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The Medical Journal of Malaysia

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Acknowledgements:
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Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia 2020; 75(6): 613-25.

NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021; 11; 398(10304): 957-80.

Books and Other Monographs:
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Goodman NW, Edwards MB. 2014. Medical Writing: A Prescription for Clarity. 4 th Edition. Cambridge University Press.

Chapter in Book
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Corporate Author
World Health Organization, Geneva. 2019. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: seventh report of a WHO study group. WHO Technical Report Series, No. 1015.

NCD Risk Factor Collaboration (NCD-RisC). Rising rural body-mass index is the main driver of the global obesity epidemic in adults. Nature 2019; 569: 260–64.

World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report 85, April 14, 2020. [cited April 2020] Accessed from: https://www.who.int/docs/defaultsource/coronaviruse/situationreports/20200414-sitrep-85-covid-19.

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Comparing fixed and auto adjusting continuous positive airway pressure (CPAP) amongst symptomatic Obstructive Sleep Apnoea patients - A randomised controlled trial

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ABSTRACT

Introduction: Continuous Positive Airway Pressure (CPAP) is required for obstructive sleep apnoea (OSA). Thisstudy compares the efficacy between Fixed Pressure CPAP (Fixed CPAP) and Auto-adjusting Pressure (APAP) based on Apnoea Hypopnoea Index (AHI), Epworth Sleepiness Score (ESS) among patients with symptomatic OSA and to ascertain their CPAP preference.

Methods: This is a prospective, randomised, crossover, single-blinded study conducted from February 2018 to February 2019 among adult subjects attending respiratory clinic Universiti Kebangsaan Malaysia Medical Centre (UKMMC).

Results: Forty-six subjects were recruited with 27 males (58.7%). The mean age was 54 (+11) year old. The baseline median Body Mass Index (BMI) was 34.2 kg/m² (Interquartile Range IQR: 30.8 kg/m² -41.7 kg/m²); baseline median AHI 28.8 /hour (IQR 21.2/hour-54.0/hour); andbaseline median ESS 15 (IQR 13-16).

After intervention, the median AHI was 5.0 / hour (IQR 4.2/hour-6.0/hour) at fixed CPAP arm; APAP arm was 5.5/ hour (IQR 4.2/hour-6.3/hour); p<0.01. The median ESS at fixed CPAP arm was 2 (IQR 0-3); APAP arm was 2 (IQR 1-3); p < 0.01. Those who preferred APAP were 22 subjects (47.8%) and had median optimal CPAP pressure 13.0 cmH_2O (IQR 12.0 cmH_2O -13.5 cmH_2O); 24 subjects (52.2%) who preferred Fixed CPAP had median optimal CPAP pressure 8.0 cmH_2O (IQR 6.3 cmH_2O -8.7 cmH_2O); p<0.01. Median baseline BMI was 37.6 kg/m² (IQR 30.8 kg/m² -43.0 kg/m²) for those who preferred APAP and 32.3 kg/m² (IQR 30.8 kg/m² - 38.4 kg/m²) for subjects preferred Fixed CPAP; p=0.03.

Discussion: Fixed CPAP maybe considered as first line therapy for symptomatic moderate and severe OSA with titrated optimal CPAP pressure less than 8 cmH2O and BMI less than 32.3 kg/m²; based on subjects' preference. Baseline AHI and average daily CPAP usage was not statisticallysignificant in affecting patient preference between fixed and auto adjusting CPAP. This is the first study of its kind conducted in Malaysia.

KEYWORDS:
Sleep Apnoea, Obstructive, Continuous Positive Airway Pressure, Mode Efficiency

INTRODUCTION

Obstructive Sleep Apnoea (OSA) is a major health burden. In Malaysia, the prevalence of OSA was estimated at 8.8% for male and 5.1% for female population.[1] Moderate to severe sleep apnoea is independently associated with increased risk of all-cause mortality.[2-5] Continuous Positive Airway Pressure (CPAP) machine therapy is the mainstay of treatment for OSA.[6] There are two modes of CPAP namely Fixed Pressure CPAP (Fixed CPAP) and Auto-Adjusting Pressure CPAP (APAP). Fixed CPAP delivers relative constant positive airway pressure throughout the respiration cycle.[7] On the other hand, the APAP delivers positive airway pressure that is dependent on respiratory event during sleep.[7] CPAP therapy improves the quality of life of sufferers and reduced all-cause mortality in symptomatic moderate to severe OSA.[4,8]

The cost of OSA treatment is substantial in Malaysia. The APAP costs Ringgit Malaysia (RM)6500-RM7500. The Fixed CPAP is relatively cheaper, costing RM4000-RM5000. CPAP machine for OSA is not covered by private medical insurance in Malaysia. Expensive treatment cost may influence patients' decisions to accept CPAP therapy in OSA.

Studies outside Malaysia have shown no difference in the efficacy between fixed CPAP and APAP for OSA.[9-11] However, there are no published data in Malaysia on the efficacy of fixed CPAP and APAP. Therefore, the objectives of our study were to evaluate the efficacy of fixed CPAP and APAP among Malaysian symptomatic OSA subjects based on Apnoea Hypopnoea Index (AHI) and Epworth Sleepiness Score (ESS) and ascertain their CPAP preference. We also looked at the key determining factors for CPAP mode device preference among recruited subjects.

MATERIALS AND METHODS

Study design

This is a prospective, randomised, crossover, single-blinded study conducted from February 2018 to February 2019 among adult subjects attending respiratory clinic Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Malaysia. This study was approved by the UKM Research Ethics Committee, Ethic code: FF-2018-207. A flow chart of the study design is shown in Figure 1.

Study subjects

We included newly diagnosed symptomatic OSA subjects aged 18 years old to 70 years old, with ESS of more than

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10/hour and sleep study AHI more than 5/hour. Subjects had no previous CPAP usage and willing to initiate long term CPAP therapy. We excluded subjects with the following comorbidities: congestive cardiac failure (CCF), severe chronic obstructive pulmonary disease with Forced Expiratory Volume in 1 second (FEV1) less than 50%, ischemic or haemorrhagic stroke, parkinsonism, neuromuscular diseases, psychiatry disorder, central sleep apnoea, craniofacial abnormalities and Pickwickian syndrome.

Sample Size

Sample size was calculated using Power and Sample Size Program (PS) version 2.1.31. Based on the reference journal Vennelle et al. with adjusted power of 80% and alpha error of 5% (p=0.05) the sample size calculated was 31.[9] To cover for 25 % drop out rate, a total sample size of 40 subjects was decided during the ethics committee meeting at UKMMC.

Procedure

A total of 50 subjects provided written consent for CPAP trial and data collection prior to enrolment into the study. Subjects were required to self-administer the validated ESS questionnaire according to their preferred language. Permission to use the validated ESS questionnaire from Mapi Research Trust France was granted. Subjects with ESS of more than 10 proceeded with sleep study. Those with high pre-test probability of moderate to severe OSA; Body Mass Index (BMI) more than 25 kg/m^2 and ESS more than 10 underwent type 3 limited sleep study at respiratory ward UKMMC. However, subjects needed to exclude other sleep breathing disorders underwent type 1 polysomnography at sleep laboratory UKMMC. Only subjects with AHI more than 5/hour were recruited.

The basic function of CPAP machine operation was explained to subjects who met the inclusion criteria and appropriate mask interface selected. Helpline provided to all subjects. They were given 3 to 5 days trial of CPAP under A-Flex mode at home to obtain the appropriate CPAP setting. Optimal pressure was taken as 95 percentiles of average CPAP pressure under A-Flex mode derived from CPAP machine memory card. Subjects were then randomised by using computer generated block of 4 randomisation by first author to either APAP (Labelled as CPAP A) or Fixed CPAP (Label as CPAP B) for 2 weeks respectively. Both groups received similar CPAP machine (Philips Respironics). Subjects were blinded to the mode of CPAP, as the CPAP screens were concealed. This was followed by 1 week of washout period. They were then crossed over to the next mode of CPAP for another 2 weeks. APAP was kept at between 4 cmH20 to 20 cmH$_2$0. The optimal pressure for fixed CPAP was derived from the 95 percentile of CPAP pressure under A-Flex mode. Subjects were followed up again at the end of respective mode of CPAP trial. Home visit was done for subjects who sought assistance via the helpline provided.

AHI and ESS changes were assessed at the end of the respective CPAP mode study. Upon completion of the study, subjects were asked for their preference between APAP and fixed CPAP machine therapy.

Statistical analysis

Statistical analysis was performed by using IBM SPSS, version 25. Demographic and baseline characteristic variables were analysed using descriptive analysis. Upon performing Shapiro Wilk normality test, baseline AHI and ESS were not normally distributed. Thus, AHI and ESS changes from baseline were analysed using Wilcoxon signed rank test, p-value less than 0.05 was considered statistically significant. Mann-Whitney test was used to compare the AHI and ESS changes between Fixed CPAP and APAP, p-value less than 0.05 was considered statistically significant. The subjects' optimal CPAP pressure, average duration of CPAP usage, baseline BMI and baseline AHI were not normally distributed. Thus, Mann-Whitney test was performed for patient CPAP mode preference in comparison with optimal CPAP pressure, average duration of CPAP usage, baseline BMI and baseline AHI. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Of the 50 subjects recruited, 46 successfully completed the study. There were no complications reported during the washout period. Four subjects withdrew from the study due to shift work and frequent traveling which contributed to 8% dropout rate. Finally,34 subjects with high pre study probability of OSA without major comorbidities underwent limited sleep study (Type 3 sleep study) at respiratory ward of UKMMC. The remaining 12 subjects who needed to exclude other sleep breathing disorders had full polysomnography (Type 1 sleep study) Among the 46 subjects who completed the study, 27 (58.7%) were males and 19 (41.3%) were females. The study population consisted of 36 (78.3%) Malays, seven (15.2%) Chinese, two (4.3%) Indians and one (2.2%) Punjabi. The mean age was 54 (+11) years, baseline median BMI 34.2 kg/m^2 (IQR: 30.8 kg/m^2 -41.7 kg/m^2), baseline median AHI of 28.8 /hour (IQR 21.2/hour-54.0/hour), baseline median ESS of 15 (IQR 13-16) (Table I).

Efficacy Between Fixed CPAP and APAP

Both fixed CPAP and APAP showed significant clinical improvement of AHI and ESS from baseline by Wilcoxon signed rank test (Table II). However, Mann-Whitney test demonstrated the efficacy between fixed CPAP and APAP were statistically not significant (Table III).

Determining factors for CPAP mode device preference

Of the 46 subjects in this study, 22 (47.8%) preferred APAP and 24 (52.2%) subjects preferred fixed CPAP. Mann-Whitney test shown that baseline BMI and optimal CPAP pressure were the determining factors for CPAP mode device preference among symptomatic OSA subjects in this study. However, baseline AHI and average CPAP usage per day were statistically not significant to affect the CPAP mode device preference among the subjects (Table IV).

DISCUSSION

The subjects in this study were mostly in their middle ages with grade 2 obesity and moderate excessive daytime sleepiness.[12,13] They had moderate to severe symptomatic OSA.[14] The ethnic composition in this study represented Malaysian demography ratio.[15]

Table I: Baseline descriptive characteristics of subjects

Characteristic	Data
Mean age + (Standard deviation)	54 (+11) year old
Gender	
Male	27 subjects (58.7%)
Female	19 subjects (41.3%)
Ethnicity	
Malay	36 subjects (78.3%)
Chinese	7 subjects (15.2%)
Indian	2 subjects (4.3%)
Punjabi	1 subject (2.2%)
Median BMI	34.2 kg/m^2 (IQR: 30.8 kg/m^2 - 41.7 kg/m^2)
Median AHI	28.8 /hour (IQR 21.2/hour-54.0/hour)
Median Epworth Sleepiness Score	15 (IQR 13-16)

*BMI: Body mass index.
*AHI: Apnoea hypopnoea index
*IQR: Interquartile range

Table II: AHI and ESS improvement from baseline between fixed CPAP and APAP

Main parameter	Baseline Median (IQR) n=46	Fixed CPAP Median (IQR) n=46	APAP Median (IQR) n=46	p value §
AHI [Events/hour]	28.8 (21.2-54.0)	5.0 (4.2-6.0)	5.5 (4.2-6.3)	<0.01
ESS	15 (13-16)	2 (0-3)	2 (1-3)	<0.01

*AHI: Apnoea hypopnoea index
*ESS: Epworth sleepiness score
*Fixed CPAP: Fixed pressure CPAP
*APAP: Auto-adjusting pressure CPAP
*IQR: Interquartile range
§ Wilcoxon signed rank test

Table III: Efficacy between fixed CPAP and APAP among symptomatic obstructive sleep apnoea

Main parameter	Fixed CPAP Median (IQR) n=46	APAP Median (IQR) n=46	p value §
AHI [Events/hour]	5.0 (4.2-6.0)	5.5 (4.2-6.3)	0.62
ESS	2 (0-3)	2 (1-3)	0.78

*AHI: Apnoea hypopnoea index
*ESS: Epworth sleepiness score
*Fixed CPAP: Fixed pressure CPAP
*APAP: Auto-adjusting pressure CPAP
*IQR: Interquartile range
§ Mann-Whitney test

Table IV: Confounding factors for CPAP device mode preference among study subjects

Parameter	Preferred Fixed CPAP Median (IQR) N 24	Preferred APAP Median (IQR) N 22	p value §
Baseline BMI [kg/m^2]	32.3 (30.8-38.4)	37.6 (30.8-43.0)	0.03
Optimal CPAP pressure [cmH^{2}0]	8.0 (6.3-8.7)	13.0 (12.0-13.5)	<0.01
Baseline AHI [event/Hour]	33.4 (21.6-59.0)	25.6 (20.7-53.1)	0.63
Average daily CPAP usage [Hours: Minutes: Seconds]	5:19:26 (5:10:15-5:38:32)	5:20:16 (4:52:51-5:37:56)	0.60

*BMI: Body mass index
*AHI: Apnoea hypopnoea index
*Fixed CPAP: Fixed pressure CPAP
*APAP: Auto-adjusting pressure CPAP
*IQR: Interquartile range
§ Mann-Whitney test

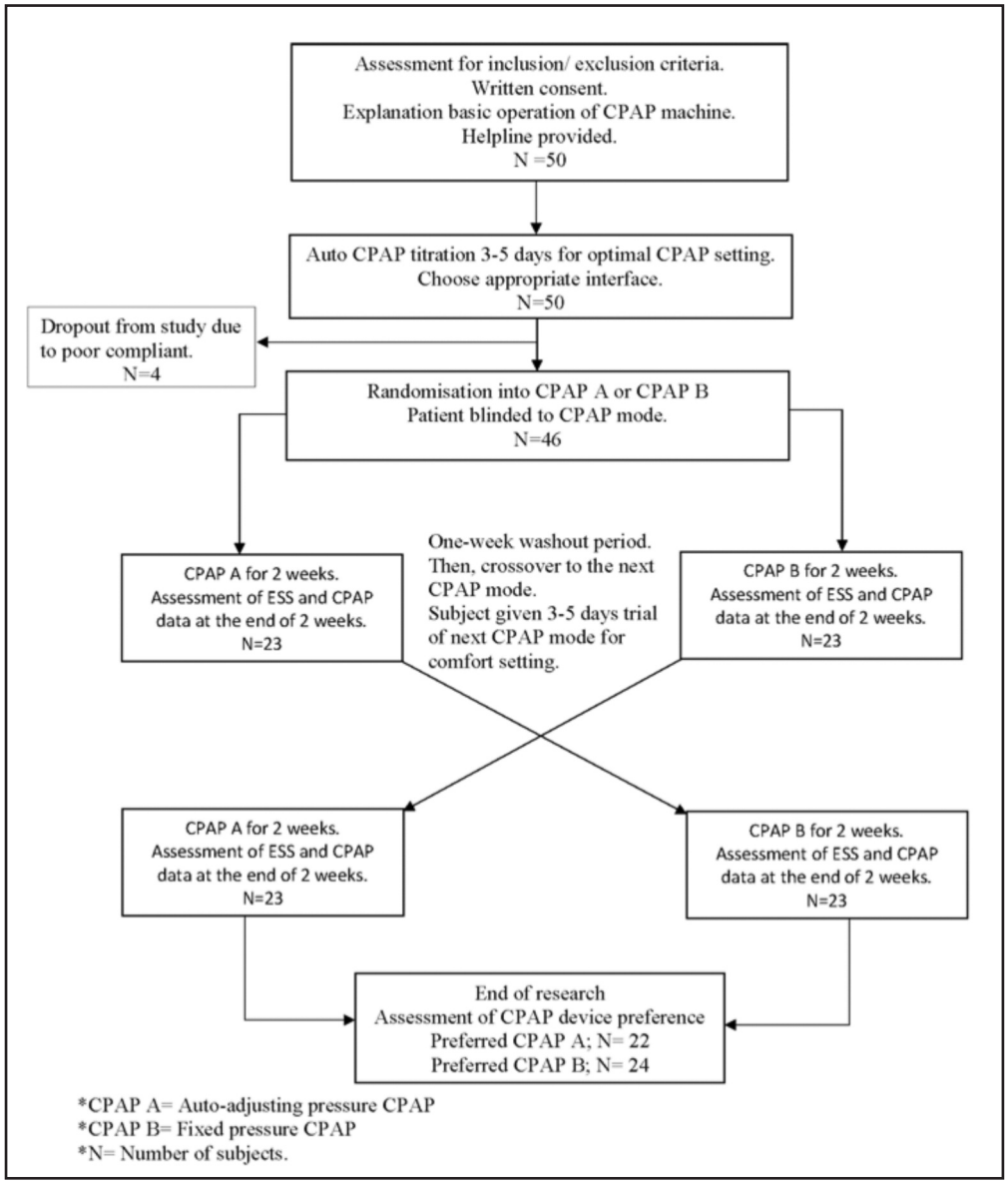

Fig. 1: Study flow chart.

In our study, 34 subjects with high pre study probability of OSA proceeded with limited sleep study (Level 3 study) at respiratory ward. However, 12 subjects who needed to exclude other sleep breathing disorders had full polysomnography at UKMMC sleep laboratory (Level 1 study). Following full polysomnography test, all these 12 subjects were diagnosed as OSA.

Our study has shown that both fixed CPAP and APAP had similar efficacy. In the fixed CPAP arm, the median AHI was 5.0 / hour (IQR 4.2/hour-6.0/hour) $p < 0.001$. In the APAP arm, the median AHI was 5.5/ hour (IQR 4.2/hour-6.3/hour) $p < 0.001$. The rate of AHI reduction between fixed CPAP and APAP (from baseline) were statistically not significant, p=0.616. Randerath et al. with almost similar study design and sample size support the outcome of our study where the AHI was obtained from polysomnography at the end of the respective mode of CPAP trial.[16] Due to our limited resources, the AHI was derived from the CPAP machine memory card at the end of the respective CPAP mode trial.

The ESS questionnaire is a simple and reliable method for measuring persistent daytime sleepiness in adults.[17] In this study, validated self-administered ESS questionnaire in English, Malay, Chinese and Tamil languages from France Mapi Research Trust were used. Both fixed CPAP and APAP demonstrated the same efficacy for improvement of ESS from baseline. The median ESS at fixed CPAP arm was 2 (IQR 0-3) and APAP arm was 2 (IQR 1-3) $p < 0.01$. Our findings show near similarity with a Hong Kong study by To et al.[11]

Contrary to our research, Noseda et al. reported that the mean ESS was significantly ($p < 0.01$) lower on APAP (5.1+ 2.8) than on fixed CPAP (6.1+ 2.8) with mean difference of 1.18 As no objective assessment of daytime vigilance was made with their small sample size, this small difference

should be interpreted with caution. Other studies, including Galetke et al. from German and Nussbaumer et al., which were double blinded studie,s have shown no statistical significance for the difference of ESS improvement among OSA patients between APAP and fixed CPAP.[19,20]

In our study, 22 subjects preferred APAP and 24 preferred fixed CPAP. Subjects who preferred APAP had higher median optimal CPAP pressure and baseline BMI compared with those patients who preferred fixed CPAP. Those preferring APAP had median optimal CPAP pressure was 13.0 cmH_2O (IQR 12.0 cmH_2O -13.5 cmH_2O) and subjects who preferred fixed CPAP had median optimal CPAP pressure of 8.0 cmH_2O (IQR 6.3 cmH_2O -8.7 cmH_2O) $p<0.01$. The median baseline BMI was 37.6 kg/m^2(IQR 30.8 kg/m^2 -43.0 kg/m^2) for those preferred APAP and 32.3 kg/m^2 (IQR 30.8 kg/m^2 -38.4 kg/m^2) for subjects preferred fixed CPAP, p 0.03. The association of optimal CPAP pressure with subjects' CPAP mode preference was similar toa study by Nolan et al. from Ireland.[10]

Contrary to our study, Nolan et al. stated that BMI was not the determining factor for CPAP mode preference among the OSA subjects.[10] However, the baseline BMI in Nolan et al. was 30.6 kg/m^2 (± 3.8 kg/m^2) for those who preferred APAP and 28.5 kg/m^2 (± 5.1 kg/m^2) for those who preferred fixed CPAP.10 The baseline BMI of subjects in Nolan et al. were relatively lower as compared to our study. The relative lower baseline BMI may have contributed to the insignificant of subjects' preference towards CPAP mode. The Randerath et al. study in 2001 found a correlation of body mass index and CPAP treatment pressures. Subjects' CPAP pressure requirement increased with higher BMI.[16] This may explain the subjects in our study with higher BMI preferred APAP. Those with higher pressure viability may do better with APAP. Further study needed in this field to define this variability.

In our study, subjects' CPAP modes preference was not affected by baseline AHI and average CPAP usage per day. We noted the compliance among those who preferred APAP and fixed CPAP were good. CPAP compliance is defined as using the therapy for an average of 4 hours a night for at least 70% of the nights.[21] In our research, those who preferred APAP had median average CPAP usage per day of 5 hours 20 minutes 16 seconds. (IQR: 4 hours 52 minutes 51 seconds- 5 hours 37 minutes 56 seconds) and 5 hours 19 minutes 26 seconds (IQR: 5 hours 10 minutes 15 seconds-5hours 38 minutes 32 seconds) for those preferred fixed CPAP. The good compliance may be due to more regular follow up by the researcher, with 24 hours helpline available for those recruited in this study. The variability of average duration of CPAP usage per day is small between those preferred APAP and fixed CPAP.

There are few limitations to our study. Firstly, our subjects were recruited from a single tertiary centre UKMMC. Besides, this is a single blinded study and manual CPAP titration was not done due to the limited resources.

CONCLUSION

In summary, APAP and fixed CPAP are equally effective in treating symptomatic OSA. If the optimal CPAP pressure is less than 8 cmH_2O and BMI less than 32.3 kg/m^2, fixed CPAP may be considered as first line modality of treatment for symptomatic OSA as it is cheaper compared with APAP.

CONFLICT OF INTEREST

None to declare.

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REFERENCES

1. Kamil MA, Teng CL, Hassan SA. Snoring and breathing pauses during sleep in the Malaysian population. Respirology 2007; 12(3): 375-80.
2. Marti S, Sampol G, Munoz X, Torres F, Roca A, Lloberes P, et al. Mortality in severe sleep apnoea/hypopnoea syndrome patients: impact of treatment. Eur Respir J 2002; 20(6): 1511-8.
3. Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. Sleep 2008; 31(8): 1079-85.
4. Yuan X, Fang J, Wang L, Yao L, Li L, Zhan X, et al. Adequate continuous positive airway pressure therapy reduces mortality in Chinese patients with obstructive sleep apnea. Sleep Breath 2015; 19(3): 911-20.
5. Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep 2008; 31(8): 1071-8.
6. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet 2014; 383(9918): 736-47.
7. Ayas NT, Patel SR, Malhotra A, Schulzer M, Malhotra M, Jung D, et al. Auto-titrating versus standard continuous positive airway pressure for the treatment of obstructive sleep apnea: results of a meta-analysis. Sleep 2004; 27(2): 249-53.
8. Batool-Anwar S, Goodwin JL, Kushida CA, Walsh JA, Simon RD, Nichols DA, et al. Impact of continuous positive airway pressure (CPAP) on quality of life in patients with obstructive sleep apnea (OSA). J Sleep Res 2016; 25(6): 731-8.
9. Vennelle M, White S, Riha RL, Mackay TW, Engleman HM, Douglas NJ. Randomized controlled trial of variable-pressure versus fixed-pressure continuous positive airway pressure (CPAP) treatment for patients with obstructive sleep apnea/hypopnea syndrome (OSAHS). Sleep 2010; 33(2): 267-71.
10. Nolan GM, Doherty LS, Mc Nicholas WT. Auto-adjusting versus fixed positive pressure therapy in mild to moderate obstructive sleep apnoea. Sleep 2007; 30(2): 189-94.
11. To KW, Chan WC, Choo KL, Lam WK, Wong KK, Hui DS. A randomized cross-over study of auto-continuous positive airway pressure versus fixed-continuous positive airway pressure in patients with obstructive sleep apnoea. Respirology 2008; 13(1): 79-86.
12. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991; 14(6): 540-5.
13. Lim TO, Ding LM, Zaki M, Suleiman AB, Fatimah S, Siti S, et al. Distribution of body weight, height and body mass index in a national sample of Malaysian adults. Med J Malaysia 2000; 55(1): 108-28.

14. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999; 22(5): 667-89.
15. Nagaraj S, Nai-Peng T, Chiu-Wan N, Kiong-Hock L, Pala J. Counting Ethnicity in Malaysia: The Complexity of Measuring Diversity. In: Simon P, Piché V, Gagnon AA, editors. Social Statistics and Ethnic Diversity: Cross-National Perspectives in Classifications and Identity Politics. Cham: Springer International Publishing 2015. p. 143-73.
16. Randerath WJ, Schraeder O, Galetke W, Feldmeyer F, Ruhle KH. Autoadjusting CPAP therapy based on impedance efficacy, compliance and acceptance. Am J Respir Crit Care Med 2001; 163(3 Pt 1): 652-7.
17. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 1992; 15(4): 376-81.
18. Noseda A, Kempenaers C, Kerkhofs M, Braun S, Linkowski P, Jann E. Constant vs auto-continuous positive airway pressure in patients with sleep apnea hypopnea syndrome and a high variability in pressure requirement. Chest 2004; 126(1): 31-7.
19. Nussbaumer Y, Bloch KE, Genser T, Thurnheer R. Equivalence of autoadjusted and constant continuous positive airway pressure in home treatment of sleep apnea. Chest 2006; 129(3): 638-43.
20. Galetke W, Anduleit N, Richter K, Stieglitz S, Randerath WJ. Comparison of automatic and continuous positive airway pressure in a night-by-night analysis: a randomized, crossover study. Respiration 2008; 75(2): 163-9.
21. Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. Am Rev Respir D 1993; 147(4): 887-95.

Reminder through mobile messaging application improves outpatient attendance and medication adherence among patients with depression: An open-label randomised controlled trial

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ABSTRACT

Introduction: Non-attendance and medication adherence are longstanding concerns in psychiatric outpatient settings. This study aimed to determine effectiveness of reminders using mobile messaging applications (messaging apps) in improving outpatient attendance and medication adherence among patients with depression.

Methods: This was a parallel, open-label randomised controlled trial with participants recruited from psychiatric outpatient services of a teaching hospital in Kuala Lumpur and a secondary hospital in Melaka. Adults (≥18 years) diagnosed with major depressive disorder; capable of reading and understanding English or Bahasa Malaysia; prescribed with at least one antidepressant and owns a smart phone were subsequently randomly assigned (1:1) to receive treatment reminders (intervention) or standard treatment without reminders (control), using a computer-generated randomisation programme. The intervention group received two reminder categories: Outpatient appointment reminders (a day before appointment); and medication reminders (weekly basis). Participants were followed-up over two months. We utilised Montgomery-Asberg Depression Rating Scale (MADRS) to measure the severity of depression; and Brief Adherence Rating Scale (BARS) to assess medication adherence. Primary outcomes were outpatient attendance rates and medication adherence assessed at two months. Secondary outcomes included changes in depression severity within each group at two months; comparison of changes in depression severity between both groups; preferences of participants towards treatment reminders, and reasons for non-attendance among participants. This trial was registered with the National Medical Research Registry, NMRR-19-3466-52001.

Results: Between February and April 2020, 183 participants were randomised to each group, of whom 179 reached study endpoint (91 [98.9%] of 92 in intervention group and 88 [96.7%] of 91 in control group). All recruited participants (n=183) were analysed using intention-to-treat approach. At two months, intervention group has significantly higher outpatient attendance rates (76.8%) than control group (56.4%) (p=0.002), and reported higher medical adherence percentage (mean difference 23.1, [95%CI 0.4, 35.8]; p<0.001). There was also significant difference in the MADRS score change between both groups (mean difference 3.4, [95%CI 0.4, 6.3]; p=0.025). Treatment reminders preferences among participants varied; forgetfulness was the most commonly reported reason (53%) for missing outpatient appointments.

Conclusion: Reminders through mobile messaging applications significantly improved outpatient attendance and medication adherence among patients with depression. Our findings support the use of messaging apps for treatment reminders in psychiatric outpatient settings. However, concerns regarding confidentiality require careful measures to be taken.

KEYWORDS:
Medication adherence, Depression, Outpatients, Mental health services, Mobile applications, Randomised controlled trial

INTRODUCTION

Non-attendance has been a longstanding issue within the healthcare system in Malaysia and is more likely to occur in the psychiatric setting compared to other specialties in medicine.[1] For psychiatric patients, non-attendance predicts higher risk of relapse and readmission.[1] A recent systematic review identified reasons for outpatients non-attendance include transportation issues, forgetfulness, poor risk perception and opportunity costs.[2]

Non-adherence to medication is another area of concern, associated with poorer prognosis and incremental differences of treatment cost. The rate of non-adherence among patients with depression ranged from 40% to 66.9% [3-5], with forgetfulness being the main reason for non-adherence in majority.[6] Antidepressants were also found to have the highest proportion (74.5%) of reporting forgetfulness as reason, among all psychotropic medications.[5]

Individuals with depressive symptoms had shown 12% reduction in memory functioning.[7] The nature of depression, such as lack of motivation, being pessimistic towards

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treatment and recovery could further contribute to non-attendance and medication non-adherence. Considering the above, reminders might not only benefit depressed individuals in terms of tackling forgetfulness, but also encourages treatment adherence.

Many studies have proven the efficacy of different reminder forms - such as phone calls, emails and short message service (SMS) - with disparities in cost-efficiency and staff dependence. However, studies on reminders utilising mobile messaging applications (messaging apps) to improve psychiatric outpatient attendance and medication adherence are relatively few. With the continuously increasing penetration of smartphones among Malaysians,[8] 97.3% of Malaysian internet users are using messaging apps in January 2021.[9] suggesting this to be the most efficient method for reminders delivery.

The primary objective of this study was to assess outpatient attendance rates and medication adherence of intervention and control group. Secondary objectives included determining changes in depression severity within each group between baseline and two months; comparing changes in depression severity between both groups; identifying preferences of participants towards treatment reminders, and exploring reasons for missing outpatient appointments among patients with depression.

MATERIALS AND METHODS

Study design

This is an open-label randomised controlled trial conducted in two psychiatric outpatient settings of different states in Malaysia: University Malaya Medical Centre (UMMC), a university hospital located in Kuala Lumpur; and Hospital Melaka (HM), a secondary hospital located in state of Malacca, approximately 150km away from Kuala Lumpur. The study was conducted between February and June 2020.

Ethical approvals for the study were obtained from Medical Research Ethics Committee of UMMC (MREC ID: 20191127-8047) and Medical Research and Ethics Committee of the Ministry of Health Malaysia, through the National Medical Research Registry (NMRR) (NMRR ID: NMRR-19-3466-52001).

Participants

Participants were 18 years old and above, newly diagnosed patients with major depressive disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria, capable of reading and understanding either English or Bahasa Malaysia, prescribed with at least one antidepressant, owns a smart phone and consented to partake in the study. Participants were excluded from the study if they were diagnosed with severe medical condition(s), which might affect their cognitive function and physical ability to travel to hospital independently; or other major psychiatric disorders with psychotic symptoms and/or severe cognitive impairment. Written informed consent was obtained from all participants, and each of them was followed up for two months.

Randomisation and Procedures

Upon recruitment, participants were required to fill up the Socio-Demographic Questionnaire and Treatment Reminder Preference Questionnaire. Baseline depression severity were then assessed using Montgomery-Asberg Depression Rating Scale (MADRS) before they were randomly assigned (1:1) to intervention or control group. Participants were randomised through block randomisation (size of 8) and random number generation using a computer-generated randomisation programme.

The intervention group received both reminder types: i) Medication adherence - at one week after last outpatient appointment and weekly thereafter; ii) Outpatient appointment - at one day before appointment. Reminders were delivered through their preferred mobile messaging applications as indicated, which comprised of either WhatsApp, WeChat, Telegram or Line. The control group did not receive any reminders. Throughout the two months of follow-up, attendance of each participant was tracked through the electronic medical record system in UMMC, and daily manual attendance records in HM. For the intervention group, those who had missed their appointments would be reminded once for rescheduling. The control group would not receive any reminder under similar circumstances.

At two months after randomisation, all participants were assessed with MADRS and Brief Adherence Rating Scale (BARS) during their outpatient appointment.

Outcomes

The primary outcomes were outpatient attendance rate and medication adherence (BARS percentage), assessed at two months. Outpatient attendance rate was calculated by dividing number of appointments attended by number of appointments scheduled within study period. Missed appointments were coded as absent, and participants who missed their appointments were contacted through phone to enquire regarding reasons for non-attendance. Appointments cancelled by psychiatrists or rescheduled ahead of time were excluded from analysis.

Brief Adherence Rating Scale (BARS) is a clinician-administered adherence assessment tool. It comprises three questions and a visual analogue scale to assess proportion of doses taken in the past month (0–100%). BARS demonstrated good sensitivity (73%) and specificity (74%) in identifying non-adherent outpatients.[10]

Secondary outcomes assessed at two months include MADRS score difference from baseline within each group; comparison of MADRS score difference between both groups; preferences regarding treatment and medication reminders; and reasons missing outpatient appointments.

Montgomery-Asberg Depression Rating Scale (MADRS) is a clinician-administered scale for depression severity assessment, particularly sensitive in evaluating treatment effects. It includes ten items rated on a 0 to 6 scale, yielding a total score from 0 to 60. Usual cut-off points are 0 to 6 for normal; 7 to 19 for mild depression; 20 to 33 for moderate depression; 34 and above for severe depression. MADRS has

Table I: Baseline socio-demographic characteristics of participants

	Total (n=183)	Intervention group (n=92)	Control group (n=91)	p value
Age, years				
Mean (SD)	29.4 (11.7)	30.5 (13.0)	28.3 (10.2)	0.618*
Median (IQR)	25 (13)	25 (17)	25 (11)	
Gender				
Male	61 (33.3%)	33 (35.9%)	28 (30.8%)	0.464**
Female	122 (66.7%)	59 (64.1%)	63 (69.2%)	
Ethnicity				
Malay	126 (68.9%)	60 (65.2%)	66 (72.5%)	0.271**
Chinese	33 (18.0%)	17 (18.5%)	16 (17.6%)	
Indian	14 (7.7%)	7 (7.6%)	7 (7.7%)	
Others	10 (5.5%)	8 (8.7%)	2 (2.2%)	
Marital status				
Single	116 (63.4%)	58 (63.0%)	58 (63.7%)	0.909**
Married/ partnership	59 (32.2%)	29 (31.5%)	30 (33.0%)	
Divorced	5 (2.7%)	3 (3.3%)	2 (2.2%)	
Widowed	3 (1.6%)	2 (2.2%)	1 (1.1%)	
Occupation				
Employed	66 (36.1%)	36 (39.1%)	30 (33.0%)	0.205**
Self-employed	8 (4.4%)	3 (3.3%)	5 (5.5%)	
Unemployed	16 (8.7%)	5 (5.4%)	11 (12.1%)	
Retired	6 (3.3%)	5 (5.4%)	1 (1.1%)	
Homemaker	14 (7.7%)	5 (5.4%)	9 (9.9%)	
Student	73 (39.9%)	38 (41.3%)	35 (38.5%)	
Education level				
Primary	3 (1.6%)	1 (1.1%)	2 (2.2%)	0.779**
Secondary	42 (23.0%)	19 (20.7%)	23 (25.3%)	
Post-secondary	16 (8.7%)	9 (9.8%)	7 (7.7%)	
Higher	122 (66.7%)	63 (68.5%)	59 (64.8%)	
Travel distance (house to hospital), km				
<5	41 (22.4%)	21 (22.8%)	20 (22.0%)	0.354**
5 – 10	41 (22.4%)	16 (17.4%)	25 (27.5%)	
10 – 15	60 (32.8%)	31 (33.7%)	29 (31.9%)	
>15	41 (22.4%)	24 (26.1%)	17 (18.7%)	

SD=Standard deviation; IQR=Interquartile range. *Mann-Whitney test **Chi-square test.

Table II: Comparison of outcome measures between intervention and control group

	Intervention group (n=92)	Control group (n=91)	Mean difference (95% CI)	t-statistic (df)	Z-statistic	p value
Primary outcomes						
Attendance percentage						
Mean (SD)	76.8 (35.3)	56.4 (44.5)				
Median (IQR)	100 (50)	67 (100)			-3.161	0.002*
BARS percentage						
Mean (SD)	60.2 (43.1)	37.1 (44.0)	23.1 (0.4, 35.8)	3.59 (181)		<0.001**
Secondary outcome						
Mean of MADRS score change (SD)	9.4 (10.8)	6.0 (9.1)	3.4 (0.4, 6.3)	2.27 (181)		0.025**

SD=Standard deviation; IQR=Interquartile range. *Mann-Whitney test **Independent t-test. CI: Confidence interval; df: Degrees of freedom; BARS: Brief Adherence Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale.

Table III: MADRS score changes within both groups

	Mean of MADRS score (SD)		Mean of MADRS score change (95% CI)	p value*
	Baseline	Two months		
Intervention group	32.7 (10.1)	23.3 (12.4)	9.4 (7.2, 11.6)	<0.001
Control group	32.6 (9.5)	26.5 (12.1)	6.0 (4.1, 7.9)	<0.001

SD=Standard deviation. *paired t-test. CI: Confidence Interval; MADRS: Montgomery-Asberg Depression Rating Scale.

Table IV: Preferences towards reminders using mobile messaging application

Variables	n (%)
Agreement towards reminders	
Yes	180 (98.4)
No	3 (1.6)
Reason agreeing	
To avoid forgetting	54 (29.5)
Being forgetful	43 (23.5)
Convenience	30 (16.4)
Being health-conscious	2 (1.1)
Feeling of concern	2 (1.1)
Others	4 (2.2)
No specific reason	45 (24.6)
Not applicable – opted for "Disagree"	3 (1.6)
Concerns regarding confidentiality	
Present	80 (43.7)
Absent	103 (56.3)
Timing for reminders (throughout the day)	
Morning	74 (40.4)
Afternoon	31 (16.9)
Evening	50 (27.3)
Office hours	5 (2.7)
Anytime	20 (10.9)
No preference	3 (1.6)
Day for appointment reminders, prior to appointment	
One day	38 (20.8)
Two days	36 (19.7)
Three days	29 (15.8)
One week	26 (14.2)
One week, along with one day	19 (10.4)
Two days, along with one day	6 (3.3)
Others	24 (13.3)
No preference	5 (2.7)
Frequency of medication reminders	
Monthly	10 (5.5)
Fortnightly	4 (2.2)
Weekly	59 (32.2)
Twice per week	14 (7.7)
Daily	20 (10.9)
Once in between appointments	9 (4.9)
No preference	4 (2.2)
Not required	63 (34.4)
Preferred mobile messenger application	
WhatsApp	160 (87.4)
Telegram	13 (7.1)
WeChat	1 (0.5)
WhatsApp or Telegram	5 (2.7)
WhatsApp or WeChat	1 (0.5)
Not applicable – opted for "Disagree"	3 (1.6)

high inter-rater reliability and validity, as its scores correlated well with scores on Hamilton Rating Scale for Depression (HAM-D), a standard rating scale for depression.[11]

Statistical Analysis

The sample size for this study was calculated using the formula as below, taking $\alpha = 0.05$, $\beta = 0.2$ and the expected proportion from previous study by Branson et al. (12)

$$n=\theta[\frac{\pi_t (1 - \pi_t) + \pi_c (1 - \pi_c)}{(\pi_t - \pi_c)^2}]$$

The smallest sample size to detect a difference between two groups was 154.

Data collected was analysed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA). The intention-to-treat approach was used to include all participants who were recruited and randomly assigned into analysis. For those who missed their appointments or were withdrawn from study, their MADRS scores and BARS percentage were imputed as the last observed value, as per last observation carried forward (LOCF) method. All statistical tests were two-tailed with alpha value of 0.05. The main study parameters analysed include: i) Outpatient attendance rate of both groups compared using Mann-Whitney test; ii) Brief Adherence Rating Scale (BARS) percentage of both groups, along with MADRS score difference between both groups compared using independent t-test; iii) MADRS score difference from baseline within each

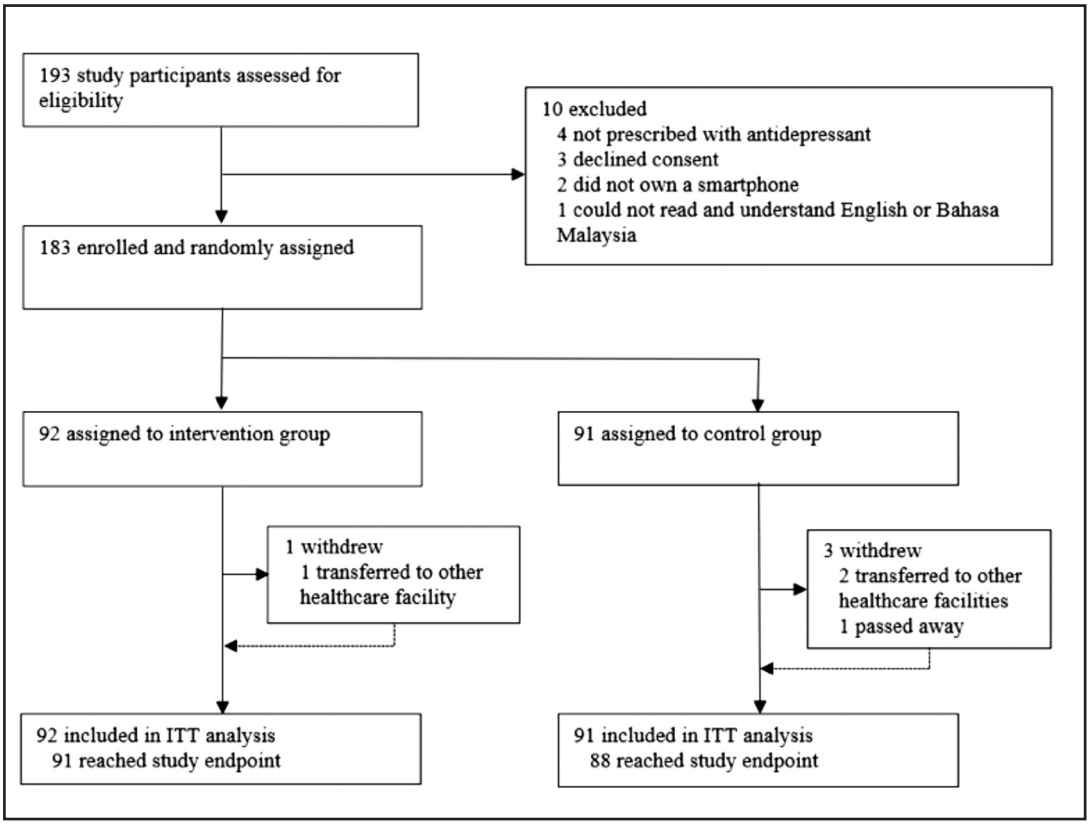

Fig. 1: Disposition of study participants.

group compared using paired t-test. Descriptive statistics were used to summarise data from Treatment Reminder Preference Questionnaire and reasons for non-attendance.

RESULTS

Between February and June 2020, from the 193 participants were assessed for eligibility in the study. 183 were recruited and 179 reached the study endpoint after two months of follow-up. All recruited participants were included for analysis, in accordance with intention-to-treat approach as shown in Figure 1.

Baseline socio-demographic data of both groups were comparable (Table I), with most participants being Malay females with higher education.

Attendance rate of intervention group (76.8%) was significantly higher than control group (56.4%) (p=0.002) (Table II). Similarly, the medication adherence (assessed using BARS) of intervention group (60.2%) was much higher than control group as well (37.1%) (p<0.001) (Table II).

For the secondary outcomes, MADRS scores had increased significantly in both groups after two months of treatment (p<0.001). The intervention group reported mean score change of 9.4 (95%CI 7.2, 11.6); while the control group reported mean score change of 6.0 (95%CI 4.1, 7.9) (Table III). Mean difference of the MADRS score change between the two groups was significant (p=0.025) at 3.4 (95%CI 0.4, 6.3) (Table II).

Our descriptive analyses show that 98.4% of participants preferred receiving reminders, with over half (53%) being concerned about forgetfulness. 43.7% (n=80) expressed concerns regarding confidentiality. 87.4% selected WhatsApp as their preferred mobile messaging application for reminders delivery (Table IV).

Forgetting the appointment was stated as the most common reason (31.0%, n=18) for participants to miss their outpatient appointments, followed by issues related with the national lockdown (20.7%) and personal issues (13.8%).

DISCUSSION

This study demonstrated that reminders through mobile messaging applications are effective in improving outpatient attendance and medication adherence among patients with depression. At two months, the increase in outpatient attendance rate of intervention group was 20% higher than that of control group (p=0.002). Interestingly, this difference is higher than recent studies which utilised short message service (SMS) reminders among general psychiatric patients: Kunigiri et al. found 8% increment of attendance rate among adult patients;[13] while Branson et al. reported 16% increment among adolescents.[12] This might be due to varying levels of non-attendance among patients with different diagnoses. For instance, Rajasuriya et al. had reported significant higher risk of non-attendance in patients with substance misuse disorders, anxiety disorders and organic disorders, including dementia.[14] Another possibility would be the higher efficacy of messaging apps in delivering reminders compared to SMS,

which would require direct comparisons in future to confirm said hypothesis.

Messaging apps reminders were effective in improving medication adherence among participants, with 60.2% of mean BARS percentage in intervention group compared to 37.1% in control group ($p<0.001$). This finding is similar to a meta-analysis focused on patients with non-communicable diseases,[15] which reported significant increase in adherence in groups receiving reminders compared to controls. Significant MADRS score changes at two months within each group ($p<0.001$) showed that antidepressant treatment would improve depressive symptoms overall. We have also discovered association between reminders and MADRS score improvement with a mean difference of 3.4 (95%CI 0.4, 6.3) ($p=0.025$), which could be explained by the synergistic effect of improved outpatient attendance and medication adherence in intervention group.

Expectedly, forgetfulness was identified as the most common reason for non-attendance in our study (31.0%). This finding is similar to that of primary care setting, which reported forgetting about the appointment or unawareness being the most common reason for non-attendance (37.6%) (16). Forgetting clinic appointments can be multifactorial including life events, perceived importance of follow-ups, and the aforementioned nature of depression.

Implementation of reminder system in psychiatric outpatient setting was well accepted by almost all participants (98.4%), however 43.7% raised concerns about confidentiality on the reminder system. While mental health awareness has greatly improved in recent years, stigmatisation still prevails in certain populations with poorer mental health literacy.[17,18] Confidentiality issues should be discussed explicitly to address these concerns and improve trust of patients. Majority of participants (87.4%) selected WhatsApp as the preferred mobile messaging application for reminders, in concordance with WhatsApp being ranked as most used messaging app among Malaysian internet users (91.9%) in first quarter of 2021.[9] Feedbacks of participants towards reminder deliveries were generally positive, with considerable variations in preferred time and frequency of reminders.

There were several limitations in this study. As we had sent out reminders manually without counterchecking, confirmation receipts for messages were not warranted in this study. The Brief Adherence Rating Scale (BARS) used in this study was only validated for oral antipsychotics use. However, the psychometric properties of BARS are well demonstrated,[10] with our data contributing to the understanding towards its adaptability in assessing antidepressant adherence. As the intervention was designed to be one-way reminders, several treatment queries (submitted as replies) were unanswered. This raised the need for an interactive platform, preferably with a triaging system to address and encourage patient engagement. Lastly, as the second half of study period coincided with national lockdown due to Coronavirus disease 2019 (COVID-19), the national lockdown acted as potential confounder in this study.

Future research could be undertaken in wider context with patients diagnosed with other psychiatric conditions, while utilising the data here as reference. Larger sample size across diverse healthcare settings, such as district hospitals and community clinics, would greatly improve the generalisability. Besides, the association between treatment reminders and greater MADRS score improvement can be formally explored. A link between hospital appointment data and messaging apps could be devised for automated reminders, with an interactive approach for patient to confirm or reschedule the appointment. Triaging system alerting medical staffs to responses with crucial health information would be useful as well. Lastly, a post-intervention feedback could be gathered to recognise and work on any issue that arises.

Treatment reminders and service response to non-attendance are vital parts of patient care for psychiatric outpatients. Utilising messaging apps for this purpose should be considered given its high penetration and proven effectiveness.

CONCLUSION

Our findings show that reminders through mobile messaging applications improved both outpatient attendance and medication adherence among patients with depression, resulting in greater improvement of depressive symptoms. Treatment reminders were generally well accepted and feasible in a psychiatric outpatient setting. However, potential issues such as confidentiality should be carefully handled while advocating reminder services.

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CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Mitchell AJ, Selmes T. Why don't patients attend their appointments? Maintaining engagement with psychiatric services. Adv Psychiatr Treat 2007; 13(6): 423-34.
2. Sheng Lee RR, Samsudin MI, Thirumoorthy T, Low LL, Kwan YH. Factors affecting follow-up non-attendance in patients with type 2 diabetes mellitus and hypertension: A systematic review. Singapore Med J 2019; 60(5):216-23.
3. Banerjee S, Varma RP. Factors affecting non-adherence among patients diagnosed with unipolar depression in a psychiatric department of a tertiary hospital in Kolkata, India. Depress Res Treat 2013; 2013: 809542.
4. Lingam R, Scott J. Treatment non-adherence in affective disorders. Acta Psychiatr Scand 2002; 105(3): 164-72.
5. Bulloch AGM, Patten SB. Non-adherence with psychotropic medications in the general population. Soc Psychiatry Psychiatr Epidemiol 2010; 45(1): 47-56.
6. Shrestha Manandhar J, Shrestha R, Basnet N, Silwal P, Shrestha H, Risal A, et al. Study of adherence pattern of antidepressants in patients with depression. Kathmandu Univ Med J 2017; 15(57): 3-9.

7. Hubbard NA, Hutchison JL, Turner M, Montroy J, Bowles RP, Rypma B. Depressive thoughts limit working memory capacity in dysphoria. Cogn Emot 2016; 30(2): 193-209.
8. Malaysian Communications and Multimedia Commission. Hand Phone Users Survey 2018 [cited Jun 2021]. Available from: https://www.mcmc.gov.my/skmmgovmy/media/General/pdf/HPUS2018.pdf
9. Global Web Index. Digital in Malaysia: All the Statistics You Need in 2021 — DataReportal – Global Digital Insights 2021 [cited Jun 2021]. Available from: https://datareportal.com/reports/digital-2021-Malaysia
10. Byerly MJ, Nakonezny PA, Rush AJ. The Brief Adherence Rating Scale (BARS) validated against electronic monitoring in assessing the antipsychotic medication adherence of outpatients with schizophrenia and schizoaffective disorder. Schizophr Res 2008; 100(1–3): 60-9.
11. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134(4): 382-9.
12. Branson CE, Clemmey P, Mukherjee P. Text message reminders to improve outpatient therapy attendance among adolescents: a pilot study. Psychol Serv 2013; 10(3): 298-303.
13. Kunigiri G, Gajebasia N, Sallah D. Improving attendance in psychiatric outpatient clinics by using reminders. J Telemed Telecare 2014; 20(8): 464-7.
14. Rajasuriya M, De Silva V, Hanwella R. Effectiveness of reminders in reducing non-attendance among out-patients. Psychiatrist 2010; 34(12): 515–8.
15. Fenerty SD, West C, Davis SA, Kaplan SG, Feldman SR. The effect of reminder systems on patients' adherence to treatment. Patient Prefer Adherence 2012; 6: 127–35.
16. Saif U, Sangeetha R, Todd L, Ellen D, Regina J, Swapna A, et al. Why do Patients Miss their Appointments at Primary Care Clinics? J Fam Med Dis Prev 2018; 4: 090.
17. Ibrahim N, Amit N, Shahar S, Wee LH, Ismail R, Khairuddin R, et al. Do depression literacy, mental illness beliefs and stigma influence mental health help-seeking attitude? A cross-sectional study of secondary school and university students from B40 households in Malaysia. BMC Public Health 2019; 19 (Suppl 4): 544.
18. Despande SRK, Ngadimon IWB, Yaacob NLC. Stigma and attitudes towards mental health disorders: A cross sectional study at a private university in Malaysia. Malaysian J Public Heal Med 2020; 20(1): 40-7.

ORIGINAL ARTICLE

Is lower dose of intramuscular dexamethasone injection beneficial in reducing neonatal respiratory morbidity for elective caesarean section deliveries at 37 to 38 weeks? An observational study

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ABSTRACT

Introduction: The use of intramuscular (IM) dexamethasone injections before an elective caesarean delivery at term has been shown in multiple randomized controlled trials to reduce the rates of transient tachypnoea of the newborn, and admission to neonatal care. Recent studies have suggested that a complete course of IM steroids can be associated with long term harmful consequences to the infants born, and there have been studies suggesting that a lower dose of IM corticosteroids can be beneficial. Therefore, we aim to establish if halving the dose of dexamethasone to 12mg can demonstrate any benefit for term elective caesarean section deliveries whilst minimizing foetal exposure.

Methods: An observational controlled study comparing neonatal respiratory morbidities before and after the single dose 12mg dexamethasone was implemented in our obstetrics and gynaecology centre for term elective caesarean section deliveries.

We included singleton pregnancies from 37+0 to 38+6 weeks undergoing elective caesarean section into our study. A total of 674 patients fulfilled the inclusion criteria and were recruited. We compared the rates and duration of admission to neonatal intensive care unit, the need for mechanical ventilation and the rate of transient tachypnoea of the newborn in the first half of 2019 without IM dexamethasone injections against the second half of the year when a single dose IM dexamethasone was given.

Results: IM dexamethasone injection did not show any significant benefit with regards to reducing the admission to neonatal care (OR 0.97, p- value 0.69), admission to neonatal intensive care unit (OR 0.91, p- value 0.80), the need for mechanical ventilation (OR 0.98, p- value 0.95), and the incidence of transient tachypnoea of the newborn (OR1.01, p- value 0.96). There was also no significant difference for the duration of admission in the neonatal intensive care unit for both groups (p- value 0.17).

Conclusions: This study showed that there was no significant benefit gained from the lower dose antenatal corticosteroids for term elective caesarean section deliveries and considering that there have been long term harmful consequences demonstrated from the higher dose of antenatal corticosteroids at term, this practice should therefore be discontinued until a larger study is done to refute these findings. The use of such dexamethasone should only be a viable option in a research setting.

KEYWORDS:
Antenatal corticosteroids, dexamethasone, transient tachypnoea of the newborn, respiratory distress syndrome

INTRODUCTION

In 1972, it was first demonstrated by Liggins and Howie that the administration of corticosteroids to preterm pregnancies prior to delivery reduces the morbidity and mortality of preterm infants. These revolutionary findings led to the widespread use of corticosteroids to reduce the risk of respiratory distress syndrome in pregnant mothers at risk of preterm delivery.[1-5]

At birth, the foetal lung is the most crucial organ for survival. The exact mechanism for the action of corticosteroid is by promoting gas exchange in the foetal lungs. Glucocorticoids causes the reduction of the distance between the blood vessels and the airway, thus providing better exchange of gas in the foetal lungs. It works by reducing the cellular proliferation rates at the mesenchymal tissue therefore reducing the distance for the gas exchange. It also increases the surfactant production and enhances the ability for the airway to remove fluid from the lungs at birth.[6]

There has since been multiple randomized controlled trials and meta- analyses demonstrating the benefits of intramuscular corticosteroids injections in reducing neonatal respiratory morbidities and including intraventricular haemorrhage and necrotizing enterocolitis in preterm infants.[7-11] It is now a recommended practice to administer intramuscular (IM) corticosteroids for pregnancies at risk of preterm delivery.

In 2005, a multicentre pragmatic randomised trial led by Stutchfield first showed that the benefits from IM corticosteroids do extend to term infants undergoing elective

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caesarean section.[12] Since then, a published Cochrane meta-analysis in 2018 combining four randomized controlled trials with a total pool of 3956 patients found that there was significant reduction in respiratory distress syndrome, transient tachypnoea of the neonate, admission to neonatal intensive care unit, admission to neonatal special care for respiratory complications.[12-16]

These randomized controlled trials used the dose for corticosteroids in either of the following regime- IM betamethasone 12mg od 48 hours and 24 hours prior to caesarean section, or IM dexamethasone 2 or 4 doses of 24mg from 48 hours prior to caesarean section or at 37 weeks. [12-16]

The optimal dose for IM corticosteroids and the superiority of individual corticosteroid regime over the other in term infants has not been clearly established.[17] The World Health Organization (WHO) recommended the use of dexamethasone instead of betamethasone as it is more widely available.[19] The 24mg dose for corticosteroids was based on animal studies and appeared sufficient to achieve the steroid concentrations observed in infants after birth during normal physiological stress. The administration of a total dose of 24 mg is most likely the most important for maximal neonatal benefits, but a lower single steroid dose may be useful to reduce maternal side effects, including those in patients with diabetes during pregnancy.[17,18,20,21] A lower dose IM corticosteroids-betamethasone injection has been shown to be beneficial in lab studies and there have also been studies suggesting that the dose of intramuscular corticosteroids should be individualized.[22,25] Additionally, the long-term effects of 24mg corticosteroids administration have not been clearly established. A questionnaire survey follow-up of the trial conducted by Stutchfield et al. suggested that there were no significant association with emotional and academic performance for the children who were given a full course of antenatal corticosteroids prior to caesarean section delivery.[26] However, a recent population-based retrospective cohort study showed that the exposure to a full course maternal antenatal corticosteroid treatment was significantly associated with mental and behavioural disorders in children.[28] It is now no longer recommended in certain centres to give a course of IM dexamethasone prior an elective caesarean section at term. Nevertheless, giving antenatal corticosteroids prior to an elective caesarean section between 37 to 38 weeks is still widely practised in this country.

Therefore, we hope to be able to establish the effectiveness of a lower dose corticosteroids by using a single 12mg IM dexamethasone dose given to mothers antenatally 24 hours prior to having an elective caesarean section. It can limit the unwanted effects of full dose dexamethasone as well as having better compliance in patients. It is thus pertinent to know if any benefit can be derived from a lower dose of IM corticosteroids in reducing neonatal respiratory morbidities and neonatal admissions.

MATERIALS AND METHODS

This was a retrospective observational controlled cohort study of patients undergoing elective caesarean section at 37 weeks to 38 weeks 6 days of gestation and comparing the respiratory morbidities before and after the implementation of 12mg IM dexamethasone in the Obstetrics and Gynaecology Department, Hospital Tuanku Ja'afar (HTJ), Seremban, Malaysia. This study compared two unpaired population sample before and after the implementation of single dose 12mg IM dexamethasone administration to elective caesarean deliveries from 1st July 2019 onwards. The 12mg IM dexamethasone would be administered at least 24 hours before the elective lower segment caesarean section delivery by a trained nurse.

The sampling of the records was done retrospectively according to the inclusion criteria from 1st January 2019 to 30th June 2019, and compared to records from 1st July 2019 to 31st December 2019, records for patients that fulfilled the inclusion criteria will be entered into this study. There were around 880 elective caesarean deliveries performed a year in HTJ therefore, the expected population size is around 880 participants. This study has been registered with NMRR with an ID NMRR-20-2198-54512 (IIR), and with a reference to the document KKM/NIHSEC/P20-2131(10).

Inclusion and exclusion criteria

This study will include patients with singleton pregnancies undergoing elective caesarean section at 37 weeks to 38 weeks 6 days between 1st January 2019 to 31st December 2019.

Under the exclusion criteria, pregnancies that have been diagnosed with foetal congenital malformations or aneuploidy were excluded from the study. Mothers with hypersensivities or were unable to tolerate dexamethasone were excluded. Patients with pre-eclampsia, foetomaternal blood immunization, chorioamnionitis, severely growth restricted foetuses with a birth weight of less than 1.8kg, macrocosmic babies with birth weight of more than 4.5kg, patients who are tested positive for HIV, hepatitis B, hepatitis C or syphilis serology were also excluded from the study. Patients with diabetes in pregnancy on insulin were excluded.

Sample Size

The population for this study was estimated to be around 880 patients undergoing elective caesarean section in a period of one year in HTJ. Therefore, each arm will have around 440 population size. Using a 95% confidence interval with a 5% margin of error from previous studies, the final sample size for each arm should be 205 or higher to give a sufficient representation. This was calculated using Epi InfoTM version 7.2.4.0.

Study outcomes

The study outcomes measured were the rates of respiratory distress syndrome and transient tachypnoea of the newborns; the rates of admission to Neonatal Intensive Care Unit (NICU) and neonatal special care, and the length of stay in the NICU.

We compared the odd ratios and mean of each arm using the Chi- square test and T- test in IBM SPSS version 26. Numerical variables were presented using mean and 95% confidence interval while the categorical variable was presented using odds ratio and their standard deviations (SD).

Table I: Summary comparing the mean age, birth weight, gestational age, and demographics comparison for both groups

	Without dexamethasone (n= 333)	With dexamethasone (n= 341)	P- value
Mean age (years)	33.0 (SD 4.58)	31.7 (SD 4.62)	0.985
Mean birth weight (kg)	2.88 (SD 0.42)	2.91 (SD 0.41)	0.346
Mean gestational age (weeks)	37+2 (SD 4.1 days)	37+3 (SD 2.7 days)	0.211
Demographics:			
Malays	262 (78.7%)	280 (82.1%)	0.261
Chinese	31 (9.3%)	22 (6.4%)	0.168
Indian	30 (9.0%)	28 (8.2%)	0.712
Foreigner	5 (1.5%)	5 (1.5%)	0.970
Other Race	5 (1.5%)	6 (1.8%)	0.792

Table II: Correlation of measured outcomes - for admission to special care nursery, NICU, neonates developing TTN, neonates that required mechanical ventilatory support, and the duration of admission in NICU - with treatment

	Without dexamethasone (n= 333)	With dexamethasone (n= 341)	Odds Ratio (95% CI)	P- value
Admission to special care nursery	29 (8.7%)	30 (8.8%)	0.970 (0.568- 1.656)	0.689
Admission to NICU	15 (4.5%)	14 (4.1%)	0.908 (0.431- 1.911)	0.799
Complications of TTN	28 (8.4%)	27 (7.9%)	1.014 (0.584- 1.760)	0.961
Requiring ventilatory support in NICU	13 (3.9%)	13 (3.8%)	0.976 (0.445- 2.137)	0.951
Duration of admission in NICU (Mean, SD)	1 week 1 day (SD 8 days)	5 days (SD 2 days)		0.172

NICU= Neonatal Intensive Care Unit; TTN= Transient Tachypnoea of the Newborn

Table III: Summary of the measured outcomes for maternal age group below 35-year-old

	Without dexamethasone (n= 233)	With dexamethasone (n= 255)	Odds Ratio (95% CI)	P- value
Admission to special care nursery	17 (7.8%)	21 (8.2%)	1.056 (0.542- 2.057)	0.873
Admission to NICU	13 (6.0%)	9 (3.53%)	0.619 (0.260- 1.477)	0.276
Complications of TTN	18 (8.3%)	17 (6.7%)	0.853 (0.429- 1.698)	0.651
Requiring ventilatory support in NICU	11 (5.1%)	10 (3.9%)	0.823 (0.343- 1.977)	0.663
Duration of admission in NICU (Mean, SD)	1 week 2 days (SD 9 days)	6 days (SD 2.5 days)		0.198

Table IV: Summary of the measured outcomes for maternal age group 35-year-old and above

	Without dexamethasone (n= 100)	With dexamethasone (n= 86)	Odds Ratio (95% CI)	P- value
Admission to special care nursery	13 (13%)	10 (11.6%)	0.881 (0.365- 2.123)	0.777
Admission to NICU	2 (2%)	3 (3.5%)	1.770 (0.289- 10.854)	0.531
Complications of TTN	9 (9%)	11 (12.8%)	1.483 (0.584- 3.768)	0.405
Requiring ventilatory support in NICU	2 (2%)	3 (3.5%)	1.771 (0.289- 10.854)	0.531
Duration of admission in NICU (Mean, SD)	1 week (SD 3.9 days)	6 days (SD 2.0 days)		0.580

RESULTS

There were 883 patients who underwent elective caesarean section in 2019. A total of 674 patients fulfilled our study criteria and was entered into our analysis. The commonest reason for exclusion in both groups was infants born to mothers with diabetes in pregnancy requiring insulin, as their newborns will require routine admission and observation in the neonatal special care for hypoglycaemia. There were 74 in the control and 68 in the treatment arm for patients who required insulin antenatally. The second commonest reason for exclusion was being beyond the studied gestational age during the caesarean section delivery. The flow chart for patient recruitment is outlined in Figure 1. The commonest indication for the elective caesarean section for both groups was having multiple previous caesarean section.

Table I shows that both groups of the study were comparable with no significant differences for the mean age, birth weight, gestational age, and demographic distribution. Therefore, there was no significant evidence of bias between the two groups. Table II summarizes the measured outcomes between the group that were given dexamethasone and the control group, without the dexamethasone injection.

As the SD for the mean age in both groups crosses 35-year-old therefore, we have done an additional analysis on the measured outcomes in different age groups, ≥35-year-old and <35-year-old. We tabulated these findings in Tables III and IV. Table III shows the summary of the measured outcomes for admission to special care nursery, NICU, rate of TTN, the need for mechanical ventilation, duration of admission in NICU with their respective p- values for maternal age group below 35-year-old whilst, Table IV shows these measured

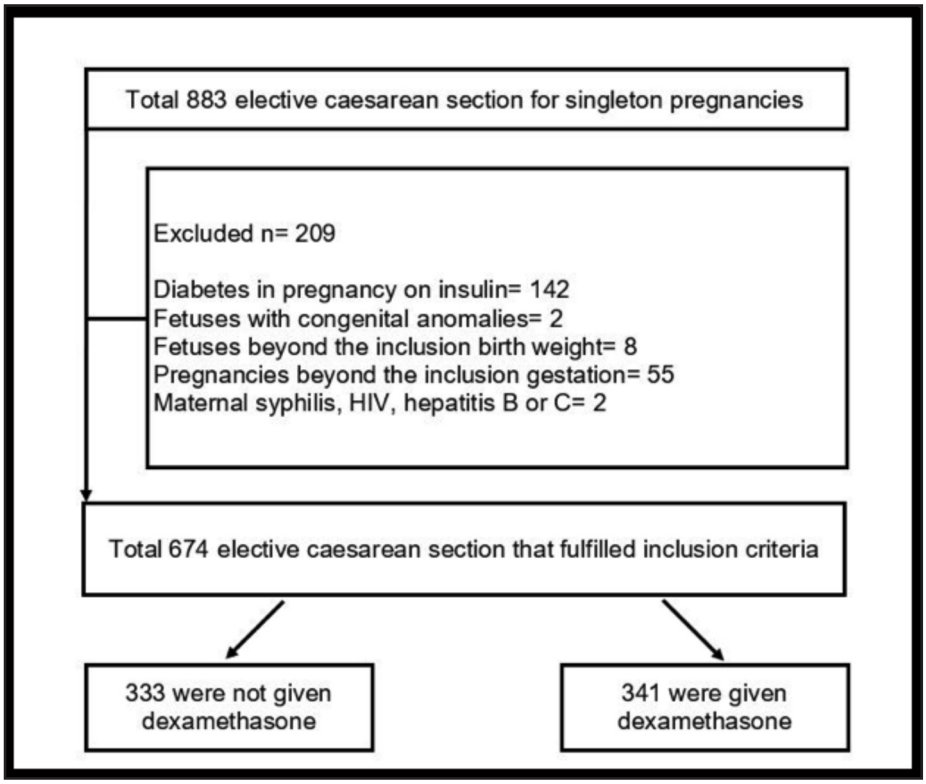

Fig. 1: Flow chart showing the participants excluded from this study.
N.B. HIV= Human Immunodeficiency Virus.

outcomes for maternal age group 35-year-old and above. The control and intervention group in both age groups were comparable with no significant differences in age, birth weights, gestational ages, and distribution of demographics. The results showed no significant differences when the age groups were separately analysed.

DISCUSSION

Caesarean section deliveries done before 39 weeks have a higher risk for transient tachypnoea of the newborn, respiratory morbidities and neonatal asphyxia compared to a vaginal delivery.[23,24,29] The rate of respiratory morbidities for caesarean section done at 39 weeks and beyond are not significantly different from vaginal deliveries but, it has a slight increased risk of antepartum stillbirth of around 0.05%. Therefore, it is recommended that consideration should be given for antenatal corticosteroids prior to an elective caesarean section before that gestation of 39 weeks.[29] For elective caesarean section done at 39 weeks and beyond, there is a high possibility that patients may present in labour before their planned caesarean section date and may end up requiring an emergency caesarean section which carries a higher risk of haemorrhage and hysterectomy.[23] Therefore, this study only included elective caesarean section done between 37 weeks to 38 weeks 6 days as their rate for respiratory morbidity is higher compared to caesarean section deliveries at 39 week and beyond.

The dose for the IM corticosteroids was derived from studies done more than half a century ago. There have not been much changes to the dosage and timing used for both drugs-betamethasone and dexamethasone.[25] The WHO recommends the use of dexamethasone as it is more widely available and more affordable particularly in countries with low resources.[19] Recent lab-based studies have demonstrated that lower doses of corticosteroids may be as effective and it can reduce unnecessary foetal exposure to the drug.[22,25] There have also been published papers suggesting that an individualized dose of antenatal corticosteroids may be needed to reduce neonatal respiratory morbidities.[27] Therefore, it was intended for our study to demonstrate benefits from a lower dose of antenatal corticosteroids whilst minimizing foetal exposure.

In our study, there was a total of 29 admissions to NICU in both groups studied, the commonest reason for admission to the NICU was transient tachypnoea of the newborns requiring mechanical ventilation, there were 11 neonates who were given this diagnosis, of which five were from the control group and six were from the treatment group. The second common reason for admission was congenital pneumonia which involved seven neonates, five of which were from the treatment group and 2 from the control group. These neonates showed radiological evidence of pneumonia which required resuscitation, intravenous antibiotics, and mechanical ventilation. Ventilatory support in the form of Continuous Positive Airway Pressure (CPAP) or Duo Positive Airway pressure were required in 13 neonates of each group.

There were 15 admissions (4.5%) to NICU in the control group, and from these admissions there was one early

neonatal death after three days of birth, the cause of death was due to severe congenital pneumonia with persistent pulmonary hypertension of the newborns. There was no post-mortem done for this case and there was also no routine anomaly scan done for the pregnancy during the antenatal period. We were therefore unable to exclude this case based on our inclusion criteria for any foetal abnormalities. There was also a neonate that developed congenital pneumonia in the control group requiring ventilation for 11 days and eventually developing complications of recurrent pneumothorax. This was the longest duration of neonatal ventilation required in the studied population. Eventually, this neonate recovered and was discharged after 30 days of admission. Apart from these two cases, the other neonates in the studied population that required ventilation recovered uneventfully without additional complications.

There were no patients documented to have developed acute reaction to the single dose intramuscular dexamethasone given. The rates of admission to neonatal special care for an elective caesarean section were 8.7% in the control group and 8.8% in the group given dexamethasone. The commonest reason for these admissions was transient tachypnoea of the newborn.

Our results showed that a lower dose IM dexamethasone did not achieve similar outcomes as the higher dose dexamethasone injections. This may be due to insufficient levels of dexamethasone in the foetal lung circulation to induce the secretion of surfactants during the time of delivery compared to betamethasone that has a longer half- life. Dexamethasone has a shorter half-life compared to betamethasone, therefore injecting the dexamethasone nearer to the time of delivery, perhaps just 12 hours or to give the injection in two separate doses of 6mg just before the planned Caesarean section may have demonstrated a clinical benefit in this study.[30,31] Additionally, in order to test for a therapeutic drug benefit, a larger randomized controlled trial with such dose would have been more appropriate only if the ethical approval is granted for such study.

Among the strength of this study was that we excluded pregnancies with maternal conditions such as diabetes on insulin, maternal syphilis, HIV, hepatitis B or C from the study population, as well as foetal anomalies and foetuses with extremes of birth weight, all of which had been poorly mentioned in previous studies. These conditions would have warranted routine admissions to special care nursery and would not have shown any possible benefit from antenatal corticosteroids injection.

Limitations of the study

One of the weaknesses found in this study was that there were a few admissions to the special care nursery, which was unrelated to respiratory morbidities, for instance a laceration wound to the foetal scalp, or hypothermia. Nevertheless, such admissions were rare and would not have affected the statistical analysis of our findings.

CONCLUSION

This study showed that there were slightly lower rates for neonatal admissions to NICU, special care nursery and the need for mechanical ventilation as well as the duration of admission in NICU when 12mg dexamethasone was given however, no statistically significant differences were demonstrated for these findings. The use of such dexamethasone should only be a viable option in a research setting. From this study, there was insufficient evidence to recommend a lower dose antenatal corticosteroid prior to an elective caesarean section for the purpose of reducing respiratory morbidities and considering that there have been long term harmful consequences demonstrated from the higher dose of antenatal corticosteroids exposure at term, this practice should therefore be discontinued until larger studies are done to refute these findings.

CONFLICT OF INTEREST

None declared

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REFERENCES

1. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972; 50(4): 515-25.
2. Cheong JL, Burnett AC, Lee KJ, Roberts G, Thompson DK, Wood SJ, et al. Victorian Infant Collaborative Study G. Association between postnatal dexamethasone for treatment of bronchopulmonary dysplasia and brain volumes at adolescence in infants born very preterm. J Pediatr 2014; 164(4): 737-43. e1.
3. Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. Am J Obstet Gynecol 1995; 173(1): 322-35.
4. Guidelines-Panel. Antenatal corticosteroids given to women prior to birth to improve fetal, infant, child, and adult health: clinical Practice Guidelines. Auckland. New Zealand: Liggins Institute, The University of Auckland; 2015.
5. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2017, Issue 3.
6. Wallace MJ, Hooper SB, Harding R. Role of the adrenal glands in the maturation of lung liquid secretory mechanisms in fetal sheep. Am J Physiol 1996; 270(1 Pt 2): R33-40.
7. Attawattanakul N, Tansupswatdikul P. Effects of antenatal dexamethasone on respiratory distress in late preterm infant: a randomized controlled trial. Thai J Obstet Gynaecol 2015; 23: 25-33.
8. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, et al. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med 2016; 374(14): 1311-20.
9. Travers CP, Clark RH, Spitzer AR, Das A, Garite TJ, Carlo WA. Exposure to any antenatal corticosteroids and outcomes in preterm infants by gestational age: prospective cohort study. BMJ 2017; 356: j1039.
10. Khazardoust S, Javadian P, Salmanian B, Zandevakil F, Abbasalizadeh F, Alimohamadi S, et al. A clinical randomized trial on endocervical inflammatory cytokines and Betamethasone in prime-gravid pregnant women at risk of preterm labor. Iran J Immunol 2012; 9(3): 199-207.
11. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2017, Issue 3. Art. No.: CD004454.

12. Stutchfield P, Whitaker R, Russell I. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. BMJ 2005; 331(7518): 662.
13. Sotiriadis A, Makrydimas G, Papatheodorou S, Ioannidis JP, McGoldrick E. Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. Cochrane Database Syst Rev 2018; 8.
14. Ahmed MR, Ahmed WAS, Mohammed TY. Antenatal steroids at 37 weeks, does it reduce neonatal respiratory morbidity? A randomized trial. J Matern Fetal Neonatal Med 2015; 28(12): 1486-90.
15. Nada AM, Shafeek MM, El Maraghy MA, Nageeb AH, Salaheldine AS, Awad MH. Antenatal corticosteroid administration before elective caesarean section et term to prevent neonatal respiratory morbidity: a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol 2016; 199: 88-91.
16. Nooh AM, Abdeldayem HM, Arafa E, Shazly SA, Elsayed H, Mokhtar WA. Does implementing a regime of dexamethasone before planned cesarean section at term reduce admission with respiratory morbidity to neonatal intensive care unit? A randomized controlled trial. J Matern Fetal Neonatal Med 2018; 31(5): 614-20.
17. Romejko-Wolniewicz E, Teliga-Czajkowska J, and Czajkowski K. Antenatal steroids: can we optimize the dose? Curr Opin Obstet Gynecol 2014, 26: 77-82.
18. Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2013(8). CD006764.
19. World Health Organisation. WHO recommendations on interventions to improve preterm birth outcomes. Geneva: WHO Publication; 2015.
20. Hrabalkova L, Takahashi T, Kemp MW, Stock SJ. Antenatal Corticosteroids for Fetal Lung Maturity- Too Much of a Good Thing? Curr Pharm Des 2019; 25(5): 593-600.
21. Briceño-Pérez C, Reyna-Villasmil E, Vigil-De-Gracia P. Antenatal corticosteroid therapy: Historical and scientific basis to improve preterm birth management. Eur J Obstet Gynecol Reprod 2019; 234: 32-7.
22. Schmidt AF, Kemp MW, Rittenschober-Bo¨hm J, Kannan PS, Usuda H, Saito M, et al. Low-dose betamethasoneacetate for fetal lung maturation in preterm sheep. Am J Obstet Gynecol 2018; 218: 132.e1-9.
23. Chongsuvivatwong V, Bachtiar H, Chowdhury ME, Fernando S, Suwanrath C, Kor-anantakul O, et al. Maternal and fetal mortality and complications associated with Caesarean section deliveries in teaching hospitals in Asia. J Obstet Gynaecol Res 2010; 36 (1): 45-51.
24. Alterman N, Kurinczuk JJ, Quigley MA. Caesarean section and severe upper and lower respiratory tract infections during infancy: Evidence from two UK cohorts. PLoS One 2021 16;16(2): e0246832.
25. Christopher JD. McKinlay and Brett J. Manley. Antenatal and postnatal corticosteroids: A swinging pendulum. Semin Fetal Neonatal Med 2019; 24(3): 167-9.
26. Stutchfield PR, Whitaker R, Gliddon AE, Hobson L, Kotecha S, Doull I. Behavioural, educational, and respiratory outcomes of antenatal betamethasone for term Caesarean section (ASTECS trial). Arch Dis Child Fetal Neonatal Ed 2013; 98: F195-F200.
27. Haas DM, Lai D, Sharma S et al. Steroid Pathway Genes and Neonatal Respiratory Distress After Betamethasone Use in Anticipated Preterm Birth. Reprod Sci 2016; 23: 680-6.
28. Räikkönen K, Gissler M, Kajantie E. Associations Between Maternal Antenatal Corticosteroid Treatment and Mental and Behavioral Disorders in Children. JAMA 2020; 323(19): 1-10.
29. Royal College of Obstetricians and Gynaecologists. Birth After previous Caesarean Birth. Green-top Guideline No. 45. [last updated in October 2015] [cited in Jan 2020].
30. Schmidt AF, Kemp MW, Kannan PS, Kramer BW, Newnham JP, Kallapur SG, et al. Antenatal dexamethasone vs. betamethasone dosing for lung maturation in fetal sheep. Pediatr Res 2017; 81: 496-503.
31. Jobe AH, Kemp M, Schmidt A, Takahashi T, Newnham J, Milad M. Antenatal corticosteroids: a reappraisal of the drug formulation and dose. Pediatr Res 2021; 89: 318-25.

ORIGINAL ARTICLE

Pseudomonas aeruginosa bacteraemia: A five-year analysis of epidemiology, clinical profiles, and outcome in a Malaysian district hospital

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ABSTRACT

Introduction: *Pseudomonas aeruginosa* is known to be the epitome of nosocomial infections associated with high morbidity and mortality. The dearth of local pseudomonal studies has prompted us to conduct this study with the following objectives: (1) to examine the local pseudomonal bacteraemia (PB) epidemiology and clinical characteristics, (2) to compare the 30-day mortality among PB of different onsets and (3) to determine the predictors of 30-day mortality outcome.

Methods: This retrospective study was conducted in Hospital Seri Manjung, Perak, Malaysia. All cases of blood culture proven PB that occurred between 1st January 2015 and 31st December 2019 were reviewed. Subjects below 12 year old and whose index blood cultures grew more than one organism were excluded. Demographic, clinical and treatment data were collected using pre-tested data collection forms and analysed using SPSS version 20.0.

Results: Among the 59 subjects included, healthcare associated (HCA) infections were the most prevalent, next to hospital onset (HO) and community onset (CO) infections. The commonest underlying comorbidities were cardiovascular disease, diabetes mellitus, and chronic kidney disease. Respiratory tract was the most frequently implicated source amongst all, while the urinary tract was more frequently implicated as the source of infection among HCA cases. Seventeen patients were admitted to ICU, and they were predominantly from the HO group. Despite having a higher rate of adequate empirical antibiotics administered, the HO group reported the lowest 30-day survival rate. Multiple logistic regression analysis demonstrated the following were independent predictors of 30-day mortality: requiring mechanical ventilator support, requiring central venous line insertion, not requiring surgery, and receiving inappropriate definite antibiotics.

Conclusion: The incidence of community onset PB was appreciably low, as cases were predominantly HCA and HO in origin. Significant morbidities were observed among pseudomonal infections, with HO infections portending the worst prognosis. Lastly, prognostic factors for determining the mortality caused by PB depended more on the severity of sepsis than the timeliness of appropriate antibiotics.

KEYWORDS:
Pseudomonas aeruginosa bacteraemia, epidemiology, clinical outcome, district hospital

INTRODUCTION

Pseudomonas aeruginosa (P. aeruginosa) is a gram-negative opportunistic pathogen in humans. Pseudomonal bacteraemia (PB) has been recognized as a serious infection that is associated with increased morbidity and mortality. Generally, empirical anti-pseudomonal antibiotic is started before the availability of microbiological results.[1] This is vital because delays in administration of appropriate anti-pseudomonal antibiotics has been reported to be associated with higher mortality outcomes.[2]

According to the unpublished data, *P. aeruginosa* only accounted for 2.92 per cent of all blood culture confirmed bacteraemia (17 out of 582 isolates) that occurred in 2018 in our hospital. Despite the low incidence of PB, we recorded a disproportionately high usage of anti-pseudomonal antibiotics in recent years due to the fear of missing out PB. The treatment was frequently used in haemodialysis patients who were admitted for catheter-related blood stream infection and cases treated for hospital acquired infections. This raised concern as injudicious use of broad-spectrum antibiotics poses the risk of inducing multidrug resistant (MDR) organisms, especially in populations where the incidence PB is relatively low.[3]

To date, there is no retrieving data regarding the epidemiology and clinical characteristics of PB in the Malaysian district population. In this study, we examined the epidemiology and clinical characteristics of PB in Malaysia. In addition, we also compared the 30-day mortality among PB of different onsets and determined the predictors of 30-day mortality outcome.

METHODOLOGY

The study was conducted at the Hospital Seri Manjung (HSM), Perak, Malaysia with 258 000 semi-urban population. Among the services provided are acute medical services, intensive care services, surgical services (general and

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orthopaedic), paediatric services, women's services, and intensive care unit services. Additionally, HSM also serves as referral center for Hospital Changkat Melintang, which is a non-specialist district hospital in Manjung District.

Study Design and data collection
In this study, a retrospective analysis was performed to review all PB cases occurring between 1st January 2015 and 31st December 2019. Demographic data, clinical details and antibiotic treatment were obtained by trained medical abstractors from laboratory records, microbiology records, medical notes, nursing notes and pharmacy notes, as well as from the patient admission system.

We included all subjects aged 12 year old and above with a positive blood culture of *P. aeruginosa*. We excluded cases with incomplete or missing medical data. Also, index blood cultures which grew more than one organism were excluded.

Community onset (CO) bacteraemia was defined as that occurring within 48 hours of admission, whereas hospital onset (HO) bacteraemia was defined as after this period or cases readmitted within 48 hours after being discharged from the hospitals. Healthcare-associated (HCA) bacteraemia was defined as either one of the following: (i) patient had been admitted to HSM in the past 3 months, excluding those who were readmitted within 48 hours after being discharged from the hospitals, or (ii) from a nursing home, or (iii) had regular healthcare contact in the past 3 months, which was adapted from Friedman et al.[4]

Inter-hospital transfer cases were included if the index blood culture was collected in the emergency department of non-specialist district hospitals within the first 48 hours of presentation. If both cultures from referral hospitals and receiving hospitals grew *P. aeruginosa*, only the first index blood culture was included for analysis.

For each patient, a primary diagnosis of the source of *P. aeruginosa* infection was determined by other cultures obtained within 48 hours of the index incident blood culture drawn. In the advent that concurrent detection of *P. aeruginosa* in other sources was not available, the source of infection was presumed based on the clinical findings.

Biochemical data such as serum haemoglobin level, serum leucocyte level, absolute neutrophil count, serum platelet level, serum albumin level and serum creatinine level collected on the same day or on the nearest date from the index blood culture date were retrieved.

Sequential Organ Failure Assessment (SOFA) scores were calculated using the necessary laboratory and clinical data from patients' medical records on the same day as the index blood culture date. If multiple values were obtained on a given day, the most abnormal value was used. If a value was missing from the day of interest, the measurement from the nearest day was used in its place. If no values were available, the measurement was assumed to be normal. The organ dysfunction scores of each system would be added, thus providing a composite SOFA score between 0 and 24, which was adapted from Hattemer et al.[5]

Microbiological data
PB or blood stream infections (BSI) was defined by its isolation from one or more sets of blood culture bottles collected using standard sterile techniques. Index blood culture growing more than one organism was defined as mixed growth and was excluded from the study. Index blood culture was defined as the first blood culture that grew *P. aeruginosa*.

In HSM, all blood cultures were processed using BACTEC fluorescent series instrument 9120 (BMS diagnostics (M) Sdn Bhd). Organisms were identified to species level by Vitek 2 – Compact Machine (Biomerieux) (Diagnostic System (M) Sdn Bhd). Routine antibiotic susceptibility testing was performed according to CLSI (Clinical and Laboratory Standards Institute). Antibiotics tested for *P. aeruginosa* included Ceftazidime, Gentamicin, Amikacin, Cefoperazone, Meropenam, Imipenam, Piperacillin/Tazobactam, Ciprofloxacin and Cefepime.

The antibiotic susceptibility test was performed in adherence to Clinical and Laboratory Standard Institute (CLSI) guidelines. Multidrug resistance was defined as resistance to three or more of the following classes of agents: anti-pseudomonal carbapenems, anti-pseudomonal beta-lactams i.e., penicillins and cephalosporins, as well as aminoglycosides, and fluoroquinolones.

Appropriate empirical antimicrobial therapy was defined as therapy administered within 48 hours after blood culture samples were obtained and consisting of an initial empirical regimen containing at least one anti-pseudomonal antibiotic that was later proven to be active in vitro against blood isolates of *P. aeruginosa*. Empirical antimicrobial therapy that demonstrated intermediate sensitivity or resistance to *P. aeruginosa* was regarded as inappropriate antimicrobial therapy. Dosages, frequency, and route of antibiotic administration were also reviewed.

A delay of appropriate antimicrobial therapy was defined as the administration of inappropriate empirical antibiotics against the *P. aeruginosa* isolate prior to the availability of the results of antibiotic susceptibility testing, with a delay of more than 48 hours after blood culture samples were obtained.

The primary outcome measure was death during hospital stay and 30-day mortality rate after the index *P. aeruginosa* blood culture collection date. Due to the retrospective nature of the study, we did not attempt to determine whether 30-day mortality was attributable to the *P. aeruginosa* BSI. Out-of-hospital death was confirmed with National Registration Department, Malaysia if such information was not available in our hospital.

All the data were analyzed using Statistical Package for the Social Sciences (SPSS) Version 20. Demographic data and clinical profiles of study subjects were presented descriptively. Categorical variables among three different onset groups were compared using Pearson Chi-Square or Fisher's Exact test while continuous variables were compared using Kruskal-Wallis H test. Kaplan-Meier curve was used to compare the 30-day mortality rates among patients with CO, HCA, and

HO bacteraemia caused by *P. aeruginosa*. The event of interest was death cases that occurred within 30 days after the index blood culture date. Multiple logistic regression was used to identify variables independently associated with 30-day mortality. All variables associated with 30-day mortality in the univariate analysis ($p<0.25$) were included at model entry. A stepwise approach was used to identify independent predictors of 30-day mortality. Variables were retained in the final model if the p value was <0.05. The results of multiple logistic regression analysis were reported as adjusted odd ratios with 95% CIs. For all statistical comparisons, a p value < 0.05 was deemed significant.

RESULTS

Demographic and clinical characteristics

During the study period, a total of fifty-nine PB were included and analyzed as per onset category. We excluded 13 cases in which two cases were due to missing medical records, seven cases due to mixed growth from index blood culture and four cases due to age below 12 year old. HCA type was the most prevalent (n=27, 45.8%) among patients with PB, next to HO (n=22, 37.3%) and CO (n=10, 16.9%) type of infections. Medical ward admissions represented 72.9% of the cases (n=43). Majority of the patients admitted to ICU at presentation were HO cases (n=6). Only two multidrug resistant PB occurred during the study period, which belonged to HCA and HO type of infections. There was a male predominance in the populations studied which detailed 62.7%. The median age for CO infections was 56.0 year old (IQR: 47.0-66.8); whilst the median age for HCA and HO infections was 65.0 year old (IQR: 47.0-69.0) and 61.5 year old (IQR: 51.8-71.0) respectively (Table I).

The percentage of patients with pre-existing comorbidities was 98.3% (n=58). Among them, the three most prevalent pre-existing comorbids were cardiovascular disease (n=42, 71.2%), diabetes mellitus (n=31, 52.5%) and chronic kidney disease (n=22, 37.3%). There was a low proportion of patients with underlying haematological malignancy (n=3, 5.1%). Nine cases had pre-existing chronic wounds or pressure sores at presentation; eight of them were from the HCA category, while the remaining one was from CO patients. Eight patients with indwelling central venous line at presentation were limited to HCA cases only; whilst seven patients with indwelling urinary catheter were observed in both HCA (n=5) and HO (n=2) cases (Table I).

Of 25 patients who had shock during index blood culture, all occurred exclusively in HCA (n=14) and HO (n=11) cases (p=0.003). The median SOFA score during index blood culture was highest among HO cases (median 6.5, IQR: 3.0-14.0) and lowest among CO cases (median 4, IQR: 1.8-5.5). Neutropaenia only occurred in 5 cases (8.5%) during index blood culture (Table I).

The respiratory tract was the most frequent source (n=22, 37.3%), followed by urinary tract (n=14, 23.7%), central venous catheter (n=10, 16.9%), skin and soft tissue (n=7, 11.9%), gastrointestinal tract (n=4, 6.78%) and unknown (n=2, 3.4%). The urinary tract was more frequently implicated as the source of infection among HCA cases (p=0.012). We recorded 17 patients admitted to ICU and they were predominantly HO patients (n=14, p<0.001) as shown in Table I.

The median SOFA scores were as follows in descending order: 7.0, among patients with appropriate empirical antibiotic use; 6.0, among patients with inappropriate empirical antibiotic with non-delayed switching; 4.0, among patients with both inappropriate empirical antibiotic but delayed switching and not switched to appropriate antibiotic groups. However, this was not statistically significant (p=0.286).

Clinical Outcomes

The median haemoglobin among HCA and HO cases ranged between 7.70 g/dL and 8.85 g/dL, which were significantly lower compared to CO cases (p=0.012), with increased blood product transfusion events (p=0.003). It is also noteworthy that all groups had severe renal impairment at presentation with median creatinine ranged 226.0 to 363.0 µmol and approximately half (n=25, 42.4%) of them required dialysis treatment. There were 24 cases (40.7%) that required mechanical ventilator support and among these, 14 cases were HO infection. To note, eight cases (13.6%) underwent surgery. Types of surgery performed included open appendectomy, arthrotomy and washout for septic arthritis, wound debridement over diabetic foot ulcer and below knee amputation, incision and drainage of right leg abscess, above knee amputation for diabetic foot ulcer as well as exploratory laparotomy (Table I).

HCA and HO cases (n=26, 53.1%) were more likely to receive appropriate antibiotics compared to CO cases (n=3, 30.0%). Of 30 cases who did not receive appropriate antibiotics, nine cases were switched to appropriate antibiotics within 48 hours; 12 cases were switched to appropriate antibiotics after 48 hours and nine cases did not undergo modification of antibiotics. For the latter, reasons of not switching to appropriate antibiotics were: 2 cases took at-own-risk discharge prior to blood culture result, 4 cases passed away within 24 hours prior to blood culture result and 3 cases improved clinically with initial empirical antibiotics (Table II). Unexpectedly, the 30-day mortality rate was the lowest (16.7%) among patients who received delayed appropriate antibiotics in comparison to patients who received appropriate empirical s (55.2%) (Table III). Further analysis demonstrated that the former group of patients had a lower SOFA score (4.0 Vs 7.0).

The in-hospital mortality rate was highest among HO cases (n=14 out of 22, 63.6%) followed by HCA cases (n=10 out of 27, 37.0%) and CO cases (n=3 out of 10, 30.0%). The 30-day survival rates, stratified according to onset categories, are presented in the Kaplan-Meier Curve. It demonstrates 30.0%, 37.0% and 63.6% 30-day mortality rate in CO, HCA, and HO pseudomonal bacteraemia respectively. The HO pseudomonal bacteraemia group had the lowest probability of 30-day survival, (overall logrank test; p=0.063) as illustrated in Figure 1.

Table I: Comparison of clinical characteristics of *Pseudomonas aeruginosa* bacteraemia cases by onset category

Characteristics	CO (n=10)	HCA (n=27)	HO (n=22)	*p* value
Admission ward specialty, n(%)				
Medical	8 (80.0)	23 (85.2)	12 (54.6)	0.064[a]
Surgical	1 (10.0)	2 (7.4)	3 (13.6)	
Orthopaedic	0 (0.0)	1 (3.7)	1 (4.5)	
Intensive care unit	1 (10.0)	0 (0.0)	6 (27.3)	
Paediatric	0 (0.0)	1 (3.7)	0 (0.0)	
Age in years, median (IQR)	56.0 (47.0-66.8)	65.0 (47.0-69.0)	61.5 (51.8-71.0)	0.652[c]
Male gender, n(%)	5 (50.0)	18 (66.7)	14 (63.6)	0.644[b]
Had shock during index blood culture, n(%)	0 (0.0)	11 (40.7)	14 (63.6)	0.003[b]
Comorbidities, n(%)				
Cardiovascular disease	7 (70.0)	17 (63.0)	18 (81.8)	0.348[b]
Diabetes mellitus	5 (50.0)	12 (44.4)	14 (63.6)	0.402[b]
Chronic kidney disease/end stage renal disease	2 (20.0)	11 (40.7)	9 (40.9)	0.463[b]
Old stroke	1 (10.0)	2 (7.4)	5 (22.7)	0.358[a]
Respiratory disease	1 (10.0)	2 (7.4)	5 (22.7)	0.358[a]
Genitourinary disease	1 (10.0)	4 (14.8)	1 (4.5)	0.540[a]
Solid tumour	0 (0.0)	4 (14.8)	1 (4.5)	0.384[a]
Orthopaedic disease	1 (10.0)	3 (11.1)	1 (4.5)	0.703[a]
Chronic liver disease	1 (10.0)	2 (7.4)	1 (4.5)	0.822[a]
Haematological malignancy	0 (0.0)	3 (11.1)	0 (0.0)	0.280[a]
Human immunodeficiency virus	1 (10.0)	1 (3.7)	1 (4.5)	0.571[a]
Autoimmune disease	2 (20.0)	0 (0.0)	1 (4.5)	0.034[a]
Others*	3 (30.0)	6 (22.2)	3 (13.6)	0.426[a]
Chronic wound/pressure sore at presentation, n(%)	1 (10.0)	8 (29.6)	0 (0.0)	0.011[a]
Indwelling devices at presentation, n(%)				
Central venous line	0 (0.0)	8 (29.6)	0 (0.0)	0.005[a]
Urinary catheter	0 (0.0)	5 (18.5)	2 (9.1)	0.371[a]
Neutropaenia, i.e. neutrophils < $0.5x10^3$/μL	1 (10.0)	3 (11.1)	1 (4.5)	0.703[a]
Haemoglobin in g/dL, median (IQR)	12.25 (9.10-12.73)	7.70 (6.50-9.40)	8.85 (7.90-10.00)	0.012[c]
Creatinine in μmol/L, median (IQR)	226.0 (112.8-329.0)	363.0 (136.0-553.0)	257.5 (65.8-553.8)	0.378[c]
SOFA score on / nearest to index blood culture date, median (IQR)	4.0 (1.8-5.5)	5.0 (4.0-11.0)	6.5 (3.0-14.0)	0.204[c]
In-patient treatment, n(%)				
Blood product transfusion	2 (20.0)	20 (74.1)	17 (77.3)	0.003[b]
Haemodialysis	2 (20.0)	14 (51.9)	9 (40.9)	0.216[b]
Mechanical ventilator	2 (20.0)	8 (29.6)	14 (63.6)	0.019[b]
Surgery	1 (10.0)	2 (7.4)	5 (22.7)	0.358[a]
Appropriate empirical antibiotic use on index bacteraemia date, n(%)	3 (30.0)	15 (55.6)	11 (50.0)	0.383[b]
Switching of inappropriate empirical antibiotic, n(%)				0.332[a]
Not applicable	3 (30.0)	15 (55.6)	11 (50.0)	
Non-delayed switching	1 (10.0)	4 (14.8)	4 (18.2)	
Delayed switching	4 (40.0)	6 (22.2)	2 (9.1)	
Not switched	2 (20.0)	2 (7.4)	5 (22.7)	
Index blood culture source, n(%)				
Respiratory tract	4 (40.0)	6 (22.2)	12 (54.6)	0.065[b]
Urinary tract	2 (20.0)	11 (40.8)	1 (4.5)	0.012[b]
Central venous catheter	0 (0.0)	8 (29.6)	2 (9.1)	0.059[a]
Skin & soft tissue	2 (20.0)	2 (7.4)	3 (13.6)	0.506[a]
Gastrointestinal tract	2 (20.0)	0 (0.0)	2 (9.1)	0.052[a]
Unknown	0 (0.0)	0 (0.0)	2 (9.1)	0.290a
ICU admission, n(%)	1 (10.0)	2 (7.4)	14 (63.6)	<0.001[b]
In-hospital death, n(%)	3 (30.0)	9 (33.3)	14 (63.6)	0.064[b]
30-day mortality, n(%)	3 (30.0)	10 (37.0)	14 (63.6)	0.097[b]

CO, Community Onset; HCA, Healthcare Associated; HO, Hospital Onset; IQR, Interquartile range; SOFA, Sequential Organ Failure Assessment; ICU, Intensive Care Unit

*Parkinson's disease, migraine, Bell Palsy, psychiatric disorder, gastritis, hypothyroidism, adrenal insufficiency, haemorrhoids

[a] Fisher's Exact test [b] Pearson Chi-square test [c] Kruskal-Wallis H test

Table II. Clinical Characteristics of Patients whose Inappropriate Empirical Antibiotics were Not Switched

No	Onset	Age In Years	Comorbids	30-Days Outcome	SOFA Score	Diagnosis
1	HCA	81	Advanced Prostate Carcinoma	Died	3	Urosepsis*
2	HO	79	Prostate Carcinoma	Died	4	Urosepsis*
3	HO	69	DM, Hypertension, Advanced CKD	Died	14	Perforated Diverticular Abscess**
4	HO	75	Hypertension, Dyslipidaemia	Died	14	Perforated Peptic Gastric Ulcer**
5	HO	63	DM, Hypertension, Hepatitis C, CKD	Died	3	Sepsis With Unknown Source**
6	CO	51	DM, Hypertension, Schizophrenia, Old PTB	Died	5	Community Acquired Pneumonia**
7	HCA	67	DM, Hypertension, Ischaemic Heart Disease, Diabetic Foot Ulcer	Survived	0	Infected Diabetic Foot Ulcer (Improved with intravenous ampicillin/sulbactam and wound debridement)
8	HO	57	DM, Hypertension, Dyslipidaemia	Survived	4	Hospital Acquired Infection (Improved with intravenous ceftazidime which showed intermediate sensitivity in vitro)
9	CO	65	Old Stroke	Survived	5	Aspiration Pneumonia (Improved clinically with intravenous amoxicillin/clavulanate)

CO, Community Onset; HO, Hospital Onset; HCA, Healthcare Associated; DM, Diabetes Mellitus; CKD, Chronic Kidney Disease; PTB, Pulmonary Tuberculosis; SOFA, Sequential Organ Failure Assessment
* Took At-Own Risk discharge
** Died before blood culture result was available

Table III: Comparison of Sequential Organ Failure Assessment (SOFA) score on / nearest to index blood culture date with regards to empirical antibiotic use and its switching vs. mortality

Empirical antibiotic use & its switching	SOFA score on / nearest to index blood culture date median (IQR)	30-day mortality rate
Inappropriate empirical antibiotic use & Non-delayed switching (n=9)	6.0 (3.0-10.0)	33.3%
Inappropriate empirical antibiotic use & Delayed switching (n=12)	4.0 (1.3-8.0)	16.7%
Inappropriate empirical antibiotic use & Not switched (n=9)*	4.0 (3.0-9.5)	66.7%
Appropriate empirical antibiotic use (n=29)	7.0 (4.0-13.0)	55.2%

*Four patients passed away within 24 hours after index blood culture; Two patients took At-Own-Risk discharge; Three patients responded to initial empirical antibiotics

Table IV: Independent predictors of 30-day mortality among *Pseudomonas aeruginosa* bacteraemia cases

	30-day mortality, n (%)		Multivariate analysis		
	No	Yes	Adj. OR	95% CI	*p* value[a]
Mechanical ventilator					
No	28 (80.0)	7 (20.0)	1.00		0.001
Yes	4 (16.7)	20 (83.3)	67.31	(5.58; 811.78)	
Central venous line					
No	20 (76.9)	6 (23.1)	1.00		0.018
Yes	12 (36.4)	21 (63.6)	17.54	(1.62; 190.20)	
Surgery					
No	26 (51.0)	25 (49.0)	182.15		0.031
Yes	6 (75.0)	2 (25.0)	1.00	(1.60; 20741.30)	
Switching of inappropriate empirical antibiotic					
Not applicable	13 (44.8)	16 (55.2)	1.00		0.012
Switched (Non-delayed & Delayed)	16 (76.2)	5 (23.8)	0.88	(0.11; 6.84)	0.900
Not switched	3 (33.3)	6 (66.7)	66.70	(3.08; 1444.46)	0.007

Adj. OR, Adjusted Odd Ratio; CI, Confidence Interval
[a] Wald test

Risk factors for 30-day mortality

Multivariate logistic regression analysis identified the following as independent predictors of 30-day mortality: requiring mechanical ventilator support (Adj. OR, 67.31;95% CI 5.58, 811.78; *p*=0.001), requiring central venous line insertion (Adj. OR, 17.54; 95% CI 1.62, 190.20; *p*=0.018), not requiring surgery (Adj. OR, 182.15; 95% CI 1.60, 20741.30; *p*=0.031) and receiving inappropriate empirical antibiotics which were not switched (Adj. OR, 66.70; 95% CI 3.08, 1444.46; *p*=0.007) (Table IV).

DISCUSSION

The findings of this study highlight the existence of several distinct clinical characteristics compared to previous works, which have only been focused on tertiary hospitals. According to the epidemiological study conducted locally in University of Malaya Medical Centre, the prevalence rate of haematological and non-haematological malignancies among the 87 PB cases reported were as high as 23% and 25% respectively.[6] On further note, the prevalence rate of solid tumours and leukaemia was reported to be 42.6% (58/136 cases) and 15% (21/136 cases) in the study conducted by Kang et al. in Seoul National University Hospital, Korea.[7]

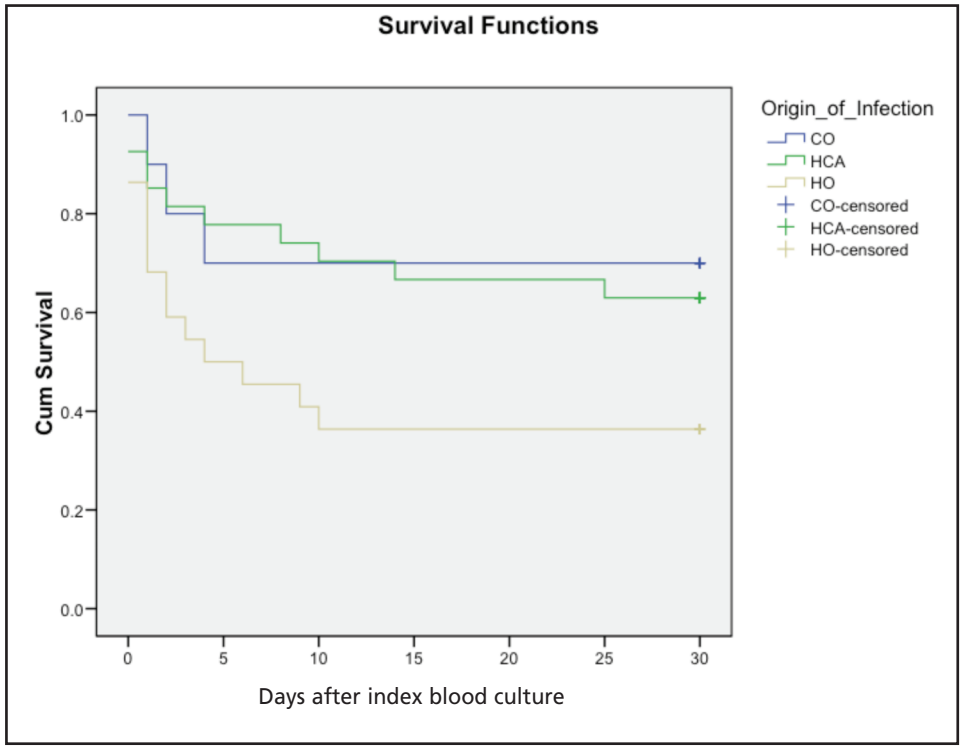

Fig. 1: Kaplan-Meier survival curve for patients with community onset VERSUS healthcare associated and hospital onset *Pseudomonas aeruginosa* bacteraemia.

In this report, we identified cardiovascular disease and diabetes mellitus as the commonest pre-existing comorbidities. The proportion of patients with underlying malignant solid tumours and haematological malignancy was considerably lower compared to available literature.[6,7] This also explains why only a minority of our cases had neutropaenia during onset of PB. These observations reflect the fact that district population clinical characteristics differ from larger hospital population characteristics in previous studies.

Apart from this slight discordance, other clinical characteristics such as male predominance and preponderance of medical admissions were similar with previous studies.[6-8] It is noteworthy that more than half of the HO cases required ICU admission. In our opinion, the actual number of pseudomonal cases requiring intensive care could be substantially higher if not for ICU bed limitations. Encouragingly, multi-drug resistant *P. aeruginosa* were appreciably low with only two cases recorded in this series. Further analysis showed that these cases had recent admission to tertiary hospitals, and this substantiates the absence of community origin MDR *P. aeruginosa* in our population.

While many studies have rigorously examined the severity of PB via sepsis scoring system, few have investigated the need of haemodialysis support and blood transfusion requirement during admission. In this study, we discovered a large number of HCA and HO pseudomonal bacteraemia requiring haemodialysis support and blood product transfusion. The detrimental impact of pseudomonal infections was also reflected from the strikingly high serum creatinine levels and profound anaemia observed during index blood culture dates. These data emphasize the importance of close monitoring of renal function and haemoglobin trend during the course of hospitalization. Also, avoidance of nephrotoxic drugs during the course of treatment is crucial as they have a predisposition to develop severe renal complications. By the same principle, our hospital antibiotic guidelines do not recommend aminoglycosides as empirical anti-pseudomonal antibiotics due to this concern.

The incidence of catheter related blood stream infections (CRBSI) among end stage renal failure (ESRF) patients are expected to be on the rising trend due to the escalating numbers of ESRF patients.[9] In this series, the incidence of pseudomonal CRBSI was considerably low with only eight HCA CRBSI in the entire five years. To date, guidelines for CRBSI treatment are largely based on empirical work done overseas.[10-13] These findings raise the question of whether *P. aeruginosa* are truly frequently accountable for CRBSI locally and the role of combination anti-pseudomonal antibiotics for all CRBSI cases. Decisions regarding whether to initiate empirical anti-pseudomonal antibiotics should reflect a balance between the risk of delayed appropriate treatment and risk of unnecessary broad spectrum antibiotic usage which promotes the emergence of MDR organisms Therefore, we recommend future studies to examine the epidemiology of CRBSI locally to identify the risk factors that predispose towards pseudomonal CRBSI that would enable restriction of usage of combination anti-pseudomonal antibiotics to the at-risk groups only.

It is well-proven and established that delayed administration of appropriate antibiotics was associated with increased mortality outcomes. This had been proven by Cheo-In et al who found increased mortality among PB cases who received delayed effective antimicrobial antibiotics which is defined as more than 24 hours after blood culture samples were taken.[2] Interestingly, our results do not appear to corroborate with their observations; in fact, we found that despite higher rate of appropriate empirical antibiotic usage among cases with HCA and HO infections, they trend towards higher mortality compared to those who received delayed effective antibiotics.

There are several possible explanations for these rather contradictory observations. First and foremost, an increased SOFA score appears to be the determinant factor for higher mortality, and timely effective antibiotics did not seem to alter the course of patients with high burden of morbidity. Nevertheless, we could not find statistical evidence of this as an independent predictor of mortality. Other factors such as morbid debility, multiple comorbidities and advanced age which could similarly have a negative influence in prognosis which would not be reflected in SOFA scores should be taken into account as well.[14] It is interesting to discover that patients who underwent surgery had a better 30-day survival. Hence, we can reasonably recommend that surgery alongside anti-pseudomonal antibiotics be considered if the pseudomonal source is surgically eradicable.

The strength of this study lies in it being the first Malaysian study in a district hospital and the results provide considerable insight into PB epidemiology in the country. The limitations of this study are that it was a single-centre retrospective study, and the number of cases was small. Therefore, it is plausible that we could have underestimated the significance of certain variables. Nevertheless, measures were taken to ensure the rigor of this study, which include use of clear variable definitions and application of statistical analysis. Importantly, clinical data abstractors comprising of trained medical officers from the Internal Medicine Department at HSM mitigated the risk of data collection errors.

In conclusion, community onset PB cases remained scarce in the district hospital, with the majority of cases belonging to healthcare associated and hospital onset infections. Also, PB was fraught with high morbidity with an increased predisposition to haemodialysis, blood transfusion, mechanical ventilator support and ICU care. Lastly, the prognostic factor for mortality of PB depended more on the severity of sepsis rather than the timeliness of appropriate antibiotics.

ETHICAL APPROVAL

This study was registered with National Medical Research register (NMRR) and approved by the Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH). MREC Approval Letter: KKM/NIHSEC/P20-100 (5) dated 21st January 2020. NMRR ID: NMRR-19-3550-52195.

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REFERENCES

1. van Delden C. *Pseudomonas aeruginosa* bloodstream infections: how should we treat them? Int J Antimicrob Agents 2007;30 Suppl 1: S71-5.
2. Kang CI, Kim SH, Kim HB, Park SW, Choe YJ. *Pseudomonas aeruginosa* Bacteremia: Risk Factors for Mortality and Influence of Delayed Receipt of Effective Antimicrobial Therapy on Clinical Outcome. Clin Infect Dis 2003; 37(6): 745-51.
3. Urba´nek K, Kola´r M, Loveckova´, Strojil J, Šantavá L. Influence of third-generation cephalosporin utilization on the occurrence of ESBL-positive *Klebsiella pneumoniae* strains. J Clin Pharm Ther 2007; 32(4): 403-8.
4. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health Care–Associated Bloodstream Infections in Adults: A Reason To Change the Accepted Definition of Community-Acquired Infections. Ann Intern Med 2002; 137: 791-7.
5. Hattemer A, Hauser A, Diaz M, Scheetz M, Shah N, Allen JP, et al. Bacterial and clinical characteristics of health care- and community-acquired bloodstream infections due to *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2013; 57(8): 3969-75.
6. Nadeem SR, Rina K, Hamimah H, Savithri DP. *Pseudomonas aeruginosa*: Epidemiology of bacteremia and antimicrobial susceptibility pattern in a teaching hospital in Kuala Lumpur. J Univ Malaya Medical Cent 2006; 9(1): 14-9.
7. Kang C-I, Kim S-H, Kim H-B, Park S-W, Choe Y-J, Oh M-D, et al. *Pseudomonas aeruginosa* bacteremia: risk factors for mortality and influence of delayed receipt of effective antimicrobial therapy on clinical outcome. Clin Infect Dis 2003; 37(6): 745-51.
8. Enoch DA, Kuzhively J, Sismey A, Grynik A, Karas JA. *Pseudomonas aeruginosa* Bacteraemia in Two UK District Hospitals. Infect Dis Rep 2013; 5(1): e4.
9. Bujang MA, Adnan TH, Hashim NH, Mohan K, Kim Liong A, Ahmad G, et al. Forecasting the Incidence and Prevalence of Patients with End-Stage Renal Disease in Malaysia up to the Year 2040. Int J Nephrol 2017; 2017: 2735296.
10. Gahlot R, Nigam C, Kumar V, Yadav G, Anupurba S. Catheter-related bloodstream infections. Int J Crit Illn Inj Sci 2014; 4(2): 162-7.
11. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 49(1): 1-45.
12. Allon M. Dialysis catheter-related bacteremia: Treatment and prophylaxis. Am J Kidney Dis 2004; 44(5): 779-91.
13. Marcos M, Soriano A, Inurrieta A, Martinez JA, Romero A, Cobos N, et al. Changing epidemiology of central venous catheter-related bloodstream infections: increasing prevalence of Gram-negative pathogens. J Antimicrob Chemother 2011; 66(9): 2119-25.
14. Pinheiro MRS, Lacerda HR, Melo RGL, Maciel MA. *Pseudomonas aeruginosa* Infections Factors Relating to Mortality with Emphasis on Resistance. Braz J Infect Dis 2008;12(6): 509-15.

Optimization of scanning time of ^{18}F-FDG whole body PET/CT imaging in obese patients using quadratic dose protocol

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ABSTRACT

Introduction: ^{18}F-FDG imaging of overweight and obese patients is often challenging due to higher scattering and attenuation. Degradation of positron emission tomography (PET) image quality as the body weight increases is best overcome by using the quadratic dose protocol. Previously the implementation of this protocol on a Bismuth Germanium Oxide (BGO) scintillation crystal-based PET/CT system at Institut Kanser Negara (IKN), Malaysia practices using the linear dose protocol (T_{min}=2.5 minutes). Hence, this study aims to optimize the T_{min} of the quadratic dose protocol for ^{18}F-FDG PET/CT.

Materials and Methods: This study was conducted based on the guideline published by the European Association of Nuclear Medicine (EANM) version 2.0 FDG-PET/CT and conducted in two phases. Firstly, 100 whole-body scan ^{18}F-FDG PET/CT images were selected for the average coefficient of variation (COV) analysis in the liver region. Second, a NEMA 2012/IEC2008 phantom was used to obtain the relationship between the $COV_{phantom}$ and the scanning time. Finally, the images acquired using the two T_{min} were quantitatively compared using contrast recovery coefficient (Q_H), signal to noise ratio (SNR), and visibility (V_H). Independent t-test between each image quality parameter performed with p-value <0.05 considered significant.

Results: The average COV of the liver was 17.7%. Currently, this value was clinically accepted to produce appropriate image quality at IKN. Interpolation at COV=17.7% gave a T_{min} value of 2.9 minutes. Comparisons show that the two T_{min} yielded equivalent PET/CT image quality (p-value of Q_H=0.774, SNR=0.780 and V_H=0.915).

Conclusion: The optimal T_{min} defined in this study was 2.9 minutes, 27.6% shorter than the T_{min} previously defined based on COV=15%. Despite the higher average COV, the shorter T_{min} beneficial in the lower total ^{18}F-FDG activity administered, reduce the internal dose to the patient while producing equivalent image quality.

KEYWORDS:
Minimal scan time, optimization, quadratic dose, ^{18}F-FDG, PET/CT

INTRODUCTION

Degradation of positron emission tomography (PET) image quality is associated with the increment of the body weights of patients. This is due to the high scattering and attenuation events.[1,2] Several methods were suggested to overcome such problems, for instance, longer scanning time,[1,3,4] time-of-flight (TOF),[5] increasing Fluorodeoxyglucose (^{18}F-FDG) dose[6] and depth of interaction (DOI) method.[7,8] For the ^{18}F-FDG dose, three dose protocols are currently practice in many PET imaging centres. The protocols are linear, constant, and quadratic dose protocols. The disadvantage of the linear and constant dose protocols was that the image quality degraded as the body mass increased. In a previous research, a comparison of the linear dose protocol and the quadratic dose protocol in obese patients turned out that the quadratic dose protocol produced constant image quality in obese patients.[6]

Currently, Institut Kanser Negara Malaysia (IKN) is implementing a linear dosing protocol for the whole-body scan (WBS) ^{18}F-FDG imaging. Based on the previous findings presented by other researchers, the implementation of this dosing protocol caused poor image quality for overweight and obese patients.[6] Hence, an attempt in implementing quadratic dose protocol at IKN institution using NEMA 2012/IEC 2008 phantom was previously performed.[9] However, implementation of the respective protocol based on the recommendation by the European Association of Nuclear Medicine (EANM) resulted in a longer scanning time compared to the current linear dose protocol practices in our institution.[9] 3.8 minutes minimal scan time (T_{min}) was previously obtained in our study compared to the current clinical practice of 2.5 minutes scanning time. In accordance with that, optimization of the quadratic dose protocol for the WBS ^{18}F-FDG was the main aim of this study. The optimization was performed based on the evaluation of the coefficient of variation (COV) value measured on the WBS ^{18}F-FDG images. The COV value is considered appropriate for the optimal image quality because it is currently accepted by the physicians at the IKN. This study provides information valuable for optimal WBS ^{18}F-FDG imaging that is likely allows optimal image quality for overweight and obese patients.

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MATERIALS AND METHODS

Study design

This was a retrospective study. The inclusion criteria included the patients who underwent WBS ^{18}F-FDG PET/CT from July to August 2019 at IKN. The exclusion criteria set was patients with cancer in the liver area. In this study, the background value was calculated in the liver due to the homogeneous tissue distribution in this area.[10] Nevertheless, for the cases of cancerous liver, the presence of cancer cells in the liver causes the uptake of the ^{18}F-FDG in the respective region to be higher and thus invalid for the normal background analysis. The WBS images of the patients were collected from the report retrieved from the picture archiving and communication system (PACS system) at IKN. All images were acquired using a PET Discovery ST scanner equipped 8 slice CT- scanner, 36 detector rings PET scanner. The detector of this scanner is a Bismuth Germanium Oxide (BGO) scintillation crystal.

Definition of optimal T_{min} for quadratic dose protocol WBS ^{18}F-FDG

This study was conducted in two phases. In the first phase, 100 WBS ^{18}F-FDG images were used for the analysis of the COV of the patient, $COV_{patient}$. To describe the prevalence of obese patients who underwent ^{18}F-FDG PET/CT, with a tolerable error of ±5% in the patients' population of ^{18}F-FDG PET/CT from the Nuclear Medicine Department, IKN with 170 patients, the sample size calculation was based on the results obtained by National Health and Morbidity Survey (NHMS) 2019, the current prevalence of obesity among Malaysian adults was 19.7%.[11] The statistically acceptable sample size was estimated to be 100 with a 10% dropout consideration. COV=15% is currently recommended by the EANM guideline as a reference value. However, this is somehow arbitrary.[12] Since we are considering the accepted image analysis and diagnosis of our institution population, the average value of the $COV_{patient}$ was used to derive the T_{min}. Other than that, at IKN, the prescribed activity to the patient is 5 MBq/kg while EANM outlines a different formulation.[13] Therefore, some modification in the definition of T_{min} is necessary to fit with the current protocol practices in our institution. During the calculation, the most uniform region in the image, which is the liver was considered for the analysis.[10] Three rectangular shapes volume of interest (VOIs), covering the maximum area of the liver were drawn on the axial, coronal, and sagittal view of the liver region by using the PMOD software Version 3.7 (Figure 1). The COV was determined by the ratio between the SD with the mean value of the VOIs (Equation 1).[14] The SD was representing as the standard deviation of the VOIs while the mean represented the mean of the pixel value.

$$COV = \frac{SD}{Mean} \times 100 \quad [1]$$

Based on the EANM recommendation, the T_{min} of the quadratic dose protocol should be defined by interpolation of the COV against the scanning time curve at COV=15%.[15] However, in this study, the definition was performed based on the average COV measured on the reconstructed images of patients at our institution. Hence, in the second phase of the experiment, we defined the relationship between the $COV_{phantom}$ and the scanning time to define the T_{min}. For this purpose, NEMA 2012/IEC 2008 image quality phantom was repeatedly scanned using six scanning times, 1, 3, 5, 7, 10, and 15 minutes. The background compartment of the phantom was considered for the COV calculation due to its homogenous character. Following that, five 30 x 30 x 30 mm VOIs were drawn at the background area as shown in Figure 1(b).

EANM guidelines version 1.0 for FDG-PET tumour imaging adhered to the PET/CT image reconstruction.[16] The image reconstruction corrected for the geometrical response, detector efficiency, system dead time, random coincidences, scatter, and attenuation. The images were reconstructed using the 3D-OSEM (ordered subset expectation maximization) algorithm in the iterative method. Two iterations and 21 subsets with the standard Gaussian post-filters with a 6.0 mm full-width half-maximum (FWHM) were used. Analysis was performed using PMOD software Version 3.7.

Estimation of ^{18}F-FDG dose activity administered

Interpolation of the $COV_{phantom}$ against the scanning time at the $COV_{patient}$ gave the T_{min} value for this imaging protocol. Substitution of this T_{min} value into Equation 2 resulted in patient-specific activity ^{18}F-FDG for the specific body weight of a patient. The respective equation is described in Equation 2, where A is the product of ^{18}F-FDG activity to be administered (in MBq), t is (in seconds) the scanning time per bed position based on the clinical setting, w_{ref} is the reference body weight, A_{ref} is the reference FDG activity.[15] For the comparison, we considered both COV=15% and COV=17.7% in the calculation.

$$A.t = \frac{w^2}{W_{ref}^2} . A_{ref} . T_{min} \quad [2]$$

The COV=17.7% used in this study was derived based on the average COV measured on the liver region of the patient reconstructed images at our department. These images were currently resulted in accepted image quality for diagnosis by the physician at IKN. Hence, adoption of this value in the T_{min} definition will result in optimal scanning time for our imaging protocol. In addition, the different COV values defined in our institution contributed by the 5 MBq/kg prescribed activity protocol practiced in IKN.

Based on the recommendation by EANM Research Ltd. (EARL), w_{ref} = 75 kg and A_{ref} = 300 MBq [16], thus can be simplified to Equation 3.

$$A = 0.053.w^2 . \frac{T_{min}}{t} \quad [3]$$

Verification of optimal T_{min} image quality

To verify the image quality obtained by using the T_{min} defined in this study, a NEMA 2012/IEC2008 phantom was repeated scanned using the respective T_{mins} and EANM recommended T_{min}. Based on a previous study, the COV=15% suggested T_{min}=3.8 minutes for the WBS PET/CT imaging.[9] This 15% COV which was recommended by EANM was regarded as the reference and standard value in this study.[15,16] Meanwhile, in the current study, COV=17.7% which was considered as the minimum and clinically acceptable COV suggested T_{min}=2.9 minutes. Quantification of the images obtained using the two T_{mins} was performed to quantitatively compared the two. The images were quantified using the following parameters:

i. Contrast recovery coefficient (Q_H)

$$Q_H \frac{\frac{Ms}{MB} - 1}{R-1} \times 100 \quad [4]$$

Where M_S and M_B were the mean count of the sphere and background respectively, and R was the tumor background ratio.[7]

ii. Signal to noise ratio (SNR)

$$SNR = \frac{T_S - T_B}{SD_B} \quad [5]$$

Where T_S was the total number of counts in spheres while T_B was the total number of counts in the background. SD_B was the standard deviation in the background.[17]

iii. Visibility (V_H)

$$V_H = \frac{M_S - M_B}{SD_B} \times \sqrt{N_{voxel}} \quad [6]$$

Where the M_S and M_B were the mean number of counts in spheres and background while N_{voxels} was the number of voxels in the spheres.[18]

Statistical Package for the Social Sciences version 26 (SPSS Inc., Chicago, IL, USA) was used to perform data analysis. Parametric analysis, independent t-test was applied to determine differences between each image quality variable and T_{min}. A p-value of <0.05 was considered statistically significant.

RESULTS

Figure 2 shows the $COV_{patient}$ measured at the liver of the patient on the reconstructed images. For the 100 samples analyzed, the $COV_{patient}$ ranged from 14% to 34%. Out of 100, only eight samples were recorded with COV>24%. 92% (92 samples from 100) of the samples were reported with COV in the ranges of 14% to 22%. The average COV was 17.7% (Σ COVpatient / 100 samples).

In Figure 3(a), the data for $COV_{phantom}$ against the scanning time was presented. The data were fitted with a power-law function, and the relationship between the two was presented by COV= 28.884 $t^{-0.457}$. At COV equal to 17.7%, the calculated T_{min} was 2.9 minutes. A similar value should be obtained if T_{min} = 17.7% is substituted into the fitted power-law function.

Referring to Figure 3(a), the power-law fitting parameters were a=28.884 and b=-0.457. Hence, by using the fitted equation y= 28.884$x^{-0.457}$ the calculated value of the T_{min} equal to 2.9 minutes. Meanwhile, at COV=15% as recommended by EANM, the T_{min} was 4.19 minutes.

Figure 3(b) shows the empirical ^{18}F-FDG activities that were estimated to be administered to the patient based on the specific body weight of the patients. The data presented here were compared for COV=15% and COV=17.7% protocols. For the ranges of body weights assumed, a consistent increment of 23% ^{18}F-FDG activity was noted between COV=17.7% and COV=15% protocol. COV=15% consistently gave higher ^{18}F-FDG activity compares to the COV=17.7%.

Figure 4 shows the analysis of the quality for the resulting images that were performed using T_{min} derived at COV=17.7% and COV=15%, resulted from T_{min}=2.9 minutes in the current study and T_{min}=3.8 minutes as reported in a previous study.[9] For the three parameters analyzed, a small percentage difference was observed between the two T_{min}s. A maximum deviation of 7.3% was reported in the Q_H of smaller spheres (5.65 ml and less). Meanwhile, the deviation was in the range of 0.6% and 2.7% for spheres 27.02 ml and 11.56 ml (Figure 4(a)). For SNR and V_H, the same pattern of results was shown in Figure 4(b) and Figure 4(c) where the percentage difference in the range of 0.2% to 5.5% was recorded. For the three image quality, independent t-test analysis indicates that all the three parameters did not significantly differ between the two T_{min} (p-value of QH=0.774, SNR=0.780 and VH=0.915) (Table I).

DISCUSSION

Degradation of PET image quality is one of the issues with the increment of the body weight of the patients, due to higher scattering and attenuation.[1,2] One of the best methods proved to produce a consistent image quality for overweight patients was the quadratic dose protocol. Nevertheless, implementation of the quadratic dose protocol suggested a longer scanning time compares to the current 2.5 minutes practices in IKN for the linear dose protocol. This finding has been published, whereby 3.8 minutes scanning time was proposed for the quadratic dose protocol.[9] However, in this study, the definition of T_{min} at COV=15% resulted in T_{min}=4.19 minutes. The difference between this T_{min} (4.19 minutes) and the T_{min} presented in the previous study (3.8 minutes) most probably due to the experimental error. In this study, we have improved the accuracy of the quantified data by repeating the measurement and data analysis three times.

Table I: Association between the T_{min} and image quality parameters

	T_{min} (minutes)	N	Mean (SD)	Std. Error Mean	F	p-value
QH	2.9	6	0.562 (0.174)	0.710	0.087	0.774
	3.8	6	0.570 (0.163)	0.664		
SNR	2.9	6	33.665 (10.302)	4.206	0.082	0.780
	3.8	6	33.583 (9.673)	3.949		
VH	2.9	6	522.083 (460.435)	187.972	0.915	0.915
	3.8	6	514.317 (443.876)	181.212		

Note: Data for T_{min}=2.9 minutes and T_{min}=3.8 minutes were expressed as mean ± SD; No significant difference between T_{min} and image quality parameters was determined by independent t-test at 0.05 level of significance.

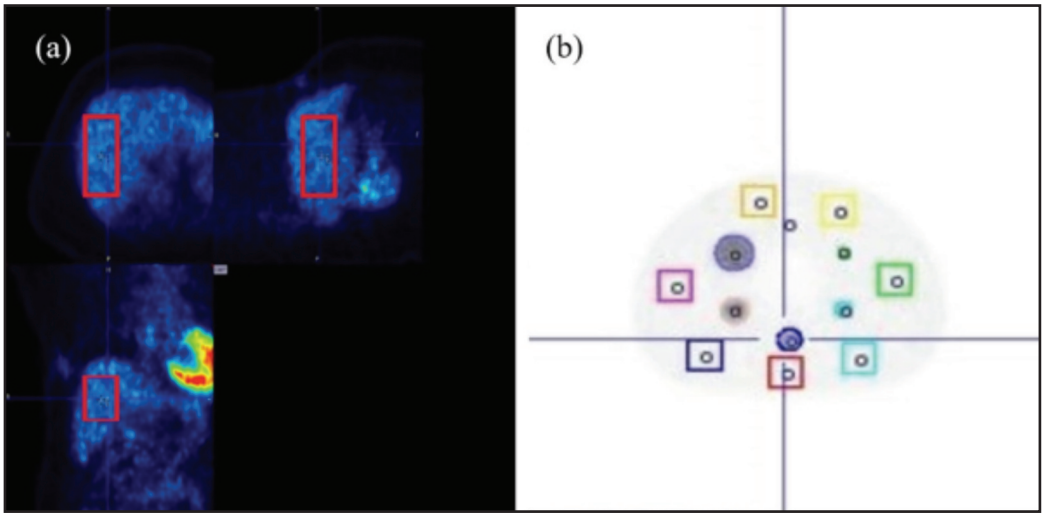

Fig. 1: The VOI defined using PMOD software (a) in the liver of the patient reconstructed image (b) at the background area of the phantom.

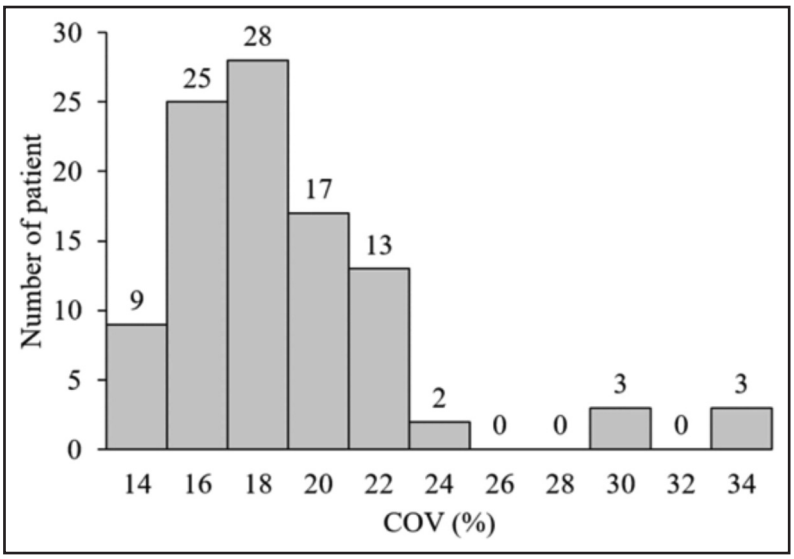

Fig. 2: Histogram of $COV_{patient}$ measured on the WBS ^{18}F-FDG PET/CT images of the patient.

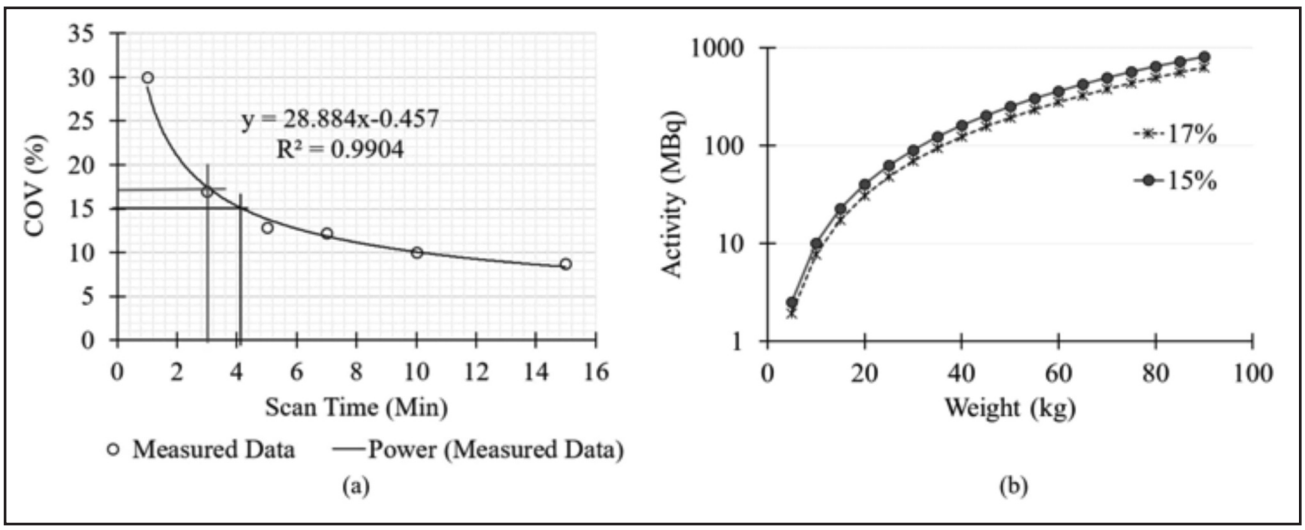

Fig. 3: (a) Comparison between the T_{mins} obtained in this study and recommendation by EANM (2015). (b) Estimated ^{18}F-FDG activity to be administered based on COV=15% and COV=17.7% quadratic dose calculation.

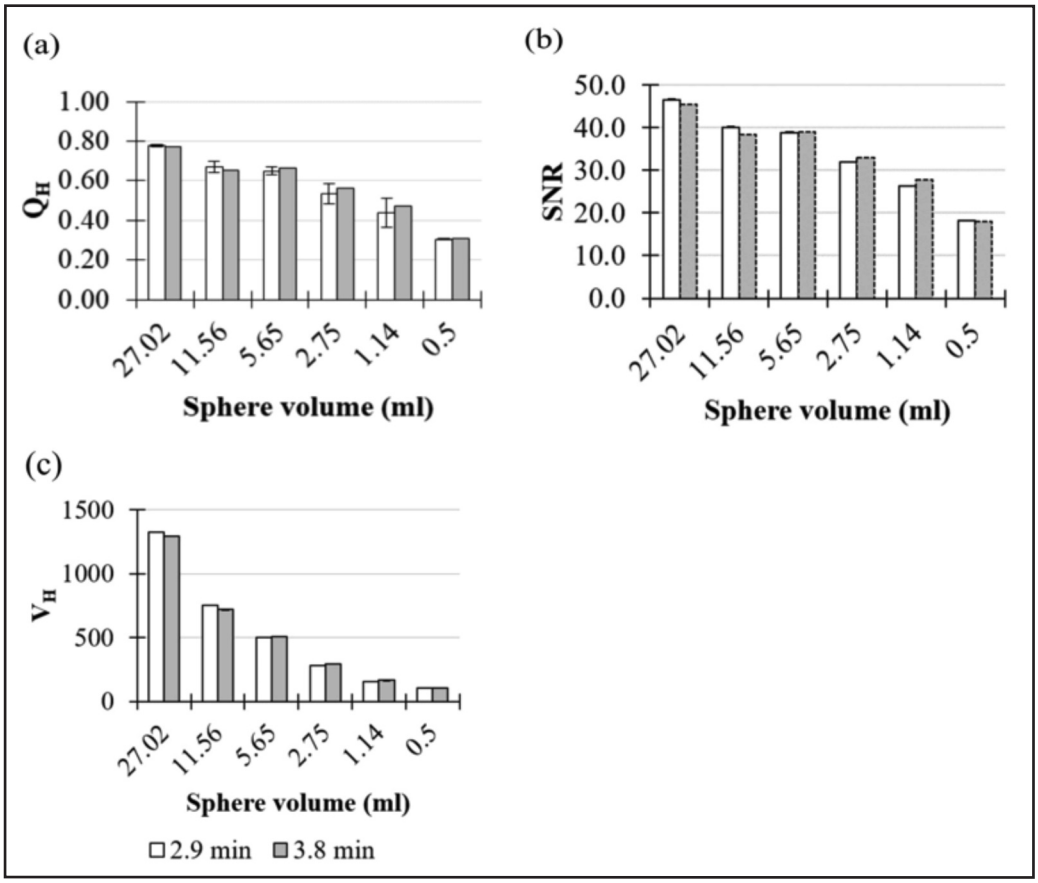

Fig. 4: Quantitative analysis of image quality for T_{min}=2.9 minutes and T_{min}=3.8 minutes. Error bar presented the percentage difference between the two data (a) contrast recovery coefficient (Q_H) (b) signal to noise ratio (SNR) (c) visibility (V_H).

This repetition can affirm the integrity of the data. To optimize the T_{min} for the WBS ^{18}F-FDG PET/CT using the quadratic dose protocol, we analyze the average COV of the WBS ^{18}F-FDG PET/CT images currently available in our PACs system. These images which were currently accepted by the physician for the analysis and diagnosis thus assumed to meet the minimal requirement for the image diagnosis. Based on the analysis, T_{min}=2.9 minutes was defined, which is 0.9 minutes or 23.68% ((0.9/3.8)x100) shorter than the T_{min} defined using COV=15%. This definition was made based on the COV=17.7% measured on the WBS ^{18}F-FDG PET/CT images. The difference in the COV values was the reason for the different T_{min} defined. Higher $COV_{patient}$ calculated on the patient images leads to a lower T_{min} as compared to the COV=15% as recommended by the EARL. The advantage of shorter T_{min} was in a shorter total acquisition time. For instance, the current WBS ^{18}F-FDG PET/CT protocol at IKN for a female patient was six bed positions. The total scanning time for the six bed positions for COV=17.7% was 17.4 minutes. Meanwhile, for COV=15%, the total scanning time was 22.8 minutes. The difference between these two COVs was 5.4 minutes. The disadvantages of longer scanning time were higher risk of movements of patients, inconvenience to the patients, artifacts and also unable to increase maximum daily scan of patients.

Based on Equation 2 and Equation 3, the amount of activity that will be administered to the patients was affected not only by the' body weight of the patients but also by the T_{min} value. Increasing the T_{min} will increase the amount of activity to be administered to the patients. The COV=17.7% of the minimal requirement for the image diagnosis in IKN suggested a lower amount of ^{18}F-FDG activity plus a shorter T_{min} as compare to the COV=15% as recommended by EANM. Since IKN is currently practicing higher COV than the recommended value, the activity administered per patient was practically reduced. For example, in Figure 3(b), for the patient with body weight of 60 kg, it is confirmed that COV= 17.7% gives less dose to the patient compared to COV=15% by 83 MBq.

In this study, the concern was not solely on the amount of activity administered to our patients but we are also considered the results of the quality of the images obtained. As stated before, the COV=17.7% practicing in IKN resulted in shorter T_{min} compares to the T_{min} derived at COV=15% as recommended by the EANM. The practicality of this T_{min} was confirmed by quantitative analysis of the images acquired using the derived T_{min}. Regarding the image analysis in this study, the results show a small percentage difference of each parameter for both T_{min}=3.8 minutes and T_{min}=2.9 minutes even in the smallest 0.5 ml sphere. Nevertheless, a slightly larger percentage deviation was recorded for the smaller sphere as compared to the larger sphere.

CONCLUSION

Analysis of the average COV on the WBS ^{18}F-FDG PET/CT images resulted in a higher average COV as compared to the recommendation by the EANM. An average COV of 17.7% was calculated from the reconstructed WBS ^{18}F-FDG PET/CT images, compares to the COV=15% recommended by the EANM. Interpolation of the T_{min} at COV=17.7% gave T_{min} =2.9 minutes, shorter than the T_{min} defined using EARL recommendation. This shorter T_{min} advantages in reducing the total scanning time, lowered the ^{18}F-FDG activity administered to the patients which reduced the internal exposure and radiation dose to the patients, and eventually more comfort to the patienst. No significant changes of Q_H, SNR and V_H were observed in the reconstructed PET/CT images of 2.9 minutes and 3.8 minutes image acquisition ($p>0.05$, respectively). Equivalent quality of images was confirmed for the two T_{mins}.

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DISCLOSURE OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Halpern BS, Dahlbom M, Auerbach MA, Schiepers C, Fueger BJ, Weber WA, et al. Optimizing imaging protocols for overweight and obese patients: a lutetium orthosilicate PET/CT study. J Nucl Med 2005; 46(4): 603-7.
2. El Fakhri G, Santos PA, Badawi RD, Holdsworth CH, Van Den Abbeele AD, Kijewski MF. Impact of acquisition geometry, image processing, and patient size on lesion detection in whole-body ^{18}F-FDG PET. J Nucl Med 2007; 48(12): 1951-60.
3. Masuda Y, Kondo C, Matsuo Y, Uetani M, Kusakabe K. Comparison of imaging protocols for ^{18}F-FDG PET/CT in overweight patients: optimizing scan duration versus administered dose. J Nucl Med 2009; 50(6): 844-8.
4. Halpern BS, Dahlbom M, Quon A, Schiepers C, Waldherr C, Silverman DH, et al. Impact of patient weight and emission scan duration on PET/CT image quality and lesion detectability. J Nucl Med 2004; 45(5): 797-801.
5. Lois C, Jakoby BW, Long MJ, Hubner KF, Barker DW, Casey ME, et al. An assessment of the impact of incorporating time-of-flight information into clinical PET/CT imaging. J Nucl Med 2010; 51(2): 237-45.
6. de Groot EH, Post N, Boellaard R, Wagenaar NRL, Willemsen ATM, van Dalen JA. Optimized dose regimen for whole-body FDG-PET imaging. EJNMMI Res 2013; 3(1): 63.
7. Yoshida E, Kitamura K, Nishikido F, Shibuya K, Hasegawa T, Yamaya T, et al. Feasibility study of a highly sensitive LaBr3 PET scanner based on the DOI-dependent extended-energy window. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip 2009; 604(1): 363-5.
8. Yoshida E, Kitamura K, Shibuya K, Nishikido F, Hasegawa T, Yamaya T, et al. A DOI-dependent extended energy window method to control balance of scatter and true events. IEEE Trans Nucl Sci 2008; 55(5): 2475-81.
9. Musarudin M, Muhammad Safwan Selvam HS, Said MA. Implementation of quadratic dose protocol for ^{18}F-FDG whole-body PET imaging using a BGO-based PET/CT scanner, GE Discovery ST. Iran J Nucl Med 2019; 27(2): 73-80.
10. Liu G, Hu Y, Pang L, Yu H, Hu P, Shi H. Variability and reliability of normal liver ^{18}F-FDG standardized uptake value in relation to placement of volume of interest. Iran J Radiol 2019; 16(2): e84881.
11. Institute for Public Health, National Institutes of Health (NIH), Ministry of Health Malaysia. National Health and Morbidity Survey (NHMS) 2019, Technical Report- Volume I: NCDs - Non-communicable diseases: risk factors and other health problems. 2019.
12. Gnesin S, Kieffer C, Zeimpekis K, Papazyan JP, Guignard R, Prior JO, et al. Phantom-based image quality assessment of clinical ^{18}F-FDG protocols in digital PET/CT and comparison to conventional PMT-based PET/CT. EJNMMI Phys 2020; 7(1): 1-16.
13. Boellaard R, Delgado-Bolton R, Oyen WJG, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015; 42(2): 328-54.
14. Abdi H. Coefficient of variation. Int Encycl Stat Sci 2011; 267.
15. Koopman D, van Osch JAC, Jager PL, Tenbergen CJA, Knollema S, Slump CH, et al. Technical note: how to determine the FDG activity for tumour PET imaging that satisfies European guidelines. EJNMMI Phys 2016; 3(1): 22.
16. Boellaard R, O'Doherty MJ, Weber WA, Mottaghy FM, Lonsdale MN, Stroobants SG, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging 2010; 37(1): 181-200.
17. Ziegler S, Jakoby BW, Braun H, Paulus DH, Quick HH. NEMA image quality phantom measurements and attenuation correction in integrated PET/MR hybrid imaging. EJNMMI Phys 2015; 2(1): 18.
18. Elschot M, Vermolen BJ, Lam MGEH, de Keizer B, van den Bosch MAAJ, de Jong HWAM. Quantitative comparison of PET and Bremsstrahlung SPECT for imaging the in vivo yttrium-90 microsphere distribution after liver radioembolization. PLoS One 2013; 8(2): e55742.

Psychosocial burden of patients with atopic dermatitis at two tertiary referral centres in Malaysia

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ABSTRACT

Background: Atopic dermatitis (AD) is a chronic pruritic skin disorder that affects up to 20% of children and 10% of adults. The disease course is unpredictable with periods of exacerbation and remission, thus having a significant impact on the mental health and quality of life (QOL). We evaluated the prevalence of anxiety and depression and their association with disease severity, QOL and their associated factors in adolescents (≥ 13 years old) and adults with AD.

Methods: A cross-sectional study was conducted involving patients aged ≥ 13 years with AD who fulfilled the Hanifin and Rajka diagnostic criteria. These patients were recruited from Hospital Queen Elizabeth, Kota Kinabalu and Hospital Kuala Lumpur between January 2020 to March 2021. Assessment instruments used were Scoring for Atopic Dermatitis (SCORAD), Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI) and Hospital Anxiety and Depression Scale (HADS).

Results: Of the 217 participants, 75 (34.6%) had mild eczema, 116 (53.5%) moderate eczema and 26 (12.0%) severe eczema with a mean SCORAD score of 30.4 (standard deviation [SD] = 4.70). Twenty-six (12.0%) and 17 (7.8%) had anxiety and depression, respectively. Patients with moderate to severe disease reported higher HADS-A (HADS-anxiety component), HADS-D (HADS-depression component), POEM, DLQI, itch, sleep loss and skin pain scores ($p < 0.001$ for all). Severe sleep loss (adjusted odd ratio [AOR] 12.41, $p < 0.001$) and hospitalisation in the past year (AOR 6.44, $p = 0.004$) were significant predictors for anxiety whereas those aged 41 to 60 (AOR 10.83, $p = 0.020$), having severe skin pain (AOR 6.12, $p = 0.028$), DLQI ≥ 10 (AOR 5.27, $p = 0.002$) and history of hospitalisation in the past year (AOR 12.73, $p = 0.002$) had increased risk for depression.

Conclusion: The prevalence of anxiety was 12.0% while depression was 7.8% in our cohort. AD renders a significant burden on mental health and QOL with a higher impact on those with more severe disease. The use of screening tools such as HADS and DLQI for assessment of mental health and QOL should be considered to address the multidimensional burden of AD.

KEYWORDS:
Psychiatric comorbidities, mental health, anxiety, depression

INTRODUCTION

Atopic dermatitis (AD) is a chronic pruritic skin disorder that affects up to 20% of children and 10% of adults.[1] In acute AD, the cutaneous lesions are characterised by weepy, oedematous and erythematous papules or vesicles. On the other hand, chronic dermatitis presents with itchy, xerotic skin with lichenification. It commonly occurs in childhood and is often associated with a personal or family history of atopy. The prevalence of AD among children in Malaysia was reported to be 12.6%.[2] As AD is a chronic disorder with periods of exacerbation and remission, it has a great impact on the patient's quality of life (QOL).[3] It does not only affect a person physically but also psychologically.[4-6]

Mental health which is recognised as an important element in comprehensive care has often been overlooked in the management of AD. The World Health Organization (WHO) defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[7] People with mental disorders are more likely to suffer from disability and have a higher mortality rate.[5] According to the National Health and Morbidity Survey (NHMS) in 2015, 29.2% of Malaysians aged 16 and above were found to have mental health problems compared to 10.7% in 1996.[8]

Previous studies demonstrated a higher prevalence of anxiety and depression in patients with AD compared to the general population,[5,6] which correlated to the severity of the AD.[9,10] A multicentre study in 13 European countries by Dalgard et al.[6] reported 10.1% of patients with AD had depression and 15% had anxiety. Moreover, a study conducted in our neighbouring country, Singapore reported that 18% had anxiety and 5% had depression in their cohort.[9] A meta-analysis by Ronnstad et al. concurred with these findings and demonstrated a positive association with suicidal behaviour.[11] In addition, Cheng CM et al. reported that having AD in adolescence or adulthood predisposes a patient to develop anxiety and depression later in life.[4] However, a causal relationship has not been established. Stressful events solely may lead to exacerbation of AD.

Sleep disturbance and the severity of itch and skin pain have been associated with impaired quality of life.[12,13] Approximately 50% of patients complain of skin itch, and 10% have sleep disturbance and skin pain.[14] Skin lesions on the head and neck and lower limbs are associated with

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inadequate control of AD.[13] Chronic itch leads to sleep deprivation and results in poor concentration at school or work. With the increasing severity, it leads to absenteeism and loss of work productivity. Ring J et al. conducted a study involving nine European countries among patients with AD and reported a high burden of disease and its negative effect on relationships, restriction to employment and leisure activities and direct and indirect financial costs imposed on the individual.[15]

In Malaysia, several studies on the impact of AD on QOL in children[16] and adults[17] have been published in the recent years. However, to date, there are no local studies assessing the association of AD with psychiatric comorbidities such as anxiety and depression. We aim to evaluate the prevalence of anxiety and depression, association of anxiety and depression with disease severity, QOL and their associated factors in adolescents (≥ 13 years old) and adults with AD in two tertiary hospitals in Malaysia.

MATERIALS AND METHODS

This was a cross-sectional study conducted from January 2020 till March 2021 at the dermatology clinics of Hospital Queen Elizabeth and Hospital Kuala Lumpur, Malaysia both which are the state dermatology referral centres. A total of 217 patients aged ≥ 13 years old who fulfilled the Hanifin and Rajka diagnostic criteria for AD (refer to Table I) were recruited during the study period. The Hanifin and Rajka criteria is a diagnostic standard published in 1980 and widely considered to be the gold standard for AD diagnosis requiring 3 of 4 major criteria and 3 of 23 minor criteria to be met for diagnosis.[18] Patients were recruited by consecutive sampling based on their clinic appointments. Those who were not able to understand the questionnaire, illiterate and declined participation were excluded.

Approval from the Malaysian Research and Ethics Committee (MREC) was obtained prior to the study commencement (NMRR-19-3035-51334). Written informed consent was obtained from all patients who agreed to participate in the study. Parental written consent was obtained for participants < 18 years old. Demographics and clinical information were obtained from each patient using a structured clinical research form by the investigators. AD severity was determined by assessment using the Scoring for Atopic Dermatitis (SCORAD). SCORAD is a widely used tool to assess disease severity in atopic dermatitis in randomised controlled trials.[19,20] The scoring includes the extent of the disease, severity of pruritus and sleep disturbance related to dermatitis with a maximum score of 103. Mild eczema is defined as a score of < 25, moderate eczema 25 to 50 and severe eczema > 50.

The average skin pain score over the past 3 days was evaluated using the visual analogue scale (VAS; 0 = no skin pain, 10 = unbearable skin pain). Average itch score and sleep loss scores over the past 3 days were also evaluated with VAS (0 = no itch/insomnia, 10 = unbearable itch/total insomnia, respectively). Subjects were questioned on the average time spent daily on topical application of medication (minutes) and the average amount of monthly expenditure spent on the treatment of AD. They were subsequently subjected to three self-administered questionnaires which were the Patient Orientated Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), and Hospital Anxiety and Depression scale (HADS) questionnaires in either Malay or English language.

POEM is a tool that is used to measure disease severity based on the patient's own experience. It has been recommended for use in the National Institute for Health and Care Excellence (NICE) guidelines.[21] It consists of seven items with each item having a score of 0 to 4; ranging from 0 (no day) to 4 (every day) with a maximum score of 28. A score of < 8 indicates clear to mild eczema, 8 to 16 indicates moderate eczema and > 16 indicates severe eczema.[22]

DLQI is a self-administered questionnaire that measures the QOL over the past one week in patients with skin disease.[23] It consists of 10 questions which cover 6 domains which are, symptoms and feeling, daily activities, leisure, work and school, personal relationships and treatment. Each question is scored 0 to 3; ranging from 0 (not at all) to 3 (very much) with a maximum score of 30. A total score of 0 to 1 indicates "no effect on patient's life", 2 to 5 "small effect on patient's life", 6 to 10 "moderate effect on patient's life", 11 to 20 "very large effect on patient's life" and 21 to 30 as "extremely large effect on patient's life". For subjects < 17 years old, the Children's DLQI was used. A DLQI score of ≥ 10 indicates significant impairment of QOL.

HADS was chosen as it has good psychometric properties and has been used in multiple studies worldwide to evaluate the psychological impact of atopic dermatitis in adults[14,24-26] and adolescents.[9] The Malay version of HADS has been validated for use in adults.[27] HADS consists of seven items that assess anxiety (HADS-A) and depression (HADS-D) separately. Each item is scored 0 to 3. Each subscale has a total score that ranges from 0 to 21. A score of ≤ 7 indicates no anxiety or depression, 8 to 10 indicates borderline anxiety or depression and ≥ 11 indicates clinical anxiety or depression. Participants with scores of ≥ 11 for either component were considered to have anxiety or depression.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences for Windows, SPSS 22.0 (SPSS Inc., IBM Corp). Categorical data were expressed as frequencies and percentages. Continuous data were expressed in means and standard deviations if they were normally distributed, or median and interquartile range if they were not normally distributed. Analysis of categorical data was done with simple logistic regression. Pearson coefficient or Kendall's tau b correlation coefficient were used to assess the correlation (r) between numerical variables. Simple Logistic Regression was run for anxiety score and depression score. A p-value of < 0.05 was considered statistically significant. In multivariate logistic regression analysis, both forward and backward Likelihood Ratio were applied for selection of independent variables. Those with p-value of < 0.05 were included in the model. The preliminary model was checked for any interaction terms between the selected variables and its multicollinearity. Hosmer-Lemeshow goodness-of-fit test was

Table I: Diagnostic criteria for atopic dermatitis[18]

Must have 3 major and ≥3 minor features for diagnosis of atopic dermatitis

Major
- Pruritus
- Typical morphology and distribution:
  - flexural lichenification or linearity in adults
  - facial and extensor involvement in infants and children
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor
- Xerosis
- Ichthyosis/ palmar hyperlinearity/ keratosis pilaris
- Immediate (type I) skin test reactivity
- Elevated serum IgE
- Early age of onset
- Tendency toward cutaneous infections (esp. Staph aureus and Herpes simplex)/ impaired cell-mediated immunity
- Tendency towards non-specific hand or foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataract
- Orbital darkening
- Facial pallor/ facial erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course influenced by environmental/ emotional factors
- White dermographism/delayed blanching

Table II: Demographic and clinical characteristics of study participants

Demographic and clinical characteristics	Number, n=217 (%)
Gender	
Male	104 (47.9)
Female	113 (52.1)
Ethnicity	
Ethnic Sabahans	111 (51.2)
Malay	42 (19.4)
Chinese	60 (27.6)
Indian	4 (1.8)
Marital status	
Single	117 (53.9)
Married	92 (42.4)
Divorced/separated	6 (2.8)
Widow/widower	2 (0.9)
Education	
Up to secondary	99 (45.6)
Tertiary and above	118 (54.4)
Employment status	
Unemployed	20 (9.2)
Employed/Student	166 (76.5)
Homemaker, retired	31 (14.3)
Monthly Income (RM)	
<RM3000	88 (40.6)
RM3000-RM9999	112 (51.6)
>RM10000	17 (7.8)
Personal history of atopy	144 (66.4)
Family history of atopy	146 (67.3)
Systemic treatment in the past 1 year	
Systemic corticosteroids	98 (45.2)
Azathioprine	31 (14.3)
Methotrexate	16 (7.4)
Phototherapy	16 (7.4)
Cyclosporin	5 (2.3)
Mycophenolate mofetil	2 (1.0)

Table III: Factors associated with anxiety, depression and significant impairment of quality of life (QOL) (using multivariate logistic regression)

	Anxiety				Depression				Significant impairment of QOL			
	Crude odds ratio (COR)	95% CI		p-value[a]	Crude odds ratio (COR)	95% CI		p-value[a]	Crude odds ratio (COR)	95% CI		p-value[a]
		Lower value	Upper value			Lower value	Upper value			Lower value	Upper value	
Age (years)				0.299		0.98	1.02	0.022				0.002
20 or less					1.00				1.00			
21-40	1.84	0.84	4.03	0.128	4.00	1.45	11.06	0.007[b]	2.46	1.28	4.85	0.009[b]
41-60	1.01	0.37	2.70	0.992	4.11	1.33	12.66	0.014[b]	1.89	0.84	4.23	0.123[b]
61 and above	1.02	0.29	3.77	0.950	1.15	0.20	6.50	0.872[b]	0.30	0.08	1.14	0.076[b]
Ethnicity				0.462				0.010[b]				0.032
Malay	1.55	0.72	3.36	0.262[b]	3.23	1.48	7.06	0.026[b]	2.04	0.97	4.26	0.059[b]
Chinese	0.95	0.45	1.97	0.881[b]	1.19	0.54	2.63	0.003[b]	0.68	0.36	1.28	0.229[b]
Others	1.00				1.00				1.00			
SCORAD score				<0.001				0.006				<0.001
Mild eczema	1.00				1.00				1.00			
Moderate eczema	3.47	1.51	8.00	0.003	3.05	1.32	7.08	0.009	3.76	2.00	7.06	<0.001[b]
Severe eczema	9.77	3.37	28.31	<0.001	5.23	1.78	15.38	0.003	15.13	4.64	49.32	<0.001[b]
Pruritus score				<0.001				0.015				<0.001
None	1.00				1.00				1.00			
Mild	1.46	0.16	13.37	0.741[b]	2.46	0.29	21.20	0.412[b]	6.86	0.84	55.68	0.072[b]
Moderate	5.90	0.74	47.25	0.095[b]	4.80	0.60	38.72	0.141[b]	15.20	1.92	120.28	0.010[b]
Severe	14.06	1.76	112.66	0.013[b]	8.80	1.09	70.85	0.041[b]	83.20	9.88	700.56	<0.001[b]
Sleep loss score				<0.001				<0.001				<0.001
None	1.00				1.00				1.00			
Mild	3.62	1.24	10.55	0.019[b]	5.50	1.82	16.63	0.003	3.93	1.75	8.83	0.001[b]
Moderate	5.65	1.96	16.32	0.001[b]	5.43	1.74	16.95	0.004	12.66	5.15	31.16	<0.001[b]
Severe	13.75	5.04	37.53	<0.001[b]	10.21	3.50	29.76	<0.001	33.27	11.87	93.30	<0.001[b]
Skin pain score				<0.001				<0.001				<0.001
No pain	1.00				1.00				1.00			
Mild	4.06[b]	1.67	9.90	0.002[b]	6.30	2.31	17.18	<0.001[b]	2.56	1.29	5.10	0.007[b]
Moderate	6.14[b]	2.48	15.21	<0.001[b]	7.91	2.84	22.06	<0.001[b]	10.91	4.63	25.70	<0.001[b]
Severe	16.38[b]	5.15	52.14	<0.001[b]	16.48	4.85	55.96	<0.001[b]	47.77	6.07	376.13	<0.001[b]
Medical conditions[c]				0.424				0.809			0.067	
No	1.00				1.00				1.00			
Yes	0.73	0.34	1.58		0.91	0.41	2.00		0.54	0.28	1.04	
Lesions at visible areas[d]				0.406				0.022				0.001
No	1.00				1.00				1.00			
Yes	1.43	0.62	3.33		4.18	1.23	14.23		3.63	1.67	7.91	
Time spent on treatment daily (mins)				0.002				0.023				0.002
≤15 mins	1.00				1.00				1.00			
16-30 mins	3.05	1.57	5.94	0.001[b]	2.20	1.10	4.41	0.023	2.51	1.38	4.56	0.003[b]
≥30 mins	3.10	1.08	8.87	0.035[b]	3.27	1.14	9.42	0.028	3.85	1.30	11.45	0.015[b]

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Table III: Factors associated with anxiety, depression and significant impairment of quality of life (QOL) (multivariate logistic regression) (cont.)

	Anxiety				Depression				Significant impairment of QOL			
	Crude odds ratio (COR)	95% CI		p-value[a]	Crude odds ratio (COR)	95% CI		p-value[a]	Crude odds ratio (COR)	95% CI		p-value[a]
		Lower value	Upper value			Lower value	Upper value			Lower value	Upper value	
Number of clinic visits in the past year				0.054				0.005				0.098
1-4	1.00				1.00				1.00			
5-8	1.45	0.72	2.92	0.305[b]	2.46	1.16	5.21	0.019	1.91	1.04	3.50	0.036
≥9	2.70	1.20	6.04	0.016[b]	3.81	1.62	9.01	0.002	1.55	0.73	3.28	0.250
Hospitalisation in the past year				<0.001				<0.001				0.015
No	1.00				1.00				1.00			
Yes	8.53	2.56	28.48		10.51	3.13	35.29		6.56	1.43	30.04	
Money spent on treatment monthly (RM)				0.874				0.046				0.003
<RM50	1.00				1.00				1.00			
RM51-150	1.21	0.59	2.50	0.605[b]	1.83	0.86	3.88	0.115[b]	2.37	1.22	1.22	0.011
>RM150	1.07	0.39	2.92	0.897[b]	2.94	1.15	7.52	0.024[b]	3.90	1.45	10.47	0.007
DLQI score				<0.001				<0.001				
< 10	1.00				1.00							
≥ 10	5.42	2.66	11.03		11.08	4.47	27.48					

[a] Likelihood Ratio (LR) test [b] Wald test

[c] Medical conditions include hypertension, dyslipidemia, ischemic heart disease, cardiac arrhythmias, gastrointestinal diseases, respiratory diseases, neurological diseases, rheumatological diseases, osteoporosis

[d] Visible areas include face, neck, hands and feet

Table IV: Factors associated with anxiety and depression (Multivariate Logistic Regression)

	Anxiety				Depression			
	Adjusted odds ratio (AOR)	95% CI		p-value[a]	Adjusted odds ratio (AOR)	95% CI		p-value[a]
		Lower value	Upper value			Lower value	Upper value	
Age group								0.020
20 or less					1.00			
21-40					6.06	1.59	23.06	0.008
41-60					10.83	2.22	52.90	0.003
61 and above					1.51	0.07	26.87	0.778
Skin pain score								0.028
None					1.00			
Mild					5.68	1.70	18.97	0.005
Moderate					4.03	1.16	13.99	0.028
Severe					6.12	1.44	25.96	0.014
Sleep loss score				<0.001				
None	1.00							
Mild	3.25	1.10	9.67	0.034[b]				
Moderate	4.58	1.54	13.66	0.006[b]				
Severe	12.41	4.49	34.30	<0.001[b]				
Hospitalisation in the past year				0.004				0.002
No	1.00				1.00			
Yes	6.44	1.79	23.21		12.73	2.62	61.80	
DLQI score								0.002
< 10					1.00			
≥ 10					5.27	1.84	15.12	

[a] Likelihood Ratio (LR) test [b] Wald test
Both models have no interaction terms, no multicollinearity and no outliers.
Hosmer-Lemeshow goodness-of-fit test for both models were not significant.
For depression model, 83.8% cases were predicted correctly whether they have depression or not and AUC of ROC was 86.5% (excellent discrimination) whereas for anxiety model, 76.5% cases were predicted and AUC of ROC was 77.7% (acceptable discrimination).

Table V: Comparison of current study with previous studies

Characteristics	Current study	Silverberg et al[14]	Dieris-Hirche et al[25]	Lim VZY et al[9]	Chiesa Fuxench et al[24]
Country	Malaysia	United States	Germany	Singapore	United States
Number of Participants	217	602	181	100	93
Female	113 (52.1%)	349 (58.0%)	137 (75.7%)	22 (22.0%)	58 (62.4%)
Age	31.0 (IQR 22.0) (range 13-87)	46.6	27.6 (SD 8.3) (range 18-60)	25.7 (SD 10.1) (range 14-58)	51.8 (SD 18.2)
Severity tool	SCORAD	PO-SCORAD	PO-SCORAD	SCORAD	POEM
Mean SCORAD	30.4 (SD 14.7)	27.5 (SD 1.8)	48.8 (SD 16.8)	55.0 (SD 16.2)	-
Severity					
Mild	75 (34.6%)	289 (59.4%)	19 (10.5%)	1 (1.0%)	362 (60.1%)
Moderate	116 (53.5%)	172 (34.8%)	73 (40.3%)	39 (39.0%)	174 (28.9%)
Severe	26 (12.0%)	34 (6.9%)	89 (49.2%)	60 (60.0%)	66 (11.0%)
Mean DLQI	10.3 (SD 6.7)	4.9 (SD 0.6)	8.3 (SD 5.9)	-	4.7 (SD 6.4)
HADS-A					
Borderline	30 (13.8%)	112 (19.8%)	-	-	-
Abnormal	26 (12.0%)	150 (28.6%)	47 (26.0%)	18 (18.0%)	23 (24.7%)
Mean HADS-A	5.3 (SD 4.1)	7.7	8.2 (SD 4.1)	7.2 (SD 3.7)	7.0 (SD 4.8)
HADS-D					
Borderline	32 (14.7%)	115 (21.0%)	-	-	-
Abnormal	17 (7.8%)	79 (13.5%)	16 (8.8%)	5 (5.0%)	13 (14.0%)
Mean HADS-D	4.6 (SD 3.8)	6.0	4.9 (SD 3.8)	5.0 (SD 3.4)	5.8 (SD 4.5)

Abbreviations: IQR, interquartile range; SD, standard deviation; SCORAD, scoring for atopic dermatitis; PO-SCORAD, patient-oriented scoring for atopic dermatitis; POEM, patient-oriented eczema measure; DLQI, dermatology life quality index; HADS-A, hospital anxiety and depression scale-anxiety component; HADS-D, hospital anxiety and depression scale-depression component

checked, not significant value means the model fits well. The sensitivity and specificity of the model's prediction of the model were determined, above 70% is considered a good model. The ROC (receiver operating characteristics) curve was checked to see the model's ability to discriminate between 2 outcomes. Finally, the Cooks influential statistic was checked and values above 1.0 were considered outliers.

RESULTS

Demographics

We recruited a total of 217 participants during the study period. Their median age was 31.0 years (interquartile range [IQR] = 22.0; range, 13 to 87). The demographics of our study participants are summarised in Table II.

Eczema severity – SCORAD and POEM tool, pruritic score, pain score and sleep loss score

The mean SCORAD score was 30.4 (standard deviation [SD] = 14.70) with 75 (34.6%) reporting mild eczema, 116 (53.5%) moderate eczema and 26 (12.0%) severe eczema. The median POEM score was 11.0 (IQR = 12.0); 72 (33.2%) mild eczema, 88 (40.6%) moderate eczema and 57 (26.3%) severe eczema. The mean pruritus score was 4.7 (SD = 2.59), median skin pain score was 2.0 (IQR = 4.0) and median sleep loss score was 2.0 (IQR = 6.0). Higher SCORAD scores were strongly correlated with higher scores for pruritus (r = 0.740, p < 0.001), sleep loss (r = 0.702, p < 0.001) and skin pain (r = 0.539, p < 0.001).

Quality of life (QOL) – DLQI tool

Sixteen (7.4%) patients reported no effect, 50 (23.0%) small and moderate effect, 83 (38.2%) very large effect and 18 (8.3%) had extremely large effect on their QOL. The mean DLQI was 10.3 (SD = 6.73). The most affected domain was symptoms (r = 0.444, p < 0.001), followed by interference with leisure activities (r = 0.390, p < 0.001), treatment-related factors (r = 0.366, p < 0.001) and effect on daily activities (r = 0.334, p < 0.001).

Anxiety and Depression - HADS tool

Our cohort had a mean HADS-A score of 5.3 (SD = 4.07) and HADS-D score of 4.6 (SD = 3.83). Thirty (13.8%) of the study participants had borderline anxiety and 26 (12.0%) had clinical anxiety whereas 32 (14.7%) had borderline depression and 17 (7.8%) had clinical depression. Eleven (5.1%) participants had both anxiety and depression, whereas fifteen (6.9%) and six (2.8%) had anxiety and depression only respectively. Of those with severe eczema, half of them (53.8%) had borderline or clinical anxiety and a third (38.5%) had borderline or clinical depression.

Logistic regression analysis of variables associated with HADS-A, HADS-D and DLQI are summarised in Table III. Unadjusted analysis revealed that patients with severe eczema were more likely to have anxiety (crude odd ratio [COR] 9.77, p < 0.001), depression (COR 5.23, p = 0.006) or significant impairment of quality of life (COR 15.13, p < 0.001) compared to those with mild eczema. Besides that, those with DLQI ≥ 10 were more likely have anxiety (COR 5.42, p < 0.001) or depression (COR 11.08, p < 0.001) compared to those with DLQI < 10.

Age group of 21 to 40, Malay ethnicity and having lesions at visible areas were associated with symptoms of depression and significant impairment of QOL. Treatment-related factors such as more time spent on treatment, hospitalisation in the past year, higher pruritus, sleep loss and skin pain scores were associated with higher risk of anxiety, depression and significant impairment of QOL. In addition, lesions at visible areas and more money spent on treatment monthly were associated with increased risk of depression or significant impairment of QOL. Increased frequency of clinic reviews was also associated with increased risk of depression. On the other hand, gender, employment status, education level, monthly household income, marital status, early onset AD (≤ 5 years old), duration of AD, personal or family history of atopy and underlying medical conditions were not associated with symptoms of anxiety or depression.

Following multivariate analysis (refer to Table IV), only severe sleep loss and hospitalisation in the past year were significant predictors for anxiety whereas age 41 to 60, severe skin pain, DLQI ≥ 10 and hospitalisation in the past year were significant predictors for depression.

The DLQI domain most affected by anxiety was symptom (r = 0.446, p < 0.001), followed by interference with leisure activities (r = 0.401, p < 0.001). For depression, the DLQI domain that was most affected was related to treatment (r = 0.431, p < 0.001), followed by symptoms (r = 0.043, p < 0.001). Anxiety scores were strongly correlated with depression scores (r = 0.751, p < 0.001). Anxiety score significantly predicted depression score (constant = 0.888, p = 0.002) and anxiety score accounted for 70.6% of the explained variability in the total depression score.

DISCUSSION

Mental health is recognised as an essential component in a person's health and well-being. Therefore, it is imperative to recognise the psychological impact of AD on patients to provide comprehensive care. This study was conducted to demonstrate the psychological impact of AD among Malaysians. HADS was selected for evaluation of anxiety and depression as it has been used in multiple similar studies.[9,14,24,25] Furthermore, validation of the Malay version of HADS in our population showed good sensitivity and specificity.[27]

The prevalence of anxiety (12.0%) in our study was lower compared to previous studies[9,14,24,25] In contrast, our prevalence of depression (7.8%) was comparable to the studies in Singapore[9] and Germany,[25] whereas a higher prevalence was reported in United States.[14,24] The mean HADS-A (5.3) and HADS-D (4.6) in our study were lower compared to the study conducted in Singapore[9] owing to the cohort in Singapore having moderate to severe eczema. Studies by Silverberg et al.[14] in The United States and Dieris-Hirche et al.[25] in Germany also documented higher anxiety and depression scores. This may be explained by the cross-cultural differences between Eastern and Western countries. A review by De Vaus et al.[28] reported differences in interpretation and response to negative emotion were critical in determining mental health well-being. Easterners have a more holistic way of thinking whereby contradictions are more accepted

resulting in adaptation to the negative emotion. In contrast, Westerners adopt a more analytical style of thinking that views positive and negative emotions as exclusive entities. In addition, Easterners are more likely to cope with high levels of negative emotions before they become overwhelmed, leading to clinical disorder. Good social support in collectivist cultures is also associated with better health outcomes.[28] Furthermore, the cost of medical treatment in Malaysia is not a barrier to obtain medical care as it is subsidised by the government. Patients only need to pay a minimal amount for medical care in the public setting thus relieving the mental stress of financial burden. Comparison of our results with previous studies are summarised in Table V.

The mean DLQI (10.3) in our study was higher compared to the studies by Silverberg et al.[14] and Chiesa Fuxench et al.[24] This could be due to the higher proportion of mild AD in their study cohorts. A study in Malaysia[17] on the impact of skin disorders on patients' QOL reported a mean DLQI of 12.9 (SD = 7.9) in AD patients. Climate differences between our country and the temperate countries may subject our patients to more AD flares due to frequent perspiration resulting in aggravation of itch and sleep disturbance thus restricting leisure, sports activities and social interactions. A review by Nguyen et al.[29] reported that with increasing temperature and humidity, sweating is enhanced which leads to skin irritation and worsening of AD. Moreover, pruriceptive nerve fibres are more activated at higher temperatures. However, ultraviolet radiation has immunosuppressive effects by enhancing T regulatory cells which leads to downregulation of T helper 2 (Th2) response. These contrasting views on the effect of climate on AD will need to be further clarified.[29,30] Additionally, our study was conducted during the COVID-19 pandemic whereby the patients may suffer from AD flares due to the use of personal protective equipment, hand sanitizers and frequent hand washing.

There was a stepwise increase in the SCORAD score with increasing anxiety, depression, DLQI, pruritus, sleep loss and skin pain scores which was also reported in previous studies [9,14,15,24,25,31] Symptoms such as itch, sleep loss, skin pain, excessive dryness, scaling and skin inflammation as well as restricted daily activities and social interactions are important factors that affect QOL, more so in those with moderate to severe disease.[14] Having AD on the visible parts of the body such as the face, neck, hands and feet were also associated with higher DLQI and depression scores. Patients often feel stigmatised, discriminated and less accepted due to the visible skin lesions. This leads to avoidance of social interaction and reduced social activities.[14] Moreover, self-esteem and confidence are affected which may lead to social isolation. Treatment-related factors such as spending more time on daily treatment, spending more money to purchase products to improve the skin condition and a higher number of clinic visits and hospitalisations were associated with greater disease severity. Understandably, patients with more severe disease will need more time to apply topical medications, to travel to the hospital for clinic reviews and blood investigations.

Besides that, with increasing AD severity, poor concentration and poor work performance at school or work leads to poor mental health.[11] Perceived social stigmatisation and the need to adapt to lifestyle changes are also contributory factors.[32] Similarly, the presence of anxiety or depression may exacerbate AD. Studies have shown that patients with psychological distress were less likely to adhere to their chronic medical illness treatment. This leads to poor control of the disease which further aggravates psychological distress.[33] Dysregulation of the hypothalamic-pituitary-adrenal axis due to chronic inflammation has been hypothesized to contribute to psychiatric comorbidities. Additionally, greater sympathetic overactivity was observed in patients with AD regardless of stress level which may lead to poor sleep quality and exacerbation of neuropsychiatric conditions.[33,34] Current data also demonstrates an increased risk of suicidal ideation in patients with severe AD.[25]

We found that AD had the highest impact on QOL and depression scores in the age group of 41 to 60 years. This age group consists of working adults. Poorly controlled AD may lead to difficulty in securing employment due to fear of stigmatisation, restricted occupational choices, presenteeism and absenteeism. A study by Andersen et al.[35] found that a higher disease severity was associated with a worse impact on work productivity. This may result in hindrance of career advancement and less fulfilling life achievements. On the other hand, the older age group was associated with lower DLQI, anxiety and depression scores. The older age group may have better coping mechanisms[17] and less daily life stress.

In our cohort, the ethnic distribution reflects the diverse ethnic groups in Malaysia. Two-thirds were recruited from Kota Kinabalu, Sabah, thus more than half of the subjects were of the ethnic groups from Sabah, followed by Chinese, Malays and Indians. In contrast, subjects from Kuala Lumpur were predominantly Malays, followed by Chinese and Indians.[36] The Malay ethnicity was associated with higher DLQI and depression scores which was also reported by Lim et al.[9] in Singapore. However, a local study on the impact of skin disorders on QOL demonstrated that QOL was most impaired in Indians followed by Malays and Chinese.[17] The differences may be due to the under-representation of the Indian and Malay ethnic groups in our cohort.

SCORAD has been widely used for the objective assessment of AD severity. However, studies have reported discrepancies between patient and clinician regarding disease severity. Those who perceived their disease to be more severe had more impaired QOL. Generally, a higher severity was reported by patients as compared to their clinicians.[37] This was also noted in our cohort where almost half of the patients who perceived they had severe disease, had moderate disease based on SCORAD assessment. These patients also had higher DLQI, anxiety and depression scores. It would be judicious then for clinicians to consider patients' perception of disease severity in deciding treatment plans as self-assessed severity has a significant impact on the psychological well-being of the patient.[38]

Awareness of the importance of recognising psychological disorders in patients with AD is essential to provide comprehensive care. The burden of disease is no longer a

measurement of physical disease only; it needs to consider the psychosocial burden and impact on QOL. Psychosocial intervention with multi-disciplinary team involvement is useful to address the psychological aspect of the disease.[10] Education on strategies to interrupt the itch-scratch cycle, good sleep habits, stress management, positive thinking and better communication skills should be incorporated in the care plan. Patient empowerment is important to equip them with the necessary resources to face challenges in their work and social life.[39] Linnet et al.[10] have reported that AD patients with high anxiety levels had improvement in mental health and skin condition after psychotherapy treatment. On the other hand, failure to recognise and provide psychological treatment to these patients may lead to poor treatment compliance.[10] Patients with anxiety and depression due to AD should be treated more aggressively as better control of AD will result in better control of the psychological comorbidities.[40] Furthermore, with new targeted treatments such as biologics and JAK (januse kinase) inhibitors, most patients can achieve good to excellent disease control.

RECOMMENDATIONS

The incorporation of screening tools such as HADS and DLQI in our daily practice should be considered especially for patients with moderate to severe disease. Patients who have abnormal anxiety or depression scores (HADS-A or HADS-D ≥ 8) should be referred for psychological assessment and counselling. These patients should be followed up closely with early consideration for systemic treatment to achieve rapid eczema control.

LIMITATIONS

As this was a cross-sectional study, we were only able to evaluate the association between psychosocial burden and AD, not causation. A study extension to compare the improvement in the SCORAD, POEM, DLQI, and HADS score after adequate control of AD would be more accurate to evaluate the impact of AD on mental health. In addition, having an age and sex-matched control group would help to better gauge the effect of AD on the psychosocial comorbidities.

CONCLUSION

This study demonstrated that AD has a significant impact on mental health and quality of life, more so with severe disease. The prevalence of anxiety was 12.0% and depression was 7.8% in our cohort. Factors that afflicted the psychological well-being of patients with AD included middle age group, higher skin pain or sleep loss scores, hospitalisation in the past year and significant impairment of QOL (DLQI ≥ 10).

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

REFERENCES

1. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet 2020; 396: 345-60.
2. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006; 368: 733-43.
3. Guo F, Yu Q, Liu Z, Zhang C, Li P, Xu Y et al. Evaluation of life quality, anxiety, and depression in patients with skin diseases. Medicine (Baltimore) 2020; 99: e22983.
4. Cheng CM, Hsu JW, Huang KL, Bai YM, Su TP, Li CT et al. Risk of developing major depressive disorder and anxiety disorders among adolescents and adults with atopic dermatitis: a nationwide longitudinal study. J Affect Disord 2015; 178: 60-5.
5. Eckert L, Gupta S, Amand C, Gadkari A, Mahajan P, Gelfand JM. The burden of atopic dermatitis in US adults: Health care resource utilization data from the 2013 National Health and Wellness Survey. J Am Acad Dermatol 2018;78: 54-61 e1.
6. Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GBE et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. J Invest Dermatol 2015;135:984-91.
7. World Health Organization. Basic documents 2020, 49th ed. World Health Organization.
8. Institute of Public Health. National Health and Morbidity Survey: Non-communicable diseases, risk factors and other health problems 2015. Malaysia: Institute of Public Health, Ministry of Health Malaysia; 2017.
9. Lim VZ, Ho RC, Tee SI, Ho MS, Pan JY, Lim YL et al. Anxiety and Depression in Patients with Atopic Dermatitis in a Southeast Asian Tertiary Dermatological Centre. Ann Acad Med Singap 2016; 45: 451-5.
10. Linnet J, Jemec GB. Anxiety level and severity of skin condition predicts outcome of psychotherapy in atopic dermatitis patients. Int J Dermatol 2001; 40: 632-6.
11. Ronnstad ATM, Halling-Overgaard AS, Hamann CR, Skov L, Egeberg A, Thyssen JP. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: A systematic review and meta-analysis. J Am Acad Dermatol 2018; 79: 448-56 e30.
12. Bridgman AC, Block JK, Drucker AM. The multidimensional burden of atopic dermatitis: An update. Ann Allergy Asthma Immunol 2018; 120: 603-6.
13. Wei W, Anderson P, Gadkari A, Blackburn S, Moon R, Piercy J et al. Extent and consequences of inadequate disease control among adults with a history of moderate to severe atopic dermatitis. J Dermatol 2018; 45: 150-7.
14. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH et al. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. Ann Allergy Asthma Immunol 2018; 121: 340-7.
15. Ring J, Zink A, Arents BWM, Seitz IA, Mensing U, Schielein MC et al. Atopic eczema: burden of disease and individual suffering - results from a large EU study in adults. J Eur Acad Dermatol Venereol 2019; 33: 1331-40.
16. Ahmad AAG NM, Rosediani M, Zulrusydi I. Quality Of Life and its Associated Factors among Children with Atopic Eczema in Kelantan, Malaysia. Int J Collab Res Intern Med Public Health 2012; 4: 1816-27.
17. Kassab YW MS, Aldahoul HK, Mohammed IK, Paneerselvam GS. The impact of skin disorders on patients' quality of life in Malaysia. J Clin Intensive Care Med 2019;4:1-9.
18. Tada J. Diagnostic Standard for Atopic Dermatitis. Japan Med Assoc J 2002; 45: 460-5.

19. Chopra R, Silverberg JI. Assessing the severity of atopic dermatitis in clinical trials and practice. Clin Dermatol 2018; 36: 606-15.
20. Schmitt J, Langan S, Deckert S, Svensson A, von Kobyletzki L, Thomas K et al. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation. J Allergy Clin Immunol 2013; 132: 1337-47.
21. National Institute of Health and Care Excellence. Atopic eczema in under 12s: diagnosis and management (Clinical Guideline 57); (updated 2 March 2021, cited 13 July 2021). Available from: https://www.nice.org.uk/guidance/cg57.
22. Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. Br J Dermatol 2013; 169: 1326-32.
23. Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol 2008; 159: 997-1035.
24. Chiesa Fuxench ZC, Block JK, Boguniewicz M, Boyle J, Fonacier L, Gelfand JM et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. J Invest Dermatol 2019; 139: 583-90.
25. Dieris-Hirche J, Gieler U, Petrak F, Milch W, Te Wildt B, Dieris B et al. Suicidal Ideation in Adult Patients with Atopic Dermatitis: A German Cross-sectional Study. Acta Derm Venereol 2017; 97: 1189-95.
26. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH et al. Measurement Properties of the Hospital Anxiety and Depression Scale Used in Atopic Dermatitis in Adults. J Invest Dermatol 2019; 139: 1388-91.
27. Fariza Y ZO. Validation of the Malay Version of Hospital Anxiety and Depression Scale (HADS) in Hospital Universiti Sains Malaysia. Int Med J April 2015; 22: 80-2.
28. De Vaus J, Hornsey MJ, Kuppens P, Bastian B. Exploring the East-West Divide in Prevalence of Affective Disorder: A Case for Cultural Differences in Coping With Negative Emotion. Pers Soc Psychol Rev 2018; 22: 285-304.
29. Nguyen GH, Andersen LK, Davis MDP. Climate change and atopic dermatitis: is there a link? Int J Dermatol 2019; 58: 279-82.
30. Kantor R, Silverberg JI. Environmental risk factors and their role in the management of atopic dermatitis. Expert Rev Clin Immunol 2017; 13: 15-26.
31. Simpson EL, Guttman-Yassky E, Margolis DJ, Feldman SR, Qureshi A, Hata T et al. Association of Inadequately Controlled Disease and Disease Severity With Patient-Reported Disease Burden in Adults With Atopic Dermatitis. JAMA Dermatol 2018; 154: 903-12.
32. Germain N, Augustin M, Francois C, Legau K, Bogoeva N, Desroches M et al. Stigma in visible skin diseases - a literature review and development of a conceptual model. J Eur Acad Dermatol Venereol 2021; 35: 1493-504.
33. Kelsay K, Klinnert M, Bender B. Addressing psychosocial aspects of atopic dermatitis. Immunol Allergy Clin North Am 2010; 30: 385-96.
34. Seiffert K, Hilbert E, Schaechinger H, Zouboulis CC, Deter HC. Psychophysiological reactivity under mental stress in atopic dermatitis. Dermatology 2005; 210: 286-93.
35. Andersen L, Nyeland ME, Nyberg F. Increasing severity of atopic dermatitis is associated with a negative impact on work productivity among adults with atopic dermatitis in France, Germany, the U.K. and the U.S.A. Br J Dermatol 2020; 182: 1007-16.
36. Department of Statistics Malaysia. Population Statistics 2019; (updated 28 April 2021, cited 30 April 2021). Available from: https://www.dosm.gov.my/v1/index.php?r=column/cthree&menu_id=UmtzQ1pKZHBjY1hVZE95R3RnR0Y4QT09.
37. Torrelo A, Ortiz J, Alomar A, Ros S, Prieto M, Cuervo J. Atopic dermatitis: impact on quality of life and patients' attitudes toward its management. Eur J Dermatol 2012; 22: 97-105.
38. Magin PJ, Pond CD, Smith WT, Watson AB, Goode SM. Correlation and agreement of self-assessed and objective skin disease severity in a cross-sectional study of patients with acne, psoriasis, and atopic eczema. Int J Dermatol 2011; 50: 1486-90.
39. Gochnauer H, Valdes-Rodriguez R, Cardwell L, Anolik RB. The Psychosocial Impact of Atopic Dermatitis. Adv Exp Med Biol 2017; 1027: 57-69.
40. Silverberg JI. Comorbidities and the impact of atopic dermatitis. Ann Allergy Asthma Immunol 2019; 123: 144-51.

Convalescent plasma as an adjunctive therapy for COVID-19: A single centre experience in Malaysia

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ABSTRACT

Introduction: The coronavirus disease 2019 (COVID-19) pandemic posed a significant and urgent threat to global health and economy. Currently, there is no effective treatment known to alter the course of COVID-19. Convalescent plasma (CP) has been used previously to treat several types of infections during pandemics. The aim of our study is to evaluate the efficacy of CP in the treatment of severe COVID-19 infections at Hospital Sultanah Bahiyah, Kedah, Malaysia.

Materials and Methods: A retrospective cross-sectional study of all severe COVID-19 patients who received CP treatment from 1st August 2020 until 31st December 2020 was conducted. Clinical outcomes were compared before and after CP transfusion.

Results: Thirty-four patients were enrolled and received CP transfusion during the study period. The most common presenting complaints were fever (64.7%) and cough (58.8%). Fourteen patients showed improvement in oxygen support after CP transfusion. Several laboratory parameters also improved such as increased lymphocyte count (1.48 vs 1.98, p=0.008) and decreased C-reactive protein levels (28.1 vs 10.6, p=0.004), and these were statistically significant. Median time from symptoms onset to CP transfusion was 6 days (range 1-11) while median time from PCR diagnosis to CP transfusion was 5 days (range 1-11). One patient developed urticaria after CP transfusion and no severe adverse events were observed. Two of our patients passed away due to secondary causes.

Conclusion: This study showed CP treatment was well tolerated and could potentially prevent progression of COVID-19 to a severe disease if administered early during the viraemic phase. Further evaluation with randomized control trial should be conducted to help ascertain the optimal dose and effectiveness of CP treatment, in correlation with the IgG titer of the donated CP.

KEYWORDS:
COVID-19, coronavirus, convalescent plasma, antibody, IgG

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is defined as an illness caused by a novel coronavirus, now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It emerged in China in late 2019 from a zoonotic source.[1] The most common transmission modality includes droplet inhalation and contact transmission. Most cases are usually asymptomatic or result in only mild symptomatic disease. However, this infection can progress to a critical illness with hypoxemic respiratory failure requiring prolonged ventilator support in a substantial percentage of susceptible patients.[2] The pathophysiological features of severe COVID-19 are dominated by an acute pneumonic process with extensive chest radiological peripheral opacities; and on autopsy, diffuse alveolar damage, inflammatory infiltrates, and microvascular thromboses are seen.[3]

Severe COVID-19 infection remains a global crisis with limited treatment options. The available antivirals could only confer benefit if administered soon after onset of illness.[4] Until an effective vaccine is developed, convalescent plasma (CP) could be a mode of adjunctive therapy to neutralise the virus and to control the overactive immune response. This was shown to be effective in treatment of various infections, including during the H1N1 influenza virus pandemic.[5] It takes approximately two to three weeks for a normal individual to mount an antibody response against pathogens. It has been postulated that patients with COVID-19 may recover faster by administering virus-neutralising antibodies in the form of CP.[6] Observational studies have shown that CP treatment has an adequate safety profile in patients with COVID-19. Besides, few initial case series suggested that CP treatment is associated with faster clinical recovery and radiological improvement.[7-9] A matched controlled study by Liu et al. also showed that CP treatment improved survival of patients.[10]

To date, multiple observational and small randomized controlled trials have demonstrated that the use of CP in treatment of COVID-19 infection remains uncertain.[11] At the beginning of the present COVID-19 pandemic, CP was transfused in patients who are more critically ill, such as those hospitalized in intensive care units (ICU) and under invasive mechanical ventilation. A randomized controlled trial (RCT) by Li and colleagues, published in August 2020, failed to demonstrate a statistically significant difference in 28-day mortality between CP-treated and standard treatment groups. However, by stratifying disease severity, the researchers observed a statistically significant difference in time to clinical improvement within a 28-day period in the

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group treated with convalescent plasma. This study highlighted that CP must be administered at an early stage of the disease in order to achieve its maximum effect.[12]

An analysis of a cohort of 3082 patients in the United States of America Expanded Access Program found that high-titre CP given less than 72 hours after hospital admission conferred a survival benefit when compared to those receiving CP later in their hospital stay.[13] It is likely that early administration of CP would be able to block viral replication during the initial phase of COVID-19, preventing the activation of inflammatory and coagulative cascade, which is often an irreversible and prominent feature of the advanced stage of disease. Any viral anti-replicative activity of CP at this stage would likely be ineffective.

The aim of our study is to evaluate the efficacy of CP transfusion in COVID-19 infection to prevent progression of illness and to obviate the need of adding immunosuppressive agents and mechanical ventilation.

MATERIALS AND METHODS

This was a single centre, retrospective cross-sectional study of 34 patients with severe COVID-19 infection who received CP treatment in Hospital Sultanah Bahiyah (HSB) Kedah, Malaysia from 1st August 2020 until 31st December 2020. All the patients were above the age of 12 years and had laboratory-confirmed SARS-CoV-2 infection by real-time reverse-transcription–polymerase chain reaction (RT-PCR) assay of either nasal or oropharyngeal swab.

In HSB, CP transfusion was given to patients with severe COVID-19 infection who had received standard of care yet noted progression of disease (e.g., >50% increase in lung infiltrates within 24-48 hours, respiratory rate more than 30/min, PaO2/FiO2 ratio of less than 300mmHg, oxygen saturation less than 93% on room air, rising CRP but < 80mg/L).

Consent was taken from all the patients prior to CP transfusion. Each patient received one (200-250ml) to two units of CP within a 12-hour interval. Corticosteroids were given to patients with rising CRP >80mg/L and worsening of PaO2/FiO2 ratio, its dose being titrated according to severity of illness. CPs were collected via apheresis method from donors who have recovered and tested positive for COVID-19 IgG, 28 days after onset of COVID-19 infection, using a point-of-care serology test, validated against the immunoassay serology.

Demographic data, clinical, radiological characteristics, co-morbidities, laboratory tests at admission and during hospitalization, treatment and outcome were retrieved from the medical records of patients. All the 34 patients were followed up during their hospitalization until they were discharged or died. Clinical symptoms (fever, cough, sore throat, anosmia, runny nose, shortness of breath, diarrhoea, and headache) and comorbidities (diabetes mellitus (DM), hypertension, chronic kidney disease, cardiovascular disease, respiratory diseases, chronic liver disease and malignancy) were also obtained. Drug treatment (antiviral, antibiotics, corticosteroid, interferon, anticoagulant), mode of oxygen therapy (standard nasal cannula, high flow oxygen, non-invasive ventilation, invasive mechanical ventilation) and need for renal replacement therapy were also collected and assessed.

Data were analysed using Statistical Package for Social Sciences software (version 21.0). Categorical data were expressed as frequencies and percentages. Wilcoxon signed-rank test were used to compare dependent variables and p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

There were 34 severe COVID-19 patients who were enrolled and received CP transfusion from 1st August 2020 until 31st December 2020. Of these, 22 were males and 12 were females with median age of 53 years old (range 35-76). The most common symptom was fever in 22 patients (64.7%), cough in 20 patients (58.8%), shortness of breath in nine patients (26.5%) and sore throat in 8 patients (23.5%). Gastrointestinal symptoms were only reported in one patient. Most of the patients had comorbidities, majority had DM (41.2%), followed by hypertension (38.2%), cardiovascular disease (17.6%) and chronic lung disease (5.9%) (Table I).

Treatment and clinical outcome

Most of the patients received off-label therapy of antiviral, interferon, and anticoagulant before the enrollment. These patients were given one or two units of CP transfusion. More than two thirds (23/34) of patients received CP transfusion within seven days from symptoms onset and PCR diagnosis with median time of 5 days (range 1-11) from PCR diagnosis, median time of 6 days (range 1-11) from symptoms onset, median CRP of 28.1 mg/L (normal value: 0-5 mg/L) and median interleukin-6 (IL-6) level of 18 pg/mL (normal value: 0-4.4 pg/mL). Among these patients who received CP transfusion, 13 of them received corticosteroids treatment post transfusion with median time of two days (range 1-4 days).

Prior to CP transfusion, three patients were on mechanical ventilation, one on non-invasive ventilation (NIV), 20 patients received high flow oxygen while ten patients received standard nasal cannula oxygenation. Our patients achieved improvement in oxygen support after CP treatment in which 14 patients were able to wean down from mechanical ventilation/NIV/high flow oxygen to standard nasal cannula oxygenation/room air (Table III). Six patients had marked improvement of oxygen support from high flow supplemental oxygen to standard nasal cannula oxygenation within 24 hours after CP transfusion.

Our study showed improvement in absolute lymphocyte count (1.48 vs 1.98, p=0.008) and CRP levels (28.1 vs 10.6, p=0.004) post CP transfusions, which were statistically significant. The median absolute lymphocyte counts were 1.48 $x10^3$ prior to transfusion, and the counts repopulated after CP transfusion. Interestingly, the CRP levels continued to rise one to two days post-CP transfusion before it fell steadily towards normal level (Figure 1). There were two

Table I: Demographic data and clinical presentation of severe COVID-19 patients who received convalescent plasma treatment

Characteristic	Value
Median age, years (range)	53 (35-76)
Gender	
Male, n(%)	22 (64.7)
Female, n(%)	12 (35.3)
Co-morbidities	
Diabetes mellitus, n(%)	14 (41.2)
Hypertension, n(%)	13 (38
Chronic kidney disease, n(%)	0 (0)
Cardiovascular disease, n(%)	6 (17.6)
Chronic lung disease, n(%)	2 (5.9)
Malignancy, n(%)	0 (0)
Presenting complaint	
Fever, n(%)	22 (64.7)
Cough, n(%)	20 (58.8)
Sorethroat, n(%)	8 (23.5)
Anosmia, n(%)	3 (8.8)
Runny nose, n(%)	6 (17.6)
Shortness of breath, n(%)	9 (26.5)
Diarrhoea, n(%)	1 (2.9)
Headache, n(%)	2 (5.9)
Treatment	
Antiviral, n(%)	34 (100)
Interferon, n(%)	24 (70.6)
Anticoagulant, n(%)	34 (100
Corticosteroids, n(%)	13 (38.2)
Median time between PCR diagnosis and CP transfusion, days (range)	5 (1-11)
Median time between symptoms onset and CP transfusion, days (range)	6 (1-11)
Median duration of ICU stays, days (range)	7 (0-34)
Outcome	
Alive, n(%)	32 (94.1)
Death, n(%)	2 (5.9)

Table II: Comparison of median laboratory parameters before and after CP transfusion

Variables	Before CP transfusion	After CP* transfusion	p value
Laboratory results			
Absolute lymphocyte count, 103/μL (range)	1.48 (0.44-2.86)	1.98 (0.43-4)	0.008
Ferritin, ng/mL (range)	459.5 (34-2578)	501 (45-1861)	0.274
C-reactive protein, mg/L (range)	28.1 (3.61-129.62)	10.6 (0.39-110.7)	0.004
Procalcitonin, ng/mL (range)	0.04 (0.01-9.33)	0.02 (0.01-3.3)	0.033
D-dimer, μg/mL (range)	0.53 (0.27-3.62)	0.76 (0.27-2.3)	0.09
IL-6	18 (2.7-692.2)	-	-

*Day 7 post CP transfusion

Table III: Comparison of oxygen requirement before and after CP transfusion

Variables	Before CP transfusion	After CP* transfusion
Oxygen supplementation		
Room air	0	15
Standard nasal cannula	10	9
High flow oxygen	20	8
Non-invasive ventilation	1	0
Mechanical ventilation	3	1

*Day7 post CP transfusion

patients who showed an increment in CRP levels after day seven due to superimposed bacterial pneumonia. The other inflammatory markers such as ferritin and D-dimer showed inconsistent response to CP treatment (Table II). Retrospectively, all stored serum were subjected to qualitative immunoassay analysis (Architect SARS-CoV2 IgG), where only three out of the 34 patients had SARS-Cov2 IgG detected prior to CP transfusion.

Thirty-two patients were discharged well from hospital, but the two others died. The two deaths were each due to hypoxic ischemic encephalopathy after a cardiac event, and a superimposed bacterial infection, respectively.

DISCUSSION

This retrospective observational study explored the feasibility and efficacy of CP therapy in viraemic phase of COVID-19

infection. Majority of enrolled severe COVID-19 patients had significant clinical and laboratory improvement after CP transfusion. All investigated patients achieved improvement in oxygen saturation, lymphocyte counts and CRP after CP transfusion in our study. After CP transfusion, we noticed that there was a sharp drop in CRP concentration, but ferritin remained elevated for a few days before decreasing in trend. This is compatible with previous studies which showed that ferritin decreased at a slower rate compared to CRP after an episode of acute infection or inflammation.[14-15]

Both the ConCovid trial by Netherlands and PLACID Trial by India demonstrated 79% and 83% of patients had various titers of baseline neutralizing antibody on enrollment. This raises the question on the value of CP as a therapy of COVID-19 infection.[16,17] Nevertheless, in resource limited countries where highly effective antivirals are not easily available or affordable, CP therapy could be a substitution of antivirals during early viraemic phase of the disease.

One of the key factors that determine the efficacy of CP therapy in COVID-19 is the timing of CP transfusion. A previous study has shown that a better treatment outcome was observed among SARS patients who were given CP before 14 days post onset of illness (58.3% vs 15.6%; p-value < 0.01), highlighting the importance of timely rescue therapy.[18] Majority of our patients received CP transfusion within seven days from symptoms onset and PCR diagnosis. A large multicenter observational study by Mayo Clinic showed that early administration of CP associated with reduction in 7-day mortality and the result was most pronounced in patients administered with CP therapy within 3 days of diagnosis as compared with patients who received treatment 4 or more days after diagnosis (8.7% vs 11.9%, p <0.001).[19] Another RCT conducted by Libster and colleagues showed that older individuals with COVID-19 who were identified in the outpatient setting within 48 hours of symptom onset and who received CP transfusion within 72 hours of symptom onset had a 48% reduced risk of progression to severe respiratory disease.[20] The case fatality rate (CFR) in our study was 5.9% (2/34), which was comparable to the CFRs in SARS infection treated with CP transfusion, which varied from 0-12.5%.[21]

Studies have shown that CRP > 97mg/L and IL-6 >80pg/mL were associated with higher risk of respiratory failure, potentially requiring mechanical ventilation. In this scenario, alternative therapies, such as corticosteroids or IL-6 antagonist need to be considered.[22] In our study, 13 patients received corticosteroids treatment where the dosage ranged from 0.5mg-1.0mg/kg/day of methylprednisolone for 5 days after CP transfusion in view of no clinical, biochemical, and radiological improvements. Possible explanation for this would be that these 13 patients did not receive convalescent plasma with high titres of neutralising antibodies as we were unable to measure the titres of neutralising antibodies in the convalescent plasma that were being given to these patients. CP transfusion is relatively safe and rarely reported to cause adverse reactions. Our findings reported only one case of allergic reaction after being given CP. Although rare, plasma transfusion has been associated with a few complications, including transfusion-related infections and transfusion related acute lung injury (TRALI). TRALI had been previously reported in an Ebola virus disease woman who received convalescent plasma therapy.[23] TRALI could pose a significant morbidity, especially in critically ill patients with COVID-19 who are experiencing significant pulmonary injury.[24] CP therapy is also associated with theoretical risk of antibody-dependent infection enhancement, which typically occurs at subneutralising concentrations, which could further suppress innate antiviral systems, allowing intracellular growth of the virus.[25-26] Ideally, only donors with high titres of neutralizing COVID-19 IgG antibodies (> 1:160) should be recruited to ensure treatment efficacy.[27] Given that neutralization assays for SARS-CoV2 neutralising antibody is not readily available, the best available method is to predict the high titer of neutralising antibody using commercial serology tests. Current data shows moderate correlation between Architect SARS-CoV2 IgG and neutralizing antibody with sensitivity of 76% in predicting antibody titer ≥1:160 when the signal cut-off is above 4.57.[28-29] Observation by investigators in China showed that middle age and elderly patients had higher level of neutralizing antibodies, and the antibody levels correlate with CRP, which is a marker of severity of COVID-19 infection.[30] Selection criteria for CP donors should include the middle age group or the fit elderly who have recovered from COVID-19 pneumonia, preferable those who required oxygen therapy.

There were several limitations in the present study. Firstly, the number of patients described is small and lacks a control group, which limits the efficacy assessment of CP therapy. Secondly, most of our patients received antiviral and interferon treatment alongside CP transfusion. We could not exclude that our observation could be the end result of the antiviral effect. Furthermore, our study did not measure the serum neutralising antibody titers of SARS-CoV-2 of our patients before and after CP transfusion. Lastly, one study has demonstrated that higher IgG levels against spike protein S1 of SARS-CoV-2 in CP may confer improved outcomes to patients with COVID-19.[31] However, this was not done in our study prior to CP transfusion. Hence, the efficacy of CP therapy in our group of patients may be varied and heterogeneous.

CONCLUSION

In our study of 34 patients with severe COVID-19, administration of CP was well tolerated, and we believe improved the clinical outcome. The optimization of CP transfusion treatment, i.e., the dose, time of administration, and established efficacy, as a potential therapy for patients with severe COVID-19 infections needs further evaluation with randomized control trials to provide a better understanding of the treatment outcomes.

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DECLARATION OF CONFLICTING INTEREST

The authors declare that there is no conflict of interest.

APPROVAL

Ethical approval of this study was obtained from Malaysia Medical Research & Ethics Committee (NMRR-20-2808-57126).

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727-33.
2. Cao J, Tu WJ, Cheng W, Yu L, Liu YK, Hu X, et al. Clinical Features and short-term outcomes of 102 patients with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 2020; 71(15): 748-55.
3. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis 2020; 20(10): 1135-40.
4. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering 2020; 6(10): 1192-8.
5. Hung IF, To KK, Lee CK, Lee KL, Chan K, Yan WW, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis 2011; 52(4): 447–56.
6. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis 2020; 398–400.
7. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A 2020; 117: 9490–6.
8. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020; 323: 1582-9.
9. Zeng H, Wang D, Nie J, Liang H, Gu J, Zhao A, et al. The efficacy assessment of convalescent plasma therapy for COVID-19 patients: a multi-center case series. Signal Transduct Target Ther 2020 6;5(1):219.
10. Liu STH, Lin HM, Baine I, Wajnberg A, Gumprecht JP, Rahman F, et al. Convalescent plasma treatment of severe COVID-19: a propensity score–matched control study. Nat Med 2020;26:1708–13.
11. Chapman S. Convalescent plasma to treat people with COVID-19: the evidence so far. Evidently Cochrane blog, https://www.evidentlycochrane.net/convalescent-plasma/ on 15 May 2020, last updated on 12 October 2020.
12. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial. JAMA 2020; 324: 460-70.
13. Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, et al. Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med 2021; 384: 1015-27.
14. Baynes R, Bezwoda W, Bothwell T, Khan Q, Mansoor N. The non-immune inflammatory response: serial changes in plasma iron, iron binding capacity, lactoferrin, ferritin and C-reactive protein. Scand J Clin Lab Invest 1986; 46: 605-704.
15. Gabay C, Kushner I. Acute phase proteins and other systemic responses to inflammation. N Engl J Med 1999; 340: 448-54.
16. Gharbharan A, Jordans CCE, GeurtsvanKessel C, den Hollander JG, Karim F, Mollema FPN, et al. Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. Nat Commun 2021; 12: 3189.
17. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ (Clinical Research ed.) 2020; 371:m3939.
18. Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur. J. Clin. Microbiol Infect Dis 2005; 24(1): 44-6.
19. Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. medRxiv 2020;2020.08.12.20169359.
20. Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. Fundación INFANT–COVID-19 Group. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. N Engl J Med 2021; 384: 610–8.
21. Yeh KM, Chiueh TS, Siu LK, Lin JC, Chan PK, Peng MY, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in Taiwan hospital. J Antimicrob Chemother 2005; 56(5): 919-22.
22. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol 2020; 146(1): 128-36.
23. Mora-Rillo M, Arsuaga M, Ramírez-Olivencia G, de la Calle F, Borobia AM, Sánchez-Seco P, et al. Acute respiratory distress syndrome after convalescent plasma use: treatment of a patient with Ebola virus disease contracted in Madrid, Spain. Lancet Respir Med 2015; 3(7): 554-62.
24. Benson AB, Moss M, Silliman CC. Transfusion-related acute lung injury (TRALI): a clinical review with emphasis on the critically ill. Br J Haematol 2009; 147(4): 431-43.
25. Halstead SB. Dengue Antibody-dependent enhancement: knowns and unknowns. Microbiology Spectrum 2014 Dec; 2(6).
26. Tirado SM, Yoon KJ. Antibody-dependent enhancement of virus infection and disease. Viral Immunol 2003; 16: 69-86.
27. Perotti C, Del Fante C, Baldanti F, Franchini M, Percivalle E, Vecchio Nepita E, et al. Plasma from donors recovered from the new Coronavirus 2019 as therapy for critical patients with COVID-19 (COVID-19 plasma study): a multicentre study protocol. Internal and Emergency Medicine 2020; 15(5): 819-24.
28. Tang MS, Case JB, Franks CE, Chen RE, Anderson NW, Henderson JP, et al. Association between SARS-CoV-2 neutralizing antibodies and commercial serological assays. Clin Chem 2020. 10.1093/clinchem/hvaa211.
29. Mendrone-Junior A, Dinardo CL, Ferreira SC, Nishia A, Salles NA, Neto CDA, et al. Correlation between SARS-COV-2 antibody screening by immunoassay and neutralizing antibody testing. medRxiv 2020.10.11.20210005.
30. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv 2020.03.30.20047365
31. Maor Y, Cohen D, Paran N, Israely T, Ezra V, Axelrod O, et al. Compassionate use of convalescent plasma for treatment of moderate and severe pneumonia in COVID-19 patients and association with IgG antibody levels in donated plasma. E Clinical Medicine 2020: 100525.

ORIGINAL ARTICLE

Development of perceptions and attitudes towards Intimate Partner Violence questionnaire for premarital young adults

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ABSTRACT

Objective: The age of young adults is a critical period as they start to explore intimate relationship and prepare for marriage. Although instruments on intimate partner violence (IPV) are available, few include potential predictors of this violent behaviors such as perceptions and attitudes. Therefore, this study aimed to develop a questionnaire to assess perceptions and attitudes toward IPV among premarital young adults.

Methods: The questionnaire was developed in two stages: item development and scale development. Two forms of validity evidence were applied, which were content validity index (CVI) and face validity index (FVI), to estimate the content validity, response process and internal structure of the tool. This cross-sectional study was conducted among premarital young adults in Kota Bharu, Kelantan. The questionnaire assessed perceptions and attitudes toward IPV on six related components, which were its forms, causes, impacts, supports, acceptance and willingness to disclose.

Results: CVI values for both perceptions and attitudes domains were more than 0.83. Five of the components have few items with low agreement by experts, hence those items were dropped. FVI values for the six domains among premarital young adults were at least 0.83, thus all these items were retained. The final result of development of this questionnaire were 64 items for perceptions and 23 items for attitudes, with five-Likert scale response option.

Conclusion: The newly developed tool, named as MY-PAIPVQ, is valid based on content validity and face validity to assess perceptions and attitudes toward intimate partner violence among premarital young adults. Before it can be used, further validation studies should be conducted to determine its psychometric properties.

KEYWORDS:
Intimate Partner Violence, Questionnaire, Young Adults, Perceptions, Attitudes

INTRODUCTION

Intimate partner violence (IPV) refers to any behavior within an intimate relationship, either actual or threatened, that causes physical, verbal, psychological, or sexual harm to those in the relationship, either in current or former spouses.[1,2] The global prevalence of physical and/or sexual partner violence among all ever-partnered women was 30.0%.[3] The prevalence was highest in the African, Eastern Mediterranean, and South-East Asia Regions, where approximately 37% of ever-partnered women reported having experienced physical and/or sexual partner violence at some point in their lives.[3] In the Western Pacific Region, specifically, the prevalence rate of intimate partner violence in 2011 was 24.6%. A few studies in Washington, Idaho and South Carolina reported that men also involved as victims in IPV with range 23% to 29% over their lifetimes among their study population.[4,5] According to the lifetime prevalence of IPV by age groups, it shows the prevalence of exposure to violence is already high among ever-partnered girls (15-19 years), which is 29.4% and 31.6% among young women (20-24 years).[3,6] This finding is suggesting that violence commonly starts early in the relationships.

Young adult (person aged 18-30 years old)7 is a critical period when they begin to explore serious relationships. This is subsequently influencing the establishment of values, patterns of behaviours, skills, and knowledge which will impact their future relationships.[8,9,10] Addressing this issue, there is a need to assess the IPV from the young adult's perspective and view to know their understandings and judgements. However, the young adults' own perception and understanding on IPV issue has rarely been sought.[11,12]

A variety of questionnaires has been designed to screen for IPV, but they were more focused to victims or married couples, hence less suitable to be used for younger adult populations.[13-15] The paucity of research concerning perceptions and attitudes toward intimate partner violence in previous studies was aimed to be complemented in this new developed questionnaire.[12-15] McCarry in her qualitative study explored on the types of violence, reasons for violence and attitudes on justifying violence.[12] Burt's Acceptance of Interpersonal Violence Scale assessed the acceptance of violence toward women.[13] A study among community in Victoria, Australia focused on general types of violence with minimal aspect on IPV.[14] Attitudes About Aggression in Dating Situations (AADS) scale focuses on the use of physical aggression in a variety of situations shown in prior work as provoking aggressive responses such as humiliation, sudden anger, and retaliation, while Justification of Verbal/Coercive Tactics Scale (JVCT) measures the respondent's attitude

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concerning the justifiability of verbal aggression, controlling behaviors, and jealous behaviors directed at their partners. Smith et al (2005) developed a toll that only measure attitudes toward various forms of IPV. Daley and Noland (2001) developed a tool to determine sexual violence in Hispanic college students' intimate relationship. Rouse (1998) used 25 items to examine dominance-possessiveness and physical force behaviors among college student's recent dating relationship.[16-18]

The existing tools on IPV have some limitations, and are also either too brief, lacking adequate cultural sensitivity or not suitable for the young adult age group. Hence, it was found necessary to develop and validate a new comprehensive questionnaire to assess IPV which is culturally appropriate for Malaysian young adults.[19] The objective of the present study was to develop a new perceptions and attitudes questionnaire on IPV among young adults.

METHODOLOGY

The development of this new tool, named as Perceptions and Attitudes toward Intimate Partner Violence Questionnaire (MY-PAIPVQ) took place in two phases. Phase 1 consisted of the item development stage, and Phase 2 comprised of scale development stage.[20,21] Item development consists of (1) identification of the domains and item generation, and (2) consideration of content validity. Scale development consists of (1) face validation and (2) pre-test. Figure 1 summarizes the methodology for developing MY-PAIPVQ questionnaire, which assess perceptions and attitudes toward IPV on components related (forms of IPV, causes of IPV, impacts of IPV, supports for IPV, acceptance of IPV and willingness to disclose). The details of each phase were elaborated in the subsequent subsections. Perceptions of IPV is defined as representation of understanding on the forms of partner violence, causes of partner violence, impacts of partner violence and supports for partner violence, and the view in their own opinion. Attitudes toward IPV defined as predispositions to respond in a positive or negative acceptance to partner violence, and willingness to disclose.

This development of questionnaire study was conducted from January until March 2020 in Kota Bharu, Kelantan using cross-sectional method. Kelantan; a northeast state of Peninsular Malaysia was chosen as the study setting as Kelantan is reported as third highest number of domestic violence (12%), after Selangor (14%) and Johor (12.4%) in 2017.[22] Kota Bharu district was chosen as it is a district with a high reported incidence of IPV cases in Kelantan.[23]

Domain identification

Thorough literature review including quantitative and qualitative studies were done to clearly define the domain and specify the purpose of the domain or construct that seek to develop.[19] A comprehensive review of the literature was also conducted to ascertain existing questionnaires, as well as to identify relevant domains in existing questionnaires on IPV. Key words used in the database searches were "intimate partner violence", "perceptions", "attitudes", "forms', "causes", "impact", "supports", "disclose", "acceptance" and "young adults".

Databases and search engines used included SAGE journals, ProQuest, PubMed, and Google Scholar. Several questionnaires that differed markedly in term of domains, as well as in their validation approaches and the quality of the validation evidence were reviewed. A meeting among the research team members was conducted to verify all the domains and some modifications from their views were considered and gathered to make sure all domains are representative, easy and understandable.[22-25]

Each contributed domain was appraised several times until all members agreed to focus on number of identified domains. Blue print of each domain was developed based on comprehensive review by research team members and two main domains (perceptions and attitudes) were identified. The perceptions domain consists of four components (forms of IPV, causes of IPV, impacts of IPV, and supports for IPV), while attitudes domains comprise of two components (acceptance of IPV and willingness to disclose).

Item Generation

Item generation was based on literature review and discussions with experts. Several guidelines and references were used to gather important information in generating appropriate items such as Understanding and Addressing Violence Against Women: Intimate Partner Violence (2012), Responding to Intimate Partner Violence and Sexual Violence Against Women: WHO Clinical and Policy Guidelines (2013), Management of Domestic Violence Cases Guideline *(Garis Panduan Pengendalian Kes Keganasan Rumah Tangga)* (2014), Domestic Violence Act (Amendment) *(Akta Keganasan Rumah Tangga (Pindaan))* 2012, Domestic Violence Guideline Book *(Buku Panduan Keganasan Rumah Tangga)* (2003), and Contemporary Family Issue: Domestic Violence *(Isu Keluarga Kontemporari: Keganasan Rumah Tangga)* (2018). [1,26-30] The development of the questionnaire was based on serial discussions, which involved a women health physician, eight public health physicians, seven premarital young adults and a biostatistician. These persons were selected based on their experience with the measured concepts in the newly developed questionnaire and discussions were conducted to explore their perceptions and attitudes towards IPV. The findings and inputs from the discussions were then used to develop relevant constructs for the questionnaire. The final number of items for perceptions and attitudes domains after completed this step was 92 items in total after rewording, rephrasing and adjustment to prevent from bias and ambiguous meaning of each item (66 items for perception domain and 26 items for attitude domain). Table I shows the objectives and items for each component for perceptions and attitudes domain.

Content validation

Content Validation Index (CVI) was assessed by the panel of expert for the relevancy and representativeness of each item to a specific domain. The panel of experts consist of four experts in women health (two experts from state women health division, a women health physician, and an expert in charge of women in crisis management), three public health physicians, and a biostatistician. The panel of experts rated each item based on a Likert scale ranging from 0 (i.e., not relevant or not represent) to 4 (i.e., highly relevant or highly

Table I: Final objectives and items for each component of perceptions and attitudes domain

Domain	Components	Objectives	Items
Perceptions	Forms of IPV	To assess the perceptions on the form of physical violence	F1, F2, F3, F4, F5
		To assess the perceptions on the form of verbal violence	F8, F9
		To assess the perceptions on the form of psychological violence	F6, F10, F11, F12, F13, F14, F15, F16, F17
		To assess the perceptions on the form of sexual violence	F7, F18
	Causes of IPV	To assess the perceptions on individual cause of IPV	C1, C2, C5, C6, C10, C12, C14, C15, C16, C17, C18
		To assess the perceptions on cultural cause of IPV	C3, C4, C7, C11, C13
		To assess the perceptions on environment cause of IPV	C8, C9
	Impacts of IPV	To assess the perceptions on physical health impact of IPV	I10, I11, I12
		To assess the perceptions on psychological health impact of IPV	I2, I3, I4, I7, I8, I9, I14, I15
		To assess the perceptions on social health impact of IPV	I1, I5, I6, I13, I16
	Supports of IPV	To assess the perceptions on informal supports for IPV	S1, S2, S3, S4, S8
		To assess the perceptions on formal supports for IPV	S5, S6, S7, S9, S10, S11, S12, S13, S14
Attitudes	Acceptance of IPV	To assess the positive acceptance of IPV	A5, A6, A9, A11, A12
		To assess the negative acceptance of IPV	A1, A2, A3, A4, A7, A8, A10
	Willingness to disclose	To assess the willingness to disclose IPV to informal persons	W1, W2, W3, W5, W10, W13, W14
		To assess the willingness to disclose IPV to formal persons	W4, W6, W7, W8, W9, W11, W12

Table II: Content Validation Index by eight experts

Components	S-CVI/UA	S-CVI/Ave	Average proportion of items judged	Number of items removed	Number of items added
Forms of IPV	0.95	0.98	0.97	1	0
Causes of IPV	0.94	0.96	0.96	1	0
Impacts of IPV	1.0	0.97	0.96	0	0
Supports for IPV	0.93	0.96	0.97	1	1
Acceptance of IPV	0.83	0.93	0.93	2	0
Willingness to disclose	0.93	0.94	0.94	2	1

*Scale-level content validity index/universal agreement method (S-CVI/UA); scale-level content validity index/averaging method (S-CVI /Ave).

Table III: Face Validation Index by 15 respondents

Components	FVI Average
Forms of IPV	0.95
Causes of IPV	0.95
Impacts of IPV	0.96
Supports for IPV	0.96
Acceptance of IPV	0.96
Willingness to disclose	0.95

Table IV: Sociodemographic characteristic of premarital young adults participated in the pre-test process in Kota Bharu (n=30)

Variables	n (%)	Mean (SD)
Age (year)		23.83 (2.37)
Gender		
Male	13 (43.3)	
Female	17 (56.7)	
Educational level		
Primary School	0 (0.0)	
Secondary School	17 (56.7)	
Diploma	5 (16.7)	
Degree/Master/PHD	8 (26.6)	
Occupational		
Unemployed	9 (30.0)	
Government worker	3 (10.0)	
Non-Government	12 (40.0)	
Self-employed	6 (20.0)	

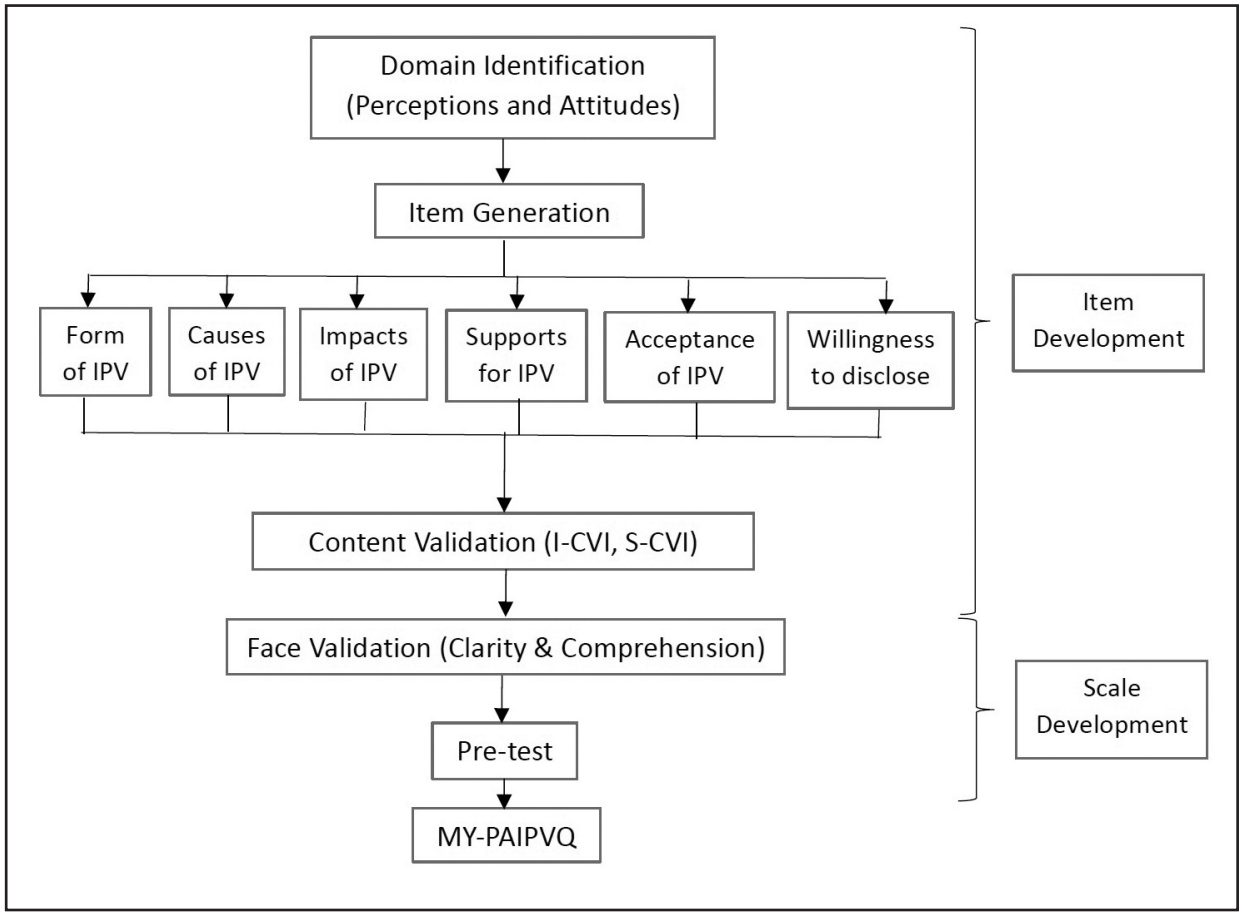

Fig. 1: The flowchart of MY-PAIPVQ development.

represent). Items were refined after a few meetings based on the panel recommendation, then rewording, rephrasing, and adjustment to prevent from bias and ambiguous meaning of each item. At the final meeting, the panel raw ratings were gathered and entered into Microsoft Excel. The calculation of item-level content validity index (I-CVI); scale-level content validity index (S-CVI); scale-level content validity index, universal agreement calculation method (S-CVI/UA); and scale-level content validity index, averaging calculation method (S-CVI/Ave); were estimated manually. S-CVI/Ave was calculated by two formulas[31] as follow:

I-CVI = (agreed item) / (number of rater)

S-CVI/Ave = (summation all I-CVI) / (number of item)

The first method was to get all I-CVI value and divide them by the number of items. The second method was to get the average proportion of each rater. Then, S-CVI/UA was calculated by getting the number of items which had 100% agreement and divided by the total number of items in that specific domain.[31] A new tool should achieve at least 80% (0.8) or higher agreement to be considered as acceptable content validity.[32]

Relevant and representative items covering both positively and negatively worded items were identified. At least ten items per component were identified to cover representativeness, relevancy, coverage, and consistency with the intended meaning of the construct.

Scale Development

Face validation was conducted to ensure that respondents interpret the items in the manner as intended. This stage highlighted items that were inappropriate at a conceptual level, besides addressing areas such as ambiguous, leading, confusing, difficult, sensitive, and missing questions.

During face validation, 15 young adults from Kota Bharu district were selected by convenience sampling and they were interviewed to check their understanding and agreement on comprehensiveness and clarity for the questionnaire items. The items were rated based on a Likert scale ranging from 0 (i.e., difficult clarity and difficult comprehensibility) to 4 (i.e., easy clarity and easy comprehensibility). The raw scores were entered in Microsoft Excel and calculated for the item-level face validity index (I-FVI) for each comprehensibility and clarity. The acceptable cut-off score of FVI is at least 0.80.[33] Formula for FVI calculation as follow:

FVI = (summation of FVI score) / (max score X number of rater)

The questionnaire was then pre-tested with 30 registered participants of premarital course from Kota Bharu district including urban (city people) and rural (villagers) settings. The pre-test served to survey and getting feedback on items prior to the launch on the data collection, especially on administrative procedures such as timing for distribution questionnaire, stationeries needed and flow of works.[34]

The standard scoring for the perceptions and attitudes domains was achieved by a meeting with the research team members. The need of scoring system and each item was examined item-by-item before the final decision. Ethical approval was obtained from the Ethical Committee, Universiti Sains Malaysia USM/JEPeM/19110807.

RESULTS

Sections of the questionnaire

The questionnaire has three sections. Section A consists of items on socio-demographic characteristics of the participants (sex, ethnicity, religion, household income, age, occupational, educational level, current relationship status and length of current relationship). Current relationship means the status of relationship, either in dating relationship, fiancé or not in any relationship. The length of current relationship was number of months of current relationship. Section B covers the perceptions towards IPV items and section C for attitudes towards IPV items. The options for the items in Section B and C responses are given by the use of 5-point Likert scale scoring system ranging from strongly agree, agree, not sure, disagree and strongly disagree. The questionnaire was written in the Malay language.

Content Validation Index (CVI)

There were four components in the domain of perception towards IPV, which were 1) forms of IPV, 2) causes of IPV, 3) impacts of IPV, and 4) supports of IPV. In addition, two components were identified for the domain of attitude towards IPV, which were 1) acceptance of IPV, and 2) willingness to disclose. Table II shows the content validation index of each component in the two domains. In the forms of IPV component, item F13 was not relevant as evident by I-CVI value of 0.63 (less than 0.8). A total 17 out of 18 items achieved acceptable universal agreement between experts (S-CVI/UA = 0.95). In the causes of IPV component, item C6 was not relevant as evident by I-CVI value of 0.63. A total 17 out of 18 items achieved acceptable universal agreement between experts (S-CVI/UA = 0.94). For the impacts of IPV component, all 16 items achieved acceptable universal agreement between experts (S-CVI/UA = 1.0). In the supports of IPV component, item S9 was not relevant as evident by I-CVI value of 0.5. A total 13 out of 14 items achieved acceptable universal agreement between experts (S-CVI/UA = 0.93).

CVI for acceptance of IPV component in the attitude domain identified two items to be removed. Item A3 and A9 were not relevant as evident by I-CVI value of 0.63 and 0.5, respectively. A total 10 out of 12 items achieved acceptable universal agreement between experts (S-CVI/UA = 0.83). In the willingness to disclose component, item W10 and W11 were not relevant as evident by I-CVI value of 0.5 and 0.63, respectively. A total 12 out of 14 items achieved acceptable universal agreement between experts (S-CVI/UA = 0.93).

The compilations of results from content validation process were discussed with the research team member. The members evaluated all the comments and suggestions given by experts, and necessary amendments were made accordingly. A total of two items were added and seven items were dropped according to the redundancy and representativeness of the content in this questionnaire.

Face validation Index (FVI)

Fifteen respondents were selected from the young adult populations living in Kelantan using convenience sampling. Most of them were female (60.0%), had secondary education and unemployed. with mean age of 22 years old (SD 1.97). FVI of clarity and comprehensive among premarital young adults was 0.95 (Table III).

Pre-test

In this study, pre-testing was done among 30 premarital young adults who attended a premarital course in Kota Bharu. The respondents were selected through purposive sampling. Sociodemographic characteristics of the respondents were summarized in Table IV. The mean of the premarital young adults participated in pre-test is 23.83 years old. Majority of them are female, had secondary education and worked in non-government sector.

Overall, comments and acceptance of the questionnaire were good. The timing for distribution was appropriate, which after a brief of introduction of research before the premarital course started. The cooperation with the organizer of the premarital courses, facilitators and the course's lecturers were excellent. The overall mean time required for respondents to answer all the items was 20.5 minutes. None of the items are ambiguous and all are understandable and clear.

The final result of development of this tool after underwent item development phase and scale development phase were 64 items for perceptions and 23 items for attitudes, with five-Likert scale response option.

DISCUSSION

IPV is an important issue to be highlighted to those who are involved in a serious relationship, especially those who already tied with marriage bond. The purpose for developing MY-PAIPVQ is to assess the perceptions and attitudes towards IPV before they get into serious relationship. All the items were developed based on established guidelines and thus providing strong evidence for its content validity. It is worthy to highlight that content validity is a prerequisite for any other forms of validity, thus should be given the highest priority during the development process of any new inventory.[35]

Seven items were removed along the development process that primarily due to poor CVI. Item F13 *(A person destroys the properties with intention to induce fear of his/her partner)* was removed from the component of form of psychological violence. The item was initially included because destroying properties may be a form of psychological violence to induce fear in the victim. The act of property destruction constitutes a form of power and control that inflicts deep, long-lasting emotional scars.[36] However, the research team members felt that the property term is unclear regarding the belonging of the properties, either public or housing properties, which lead to ambiguous statement.

Item C6 *(Both partners are working outside the house)* was considered not relevant as the individual causes of IPV by the expert panel. This is because of both partners working outside the house is common nowadays. Higher income was associated with several potential pathways to reduced IPV, including reduced household hardship, fewer arguments over the partner's inability to provide for the family, and increased relationship dissolution.[37] Conversely, some studies mentioned that women's employment or working for money has been associated with higher violence in some settings.[38-39] In addition, for the support of IPV component, Item S9 *(Counsellor is one of IPV emotional supports)*, mentioned on emotional therapy supports from counsellors. This item was detached out from the item list as counsellors support is well understood by public.

For attitudes section, item A3 and item A9 were reversed statements. Item A3 stated a person who hit her/his partner actually love her/him so much, while item A9 stated that violence is an appropriate action if child negligence happens. Experts did not agree with both reversed statements as they sound like promoting and encouraging the violence to occur in future. Item W10 *(I will disclose the IPV to religious person)* was agreed to be removed as the willingness to inform the religious person is common in Malaysian community, which may lead to biased answer. Item W11 *(I will disclose the IPV to women state development officer)* was cancelled from the questionnaire in view of gender bias.

The final number of items for both domains at the end of development stage was 87 items from 92 items. For perceptions domain, it contains four components: 17 items for forms of IPV, 17 items for causes of IPV, 16 items for impacts of IPV and 14 items for supports of IPV. While attitude domain consists of 10 items for acceptance of IPV and 13 items for willingness to disclose of IPV. The CVI of the final items was more than 0.83, indicating an acceptable level of content validity.[39] Pertaining to the response process as represented by FVI, the 87 items scored a high level of face validity in term of its clarity and comprehensibility, indicating a good response process.[39-40] A new thing introduced by MY-PAIPVQ is the broader scope and covered various aspects of intimate partner violence. Previously, existing questionnaires mostly had limited scope and more focus on violence against women.

This study has shown that MY-PAIPVQ has a good content and face validity in assessing perceptions and attitudes towards IPV among Malay population in our setting. However, further assessment is required to verify its construct validity. MY-PAIPVQ is potential to be a good tool for measuring perceptions and attitudes toward violent behaviors in intimate partner relationships. The questionnaire also might prove useful to health promotion professionals who need to identify those at risk of becoming perpetrators or victims of IPV. It can also be used as outcome measures in experimental and program evaluation research to determine effectiveness of violence interventions. In addition, the scales might possibly be used to detect favorable attitudes toward violent behaviors, which might be seen as early warning signs of potential violent behavior. Preventative interventions among young adults are more cost-effective[17], when we consider the costs of social care, health care and the criminal justice system. This questionnaire also can serve as the baseline assessment in a young adult setting or as a tool for assessing the success of IPV prevention programs, including premarital courses and school initiatives.

CONCLUSION

MY-PAIPVQ, the newly developed tool, has shown to have good content and face validity to assess perceptions and attitudes towards intimate partner violence among premarital young adults. The validity has been tested by content validation by expert panels and face validation by premarital young adults.

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CONFLICT OF INTEREST

None to declare.

REFERENCES

1. World Health Organization, Geneva. 2012. Understanding and addressing violence against women: Intimate partner violence.
2. Centers for Disease Control and Prevention. Preventing intimate partner violence across the lifespan: A technical package of programs, policies, and practices. Government Printing Office; 2017.
3. World Health Organization, Geneva. 2013. Global and regional estimates of violence against women: prevalence and health effects of intimate partner violence and non-partner sexual violence.
4. Reid RJ, Bonomi AE, Rivara FP, Anderson ML, Fishman PA, Carrell DS, et al. Intimate partner violence among men: Prevalence, chronicity, and health effects. Am J Prev Med 2008; 34(6): 478-85.
5. Coker AL, Davis KE, Arias I, Desai S, Sanderson M, Brandt HM, Smith PH. Physical and mental health effects of intimate partner violence for men and women. Am J Prev Med 2002; 23(4): 260-8.
6. Lundgren R, Amin A. Addressing intimate partner violence and sexual violence among adolescents: emerging evidence of effectiveness. J Adolesc Health 2015; 56(1): S42-50.
7. Gibbs A, Jewkes R, Willan S, Washington L. Associations between poverty, mental health and substance use, gender power, and intimate partner violence amongst young (18-30) women and men in urban informal settlements in South Africa: A cross-sectional study and structural equation model. PLOS ONE 2018; 13(10): e0204956.
8. Indermaur D. Young Australians and domestic violence. Canberra: Australian Institute of Criminology 2001.
9. Flood M. Why violence against women and girls happens, and how to prevent it. Redress 2007; 16(2): 13-9.

10. Mikton C. Preventing intimate partner and sexual violence against women: taking action and generating evidence. Inj Prev 2010: 359-60.
11. Burman M, Cartmel F. Young people's attitudes towards gendered violence. National Health Survey 2005.
12. McCarry MJ. Justifications and contradictions: understanding young people's views of domestic abuse. Men Masc 2009; 11(3): 325-45.
13. Ogle RL, Noel NE, Maisto SA. Assessing acceptance of violence toward women: A factor analysis of Burt's Acceptance of Interpersonal Violence scale. Violence against women 2009; 15(7): 799-809.
14. Taylor NM, Mouzos J. Community attitudes to violence against women survey: A full technical report. Melbourne: Victorian Health Promotion Foundation 2006.
15. Slep AM, Cascardi M, Avery-Leaf S, O'Leary KD. Two new measures of attitudes about the acceptability of teen dating aggression. Psychol Assess 2001; 13(3): 306.
16. Smith BA, Thompson S, Tomaka J, Buchanan AC. Development of the intimate partner violence attitude scales (IPVAS) with a predominantly Mexican American college sample. Hisp J Behav Sci 2005; 27(4): 442-54.
17. Daley EM, Noland VJ. Intimate partner violence in college students: A cross-cultural comparison. Int Electron J Health Educ 2001; 4: 35-40.
18. Rouse LP. Abuse in dating relationships: A comparison of Blacks, Whites, and Hispanics. J Coll Stud Dev 1988; 29: 312-9.
19. Straus MA, Douglas EM. A short form of the Revised Conflict Tactics Scales, and typologies for severity and mutuality. Violence Vict 2004; 19(5): 507-20.
20. Gjersing L, Caplehorn JR, Clausen T. Cross-cultural adaptation of research instruments: language, setting, time and statistical considerations. Med Res Methodol 2010; 10(1).
21. Simoens S. The cost-effectiveness of prevention: is an ounce of prevention worth a pound of cure?. Farmeconomia. Health economics and therapeutic pathways 2012; 13(1): 5-6.
22. Royal Malaysia Police Statistics. Number of Domestic Violence Cases by States. Malaysia, 2017.
23. Abdullah SM. Kelantan police: Sexual crimes, domestic abuse surge during MCO [cited May 2021]. Available from: https://www.nst.com.my/news/nation/2021/01/660746/kelantan-police-sexual-crimes-domestic-abuse-surge-during-mco-nsttv.
24. Boateng GO, Neilands TB, Frongillo EA, Melgar-Quiñonez HR, Young SL. Best practices for developing and validating scales for health, social, and behavioral research: a primer. Front Public Health 2018; 6: 149.
25. Raykov T, Marcoulides GA. 2011. Introduction to psychometric theory. Routledge.
26. Artino Jr AR, La Rochelle JS, Dezee KJ, Gehlbach H. Developing questionnaires for educational research: AMEE Guide No. 87. Medical teacher 2014; 36(6): 463-74.
27. Morgado FF, Meireles JF, Neves CM, Amaral A, Ferreira ME. Scale development: ten main limitations and recommendations to improve future research practices. Psicologia: Reflexão e Crítica 2017; 30.
28. World Health Organization, Geneva. 2013. Responding to intimate partner violence and sexual violence against women: WHO clinical and policy guidelines.
29. Kementerian Pembangunan Wanita, Keluarga dan Masyarakat. 2014. Garis Panduan Pengendalian Kes Keganasan Rumah Tangga.
30. Jabatan Bantuan Guaman. 2012. Akta Keganasan Rumah Tangga (Pindaan). PNMB.
31. Persatuan Pendidikan dan Penyelidikan Pengguna-Pengguna Malaysia. 2003. Buku Panduan Keganasan Rumah Tangga. ERA Consumer.
32. Ahmad, Sa'odah & Mansor, Mariani. 2007. Isu Keluarga Kontemporari: Keganasan Rumah Tangga.
33. Davis LL. Instrument review: Getting the most from a panel of experts. Appl Nurs Res 1992; 5(4): 194-7.
34. Marzuki MF, Yaacob NA, Yaacob NM. Translation, cross-cultural adaptation, and validation of the Malay version of the system usability scale questionnaire for the assessment of mobile apps. JMIR human factors 2018; 5(2): e10308.
35. Dunning T, Martin M. Developing a questionnaire: some methodological issues. Aust J Adv Nurs 1996; 14(2): 31-8.
36. Zamanzadeh V, Ghahramanian A, Rassouli M, Abbaszadeh A, Alavi-Majd H, Nikanfar AR. Design and implementation content validity study: development of an instrument for measuring patient-centered communication. J Caring Sci 2015; 4(2): 165.
37. Weisberg DK. Property Damage in the Domestic Violence Context. Domestic Violence Report. 2016; 22: 17.
38. Abramsky T, Lees S, Stöckl H, Harvey S, Kapinga I, Ranganathan M, Mshana G, Kapiga S. Women's income and risk of intimate partner violence: secondary findings from the MAISHA cluster randomised trial in North-Western Tanzania. BMC Public Health 2019; 19(1): 1108.
39. Krishnan S, Rocca CH, Hubbard AE, Subbiah K, Edmeades J, Padian NS. Do changes in spousal employment status lead to domestic violence? Insights from a prospective study in Bangalore, India. Soc Sci Med 2010; 70(1): 136-43.
40. Naved RT, Persson LÅ. Factors associated with spousal physical violence against women in Bangladesh. Stud Fam Plann 2005; 36(4): 289-300.

Assessing bone marrow involvement in diffuse large B-cell lymphoma with 18F-FDG PET/CT: A preliminary experience at Hospital Pulau Pinang

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ABSTRACT

Background: Bone marrow biopsy (BMB) is the standard of care for detecting bone marrow involvement (BMI) in newly diagnosed diffuse large B-cell lymphoma (DLBCL). The role of 18F-FDG PET/CT has been explored as a non-invasive method for detecting BMI in newly diagnosed DLBCL. Due to limited evidence, this method has not been adopted as a mainstream investigation for BMI in Malaysia. The aim of this study was to identify the role of 18F-FDG PET/CT for the detection of BMI in newly diagnosed DLBCL patients at Hospital Pulau Pinang (HPP).

Methods: DLBCL patients at HPP who underwent 18F-FDG PET/CT and BMB were recruited between November 2016 to February 2018. Two reviewers, blinded to the BMB results, evaluated the 18F-FDG PET/CT scans to identify and characterize BMI. The diagnostic performance of 18F-FDG PET/CT was calculated using the BMB histopathological evaluation as the reference standard.

Results: A total of 21 DLBCL patients were enrolled. Seven patients demonstrated BMI on PET/CT (3 with multifocal uptake were concordant with BMB). Fourteen scans were negative for BMI and concordant with BMB. The sensitivity and specificity of 18F-FDG PET/CT scans for detecting BMI is 100% and 77.8%, respectively.

Conclusion: 18F-FDG PET/CT is excellent for ruling-out the presence of BMI. A negative 18F-FDG PET/CT scan for BMI can preclude the need for BMB in certain cases. Although 18F-FDG PET/CT can accurately detect BMI in multifocal pattern of infiltration, it cannot fully replace BMB, which is still considered as the gold standard for evaluating BMI in DLBCL.

KEYWORDS:
BMB, Deauville's criteria, DLBCL, Nuclear Medicine, Staging

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin's lymphoma (NHL) worldwide.[1] Two separate studies in Malaysia identified that DLBCL has a higher prevalence compared to other types of NHL.[2,3] DLBCL is a highly aggressive disease that needs to be detected and treated immediately. The clinical course of the disease is highly variable based on the various subtypes and most patients present late at Stage III or IV.[4] Furthermore, up to 40% of patients have been reported to have relapsing disease after the 1st line of chemotherapy.[5]

DLBCL is divided into concordant and discordant types based on the histology. Concordant histology refers to a worse overall survival and prognostic outcome which occurs when cancer cell histopathology is similar in the marrow and nodal site. Opposite to discordant histology, it refers to differing histopathology between the marrow and nodal site, however it carries lesser impact on overall prognosis of the patients.

Aggressive histopathology is described as a high number of lymphoproliferative cells and T-cell rich nodules. Whereas immunohistochemical features of aggressive disease include diffuse leukocyte common antigen (LCA) and CD20 positivity as well as the presence of MIB, a proliferation marker index that is more than 80%.[6]

The clinical practice guideline by the European Society of Medical Oncology (ESMO) is commonly utilised as the standard of care for diagnosing DLBCL.[7] Additionally, the International Prognostic Index (IPI) was introduced to determine the prognostic factors for DLBCL patients. Based on the IPI, five characteristics were used to score and classify the disease prognosis, among which included bone marrow involvement (BMI).[1] The treatment given for DLBCL is based on the age and IPI index score of the patients, whereby the classification is (i) young low-risk without bulky disease (IPI=0), (ii) young low-risk with bulky disease (IPI=0), (iii) young low-intermediate risk (IPI=1), (iv) young high and high-intermediate risk (IPI=2), (v) patient aged 60-80 years old, and (vi) patient >80 years old with CNS involvement.[8]

Until recently, bone marrow biopsy (BMB) has been the undisputed standard of care for identifying BMI to stage the extra-nodal involvement of DLBCL.[9] A blind posterior iliac crest trephine biopsy and aspirate is routinely performed in newly diagnosed DLBCL. Subsequently, morphological and immunohistochemical evaluation are conducted on the BMB specimens to identify BMI using the Ann Arbor staging.[9] Ann Arbor Stage I is the presence of a single lymphatic region involvement or involvement of a single extra-lymphatic site

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involvement, Stage II is the involvement of ≥ 2 lymphatic regions or extra-lymphatic site(s) involvement on the same side of the diaphragm, Stage III is lymphatic involvement on both sides of the diaphragm, and Stage IV is diffuse or disseminated involvement of ≥ 1 extra-lymphatic organs with or without lymphatic involvement.[8]

Despite the widely acceptable practice of BMB, currently there is a move towards adopting less invasive means of evaluating BMI in DLBCL. In the latest consensus established by international working groups, the Lugano classification has been proposed to incorporate the role of 18-Fluorine-Fluorodeoxyglucose positron emission tomography / computed tomography (^{18}F-FDG PET/CT) scans in the staging and restaging of DLBCL.[8] ^{18}F-FDG PET/CT allows for a physiological response assessment based on the tumour metabolism itself, whereby it enters the tumour cells via sodium-independent glucose transporter receptors (GLUT-1, GLUT-3 and GLUT-12) by facilitated diffusion, and is then transported within the cells and phosphorylated, hence becoming trapped as FDG-6-phosphate.[10] The 18F-FDG PET/CT scans are evaluated based on the size and intensity of radiotracer uptake, where a visual assessment is conducted to identify patterns of abnormally high radiotracer uptake in the marrow.[11] Quantitative assessment using the maximum Standard Uptake Value (SUV_{max}) can also be employed to determine any abnormal FDG accumulation in volumes of interests (VOIs) at pertinent sites of the whole body.[12]

Nevertheless, there is still much debate on the visual assessment of BMI (qualitative analysis) and SUVmax evaluation of uptake at VOIs (quantitative analysis) on the ability of ^{18}F-FDG PET/CT scans to fully replace BMB for the assessment of BMI in patients with DLBCL.13,14 The conflicting results, together with the limitations due to the cost and availability of ^{18}F-FDG PET/CT scans were the main reasons as to why BMB was still mandated for assessing BMI.[15] In Malaysia, there is no local data available regarding the potential role of ^{18}F-FDG PET/CT scans to preclude the need for BMB in excluding BMI among newly diagnosed DLBCL patients. Thus, the aim of this study was to conduct qualitative and quantitative assessment of ^{18}F-FDG PET/CT radiotracer uptake characteristics for the evaluation of BMI among DLBCL patients. We also aimed to identify the role of ^{18}F-FDG PET/CT, including its diagnostic accuracy, compared to BMB for the detection of BMI in newly diagnosed DLBCL patients at a northern region Malaysian hospital, i.e., Hospital Pulau Pinang (HPP).

MATERIALS AND METHODS

Ethical clearance, study design and subject recruitment

This study was approved by the Medical Research Ethics Committee (MREC) of the Kementerian Kesihatan Malaysia and registered with the National Medical Research Register (NMRR ID: NMRR-16-1950-32951). This study was also approved by the Jawatankuasa Etika Penyelidikan Manusia (JEPeM) of Universiti Sains Malaysia (USM JEPeM ID: USM / JEPeM / 17050261) A prospective study with universal sampling method was carried out in the Nuclear Medicine Department, HPP from November 2016 to February 2018. The study subjects were newly diagnosed pre-treated "chemo naïve", adult DLBCL patients in the northern region of Malaysia, who were referred to HPP for therapeutic management. All patients underwent diagnostic pre-chemotherapy ^{18}F-FDG PET/CT scan and BMB within an interval of 60 days apart between the two tests. A delay period interval of more than 60 days may result in morphological histopathological changes leading to invalidity of results.[16] Patients who had received haematopoietic growth factor injections as a prophylaxis prior to receiving chemotherapy,17 in a period of less than 48 hours prior to the first ^{18}F-FDG PET/CT scan, were excluded from this study because this could result in false positive findings caused by an inflammatory reaction in the bone marrow.

^{18}F-FDG PET/CT imaging protocol

The preparation for ^{18}F-FDG PET/CT scans, for a total of 28 subjects who fulfilled the inclusion and exclusion criteria and were initially enrolled into this study, were performed as per the HPP department protocol. Subjects were advised to be fasted for 4-6 hours before the scan to limit the impact of dietary glucose to compete with the glucose analogue, i.e., ^{18}F-FDG. The patients were also instructed to avoid any strenuous exercise for few days prior to the scan in order to reduce skeletal muscle uptake of the glucose analogue. The subjects with Type 2 diabetes mellitus were carefully scheduled in the morning before taking their insulin. Whereas the subjects on oral hypoglycaemia agents, i.e., metformin were advised to withhold medication on the morning of the scan to decrease bowel background activity caused by the drug. Before injecting ^{18}F-FDG intravenously, all the subjects were ensured that their blood glucose levels were less than 11 mmol/L as indicated by the department protocol. After injection, the subjects were kept rested in a dimly lit room to allow for the uptake time. Subsequently, PET/CT scanning was conducted at approximately 60 minutes post-injection. PET/CT scans were conducted using a GE Discovery scanner (General Electric Company (GE), Boston, USA). Scans were performed from mid femur to the vertex with duration of 3 minutes per bed position. A transmission date acquisition of 40-minutes attenuation data acquisition using a built-in CT scanner was done along with 1-hour attenuation data acquisition using radioactive sources with 2D mode (in septa) collimator and 30% energy window of 511kev. Low-dose CT data was used for attenuation correction and anatomical localization of the PET images. Images were reconstructed in axial, sagittal and coronal fused PET/CT images and viewed on a dedicated PET/CT GE workstation.

Interpretation of ^{18}F-FDG PET/CT scans

The ^{18}F-FDG PET/CT scans were evaluated by two experienced nuclear medicine physicians at HPP, who were blinded to the subsequent BMB results. Both readers evaluated the images qualitatively for the presence of BMI as evidenced by radiotracer uptake in the bone marrow that was of higher intensity than the liver. They then characterised the pattern of uptake into focal (one area of discrete uptake), multifocal (presence of two or more regions of well-circumscribed uptake), diffuse (widespread regions of uptake involving the whole bone marrow), or mixed focal and diffuse uptake (Figure 1 A, B, C). In the instance that there were no bone marrow regions with radiotracer uptake higher than the

Table I: Sociodemographic factors and clinical data of the study subjects

Patient factors	Number of patients (Percentage (%))
Gender	
Male	13 (61.9)
Female	08 (38.1)
Race	
Malay	12 (57.1)
Chinese	06 (28.6)
Indian	03 (14.3)
Others	Nil
Ann Arbor Stage	
I	02 (9.5)
II	06 (28.6)
III	05 (23.8)
IV	08 (38.1)

Table II: Qualitative and quantitative 18F-FDG PET/CT results in DLBCL subjects

Num.	Quantitative		Qualitative	Type of uptake	BMB
	BM SUVmax	L SUVmax	BMI		
1	6.32	1.27	+	MF	+
2	11.23	2.16	+	MF	+
3	12.8	2.2	+	MF	+
4	4.79	2.32	+	D	-
5	4.77	2.68	+	D	-
6	2.65	2.1	+	D	-
7	3.5	2.5	+	F & D	-
8	1.09	2.02	-	N	-
9	0.94	3.5	-	N	-
10	1.31	2.21	-	N	-
11	3.11	4.11	-	N	-
12	2.28	3.09	-	N	-
13	2.26	2.47	-	N	-
14	2.01	2.7	-	N	-
15	2.37	2.5	-	N	-
16	1.69	3.02	-	N	-
17	3.48	3.72	-	N	-
18	1.85	2.74	-	N	-
19	1.37	2.03	-	N	-
20	1.7	2.1	-	N	-
21	3.4	3.8	-	N	-

*BM = Bone marrow; L = Liver; BMI = Bone marrow involvement; BMB = Bone marrow biopsy; *MF = Multifocal; D = Diffuse; F&D = Focal & diffuse; N= Negative.

Table III: Pattern of uptake on 18F-FDG PET/CT scan correlated with bone marrow biopsy

		18F-FDG PET/CT				
		Negative	Positive			
			Multifocal	Diffuse	Mixed Focal & Diffuse	Total
BMB	Negative	14	0	3	1	18
	Positive	0	3	0	0	3
	Total	14	3	3	1	21

liver, the scan was considered negative for BMI (Figure 1D). Any disagreement in the results was resolved by a third reader, a senior consultant of Nuclear Medicine, to attain a consensus on the evaluation of the presence of BMI. The readers also placed VOIs at selected marrow uptake sites to record the automated SUV_{max} for the quantitative analysis. A similar VOI was also placed at in the liver at the region of highest SUVmax avoiding vascular territories. According to the 5-point Deauville's scoring criteria which was recommended for standardization of ^{18}F-FDG PET/CT method for quantitative approach, marrow uptake positivity is considered when the SUVmax within the marrow is higher than the SUVmax of the liver.[18] Moreover, the liver can be a surrogate of arterial radiotracer uptake for SUV normalization, enabling reliable measurements of background radiotracer uptake provided that a consistent volume of interest (VOI) site is utilised to achieve standardization.[19]

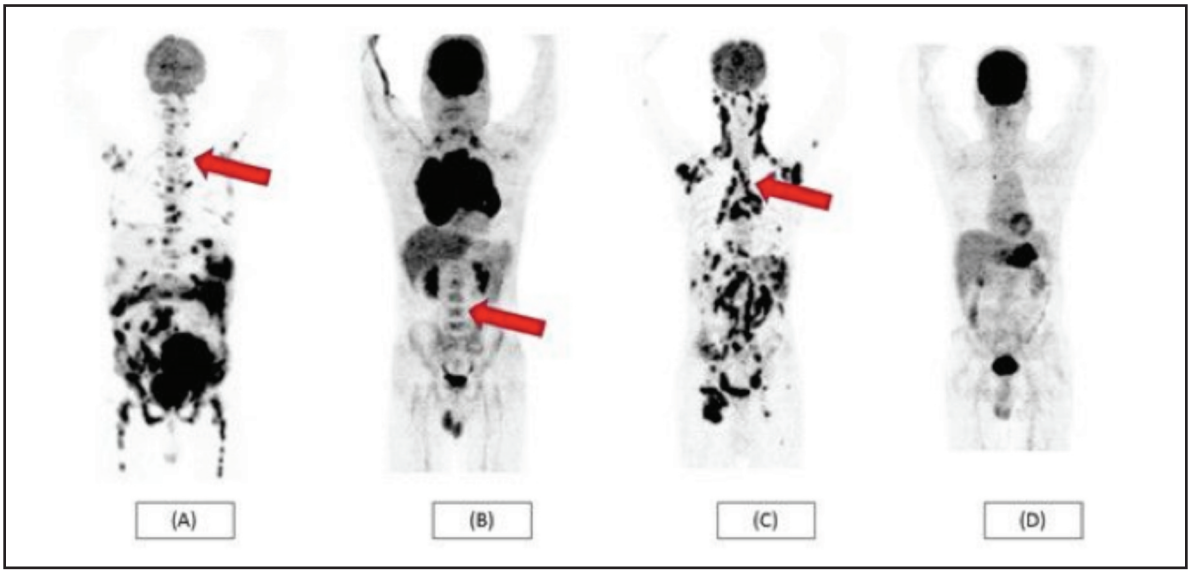

Fig. 1: Maximum Intensity Projection (MIP) images in coronal view showing various patterns of bone marrow uptake on 18F-FDG PET/CT scans. (A) Focal/multifocal uptake. (B) Diffuse uptake. (C) Mixed multifocal & diffuse uptake. (D) Negative study indicative of no bone marrow involvement.

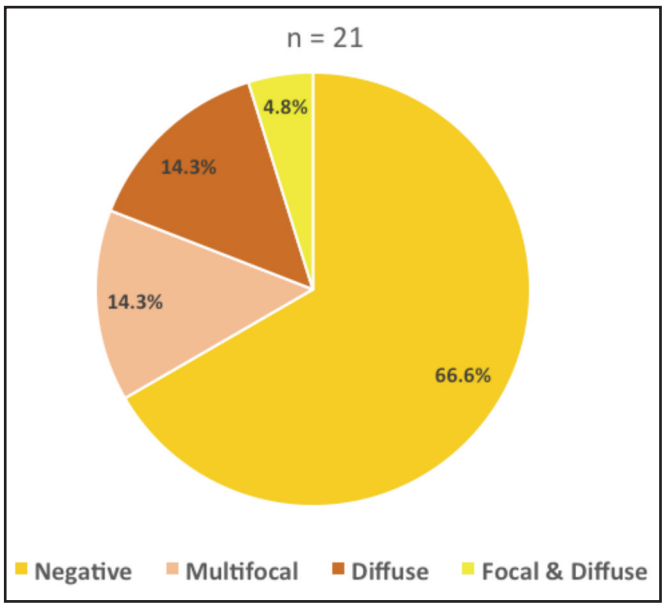

Fig. 2: Pattern of tracer uptake in ^{18}F-FDG PET/CT scans of the DLBCL subjects.

Equation 1:
SUV_{max} = Maximum tissue activity per volume of interest (millicurie/mL) / Total injected dose per body weight (millicurie)/gram)

Data analysis and statistical tests
The results of the ^{18}F-FDG PET/CT scan findings were then compared with the BMB results as the reference standard for the evaluation of BMI. Statistical analyses were performed using IBM Statistical Package for Social Science software version 24.0 for Mac (SPSS, 2016). Descriptive studies were expressed as frequency (percentage), mean ± standard deviation for normally distributed data or median (IQR) for skewed data. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy were calculated based on statistical formulas. A Cohen's kappa test was used to determine the validation and agreement between 18F-FDG PET/CT scan and BMB for BMI in DLBCL cases involving a statistical significance of $p<0.05$.

RESULTS

Subject demographics and clinical data
A total of 28 subjects who fulfilled the inclusion and exclusion criteria were initially enrolled in this study. However, only 21 subjects completed both 18F-FDG PET/CT scan and BMB within the time frame required. Thus, seven subjects had to be dropped out from this study due to the reason that the BMB and ^{18}F-FDG PET/CT scan were not conducted within a maximum period of 60 days apart. Seven subjects had to be dropped out due to the reason that BMB was not completed within the stipulated period after patients had their pre-chemotherapy ^{18}F-FDG PET-CT scan done.
The mean± standard deviation for the age of the 21 subjects was 45.6 ± 18.5 years old, ranging from 18 years old to 80 years old. Thirteen (61.9%) out of the 21 patients were males and the remaining 38.1% were females. The majority of these patients were Malays, followed by Chinese and Indians (Table I). As for the stage of disease, most of the subjects were in the category of Ann Arbour Stage IV disease (n=8, 38.1%) (Table I). There was a male preponderance for more advanced stage of DLBCL. All patients received rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone chemotherapy (R-CHOP) regime.

Qualitative analysis determination of BMI
We detected radiotracer uptake that was higher than the liver uptake in seven out of 21 subjects (33.4%). The pattern of bone marrow uptake was variable among these patients; whereby three patients showed multifocal uptake, one

patient showed mixed focal and diffuse uptake, whereas another three patients showed diffuse uptake alone (Figure 2). The majority of the ^{18}F-FDG PET/CT scans were negative for BMI.

Quantitative analysis determination of BMI

Most ^{18}F-FDG PET/CT scans that were evaluated to be negative for BMI had bone marrow SUVmax of ≤ 2.0 g/mL. The commonest radiotracer uptake pattern that was positive for BMI was multifocal bone marrow uptake, which had SUV_{max} measurements of ≥ 6.0g/mL, with the highest recorded SUV_{max} uptake of 12.8 g/mL (Table II).

Diagnostic performance of 18F-FDG PET/CT scan compared to BMB

There was moderate agreement between ^{18}F-FDG PET/CT scan and BMB which showed significant concordance (kappa k-value: 0.500, p<0.008) By comparing ^{18}F-FDG PET/CT scans with BMB as the reference standard for detecting BMI, the results showed three truly positive scans and no falsely negative scans (Table III), thus giving a sensitivity of 100% (95%CI 29.2 - 100.0). There were 14 truly negative and four false positive scans (Table III), giving a specificity of 77.8% (95% CI of 52.4 - 93.6). The PPV is 42.9% (95% CI of 24.0 - 64.0) and the NPV is 100%. Therefore, the diagnostic accuracy of ^{18}F-FDG PET/CT for detecting BMI in DLBCL is 80.9% (95% CI of 58.1 - 94.6).

DISCUSSION

This study evaluated the role of ^{18}F-FDG PET/CT in determining the presence of BMI and uptake pattern in newly diagnosed DLBCL. The mean age of the subjects in this study was mid-40s, which is comparable to a study of DLBCL patients conducted in Sabah Malaysia, by Peh et al.[3]

Most of the subjects recruited in this study were in advanced Ann Arbor Stage IV disease. This is similar to another cohort study by Khan et al that had a high prevalence rate of 45% patients staged in Ann Arbor stage IV at presentation.[20] Our cohort study also showed that an advanced stage of DLBCL, i.e., Ann Arbor Stage III and IV, was more prevalent among the male gender. The higher mortality rate in the male gender compared to females, indicating that the majority of males were diagnosed at a late stage of disease has also been previously reported.[21]

On analysis of the pattern of marrow uptake on ^{18}F-FDG PET/CT scans, the commonest pattern of uptake was the multifocal type of uptake pattern (14.3%). compared to those with positive ^{18}F-FDG PET/CT scan and negative BMB study which showed 1 mixed focal and diffuse type of uptake (4.8%) and the remaining 3 (14.3%) showed only diffuse type of uptake. In the quantitative analysis, the bone marrow SUVmax for the 3 positive multifocal type of pattern of uptake in ^{18}F-FDG PET/CT scans showed a markedly high SUVmax uptake of 6.32-12.8 which is more than 70% of the mean liver SUVmax. Additionally, it has been reported that DLBCL with focal pattern of marrow uptake on ^{18}F-FDG PET/CT scans have a worse prognosis compared to the other patterns of uptake.[22] In fact Berthet et al identified that 2 of their study subjects had positive multifocal type of bone marrow uptake on the ^{18}F-FDG PET/CT scans with concordant BMB results. The subjects were then upstaged to Ann Arbor Stage IV and received intensified chemotherapy followed by autologous stem cell transplant, which improved their prognostic outcome.[1] Therefore, this may imply that multifocal type of bone marrow uptake may place these DLBCL patients in a more advanced disease stage.

There was one positive mixed focal and diffuse type detected, as well as 3 positive diffuse bone marrow uptake patterns seen on the ^{18}F-FDG PET/CT scans in this cohort study. The corresponding subjects were identified with a lower bone marrow SUVmax uptake of 2.65- 4.79 g/mL, which is less than 50% of the liver SUV_{max}. An explanation as to the reason for the diffuse uptake on ^{18}F-FDG PET/CT scans is likely due to the concurrent presence of other medical conditions such as anaemia (91.3%), elevated C-reactive protein levels (81.0%), leucocytosis (47.8%), thrombocytopenia (39.1%) and thrombocytosis (21.7%), as observed by Adams et al.[23] Furthermore, this medical manifestation is likely due to an alteration in the composition of the blood and reactive bone marrow processes besides a lymphomatous BMI.[1]

According to the Ann Arbor classification, the presence of BMI will automatically upgrade the patient to an advanced stage of the disease.[1] The subjects will then be subjected to additional more intensive treatment regimens such as doxorubicin, vindesine, cyclophosphamide, bleomycin and prednisone (ACVBP); involved-field radiotherapy (IF-RT), or autologous stem-cell transplantation (ASCT).[8] Furthermore, as noted in this study all thee multifocal type of uptake pattern on ^{18}F-FDG PET/CT with concordant BMB results were noted to be at Ann Arbor Stage IV disease. This strongly agrees with a paper by Tilly et al which stated that a focal or multifocal pattern of uptake is usually seen in advanced stages of DLBCL disease.[8]

In this cohort study, all 14 out of 21 ^{18}F-FDG PET/CT scans were correctly assessed as negative for BMI. The average value of the liver SUV_{max} for all these negative scans was 2.5 g/mL and most patients had bone marrow SUV_{max} of ≤ 2.0 g/mL. A previous study by Chen et al revealed that there were 147 subjects that had ^{18}F-FDG PET/CT scans that were negative for BMI with concordant BMB results.[24]

Our cohort study showed a high NPV and a sensitivity of 100%, respectively. The findings from this study is in agreement with results from Berthet et al as their results reported negative BMI in ^{18}F-FDG PET/CT scans performed for 101 cases, 99 cases of which were concordant with negative BMB results, achieving a sensitivity and a NPV of 90.4% and 95.8%, respectively.[1] These results were also in line with a meta-analysis reported by Adams et al whereby the pooled sensitivity and specificity were 96.9% and 99.7%, respectively.[25]

In addition to that, our current cohort study has managed to prove a moderate agreement between our ^{18}F-FDG PET/CT scan and BMB with a significant p value of 0.008 and k-value of 0.500. Furthermore, a recent study done in 2017 by El Karak et al. had also demonstrated a weak but significant concordance between ^{18}F-FDG PET/CT scan and BMB using Receiver Operating Characteristic curve (kappa=0.391, with p=0.001).[26]

Many previous studies have recommended that BMB may be replaced by ^{18}F-FDG PET/CT in Hodgkin's lymphoma (HL).[14, 27] The low incidence rate of BMI and lack of treatment consequences in advanced HL disease makes it more permissible for BMB to be omitted in assessing for BMI provided that a pre-chemotherapy ^{18}F-FDG PET/CT scan is done.[15] In a recent study by Chen et al it is recommended that in view of BMB's unfavourable accuracy and limitation of predicting patient prognosis compared to ^{18}F-FDG PET/CT scans, the role of BMB is unnecessary in assessing BMI.[24]

Despite multiple studies done in assessing BMI with 18F-FDG PET/CT scan, the role of pre-chemotherapy ^{18}F-FDG PET/CT in assessing BMI in Malaysia has yet to be enforced in view of limited sources i.e., the limited availability of PET/CT scans, as well as the affordability and awareness of its role by primary physician teams. All lymphoma patients in Malaysia are still subjected to BMB despite many current reports recommending practitioners to be more selective in deciding which patients are suitable for BMB if the results of ^{18}F-FDG PET/CT are indeterminate. The motive of this study is to explore the complementary role of ^{18}F-FDG PET/CT as well as to collate the sensitivity and specificity between ^{18}F-FDG PET/CT scan and BMB in assessing BMI, specifically in DLBCL.

One of the limitations of our study is the relatively small sample size. Thus, we recommend a longer duration for patient recruitment to obtain larger datasets. The second limitation is the lack of follow-up scans, which can be rectified by conducting a future longitudinal study. Thirdly, no medical data regarding the anaemic status of our patients was included. Moreover, it is a challenge to diagnose BMI in anaemic patients considering that the SUVmax is not a reliable indicator of BMI in this group of patients. Additionally, when these patients have a diffuse pattern of ^{18}F-FDG uptake as opposed to focal, it gives rise to equivocal diagnostic accuracy. In the instance of a relatively lower BM SUVmax with diffuse pattern of uptake, a BMB becomes mandatory to exclude BMI. This will then allow for the assessment of progression free survival and overall survival of DLBCL patients in the northern region of Malaysia. Multicentre studies need to be considered, by including patients from all regions in Malaysia, which can truly represent the whole population in this country and reflect a more accurate clinical scenario.

In view of achieving a strong NPV and excellent sensitivity of ^{18}F-FDG PET/CT in excluding or detecting BMI respectively, we recommend that a negative bone marrow infiltration finding on an ^{18}F-FDG PET/CT scan should be able to preclude the need for BMB. However, in discordant histology i.e., aggressive tumour, the role of BMB may be crucial to be performed with the role of ^{18}F-FDG PET/CT being complementary.

CONCLUSION

^{18}F-FDG PET/CT is excellent for excluding the presence of BMI in DLBCL. A negative ^{18}F-FDG PET/CT scan for BMI can preclude the need for BMB in certain cases. Although ^{18}F-FDG PET/CT can accurately detect BMI in multifocal pattern of BM infiltration, it cannot fully replace BMB, which is considered as the gold standard for evaluating BMI in DLBCL.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

REFERENCES

1. Berthet L, Cochet A, Kanoun S, Berriolo-Riedinger A, Humbert O, Toubeau M, et al. In newly diagnosed diffuse large B-cell lymphoma, determination of bone marrow involvement with 18F-FDG PET/CT provides better diagnostic performance and prognostic stratification than does biopsy. J Nucl Med 2013; 54(8): 1244-50.
2. Chang K, Lau N, Chew L, Tan S, Jameela S, Puru V. Incidence and Outcome of T-Cell Lymphomas in Malaysia. Blood 2006; 108(11): 4684.
3. Peh S, Shaminie J, Jayasurya P, Hiew J. Spectrum of malignant lymphoma in Queen Elizabeth Hospital, Sabah. Med J Malaysia 2003; 58(4): 546-55.
4. Hoefnagel J, Dijkman R, Basso K, Jansen P, Hallermann C, Willemze R et al. Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. Blood 2005; 105(9): 3671-8.
5. Johnson SA, Kumar A, Matasar MJ, Schöder H, Rademaker J. Imaging for Staging and Response Assessment in Lymphoma. Radiology 2015; 276(2): 323-38.
6. Ali AE, Morgen EK, Geddie WR, Boerner SL, Massey C, Bailey DJ, et al. Classifying B-cell non-Hodgkin lymphoma by using MIB-1 proliferative index in fine-needle aspirates. Cancer Cytopathol 2010; 118(3): 166-72.
7. Tilly H, Vitolo U, Walewski J, da Silva MG, Shpilberg O, André M, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23 Suppl 7: vii78-82.
8. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26: v116-v25.
9. Alzahrani M, El-Galaly TC, Hutchings M, Hansen JW, Loft A, Johnsen HE, et al. The value of routine bone marrow biopsy in patients with diffuse large B-cell lymphoma staged with PET/CT: a Danish-Canadian study. Ann Oncol 2016; 27(6): 1095-9.
10. Farwell MD, Pryma DA, Mankoff DA. PET/CT imaging in cancer: Current applications and future directions. Cancer 2014; 120(22): 3433-45.
11. Adams HJ, De Klerk JM, Fijnheer R, Heggelman BG, Dubois SV, Nievelstein RA, et al. Bone marrow biopsy in diffuse large B-cell lymphoma: useful or redundant test? Acta Oncol 2015; 54(1): 67-72.

12. Boellaard R, O'Doherty MJ, Weber WA, Mottaghy FM, Lonsdale MN, Stroobants SG, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nuc Med Mol Im 2010; 37(1): 181-200.
13. Alzahrani M, El-Galaly TC, Hutchings M, Hansen JW, Loft A, Johnsen HE, et al. The value of routine bone marrow biopsy in patients with diffuse large B-cell lymphoma staged with PET/CT: a Danish-Canadian study. Ann Oncol 2016; 27(6): 1095-9.
14. Vishnu P, Wingerson A, Lee M, Mandelson MT, Aboulafia DM. Utility of Bone Marrow Biopsy and Aspirate for Staging of Diffuse Large B Cell Lymphoma in the Era of Positron Emission Tomography With 2-Deoxy-2-[Fluorine-18]fluoro-deoxyglucose Integrated With Computed Tomography. Clin Lymphoma Myeloma Leuk 2017; 17(10): 631-6.
15. El-Galaly TC, Hutchings M, Mylam KJ, Brown Pde N, Bukh A, Johnsen HE, et al. Impact of 18F-fluorodeoxyglucose positron emission tomography/computed tomography staging in newly diagnosed classical Hodgkin lymphoma: fewer cases with stage I disease and more with skeletal involvement. Leuk Lymphoma 2014; 55(10): 2349-55.
16. Dupas B, Augeul-Meunier K, Frampas E, Bodet-Milin C, Gastinne T, Le Gouill S. Staging and monitoring in the treatment of lymphomas. Diagn interv Imaging 2013; 94(2): 145-57.
17. Demetri GD. Hematopoietic growth factors. Defining the appropriate clinical role in multimodality cancer therapy. Chest 1995;107(6 Suppl):255s-60s.
18. Hasenclever D, Kurch L, Mauz-Körholz C, Elsner A, Georgi T, Wallace H, et al. qPET – a quantitative extension of the Deauville scale to assess response in interim FDG-PET scans in lymphoma. Eur J Nuc Med Mol Imaging 2014; 41(7): 1301-8.
19. Azmi NHM, Suppiah S, Liong CW, Noor NM, Said SM, Hanafi MH, et al. Reliability of standardized uptake value normalized to lean body mass using the liver as a reference organ, in contrast-enhanced 18F-FDG PET/CT imaging. Radiat Phys Chem 2018; 147: 35-9.
20. Khan AB, Barrington SF, Mikhaeel NG, Hunt AA, Cameron L, Morris T, et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. Blood 2013; 122(1): 61-7.
21. Nair R, Arora N, Mallath MK. Epidemiology of Non-Hodgkin's Lymphoma in India. Oncology 2016; 91(suppl 1)(Suppl. 1): 18-25.
22. Lee JW, Lee SC, Kim HJ, Lee SM. Prognostic value of bone marrow (18)F-FDG uptake on PET/CT in lymphoma patients with negative bone marrow involvement. Hell J Nucl Med 2017; 20(1): 17-25.
23. Adams HJA, Kwee TC, Fijnheer R, Dubois SV, Nievelstein RAJ, de Klerk JMH. Diffusely increased bone marrow FDG uptake in recently untreated lymphoma: incidence and relevance. Eur J Haematol 2015; 95(1): 83-9.
24. Chen Y, Zhou M, Liu J, Huang G. Prognostic Value of Bone Marrow FDG Uptake Pattern of PET/CT in Newly Diagnosed Diffuse Large B-cell Lymphoma. J Cancer 2018; 9(7): 1231-8.
25. Adams H, Kwee T, De Keizer B, Fijnheer R, de Klerk J, Littooij A, et al. Systematic review and meta-analysis on the diagnostic performance of FDG-PET/CT in detecting bone marrow involvement in newly diagnosed Hodgkin lymphoma: is bone marrow biopsy still necessary? Ann Oncol 2014; 25(5): 921-7.
26. El Karak F, Bou-Orm IR, Ghosn M, Kattan J, Farhat F, Ibrahim T, et al. PET/CT Scanner and Bone Marrow Biopsy in Detection of Bone Marrow Involvement in Diffuse Large B-Cell Lymphoma. PloS One 2017; 12(1): e0170299.
27. Elamir Y, Elazab M, Owis AS, Elsayed HF. PET/CT and bone marrow biopsy (BMB) in evaluating bone marrow in lymphoma. Egypt J Radiol Nucl Med 2020; 51(1): 201.

ORIGINAL ARTICLE

Psychometric properties of the Malay inventory for the perception of Muslims with hearing impairment

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ABSTRACT

Objective: The aims of this study are to measure the psychometric properties of the newly developed preliminary version of hearing impairment inventory for religious duties for Muslim adults, i.e., the *Inventori Persepsi Bagi Muslim Yang Memiliki Masalah Pendengaran (IPM3P)*, and to produce a final version of IPM3P.

Methods: The preliminary version of IPM3P that is used to investigate the perception of Muslim adults with hearing impairment towards Islamic understanding and practice has been tested in this study. The preliminary version of IPM3P consists of three domains (obligation, practice, and difficulty) with 59 items in total. Four phases of validity and reliability testing involved were: i) Content validation, ii) Pre-testing, face validity and proofreading, iii) Pilot study, and iv) Psychometric evaluation.

Results: The final version of IPM3P consists of 36 items. The findings from the present study suggest that the final version of IPM3P has excellent psychometric properties manifested by: i) good content validity, ii) excellently pretested, iii) good face validity, iv) good construct validity shown by principal component analysis and convergent validity, and v) good discriminant validity showed by divergent validity.

Conclusion: IPM3P shows good potential to be used as a tool in investigating perception of Muslim adults towards Islamic understanding and practice.

KEYWORDS:
Questionnaire development, effects of hearing loss, Islamic understanding and practice, psychometric properties

INTRODUCTION

Hearing loss was proven to affect quality of life including the religious life. Previous studies investigating the effect of heairng loss towards religous life among Muslim showed that hearing loss was proven to affect certain areas of Islamic understanding and practice, including prayers, and quranic recitation.[1–3] Previously, investigations on impact of hearing loss on Islamic practice were mainly concentrated on students and children population.[1–4] To our knowledge, there was no study investigating the effect of hearing loss towards Islamic understanding and practice among the Muslim adult population. The absence of tools to measure the effects of hearing loss on Islamic understanding and practices among Muslim adults is among the factors contributing to the limited investigation in the area. As a solution, a preliminary version of a questionnare to investigate the impact of hearing loss among adults in varoius area of Islamic understanding and practices, that is known as *'Inventori Persepsi Bagi Muslim Yang Memiliki Masalah Pendengaran' (IPM3P)* has been previously developed.[5,6] The preliminary version of IPM3P consists of three domains (obligation, practice and difficulty) with 59 items in total, but has yet to be validated. The aims of this study were to finalize the development of IPM3P and subsequently to measure the psychometric properties of the final version of IPM3P. This was conducted by performing content validity, face validity, pre-testing, pilot study, and by distributing the IPM3P to a larger scale for psychometric evaluation. With the validation and reliability analysis, it is hoped that the IPM3P can be used as one of the tools to measure the impact of hearing loss on the various aspects of Islamic understanding and practice, as well as to serve as a rehabilitative tool in measuring the effectiveness of an intervention strategy, specifically for the Muslim adult population.

MATERIALS AND METHODS

There were four stages involved in this study. In stage 1, the first preliminary version of IPM3P that was developed by Rahmat et al. was content validated to produce the second preliminary version of IPM3P.[5] In stage 2, the second preliminary version of IPM3P was pre-tested, face validated and proofread to produce the initial version of IPM3P. In stage 3, the initial version of IPM3P was piloted. In stage 4, the initial version of IPM3P undergo psychometric evaluation and was further finalized to produce the final version of IPM3P. Figure 1 shows the workflow involved in this study.

Materials

The first preliminary version of IPM3P which consists of 59 items - 18 items for obligation domain, 20 items for practice domain and 21 items for difficulty domain, was used as the questionnaire for this study.[5] The items under obligation domain were mainly assessing the perception of Muslim with hearing impairment towards their obligation to understand Islamic teaching, and performing Islamic practice. The items

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under practice domain were designed to investigate the perception of Muslim with hearing impairment regarding their Islamic practice (i.e., how frequent they perform the Islamic practice). On the other hand, the items under difficulty domain were designed to assess the difficulty level faced by the subject in understanding and practice Islam. There were seven (7) sub-domains under each domain i.e., *'Aqidah', 'Ibadah', 'Muamalat', 'Da'wah', 'Akhlak', 'Tasawwuf, 'Sirah'*, with the exception to domain practice which contained all similar sub-domains as in the obligation and difficulty domain except *'Sirah'*(refer to Table I in Rahmat et al. for the definition of each sub-domain).[5] The inclusion of different sub-domain which represent different area of Islamic understanding and practice was to assess a wide area of Islamic understanding and practice in respect to the assigned domains. The preliminary version of IPM3P were made from a total of 36 positive and 23 negative statements. For the domain 'obligation' and 'difficulty', the response is rated as (1) *'sangat tidak setuju'* (totally disagree), (2) *'tidak setuju'* (disagree), (3) *'tidak pasti'* (not sure), (4) *'setuju'* (agree), to (5) *'sangat setuju'* (totally agree). For the domain 'practice', the response is rated as (1) 'sangat tidak kerap' (very rarely), (2) 'tidak kerap' (Rarely), (3) 'tidak pasti' (not sure), (4) 'kerap' (frequent), to (5) 'sangat kerap' (very frequent).

Stage One: Content validation

Qualitative Content validation was conducted to assess if the items that were generated for the preliminary version of IPM3P were representative of the content and the respective domain.

Participants

A total of six content experts from two different academic backgrounds were involved for this stage, two experts from Islamic studies and four (4) experts from speech and hearing sciences. All the content experts hold at least a master's degree in their respective field.

Procedure

Six experts were given the content validation form and they were requested to specify whether an item is relevant or not relevant, in addressing: i) the issue that need to be investigated (i.e., the perception of Muslims with hearing impairment in understanding their obligation as a Muslim, and how they perceive their practice as a Muslim), ii) whether the item suits the respective domain, and iii) clarity of the item. The content experts were also asked to give their comment and recommendation for further improvement of the items. The recommendations from the content experts were considered and were taken into account to produce the second preliminary version of IPM3P (60 items) which was later pre-tested on Muslim adults with hearing impairment.

Data analysis

The percentage of agreement by the experts on the relevancy of each of the item was calculated using the following formula:

$$\textit{Percentage of agreement} = \frac{\textit{No of expert agreed that item is relevant}}{\textit{Total number of content expert}} \times 100$$

The number of changes, item deletion and item that remained followed the suggestion that was given by the content expert was recorded.

Stage Two: Pre-testing, face validity & Proofreading

Before the initial version of the IPM3P was piloted to the target population (Muslim adults with hearing impairment), the 60 items of the second preliminary version of IPM3P that had been content validated was pre-tested and face validated to a group of Muslim adults. These stages were conducted to gauge the participant's understanding of the IPM3P's items and to probe the problems that the respondents encountered when responding to the items.[7]

Participants

The two groups of participants who were involved in this stage were a laymen group and an expert group. A total of twelve individuals consisting of two experts from an audiology background and ten laymen without specialized knowledge in hearing related sciences (audiology or speech language pathology) and Islamic studies were recruited for this stage. The laymen came from various occupation and education background, including cleaner, housewife, university students and professionals (engineers, administrative officers & teacher).

Procedure

A Pre-testing and face validity form was distributed to all the participants. Each of the participants were asked to rate the agreement on each item (yes/no) based on readability of the items, suitability of an item, layout and style, and clarification of words. The subjects were also asked if they understand each of the items, and if they had any comments and suggestions to improve the items. The comments and suggestions were taken into account in modifying the item before the items were sent for proofreading and distributed for pilot study. Before the pilot study was conducted, the modified second preliminary draft of IPM3P was proofread by a professional proofreader who has been working in the proofreading services for more than five years. There were some minor grammatical errors that had been identified based on the proofreading process and changes were made accordingly to produce the initial version of the IPM3P.

Data analysis

Pre-testing analysis was conducted based on three criteria: i) readability of an item, ii) clarity of words and, iii) layout and style. The face validity analysis was conducted based on the criteria of 'suitability of an item' to represent the IPM3P questionnaire and objectives. The percentage of experts' agreement on each criterion of pre-testing and face validity assessment was calculated using the following formula:

$$\textit{Percentage of agreement for each criteria} = \frac{\textit{No of subject agreed that item is relevant for the criteria}}{\textit{Total number of subject)}} \times 100$$

Number of changes, item deletion and item remained, following suggestion by the subject was recorded. Items that achieve < 80% of agreement in any of the assessed criteria was considered for deletion during stage five.[8]

Table I: Percentage of Experts Agreement on Item Relevancy for Content and face validity and pre-testing

Type of assessment	Criteria of assessment	Item Number	Percentage of subject who agreed with the item (%)
Content validity	Content	1-18, 20-24, 26-32, 34-49, 51-57, 59	100%
		19,33,50,58	83.3%
		25	66.7%
Face validity	Suitability of an item	1-12, 14-20, 22-24, 26-28, 30-38, 40-42, 46-52, 54-57, 59-60	100%
		13,21,29,39,43,44,45,53,58	91.7%
		25	83.3 %
Pre-testing	Readability of item	1-60	100%
	Clarity of words	4-6, 9-11, 13, 15, 16, 19, 22-39, 41, 42, 46-52, 54, 55, 57, 59	100%
		1-3, 8, 14, 18, 20-21, 40, 43-45, 53, 56, 58, 60	91.7 %
		7, 12, 17	83.3 %
	Layout & Style	1-6, 8-11, 13,14, 16,19,20,22-24, 26-31,33-38,40-42, 46-53, 55-57	100%
		7,12,15, 17, 18, 21, 25, 32, 39, 43-45, 54, 58, 60	91.7 %

Table II: Result of the first and second internal reliability analysis of stage 5

Domain	Cronbach alpha (α), n=77	
	First reliability analysis	Second reliability analysis
Overall internal reliability	0.95	0.94
Obligation domain	0.84	0.90
Practice domain	0.87	0.90
Difficulty domain	0.92	0.93

Table III: Criteria for removal of item or modification of domain and list of items involved

No	Criteria for removal of item or modification of domain.	Item number_original domain
1.	Remove items that does not achieve 0.3 component loading.	29_P
2.	Remove item that has negative component loading.	13_O, 34_P
3.	Remove item that does not seem to represent the original domain from subjective evaluation, or/ and has poor component loading (e.g 0.4).	4_O, 9_O, 12_O, 18_O
4.	Remove item that does not really indicate the original domain based on PCA, and subjective evaluation shows that it does not suit the other suggested domain.	3_O, 25_P, 32_P, 33_P, 40 _D, 41_D, 42_D, 46_D, 49_D, 60_D
5.	Remove item that has ambiguous domain based on PCA (e.g. component loading load into two or three components on less or similar strength).	12_O, 45_D, 47_D, 30_P
6.	Remove item that carries slightly similar meaning/ aspect to other item/s	53_D, 20_P
7.	Remove items based on the expert's comment from content validation	19_P, 26_P
8.	Rearrange item into another domain if subjective evaluation and component loading indicate that the item suits better in the suggested new domain, i.e., items load higher into the new suggested domain as compared to the original domain.	39_P, 57_D

a. The abbreviation of the original domain of the item. O: Obligation, P: Practice, D: Difficulty

Stage Three: Pilot study

To initially test the reliability of the initial version of the IPM3P in order to ensure that it is ready to be used in a larger scale, a pilot study was conducted on a small group of Muslim adults with hearing impairment.[9] The process of the pilot study is discussed as follows.

Participants

A total of forty (40) Malay Muslim adults (>18 years old) with hearing impairment (pure tone average of air conduction above 25 dB HL at 0.5kHz, 1kHz, 2kHz and 4 kHz) were recruited from Kuantan, Pahang, Malaysia. The subjects consist of twenty three (23) males and seventeen (17) females with the age ranging from 19-75 years old. The degree of hearing loss among the subjects ranged from mild to profound hearing loss.

Procedure

The initial version of IPM3P questionnaire was distributed to the subjects. The subject was asked to rate their response for every item based on the Likert scale described in Materials. An informed consent was obtained from the subjects prior to their participation.

Data analysis

Reverse scoring was applied for all negative statements. Internal consistency of the initial version of IPM3P was calculated using the Cronbach's alpha value through the SPSS statistical 20. An Alpha value of > 0.7 was considered as acceptable.[10]

Stage Four: Further psychometric evaluation and finalisation of IPM3P

Further psychometric testing was conducted on a larger population to further evaluate the psychometric properties of

Table IV: Result of rotated component matrix from second principal component analysis (PCA)

Original Item number_original domain _revised domain[a]	Revised item number	Sub-domain	Component 1 (Obligation domain)	Component 2 (Practice domain)	Component 3 (Difficulty domain)
1_O	1	Ibadah	0.68		
2_O	2	Ibadah	0.58		
5_O	3	Akidah	0.68		
6_O	4	Akidah	0.69	0.37	
7_O	5	Muamalat	0.61		0.32
8_O	6	Akidah	0.68	0.41	
10_O	7	Tasawwuf	0.64	0.37	
11_O	8	Tasawwuf	0.62	0.43	
14_O	9	Akhlak	0.55	0.41	
15_O	10	Akhlak	0.51	0.32	
16_O	11	Da'wah	0.75		
17_O	12	Da'wah	0.66		
21_P	13	Ibadah	0.31	0.67	
22_P	14	Ibadah		0.67	
23_P	15	Ibadah		0.65	
24_P	16	Akidah		0.80	
27_P	17	Muamalat	0.34	0.68	
28_P	18	Muamalat	0.35	0.68	
31_P	19	Muamalat		0.68	
35_P	20	Tasawwuf		0.67	
36_P	21	Akhlak		0.70	
37_P	22	Akhlak		0.74	
38_P	23	Da'wah		0.76	
57_D_P	24	Da'wah		0.52	
39_P_D	25	Da'wah			0.74
43_D	26	Ibadah			0.65
44_D	27	Ibadah			0.80
48_D	28	Akidah	0.46		0.61
50_D	29	Muamalat			0.76
51_D	30	Muamalat	0.54		0.69
52_D	31	Muamalat	0.60		0.61
54_D	32	Tasawwuf	0.45		0.61
55_D	33	Tasawwuf			0.66
56_D	34	Akhalak	0.61		0.47
58_D	35	Da'wah			0.76
59_D	36	Da'wah			0.81

a. The abbreviation of the original and revised domain of the item. O: Obligation, P: Practice, D: Difficulty.

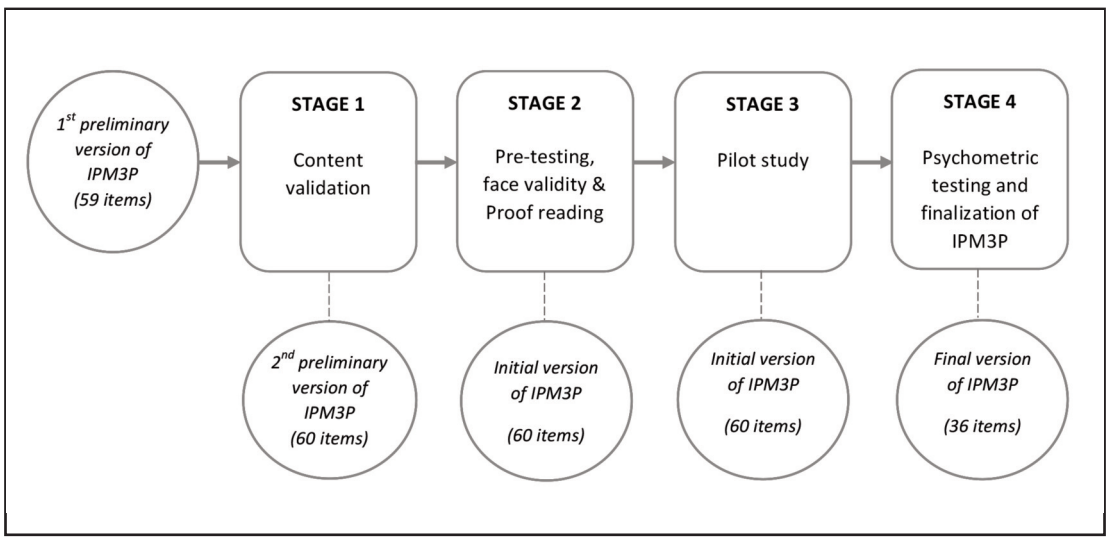

Fig. 1: Workflow of IPM3P development.

the items. The input from the psychometric analysis, together with the input from stage two to four was taken into account to produce the final version of the IPM3P.

Participants

A total of seventy-seven (77) Muslim adults with hearing impairment (similar criteria as in the pilot study) were recruited from Kuantan, Pahang, Malaysia. Subjects consist of thirty-eight (38) males and thirty-nine (39) females with the age ranging from 18-79 years old. The degree of hearing loss among the subjects ranged from mild to profound hearing loss.

Procedure

Informed consent was obtained from the subjects prior to their participation. The initial version of IPM3P questionnaire was distributed to the subjects. The subject was asked to rate their response for every item based on the Likert scale described in Materials section.

Data analysis

All the responses and data were analysed using SPSS statistical 20 for psychometric properties evaluations. To measure the psychometric properties of this new scale, three statistical analyses were performed:

i) Internal reliability analysis using Coefficient alpha: similar criteria as described in pilot study was used.
ii) Factorial analysis using principal component analysis (PCA): The PCA was conducted to assess the construct validity of the questionnaire. Two assumption of PCA were checked before proceeding the analysis- i) Kaiser-Meyer-Olkin (KMO) value should be > 0.5, and ii) the p-value of Bartlett's test of sphericity should be <0.05.[11]
iii) Inter-item correlation analysis (for convergent and divergent validity): Pearson correlation was used to analyse the data and correlation coefficient (r) value was noted to determine the correlation strength.

A few steps of psychometric evaluation and modification of questionnaire were involved in this stage:

i) First psychometric evaluation: The internal reliability analysis and PCA were conducted on the initial version consisting of 60 items (similar version as in the pilot study).
ii) Removal of item and modification of domain based on the first psychometric result with additional input from stage two to four: the identification of domain was made based on the subjective evaluation and value of component loading. A few criteria (as listed in Table III) were set in order to decide whether an item should be removed or if the original domain needed to be changed. A total of 36 items were finally selected during this step to proceed with the second psychometric evaluation.
iii) Second psychometric evaluation: second internal reliability analysis, PCA, and inter-item correlation (for convergent and divergent validity) were performed on the new set of 36 items.
iv) Finalisation of IPM3P: Based on the result from the second psychometric evaluation, the new set of 36 items of IPM3P was finalised.

RESULTS

Stage One: Content validity

Six experts were asked to specify the relevancies of each item and the responses were tabulated in Table I. Overall, >80 % of the expert agreed that majority of the items were relevant, with the exception to item number 25 which only obtained 66.7% of experts agreement. Item number 25 will be considered for removal following other validation and reliability analysis in stage five. Based on the analysis of the original 59 items, 25 items remained, 33 items had been modified, and one item had been split into two items. These yielded a new total of 60 items (18 items for obligation domain, 21 items for practice domain, and 21 items for difficulty domain) for the second preliminary draft of IPM3P. The suggestions by experts had included: changing of words to make the item more clear and specific, addition of phrase to suit the meaning, deletion of words to make the item shorter and more precise, and separation of item as the original item consisted of two different aspects; these were taken into account in modifying the items.

Stage Two: Pre-testing, face validity & Proofreading

The percentage of experts' agreement on each criterion of pre-testing and face validity assessment was calculated and presented in Table I. From the analysis of 60 items, 48 items remained and 12 items had been modified with no changes to the distributions of domains. The modification was based on the comment given by the subjects including the addition of some phrases to make the items more structured, and changing of words to make the items more understandable and simple. None of the items achieved <80% of agreement and were considered to be removed based on face validity and pre-testing result. Following the proofreading process, 55 items had been modified and 5 items remained. The modification was based on some minor grammatical errors that had been identified by the proofreader and the changes were made prior to pilot study.

Stage Three: Pilot study

The internal reliability analysis of the initial version of IPM3P yields an excellent overall Cronbach alpha value (α: 0.91), with questionable to a good level of Cronbach alpha for the respective domains (obligation, α: 0.62; Practice, α: 0.82; difficulty, α: 0.89). Although domain obligation has a questionable level of Cronbach alpha value, the overall internal consistency of the initial version of IPM3P was α: 0.91. This shows that the initial version of IPM3P has good potential and is ready to be tested to a larger population for further psychometric testing.

Stage Four: Further psychometric evaluation and finalisation of IPM3P

a) First psychometric evaluation

The first psychometric evaluation was conducted on the initial version consisting of 60 items (similar version as in the pilot study). The internal reliability analysis and PCA were performed for the first psychometric evaluation.

i) Internal reliability analysis

The first reliability analysis on the initial 60 items yields an excellent overall Cronbach alpha value, with a good to excellent alpha value for each respective domain. The result

of the first and second reliability analysis was tabulated in Table II for easy comparison.

ii) First principal component analysis (PCA)
The first principal component analysis (PCA) was conducted to study the construct of the initial version of IPM3P. The analysis revealed a Kaiser-Meyer-Olkin (KMO) value of 0.64 suggesting that the degree of common variance among the variables was 'mediocre' bordering on 'middling', indicating an adequate sample size for conducting the PCA. The Bartlett's test of sphericity showed $p<0.001$, suggesting that the domains of IPM3P were independent of each other.

The PCA with Varimax rotation was conducted using the extraction method based on a fixed number of domain (3) that was previously set for IPM3P (obligation, practice and difficulty). Items with coefficient value <0.3 was suppressed. The cumulative percentage of variance explained by the three components was 49.02%. A majority of the items under the practice domain load to component one, while the majority of items under the obligation domain load into component two, and a majority of items under the difficulty domain load into component three. From the first PCA, it can be seen that all of the items with the exception of two (item 29& 34) have a component loading of > 0.3 in at least one of the components.

b) Removal of item and modification of domain based on the first psychometric result with additional input from stage two to four.
In this step, discussion with the experts from the research team was conducted to evaluate the items and finally a consensus was achieved either to retain, or to remove the item, or to change the domain of the item. A few criteria were set in order to decide whether an item should be removed or if the original domain needed to be changed. The criteria are listed in Table III, together with the number of items that was involved. A total of 24 items 24 items were deleted (Obligation-6 items, Practice – 9 items, Difficulty – 9 items), and 2 items were rearranged into new domain. A total of 36 items (12 items for each- obligation, practice and difficulty, domain) were finally selected during this step to proceed with the second psychometric evaluation.

c) Second psychometric evaluation
Second psychometric evaluation was conducted to the new set of IPM3P which consisted of 36 items (12 items for each- obligation, practice and difficulty, domain). The psychometric evaluation includes internal reliability analysis, PCA, and inter-item correlation.

i) Second internal reliability analysis
The second reliability analysis on the final 36 items yields an excellent overall Cronbach alpha value, with an excellent alpha value for each respective domain. From Table II, it can be seen that the result for the second reliability analysis on the new set of 36 items of IPM3P has improved as compared to the first reliability analysis on the 60 items, particularly on the alpha value for each domain. The new set of 36 items of IPM3P shows excellent internal consistency and could be considered as the final version of the IPM3P depending on the result from the second PCA below.

ii) Second principal component analysis
A second PCA was conducted to see if the results would improve with the final set of 36 items of IPM3P. The analysis revealed that the Kaiser-Meyer-Olkin (KMO) value improved to 0.78 compared to that of 0.64 from the first PCA analysis, suggesting that the degree of common variance among the variables was 'middling', indicating an adequate sample size for conducting the PCA. The Bartlett's test of sphericity showed $p<0.001$, suggesting that the domains of IPM3P were independent of each other.

The PCA with Varimax rotation was conducted again using similar method as in the first PCA analysis. The cumulative % of variance explained by the three components was improved to 56.20% compared to 49.02% from the first analysis. The results of the PCA based on the three components or domain were presented in Table IV. A much clearer separation of domains can be seen, with all the revised items under the obligation, practice and difficulty domain loaded to component one, component two, and component three, respectively. Similar to the first PCA analysis, identification of the domain that suited the items was made based on subjective evaluation, supported by the value of component loading. In the case of an item that loaded into two components, the component with the higher component loading was chosen to represent the domain of the item- provided that the subjective evaluation showed that the item suited the suggested domain (the value of the dominant component loading is bolded in Table IV). This rule was particularly applicable for all items except for item number 56_D where the component loading loaded higher into component one (obligation), as compared to component three (difficulty). However, the item was retained in the difficulty domain since the subjective evaluation showed that the item was better suited in the difficulty domain. None of the items have either a negative or <0.3 component loading value.

iii) Inter-item correlation for convergent and divergent validity
Inter-item correlation was performed to measure the convergent and divergent validity of the questionnaire. For convergent validity, inter-item correlation was performed between item with the same domain, and convergent validity was met when the inter-item correlation was found to be significant ($p<0.05$) and $r > 0.03$.[10] A majority (93.43%) of the inter-item pair for the overall IPM3P met the convergent validity ($p<0.05$, $r> 0.03$), with the percentage of inter-item pair that met the convergent validity for all the domains ranging between 86.36%- 96.97%. The result for the convergent validity analysis was excellent, and thus the convergent validity for IPM3P was established.

For divergent validity, inter-item correlation was performed between items from different domain (obligation vs. practice, obligation vs. difficulty, and practice vs. difficulty). Divergent validity was met when the inter-item correlation was found to be insignificant ($p<0.05$), or when correlation coefficient is not strong ($r < 0.8$), and/ or when a difference was observed when comparing the correlation coefficient (r) and p-value to that of convergent validity result.[10,12] 100% of the inter-item pairs had correlation coefficient (r) < 0.8. In addition, 44% of the inter-item correlation was not significant, as compared to

only 2.5 % of non-significant inter-item correlation for convergent validity. The result for divergent validity analysis was excellent and thus the divergent validity for IPM3P was established.

d) Finalisation of the IPM3P

Looking at the result from the second psychometric evaluation, the new set of 36 items (12 items for each obligation, practice, and difficulty domain) of IPM3P shows good content validity, excellent internal reliability as well as excellent construct validity from the PCA, and inter-item correlation for convergent and divergent validity. Thus, the research team came to a consensus to use the new set of 36 items of IPM3P as the final version of IPM3P. The revised item number was assigned for each item as listed in Table IV.

DISCUSSION

The aims of this study were achieved, i.e., to finalise the development of IPM3P, and to measure the psychometric properties of the final version of IPM3P. During the initial stage of IPM3P item development, the initial version of IPM3P consisted of quite a large number of items representing each domain and sub-domain (59 items). The development of a large number of items during initial stage was recommended as to prepare for any item deletion following the later stage of psychometric analysis. 13 During the selection of items in stage four, the item with a good component loading was selected and the selection was performed with the aim to have at least one item representing each sub-domain. The research committee had managed to include at least one or more items representing all sub-domains that were identified during the sub-domain generation, i.e., *'Akidah', 'Ibadah', 'Muamalat', 'Da'wah', 'Akhlak',* and *'Tasawwuf'*, with the exception of the sub-domain *'Sirah'*. The final version of IPM3P (a set of 36 items) does not include any item under the domain *'Sirah'* as all of the items (two items) under this sub-domain have poor construct validity (based on the PCA); however, the exclusion of this sub-domain from the final version of IPM3P was not an issue as the aim to have items representing the different sub-domains was to assess a wide area of Islamic understanding and practice, which could be achieved through the items from the other remaining sub-domains.

Hearing is an important sense that is involved in gaining a good Islamic understanding and is important in performing Islamic obligation.[14] According to the principle of Islamic law *(Maqasid As-Shariah)*, providing the means to understand and practice religion becomes a necessity as a way to protect faith. Therefore, an establishment of welfare and support system (including providing treatment and assistance) for Muslims with hearing impairment to understand and practice Islam (despite their disability) becomes a collective Islamic responsibility that is shared by the government, the community (including the hearing care professionals), the family, and the individuals themselves.[14] Such support could be better provided when the perception of Muslims with hearing impairment has been enlightened and their practice is well understood, which could possibly be achieved through the development of IPM3P.

The psychometric evaluations have revealed that the IPM3P has the potential to be used as a tool to investigate the perception of Muslim adults with hearing impairment towards Islamic understanding and practice. Further confirmatory factor analysis (CFA) among larger samples (n>100) could be conducted to further confirm the three domain of IPM3P. Using the validated version of IPM3P, further investigation to probe the perception of adult Muslim with hearing impairment towards Islamic understanding and practice is needed. In addition, further study is needed to investigate the relationship between the factors that might be affecting the perception of adult Muslim with hearing impairment towards Islamic understanding and practice (as proposed in the theoretical framework of IPM3P development); i.e. attitude (obligation), perceived behavioral control (difficulty), and behavior (practice).[5] In addition, the effect of hearing amplification in alleviating the difficulty faced by Muslim adult with hearing impairment in performing Islamic obligation should be further investigated.

CONCLUSION

The development of IPM3P serves as the preliminary work to further understand the religious need and religious difficulty among Muslim adults with hearing impairment. Findings from the present study suggests that the final version of IPM3P has excellent psychometric properties that have been manifested by: i) good content validity, ii) excellently pretested, iii) good face validity, iv) good construct validity that is shown by factorial analysis and convergent validity, and v) good discriminant validity that is shown by divergent validity. The psychometric evaluations have revealed that the IPM3P has the potential to be used as a tool to investigate the perception of Muslim adults with hearing impairment towards Islamic understanding and practice. Such understanding of the phenomenon may give an input on how this population could be assisted in terms of their religious duties.

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CONFLICT OF INTEREST

None to declare.

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REFERENCES

1. Awang@Husain MH, Zakaria HB, Abd Rahim RA. Pendidikan Islam Golongan Masalah Pendengaran : Tinjauan Awal Isu dan Cabaran daripada Perspektif Guru. J Teknol Social Sci 2012; 58: 135-9.

2. Abdullah AY, Ali MM. Mastery of Pillars of Prayer Among the Hearing-Impaired Students. J Penelit dan Pengemb Pendidik Luar 2018; 5(1): 1–6.
3. Saari NH, Cila U, Mat Teh KS. Factors Affecting the Learning of the Holy Quran among Severely and Profoundly Hearing-Impaired Children with a Cochlear Implant. IOSR J Humanit Soc Sci 2012; 2(1): 85–92.
4. Ishak H, Tamuri AH, Majid RA, Bari S. Amalan Pengajaran Guru dalam Pengajaran dan Pembelajaran Pendidikan Islam di Sekolah Kebangsaan Pendidikan Khas (Masalah Pendengaran). J Islam Arab Educ 2012; 4(2): 11–24.
5. Rahmat S, A Rahman S, Tukiran N, Musa R, Othman N, Dzulkarnain A. Development of hearing impairment inventory for religious duties of muslim adult. Med J Malaysia 2021; 76(2): 205-11.
6. Yati IES, Rahmat S, Tukiran NH, Musa R. A pilot study for preliminary version of 'inventori persepsi bagi muslim yang memiliki masalah pendengaran (IPM3P).' Int J Allied Heal Sci 2019; 3(1): 564.
7. Ruel E, Wagner III WE, Gillespie BJ. The Practice of Survey Research: Theory and Applications. The Qualitative Report. Los Angeles: SAGE Publications; 2016.
8. Perneger T V, Courvoisier DS, Hudelson M P, Gayet-Ageron A. Sample size for pre-tests of questionnaires. Qual Life Res 2014; 24(1): 147-51.
9. Gudmundsson E. Guidelines for translating and adapting psychological instruments. Nord Psychol 2009; 61(2): 29-45.
10. Devon HA, Block ME, Moyle-Wright P, Ernst DM, Hayden SJ, Lazzara DJ, et al. A psychometric toolbox for testing validity and reliability. J Nurs Scholarsh 2007; 39(2): 155-64.
11. Shrestha N. Factor Analysis as a Tool for Survey Analysis. Am J Appl Math Stat 2021; 9(1): 4-11.
12. Chan YH. Biostatistics 304. Cluster analysis. Singapore Med J 2005; 46(4): 153-60.
13. Artino AR, La Rochelle JS, Dezee KJ, Gehlbach H. Developing questionnaires for educational research: AMEE Guide No. 87. Med Teach 2014; 36(6): 463-74.
14. Rahmat S, Othman N, Sulaiman N, Jusoh M, Mohammad H, Dzulkarnain A, et al. Hearing Impairment from the Islamic Perspective: A Review. IIUM Med J Malaysia 2018; 17(2): 35-47.

ORIGINAL ARTICLE

Translation, validation and cross-cultural adaptation of the Malay emotion regulation checklist (ERC-M): A preliminary study

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ABSTRACT

Introduction: Emotion Regulation Checklist (ERC) has been used globally and translated to several languages, including Brazilian Portuguese, Italian and Persian. The aim of this study is to translate and validate ERC to the Malay language and to measure the reliability and validity of the translated version of this scale among Malaysian parents.

Methods: This study involved forward and back translation method. The translated questionnaire was then pretested and piloted among 10 parents and 50 participants, respectively. The procedure was repeated using the same questionnaire to evaluate the test-retest reliability.

Results: The ERC-Malay (ERC-M) has excellent qualitative and quantitative measurements in both item-level content validation index (I-CVI) and scale-level content validation index (S-CVI). In addition, the ERC-M demonstrated good internal consistency from Cronbach's alpha and test-retest reliability based on the Intraclass Correlation Coefficient (ICC) in all domains.

Conclusion: ERC-M can potentially be used as a tool to evaluate emotion for the population with emotional dysregulation issue, such as autism spectrum disorder.

KEYWORDS:
Autism, Emotional Regulation, Malay, Translation, Validation

INTRODUCTION

Emotion is a fundamental aspect in generating information-processing in the brain of humans. Emotion is generated through one's environment, experience and stimulation, which is later processed and receptively seen through expressions. The regulation of emotions is influenced by three response mechanisms that include neurophysiological-biochemical, motor expressive and cognitive experience.[1] These three mechanisms are interrelated; for example, any changes in the neurophysiological system may lead to changes in both motor and cognitive mechanisms. When there is any disruption of these mechanisms, it could lead to emotional dysregulation. Emotion dysregulation can occur in typically developing children, and more frequently in children with certain disorders, such as those with Autism Spectrum Disorder (ASD). According to Shields and Cicchetti,[2] school-aged children are prone to have difficulty in controlling their emotions, especially in unfavorable situations. Therefore, it is crucial to identify any emotion dysregulation in school children for immediate intervention. In response to this issue, several tests have been developed to evaluate emotion dysregulation concurrent with other behavioral issues among school children using general physiological tests, observational methods, interviews and questionnaires.[3-5] However, these assessments only cover the gross information on behavioral, psychosocial, intellectual, and academic functioning but not specifically evaluating the emotional aspect.[5] Dante and Shields developed a parental/teacher reported questionnaire that specifically assesses the emotional aspects of children, known as the Emotion Regulation Checklist (ERC). ERC allows clinician or researchers to evaluate the personality of an individual and to understand their emotion regulation abilities. The checklist is rated by parents or teachers, thus, minimizing clinician bias and has excellent internal consistency, reliability, and validity.[2]

Whilst several questionnaires are available to evaluate emotional regulation,[6,7] Emotion Regulation Checklist (ERC) has been proven to truly reflect the overall children emotional behaviour by giving information on emotional characteristics that are mostly possessed or least possessed in them.[2] In addition, ERC has excellent criterion validity where it can distinguish emotion regulation between maltreated (abused) children with non-maltreated children.[8] ERC has been used worldwide and has been translated into several languages, including Brazilian Portuguese, Italian and Persian.[9-11] Till now, no publication has translated and validated neither the ERC questionnaire nor other emotion regulation questionnaire into the Malay language for the use of Malay-speaking parents and teachers especially for children. Therefore, the aim of this study was to translate the ERC to the Malay language and validate and measure the reliability of the translated version among Malaysian parents.

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MATERIALS AND METHODS

Study Design

The authors used forward and back translation processes followed by the validation study design. Figure 1 shows the summary of the translation and validation process of ERC. This study was approved by the International Islamic University Malaysia (IIUM) Research Ethics Committee (IREC). Permission was obtained from the original author of ERC (Dante Cicchetti) before the whole process initated. In addition, all parents consented to participate after the explanation of the research was given.

Materials

ERC developed by Shields and Cicchetti and the questionnaire contains 24 items of two domains (negative liability domain and emotion liability domain). This questionnaire accurately measures the positive and negative liability of an individual as it comprises both positive and negative weighted items.[12] This questionnaire targeted only school-aged children of up to 16 years old that included important items in assessing emotion regulation for this population.[2,13]

Forward and Back Translation Process

The translation process started with forward translation. The original English Version of ERC was translated into the Malay language following the guidelines by Guillemin, Bombardier, and Beaton.[14] The authors used the forward and back translation method where the forward translation was performed by two independent Malay native speakers with good command in English and health sciences background related to the context of the questionnaire (Psychology and Speech-language Pathology).[15] The forward translation proceeded from the original English version of ERC to the target mother tongue language, the Malay language. The translators were not aware of the original version of ERC.[14] Next, the translations from both translators were then harmonized and re-conciliated to produce a harmonized version (ERCBMH1).

For the back translation process, another two expert language translators translated back the harmonized version, ERCBMH1 into the original language independently.[15] Using the same procedure in the forward translation, both back translators were also not aware of the existence of the original version of the questionnaire to prevent any information bias.[14] The back translations were later harmonized into ERCH after discussion between both translators.

Expert Committee Review

The third stage was the committee review and cross-cultural adaptation of the ERC-M. The roles of the experts in the committee were to consolidate all the version of questionnaires and develop the pre-final version to be used in the pre-testing stage.[15] For this stage, three committee members reviewed and compared the ERCH version and the original ERC version. The three committee members were working as academicians with a PhD degree in the field of Health Sciences (audiology, speech-language pathology, and psychology). The expert committee were not involved in the forward and back translational process, do not know each other before and they had good command in both Malay and English languages. All the items were reviewed in a group discussion among the panels that consisted of different ethnics who understood the Malaysian context to avoid any potential cultural bias. For the group discussion, they were asked to check : (a) the comprehension, semantics and content of the ERCBMH1 so that the instrument has equivalent meaning to the original ERC version despite alterations in the sentence construction to make adaptation easier[14] and thus, producing ERCBMH2; and (b) to identify the translated items were acceptable to the target culture or if they require additional modification to enhance their relevance to the target culture. No items required any modification for cultural adaptation since all translated items were relevant to Malaysian context as agreed by the expert committee.

Face Validation of ERCBMH2

The newly translated questionnaire was pre-tested among ten parents with children aged 6 to 17 years, and the children met the following criteria: i) bilateral normal hearing and ii) normal physical development. To check the face validity at this stage, three aspects was considered as follows: i) clear and concise sentences, ii) easy to understand and iii) free from typographical errors. Once the pre-testing stage was completed, the face validity score was then calculated. Next, the ERCBMH2 was sent to two independent proofreaders for editorial check to correct any punctuation and grammatical errors in the questionnaires, thus producing the final version known as ERC-Malay (ERC-M) .

Pilot Study and Test-Retest Reliability

This study was then administered among 50 parents to check for internal consistency and was repeated twice using the same questionnaire to check the test-retest reliability between two intervals (Test 1 and Test 2) of 7 to 14 days after the first test (Test 1).

Data Analysis

The content validation index (CVI) of the questionnaire was computed specifically for item-level CVI (I-CVI) and scale-level CVI (S-CVI). For I-CVI, the items were scored according to the relevance scale by three expert committees. If the relevance scale was given as 3 or 4, the rating score will be taken as 1, whereas, if the relevance scale was given as 1 or 2, the rating score will be taken as 0.[16] To obtain S-CVI, all I-CVI scores were averaged and divided by three (number of our expert committees). A good and excellent I-CVI had to be more than 0.78 and more than 0.9 for S-CVI.[17] The face validity index was calculated by taking the item agreement across ten participants for each aspect; i) sentence clearer and concise, ii) easy to understand and iii) free from typographical errors. A value of 80% and above was considered as a satisfactory level of face validity.[18] The Cronbach's alpha and Intraclass Correlation Coefficient (ICC) values were analyzed using IBM SPSS Statistic Version 26. The recommended value for Cronbach's alpha and ICC for this study is summarized in Table I.[19,20]

Table I: The cut-off score of the acceptable Cronbach's alpha[19] and ICC value.[20]

Cronbach's alpha		ICC	
More than 0.9	Excellent	More than 0.9	Excellent
More than 0.8	Good	0.75-0.9	Good
More than 0.7	Acceptable	0.5-0.75	Moderate
More than 0.6	Questionable	Less than 0.5	Poor
More than 0.5	Unacceptable		
Less than 0.5	Poor		

Table II: The summary of validity and reliability analysis findings of the ERC-M (ERC-M, Emotion Regulation Checklist Malay version; α, Cronbach's Alpha; I-CVI, item level content validity index; S-CVI, scale level content validity index). Note that item no 12 is not scored in either domain as it was initially not added to the validation process of ERC original version

Domains	Item No.	Content Validity Analysis (I-CVI)	Reliability Analysis (Cronbach's Alpha)	
Negative Liability	2.	1.00	Domain Level	Scale level
	4.	1.00	0.75	0.78
	5.	1.00		
	6.	1.00		
	8.	1.00		
	9.	1.00		
	10.	1.00		
	11.	1.00		
	13.	1.00		
	14.	1.00		
	17.	1.00		
	19.	1.00		
	20.	1.00		
	22.	1.00		
	24.	1.00		
Emotion Regulation	1.	1.00	0.69	
	3.	1.00		
	7.	1.00		
	15.	1.00		
	16.	1.00		
	18.	1.00		
	21.	1.00		
	23.	1.00		
Average I-CVI or S-CVI	1.00			

Table III: Intraclass Correlation Coefficient (ICC) between two domains (negativity liability domain and emotion regulation domain) and overall score

Items	ICC
Negative Liability	0.762
Emotion Regulation	0.772
Overall	0.814

RESULTS

ERC-M had a satisfactory level of face validity with a value of 98% to 99% for three aspects (sentence clearer and concise, easy to understand and free from typographical errors). The ERC-M had excellent qualitative and quantitative measurements in both I-CVI and S-CVI analyses, as shown in Table II. In addition, the ERC-M demonstrated a good internal consistency for the overall scale (Cronbach's alpha, α = 0.78). The Cronbach's alpha for the negative liability domain was 0.75 and the emotion regulation domain was 0.69. A good test-retest reliability was also obtained between Test 1 and Test 2, where the ICC value for the negative liability domain = 0.76, emotion regulation = 0.77 and an overall ICC = 0.81, as shown in Table III. All these findings concluded that the validity, reliability, and test-retest reliability of ERC-M was established.

DISCUSSION

This study aimed to translate and validate the Malay version of ERC. The findings suggest that ERC-M has a good face and content validity, internal consistency and test-retest reliability, which indicates that this translated version of the checklist is appropriate and has the potential to be used among school-aged children in Malaysia. These findings were consistent with previous cross-cultural adaptation and

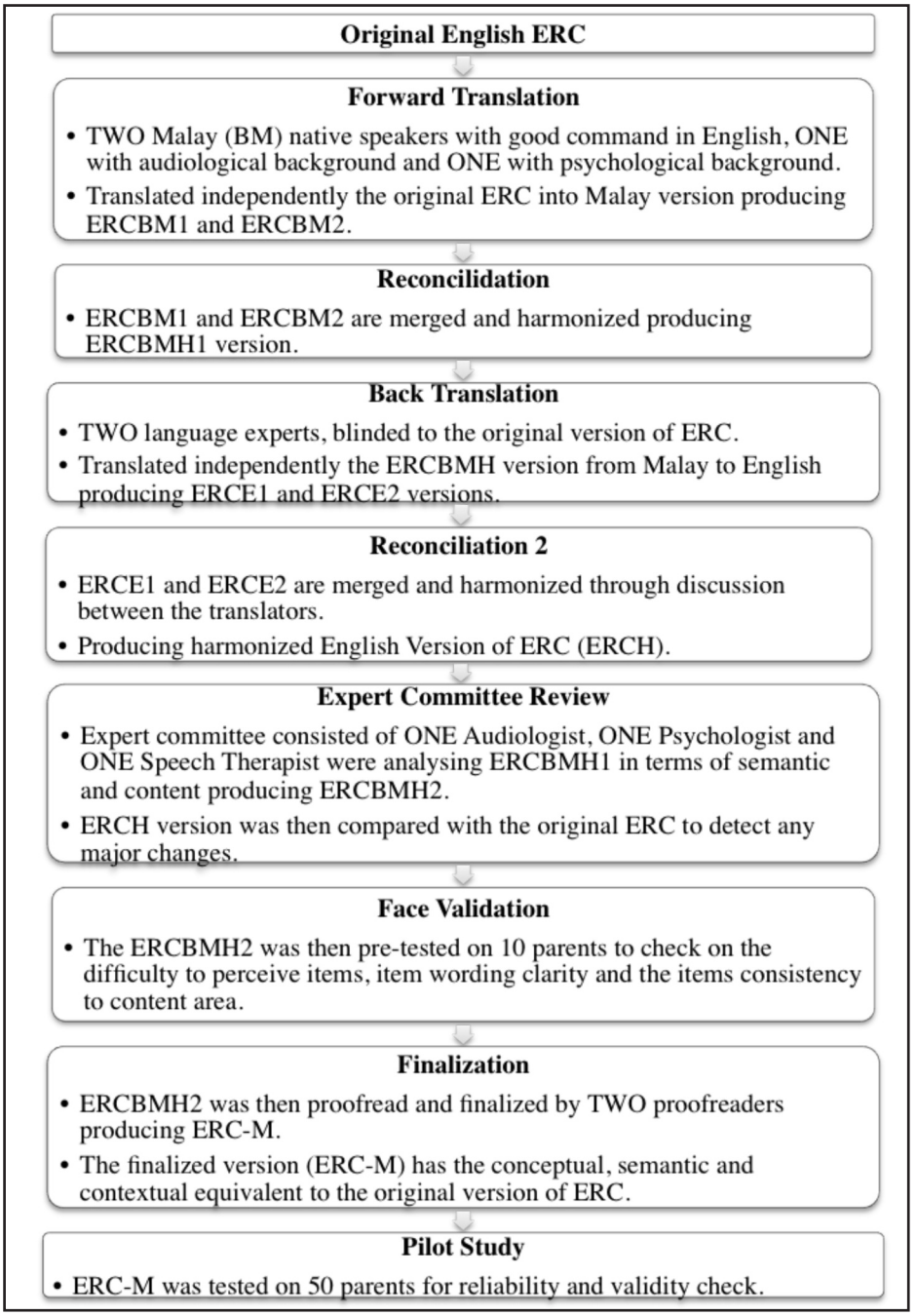

Fig. 1: Overview of the whole process of translation, cross cultural adaptation, and validation of ERC-M.

validation of ERC in Brazilian Portuguese, Italian and Persian language.[9-11] The ERC has been designed as an early detection tool to monitor the emotion regulation of school-aged children based on the perception reported by teachers and parents. The ERC results may suggest further diagnosis or referral to the related medical or healthcare professionals. From this study, it was observed that it only required about 15 minutes to complete the parental report questionnaire without the need for further assistance from the researcher. This suggested that the questions are understandable and easy to administer.

The findings of this study indicates that the ERC questionnaire represents a simple and quick instrument to detect which part of liability possessed more by a child. In other words, this instrument can be easily implemented by professionals, including general practitioners, psychiatrists, psychologists, pediatricians, speech therapists, audiologists, and teachers to measure the emotional regulation in children with emotional issues, such as among Autism Spectrum disorder (ASD) children. This study is limited to only 50 respondents and in future, further psychometric validation and criterion validity studies should be conducted in a larger population to ensure and reaffirm the validity of this checklist.

CONCLUSION

In this study the Malay version of ERC was successfully translated and validated. The ERC-M shows good to excellent reliability to be used as an early detection tool for emotional regulation in children and for the known population to have poor emotional regulation, such as ASD children. This ERC scale, therefore, can be used for screening or as a diagnostic tool in identifying the emotional status of children for further intervention strategies in regulating their emotions. In future, this translated Malay version of ERC can also be used not only in Malaysia, but also in neighbouring countries such as Indonesia, Brunei, and Singapore that use the Malay language.

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CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Dodge KA. Emotion and social information processing. 1991: 159-81.
2. Shields A, Cicchetti D. Emotion Regulation Among School-Age Children: The Development and Validation of a New Criterion Q-Sort Scale. Dev Psychol 1997; 33: 906-16.
3. Al-Ayadhi L, Alhowikan AM, Halepoto DM. Impact of Auditory Integrative Training on Transforming Growth Factor-beta1 and Its Effect on Behavioral and Social Emotions in Children with Autism Spectrum Disorder. Med Princ Pract,2018; 27: 23-9.
4. Jane E, Thomas B. Music Therapy for People with Autism Spectrum Disorder: Oxford University Press 2015.
5. Maedgen JW, Carlson CL. Social Functioning and Emotional Regulation in the Attention Deficit Hyperactivity Disorder Subtypes. J Clin Child Psychol 2000; 29: 30-42.
6. Petrides KV. Psychometric Properties of the Trait Emotional Intelligence Questionnaire (TEIQue). J Pers Assess 2009; 88: 85-101.
7. Williams JH, Cameron IM, Ross E, Braadbaart L, Waiter GD. Perceiving and expressing feelings through actions in relation to individual differences in empathic traits: the Action and Feelings Questionnaire (AFQ). Cogn Affect Behav Neurosci 2016; 16: 248-60.
8. Shields A, Cicchetti D. Parental Maltreatment and Emotion Dysregulation as Risk Factors for Bullying and Victimization in Middle Childhood. J Clin Child Psychol 2001; 30: 16.
9. Meybodi FA, Mohammadkhani P, Pourshahbaz A, Dolatshahi B, Mousavi ME, Heydari H. Psychometric Properties of the Persian Version of the Emotion Regulation Checklist. World Family Medicine Journal: Incorporating the Middle East Journal of Family Medicine 2018; 99: 1-6.
10. Molina P, Sala MN, Zappulla C, Bonfigliuoli C, Cavioni V, Zanetti MA, et al. The Emotion Regulation Checklist–Italian translation. Validation of parent and teacher versions. Eur J Dev Psychol 2016; 11: 624-34.
11. Reis AH, Oliveira SES, Bandeira DR., Andrade NC, Abreu N, Sperb TM. Emotion Regulation Checklist (ERC): Preliminary studies of cross-cultural adaptation and validation for use in Brazil. Temas em psicologia 2016; 24: 97-116.
12. Cicchetti D, Ganiban J, Barnett D. Contributions from the study of high-risk populations to understanding the development of emotion regulation. Cambridge University Press, UK 1991: 15-48.
13. Weiss JA, Thomson K, Chan L. A Systematic Literature Review of Emotion Regulation Measurement in Individuals With Autism Spectrum Disorder. Autism Res 2014; 7: 629-48.
14. Guillemin F, Bombardier C, Beaton D. Cross-Cultural Adaptation of Health-Related Quality of Life Measures: Literature Review and Proposed Guideliness. J Clin Epidemiol 1993; 46: 16.
15. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the Process of Cross-Cultural Adaptation of Self-Report Measures. SPINE 2000; 25: 3186-91.
16. Yusoff MS. ABC of content validation and content validity index calculation. Resource 2019; 11: 49-54.
17. Polit DF, Beck CT, Owen SV. Is the CVI an acceptable indicator of content validity? Appraisal and recommendations. Res Nurs Health 2007; 3: 459-67.
18. Andrew Chin RW, Chua YY, Chu MN, Mahadi NF, Wong MS, Yusof MSB, et al. Investigating validity evidence of the Malay translation of the Copenhagen Burnout Inventory. J Taibah Univ Med Sci 2017; 13: 1-9.
19. George D, Mallery P. SPSS for Windows Step by Step; A Simple Guide and Reference Fourth Edition (11.0 update) 4th Edition. Boston: Allyn & Bacon 2003
20. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med 2016; 15: 155-63.

Malaysian consensus statement on FDG PET-CT reporting format for lymphoma

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ABSTRACT

Over the past decade, 18F-Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) has emerged as an important imaging modality in the management of lymphoma. Since the introduction of Deauville scoring system (2009) and the Lymphoma Response Assessment Criteria (2014), clinicians are now sharing a common language in the management of lymphoma. In Malaysia, nearly a third of PET-CT request is related to lymphoma imaging. Though there are extensive publications regarding these scoring systems and assessment criteria for lymphoma, there are hardly any literature on the reporting format for the 18F-FDG PET-CT in this disease. The variable reporting formats have on many occasions caused confusion not only to the referring clinicians but also to nuclear medicine physicians. Thus, a working committee comprising experienced nuclear medicine physicians and haematologists in Malaysia have agreed and made a joint recommendation on the standard reporting format for 18F-FDG PET-CT in Lymphoma. This recommendation will minimize inter-observer discrepancies in reporting, facilitate the understanding of the report of the referring clinicians as well as facilitate counseling between patients and clinicians in the management of the disease.

KEYWORDS:
Consensus; lymphoma; 18F-Fluorodeoxyglucose PET-CT; reporting

INTRODUCTION

Lymphoma ranks fourth among males and sixth in females for the most common cancer among Malaysians according to the Malaysian National Cancer Registry Report 2007-2011.[1] Over the last two decades, 18F-Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) has emerged as an important imaging modality in lymphoma management.[2] PET-CT has been shown to improve the accuracy in staging, treatment response assessment, surveillance, detection of transformation and, as a surrogate marker in new drug development in assessing FDG-avid lymphoma.[3,4]

Since the introduction of Deauville five-point score (5-PS) at the first International Workshop on PET in Lymphoma in 2009, PET-CT has been recommended, as an imaging biomarker, in the risk-adapted strategies in the management of lymphoma.[5] In 2011 and 2013, following the 11th and 12th International Conferences on Malignant Lymphoma in Lugano, a consensus was reached among haemato-oncologists and nuclear medicine physicians to accept PET-CT in lymphoma evaluation and to harmonise PET reporting.[6]

The Deauville (5-PS) scoring system (Table II) was adopted by nuclear medicine physicians in Malaysia shortly after the publication of Lugano Criteria in 2014.[6] Nevertheless, there is still a lack of standardised format for PET-CT reporting in lymphoma cases using the published guideline. Therefore, there is a need to standardise the reporting format by outlining the minimum expectation in reporting the findings for patients in Malaysia.

AIM OF THIS CONSENSUS

The aim of this paper is to standardise the FDG PET-CT reporting format for lymphoma in Malaysia. This will (i) minimise inter-personal discrepancies in reporting; (ii) facilitate the reading and understanding of the reports by the referring clinicians; (iii) facilitate counselling of patients in planning the subsequent therapeutic management; (iv) standardise clinical trial.

In this report, a multidisciplinary panel was established with representatives from nuclear medicine physicians and clinical haematologists from public, private and university hospitals. The initial draft was prepared by the nuclear medicine physicians based on the existing guidelines.[7,8] Subsequently, this draft was presented and discussed with clinical haematologists according to clinical settings in Malaysia.

Of note, in order to adapt to the Malaysian needs and for practicality reasons (e.g. regions without the availability of the PET-CT service), it is important to note that some of the recommendations were based on the consensus of the committee based on the current accepted practice in Malaysia.

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PREPARATIONS FOR FDG PET-CT IMAGING

The recommended timing for performing PET-CT for patients is summarized in Table III. Optimal patient preparation for PET-CT examination is essential to obtain good-quality images for accurate interpretation. Patients are required to fast for at least 4 hours before the procedure with only plain water intake permitted. Serum glucose levels of patients need to be assessed prior to PET-CT examination. The optimal glucose level prior to FDG injection needs to be below 11.1mmol/l. In patients with diabetes, anti-diabetic medication may need to be adjusted at the discretion of the attending physician. Rescheduling of the procedure may be necessary if the glucose level of the patient is too high.

In addition to the dietary restrictions, patients are also required to avoid strenuous exercise a day before the procedure. Physiological brown fat uptake can occur when patients are exposed to the cold environment during the procedure. Medications such as oral propranolol and benzodiazepine can be used to minimise this problem.

LYMPHOMA UPTAKE, PHYSIOLOGICAL DISTRIBUTION AND PITFALLS OF FDG PET-CT

Lymphomas comprise a heterogeneous group of histological subtypes with various genetic, molecular characteristics and biological behaviours. Most of the common lymphoma subtypes demonstrate high FDG avidity but particular attention needs to be paid to several less common subtypes with variable FDG avidity as shown in Table IV.

It is important to take note of the patterns of normal physiological FDG uptake in the brain, nasopharynx, liver, spleen, bone marrow and brown fat.[9] Brown fat activity, due to cold stimulation, is commonly seen at bilateral neck, shoulder, mediastinal, perirenal and paraspinal areas.[10,11] The uptake in these organs may occasionally mask small nodal and extranodal lesions. Therefore, CT component of PET-CT images should be scrutinised for any potential lesions. Specific measures such as drug administration (propranolol or benzodiazepine) or keeping the patients warm should also be undertaken to reduce brown fat activity and improve image quality.[10,11] Diffuse splenic FDG uptake is physiological but if the intensity is higher than the liver, it is suggestive of splenic involvement.[9]

Focal uptake in the bone marrow (BM) is highly predictive of lymphoma infiltration, which has been validated by various studies.[13] Therefore, it is suggested that definite FDG uptake in the marrow can help to obviate the need for bone marrow biopsy (BMB) in Hodgkins' lymphoma (HL) and to a certain extent, diffuse large B cell lymphoma (DLBCL).[13] For HL, in the absence of B symptom and with a negative PET-CT, BMB can be omitted. For DLBCL, BMB may still be required when PET-CT shows no evidence of marrow involvement because identification of low volume disease is clinically important for subsequent treatment planning.[14-17] BMB is also recommended for the staging of other histological types.[4] On the other hand, diffuse intense bone marrow uptake in DLBCL patients, especially following institution of therapy, is usually attributable to hyper-reactive marrow (result of disease or treatment related factors) and should not be reported as definitive lymphomatous involvement.

Recommendation: *Bone marrow biopsy should be performed in any case when confirmation of marrow involvement is clinically important for treatment planning.*

Diagnosing the lung involvement in lymphoma is a challenge.[18] Lung lymphomas may present as nodules, consolidation, or interstitial infiltrates with moderate to high FDG uptake. False positive findings due to bacterial pneumonia, granulomatous disease such as tuberculosis or sarcoidosis and bleomycin-induced pneumonitis have been well-documented.[19] Clinical, histopathological correlation, or follow-up study may be needed to establish the diagnosis. Lymphomatous infiltration and extension from adjacent mediastinal or hilar adenopathy (E lesion) should be differentiated from non-contiguous lymphomatous involvement of the lung parenchyma (Stage IV).

Increased FDG activities in the activated lymphoid tissues are another common pitfall in PET-CT scans.[19,20] Rebound thymic hyperplasia can be observed in children and younger adults after chemotherapy, and thus needs to be distinguished from the residual mediastinal lymphoma. FDG uptake in the reactive lymph nodes especially at upper jugular chains are often seen on the end-of-treatment PET-CT scans. Comparison of these findings with the baseline study and recognition of the specific patterns are useful to derive the accurate conclusion.[21]

False positivity can also occur due to the presence of concurrent infection, inflammation during PET-CT examination or the patient receiving the immunotherapy. Referring clinicians should inform any conditions that may result in false positive results in the request form. Reporting doctors should also be aware of these conditions.

Recommendation: *FDG uptake should be interpreted in conjunction with CT morphology when writing a PET-CT report. Indeterminate lesion should be clearly stated. Clinical and histopathological correlation should always be taken into consideration when reading and interpreting the PET-CT report.*

USE OF STANDARDIZED UPTAKE VALUE AND DEAUVILLE CRITERIA

FDG uptake is commonly presented semi-quantitatively by the Standardised Uptake Value (SUV).[9,23] However, SUV may vary as it is subjected to the injected FDG dose, time-to-image, scanner, and other factors.[21] To avoid such variations and to ensure consistencies in reporting, it is recommended that serial studies are performed on the same PET-CT scanner.[9]

Despite standardization of PET-CT imaging techniques, inter-observer agreement on PET response in lymphoma treatment is not satisfactory, leading to concerted efforts for improvement, known as the International Harmonization Project. The previous shortcoming was partly due to lack of a reliable SUV cut-off value in differentiating active versus non-active lesions, especially in the category of 'minimal residual uptake'.[3,6] This problem has been overcome by the five-point scale grading or Deauville Criteria, which has been shown to be more reproducible by incorporating the use of mediastinum blood pool and liver as "reference tissues" and normalization of lesion/target SUV measures to the selected reference tissues.[3,5,6]

Table I:

Sections of the Report	Details of the Content
Demographics	Patient's identifiers, the referring doctor's name, date of the study and type of the examination (FDG PET-CT).
Clinical summary	Histologic subtype of lymphoma, the primary sites of disease, initial staging and treatment history (including dates of last cycle of chemotherapy, immunotherapy, or radiotherapy, stem cell transplant), recent investigation results (tumour markers), recent procedures, past or co-existing medical illnesses and drug history (GCSF administration, metformin etc), previous imaging studies.
Study indication Procedure	Baseline, interim, end-of-treatment or surveillance scan (specify the purpose of the surveillance study). Name of the radiopharmaceutical, the administered activity (total activity or per body weight), anatomical site of injection (optional), time from injection to imaging, pre-injection blood glucose level, oral or intravenous CT contrast (if given), other medication administered e.g., diuretics, benzodiazepines, propranolol (if given), additional regional or delayed scanning (if performed).
Findings	• There are two ways of reporting the findings of PET/CT: arrange the findings in descending order of clinical importance (preferred by majority of the clinicians) or according to successive structured anatomical regions. Both reporting styles are acceptable and endorsed by International Atomic Energy Agency (IAEA).[25] • When comparing two or more studies, it should be clearly stated *"Comparison was made with previous PET-CT(s) dated ....."*. • Potential limitations such as intense brown fat uptake and patient's motion artefact should be stated. Non-FDG avid proven or suspicious lymphoma lesions should also be included. • Lymphoma typically involves multiple groups of lymph nodes at multiple regions. The reporting nuclear medicine physicians should specify each regional involvement (e.g., unilateral/ bilateral cervical, mediastinal, axillary, retroperitoneal, pelvic, inguinal regions) and any extra-nodal or bone marrow involvement • In each region (cervical, mediastinal, retroperitoneal, etc), SUV with Deauville score of the representative lymph node (typically the most metabolically active one) should be stated. Tumour size, and if possible, tumour volume, should be stated together with SUV. For example: *"Intense FDG uptake is demonstrated at large lobulated mediastinal mass (SUVmax 15.7 (Deauville 5), measuring 3.5 × 1.7cm)".* • In assessment of the therapy response, changes of uptake intensity and CT size of the target lesions should be clearly stated. For example: *"Previous mediastinal mass has markedly reduced in hypermetabolic intensity and CT size (current SUVmax 4.0 (Deauville 4), measuring 3.8 × 1.9cm; previous SUVmax 15.7 (Deauville 5), measuring 8.5 × 3.2cm)"*. • CT component should be examined. Any bulky lymph nodes or lesions compromising critical structures must be stressed to the referring physicians. • Non-oncologic incidental findings e.g., pneumonia, chemotherapy/ radiation-induced lung fibrosis, vascular aneurysm, thromboembolism, obstructive uropathy, gynaecological masses etc. should be reported.
Conclusion	• A brief conclusion to answer the clinical questions of the referral. For example: *"Current study demonstrates active lymphoma at bilateral cervical and right axillary regions (Ann Arbor stage II). No demonstrable bulky disease or extra-nodal lesion."* • In response assessment, it may be concluded that: *"The findings are consistent with complete metabolic response/ partial metabolic response/stable metabolic disease/ progressive metabolic disease."* • If baseline study is not available for comparison, the term *"residual active lymphoma"* if presence of active disease. • It is advisable to avoid the term of *"mixed response"* which may result in confusion. • The strength of evidence indicative of active lymphoma present on the current study can be reflected by using the terms such as *"highly suggestive of"*, *"suggestive of"* or *"less likely"*. • If there is an indeterminate lesion *"suggestive of"* residual lymphoma, the nuclear medicine physician should suggest an appropriate subsequent action(s) such as a suitable site for biopsy. If active lymphoma is *"less likely"*, then an alternative differential such as infection should be given. • Verbal communication of the critical finding e.g., airway compromise, cord compression, thrombosis or impending fracture to the referring doctor must be recorded.
Addendum	Following the issuance of the initial official report, any discrepancies, variation in findings and/or conclusions, additional amendment, comments or feedbacks should be recorded in this section.

Table II: The definitions of Deauville five-point score

Score	Definitions
1	No FDG uptake
2	FDG uptake ≤ mediastinal blood pool
3	FDG uptake > mediastinal blood pool but ≤ liver
4	Moderately increased FDG uptake compared to the liver (< 3 × SUV liver)*
5	Markedly increased FDG uptake compared to the liver (≥ 3 × SUV liver)* or new lesion
X	New areas of FDG uptake unlikely to be related to lymphoma

Note: * The 3 times SUV of liver as the cut-off to classify Deauville Score 4 and 5 is recommended by our working committee based on our expert opinions.

Table III: Terminology of indications of PET-CT scan in lymphoma

Baseline scan: It is performed prior to institution of the definitive therapy to provide information about the staging and the prognosis. It also enables comparison with the subsequent study to facilitate evaluation of treatment response.

Interim scan: It is the mid-treatment scan frequently done after the second or third cycle of therapy, at timing just before the start of the following cycle. It must be performed at least 14 days after the previous chemotherapy cycle. It is useful to predict the response to the current regime so that early treatment adaptation can be performed.

End-of-treatment scan: It is used to evaluate response following the completion of the predefined treatment regime, usually within 6 months after treatment. The scan is recommended to be performed at the following time frame to avoid false positive flare reaction:

- At least 2 weeks after GCSF
- At least 4 weeks post-surgery
- At least 6 weeks post chemotherapy including immunomodulator
- At least 8 weeks after PD-1/ PDL-1 immunotherapy
- At least 12 weeks post radiotherapy

Surveillance scan: It refers to the follow-up scan which is done:

i) to assess the equivocal findings on the end-of-treatment scan, or
ii) more than 6 months after completion of the definitive treatment with the purpose of screening to ensure remission, or
iii) to evaluate the suspicion of relapse after achieving complete remission

Table IV: 18F-FDG avidity of various subtypes of lymphoma [4,6]

	FDG avidity (%)
High avidity	
Hodgkin Lymphoma	97 – 100
Diffuse Large B Cell Lymphoma	97 – 100
Follicular Lymphoma	97 – 100
Mantle-cell lymphoma	100
Marginal zone lymphoma, nodal	100
Lymphoblastic lymphoma	100
Sezary syndrome	100 +
Anaplastic large T-cell lymphoma	94 – 100 *
Natural Killer/ T-cell lymphoma	83 – 100
Mycosis fungoides	83 – 100
Angioimmunoblastic T-cell lymphoma	78 – 100
Enteropathy-type T-cell lymphoma	67 – 100
Peripheral T-cell lymphoma	86 – 98
Moderate to High Avidity	
MALT marginal zone lymphoma	54 – 81
Small lymphocytic lymphoma	47 – 83
Mild to Moderate Avidity	
Subcutaneous panniculitis-like T-cell lymphoma	71
Marginal zone lymphoma, unspecified	67
Marginal zone lymphoma, splenic	53 – 67
Primary cutaneous anaplastic large T-cell	40 – 60
Lymphomatoid papulosis	50
Poor FDG Avidity	
Cutaneous B-cell lymphoma	0

Note: + only 62% of cutaneous sites
* only 27% of cutaneous sites

Table V: The definitions of metabolic response criteria based on Lugano Classifications 3,6

Categories of response	Definitions
Complete metabolic response (CMR)	• Score 1, 2 or 3 in the nodal or extranodal sites, with or without residual mass(es).
Partial metabolic response (PMR)	• Score 4 or 5, with reduced uptake compared with baseline and residual mass(es) of any size. • SUV of the baseline target lesion+ is reduced by > 30%. # • None of the other less active non-target lesions showing SUV increment of > 30%. # • Bone marrow metastases uptake > normal marrow but reduced compared with baseline scan. • At interim scan, PMR may suggest responding disease but at the end-of-treatment scan it indicates residual active lymphoma.
No metabolic response (NMR)	• Score 4 or 5 on the interim or end-of-treatment scan, with no significant change in target lesion uptake from baseline. • None of the other less active non-target lesions showing SUV increment of >30%. #
Progressive metabolic disease (PMD)	• Score 4 or 5 on the interim or end-of-treatment scan, with an increase in uptake from baseline. • New FDG-avid foci consistent with lymphoma. • SUV of the baseline target lesion is increased by > 30%. # • Any of the other less active non-target lesions showing SUV increment of > 30%. * #

Note: + Target lesion is the most metabolically active lymphoma lesion
The 30% cut-off value is based on the expert opinions of our working committee
* The increase in FDG uptake may be due to inflammation, thus biopsy may be necessary to confirm PMD

Deauville Criteria is recommended for response assessment at interim as well as end of treatment PET.[5] Score 1 and 2 represent complete metabolic response (CMR). When a target lesion demonstrates score 4 and 5 during interim or end-of-treatment study, a SUV of more than 30% reduction from baseline study represents partial metabolic response (PMR); whereas more than 30% increment from baseline study is considered progressive metabolic disease (PMD). Change of SUV that does not meet the above criteria is considered no metabolic response (NMR) or stable metabolic disease (SMD). In additional, any new metabolically active lesions represent progressive metabolic disease (PMD) (Table V).[3,6]

In order to avoid missing small residual disease, Score 3 should be interpreted with anticipated prognosis, lymphoma subtype, clinical findings, other markers (such as CT size reduction) and decision on escalation/ de-escalation of treatment. For instance, score 3 is likely to represent CMR in interim PET in HL receiving standard induction therapy. However, score alone should not be used to decide on de-escalation of treatment.

For the lesion occurring in the regions with high physiological FDG uptake i.e., bowel, spleen and bone marrow, a reduction of the previous uptake to the level not exceeding the current surrounding normal tissue activity can be regarded as a CMR.

Recommendation: *Deauville score should be provided together with SUV when reporting FDG PET-CT in lymphoma. Although Deauville Criteria is useful when comparing serial studies, it is recommended to state the Deauville score in the baseline study. If there are multiple lesions in a particular nodal region, the highest Deauville score lesions should be provided at each region.*

NOTE 1: *Deauville Criteria provides the metabolic response of the target lesions. Morphologic (tumour size and volume) response and other blood parameters should be taken in consideration when assessing overall clinical response.*

NOTE 2: *When measuring tumour size, bi-dimensional measurement is recommended by the panel for routine clinical use. The measurements should include the longest diameter of the target lesion as recommended by RECIL 2017.[23] We take note that uni-dimensional short axis nodal measurement recommended by RECIST 1.1 is usually used in clinical research.[24] Although CT tumour volume, metabolic tumour volume or total lesion glycolysis has been well studied in evaluating tumour response, it is not yet incorporated in the general guidelines.*

INDICATIONS OF FDG PET-CT IN LYMPHOMA

PET-CT is considered the standard-of-care imaging for staging, response assessment and surveillance of lymphomas (Table III). When the initial PET-CT demonstrates low FDG avid nodes, subsequent diagnostic CT should be used to monitor morphological response.

Recommendation: *FDG PET-CT should not be used to diagnose lymphoma in suspected cases. Histopathological results remain the gold standard. However, PET-CT may be useful to map the distribution of active lesions and identify the optimal biopsy site for histopathologic confirmation.*

Terminology such as "baseline scan", "interim scan" and "end-of-treatment scan" are widely used in clinical practice. (Table III) However, some clinicians prefer terminologies like "pre-treatment scan" and "post-treatment scan". It is important that both the referring clinicians as well as the reporting nuclear medicine physicians share the same understanding of the terminologies used.

STRUCTURED FDG PET-CT REPORT FOR LYMPHOMA

The report usually contains the following sections:

CONCLUSION

This document provides essential elements and standardized terminologies used in PET-CT reporting in lymphoma. It is intended to provide a practical guide to Malaysian

physicians involved in lymphoma management in reporting, interpreting, and understanding the PET-CT report. We hope that these joint statements will lead to more collaboration and cross-disciplinary input among all parties in optimising lymphoma management in future. In view of rapid progress in lymphoma imaging and therapy, these recommendations will be reviewed within 5 years.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

REFERENCES

1. Azizah Ab M, Nor Saleha I T, Noor Hashimah A, Asmah Z A, Mastulu W. Malaysia National Cancer Registry Report (2007 to 2011). National Cancer Institute. Ministry of Health.
2. Weiler-Sagie M, Bushelev O, Epelbaum R, Dann EJ, Haim N, Avivi I, et al. (18)F-FDG avidity in lymphoma readdressed: a study of 766 patients. J Nucl Med 2010; 51: 25-30.
3. Barrington SF, Mikhaeel NG, Kostakoglu L, Hutchings M, Mueller SP, Schwartz H, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 2014; 32: 3048-58.
4. Barrington SF, Johnson PWM. 18F-FDG PET/CT in Lymphoma: Has Imaging-Directed Personalized Medicine Become a Reality? J Nucl Med 2017; 58(10): 1539-44.
5. Meignan M, Gallamini A, Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on Interim-PET-Scan in Lymphoma. Leukemia Lymphoma 2009; 50: 1257-60.
6. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014; 32: 3059-68.
7. Haematological cancers. NICE guideline QS150. 2017.
8. Zelenetz AD, Gordon LI, Abramson JS, Advani RH, Bartlett NL, Caimi PF, et al. NCCN Guidelines Insights: B-Cell Lymphomas, Version 3.2019. J Natl Compr Canc Netw 2019;17(6):650-61.
9. Hofman MS, Hicks RJ. How We Read Oncologic FDG PET/CT. Cancer Imaging 2016; 16: 35.
10. Paidisetty S, Blodgett TM. Brown Fat: Atypical Locations and Appearances Encountered in PET/CT. AJR Am J Roentgenol 2009; 193: 359-66.
11. Gerngrob C, Schretter J, Klingenspor M, Schwaiger M, Fromme T. Active Brown Fat During 18F-FDG PET/CT Imaging Defines a Patient Group with Characteristic Traits and an Increased Probability of Brown Fat Redetection. J Nucl Med 2017; 58: 1104-10.
12. Dubreuil J, Salles G, Bozzetto J, Tordo J, Djaileb L, Berriolo-Riedinger A, et al. Usual and unusual pitfalls of 18F-FDG-PET/CT in lymphoma after treatment: a pictorial review. Nucl Med Commun 2017; 38: 563-76.
13. El-Galaly TC, d'Amore F, Mylam KJ, de Nully Brown P, Bogsted M, Bukh A, et al. Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography staged treatment-naive patients with Hodgkin lymphoma. J Clin Oncol 2012; 30: 4508-14.
14. Richardson SE, Sudak J, Warbey V, Ramsay A, McNamara CJ. Routine bone marrow biopsy is not necessary in the staging of patients with classical Hodgkin lymphoma in the 18F-fluoro-2-deoxyglucose positron emission tomography era. Leukemia Lymphoma 2012; 53: 381-5.
15. Khan AB, Barrington SF, Mikhaeel NG,Hunt AA, Cameron L, Morris T, et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. Blood 2013; 122: 61-7.
16. Adams HJ, Kwee TC, de Keizer B, Fijnheer R, de Klerk JM, Nievelstein RA. FDG PET/ CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 2014; 41: 565-74.
17. Berthet L, Cochet A, Kanoun S, Berriolo-Riedinger A, Humbert O,Toubeau M, et al. In newly diagnosed diffuse large B-cell lymphoma, determination of bone marrow involvement with 18F-FDG PET/CT provides better diagnostic performance and prognostic stratification than does biopsy. J Nucl Med 2013; 54: 1244-50.
18. Sirajuddin A, Raparia K, Lewis VA, Franks TJ, Dhand S, Galvin JR, et al. Primary Pulmonary Lymphoid Lesions: Radiologic and Pathologic Findings. Radiographics 2016; 36: 53-70.
19. Kis A, Eszes N, Tamasi L, Losonczy G, Csekeo A, Csomor J, et al. Sarcoidosis lymphoma syndrome - the value of PET-CT in the diagnosis. World J Surg Oncol 2013; 11: 235.
20. Hu YY, Zhang X, Long W, Lin XP, Zhang YR, Li YH, et al. Cervical lymph node hyperplasia on [(18)F]- fluorodeoxyglucose positron emission tomography/computed tomography scan after treatment of children and adolescents with malignant lymphoma. Eur J Radiol 2015; 84: 1378-82.
21. Kinahan PE, Fletcher JW. PET/CT Standardized Uptake Values (SUVs) in Clinical Practice and Assessing Response to Therapy. Semin Ultrasound CT MR 2010; 31: 496-505.
22. Weiss GJ, Korn RL. Interpretation of PET scans: do not take SUVs at face value. J Thorac Oncol 2012; 7: 1744-6.
23. Younes A, Hilden P, Coiffier B, Hagenbeek, A., Salles, G., Wilson, W., et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Ann Oncol 2017; 28(7): 1436-47.
24. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): 228-47.
25. Standard operating procedures for PET/CT: a practical approach for use in adult oncology. Vienna: International Atomic Energy Agency 2013.

Esophageal cancer epidemiology, diagnosis, and management in Sudan - A review

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ABSTRACT

Introduction: In Sudan, cancer a common health challenge, is the leading cause of death after malaria and viral pneumonia. The aim of the review is to determine the risk factors associated with esophageal cancer (EC) among Sudanese population.

Methods: All published online data concerning EC epidemiology, diagnosis, and management in Sudan were studied.

Results: The prevalence of EC in Sudan is ranked fourth among cancer types in males and fifth in females. The squamous cell carcinoma is more predominant than adenocarcinoma. The dietary, dysplasia and teeth loss, cigarette smoking, age, sex, GERD, genetic and environmental interactions remain a risk for developing EC in clinical practice. A significant challenge for treatment is that most of EC patients were often diagnosed in advanced stages due to the lack of early clinical symptoms. Management of EC depends on patient fitness and tumor stage, endoscopic removal was used for early tumors, while chemotherapy, chemo-radiotherapy, surgical resection, or combinations of these were used for advanced tumors. Despite improvements in the management and treatment of EC patients, the general outcome remains very poor. Furthermore, using molecular techniques to better understand the etiology of EC, it may assist in identifying complicated and critical issues and improve therapy towards a new treatment strategy.

Conclusion: The remarkable factors associated with EC among Sudanese are geographical variation, environmental factors, ethnic differences, dietary and social habits.

KEYWORDS:
Esophageal cancer, epidemiology, diagnosis, management, Sudan

INTRODUCTION

Esophagus cancer (EC) is ranked sixth in causing cancer death worldwide.[1] Squamous cell carcinoma and adenocarcinoma are the two histological subtypes, varying in geographical and racial distribution.[2] Etiologically adenocarcinoma is primarily associated with gastric reflux, and Barrett's esophagus is a more common cancer type in developed countries that increased significantly to the global health burden.[3] In contrast, squamous cell carcinoma was associated with red meat consumption, low intake of fresh fruit and vegetables, drinking hot tea, smoking, alcohol consumption, poor oral health, is more prevalent in a lower socioeconomic group and among those in developing countries.[4]

In our previous study we found that EC was associated with many risk factors such as age, sex, alcohol smoking, tobacco use, red meat, poor oral health, low intake of fresh food, and socioeconomic status. The study demonstrated that the literature on EC was continuously growing, in the field of squamous cell, carcinoma and adenocarcinoma. Research in EC was supported by China and United States of America (USA) funding agencies. Therefore, China, USA and Japan are the top productive countries on EC research.[5]

EC is a fatal disease among Sudanese populations and sub-Saharan Africa concerning prognosis and mortality rate.[6] It is the most reported gastrointestinal cancer,[7] with approximately 5.8 per 100000 cases in the general Sudanese population.[7] EC cases were relatively increased since 1993, with an estimated rate of 4.6% among Sudanese[7] to 5.4% in the year 2006.[7] In 2000, cancer was the third leading cause of death after malaria and viral pneumonia, accounting for 5% of all deaths.[7] EC ranks the 4th among Sudanese males and 5th cancer among females.[8] The incidence of adenocarcinoma was increased by 11% from 1986 to 1991[7] to 44.5% in 2010.[9] The remarkable factors associated with EC among Sudanese are geographical variation, environmental factors, ethnic differences, dietary and social habits, in addition, genetic factors.[10,11]

Cancer registry in Sudan

Sudan is like other developing countries where the primary health system focuses against infectious diseases with less attention given to non-communicable diseases owing to an increase in EC cases.[2] The first national cancer registry was started in 1967, supported with a grant from the International Union against Cancer (IUAC) in cooperation with University of Khartoum, Stack Medical Research Laboratory, and the Ministry of Health, Sudan.[2] Recently, the primary cancer data are obtained from the hospital-based cases at only two oncology centers.[6] The first is the "Radiation and Isotope Center in Khartoum State, and the second is "National Cancer Institute in Gezira State established in 1992 by the University of Gezira. These centers were still facing

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Table I: Gender ratio and age distribution of esophageal cancer patients in Sudan

Gender	Male: Female ratio	Country	References
	1:3.3	Sudan	Mohammed et al., 2012
	1.3:1.0	Sudan	Mahmoud et al., 2014
	0.7:1.5	Sudan	Elhadi et al., 2016
	2:1	African Sub-Sahara region	Kachala, 2010
Age (year)	**Range**	**Country**	**References**
	52-66	Sudan	Mohammed et al., 2012
	45-64	Sudan	Mohammed et al., 2014
	50-80	Sudan	Ali and Ibrahim, 2014
	31-93	Sudan	Elhadi et al., 2016

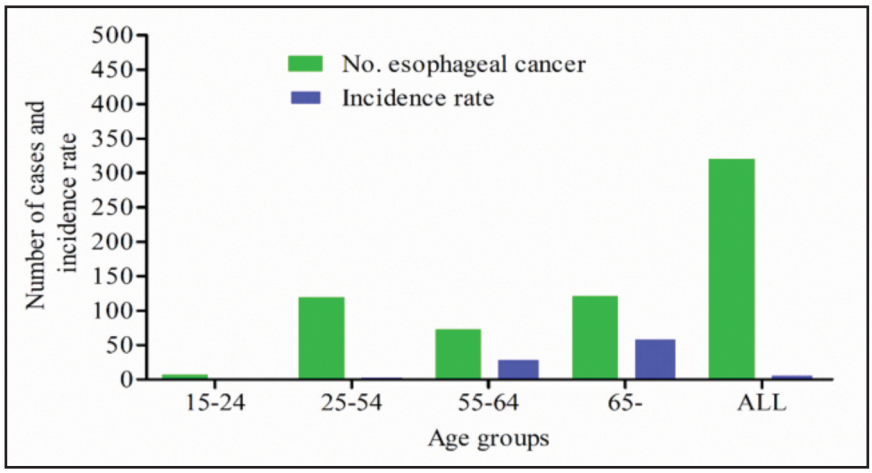

Fig. 1: Age-wise distribution of esophageal cancer incidence among the top 10 cancer reported during the year 2009-2010 Saeed et al.[8]

many problems, such as lack of running cost and research activities, budget to support professional medical care staff, the fund for expansion of cancer registration at the state level, qualified oncologist, the fund for carryout health awareness, week health information system, insufficient cancer diagnostic facilities, lack of a national population-based cancer registry and standardized pathological reporting.[12]

Geographical distribution of esophageal cancer

Sudan is a large country with diversity in the population and the environment.[13] The change face EC presents a vast challenge in the management and control. The incidence of EC in Western Sudan was 38.9%, Khartoum state 30.5%, White Nile 18.1%, Eastern Sudan 5.5%, Northern Sudan 4.5%, and Blue Nile state 2.8%.[11] In the Gadarif State in Eastern Sudan, the EC cases are slightly higher among people living in town compared with the rural area, and the reason is that urban area has better health services and diagnostic tools.[14] Ali and Ibrahim[15] indicated that Khartoum and North Kordofan were the most geographical areas in Sudan affected by cancer. The population of the Southern and Eastern African Sub-Regions had ten times higher age-gender incidence and prevalence rates compared with the Western African Sub-Region.[16]

The incidence of esophageal cancer in Sudan

The incidence of EC was 1.4% in early 1977. Recently, 9.6% of patients referred for endoscopy units in Gezira state were proved to have EC.[17] Incidence data derive from population-based cancer registries reported as 5.8 per 100000 in the general Sudanese population and 8.9 per 100000 in adults more than 15 years were at risk with EC.[8] The highest incidence was reported in the Northern region than in South Sudan.[8] In Sudan, the prevalence of the EC is generally higher among males.[17] The incidence of EC is high at the age of more than 15 years.[7] A recent study showed the incidence rate was higher in adults at 65 years (Figure 1).[8] The mortality rate of 10% indicated a remarkable improvement compared with the previous reports back to fifteen years ago.[7]

Clinical presentation of the esophageal cancer

In Sudan, the most common clinical presentation was dysphagia, followed by loss of body weight.[18] A few patients presented with epigastric pain and back pain,[11] pressure or burning, worsening indigestion or heartburn, and coughing or hoarseness.[18] The mean duration of dysphagia was 120 days.[11]

Squamous cell carcinoma was the common type of EC 92.5% compared to adenocarcinoma 4.7%.[11,19] In contrast, Elhadi et al.[18] reported 80.6% were adenocarcinoma, and 19.4% were squamous cell carcinoma. Adenocarcinoma was more frequent in males 75%, compared with females 25%, whereas Squamous cell carcinoma was more frequent in females 63.6%, compared to males 36.4%.[2]

The well-differentiated tumors were most common among the patients with Squamous cell carcinoma, in both males, 42.9%, and females 51.8%.[11] Whereas, poorly differentiated

tumors were predominant among the patients with Adenocarcinoma, representing 32.1% and 42.8% of the Adenocarcinoma in male and female patients, respectively.[11]

In general, the site of the tumour was located in the middle and lower third of the esophagus.[18,19] Gasmeseed et al.[11] indicated that squamous cell carcinoma cases were located in the middle and lower third of the esophagus, while most adenocarcinomas were located in the lower third.[10]

Risk factors associated with esophageal cancer

EC and gastrointestinal malignancies are the most common cancer, caused risk for up to 25.3% of people.[20] The rich diet in red and processed meat, saturated fats, and low intake fruits and vegetables, dysplasia, and teeth loss remain a risk for developing esophageal adenocarcinoma in clinical practice.[18,21] The incidence of esophageal carcinoma is rare in young people, and increases with age, reach the peak in 70 to 80 years of age.[22] GERD, cigarette smoking, and sex are also associated with esophageal adenocarcinoma.[22,23]

Gender

EC ranks fourth in Sudanese males, and the fifth in females[7], it was more predominant in females.[2,15,18-20] The male-to-female ratio was 1:2 for squamous cell carcinoma and 2:1 for adenocarcinoma.[11] A minor female predominance was reported in Uganda in East Africa and Guinea in West Africa.[13] In contrast, Mahmoud et al.[24] indicated that EC is more prevalent in males (Table I). In African countries, the male-to-female ratio for EC was closer to 2:1 Tanzania,[25] Kenya,[26] and South Africa.[27] The reason for male-dominant is that smoking and alcohol drinking were more prevalent among males.[28] In addition, the inhibitory effect of estrogen in the growth of EC cells was reported. However, there is no documented role of estrogen in human EC etiology.[29] On the other hand, women with EC tend to have a better prognosis than men.[30]

Age

The maximum incidence of EC was in the 6th and 7th decades.[10] Previous studies have shown that the average age of females was 52.75 ± 11.66 years, and that of males was 66.11 ± 9.52,[19] while the average age for both male and female was 62.57±15.1years,18 and 47.3% of women were in the age between 50 and 80 years old.[15] A recent study has shown that the peak was in the age 65 -69 years 40%, followed by 50 -54 years 27%, and over 70 years old 8.1%.[2]

Nutrition

Several studies reported a positive association between EC and alcohol and tobacco consumption,[31] low intake of fresh fruit and vegetables,[4] exposed to the hot drinks and food,[14] achalasia, lime, and caustic fluids ingestion.[19] Poor nutritional status, low fruits and vegetables intake are suggested to be partially responsible for EC. The nutritional status of EC patients was associated with surgical resectability, response to chemotherapy, length of hospital stays, and survival rate.[32] Patients on jejunostomy catheter feeding were considered optimized to receive neo-adjuvant therapy based on clinical assessment. A recent study revealed that feeding jejunostomy catheter combined with a locally prepared feeding formula was provided a reliable nutritional option for esophageal cancer patients in developing countries.[9]

Smoking and Alcohol consumption

Smoking is a risk factor, especially for people living in Western countries, and the risk increases by three-fold to sevenfold for smokers compared with non-smokers people.[33] However, smoking on EC is considerably higher among Asian populations compared with Western populations. In China, poor oral health, cigarettes, and hookah smoking, and smoking were not significantly associated with the risk of EC in the long-term.[4]

The incidence of tobacco smoking use among urban adult males is increasing in Sudan.[7] Among the male EC patients, the manual laborers had the highest percentage of ever tobacco use and alcohol consumption 66.1%, followed by the office workers 50% and farmers 37.3%.[11] Ever tobacco use was most common among patients who come from the Nilotic, Nubian, and Guhaina tribal backgrounds.[11] Ever tobacco use was frequently reported by males with adenocarcinoma 57.1% and squamous cell carcinoma 47.7%.[11] Alcohol is a risk for developing upper aero-digestive tract cancer.[34]

Socioeconomic status

The socioeconomic status of the population was associated with a higher risk of EC in both developed and developing countries.[35] In Sudan the daily diet components intake by people are poor, only few people have access to fruits and vegetables, which may have suggested to be partially responsible for EC. In Gezira State, EC patients who had occupations typically associated with the low socioeconomic status was associated with a higher risk of EC incidence.[11] In China, low socioeconomic status and obesity were associated with a higher risk of esophageal squamous cell carcinoma.4 In addition, people's lifestyles, environmental and socioeconomic factors, such as reproductive and access to medical and health care services, were associated with EC.[36] Both body mass index and abdominal obesity were associated with the risk of cancer.[37] Obesity is a major pubic-related disease in developed countries.[38] Tooth loss was positively associated with squamous dysplasia of the esophagus, while good oral hygiene was negatively associated.[39]

Gastro-esophageal reflux disease

Gastro-esophageal reflux disease is the main esophagus adenocarcinoma risk factors.[18,24] Weekly GERD symptoms increase the odds of esophagus adenocarcinoma five-fold, and daily symptoms increased the odds seven-fold compared with those with less frequent episodes.[40] In Sudan, gastrointestinal malignancies are the most common cancer; 25.3% is EC.[10] Gastro-esophageal reflux disease (GERD) and Barrett's esophagus are associated mainly with adenocarcinoma.[3,19] Other studies also indicated that GERD is more common in patients with adenocarcinoma than squamous cell carcinoma, representing 5.5% for squamous cell carcinoma and 34.7% for adenocarcinoma.[41] GERD can cause and exacerbate mental complications in patients. Mental factors (anxiety and depression) play important roles in the development of GERD, especially non-erosive esophagitis.[42] In addition, anxiety and depression levels were significantly higher in subjects with GERD than in controls.[43]

Infectious pathogens

Helicobacter pylori infection was negatively associated with esophageal adenocarcinoma. The infection confers a

protective effect for esophageal adenocarcinoma.[24] *H. pylori* infection leads to atrophic gastritis and decreased gastric acid production, neutralizes the acid through the production of ammonia, decreased acid exposure of the distal esophagus, which reduces the chances of esophagitis and esophageal adenocarcinoma.[44] Xie et al.[45] indicated that *H. pylori* infection decrease the risk of esophageal adenocarcinoma by 41% through gastric atrophy, which leads to acid reduction.

In patients with GERD, the prevalence of *H. pylori* infection was higher among patients with than without peptic ulcers.[46] Early studies revealed that *H. pylori* eradication was positively associated with reflux esophagitis or GERD symptoms in patients with gastric and duodenal ulcer diseases.[46] A recent meta-analysis demonstrated that eradication therapy of *H. pylori* was related to a higher risk of developing de novo GERD in Asian studies.[47]

Human papillomavirus (HPV) is one of many factors contributing to EC.[48] HPV16 and HPV18 are the most detected types associated with cancers.[49] These serotypes have a strong association with vulva, anus, penis, and oropharynx cancers.[49] The wide range in HPV positivity could reflect, in part, differences in the sensitivity of the various detection methods used (PCR, In-situ hybridization, Southern blot hybridization, and Immunohistochemistry), and also differences in the incidence of HPV in the tumour samples examined.[62] There is no study to confirm the association of HPV with cancer in the Sudanese population.[6]

Epstein Barr Virus (EBV) infection and exposure to Plasmodium falciparum are cofactors in the pathogenesis of Burkitt's lymphoma, the most common pediatric cancer in equatorial Africa.[51] Furthermore, immunocompromised hosts and EBV have associated nasopharyngeal carcinoma and B cell lymphoma in the Sudanese population.[6] The etiological effects of EBV might cause EC in Sudan.[52]

Human immunodeficiency virus (HIV) related immunosuppression is a strong risk factor for Kaposi's sarcoma, associated with its specific herpesvirus, and non-Hodgkin lymphoma, associated with Epstein Barr virus.[53] HPV-associated cervical carcinoma is also considered an AIDS-defining malignancy.[53,54] AIDS-defining malignancies were reported in Zimbabwe, Zambia, Uganda, Rwanda, and South Africa.[55]

Schistosomiasis is endemic in Sudan, Schistosoma. haematobium was associated with bladder cancer.56 Recently a case of sigmoid colonic adenocarcinoma coexisting with schistosomiasis was reported.[57] Schistosoma mansoni ova were seen in the tumor tissue.[57] An astomotic esophageal leak due to Taenia saginata following esophagectomy for esophageal cancer in a 50-year-old female with squamous cell carcinoma at the lower third site was reported.[58]

Genetic factors

Genetic and environmental interactions play a role in the incidence of EC progression.[59] Host genetics contribute up to one-third of the risk for sporadic Barretts esophagus and esophageal adenocarcinoma development, and 7% of Barretts esophagus and esophageal adenocarcinoma cases are familial.[60] In the USA, the incidence rate was greatest for each stratification in males, blacks, distant disease, and adenocarcinoma.[61] Familial aggregation of esophageal carcinoma in northern regions of China was reported.[62] Ethnic and genetic factors are stand towards an increase the cancer cases in Sudan and Africa region.[36,63] There was an association between family history and EC.[14] Guhaina was the most prevalent tribal origin for cancer in Sudan 42.2%, followed by Jaali 23.9%, Beja 11.2% and Darfurian 5.6%.[11]

Tylosis, an autosomal dominant disease, was related to esophageal squamous carcinoma.[53] Somatic mutations in TP 53 and other tumor suppressor genes were reported in esophageal squamous cell carcinomas.[63] There is a mutational profile of EC that closely resembles those of squamous cell carcinomas.[64]

The p53 arg/pro polymorphism has a different pattern of frequency in various types of cancer in Sudanese patients, indicating different etiology and biology of these tumors.[65] Overexpression of TP53 protein and mutation in exon 4 and 8 were associated with EC in Sudanese patients.[63]

Genome-wide association studies (GWAS) identified loci linked to esophageal embryonic development (FOXF1, BARX1), host immune response (MHC locus 16.24), and cellular proliferation and transformation (CRTC1 (19p13)).[66] Epigenetic was associated with the development of esophageal adenocarcinoma.[67] Identification of susceptible genes and biomarkers will predict the treatment response of patients and improve their survival rates. [68]

Environmental factors

There is evidence of the association between environmental and occupational exposures and specific cancer types.[69] In Sudan it is difficult to assess the possible role of air pollution in the disease. Air pollution in rural areas is low to moderate, and in the urbanized areas is moderate to high.[6] In general, air pollution was derived from industries, oil-producing facilities, and traffic. Whereas, in Sudan and other African countries, fires lit for cooking within poorly ventilated mud huts and the habit of burning trash were main factors.6 Active pesticide ingredients used to control mosquito, pests of cotton, and other rotation crops were risks for cancer.[6]

Common hazardous substances in the workplace include acids, caustic substances, disinfectants, heavy metals, including mercury, lead, cadmium and aluminum, paint, pesticides, petroleum products and solvents. Health effects depend on the type of hazardous substance and the level of exposure (concentration and duration). Occupational exposures such as polycyclic aromatic hydrocarbons, silica, and mixed dusts have been consistently shown to increase risk of esophageal cancer, while the risk has decreased among education employees and technical workers.[70] In contrast, specific airborne occupational exposures do not seem to be of major importance in the aetiology of EC.[71]

Diagnosis of Esophageal cancer

Delay in the diagnosis of EC caused a potentially life-threatening condition and increased mortality. The poor diagnosis of EC highlights the need to improve detection and prediction methods. A challenge facing proper diagnosis is

the lack or availability of reagents of poor quality, which effect diagnosis and later improper treatment of cancer.[13] Very few specialist doctors are working on EC and they are only in Khartoum, the Capital of Sudan, so those in other cities are facing poor diagnosis problems. The local training for clinical oncologists is started in the late 1990s, provided trained staff committed to work in the country.[13] EC is often diagnosed in its advanced stages due to the lack of early clinical symptoms.[68] Patients with the same clinical features and treatments may have different clinical outcomes, indicating that genetic variants may effect EC prognosis.[34] Squamous cell carcinoma of the esophagus presents as asymptomatic, lead to late diagnosis with a poor prognosis.[62]

Management of esophageal cancer

EC is a fatal malignant worldwide, increased dramatically in the Western world.[68] Despite improvements in the management and treatment of EC patients, the general outcome remains very poor for over 5-year survival rates 10% and 5-year post-esophagectomy survival rates 15-40%.[68] Primary prevention of EC includes tobacco avoidance and alcohol intake, maintenance of a healthy weight, increasing fresh fruit and vegetable intake, and reduction in red meat consumption.[1]

Management of EC depends on patient fitness and tumor stage. Early tumors may be suitable for endoscopic removal, and locally advanced cancers are treated with chemotherapy, chemo-radiotherapy, surgical resection, or combinations of these.[1] Patients with EC that are not suitable for operative management are treated with systemic chemotherapy.[1] In Sudan, patients often have advanced disease at presentation, they are dehydrated and malnourished, making rehydration and feeding an emergency initial step in the management.[8]

Treatment of esophageal cancer

The crucial point of EC management is the time from the initiation of symptoms to admission to primary health care centers or hospitals. In Sudan, Radiation and Isotope Center in Khartoum, established in 1959, and National Cancer Institute, established in 1999, were provide chemotherapy and radiation treatment for cancer patients.[11] The early detection of cancer requires early diagnosis for symptomatic patients and screening of asymptomatic patients at risk.[7] A significant challenge to the treatment of cancer is that most patients present with advanced-stage disease. In Sudan, 78% of patients seek first medical treatment at stage III or IV of disease. In these stages, treatment involves multiple modalities, including surgery, radiotherapy, chemotherapy, and hormone therapy.[15] Patients with advanced or metastatic EC are treated with cytotoxic chemotherapy; those who are HER2 positive may also benefit from trastuzumab treatment.[1] Immuno-oncology therapies have promising early results in squamous cell carcinoma and adenocarcinoma.[1] Neo-adjuvant concurrent chemo-radiotherapy has been increasingly administered to treat EC.[72]

Clinic-based cohort studies have shown a significant association between treatment with proton-pump inhibitors and a decreased risk of high-grade dysplasia and adenocarcinoma in patients with Barrett's esophagus.[24] Cervical esophageal squamous cell cancers are treated with chemotherapy and radiation therapy. Mid and lower esophagus and gastric cardia were treated with induction therapy and esophageal resection.[3] Endoscopic therapies, including radiofrequency ablation, endoscopic mucosal resection, and endoscopic sub-mucosal dissection, have become the standard treatment modality for Barrett's esophagus and early carcinoma.[3] Observational studies with a large number of patients showed that the use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and statins in patients with Barrett's esophagus, reduced the progression to adenocarcinoma.[79] Minimally invasive esophagectomy by thoracotomy is gaining acceptance due to advantages in short-term outcomes.[73]

Radiation therapy in Sudan was started in Khartoum Teaching Hospital in 1959, with a superficial x-ray machine and deep x-ray machine. In 1967, the work was started in a new oncology hospital in Khartoum. Brachytherapy using radium-226 was first used in the same hospital. Later in the 1990s, the old name of the hospital was changed to Radiation and Isotopes Center of Khartoum (RICK). In 1999 radiation therapy was started in the Institute of Nuclear Medicine and Molecular Biology, the University of Gazira in Madani. Since then, radiation therapy Divisions have been established in the College of Medical Radiologic Sciences, Sudan University of Science and Technology, and cancer centers all over Sudan.[69]

CONCLUSIONS

As a result of increasing EC cases in Sudan, there is an urgent need for early detection programs for patients to attend the cancer center for treatment and make the EC treatment more effective, less costly and invasive, and conduct rapid confirmed and appropriate therapy for patient diagnoses with EC. Furthermore, understanding the etiology of EC using molecular techniques may assist in the management and identifying complicated and critical issues and improve therapy towards a new treatment strategy. Understand a significant impact of changes in community dietary behaviors, eco-environmental effects, ethnic, dietary, and cultural, and other factors associated with increased EC incidence.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Smyth EC, Lagergren J, Fitzgerald RC, Lordick F, Shah MA, Lagergren P, et al. Oesophageal Cancer. Nat Rev Dis Primers 2018; 3: 17048.
2. Hamad AM, Ahmed ME, Abdelgadir A, Suliman IB. Esophageal Cancer in Sudan: Demographic and Histopathlogical Variations. Open J Gastroenterol 2017; 7(3): 124-9.
3. Abbas G, Krasna M. Overview of esophageal cancer. Ann Cardiothorac Surg 2017; 6(2): 131-6.
4. Mao WM, Zheng WH, Ling ZQ. Epidemiologic risk factors for esophageal cancer development. Asian Pac J Cancer Prev 2011; 12: 2461-6.
5. Musa IH, Musa TH, Ahmed ME, Musa HH. Narrative review article on epidemiology, diagnosis, treatment: a bibliometric analysis of the global scientific research progress on esophageal cancer. Dig Med Res 2020. http://dx.doi.org/10.21037/dmr-20-121

6. Awadelkarim KD, Mariani-Costantini R, Elwali NE. Cancer in the Sudan: an overview of the current status of knowledge on tumor patterns and risk factors. Sci Total Environ 2012; 15: 423: 214-28.
7. Ahmed ME, Mahadi SI, Ali BM. The surgical treatment of esophageal cancer in Sudan: A 100 consecutive cases. Inter J Surg 2016; 29: 101-7.
8. Saeed IE, Weng HY, Mohamed KH, Mohammed SI. Cancer incidence in Khartoum, Sudan: first results from the Cancer Registry, 2009-2010. Cancer Med 2014; 3(4): 1075-84.
9. Abdelgadir MA, Mahadi SI, Nasr AO, Ahmed ME. Role of jejunostomy feeding catheter as a model for nutritional support. Inter J Surg 2010; 8: 439-43.
10. Doumi EA, Ahmed MA, Hamad AM. Pattern and incidence of cancer at El Obeid Hospital, Western Sudan. Sudan JMS 2009; 4 (1): 43-6.
11. Gasmelseed N, Abudris D, Elhaj A, Eltayeb EA, Elmadani A, Elhassan MM, et al. Patterns of Esophageal Cancer in the National Cancer Institute at the University of Gezira, in Gezira State, Sudan, in 1999-2012. Asian Pac J Cancer Prev, 2015; 16(15): 6481-90.
12. Saeed IE, Elmustafa AD, Mohamed KE, Mohammed SI. Cancer registry in Sudan: a brief overview. The Internet J Epid 2013; 11(2).
13. Gafer N, Walker E, Khair Allah M, Elbaghir A. Chapter 13 Cancer Care in Sudan: Current Situation and Challenges. in M. Silbermann (ed.), Cancer Care in Countries and Societies in Transition, 2016.
14. Alamin NAM, Elsharief UA, Babiker RA, Abubaker YF, Hamid Y, Karoum AO, et al. Risk Factors for Esophageal Cancer in Gadarif State in Eastern Sudan. Int J Curr Res Med Sci 2019; 5(9): 20-31.
15. Ali AA, Ibrahim FE. Incidence and geographical distribution of cancer in Radiation and Isotopes Center in Khartoum. Sudan Med Monit 2014; 9(3): 109-11.
16. Kachala R. Systematic review: epidemiology of Oesophageal Cancer in Sub-Saharan Africa. Malawi Med J 2010; 22(3): 65-70.
17. Moawia EM, Daffala OA, Elgaili ME, Nagla G. Predominance of Females with Oesophageal Cancer in Gezira, Central Sudan. Arab J Gastroenterol 2012; 13: 174-7.
18. Elhadi AA, Mirghani HO, Ibrahim Y, Albalawi IA. Pattern of Esophageal Cancer in Sudan. Ameri J Clin Exper Med 2016; 4(6): 166-9
19. Mohammed ME, Abuidris DO, Elgaili EM, Gasmelseed N. Predominance of females with oesophageal cancer in Gezira, Central Sudan. Arab J Gastroenterol 2012; 13: 174-7.
20. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65:87-108.
21. Jemal A, Bray F, Forman D, O'Brien M, Ferlay J, Center M, Parkin DM. Cancer Burden in Africa and Opportunities for Prevention. Cancer 2012;118(18): 4372-84.
22. Rustgi AK, El-Serag HB. Esophageal carcinoma. N Engl J Med 2014; 371: 2499-509.
23. Simard EP, Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. CA Cancer J Clin 2012; 62: 118-28.
24. Mahmoud K, Musaad A, Alawad AA. Pattern of Primary Gastrointestinal Tract Cancer in a Tertiary Central Hospital in Sudan: A Prospective Study. Medicine 2014; (4): 34-7.
25. McHembe MD, Rambau PF, Chalya PL, Jaka H, Koy M, Mahalu W. Endoscopic and clinicopathological patterns of esophageal cancer in Tanzania: experiences from two tertiary health institutions. World J Surg Oncol 2013; 11: 257.
26. Dawsey SP, Tonui S, Parker RK, Fitzwater JW, Dawsey SM, White RE, et al. Esophageal cancer in young people: a case series of 109 cases and review of the literature. PLoS One 2010; 5: 14080.
27. Tettey M, Edwin F, Aniteye E, Sereboe L, Tamatey M, Ofosu-Appiah E. et al. The changing epidemiology of esophageal cancer in sub-Saharan Africa the case of Ghana. Pan Afr Med J 2012; 13: 6.
28. Khushalani N. Cancer of the esophagus and stomach. Mayo Clin Poc 2008; 83: 712-722.
29. Chandanos E, Lagergren J. The mystery of male dominance in oesophageal cancer and the potential protective role of oestrogen. Eur J Cancer 2009; 45: 3149-55.
30. Crane SJ, Locke GR, Harmsen WS, Zinsmeister AR, Romero Y, Talley NJ. Survival Trends in Patients with Gastric and Esophageal Adenocarcinomas: A Population-Based Study. Mayo Clin Proc 2008; 83: 1087-94.
31. Sardana RK, Chhikara N, Tanwar B, Panghal A. Dietary impact on esophageal cancer in humans: a review. Food Funct 2018; 9(4): 1967-77.
32. Steenhagen E. Preoperative nutritional optimization of esophageal cancer patients. J Thorac Dis 2019; 11(Suppl 5): 645-53.
33. Kamangar F, Chow WH, Abnet CC, Dawsey SM. Environmental causes of esophageal cancer. Gastroenterol Clin North Am. 2009; 38: 27-57.
34. Toh Y, Oki E, Ohgaki K, Sakamoto Y, Ito S, Egashira A, et al. Alcohol drinking, cigarette smoking, and the development of squamous cell carcinoma of the esophagus: molecular mechanisms of carcinogenesis. Int J Clin Oncol 2010; 15: 135-44.
35. Blot WJ, McLaughlin JK, Fraumeni JF. Esophageal cancer. In: Schottenfeld D, Fraumeni JF, editors. Cancer Epidemiology and Prevention. New York: Oxford University Press; 2006: 697-706.
36. Hamidi Y, Abdeljaoued-Tej I, Zatchi AA, Abdelhak S, Boubaker S, Brown JS, Benkahla A. Cancer in Africa: The Untold Story. Front Oncol 2021; 11: 650117.
37. Corley DA, Kubo A, Levin TR, Block G, Habel L, Rumore G, et al. Helicobacter pylori and gastroesophageal reflux disease: a case-control study. Helicobacter 2008; 13(5): 352-60.
38. Domper Arnal M J, Arenas AF, Arbeloa AL. Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol 2015; 21(26): 7933-43.
39. Sadjadi A, Marjani H, Semnani S, Nasseri-Moghaddam S. Esophageal Cancer in Iran: A Review. Middle East J Cancer 2010; 1(1): 5-14.
40. Rubenstein JH, Taylor JB. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Aliment Pharmacol Ther 2010; 32: 1222-27.
41. Ali AE, Hyder OMi, Yassin I, Ibrahim AA. Pattern of Esophageal Cancer in Sudan. Amer J Clin Exper Med 2016;4 (6): 166-9.
42. Javadi SAI, Shafikhani AA. Anxiety and depression in patients with gastroesophageal reflux disorder. Electronic Physician 2017; 9(8): 5107-12.
43. Choi JM, Yang JI, Kang SJ, Han YM, Lee J, Lee C, et al. Association between anxiety and depression and gastroesophageal reflux disease: Results from a large cross-sectional study. J Neurogast Motility 2018; 24(4): 593-602.
44. McColl KE, Watabe H, Derakhshan MH. Role of gastric atrophy in mediating negative association between Helicobacter pylori infection and re ux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma. Gut 2008; 57: 721-3.
45. Xie FJ, Zhang YP, Zheng QQ, Jin HC, Wang FL, Chen M, et al. Helicobacter pylori infection and esophageal cancer risk: an updated meta-analysis. World J Gastroenterol 2013; 19: 6098-107.
46. Jie W, Qinghong X, Zhitao C. Association of Helicobacter pylori infection with gastroesophageal reflux disease. J Inter Med Res 2019; 47(2): 748-53.
47. Hong SJ, Kim SW. Helicobacter pylori Infection in Gastroesophageal Reflux Disease in the Asian Countries. Gastroenterol Res Pract 2015; 2015: 985249.
48. Beely MAB, Abdelaziz MS, Elemam IBY, Zulfa AA, Ahmed HG. Identification of Human papilloma virus esophageal cancer in Sudan. EJBPS 2016; 3(9): 139-42.
49. Zhang SK, Guo LW, Chen Q, Zhang M, Liu SZ, Quan PL, et al. The association between human papillomavirus 16 and esophageal cancer in Chinese population: a meta-analysis. BMC Cancer 2015; 15:1096.

50. Asombang AW, Chishinga N, Nkhoma A, Chipaila J, Nsokolo B, Manda-Mapalo M, et al. Systematic review and meta-analysis of esophageal cancer in Africa: Epidemiology, risk factors, management and outcomes. World J Gastroenterol 2019; 24: 4512-33.
51. Chene A, Donati D, Guerreiro-Cacais AO, Levitsky V, Chen Q, Falk KI, et al. A molecular link between malaria and Epstein-Barr virus reactivation. PLoS Pathog 2007; 3: e80.
52. Beely MABI, Ahmed HG, Aziz MSAE, Eldour AAA, ALmutlaq BA, et al. Molecular detection of Epstein Barr Virus (EBV) among Sudanese patients with esophageal cancer. J Cancer Prev Curr Res 2017; 7(1): 00219.
53. Strickler HD. Does HIV/AIDS have a biological impact on the risk of human papillomavirus-related cancers. J Natl Cancer Inst 2009;101: 1103-5.
54. Chaturvedi AK, Kleinerman RA, Hildesheim A, Gilbert ES, Storm H, Lynch CF, et al. Second cancers after squamous cell carcinoma and adenocarcinoma of the cervix. J Clin Oncol 2009; 27: 967-73.
55. Ahmed A, Muktar HM, Bugaje MA. Epidemiological and clinical features of AIDS-Associated Kaposi's sarcoma in Northern Nigeria. Arch Inter Surg 2013; 3:29-34.
56. Sitas F, Parkin DM, Chirenje M, Stein L, Abratt R, Wabinga H. Part II: cancer in indigenous Africans causes and control. Lancet Oncol 2008; 9: 786-95.
57. Salim OEH, Hamid HK, Mekki SO, Suleiman SH, Ibrahim SZ. Colorectal carcinoma associated with schistosomiasis: a possible causal relationship. World J Surg Oncol 2010; 8: 68.
58. Baleela RM, Huessain MY, Ahmed ME. Anastomotic esophageal leak due to Taenia saginata following esophagectomy for esophageal cancer. Saudi Med J 2006; 27: 241-3.
59. Qu Y, Zhang S, Cui L, Wang K, Song C, Wang P, et al. Two novel polymorphisms in PLCE1 are associated with the susceptibility to esophageal squamous cell carcinoma in Chinese population. Dis Esophagus. 2017; 30: 1-7.
60. Vaughan TL, Fitzgerald RC. Precision prevention of oesophageal adenocarcinoma. Nat Rev Gastroenterol Hepatol. 2015; 12: 243-8.
61. Patel N, Benipal B. Incidence of Esophageal Cancer in the United States from 2001- 2015: A United States Cancer Statistics Analysis of 50 States. Cureus 2018; 10(12): e3709.
62. Wheeler JB, Reed CE. Epidemiology of esophageal cancer. Surg Clin North Am 2012; 92: 1077-87.
63. Eltaher SM, Idris AB, Mahmoud AH, Yousif MY, Mohamed NS, Hamid MM, et al. Genetic analysis of TP53 gene mutations in exon 4 and exon 8 among esophageal cancer patients in Sudan. BioRxiv 2019: 572214.
64. Gao YB, Chen ZL, Li JG, Hu XD, Shi XJ, Sun ZM, et al. Genetic landscape of esophageal squamous cell carcinoma. Nat Genet 2014; 46(10): 1097-102.
65. Eltahir HA, Adam AAM, Yahia ZA, Ali NF, Mursi DM, Higazi AM, et al. p53 Codon 72 arginine/proline polymorphism and cancer in Sudan. Mol Biol Rep 2012; 39: 10833-6.
66. Su Z, Gay LJ, Strange A, Palles C, Band G, Whiteman DC. et al. Common variants at the MHC locus and at chromosome 16q24.1 predispose to Barrett's esophagus. Nat Genet 2012; 44: 1131-6.
67. Xu E, Gu J, Hawk ET, Wang KK, Lai M, Huang M, et al. Genome-wide methylation analysis shows similar patterns in Barrett's esophagus and esophageal adenocarcinoma. Carcinogenesis. 2013; 34: 2750-6.
68. Huang F, Yu S. Esophageal cancer: Risk factors, genetic association, and treatment. Asian J Surg 2018; 41: 210-5.
69. Abdullah YM, Khalifa AA. Estimating Environmental and Occupational Factors that Contribute to Cancer in Sudan. Inter J Health Rehab Sci 2015; 4(2): 115-21.
70. Wernli KJ, Fitzgibbons ED, Ray RM, Gao DL, Li W, Seixas NS, et al. Occupational Risk Factors for Esophageal and Stomach Cancers among Female Textile Workers in Shanghai, China. Am J Epidemiol 2006; 163: 717-25.
71. Jansson C, Plato N, Johansson ALV, Nyren O, Lagergren J. Airborne occupational exposures and risk of oesophageal and cardia adenocarcinoma. Occup Environ Med 2006; 63: 107-12.
72. Merkow RP, Bilimoria KY, McCarter MD, Chow WB, Ko CY, Bentrem DJ. Use of multimodality neoadjuvant therapy for esophageal cancer in the United States: assessment of 987 hospitals. Ann Surg Oncol. 2012; 19: 357-64.
73. Sohda M and Kuwano H. Current Status and Future Prospects for Esophageal Cancer Treatment. Ann Thorac Cardiovasc Surg 2017; 23(1): 1-11.

SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Trends in antimicrobial resistance in Malaysia

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ABSTRACT

Introduction: Antibiotic resistance is a burgeoning problem worldwide. The trend of bacterial resistance has increased over the past decade in which more common bacteria are becoming resistant to almost all the antibiotics currently in use, posing a threat to humans and even livestock.

Methods: The databases used to search for the relevant articles for this review include PubMed, Science Direct, and Scopus. The following keywords were used in the search: Antimicrobial resistance, Malaysian action plan, antibiotic-resistant bacteria, and Malaysian National Surveillance on Antimicrobial Resistance (NSAR). The relevant articles published in English were considered.

Results: The antibiotic-resistant bacteria highlighted in this review showed an increase in resistance patterns to the majority of the antibiotics tested. The Malaysian government has come up with an action plan to create public awareness and to educate them regarding the health implications of antibiotic resistance.

Conclusion: Antimicrobial resistance in Malaysia continues to escalate and is attributed to the overuse and misuse of antibiotics in various fields. As this crisis impacts the health of both humans and animals, therefore a joined continuous effort from all sectors is warranted to reduce the spread and minimize its development.

KEYWORDS:
Antimicrobial resistance, Malaysian action plan, antibiotic-resistant bacteria

INTRODUCTION

Antimicrobial resistance arises as microorganisms survive and reproduce when exposed to antimicrobial drugs. Back in 1907, Paul Ehrlich, the father of modern chemotherapy observed that the organism in trypanosome infections sometimes appears to be resistant to the agent used. Due to specific resistance, he observed that fuchsin dye-resistant strain was still susceptible to an arsenic compound, while a strain resistant to the arsenic compound retained sensitivity to the dye. Later in 1908, he proposed that the resistance can be steadily inherited once it is acquired.[1]

This review provides a general overview of the antimicrobial resistance trends of selected clinical isolates in Malaysia which were obtained from various studies, as well as the Malaysian National Surveillance on Antimicrobial Resistance (NSAR) annual reports.

Antibiotic Resistance Trends

The emergence of antibiotic-resistant microorganisms is a serious public health problem.[2] Developed countries have shifted their drugs towards more expensive one due to the lack of potency of the drugs towards common pathogens. Meanwhile, the developing and least developed countries opt for alternative drugs due to financial constraints which has led to the increased morbidity and mortality.[3]

The World Health Organization (WHO) has come up with a surveillance system called the Global Antimicrobial Surveillance System or GLASS. An early release of the data has shown that there was high antibiotic resistance incidence in both high-income and low-income countries with the occurrence of up to 500,000 cases across 22 countries.[4]

A report by World Bank in 2016 on antimicrobial resistance had predicted that financial burden will mostly be felt by low-income and middle-income countries.[5] The antimicrobial resistance rate has increased by two folds in the last 20 years and has killed approximately 700,000 people per year globally. The number is estimated to escalate to 10 million deaths annually by 2050 whereas the financial burden could cost up to US$100 trillion (RM416.65 trillion).[6] This situation highlights the urgency of an action plan to combat the issue comprehensively.

Prevalence of Antibiotic-Resistant Bacteria in Malaysia

Escherichia coli

The urinary tract infections caused by *Escherichia coli (E. coli)* is the most common bacterial infection in patients worldwide[7] and its occurrence is estimated to be up to 88.0%.[8] Malaysia is one of the countries with higher *E. coli* resistance towards aminopenicillin.[9] Data from various public hospitals in Malaysia revealed that the majority of the tested *E. coli* isolates showed the highest resistance rate to penicillins ranging from 68-100% (Table I). This resistance pattern remains for years and in fact, some of the isolates were also resistant to two or more antibiotics (multidrug-resistant).[10] Data also showed that from the year 2004 to 2018, the resistance of *E. coli* to carbapenems remains low within the range of 0-5%, with a steady increment reported over the years.[11-16]

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Additionally, an imipenem-resistant *E. coli* was reported between 2006 and 2009 and were among the first resistant isolates reported in the country.[12] Resistance rates of more than 85% for ciprofloxacin and cefuroxime were also reported between 2017 and 2018.[15] The data presented showed that *E. coli* is resistant to antibiotic groups that have been widely used for the longest time, although some fluctuations were observed which is due to the number of isolates tested in the individual hospitals. Many studies have suggested that the intrinsic resistance and the expression of numerous efflux pumps could be the major contributors to the resistance patterns observed in this organism.

Acinetobacter baumannii

Acinetobacter baumannii (A. baumannii) is an opportunistic pathogen that can easily acquire resistance elements such as plasmids and conjugative transposons.[17] The broad-spectrum carbapenems are the antibiotic of choice for complications associated with *A. baumannii* although the resistance rate has been increasing in the last two decades.

A report by University Malaya Medical Centre (UMMC) between 1996 and 1998 showed a 100% carbapenems-resistant *Acinetobacter baumannii* (CRAB) resistance towards amoxicillin-clavulanate, ampicillin, cefoperazone, and cefuroxime. Additionally, more than 90% resistance was observed for cephalosporins, gentamicin, and ciprofloxacin.[18] Over the years, the resistance rates for penicillins showed a decrement up to 50%.[13,16,19-23]

The resistance rates for cephalosporins do not show substantial change, although in 2018 for the first time in several years, the resistance rate plummeted to 37.9% (Table II). Conversely, the resistance rates to carbapenems and aminoglycosides fluctuated with the highest rates reported between 2017 and 2018. The data also showed an increasing trend of resistance to fluoroquinolones with an average of 93% in the last two years.[16,23]

Klebsiella pneumoniae

Klebsiella sp. are a reservoir for antibiotic-resistant genes and can transfer the gene to other Gram-negative bacteria. Studies on *Klebsiella pneumoniae (K. pneumoniae)* infections and antibiotic resistance in Malaysia are scanty. Between 2010 and 2012, the majority of the *K. pneumoniae* isolates tested were resistant to second and third generations cephalosporins (97-100%).[24,25] As shown in Table III, the ampicillin, amoxicillin-clavulanate acid and aztreonam resistances were high among *K. pneumoniae* species with an average of 94-100%.[25] The trends plunged drastically in 2013 and 2017 [13] with the lowest resistance rates recorded that is possibly due to the significant number of isolates tested as compared to the earlier years. The resistance rate to gentamicin was recorded between 2010 and 2017, with the lowest resistance rate recorded in 2017 (8.5%).[13] Data also revealed a steady increase in the resistance pattern to carbapenems.[13]

Staphylococcus aureus

Staphylococcus aureus (S. aureus) possesses the ability to develop a resistance mechanism to various antibiotics [26] and its resistance towards β-lactams is due to the presence of the mecA gene.[27] One of the earliest reports from Hospital Kuala Lumpur (HKL) recorded all 539 MRSA isolates were resistant to penicillin.[28] The resistance rates remained constant until 2018 with 100% isolates were resistant (Table IV). Likewise, the resistance rates to gentamicin persisted over the years with the highest rates reported between 1990-1991 and 2002-2007.[28,29] Resistance to erythromycin showed a steady declined over the years, while the isolates showed an increase in resistance patterns to clindamycin, from 0% in 2006-2007 to an average of 83% in 2011-2013.[30-32] Until 2018, none of the *S. aureus* isolates is resistant to linezolid or vancomycin.[28-33]

Enterococcus sp.

Enterococcus sp. are part of the normal flora and are natural inhabitants of nature. They are also opportunistic pathogens that can pose serious threats to human life. Treatment for enterococci infections is challenging as they are intrinsically resistant to multidrug and can develop resistance to other classes of antibiotics. From the year 2007 to 2008, *Enterococcus faecium (E. faecium)* isolates showed complete resistance to vancomycin, ampicillin, and teicoplanin.[34] Although ampicillin-resistant *Enterocccus faecalis (E. faecalis)* was also reported, the rates were much lesser than the ones reported in *E. faecium*.[13,35-36]

Despite that 100% vancomycin-resistant *E. faecium* was reported between 2007-2008, the rates fall to 14.1% in 2018. Unlike *E. faecium*, the number of vancomycin-resistant *E. faecalis* isolates were very less, with the highest rate of 6% reported over the years.[13,35-36] The resistance rates for gentamicin and linezolid were reasonably constant over the years for both *E. faecium* and *E. faecalis* isolates.[13,16,34-36] Conversely, the resistance rates of erythromycin and tetracycline among the enterococci isolates were high with an average of 98% (Table V).[36]

The Contributing Factors

According to WHO, misuse and overuse of antimicrobial agents are the main causes of antibiotic resistance.[4] As of 2016, the National Medical Care Survey (NMCS) has gathered data of 27,587 patients from 545 healthcare clinics and 5810 (21.1%) patients that received antibiotic prescriptions through which 197 (3.4%) of them were prescribed with more than one antibiotic.[37]

Another observation revealed that the rate of antibiotic prescriptions in private clinics (30.8%) is higher than in public or government clinics (6.8%). Almost half of the prescribed antibiotics are for acute upper respiratory tract infections (URTI) followed by other diagnoses such as fever and gastroenteritis.

Consumption of foods contaminated with pathogenic *E. coli* may lead to bacterial infections and many studies on *E. coli* are concerned with beef samples. A study isolated 55 *E. coli* strains from ducks in Penang and showed that they are completely resistant to vancomycin and more than 60% are resistant to tetracycline, ampicillin, and streptomycin.[38] Another study reported that out of 40 beef samples taken from two local abattoirs in Selangor contains Enterobacteriaceae (82.5%) and *E. coli* (55%).[39] Although a total of 97 antibiotics have been approved in Malaysia and

Table I: The Prevalence of Antibiotic-Resistant *Escherichia coli* in Malaysia

Year	Type of Antibiotics												Source*
	Ampicillin %	Piperacillin %	Amoxicillin %	Cefuroxime %	Ceftazidime %	Cefepime %	Imipenem %	Meropenem %	Amikacin %	Gentamicin %	Ciprofloxacin %	Trimethoprim-sulfamethoxazole %	
2004	77 (47)	64 (47)	17 (47)			6 (47)	0 (47)		2 (47)	21 (47)	33 (47)		10
2006-2008		48.9 (45)					0 (45)		11.1 (45)	56 (45)	71.1 (45)	97.8 (45)	11
2006-2009	71.7 (1642)			5.6 (1642)	5.6 (1642)		4.9 (1642)		3.8 (1642)	8.4 (1642)	9.7 (1642)		12
2013	68.9 (28720)			22.6 (12974)			0.3 (28696)	0.3 (27759)	0.8 (11924)		23.4 (29400)		13
2014	69.8 (149)						0 (149)	0 (149)	0 (149)				14
2016							0.8 (29312)	0.9 (28602)	1.5 (28139)				13
2017-2018	100 (100)			95 (100)							86 (100)		15
2018				24.5 (31817)				0.7 (30153)			23.0 (31150)		16

*The source of isolates is listed in the respective references.
**No. of isolate tested is represented in the bracket.

Table II: The Prevalence of Antibiotic-Resistant *Acinetobacter baumannii* in Malaysia

Year	Type of antibiotics														Source*
	Amoxicillin-Clavulanate %	Ampicillin %	Piperacillin %	Cefoperazone %	Cefuroxime %	Ceftazidime %	Ceftriaxone %	Cefotaxime %	Imipenem %	Ciprofloxacin%	Amikacin %	Gentamicin %	Netilmicin %	Colistin %	
1996-1998	100 (88)	100 (88)		100 (88)	100 (88)	97.7 (88)	97.7 (88)	97.7 (88)	36.4 (88)	90.9 (88)		95.5 (88)			18
2008-2009		92 (100)	60 (100)			59 (100)			55 (100)			48 (100)		0 (100)	20
2009	63 (111)	90 (111)	68 (111)	95 (111)	79 (111)			87 (111)		22 (111)			21 (111)		21
2010-2011						78.4 (162)			79 (162)	79.6 (162)					22
2017		57.1 (7627)		46.8 (5655)		58 (8183)			61.7 (7795)		49.8 (8155)	53.2 (7860)			13
2017-2018						99.06 (102)			100 (102)	95.6 (102)	63.73 (102)	81.11 (102)			23
2018		56.0 (7272)				37.9 (7377)			41.3 (7261)	90.9 (88)	31.5 (7348)	31.5 (7202)			16

*The source of isolates is listed in the respective references.
**No. of isolate tested is represented in the bracket.

Table III: The Prevalence of Antibiotic-Resistant *Klebsiella pneumoniae* in Malaysia

Year	Type of antibiotics											Source*
	Ampicillin %	Amoxicillin + clavulanic acid %	Aztreonam %	Cefepime %	Ceftriaxone %	Cefuroxime %	Cefoperazone %	Cefotaxime %	Ceftazidime %	Imipenem %	Gentamicin %	
2010-2012		86.7 (321)									61.5 (321)	24
2010-2012	100 (93)	94.6 (93)	98.9 (93)		100 (93)	100 (93)	100 (93)	100 (93)	97.8 (93)	1.1 (93)	74 (93)	25
2013		18.3 (25916)		15.5 (19158)		25.9 (26127)		27 (21453)	24.2 (24691)	1.5 (24477)		13
2017		20.1 (30470)		16.4 (29798)		25.1 (31104)		22.2 (30840)		1.7 (31143)	8.5 (30801)	13

*The source of isolates is listed in the respective references.
**No. of isolate tested is represented in the bracket.

Table IV: The Prevalence of Antibiotic-Resistant *Staphylococcus aureus* in Malaysia

Year	Type of antibiotics												Source*
	Penicillin %	Oxacillin %	Ampicillin %	Cefoxitin %	Amikacin %	Gentamicin %	Erythromycin %	Ciprofloxacin %	Co-Trimoxazole %	Clindamycin %	Linezolid %	Vancomycin %	
1990-1991	100 (539)					92 (539)	98 (539)		94 (539)			0 (539)	28
2002-2007	100 (1979)					92 (1979)	98 (1979)		94 (1979)			0 (1979)	29
2006-2007	100 (32)	100 (32)	100 (32)	100 (32)	78.1 (32)	78.1 (32)				0 (32)	0 (32)	0 (32)	30
2011-2012	100 (175)	100 (175)				88 (175)	93.7 (175)			88 (175)	0 (175)	0 (175)	31
2013	100 (66)	87.9 (66)				59.1 (66)	87.9 (66)	83.3 (66)		78.8 (66)		0 (66)	32
2018	100 (36)	100 (36)				88.8 (36)	33.3 (36)					0 (36)	33

*The source of isolates is listed in the respective references.
**No. of isolate tested is represented in the bracket.

Table V: The Prevalence of Antibiotic-Resistant Enterococci in Malaysia

Year	Type of antibiotics								Source*
	Ampicillin %	Vancomycin %	Teicoplanin %	Gentamicin %	Linezolid %	Tazobactam-piperacillin %	Erythromycin %	Tetracycline %	
					Enterococcus faecium				
2007-2008	100 (3)	100 (3)	100 (3)	50 (3)	0 (3)				34
2009-2010	92.9 (28)	0 (28)	0 (28)	82.1 (28)		96.4 (28)			35
2013	84 (25)			84 (25)	0 (25)		100 (25)	100 (25)	36
2013	83.3 (653)	8.4 (667)		43 (393)	1.1 (540)				13
2017	87.5 (1050)	15.6 (1033)		42.7 (655)	1.5 (876)				13
2018	89.8 (996)	14.1 (1037)		43.5 (614)	1.0 (878)				16
					Enterococcus faecalis				
2009-2010	3.2 (31)	0 (31)	0 (31)	38.7 (31)		3.2 (31)			35
2009-2010	24 (50)	6 (50)		48 (50)	0 (50)		96 (50)	98 (50)	36
2013	5.5 (1356)	1.4 (1359)		19.4 (806)	4.7 (1029)				13
2017	6 (2374)	1.3 (2313)		23.7 (1513)	2.2 (1905)				13

*The source of isolates is listed in the respective references.
**No. of isolate tested is represented in the bracket.

registered with the Ministry of Health for food and animal practice, the majority of these antibiotics are not advisable for veterinary purposes by WHO. It was suggested that the growth of promoter agents that are not used for human therapeutic reasons should be used in livestock farming instead of antibiotics used in human therapy.

Malaysian Action Plan on Antimicrobial Resistance

The Malaysian government has revised several strategies to curb the spread of fatal diseases and minimize the threat of antimicrobial resistance. The action plan on antimicrobial resistance (MyAP-AMR) is structured based on four key areas: (1) public awareness and education, (2) surveillance and research, (3) infection prevention and control, and (4) appropriate use of antimicrobials.

Significant measures have been developed to slow down the emergence of antimicrobial resistance and to avert its spread. This includes increasing public awareness and understanding regarding antimicrobial resistance, particularly among healthcare workers, those under nursing care, in food and livestock production, and aquaculture. It is important to comprehend the emergence of antimicrobial resistance through surveillance, monitoring and research thus, providing information on antimicrobial issues and the proposed risk of antimicrobial resistance. The government is also focused on infection prevention and control through enforcement of appropriate antimicrobial uses to reduce antibiotic-resistant bacteria.[40]

Research findings have suggested that more educational campaigns need to be organized to improve public awareness and promote the rational use of antibiotics as many Malaysians were found to have inadequate knowledge and attitudes concerning both antibiotic use and antibiotic resistance. Aside from that, antimicrobial stewardship and infection control programs have been designed to optimize the appropriate use of antimicrobials by ensuring that every patient receives an antibiotic only when one is needed, with the right dose and within the exact duration. This is to optimize clinical outcomes and minimize unintended consequences of antimicrobial use.

CONCLUSION

Antimicrobial resistance is a serious threat to human health and this review has revealed the trends of antibiotic resistance in Malaysia over the years. Major drivers of antimicrobial resistance include inappropriate uses of antibiotics in healthcare practices as well as in animal production. A continuous effort from the related agencies to combat antimicrobial resistance in every aspect is essential to prevent bacteria from becoming resistant, henceforth causing severe impacts on human health and the future economy.

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CONFLICTS OF INTEREST

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REFERENCES

1. Ehrlich P. Über den jetzigen stand der chemotherapie. Berichte Der Deutschen Chemischen Gesellschaft 1909; 42:17-47.
2. World Health Organisation (WHO). Antimicrobial resistance factsheet; [cited Dec 2019]. Available from: http://www.who.int/mediacentre/factsheets/fs194/en/.
3. Van Boeckel T, Gandra S, Ashok A, Caudron Q, Grenfell B, Levin S, Laxminarayan R. Global antibiotic consumption from 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis 2014; 14:742-50.
4. World Health Organization. Antibiotic resistance. Available from: https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance.
5. World Health Organization. Situational analysis on antimicrobial resistance in the south-east Asia region; [cited Dec 2019]. Available from: https://apps.who.int/iris/rest/bitstreams/1171693/retrieve.
6. Holt E. 'Anti-microbial resistance on the rise'. New Straits Times; [cited Dec 2019]. Available from: https://www.nst.com.my/opinion/columnists/2018/12/438444/anti-microbial-resistance-rise.
7. Hryniewicz K. Antibiotic susceptibility of bacterial strains isolated from urinary tract infections in Poland. J Antimicrobial Chemother 2001; 47:773-80.
8. Frederick A. Escherichia coli, its prevalence and antibiotic resistant in Malaysia: a mini review. Microbiol 2011; 1:47-53.
9. The Center for Disease, Dynamics Economics & Policy Resistance Map: Antibiotic resistance. Available from: https://resistancemap.cddep.org/AntibioticResistance.php.
10. Lim K, Yasin R, Yeo C, Puthucheary S, Thong K. Characterization of multidrug resistant ESBL-producing Escherichia coli isolates from hospitals in Malaysia. J Biomed Biotechnol 2009; 165637.
11. Ibrahim N, Wajidi MF, Yusof MY, Tay, ST. The integron prevalence of extended-spectrum beta lactamase producing enterobacterial isolates in a Malaysian teaching hospital. Trop Biomed 2011; 28(3): 668-71.
12. Mustafa M, Balingi J. Urinary tract infections in a Sabah general hospital. J Pharm Biol Sci 2012; 1(6): 44-8.
13. Ministry of Health Malaysia. National Surveillance of Antimicrobial Resistance. Available from:https://www.imr.gov.my/images/uploads/NSAR/NSAR_2015/edited_251616_NSAR_Antibiotic_Resistance_Surveillance_data_2015.pdf.
14. Mohsen SMY, Hamzah HA, Al-Deen MMI, Baharudin R. Antimicrobial susceptibility of Klebsiella pneumoniae and Escherichia coli with extended-spectrum β-lactamase associated genes in Hospital Tengku Ampuan Afzan, Kuantan, Pahang. Malays J Med Sci 2016; 23(2):14-20.
15. Fazlul MKK, Farzana Y, Najnin A, Rashid MA, Nazmul MHM. Detection of CTX-M-type ESBLs from Escherichia coli Clinical Isolates from a Tertiary Hospital, Malaysia. Baghdad Sci J 2019; 16(3): 682-8.
16. Institute for Medical Research, National Antibiotic Resistance Surveillance Report 2018. Institute for Medical Research, 2020.
17. Doi Y, Murray GL, Peleg AY. Acinetobacter baumannii: evolution of antimicrobial resistance-treatment options. Semin Respir Crit Care Med 2015; 36(1): 85-98.
18. Misbah S, Abu Bakar S, Hassan H, Hanifah YA, Yusof MY. Antibiotic susceptibility and REP-PCR fingerprints of Acinetobacter spp. isolated from a hospital ten years apart. J Hosp Infect 2004; 58(4): 254-61.
19. Loh LC, Yii CTJ, Lai KK, Seevaunnamtum SP, Pushparasah G, Tong JMG. Acinetobacter baumannii respiratory isolates in ventilated patients are associated with prolonged hospital stay. Clin Microbiol Infect 2006; 12(6): 597-8.

20. Dhabaan GN, Abu Bakar S, Shorman MA, Hassan H. In vitro activity of tigecycline against Acinetobacter baumannii isolates from a teaching hospital in Malaysia. J Chemother 2012; 24(2): 87-92.
21. Deris ZZ, Harun A, Omar M, Johari, MR. The prevalence and risk factors of nosocomial Acinetobacter blood stream infections in tertiary teaching hospital in north-eastern Malaysia. Trop Biomed 2009; 26(2): 123-9.
22. Biglari S, Hanafiah A, Mohd Puzi S, Ramli R, Rahman M, Lopes BS. Antimicrobial resistance mechanisms and genetic diversity of multidrug-resistant Acinetobacter baumannii isolated from a teaching hospital in Malaysia. Microb Drug Resist 2017; 23(5): 545-55.
23. Nor FM, Shahari AS, Palaniasamy NK, Mohd Rustam FR, M-Zain Z, Lee BPK, Soh T. Multidrug resistant (MDR) Acinetobacter baumannii: rate of occurrence from a tertiary hospital, Malaysia. Int J Infect Dis 2019; 79: 46-7.
24. Hamzan N, Yean C, Rahman R, Hasan H, Rahman Z. Detection of blaIMP4 and blaNDM1 harboring Klebsiella pneumoniae isolates in a university hospital in Malaysia. Emerg Health Threats J 2015; 8(1): 26011.
25. Al-Marzooq F, Mohd Yusof MY, Tay ST. Molecular analysis of antibiotic resistance determinants and plasmids in Malaysian isolates of multidrug resistant Klebsiella pneumoniae. PLoS One 2015; 10(7): e0133654.
26. Kaur D, Chate S. Study of antibiotic resistance pattern in methicillin resistant Staphylococcus aureus with special reference to newer antibiotic. J Glob Infect Dis 2015; 7: 78.
27. Wielders CLC, Fluit AC, Brisse S, Verhoef J, Schmitz FJ. MecA gene is widely disseminated in Staphylococcus aureus population. J Clin Microbiol 2002; 40: 3970-5.
28. Cheong I, Tan SC, Wong YH, Zainudin BM, Rahman MZ. Methicillin-resistant Staphylococcus aureus (MRSA) in a Malaysian hospital. Med J Malaysia 1994; 49: 24-8.
29. Al-Talib H, Chan YY, Al-Jashamy K, Hasan H. Methicillin-resistant Staphylococcus aureus nosocomial infection trends in Hospital Universiti Sains Malaysia during 2002–2007. Ann Saudi Med 2010; 30: 358–63.
30. Neela V, Sasikumar M, Ghaznavi G, Sekawi Z, Mariana S. In vitro activities of 28 antimicrobial agents against methicillin-resistant Staphylococcus aureus (MRSA) from a clinical setting in Malaysia. SE Asian J Trop Med 2008; 39(5): 85-92.
31. Ho W, Choo Q, Chew C. Predominance of three closely related methicillin-resistant Staphylococcus aureus clones carrying a unique ccrC-positive SCCmec type III and the emergence of spa t304 and t690 SCCmec type IV pvl+ MRSA isolates in Kinta Valley, Malaysia. Microb Drug Resist 2017; 23(2): 215-23.
32. Sit P, Teh C, Idris N, Ponnampalavanar S. Methicillin-resistant Staphylococcus aureus (MRSA) bacteremia: correlations between clinical, phenotypic, genotypic characteristics and mortality in a tertiary teaching hospital in Malaysia. Infect Genet Evol 2018; 59: 132-41.
33. Bariman MH, Mustafa-Mahmoud MIA, Hamzah HA. Phenotypic and genotypic characterization, and detection of PVL encoding gene in methicillin resistant Staphylococcus aureus strains isolated from patients admitted to a tertiary hospital in Kuantan, Malaysia. IIUM Med J Malaysia 2019; 18: 2.
34. Weng PL, Hamat RA, Cheah YK, Zainol N, Aziz MN, Shamsudin MN. Vancomycin-resistant Enterococcus faecium of multi locus sequence type 18 in Malaysia. Med J Malaysia 2012; 67(6): 639-40.
35. Weng PL, Ramli R, Shamsudin MN, Cheah YK, Hamat RA. High genetic diversity of Enterococcus faecium and Enterococcus faecalis clinical isolates by pulsed-field gel electrophoresis and multilocus sequence typing from a hospital in Malaysia. Biomed Res Int 2013; 2013: 938937.
36. Moussa AA, Md Nordin AF, Hamat RA, Jasni AS. High level aminoglycoside resistance and distribution of the resistance genes in Enterococcus faecalis and Enterococcus faecium from teaching hospital in Malaysia. Infect Drug Resist 2019; 12: 3269-74.
37. Ab Rahman N, Teng CL, Sivasampu S. Antibiotic prescribing in public and private practice: a cross-sectional study in primary care clinics in Malaysia. BMC Infect Dis 2016; 16: 1.
38. Adzitey F, Rahmat Ali GR, Huda N, Cogan T, Corry J. Prevalence, antibiotic resistance and genetic diversity of Listeria monocytogenes isolated from ducks, their rearing and processing environments in Penang, Malaysia. Food Control 2013; 32(1): 607-14.
39. Chong ES, Bidin ZF, Abu Bakar NF, Zulfakar SS. Bacterial contamination on beef carcass at selected abattoirs located in Selangor, Malaysia. Malays Appl Biol 2017; 46(1): 37-43.
40. Ministry of Health Malaysia. Malaysian Action Plan on Antimicrobial Resistance (MyAP-AMR) 2017–2021. Ministry of Health Malaysia: 2017.

SYSTEMATIC / NARRATIVE REVIEW ARTICLE

CT and MRI findings of acute calculous cholecystitis and its complications in Singapore: A pictorial review

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ABSTRACT

Introduction: Acute cholecystitis (AC) is a common problem encountered in surgical practice. This occurs due to obstruction of the cystic duct by calculi resulting in inflammation of the gallbladder. Increasingly, contrast enhanced computed tomography (CECT) and Magnetic Resonance Imaging (MRI) scans are being used for assessment. While the imaging features of AC are well recognized and extensively described in the literature, radiological features of the rarer complications related to AC such as pseudoaneurysm formation and gallbladder volvulus are less well known. We aim to describe these rarer findings in our pictorial review, to better educate the clinician and radiologist, such that timely diagnoses can be reached, and relevant management can be affected.

Methods: A collection of cases showing the common acute gallbladder pathologies and complications such as acute cholecystitis, gangrenous cholecystitis, emphysematous cholecystitis, haemorrhagic cholecystitis, Mirizzi's syndrome, gallbladder perforation and abscess formation, were collected between July 2016 and March 2018 at two different medical institutions in Singapore. In addition, rarer cases of gallbladder volvulus and vascular complications such as cystic artery pseudoaneurysms and vessel erosions, were also followed up.

Results: The CT and MRI imaging features of these conditions were discussed, with key diagnostic imaging features emphasized.

Conclusion: Acute gallbladder pathologies are commonly encountered in day-to-day radiology practice. Knowledge of the rarer gallbladder pathologies and their key imaging features will help the radiologist, in particular, the on call radiologist in training, improve diagnostic accuracy and allow for timely management.

KEYWORDS:
Acute calculous cholecystitis, computed tomography, magnetic resonance imaging, complications

INTRODUCTION

Acute cholecystitis (AC) is a common problem encountered in surgical practice and it occurs due to obstruction of the cystic duct by calculi resulting in inflammation of the gallbladder. Gallstones affect 10-15% of the adult population in developed countries, with 1-4% of such patients developing symptoms each year.[1] In the United States, AC occurs in up to 1% of patients with known gallstones per annum.[2]

Radiological examinations are a cornerstone in the evaluation of patients who present with AC. Traditionally, ultrasound is the modality of choice in the investigation of patients who are suspected to have an acute gallbladder pathology. However, the images obtained with ultrasound is operator and patient dependent. Furthermore, ultrasound may not detect complications such as perforation or gangrene.

Contrast-enhanced computed tomography (CECT) scans of the abdomen and pelvis are increasingly being performed in patients with suspected acute cholecystitis, due to the short scan time and increasing availability in most departments. CECT is also able to detect complications of AC such as perforation or gangrene. Magnetic Resonance Imaging (MRI) is not commonly used as a primary imaging modality to image patients with acute gallbladder pathologies. However, magnetic resonance cholangiopancreaticogaphy (MRCP) is useful in the detection of choledocholiathiasis and variant biliary anatomy which would be helpful in preoperative planning. Complications such as gangrene and abscess formation may also be more discernible on MRI.

The imaging features of AC are well recognized and extensively described in literature. However, the radiological features of the complications related to acute cholecystitis such as pseudoaneurysm formation are less well described on CECT and MRI. These complications may be difficult to diagnose prospectively if the radiologist is unaware of their appearances. Accurate diagnosis is imperative for timely and appropriate management.

A. Acute calculous cholecystitis

An impacted gallstone in the gallbladder neck or cystic duct accounts for approximately 90-95% of cases of acute cholecystitis. The proposed pathophysiology of cholecystitis is as follows: the impacted stone leads to biliary stasis followed by inflammation of the gallbladder secondary to bacterial overgrowth. Distension of the gallbladder also causes reduced perfusion from the cystic artery and resultant ischaemia. The gallstones may also contribute to the inflammatory response by stimulating prostaglandins.[3]

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Patients characteristically present with a history of severe, sudden onset of constant or colicky pain in the right hypochondrium with nausea with vomiting. Clinical examination may reveal a positive Murphy's sign and peritonitis. Patients are usually more than 25 years old with a female preponderance (1:3 ratio).[4]

On CECT imaging, radiodense cholecystolithiasis is found 15-20% of the time,[3] associated with mural hyperenhancement, pericholecystic fluid and inflammatory fat stranding. The gallbladder is often distended and demonstrates mural thickening of more than 3mm.[5] Occasionally, enhancement of the adjacent liver parenchyma due to reactive hyperaemia may be present.

On MR imaging, gallstones were recognized as dependent signal voids on T2w imaging. Cholesterol stones may appear as T1 hyperintense foci. Similar to CECT, the gallbladder is often distended. The walls of the gallbladder were thickened and hyperintense on T2. In such instances, MRCP may be useful to show retained calculi within the common bile duct which may predispose the patient to cholangitis and biliary obstruction.

Cholecystectomy is the definitive management, with percutaneous cholecystostomy as an alternative should the patient be a poor surgical candidate. A small percentage of patients may develop potentially lifethreatening complications, which will be further elaborated later in this paper. With prompt surgical intervention, the prognosis for uncomplicated cases of acute calculous cholecystitis is excellent, with a low mortality rate of 3-4%.[6] Majority of the patients with AC do not experience complications. However, a small percentage of patients who may develop potentially life threatening complications such as gallbladder empyema, gangrenous cholecystitis and gallbladder perforation. Recognition of these entities is important as prompt surgical intervention would be required.

B. Complications of acute calculous cholecystitis

1. Gallbladder Empyema

Gallbladder empyema is a severe form of AC resulting from stagnant bile in the gallbladder superinfected with microorganisms that lead to pus formation in an acutely inflamed gallbladder. It is estimated to occur in 5 % to 15% of cases diagnosed to have acute cholecystitis.[7] Pus in the gallbladder increases the intraluminal pressure and may lead to wall necrosis and perforation if there is no prompt intervention. The CECT findings of gallbladder empyema are indistinguishable from that of acute cholecystitis.

On MR imaging, pus or purulent bile demonstrates restricted diffusion due to the large quantities of inflammatory cells within the purulent fluid. The diagnosis of empyema can thus be suggested by presence of fluid demonstrating diffusion restriction, when accompanied by an inflamed wall of a distended gallbladder.

Identification of these findings by the radiologist would enable prompt treatment, as this is a surgical emergency with a high propensity for septic shock.[8-10]

2. Gangrenous cholecystitis

Gangrenous cholecystitis is a relatively common complication of AC, affecting approximately 39% of patients with acute calculous cholecystitis.[11] Elderly patients, and patients with a history of diabetes mellitus and white blood cell count > 15,000 cells/mL are at an increased risk of having gangrenous changes at presentation. It occurs due to ischaemia and necrosis of the gallbladder wall. This can be further complicated by perforation, sepsis, abscess formation. Thus, it carries a high rate of mortality and morbidity.[11] CT is known to have high specificity but low sensitivity for acute gangrenous cholecystitis.

The commonest CECT finding of gangrenous cholecystitis would be lack of gallbladder wall enhancement. The gallbladder wall is often thin and irregular in appearance.

On MR imaging, there is usually asymmetric irregular wall thickening with inhomogeneous or absence of wall enhancement on post-contrast sequences. Mural ulcers may be present appearing as concave hyperintense areas on T2 fat saturated sequences. The presence of intramural membranes is the most specific sign of gangrenous cholecystitis and this is demonstrated very well on MRI, where the intraluminal membranes appear as linear T2 hypointense filling defects within the lumen of the gallbladder.

Patients are often treated with an emergent cholecystectomy under the cover of broad spectrum intravenous antibiotics. Percutaneous cholecystostomy may be performed in patients who are not eligible for emergent cholecystectomy to relieve the infection and act as a bridge to definitive surgery.

3. Emphysematous cholecystitis

Emphysematous cholecystitis is a potentially life threatening anaerobic infection of the gallbladder. It is defined as presence of intramural or intraluminal gas in the setting of AC without demonstrable communication to the gastrointestinal tract.

It is more commonly seen in men and typically occurs in diabetic patients.[12] Clostridium welchii is the most frequently cultured organism.[13-14] Vascular compromise of the cystic artery is thought to be one of the contributing factors, leading to gallbladder ischaemia. This can result in increased incidence of complications such as gallbladder wall gangrene and perforation, causing mortality rates to rise as high as 15-25%.[12-15] There are also cases of emphysematous cholecystitis in cancer patients on sunitinib, a tyrosine kinase inhibitor.

Gas foci can be seen within the gallbladder wall or lumen or pericholecystic tissues in emphysematous cholecystitis on CECT imaging.

On MR imaging, intramural gas is seen as signal voids along the non dependent aspect of the gallbladder. This is in contrast with gallstones which will be seen at the dependent portions. This feature helps distinguish intramural gas from an intramural stone. Other MR imaging findings of emphysematous cholecystitis resemble those of gangrenous cholecystitis, including irregular or asymmetric thickening of the wall with heterogeneous high signal intensity on fat suppressed T2 weighted images and fat suppressed T1

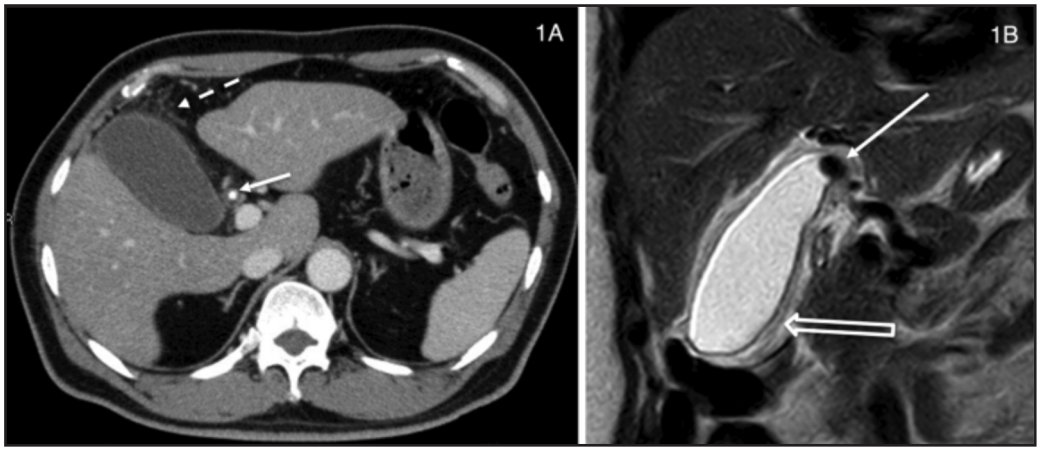

Fig. 1: (A) is a CT scan of of a middle aged gentleman who presented with 2 days history of right sided abdominal pain and fever. Axial CECT showed a distended gallbladder secondary to an impacted gallstone at the cystic duct (arrow), associated with pericholecystic fat stranding (dashed arrow) and mild gallbladder wall thickening. (B) is an MRI of a middle aged Chinese lady who presented with right upper quadrant pain. Coronal T2 HASTE sequence showed a calculus (arrow) in the neck of the gallbladder associated with mural thickening (open arrow), typical for acute calculous cholecystitis.

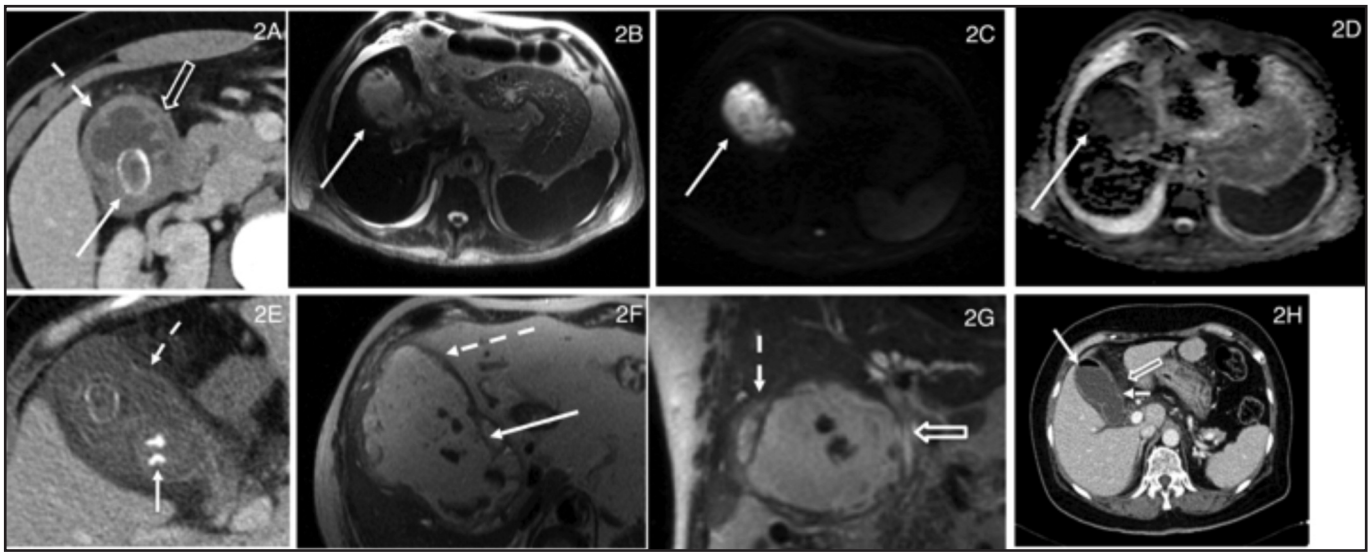

Fig. 2: (A) is a CT scan of a middle aged gentleman who presented with right hypochondrial pain. Axial CECT showed a calculus (arrow) lodged in the neck of the gallbladder. The gallbladder wall was thickened (dashed arrow) and also showed irregular mural outpouchings (open arrow) which suggests mural ulceration. During surgery, the lumen of the gallbladder was filled with pus. On CECT, AC is indistinguishable from gallbladder empyema. (B-D) are MRI images demonstrating the presence of T2w hypointense material layering within the dependent aspect of the gallbladder, representing calculi. In the non dependent aspect of the gallbladder, there is T2w hyperintense material (arrow, Fig 2B) demonstrating restricted diffusion (arrow, Fig 2C, 2D). During surgery, the lumen of the gallbladder was filled with pus, corresponding to the T2w hyperintense material showing restricted diffusion. On CECT, acute cholecystitis is indistinguishable from gallbladder empyema. (E) is a CT scan image of a middle aged lady presented with abdominal pain and septic shock. Axial CECT showed that the gallbladder contained multiple calculi (arrow). The wall of the gallbladder was irregular, thin and poorly enhancing (dashed arrow), in keeping with gangrenous change. Intraoperatively, the gallbladder showed patchy areas of gangrene. (F-G) are images of a middle aged gentleman was in a subacute inpatient ward for rehabilitation after a motor vehicle accident. He developed fever and abdominal pain. Axial T2 HASTE sequence showed the gallbladder to be markedly distended. Multiple linear striations are seen along the wall of the gallbladder which are suggestive of intraluminal membranes (arrow). Note that the gallbladder wall is also thinned (dashed arrow). The contour of the gallbladder is distorted with an outpouching seen posteriorly, worrisome for focal perforation (open arrow). (H) is a CT scan image of a middle aged gentleman who presented with acute onset of epigastric pain radiating to the back. Axial CECT showed intraluminal gas with gas fluid level (arrow). The gallbladder wall is thickened with areas of ulceration (dashed arrow) with surrounding fat stranding (open arrow). No abnormal communication with the gastrointestinal tract is seen on the rest of the images. There was no history of prior biliary surgery or instrumentation. Findings are in keeping with emphysematous cholecystitis, which was confirmed intra-operatively.

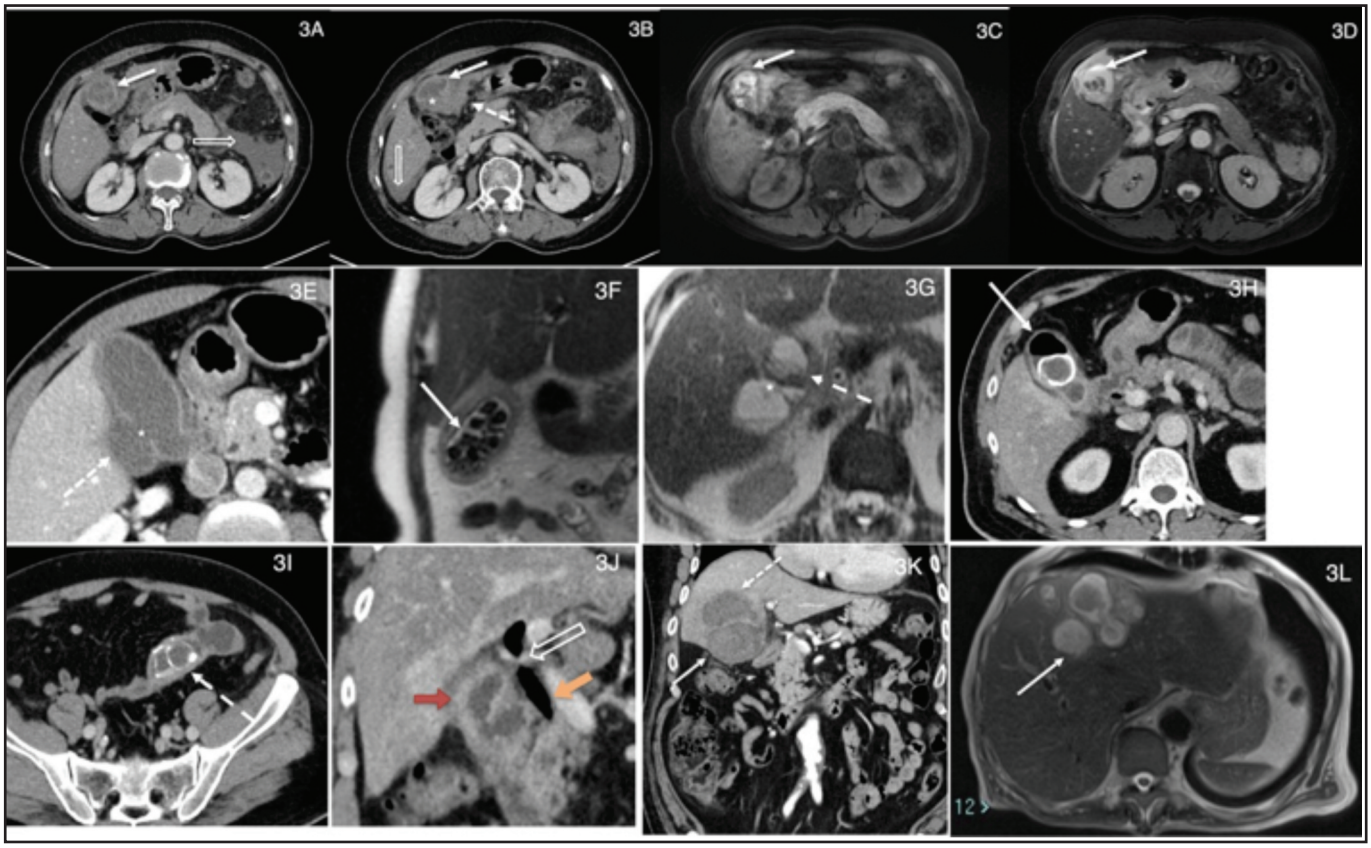

Fig. 3: (A-D) are abdominal CT scan sections of an elderly lady who was on antiplatelets for ischemic heart disease and presented with acute right abdominal pain and vomiting. (A-B) are axial CECT scans that showed heterogenously dense content within the gallbladder with thickened gallbladder wall (arrow), worrisome for intraluminal haemorrhage. Within the medial aspect of the wall, there was focal mural defect (asterisk) with an adjacent haematoma (dashed arrow). A small amount of hyperdense ascites was noted, which appeared as suspicious for haemoperitoneum (open arrow). (C-D) show the subsequent T1w MRI and T2w MRI images, respectively that demonstrated heterogeneous T1w hyperintense and T2w hypointense material within the gallbladder (arrow). Haemorrhagic cholecystitis with focal perforation and haemoperitoeum was confirmed intra-operatively. (E) is that of a patient who presented with right upper quadrant pain for 5 days. Axial CECT showed a focal outpouching at the lateral wall of the gallbladder, in keeping with a focal region of perforation (dashed arrow). A definite mural defect (asterisk) can also be seen. (F-G) are MRI images of an elderly lady who presented with fever and right upper quadrant pain. F is a coronal T2 HASTE image that showed multiple signal voids within the gallbladder in keeping with calculi. (G) is an axial T2 HASTE image that shows a focal mural defect (asterisk) and pericholecystic collection (dashed arrow). Findings are in keeping with perforation. (H-J) are CT scan images of a patient who presented with symptoms of small bowel obstruction. H is an axial CECT scan that showed the presence of gas and calculi within the gallbladder (arrow). (I) is an axial CT scan that shows a calculus that was detected in the ileum (dashed arrow) which was causing intestinal obstruction. (J) indicates that a closer evaluation of the gallbladder on coronal CECT showed a small cholecystoduodenal fistula (open arrow) between the gallbladder (red arrow) and the air filled duodenum (yellow arrow). These findings in (H-J) are in keeping with gallbladder perforation complicated by gallstone ileus. (K) shows coronal CECT showed a distended and inflamed gallbladder with heterogeneously dense intraluminal content and indistinct wall (arrow). An adjacent multi loculated intrahepatic abscess (dashed arrow) is noted with hyperdense material within it, likely secondary to debris or blood product. Pericholecystic inflammatory stranding is also detected. These findings suggest acute cholecystitis with hepatic abscess formation. (L) is that of subsequent MRI of the same patient with perforated cholecystitis showed a large, multi loculated T2 weighted hyperintense fluid collection (arrow), compatible with a hepatic abscess secondary to perforated acute cholecystitis.

weighted images, indicative of intramural hemorrhagic necrosis and formation of micro abscesses.[16]

Similar to gangrenous cholecystitis, cholecystectomy is the definitive treatment for emphysematous cholecystitis. Emphysematous cholecystitis generally carries with it a poorer prognosis, and the mortality rate in emphysematous cholecystitis as high as 25%, compared with 4% in acute cholecystitis.[6]

4. Hemorrhagic cholecystitis

Hemorrhagic cholecystitis refers to haemorrhage into the gallbladder lumen as a result of mucosal ulceration and necrosis. A few isolated cases of haemorrhagic cholecystitis occurring in patients with haemophilia or on anticoagulation have been described.[17-19] However, bleeding due to cholecystitis is extremely rare and is postulated that the inflammation associated with cholecystitis may cause vascular thrombosis.[20-22]

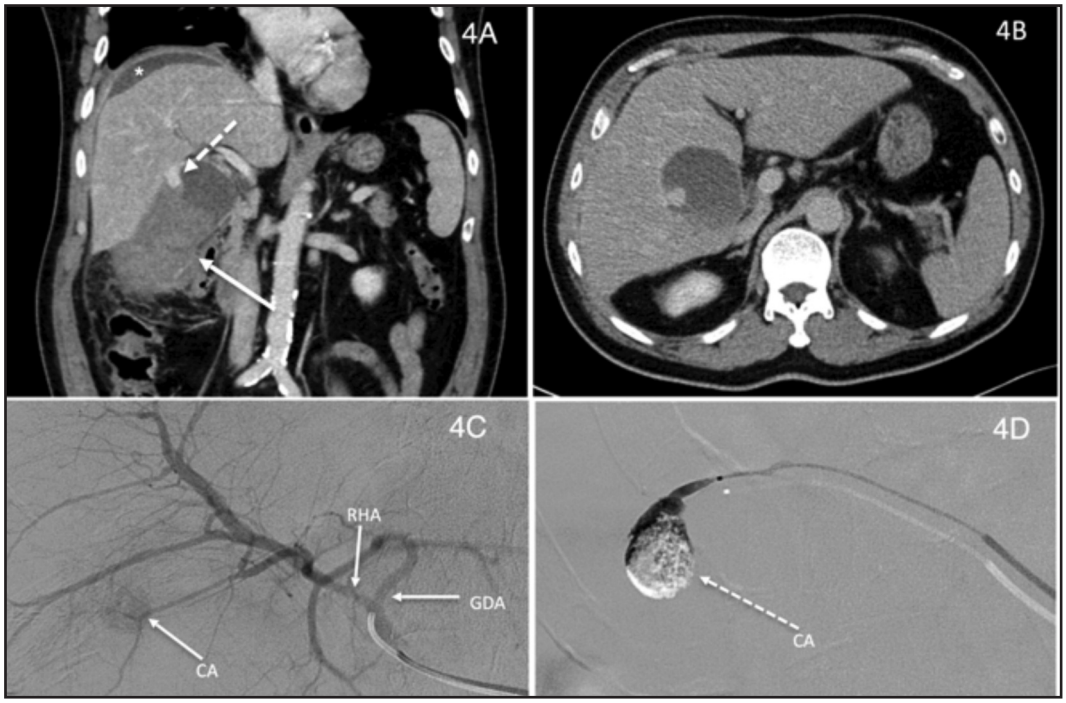

Fig. 4: (A) 60 year old male patient presented with three days duration of right hypochondrial pain. (A-B) are coronal and axial CECT, respectively that showed a distended gallbladder with layering hyperdensity (arrow) due to the presence of blood / sludge. There was a focal nodular hyperdensity at the lateral gallbladder wall in a non dependent aspect which was similar in configuration on the venous and delayed phases, suspicious for a pseudoaneurysm (dashed arrow). There was also a right subdiaphragmatic collection of low attenuation, possibly representing ascites (asterisk). The patient subsequently underwent angioembolisation. (C) is a selective angiogram of the hepatic artery that showed contrast blush from the cystic artery. (D) shows the super selective angiogram of the cystic artery that revealed a widenecked pseudoaneurysm (dashed arrow), which was embolised using glue. *RHA = right hepatic artery, GDA = gastroduodenal artery, CA = cystic artery

The presenting features of hemorrhagic cholecystitis are similar to AC, with right hypochondrial pain being a dominant feature. Where blood is passed through the biliary tree into the gut, the patient also may have additional symptoms of haematamesis or melena. Furthermore, blood clots may form, giving rise to mechanical obstruction of the bile ducts, resulting in painful jaundice, and mimicking the passage of gallstones. This oozing of blood via the ampulla of Vater, known as hemobilia, can be visualised on endoscopy.[23] On CECT imaging, debris and blood products are seen as high density material layering within the gallbladder lumen. The presence of gallstones may be obscured by the intra luminal blood. Free fluid seen elsewhere in the abdomen and pelvis may be simple or high in density, depending on whether hemoperitoneum is present due to perforation. As in majority of patients with AC, there is often free pericholecystic fluid and gallbladder wall thickening.

On MR imaging, blood in the wall and lumen of the gallbladder is T1w hyperintense due to the presence of methemoglobin. A fluidfluid level may be seen in the lumen of the gallbladder and extrahepatic bile ducts. Haemoperitoneum or free fluid can be seen in the peritoneal cavity if the gallbladder is perforated.

Angioembolisation of the bleeding vessel may be undertaken to stop the bleed and to stabilize the patient.[23] Subsequently, an elective cholecystectomy can be performed when the patient had recovered from the acute episode.

5. Perforated cholecystitis

Gallbladder perforation is a potential complication of AC, with a reported mortality rate ranging from 12-42%.[24] Increased intraluminal pressure within the gallbladder lumen results in ischaemia of the gallbladder wall, rendering it susceptible to perforation. Perforation occurs in 2-11% of acute cholecystitis patients.[11]

The fundus is the commonest site of perforation, given that it is the most distal part of the gallbladder with the least blood supply.[25] Fundal perforations are less likely to be covered by the omentum.[25] As a result, bile drains into the peritoneal space, resulting in free biliary peritonitis and stones within the peritoneal cavity. Non fundal perforations are easily sealed by the omentum or the surrounding intestines. Hence, the inflammatory process is confined to the right upper quadrant with formation of a pericholecystic abscess.[25]

CECT may show visible defect in the wall of the gallbladder. More commonly, a focal outpouching is seen which suggests the presence of a defect. Patients often have bile leakage as a result of perforation and a pericholecystitic fluid collection with adjacent inflammatory fat stranding may result.

On MR imaging, there was disruption of the gallbladder wall, which shows up as a mural defect. Often, a pericholecystic abscess is seen adjacent to the site of perforation. When a pericholecystic abscess is present, the gallbladder lumen communicates with the abscess through the disrupted gallbladder wall.

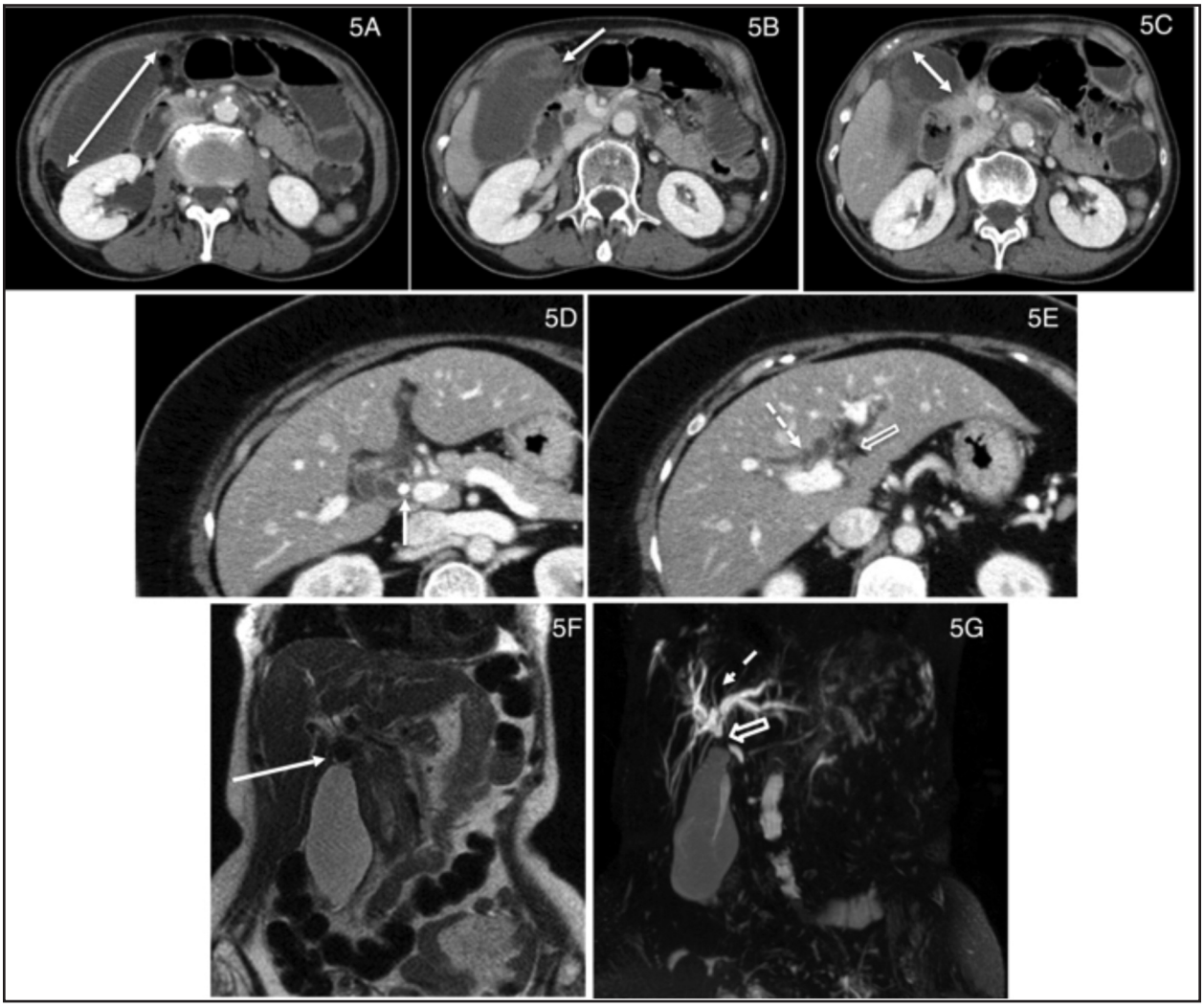

Fig. 5: (A-C) are axial CECT images of an elderly female who presented with right upper quadrant pain and vomiting. The gallbladder was markedly distended with a change in axis at the mid body (double headed arrow in Fig 5A and 5C). Enhancing soft tissue is noted at the point of axis change (Fig 5B, arrow). There was gallbladder torsion noted intra-operatively. (D-E) are those of an elderly lady presented with epigastric pain and vomiting. Axial CECT (Fig. 5D) showed an impacted gallstone within the cystic duct (arrow) compressing on the common hepatic duct (open arrow). (E) shows that the common hepatic duct (open arrow) and intrahepatic biliary tree (dashed arrow) were dilated (Fig. 5E). Findings were consistent with Mirizzi's syndrome.
Figure 5(F-G) are those of a patient who presented with right upper quadrant pain and jaundice. Coronal T2 HASTE image showed a calculus is lodged in Hartmann's pouch of the gallbladder (arrow in Fig. 5F). As a consequence of the mass effect, this had caused compression on the common hepatic duct (open arrow), with resultant dilation of the intra hepatic biliary ducts (dashed arrow) as demonstrated on the 3D MRCP images (Fig. 5G), accounting for the patient's jaundice.

The inflamed gallbladder can also perforate into the adjacent liver parenchyma, resulting in the formation of an intrahepatic abscess.

The treatment for perforated cholecystitis is that of an emergent cholecystectomy with abdominal lavage to treat peritonitis.[25,26] Drainage of the abscess if present, should also be performed in the same setting.

6. Cystic artery pseudoaneurysms

Formation of a cystic artery pseudoaneurysm is a very rare complication of AC. Typically patients present with a combination of upper abdominal pain, hematemesis and jaundice, known as Quinke's triad.[27,28] Approximately 50 cases have been reported worldwide.[29] More than half these cases were associated with cholecystitis or cholelithiasis, and more than 75% of these patients presented with haemobilia resulting from rupture of the aneurysm.

In AC inflammatory changes surrounding the gallbladder can result in fibrosis encasing the cystic artery and weakening its wall, giving rise to aneurysm formation.[29] These aneurysms are likely to rupture when the tamponade effect of the surrounding inflammatory fluid tension is lost. Hence, drainage of the pericholecystic fluid via cholecystostomy is usually delayed until embolisation of the pseudoaneurysm is completed.[30,31]

On CECT imaging, the pseudoaneurysm appears as a well circumscribed hyperattenuating lesion on the plain phase.

This lesion subsequently opacifies in the arterial phase and remains persistently hyperattenuating on delayed images. High density material in the lumen of the gallbladder and biliary ducts (haemobilia) may be seen with pericholecystic inflammatory changes.

As cystic artery pseudoaneurysm is a rare entity, there is currently no consensus for its clinical management, although it may range from the minimally invasive selective angioembolisation for unstable patients, to definitive cholecystectomy.

C. Others

1. Gallbladder volvulus

Gallbladder volvulus or torsion is an uncommon cause of acute abdomen. It occurs along the axis of the cystic duct and artery, compromising vascular supply.[32] It occurs when there is enough mobility of the gallbladder to allow it to rotate around a fixed pedicle by at least 180 degrees. While it has been postulated that precipitating factors for gallbladder volvulus or torsion include intense peristalsis of the neighboring organs, kyphoscoliosis of the spine and tortuous atherosclerotic cystic artery, no real cause has been identified to date.[33,34]

The entity is commonly misdiagnosed as cholecystitis before surgery, although some imaging findings are present which may assist the radiologist in reaching the right diagnosis.

CECT often demonstrates a large, distended gallbladder with loss of normal enhancement and abrupt tapering of the cystic duct. The 'beak and twirl' sign immediately distal to the point of torsion as well as a change in the anatomical position of the gallbladder from vertical to horizontal can be demonstrated.[35,36] The gallbladder may also be seen outside of its anatomical fossa with surrounding inflammatory changes.

On MR imaging, there is high signal intensity in the wall on T1w imaging as a result of coagulation necrosis with intramural haemorrhage. This diagnosis can be confirmed with contrast enhanced images. The treatment for gallbladder volvulus is emergent cholecystectomy to prevent ischaemia, infarction and overwhelming sepsis.[32]

2. Mirizzi syndrome

Mirizzi syndrome is defined as common hepatic duct (CHD) obstruction caused by an extrinsic compression from an impacted stone in the Hartmann's pouch of the gallbladder or in the cystic duct. Obstruction may be due to direct mass effect or stricture formation in the CHD due to repeated inflammation. Predisposing factors include long cystic duct running parallel to the CHD or low insertion of cystic duct into common bile duct.

Patients typically present with jaundice, fever, and right upper quadrant pain. It has been postulated that patients with Mirizzi syndrome are predisposed to gallbladder malignancy due to recurrent inflammation and biliary stasis. Cholecystocholedochal fistula may develop due to chronic inflammation/pressure necrosis, with gallstones eroding from cystic duct into bile duct.

CECT and MR findings for Mirizzi's syndrome are similar, with the presence of a large, impacted gallstone in the gallbladder neck. Dilated intra and extrahepatic biliary ducts are seen, with the former more commonly noted. The gallbladder wall may be diffusely thickened and enhance with contrast.

The treatment for Mirizzi syndrome include endoscopic removal of the obstructing calculus and subsequent definitive cholecystectomy.

CONCLUSION

Acute gallbladder pathologies are commonly encountered in surgical practice. As CECT and MRI are increasingly performed and image quality on CECT improves, acute gallbladder pathologies are increasingly and more confidently diagnosed. There is a paucity of published literature on the complications of AC, which includes erosion of the adjacent vessels, cystic artery pseudoaneurysm formation and gallbladder volvulus. Knowledge of the rarer gallbladder pathologies and their key imaging features will help the radiologist and residents in training improve diagnostic accuracy. This would assist the surgeon in either planning the surgery or in guiding further management.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Sanders G, Kingsnorth AN. Gallstones. BMJ 2007; 335(7614): 295-9.
2. Tanaja J, Lopez RA, Meer JM. Cholelithiasis StatPearls Treasure Island (FL): StatPearls Publishing; 2021.
3. Adrian A. Indar, Ian J Beckingham, Clinical Review: acute cholecystitis. BMJ. 2002; 325(7365): 639-43.
4. Njeze GE. Gallstones. Niger J Surg 2013; 19(2): 49-55.
5. Fidler J, Paulson EK, Layfield L. CT evaluation of acute cholecystitis: findings and usefulness in diagnosis. AJR Am J Roentgenol 1996; 166(5): 1085-8.
6. Smith EA, Dillman JR, Elsayes KM, Menias CO, Bude RO. Cross-sectional imaging of acute and chronic gallbladder inflammatory disease. AJR 2009; 192(1): 188-96.
7. Ambe PC, Jansen S, Macher-Heidrich S, Zirngibl H. Surgical management of empyema-tous cholecystitis: a register study of over 12,000 cases from a regional quality control database in Germany. Surg Endosc 2016; 30(12): 5319–24.
8. Supit C, Supit T, Mazni Y, Basir I. The outcome of laparoscopic subtotal cholecystectomy in difficult cases - A case series. Int J Surg Case Rep 2017; 41: 311-4.
9. Pant G, Kumar A, Verma N, Sharma A. Gallbladder empyema complicating acute myeloid leukaemia in an adolescent boy. BMJ Case Rep 2018; 2018: bcr2018224359.
10. Mehta V, Yarmish G, Greenstein J, Hahn B. Gallbladder Empyema. J Emerg Med 2016; 50(6): 893-4.
11. Chawla A, Bosco JI, Lim TC, Srinivasan S, Teh HS, Shenoy JN. Imaging of acute cholecystitis and cholecystitis associated complications in the emergency setting. Singapore Med J 2015; 56(8): 438-43.
12. Rosenberg AA, Cherry Bukowiec JR, Li SH, Napolitano LM. Emphysematous cholecystitis. Surg Infect (Larchmt) 2013; 14(5): 483-5.
13. Grayson DE, Abbott RM, Levy AD, Sherman PM. Emphysematous infections of the abdomen and pelvis: a pictorial review. Radiographics 2002; 22(3): 543-61.

14. Garcia-sancho tellez L, Rodriguez-montes JA, Fernandez de lis S., et al. Acute em-physematous cholecystitis. Report of twenty cases. Hepatogastroenterology 1999; 46(28): 2144-8.
15. Mentzer RM Jr, Golden GT, Chandler JG, Horsley JS 3rd. A comparative appraisal of emphysematous cholecystitis. Am J Surg 1975; 129(1): 10-5.
16. Miller RE, Kimmelstiel FM. Laparoscopic cholecystectomy for acute cholecystitis. Surg Endosc 1993; 7(4): 296-9.
17. Kwon JN. Hemorrhagic cholecystitis: report of a case. Korean J Hepatobiliary Pancreat Surg 2012; 16(3): 120-2.
18. Morris DS, Porterfield JR, Sawyer MD. Hemorrhagic cholecystitis in an elderly patient taking aspirin and cilostazol. Case Rep Gastroenterol 2008; 2(2): 203-7.
19. Chen YY, Yi CH, Chen CL, Huang SC, Hsu YH. Hemorrhagic cholecystitis after anticoagulation therapy. Am J Med Sci 2010; 340(4): 338-9.
20. Reddy SC. Pseudoaneurysm of cystic artery with upper gastrointestinal hemorrhage. South Med J. 1983; 76(1): 85-6.
21. Smague EA, Schulte F, Guse S. Recurrent hemobilia caused by a ruptured pseudoaneurysm of the cystic artery in the gallbladder. Chirurg 1990; 61: 199-200.
22. England RE, Marsh PJ, Ashleigh R, Martin DF. Case report: pseudoaneurysm of the cystic artery: a rare cause of haemobilia. Clin Radiol 1998; 53(1): 72-5.
23. Hicks N. Haemorrhagic cholecystitis: an unusual cause of upper gastrointestinal bleeding. BMJ case reports 2014; (17)2014: bcr2013202437.
24. Date RS, Thrumurthy SG, Whiteside S, Umer MA, Pursnani KG, Ward JB, et al. Gallbladder perforation: case series and systematic review. Int J Surg 2012; 10(2): 63-8.
25. Derici H, Kara C, Bozdag AD, Nazli O, Tansug T, Akca E. Diagnosis and treatment of gallbladder perforation. World J Gastroenterol 2006; 12(48): 7832-6.
26. Gunasekaran G, Naik D, Gupta A, Bhandari V, Kuppusamy M, Kumar G, et al. Gallbladder perforation: a single center experience of 32 cases. Korean J Hepatobiliary Pancreat Surg 2015; 19(1): 6-10.
27. Saluja SS, Ray S, Gulati MS, Pal S, Sahni P, Chattopadhyay TK. Acute cholecystitis with massive upper gastrointestinal bleed: a case report and review of the literature. BMC Gastroenterol 2007; 7(1): 12.
28. Maeda A, Kunou T, Saeki S, Aono K, Murata T, Niinomi N, et al. Pseudoaneurysm of the cystic artery with hemobilia treated by arterial embolization and elective cholecystectomy. J Hepatobiliary Pancreat Surg 2002; 9(6): 755-8.
29. Fujimoto Y, Tomimaru Y, Hatano H, Noguchi K, Nagase H, Hamabe A, et al. Ruptured Cystic Artery Pseudoaneurysm Successfully Treated with Urgent Cholecystectomy: A Case Report and Literature Review. Am J Case Rep. 2018; 19: 187-93.
30. Fung AK, Vosough A, Olson S, Aly EH, Binnie NR. An unusual cause of acute inter-nal haemorrhage: cystic artery pseudoaneurysm secondary to acute cholecystitis. Scott Med J 2013; 58(2): e23-6.
31. Nkwam N, Heppenstall K. 10.Nkwam N, Heppenstall K. Unruptured Pseudoaneurysm of the cystic artery associated with acute calculus cholecystitis. J Surg Case Rep 2010; 2010(2): 4.
32. Kashyap S, Mathew G, Abdul W, et al. Gallbladder Volvulus. StatPearls Treasure Is-land (FL): StatPearls Publishing; 2020.
33. Musthafa S, Aftab Z, Ali SM, Khanna M. Gallbladder volvulus with segmental right liver lobe hypoplasia/atrophy: a preoperative diagnostic dilemma. BMJ Case Rep 2018; 2018: bcr 2018-224474.
34. Abadía Barnó P, Coll Sastre M, Picón Serrano C, Sanjuanbenito Dehesa A, Cabañas Montero J. [Gallbladder volvulus: diagnostic and surgical challenges]. Cir Cir. 2017; 85 Suppl 1: 89-92.
35. Younan G, Schumm M, Ali F, Christians KK. Gallbladder Volvulus in a Patient with Type I Choledochal Cyst: A Case Report and Review of the Literature. Case Rep Surg 2016; 2016: 5626531.
36. Grock A, Chan W, deSouza IS. A Curious Case of Right Upper Quadrant Abdominal Pain. West J Emerg Med 2016; 17(5): 630-3.

SHORT COMMUNICATION

Modifications to Hepatopancreatobiliary surgical services during COVID-19 partial lockdown in a hospital in northern Malaysia

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SUMMARY

Maintaining hepatopancreatobiliary (HPB) services during the initial phase of a pandemic in a state referral hospital for COVID-19 presents a few challenges, especially when a nationwide, government-issued partial lockdown is in enforcement. We describe the adaptations to our practice to maintain the services whilst ensuring safety of patients and staff, by postponing non-urgent clinic cases, grouping our staff to two mutually exclusive teams that work on alternate shifts and selecting HPB operative cases according to the modified Risk Urgency Decision Matrix.

KEYWORDS:
Hepatopancreatobiliary, COVID-19, movement control order, lockdown, social distancing

INTRODUCTION

To curb the spread of COVID-19 outbreak, the Malaysian government implemented the Movement Control Order (MCO) on 18th March 2020 – a nationwide *cordon sanitaire*, extended in two-weekly phases to temporarily restrict mass gathering, interstate travel, as well as non-essential public and private services.[1]

This article discusses the modifications that were made during the COVID-19 lockdown period in Hospital Sultanah Bahiyah (HSB), Kedah, Malaysia. HSB is a 923-bedded state hospital with three surgical wards, receiving all COVID-19 referrals in Kedah and hepatopancreatobiliary (HPB) referrals from the northern region of Malaysia with a combined population of 6.7 million. Most of the essential resources such as personal protective equipment (PPE), intensive care unit (ICU) beds, ventilators and haemodialysis machines were reserved for the care of COVID-19 patients, leaving limited resources for elective HPB surgeries. Patients must make interstate travels against the MCO to attend their appointments, which risks crowding and contracting COVID-19. Therefore, the management of HPB surgical and endoscopic services were innovated according to international advisory guidelines to deliver safe and timely treatment to patients.[2-3]

METHODS

Staff Management

During the partial lockdown, one HPB consultant was assigned as the resident consultant to manage cases. Another consultant worked from the Advanced Medical and Dental Institute (AMDI), Penang by conducting emergency surgeries and endoscopic retrograde cholangiopancreatography (ERCP) at referral hospitals with the available resources, to reduce movement of patients to HSB. A third consultant oversees the services, scrubs in for elective surgeries and replaces any consultant who gets infected with COVID-19.

The remaining HPB and endoscopy staff were divided into 2 teams that work on alternate 48-hour shifts without contact with each other. All clinic, ward and endoscopy personnel were required to wear face masks and maintain social distance of 1 metre apart. If any staff becomes infected with COVID-19, the entire team is quarantined while the other team takes over the HPB services, hence avoiding total shutdown. At the end of the MCO period stated above, none of the staff involved was infected with COVID-19.

Outpatient Clinic Management

We ran a twice-a-week clinic with 83 to 114 patients a week from August-December 2019. Clinic load was reduced to 22-38 patients a week via phone calls made to the patients to reschedule their appointments, during the initial stages of MCO. This reduction of appointments avoided crowding at the hospital and minimised movement across cities. Patients with postponed appointments had their prescriptions extended and dispensed at the hospital drive-through pharmacy.

All outpatient referrals were triaged according to urgency; HPB cancer cases were seen within two weeks while benign, non-urgent diseases (gallstones, liver cysts, chronic pancreatitis) were seen after a month.

Surgical Services Management

HPB elective cases were conducted in one operation theatre (OT) twice a week while emergency cases were called to a common OT shared with other specialties. All COVID-19 positive cases were conducted in an OT with stand-alone air-conditioning system and distinct air-handling unit located at

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Table I: List of HPB surgeries and ERCPs done at HSB during the MCO period

Surgery		ERCP	
Elective (n=14)	**Emergency (n=14)**	**Elective (n=9)**	**Emergency (n=36)**
Non-anatomical liver resections (NAR) (2)	Open cholecystectomy (8)	Stent removal (3)	Stent insertion (19)
NAR and cholecystectomy (1)	Open cholecystectomy with right psoas abscess drainage (1)	Stent exchange (2)	Stone clearance (4)
Whipple's procedure (2)	Whipple's procedure with extended right hemicolectomy (1)	Stent exchange (2)	Stone clearance (4)
Right hemihepatectomy (3)	Whipple's procedure with take-down anastomosis post-right hemicolectomy (1)	Cholangiography (1)	Ampullary biopsy (1)
Left lateral sectionectomy (2)	Distal gastrectomy (1)	Self-expanding metallic stent (SEMS) insertion (1)	Cholangiography (3)
Open cholecystectomy (2)	Left lateral sectionectomy (1)		Abandoned procedure – failed ampullary cannulation, food in stomach (5)
Staging laparotomy (2)	Laparotomy and peritoneal washout (1)		

the ground floor by a separate team within the surgical department.

All elective surgeries were withheld at the start of the MCO period. Despite the recommendations of Society of American Gastrointestinal and Endoscopic Surgeons and European Association for Endoscopic Surgery to postpone all elective surgeries and endoscopies[4] we resumed elective surgery in the second week of MCO by selecting cases guided by the modified Risk Urgency Decision Matrix (RUDM) (Fig. 1) of the Philippines Association of HPB Surgeons (PAHPBS) Recommendations in Time of COVID-19 Pandemic.[5]

RESULTS

We performed 14 emergency and 14 elective HPB surgeries between 23/3/2020-5/5/2020 (Table I). Urgent and life-threatening cases were performed as emergency surgeries. Urgent and non-life-threatening cases were performed electively if deemed to be at low risk for post-operative ICU admission or ventilator requirement. Non-urgent and ambulatory care cases (including elective cholecystectomy) were listed in a ledger and rescheduled later.

Initially, only one elective liver carcinoma case requiring minor resection with anticipated low blood product requirement was scheduled a day. As the MCO period progressed and COVID-19 incidence reduced, the number and complexity of elective cases were increased; left lateral sectionectomy (week 2 of MCO), Whipple's procedure (week 4) and right hemihepatectomy in a lady with massive saddle pulmonary embolus (week 6).

Patients were screened for COVID-19 as per MOH Guidelines of Management of COVID-19 Disease in Surgery.[6] Elective patients were required to sign the COVID-19 health declaration form and partake single SARS-CoV-2 nasopharyngeal and oropharyngeal rapid-test kit antigen (RTK-Ag) swab on admission the day before surgery.

Only open surgical procedures were performed during the early stage of pandemic to reduce operating time and to mitigate the risk of SARS-CoV-2 aerosolisation, in the absence of clear evidence regarding the risk at that moment.

Endoscopic Services Management

Initially, all elective scopes and endoscopic ultrasound (EUS) were withheld. All 45 ERCPs were performed on patients with obstructive jaundice or bile leakage, between 23/3/2020-5/5/2020 (9 elective and 36 emergency cases) (Table I).

Endoscopy assistants donned full PPE (Fig. 2) to reduce risk of aerosol-generating positive insufflation during endoscopy.[9] Suspected or confirmed COVID-19 patients were scoped in a negative pressure room. Standard endoscope disinfectant (Anioxyde 1000™ (5% hydrogen peroxide)) was used for all scopes as per the Asian Pacific Society for Digestive Endoscopy guidelines.[7] The fluoroscopy room was disinfected at the end of each ERCP session.

DISCUSSION

The staff should ideally be grouped into two teams that work in separate shifts to prevent contact between both teams. The limitation in our number of consultants prevented exclusive supervision by one consultant for each team, which may potentially allow cross-contamination through the consultant who works with both teams.

At the start of the pandemic, our personnel donned full PPE for all cases, despite the negative RTK-Ag swab results, due to the low sensitivity (84.4%) of the RTK-Ag kits.[8] We revised our practice in July 2020 to wearing face masks, goggles and disposable gowns in RTK-Ag negative cases, upon report of improved sensitivity (84.4 to 90%) and specificity (100%) of the RTK-Ag kits by the Institute of Medical Research (IMR). We currently test all elective patients with reverse transcriptase polymerase chain reaction (RT-PCR) and emergency patients with RTK-Ag swabs.

An online survey involving 145 European and African HPB Association (E-AHPBA) members reported postponements of non-essential surgeries by 83% of members,[9] which concurs with our practice during the partial lockdown. Most

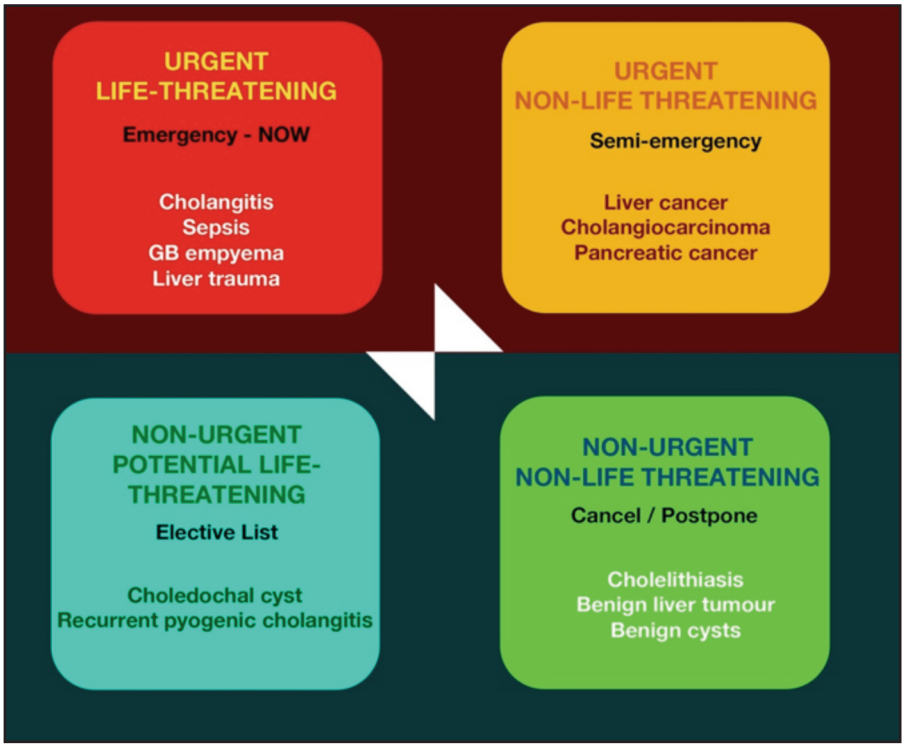

Fig. 1: Modified Risk Urgency Decision Matrix.

Policies Adapted for HPB Elective OT Cases

- Minimal essential staff
- The HPB Fellow leads the surgery and calls in the consultant when needed, to reduce patient exposure and use of PPE
- Full PPE (N95 masks, Tyvek suits, double gloves, shoe protectors and goggles) donned by the operating team
- Disposable gowns and drapes for all cases

Fig. 2: Policy for all HPB elective surgeries based on the MOH Guidelines[6]

respondents however, reported a reduction in resectable HPB cancer surgeries due to limited life support resources and institutional policies. Hence, they subjected these patients to chemotherapy instead, followed by ablation in colorectal liver metastases cases. In contrast, we strictly maintained our standards of practice. In particular, we avoided neo-adjuvant chemotherapy for resectable HPB cancer cases due to the lack of evidence regarding the impact of delay in surgery on the morbidity and long-term survival of patients.

A systematic review reported a reduction in interdisciplinary surgical clinic volume by 50-75% with the use of virtual clinics in centres during lockdown.[10] Although we reduced the clinic load, we opted for patients to be physically present in our clinic for important pre-operative clinical assessment and counselling for major elective cancer surgeries as most of our patients were elderly with digital illiteracy.

CONCLUSION

HPB practitioners must contemporaneously innovate their practice according to the latest COVID-19 trend and local guidelines. Clinic volume should be reduced during lockdown to avoid interstate travel of patients with non-urgent diagnoses. HPB staff may be grouped into two mutually exclusive teams to reduce risk of total shutdown of services, in the event of COVID-19 infection among any staff member. Elective HPB surgeries may resume during the pandemic and cases selected according to the RUDM by PAHPBS, information based on the latest COVID-19 trend and the availability of life support resources.

REFERENCES

1. Prime Minister Office of Malaysia. Press Release: Restriction of Movement Order [cited 16 March 2020]. Available from: https://www.pmo.gov.my/2020/03/movement-control-order/
2. Royal Colleges of Surgeons. Updated Intercollegiate General Surgery Guidance on COVID-19, [cited 6 April 2020]. Available from: https://www.rcseng.ac.uk/coronavirus/joint-guidance-for-surgeons-v2/
3. Hettiaratchy S, and Deakin D. Guidance for Surgeons Working During The COVID-19 Pandemic, Royal Colleges of Surgeons. [cited 20 March 2020]. Available from: https://www.rcseng.ac.uk/coronavirus/joint-guidance-for-surgeons-v1/
4. Pryor A. SAGES and EAES Recommendations Regarding Surgical Response to COVID-19 Crisis. [cited 29 March 2020]. Available from: https://www.sages.org/recommendations-surgical-response-covid-19
5. Philippines Association of HPB Surgeons. Philippines Association of HPB Surgeons Recommendations in Time of COVID-19 Pandemic. [cited 21 March 2020]. Available from: https://drive.google.com/file/d/1X7hvDacbpupydE__TmMpaEBBVf4ChskQ/view?fbclid=IwAR1V4qyUOtYBwDvsLUldgqwPCNaDWIbUPN1LZx0PEx3ZfPm5ZDqzU3Vn5As
6. Ministry of Health Malaysia. Guidelines on Management of Coronavirus Disease 2019 (COVID-19) in Surgery. [cited 25 March 2020]. Available from: https://www.moh.gov.my/moh/resources/Penerbitan/Garis%20Panduan/COVID19/annex_22_COVID-19_Guidelines_Surgical_ 22032020.pdf
7. Chiu PW, Chiu PW, Ng SC, Inoue H, Reddy DN, Hu EL, et al. Practice of Endoscopy During COVID-19 Pandemic: Position Statements of The Asian Pacific Society for Diges-tive Endoscopy (APSDE-COVID Statements), Gut 2020; 69(6): 991-6.
8. Ministry of Health Malaysia. Press Release: Updates on The Coronavirus Disease 2019 (COVID-19) Situation in Malaysia. [cited 16 July 2020]. Available from: http://covid-19.moh.gov.my/terkini/072020/situasi-terkini-16-julai-2020/PS%20DG,%20COVID-19%20updates%20(16%20July%202020).pdf
9. Balakrishnan A, Lesurtel M, Siriwardena AK, Heinrich S, Serrablo A, Besselink MG, et al. Delivery of hepato-pancreato-biliary surgery during the COVID-19 pandemic: an Euro-pean-African Hepato-Pancreato-Biliary Association (E-AHPBA) cross-sectional survey. HPB 2020; 22(8): 1128-34.
10. Lee Y, Kirubarajan A, Patro N, Soon MS, Doumouras AG, Hong D. Impact of hospital lockdown secondary to COVID-19 and past pandemics on surgical practice: A living rapid systematic review. Am J Surg 2021; 222(1): 67-85.

LETTER TO THE EDITOR

Human papillomavirus assay design is a crucial consideration for self-collection based cervical screening

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Dear Editors,

Tan and colleagues recently published an interesting study [1] which used self-collection in a remote region of Malaysia during the first wave of the COVID19 pandemic in May, 2020. The study design involved participants collecting their own specimen which was then transported to the Universiti Malaysia Sarawak for testing using the careHPV test. The primary finding of the study was that only one out of 55 (1.82%) participants returned a positive high-risk Human papillomavirus (HPV) result. The incorporation of self-collection into the testing paradigm should be applauded but there are some critical technical issues which the authors didn't address. careHPV has met the World Health Organization (WHO) standard for pre-qualification with a positive agreement of 74.42%, however wasn't able to meet international standards for clinical validation, primarily due to a lack of sensitivity compared to a reference assay (0.86 (95%CI 0.79 – 0.94)) for cervical intraepithelial neoplasia grade 2+ (CIN2+).[2] careHPV has an European claim for self-collection, however independent studies have shown that it, along with other signal amplification assays, are not suitable for self-collection due to insufficient sensitivity.[3]

Another aspect of careHPV, which the authors acknowledge as a limitation, is the lack of a control for sample adequacy. Pragmatically, this means that if a collection device is returned without any specimen being collected, careHPV would produce a negative result, rather than an error noting insufficient material to test. If participants in a study didn't engage with the process it may produce samples which lack any clinical specimen.

The authors have previously undertaken a study in the same region of Sarawak which used the careHPV test, but with clinician-collected specimens. The oncogenic HPV positivity rate for this earlier study was 8% (6/75). The obvious difference in protocol between these two studies is that of clinician-collected vs self-collected specimens. The author's highlight this as a possible limitation but provided citations to suggest that other studies have shown strong concordance between self- and clinician collected specimens for the same patient. As no clinician-collected specimens were obtained during the current study it is difficult to draw the same conclusions on concordance between sample types when they are taken from different people. Another outcome of this study was that only 10 participants completed the self-sampling perception survey, compared with 55 who undertook the initial HPV literacy study. This raises the possibility that participants may not have been engaged with the self-collection process.

The evidence highlighted above provides a rationale for why this study found so few positive results. A combination of participants returning swabs without clinical specimens, and the use of a HPV test which is less sensitive and lacks a sample adequacy control, could produce an outcome which underestimates the prevalence of oncogenic HPV.

REFERENCES

1. Tan CS, Hamzah ND, Ismail ZHF, Jerip AR, Kipli M. Self-sampling in Human Papillomavirus screening during and post-COVID-19 pandemic. Med J Malaysia 2021; 76(3): 298-303.
2. Arbyn M, Simon M, Peeters E, Xu L, Meijer CJLM, Berkhof J, et al. 2020 list of human papillomavirus assays suitable for primary cervical cancer screening. Clin Microbiol Infect 2021; 27(8): 1083-95.
3. Arbyn M, Smith SB, Temin S, Sultana F, Castle P, Testing CoS-SaH. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. BMJ 2018; 363: k4823.

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Lessons learned from chemotherapeutic and immunosuppressant induced Hepatitis B reactivation - a case series

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SUMMARY

This case series is to create awareness among clinicians on the importance of Hepatitis B screening prior to administration of chemotherapeutic agents and immunosuppressant in preventing Hepatitis B reactivation (HBVr). We also highlight the importance of identifying patients who are at risk of HBVr and when to initiate antiviral prophylaxis based on the current evidence-based guidelines. The case series consists of four patients seen in Hospital Selayang, Malaysia who developed fulminant liver failure secondary to chemotherapeutic agents or immunosuppressant induced HBVr. HBVr is likely to be of increasing clinical significance as potent immunosuppressive regimens are used more widely across all medical specialties. Clinicians should be made aware of the potential risk of patients developing fulminant liver failure following HBVr and its association with high morbidity and mortality. In the era of inexpensive Hepatitis B blood screening tests and safe potent antivirals, there is now a paradigm shift to make the test compulsory to screen all patient prior to initiation of chemotherapeutic agents or immunosuppressive therapy. Antiviral prophylaxis may be offered to more patients who are at risk of HBVr and the duration of both prophylaxis and subsequent monitoring may be extended until 6 to 18 months following completion of treatment.

KEYWORDS:
Hepatitis B reactivation, Chemotherapeutic induced Hepatitis B, Immunosuppressant induced Hepatitis B, Acute liver failure, Fulminant liver failure

INTRODUCTION

Hepatitis B virus (HBV) infection is a worldwide disease associated with significant morbidity and mortality. After acute infection, HBV infection can persist in about 1-2% of immunocompetent hosts.[1] In Malaysia, the incidence of hepatitis B was reported to have increased from 2.26 per 100,000 in 2010 to 12.65 per 100,000 population in 2015.[1] Most hepatitis B patients diagnosed now were born in the pre-vaccination era, with approximately 45% to 50% of them aged between 20 to 40 years.[1] Chemotherapeutic and immunosuppressant induced Hepatitis B reactivation (HBVr) is a life threatening complication leading to discontinuation of the required definitive treatment, fulminant hepatitis with severe acute liver failure and death. We present a case series of four patients who were seen in Hospital Selayang, Malaysia to illustrate the lessons learned.

CASE REPORTS

Case 1

A 35-year-old Malay gentleman who was diagnosed with Nasopharyngeal Carcinoma stage IVB (T3N3aM0) and who underwent 3 cycles of neo-adjuvant chemotherapy, given Cisplatin and 5-florouracil (Table I). Subsequently, was planned for his first fraction of radiotherapy but was noted to be deeply jaundiced with deranged liver enzymes. Hepatitis screening was done and his HBsAg came back as reactive. Of note, he had a strong family history of Hepatitis B, but he had never been screened before. He was admitted for close monitoring and initiation of anti-viral therapy.

Clinically he was jaundiced with no signs of hepatic encephalopathy and no stigmata of chronic liver disease. His vital signs were stable and systemic examination were unremarkable. Blood tests were as shown in Table II. Ultrasound Abdomen showed normal liver size with coarse echotexture and irregular margin. No splenic varices or ascites were present.

He was started on oral Tenofovir 300mg daily and transferred to our Liver centre. On day 13 of his admission, he decompensated further whereby he developed ascites and subsequently Grade I hepatic encephalopathy. At this point he was diagnosed to have acute on chronic liver failure (ACLF) Grade I with AARC score of 7. He was treated aggressively with ACLF management which included corrections of his electrolytes, fluid management, IV human albumin, IV N-Acetyl Cysteine and broad-spectrum antibiotic. Initially he responded well and had reversal of his encephalopathy after 2 days. However, his prolonged hospitalisation had led to septicaemia, and he succumbed subsequently.

Case 2

A 27-year-old Chinese lady with underlying vertically transmitted Chronic Hepatitis B (CHB) diagnosed at birth and diagnosed with Myasthenia Gravis aged 25. She was a treatment naïve Hepatitis B carrier with baseline HBV DNA of 24 IU/ml. She was a non-smoker, teetotaler with no history of drug abuse. She was single and not sexually active.

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Table I: Summary of patient's demographic, treatment, risks of HBVr and mortality outcome

Case	1	2	3	4
Age	35	27	52	61
Gender	Male	Female	Female	Female
Ethnicity	Malay	Chinese	Malay	Chinese
Co-morbidity	Nasopharyngeal carcinoma	Myasthenia gravis	Invasive breast Icarcinoma	Non hodgkin lymphoma
Known Hepatitis B	No	Yes	No	No
Family history of Hepatitis B	Yes	Yes	Yes	Yes
Chemotherapeutic Agents or Immunosuppressant received	Cisplatin 5-florouracil	High dose Corticosteroid	5-fluorouracil Epirubicin Cyclophosphamide	Rituximab Cyclophosphamide Doxorubicin Vincristine Prednisolone
Risk of HBVr	Moderate	High	High	High
Mortality at Day 90 from onset of jaundice	Deceased	Deceased	Alive (Palliative Care)	Deceased

Her myasthenic crisis was treated with plasma exchange and high dose corticosteroid. Initially she was prescribed with intravenous hydrocortisone 100mg 8 hourly and then it was changed to oral prednisolone at 1mg/kg/day. She was discharged well on tapering dose of oral prednisolone, oral Mycophenolate Mofetil 1g twice daily and oral pyridostigmine 60mg 6 hourly.

She presented 6 months later with 3-day history of jaundice, coagulopathy, and markedly elevated transaminases. Blood tests were compatible with acute flare of Hepatitis B (Table II). On day 5 of admission, she clinically deteriorated and developed Grade I hepatic encephalopathy. She was transferred to our liver center for further management and an emergency liver transplant work out was activated. Her AARC score was 10 at Day 0 with Grade II ACLF. Her condition continued to worsen despite optimal care and treatment. Unfortunately, she finally succumbed due to multi-organ failure while awaiting a cadaveric liver transplant.

Case 3

This was a 52- year-old Malay lady with underlying toxic multi-nodular goiter post radioactive iodine therapy. She had defaulted her thyroid hormone replacement therapy having been asymptomatic despite biochemically being hypothyroid with TSH 7.28mU/L and FT4 7.0 pmol/L. She was diagnosed to have Left breast invasive carcinoma Stage IV (T2N0M1) with bilateral lung nodules suggestive of metastasis. Histopathology examination revealed positive estrogen and progesterone receptors with negative C-erb-B2 receptor. She was started on 6 cycles of neo-adjuvant chemotherapy containing 5-fluorouracil, Epirubicin and Cyclophosphamide. During her admission for the 6th cycle of chemotherapy, she was noted to be jaundiced and was scheduled for repeat of her blood tests.

She was called in for admission when her blood tests showed features of acute flare of Hepatitis B. She was not known to have Hepatitis B before but had a very strong family history of Hepatitis B. She was initiated on anti-viral therapy, oral Tenofovir 300mg daily but continued to be further decompensated throughout the first month of therapy with refractory ascites which responded poorly to diuretics and regular peritoneal paracentesis.

Further assessment by our multi-disciplinary team, we decided that she was no longer a candidate for surgical intervention for a left breast mastectomy and axillary clearance nor chemotherapy. She finally opted for palliative care and currently having limited mobility with dependent basic activity of daily livings.

Case 4

A 61-year-old Chinese lady with history of previous Hepatitis B infection, her last HBsAg taken more than 10 years ago during her insurance medical check-up was non-reactive. Her father had Chronic Hepatitis B hence giving a strong family history. She had history of prolonged cough and treated as steroid dependent pneumonitis. Computed tomography (CT) imaging of her lungs showed right middle lobe consolidation; a core biopsy was done, and histopathology examination revealed the diagnosis of Extra Nodal Marginal Zone Lymphoma, a subtype of non-Hodgkin Lymphoma (stage IV).

In view of the site of interest and her performance status, she was subjected to 6 cycles of induction chemotherapy with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone (R-CHOP regime). She had excellent metabolic response and attained complete metabolic remission at the end of her treatment. Subsequently, she received further consolidation chemotherapy of Rituximab but unfortunately then she developed HBVr.

A week following her second dose of Rituximab, she presented with symptoms of jaundice, tea colored urine, lethargy, nausea, abdominal distention and reduced oral intake. Clinically she was afebrile, deeply jaundiced with no evidence of hepatomegaly or splenomegaly. Ultrasound abdomen showed normal liver size with smooth margin and relatively hypoechoeic liver parenchyma with prominent periportal echoes consistent with inflammation. Blood investigations revealed HBV DNA of 142,196,020 IU/ml and both reactive HBsAg and HBeAg. She was started on T. Entecavir 0.5mg daily but went into fulminant liver failure and ACLF shortly after and finally succumbed.

DISCUSSION

The definition of HBV reactivation (HBVr) varies between guidelines, but the basic concept is the same. Individuals with

Table II: Summary of blood investigations trend and AARC scores of all 4 cases

Case 1	**Chronology of results**						
Day(s) of jaundice	1	7	19	23	26	35	41
Day(s) after anti-viral treatment		1	13	17	20	29	35
Day(s) of ACLF							
AARC* Score (Grade)			**Day 0 7 (I)**	**Day 4 8 (II)**	**Day 7 10 (II)**		
Total Bilirubin (umol/L)	18.6	166.9	630	446	491	630	707
INR		2.2	4.6	4.0	3.7	4.8	9.0
Lactate (mmol/L)			0.96	0.64	1.69		
Creatinine (umol/L)		49	47	54	60	54	52
Hepatic encephalopathy (Grade)	Nil	Nil	Grade II	Nil	Nil	Grade III	Nil
HBV DNA (IU/ml)							
Log		68,542 4.84					
Case 2							
Day(s) of jaundice	3	4	6	11	14	16	19
Day(s) after anti-viral treatment		1	3	8	11	13	16
Day(s) of ACLF							
AARC Score (Grade)			**Day 0 10 (II)**	**Day 4 10 (II)**	**Day 7 11 (III)**		
Total Bilirubin (umol/L)	193	305	408	483	471	438	-
INR		5.78	4.8	4.1	3.8	5.3	8.4
Lactate (mmol/L)			1.84	1.96	2.7	8.01	4.26
Creatinine (umol/L)	54	43	40	48	41	29	109
Hepatic encephalopathy (Grade)	Nil	Nil	Grade II	Nil	Nil	Grade III	Grade IV
HBV DNA (IU/ml)							
Log (log10)				7,055 3.85			
Case 3							
Day(s) of jaundice	3	5	30	34	38	43	91
Day(s) after anti-viral treatment		1	26	30	34	39	87
Day(s) of ACLF							
AARC Score (Grade)				**Day 0 8 (II)**	**Day 4 8 (II)**	**Day 4 8 (II)**	
Total Bilirubin (umol/L)	347	446.9	421.2	333	370	386	240
INR	1.9	1.7	1.9	1.8	1.9	2.1	2.4
Lactate (mmol/L)				1.82	1.14	1.37	
Creatinine (umol/L)				56	68	139	78
Hepatic encephalopathy (Grade)	Nil	Nil	Nil	Nil	Nil	Nil	Nil
HBV DNA (IU/ml)							
Log (log10)		40,900,000 -		4,299 3.63			
Case 4							
Day(s) of jaundice	7	15	20	24	27	28	33
Day(s) after anti-viral treatment	1	9	14	18	21	22	27
Day(s) of ACLF							
AARC Score (Grade)			**Day 0 11 (III)**	**Day 4 11 (III)**	**Day 7 9 (II)**		
Total Bilirubin (umol/L)	46.9	230.9	367.8	477	475	595	509
INR	1.5		5.0	7.3	9.1	10.3	7.5
Lactate (mmol/L)	2.31		2.22	6.28	1.27		
Creatinine (umol/L)	35	46	64	58	59	151	199
Hepatic encephalopathy (Grade)	Nil	Nil	Grade I	Nil	Nil	Grade III	Grade IV
HBV DNA (IU/ml)							
Log (log10)	142,196,020 10		257,934 5.41				

*AARC: APASL ACLS Research Consortium

Table III: Risk of Hepatitis B reactivation stratified by immunosuppressive regimen

	HBsAg positive	HBsAg negative, anti-HBc positive
Low Risk < 1%	• Traditional immunosuppressive agents (e.g.: azathioprine, methotrexate) • Intra-articular corticosteroids • Any dose of oral corticosteroids daily for <1 week	• Traditional immunosuppressive agents (e.g.: azathioprine, methotrexate) • Intra-articular corticosteroids • Low-dose corticosteroids for ≥4 weeks (e.g.: prednisolone <10 mg or equivalent) • Any dose of oral corticosteroids daily for <1 week
Moderate Risk 1-10%	• Less potent TNF-α inhibitors (e.g. etanercept) • Cytokine or integrin inhibitors (e.g. abatacept, natalizumab) • Tyrosine kinase inhibitors (e.g. imatinib, nilotinib) • Immunophilin inhibitors, including cyclosporine • Proteasome inhibitors (e.g.: bortezomib) • Histone deacetylase inhibitors • Low dose corticosteroids for duration of ≥4 weeks (e.g.: prednisolone <10mg daily or equivalent) • Systemic chemotherapy	• TNF-α inhibitors (e.g., etanercept, adalimumab, infliximab) ☒ • Cytokine or integrin inhibitors (e.g., abatacept, natalizumab) • Tyrosine kinase inhibitors (e.g. imatinib, nilotinib) • Moderate to high dose corticosteroids daily for ≥4 weeks Moderate dose (e.g.: prednisolone 10-20mg daily or equivalent) or high-dose (e.g.: prednisolone >20 mg daily or equivalent) • Anthracycline derivatives (e.g., doxorubicin, epirubicin) • Immunophilin inhibitors, including cyclosporine • Proteasome inhibitors (e.g.: bortezomib) • Histone deacetylase inhibitors • Systematic chemotherapy, including HCC
High Risk > 10%	• B-cell depleting agents (e.g.: rituximab) • Anthracycline derivatives (e.g.: doxorubicin, epirubicin) • Moderate to high dose corticosteroids daily for ≥4 weeks Moderate dose (e.g.: prednisolone 10-20mg daily or equivalent) or high-dose (e.g.: prednisolone >20 mg daily or equivalent) • Potent TNF-α inhibitors, (e.g.: adalimumab, infliximab) • Local treatment for HCC (e.g.: TACE)	• B-cell depleting agents (e.g.: rituximab)

Note: Anti-HBc = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBVr = hepatitis B virus reactivation; HCC = hepatocellular carcinoma; TACE = trans arterial chemoembolization; TNF = tumour necrosis factor
Source referenced from [4].

CHB (HBsAg positive for at least 6 months and measurable HBV DNA in the blood) and previously infected but serologically cleared HBV infection (HBsAg negative, anti-HBV-core antibody (anti-HBc) positive) are both susceptible to HBVr. In patients with CHB, reactivation is defined by a rise in HBV DNA above baseline.[2] In patients with previous HBV, reactivation is defined by either the appearance of HBV DNA in the blood or conversion to the reactive HBsAg state.[2] The latter process is known as reverse seroconversion.

Advancement in the treatment of inflammatory and malignant diseases have led to the upsurge use of chemotherapeutic and immunosuppressant as the treatment of a wide range of medical specialties. These advancements in treatment options have been met with the challenge of increased risk of HBVr. It is important to recognize that HBVr in this clinical setting is potentially preventable. Therefore, screening (Figure 1) and identifying patients at risk of HBVr as well as institution of prophylactic antiviral therapy prior to initiation of immunosuppression is essential.[2] HBsAg and anti-HBc (total or immunoglobulin G) testing should be performed in all patients before initiation of any chemotherapeutic agents or immunosuppressant.

The subsequent step after screening is risk stratification based on virological status and chemotherapeutic or immunosuppressant regimen. The magnitude of risk of HBVr is associated with the HBV serological status of the individuals (Figure 1) and the potency and duration of immunosuppression (Table III). Patients with CHB have a higher risk than patients with previous HBV.[3,4,5] Hematopoietic stem cell transplant recipients (HSCT) and B cell–depleting therapies (e.g., rituximab) confer the highest risk among chemotherapeutic regimens.[5] The American Gastroenterological Association (AGA) suggests that anthracyclines (e.g., doxorubicin) and moderate-dose corticosteroids (≥10 mg of daily prednisone or equivalent for ≥4 weeks) confer higher risk than other immunosuppressant agents.[3,6]

The final step in preventing HBV reactivation is tailoring management based on risk stratification. For patients with CHB, prophylactic antiviral therapy should be administered for at least a week before the initiation of chemotherapeutic agents or immunosuppressive therapy, regardless of baseline serum HBV-DNA level.[7] First line nucleoside analogue (NA) for example Entecavir or Tenofovir was preferred over other

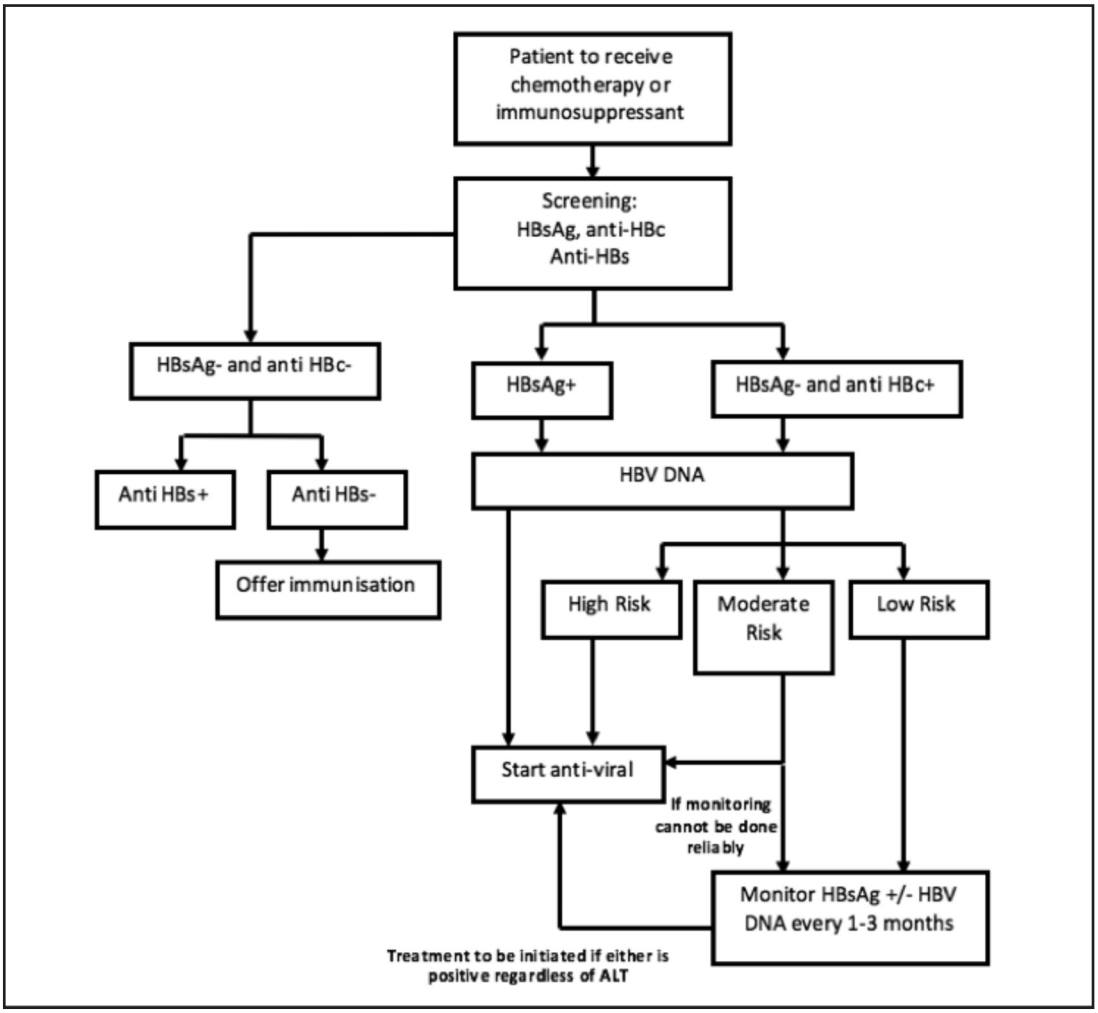

Fig. 1: Screening algorithm for management of patients who are planned to receive chemotherapy or immunosuppressant and are at risk of Hepatitis B reactivation.

NAs because of their higher potency and high resistance barrier, as multiple meta-analyses have shown reduction in reactivation, hepatitis, mortality, and anticancer therapy interruption.[6,7]

Antiviral prophylaxis should be continued well after cessation of immunosuppression, generally 12 to 18 months if high-potency therapies are used, particularly for patients who undergo HSCT or received B cell–depleting therapies[7] and 6 to 12 months for other agents.[3,5] Once prophylaxis treatment is withdrawn, it is recommend for clinicians to continue biochemical monitoring as there were large percentage of reactivation cases occurring after antiviral withdrawal. However, for patients receiving chronic immunosuppression, for example transplantation and biological therapy, much less is known about the optimal duration of prophylaxis that is needed.

CONCLUSION

Hepatitis B reactivation is preventable if patients who are at risk are appropriately identified through screening and triaged to an appropriate treatment strategy. This case series highlights the importance of HBV screening in patients who are planned for chemotherapeutic or immunosuppressive therapy. We suggest that there is more work to be done to improve HBV screening rates and education on preventing Hepatitis B virus reactivation.

CONSENT TO PARTICIPATE

This study was registered under National Medical Research Register (NMRR ID: 20-2546-57421) dated 27th November 2020 and the patients gave written informed consent for the use of the data in this publication.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

FUNDING

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REFERENCES

1. Malaysia National Strategic Plan for Hepatitis B & C 2019-2023 Jan 2019 [cited Nov 2020]. Available from: https://www.moh.gov.my/moh/resources/Penerbitan/Pelan%20Strategik%20/NSP_Hep_BC_2019_2023.pdf.
2. Patullo V. Prevention of Hepatitis B reactivation in the setting of immunosuppression. Clin Mol Hepatol 2016; 22(2): 219-37.
3. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy. Gastroenterology 2015; 148(1): 215-9.
4. Koffas A, Dolman GE, Kennedy PTF. Hepatitis B virus reactivation in patients treated with immunosuppressive drugs: a practical guide for clinicians, Clinical Medicine 2018; 18(3): 212-8.
5. Myint A, Tong MJ, Beaven SW. Reactivation of Hepatitis B virus: a review of Clinical Guidelines. Clin Liver Dis 2020; 15(4): 162-7.
6. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection, J Hepatol 2017; 67: 370-398.7.
Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM et al. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance, Hepatology 2018; 67(4): 1560-99.

CASE SERIES

Temporal bone squamous cell carcinoma: A change in treatment

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SUMMARY

Temporal bone squamous cell carcinoma (TBSCC) is a rare head and neck malignancy with the incidence 0.8 –1.0 cases in 1 million population. We are reporting a case series on the TBSCC cases that were operated on at Sarawak General Hospital, Malaysia. Ten patients were identified and collected with the presentation and type of surgery performed. It has been challenging for us to manage with recorded 2 years surviving in 6 out of 10 patients operated within this period. An adequate management with proper surgical resection of tumour and radiotherapy can extend the life expectancy for TBSCC patients.

KEYWORDS:
Temporal bone, Squamous cell Carcinoma, Resection

INTRODUCTION

Malignant neoplasm of temporal bone is a rare disease with an incidence of 0.8 – 1.0 cases per million population per year.[1,2] Squamous cell carcinoma is one of the most common reported variants. Nonetheless, it only constitutes 0.2% of the total head and neck malignancy.[3] Other variants of this malignancy that have been reported include basal cell carcinoma, adenoid cystic, melanoma chondrosarcoma, Ewing's tumour and fibroxanthoma.[2] Temporal bone squamous cell carcinoma (TBSCC) has always been described for its aggressive behaviour with invasion to the surrounding structure via bony canals or intraosseous vessels.[4]

To date, to our best knowledge, there is no consensus on the management of this rare disease. There is still an ongoing debate with regards to the preferred staging method that should be used for TBSCC. In particular, Sarawak General Hospital (SGH), Malaysia is a tertiary healthcare centre in the state of Sarawak. SGH receives all the complicated surgery cases from all over the state. We aimed to review the outcome of the temporal bone surgeries in treating TBSCC in SGH, Malaysia.

MATERIALS AND METHODS

We retrospectively reviewed and audited 10 patients who were diagnosed with TBSCC from the years 2014 to 2019. Data was traced from the SGH record unit. All the patients were operated by the same surgeon. All patients went through regular Ear Nose Throat (ENT) examination. Patients who were confirmed with squamous cell carcinoma from the histopathological examination (HPE) of the external auditory mass were arranged for computed topography (CT) imaging of temporal bone as well as whole body staging. Modified Pittsburgh system was used to stage our patients.5 Operation was planned and introduced to all patients who were confirmed to have TBSCC from the biopsy of their external auditory canal tissue. During the review, we excluded those patients who were diagnosed with TBSCC but not fit for surgery after anaesthetist review, as well as patients who did not agree for any intervention. Surgical resection was deployed as the treatment for all the patients, followed by radiotherapy with or without chemotherapy. LTBR was performed on patients with T1 and T2 lesions, whereas STBR was performed in T3 and T4 lesions (Figure 1A).

RESULTS

The median age for this case series was aged 50 years with a male predominance. Of note, the youngest patient in our case series was only 13 years old. More than half of our patients presented with otorrhoea (n=7) and otalgia (n=6). Three patients reported hearing loss or reduced hearing, and external auditory canal mass was seen in two patients. Only one of our patients presented with facial nerve palsy. Most of our patients presented at stage III of the disease. One patient had a history of nasopharyngeal carcinoma with head and neck radiotherapy performed. Two patients had history of chronic otitis media for more than six months. Details of our patients is shown in Table I.

All the patients had lateral and subtotal temporal bone resection done as stated in Table I. A modified radical neck dissection was planned for patients who were noted to have cervical lymph node involvement in CT scan. Six of 10 patients had neck dissection performed, and one patient had HPE confirmed neck involvement. One of our patients did not go for radiotherapy as he had recently received radiotherapy for concurrent nasopharyngeal carcinoma.

DISCUSSION

Primary squamous cell carcinoma (SCC) of the temporal bone is an uncommon head and neck malignancy with aggressive behaviour. It was first described by Schwartze and

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Table I: Patients' data

No.	Age	Gender	Race	Comorbidities	Duration of presentation	Presentation	Side	Staging	HPE	Surgery	Parotid involvement from HPE	Radiotherapy	Status
1	13	M	Iban	Resolved otitis media	1 week	Otalgia	Right	T1N0M0	Moderately differentiated squamous cell carcinoma	Right lateral TBR, right Selective neck dissection	No	Yes	No recurrence for 2 years
2	46	M	Chinese	Diabetes mellitus, hypertension, end stage renal failure	1 month	Otalgia, otorrhea	Right	T1N0M0	Squamous cell carcinoma	Right lateral TBR	No	Yes	Death due to other disease after 1 year, i.e., Pneumonia
3	45	M	Iban	Nasopharyngeal carcinoma treated in year 2009	1 month	Otalgia, otorrhea, hearing loss	Right	T2N0M0	Moderately differentiated squamous cell carcinoma	Right lateral TBR	No	No	No recurrence for 5 years
4	53	M	Chinese	No comorbid	NA	Hearing loss	Left	T3N0M0	Invasive, moderately differentiated squamous cell carcinoma	Left subtotal TBR	No	Yes	No recurrence for 5 years
5	48	M	Bidayuh	Chronic otitis media for 6 years	3 months	Otorrhea, otalgia	Right	T3N0M0	Poorly differentiated squamous cell carcinoma	Right subtotal TBR	Yes	Yes	No recurrence for 3 years
6	68	F	Iban	No comorbid	6 months	Otalgia, otorrhea, facial weakness, vertigo	Left	T3N0M0	Well differentiated squamous cell carcinoma	Subtotal TBR, left parotidectomy, left MRND	No	Yes	Death due to disease
7	58	M	Chinese	No comorbid	2 months	Ear mass, otorrhea, postauricular fungating ulcer	Left	T3N0M0	Well differentiated squamous cell carcinoma	Right subtotal TBR, right total parotidectomy, right MRND	No	Yes	Death due to disease
8	62	M	Iban	No comorbid	3 months	Otorrhoea	Right	T3N0M0	Moderately differentiated squamous cell carcinoma	Right subtotal TBR, right parotidectomy and right MRND	No	Yes	No recurrence for 3 years
9	48	M	Malay	Diabetes mellitus, dyslipidaemia	10 years	Ear mass, bleeding, otalgia	Left	T3N0M0	Well-differentiated squamous cell carcinoma	Left subtotal TBR, left total parotidectomy, left MRND and pectoralis major free flap	Yes	Yes	No recurrence for 2 years
10	52	F	Iban	Hypertension	4 months	Ear mass, otorrhea, reduced hearing	Left	T4N1M0	Well differentiated SCC	Left subtotal TPR, total parotidectomy, left MRND	Yes	Yes	Death due to disease after 2 years

N.B.: MRND: Modified radical neck dissection, SCC: squamous cell carcinoma, TBR: Temporal bone, resection, SCM: sternocleidomastoid, NA: not available

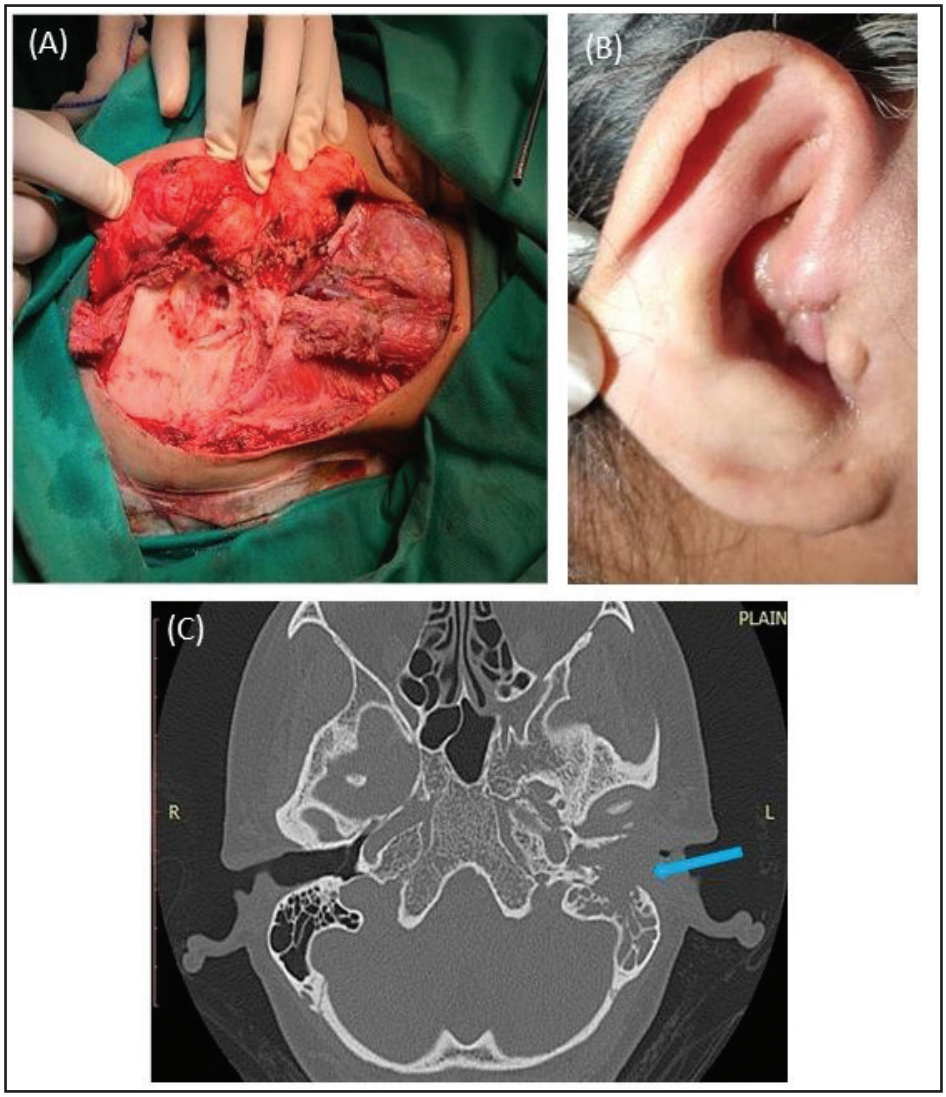

Fig. 1: Images of patients with temporal bone squamous cell carcinoma. (A) Intra-operative image of right subtotal temporal bone resection (B) External auditory mass (C) Computed tomography imaging at the base of skull in bone window, showing a mass in the external auditory canal of the left ear (blue arrow) that is invading into the left mastoid air cells.

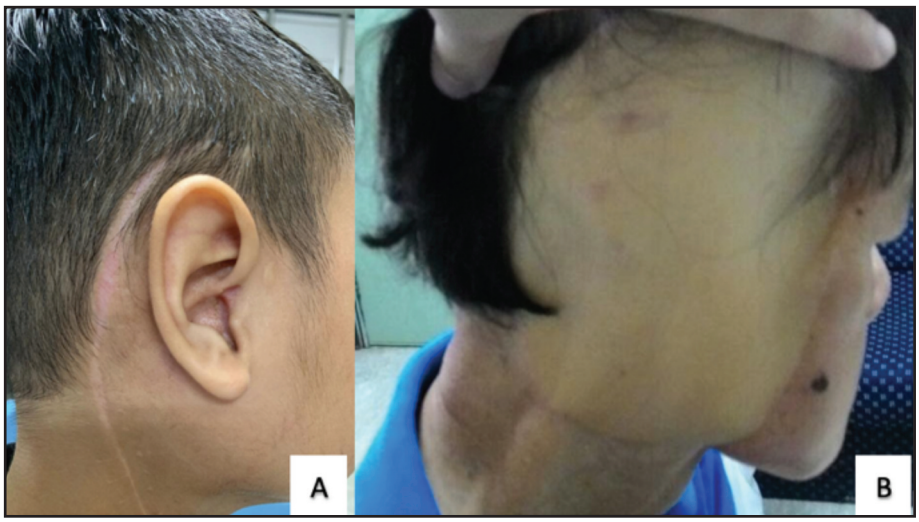

Fig. 2: Post-operative wound with (A) primary closure and (B) reconstruction with pectoralis major free flap.

Wide in 1775, but the first publication about TBSCC was only presented by Newhart in his case series in 1917.6 Due to the rarity of this condition, it remains a challenge to clinicians in diagnosing and managing the TBSCC. The incidence of TBSCC was reported to peak in the 6th decade of life with male predominance (male: female ratio of 1.7:1).[1,7] However, in our case series, the youngest patient was 13 years old and this raises the question of whether advanced age is truly a contributing risk factor for this rare malignancy.

The exact aetiology of TBSCC remains unknown. Whilst the use of alcohol and tobacco have always been related with SCC in head and neck, this cannot be applied to TBSCC.[8] More than half of our patients in this case series presented to us with otorrhoea and otalgia, with duration ranging from 1 months to as long as 6 months. One of them was treated as chronic otitis media for 6 years, and recently presented with bleeding from the ear with scanty foul-smelling discharge for 3 months with high suspicion of malignancy. Modified mastoidectomy was performed and revealed inflammatory granulation. Our findings correlate with previous studies, which show that chronic inflammatory process and chronic otorrhoea are risk factors for TBSCC.[9] It is postulated that chronic inflammation undergoes malignancy transformation when recovery fails.[10] Other symptoms such as facial nerve palsy, external auditory mass (Figure 1B), hearing loss with tinnitus are also found to be associated with TBSCC. History of radiation has been proposed as one of the causes of TBSCC.[11] Lending support to this, one patient in our case series had a history of nasopharyngeal carcinoma and completed radiotherapy was found to have TBSCC. Interestingly, human papillomavirus (HPV) exposure with detection of high-risk genotype HPV 16 and HPV 18 in chronic otitis media and cholesteatoma gave a hypothesis of relation between HPV with TBSCC.[12] The above mentioned presentations, however, are insidious presentations of temporal bone SCC that cause delays in seeking treatment.[13] The spread of TBSCC to cervical lymph nodes have also been reported. The pathway through which TBSCC spread is through the tegmen tympani, fissure of Santorini and foramen of Huschke into the middle cranial fossa or infratemporal fossa, thus causing headache, parotid swelling and ulceration in the surrounding skin.[1]

Imaging investigation helps clinician to evaluate extension of malignancy. High resolution computed tomography (HRCT) scan of the temporal bone provides useful information of the tumour and the surrounding bony erosion (Figure 1C).[13] However CT scan was reported to have limited role in identifying soft tissue involvement.[14,15] Magnetic resonance imaging (MRI) overcomes this limitation by giving information on perineural, parotid gland and any regional lymph node invasion as well as vascular and dural involvement.[15] Therefore, both HRCT and MRI are required for staging the disease. Biopsy is mandatory in order to establish the diagnosis of TBSCC.16 Additionally, imaging enables clinicians to precisely locate and obtain tissue biopsy for histopathological examination. The presence of inflammation and oedema may hinder the success of an accurate biopsy; thus, a deep tissue biopsy is often required to yield a positive result.[16] Further investigation with arterial or venous angiography can be arranged when there is vascular invasion seen on MRI. Imaging is also useful for disease staging and to guide the management or treatment planning for patients with TBSCC. Unfortunately, in SGH, MRI is usually approved for cases suspicious of neurological involvement only. CT scan is, thus far, sufficient in our setting to confirm the origin as well as the location of the tumour. Ninety percent of our operated patients were at disease stage ≤T3.

To date, the Modified Pittsburgh Staging system is widely used in staging TBSCC. American Joint Committee of Cancer (AJCC) staging for head and neck malignancies was used before the Pittsburgh system was introduced by Arriaga et al. in 1990 with accuracy of 98%.[14,17] Our centre is mainly operating on patient with tumour staging of T3 and below. Patient with stage T4 malignancies was reported to have 5 years survival rate < 30%.[7,18] The only stage 4 patient that had operation performed was noted to have T3 preoperative and patient succumbed within 1 year postoperatively.

Surgery is the mainstay treatment for TBSCC.[1] The primary consideration that a surgeon has to bear in mind is when and what kind of resection is adequate in treating the patient. In the current era of oncology surgery, a proper multidisciplinary discussion is required for patients before surgery, which involve otorhinolaryngology, oncology and plastic and reconstructive surgery. This helps in the designing and explaining the method of surgery and planned post-operative management for the understanding of patients towards their disease. The diminished hearing observed postoperative as well as the swallowing rehabilitation need to be explained to the patients, as this might give a huge impact to the quality of life of patients after the treatment.

The principle of *en bloc* resection is to maximise the negative surgical margin, at the same time preserving the function of unaffected structures.[4,10] Unlike cutaneous SCC, a definite margin of tumour could not be clearly resected during the burring.[19] Intraoperative frozen section maximise the benefit in assurance of negative margin during single operative setting. Depending on the anatomical extension of malignancy, options for temporal bone resection (TBR) that have been introduced, which include lateral temporal bone resection (LTBR), subtotal temporal bone resection (STBR) (Figure 1A). and total temporal bone resection (TTBR).[1] Wound closure post resection should also be included as part of the surgical planning. Flap reconstruction will be necessary if the resected wound is not able to close primarily (Figure 2). Patient should not only be counselled on the complications of wound breakdown and disease recurrence postoperatively, but also the cosmetic outcome post-surgery.[20]

The decision of parotidectomy during TBR is remains inconclusive.[21] Due to the vicinity of parotid gland and temporal bone, direct spread of this malignancy is of high index of suspicion. Although the percentage is reported < 50% in T1 and T2 lesions, it is advised not to take the risk to exclude parotidectomy.[18,21] Suggestions have been given to perform superficial parotidectomy in patients with T1 and T2 lesions, and total parotidectomy in T3 and T4 lesions during an extended TBR.[10,21] In our retrospective review, 6 of patients with T3 had total parotidectomy performed in which 4 had

positive malignancy seen (67%). We performed biopsy of parotid tissue for T1 and T2 lesions, with no parotid involvement. However, if CT imaging and intraoperative revealed parotid involvement, parotidectomy is performed intraoperatively. These patients also had neck dissection done under the same setting, and it was noted that none has positive lymph node involvement. There was only one patient who had lymph node involvement in advanced (T4) temporal bone SCC. As most patient might have problem in travelling to SGH, we had performed functional neck dissection under same general anaesthesia setting in our patients based on presence of enlarged cervical lymph node in both the CT and MRI scan, to prevent patient go for a second surgery.

Postoperative prognosis is said to be good in patient with early stage (T1 and T2). Most review show drastically higher mortality rate for T3 and T4. The 5-year survival is 100% in T1 and T2, but 69% in T3 and only 20% in T4.[10,18] Lymph node involvement is also an indicator of poor prognosis and higher recurrence rate.[8] In our series, adjuvant radiotherapy played an important role in the management as a clear margin is hard to identified during burring. Six out of 8 patients who went through radiotherapy showed no recurrence for at least 2 years. There was one patient with a T3 lesion who defaulted the planned radiotherapy and succumbed 6 months later. To date, there is no definite conclusion regarding the effectiveness of postoperative adjuvant radiotherapy in temporal bone SCC. Our patients, however, were further discussed with the oncology team post-operative and radiotherapy was given to most of our patients, as our HPE could not provide clear information on tumour free margin.

In SGH, surgical management was planned to patient with T1 – T3. As mentioned earlier, logistic issue is also a problem in Sarawak because the patients come from remote areas and often present to us at an advanced stage of disease. Hence, it becomes challenging to perform both advanced resection and regular radiotherapy in managing our patients. Nevertheless, the survival rate at >2 years in postoperative temporal bone SCC at SGH is 70%. Patients need to be briefed regarding the indication, complications, as well as the compliance with clinic review so that recurrence can be detected earlier. The aetiology of human papilloma virus should also be studied further in the future.

CONCLUSION

This case series does not represent a standard management in treating temporal bone squamous cell. However, it is aimed at sharing our surgical experience in treating this malignancy. Patients with severe painful non-traumatic, bleeding ear should always be alert to the possibility of malignancy, and an earlier intervention with well-designed resection could provide a better prognosis for the patient. Despite limited resources, the properly planned resection of tumour along with radiotherapy can help to extend the life expectancy of these patients. The challenging part in managing TBSCC is the experience of the surgeon in identifying a normal and tumour infiltrated margin intraoperatively for adequate resection. The compliance of the patients with the treatment and follow up is needed for regular monitor and keeping them disease-free in future.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Lovin BD, Gidley PW. Squamous cell carcinoma of the temporal bone: A current review. Laryngoscope Investig Otolaryngol 2019; 4(6): 684-92.
2. da Silva AP, Breda E, Monteiro E. Malignant tumors of the temporal bone – our experience. Braz J Otorhinolaryngol 2016; 82(4): 479-83.
3. Zanoletti E, Marioni G, Stritoni P, Lionello M, Giacomelli L, Martini A, et al. Temporal bone squamous cell carcinoma: analyzing prognosis with univariate and multivariate models. Laryngoscope 2014; 124(5): 1192-8.
4. Martinez-Devesa P, Barnes ML, Milford CA. Malignant Tumors of the Ear and Temporal Bone: A Study of 27 Patients and Review of Their Management. Skull Base 2008; 18(01): 1-8.
5. Breen JT, Gidley PW. Evaluation and Staging of Temporal Bone Tumors. In: Gidley PW, DeMonte F, editors. Temporal Bone Cancer. Cham: Springer International Publishing; 2018. p. 15-28.
6. Gidley PW. Overview and Historical Developments. In: Gidley PW, DeMonte F, editors. Temporal Bone Cancer. Cham: Springer International Publishing; 2018. p. 1-13.
7. Yin M, Ishikawa K, Honda K, Arakawa T, Harabuchi Y, Nagabashi T, et al. Analysis of 95 cases of squamous cell carcinoma of the external and middle ear. Auris Nasus Larynx 2006; 33(3): 251-7.
8. McRackan TR, Fang T-Y, Pelosi S, Rivas A, Dietrich MS, Wanna GB, et al. Factors Associated With Recurrence of Squamous Cell Carcinoma Involving the Temporal Bone. Ann Otol Rhinol Laryng 2014; 123(4): 235-9.
9. Gamra OB, Abid W, Nacef I, Kdous S, Romdhane N, Chammakhi C, et al. Cholesteatoma associated with squamous cell carcinoma of the external auditory canal: Case report and literature review. Egypt J Ear Nose Throat Allied Sci. 2015; 16(3): 269-74.
10. Gidley PW, Roberts DB, Sturgis EM. Squamous cell carcinoma of the temporal bone. Laryngoscope 2010; 120(6): 1144-51.
11. Lo W-C, Ting L-L, Ko J-Y, Lou P-J, Yang T-L, Chang Y-L, et al. Malignancies of the Ear in Irradiated Patients of Nasopharyngeal Carcinoma. Laryngoscope 2008; 118(12): 2151-5.
12. Malagutti N, Rotondo JC, Cerritelli L, Melchiorri C, De Mattei M, Selvatici R, et al. High Human Papillomavirus DNA loads in Inflammatory Middle Ear Diseases. Pathogens 2020; 9(3): 224.
13. Allanson BM, Low T-H, Clark JR, Gupta R. Squamous Cell Carcinoma of the External Auditory Canal and Temporal Bone: An Update. Head Neck Pathol 2018; 12(3): 407-18.
14. Arriaga M, Curtin HD, Takahashi H, Kamerer DB. The Role of Preoperative CT Scans in Staging External Auditory Meatus Carcinoma: Radiologic-Pathologic Correlation Study. Otolaryngol Head Neck Surg 1991; 105(1): 6-11.
15. Gillespie MB, Francis HW, Chee N, Eisele DW. Squamous cell carcinoma of the temporal bone: a radiographic-pathologic correlation. Otolaryngol Head Neck Surg 2001; 127(7): 803-7.
16. Moffat DA, Wagstaff SA. Squamous cell carcinoma of the temporal bone. Curr Opin Otolaryngol Head Neck Surg 2003; 11(2): 107-11.
17. Arriaga M, Curtin H, Takahashi H, Hirsch BE, Kamerer DB. Staging proposal for external auditory meatus carcinoma based on preoperative clinical examination and computed tomography findings. Ann Otol Rhinol Laryng 1990; 99(9 Pt 1): 714-21.

18. Zhang B, Tu G, Xu G, Tang P, Hu Y. Squamous cell carcinoma of temporal bone: Reported on 33 patients. Head Neck 1999; 21(5): 461-6.
19. Kunst H, Lavieille JP, Marres H. Squamous cell carcinoma of the temporal bone: results and management. Otol Neurotol 2008; 29(4): 549-52.
20. Homer JJ, Lesser T, Moffat D, Slevin N, Price R, Blackburn T. Management of lateral skull base cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol 2016; 130(S2): S119-24.
21. Lee JM, Joo JW, Kim SH, Choi JY, Moon IS. Evidence Based Tailored Parotidectomy in Treating External Auditory Canal Carcinoma. Sci Rep 2018; 8(1): 12112.

Group A *Streptococcus* puerperal sepsis with invasive neonatal infection: A fatal case

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SUMMARY

Neonatal invasive Group A *Streptococcus* (GAS) infection is a rare occurrence nowadays. Prior maternal vaginal colonization is an important factor in early neonatal disease. We report a case of invasive and fatal infection in a neonate. At Day 1 of life, a term baby was found to be lethargic, with poor feeding, and later became unresponsive. Consequently, the baby was immediately brought to the Emergency Department of Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan via ambulance. Despite the active resuscitation efforts in the hospital, the baby died. An autopsy was carried out to determine the cause of death. The mother was noted to have puerperal pyrexia secondary to vaginal discharge. Her high vaginal swab culture was positive for GAS. GAS was also isolated from the intracardiac blood, pleural fluid, peritoneal fluid, and umbilical swab of the baby, giving evidence to the aetiology of the mortality. Vaginal colonization of GAS is an important factor for high morbidity and mortality for both mother and infant due to its invasiveness and virulence.

KEYWORDS:
Streptococcus pyogenes, Group A Streptococcus, GAS, neonate, puerperal sepsis

INTRODUCTION

Streptococcus pyogenes, also known as Group A *Streptococcus*, is a Gram positive, beta-haemolytic bacteria, and a significant human pathogen capable of causing broad range of infections from mild infections such as pharyngitis and impetigo to severe infections like necrotizing fasciitis and streptococcal toxic shock syndrome (STSS). An immune-mediated non-pyogenic complications such as acute rheumatic fever, post streptococcal acute glomerulonephritis, and post streptococcal reactive arthritis are also parts of the disease spectrum. In the United States, the incidence of Group A *Streptococcus* postpartum infection is 6 per 100 000 live births with 2% maternal mortality.[1] It is estimated that there is a 20-fold increased risk of invasive GAS in pregnant women compared to non-pregnant women.[2] The reported prevalence of vaginal-rectal colonization of GAS during pregnancy is very low as compared to Group B *Streptococcus*, 0.03% and 20% respectively.[3] Due to the rarity of GAS vaginal colonization and its low incidence of postpartum infection, a screening-based approach is not commonly done. We report here a case of invasive neonatal streptococcal disease resulting in a neonatal death and simultaneously illustrated a classical case of puerperal sepsis in her mother.

CASE PRESENTATION

A term baby girl, birth weight of 2.46 kg, was delivered by spontaneous vaginal delivery with an Apgar score of 9 in 1 minute. The baby was discharged home the next day. However, at home, the baby was not breastfeeding well throughout the evening until night. At 26 hours of life, the baby became more lethargic and grunting, hence brought to a hospital. Upon arrival at the Emergency Department of Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan, the baby was unresponsive with neither spontaneous breathing nor heart rate detected. Cardiopulmonary resuscitation was immediately commenced and the baby was intubated. The blood sugar level was low 2.3mmol/L hence 12 mL D10% bolus and 60 mL normal saline were administered intravenously. However, after 30 minutes of resuscitation, there was no return of spontaneous circulation and the baby succumbed. The baby was subjected to post-mortem examination due to undetermined cause of death.

At post-mortem examination, the external appearance of the baby was unremarkable. However, upon opening of the thoracic cavity, there was a diffuse area of patchy light brown discolouration over the inferior part of the right upper and middle lobe of the lungs. The pleural cavity was filled with a significant amount of thickened and cloudy fluid. There was presence of dilated alveolar air spaces at the periphery of the left lung with area of petechiae seen on the surface of the superior part of the left upper and lower lobes. The brain, lung and liver tissues were sent for histopathological examination. The histopathology result of the lung tissue showed scattered cocci-shaped bacteria and patchy intra-alveolar fibrinopurulent exudates with associated septal wall necrosis (Figure 1) as well as evidence of congestion in the background. Sections from the brain and liver showed

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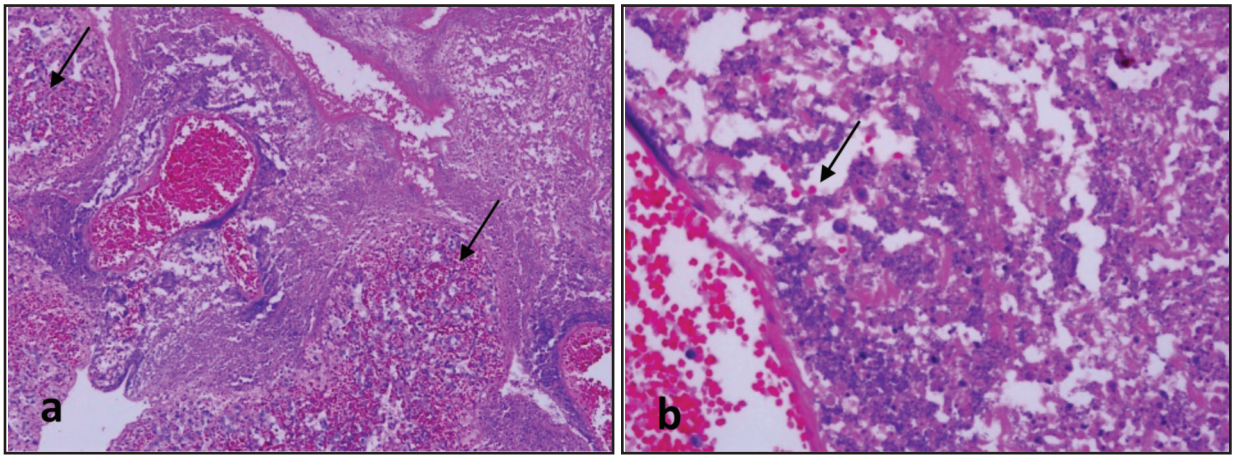

Fig. 1: Histopathological images showing fibrinopurulent exudates and scattered cocci-shaped bacteria (arrows) (a) Haematoxylin and Eosin (H&E) stain, magnification x 100, (b) H&E stain, magnification x 400.

congested tissues with no evidence of infection. Bacterial cultures of the peritoneal fluid, pleural fluid and intracardiac blood were positive for Group A *Streptococcus*.

Retrospectively, the baby was born to a 24-year-old housewife, a primigravida at 37 weeks' period of amenorrhoea. Apart from symptoms of labour, she also complained of vaginal itchiness associated with vaginal discharge for 6 days. She had a risk factor for gestational diabetes mellitus (DM) with family history of DM and hypertension. However, her oral glucose tolerance test (OGTT) done twice were normal. Her body mass index (BMI) at booking was 34.6.

She was admitted in the active phase of labour. On vaginal examination, her cervix was effaced with 5cm dilatation. Per speculum examination revealed minimal vaginal discharge and high vaginal swab sample was taken for culture. Later, she experienced spontaneous rupture of membrane with clear liquor, and labour progressed well in five hours without any complications. Finally, she delivered a baby girl via spontaneous vaginal delivery. Postpartum, she was afebrile, able to tolerate orally and was discharged home with her baby girl in the afternoon.

At day three postnatal, the mother experienced fever associated with chills and rigors for two days. There was no other symptom such as abdominal pain or foul smelly vaginal discharge. She visited local health clinic and was referred to a tertiary hospital for puerperal pyrexia. Her temperature was 39.9°C and tachycardic with heart rate of 148 bpm. However, other vital signs were stable. Transabdominal sonography was unremarkable. Her arterial blood gas showed respiratory alkalosis and the full blood count examination showed an elevated total white count of 22 x 10^9/L, with 90% neutrophils, haemoglobin level of 11.9 g/dL and platelet count 244 x 10^9/L. Her C-reactive protein (CRP) was more than 200 mgL. Her renal profile and coagulation study were normal. Her high vaginal swab culture was positive for Group A Streptococcus. However, the blood culture did not grow any organism. She was treated with IV piperacillin-tazobactam and clindamycin for 10 days and was discharged well. On the next clinic visit, she had no further complaints and was discharged from follow-up.

DISCUSSION

Neonatal infections are commonly caused by Group B *Streptococcus* and *Escherichia coli*. Group A *Streptococcus* is a rare causative agent but the infection can be invasive and fatal.[4] Invasive Group A streptococcal disease was defined as isolation of GAS from a normally sterile sites such as blood, CSF, joint, pleural and peritoneal fluid. The incidence of invasive neonatal GAS infection in the United Kingdom was 1.5 per 100 000 person years while in the United States of America, an increasing incidence of invasive GAS infections in children from 0.16 to 0.37 per 1000 admissions was observed within the 7-year period.[4,5]

The major virulence factor for GAS infection is M protein, encoded by emm gene. More than 125 emm gene types have been discovered, with certain types causing specific diseases. The predominant M serotypes causing invasive infections are M1 and M3 types. M protein is a major surface antigen that is capable of inhibiting the immune response and interferes with phagocytosis.[6]

Almost half of infants less than 3 months or early neonatal sepsis diagnosed with invasive GAS infection are severely ill, with the most common clinical presentation were respiratory distress, bacteraemia and non-specific signs of sepsis with rapid deterioration and high mortality similar to this case.[4,6] The overall mortality rate was as high as 31%.[6] Vertical transmissions via ascending spread from the vagina colonized by *Streptococcus pyogenes* during delivery is a possibility in this case. As reported by a previous study, vertical transmission accounted for 75% cases of early onset neonatal GAS disease.[6]

The management of severe invasive GAS disease involves mainly specific antimicrobial therapy, supportive treatment with fluid and electrolytes, minimizing or neutralizing the toxin effects and other measures on specific situation for example controlling the source of infection by extensive

surgical debridement in deep-seated abscess. Penicillin remains the treatment of choice and no resistance strain to this antibiotic has been encountered yet. The addition of clindamycin is beneficial especially in the case of streptococcal toxic shock as it can suppress exotoxin and M-protein production by GAS. Besides, it has longer half-life with no antagonist effect with penicillin.[7]

Unlike *Streptococcus* Group B that is common in causing neonatal sepsis, more extensive screening measures and aggressive maternal prophylaxis has been adopted as compared to maternal GAS, which is rarely detected due to its low prevalence of vaginal colonization, and rarely cause maternal and neonatal disease. So far, there has been no specific guidelines and recommendations on chemoprophylaxis for maternal GAS vaginal colonization or asymptomatic carriage. However, considering its nature of invasiveness and interaction with immunocompromised host, resulting in high morbidity and mortality, a more aggressive approach and intrapartum antibiotic prophylaxis should be considered whenever GAS is isolated from pregnant women.

Puerperal sepsis due to GAS infection may present with two or more of the following clinical manifestations: pelvic pain, fever, abnormal vaginal discharge, abnormal smell/foul odour discharge or delay in uterine involution.[7] Some of the identified host risk factors for perinatal infections are prolonged ruptured of membranes or prolonged labour, pre-existing comorbidities such as malnutrition, diabetes, severe anaemia, obesity, prior vaginal infections as well as repeated vaginal examinations and Caesarean section.[2] In our case, the mother had no identified risk factors except maternal obesity. It was postulated that women who are obese had elevated levels of inflammatory cytokines and monocytes, resulting in chronic state of inflammation causing the immune systems to be less responsive to the threat of infection and diminished their ability to mount an acute cytokines response to an infection.[8]

The less severe clinical presentation of the mother raised possibility of prior colonization or state of asymptomatic carriage before the onset of delivery as most patients with GAS colonization are asymptomatic. GAS can become the colonizer of oropharyngeal tract, vagina and even skin. The mechanism of colonization is poorly understood, it is suggested that GAS virulence factors and certain mutations leads to its ability to escape phagocytosis, simultaneously increasing its capacity in adherence to host cells.[9] In this patient (mother), the most striking symptom that she presented was per vaginal discharge several days before labour. Although this may appear common among pregnant ladies, this history should not be taken lightly. A study on pregnancy-related *S. pyogenes* revealed that 38.5% of patients with early puerperal sepsis presented with purulent vaginal discharge. GAS was isolated from the genitourinary tract in 76.9% of the cases, suggestive of prior vaginal colonization.[1] In conclusion, although routine screening for asymptomatic vaginal GAS carriage in pregnancy may not be indicated, isolation of GAS from vaginal specimens should prompt early clinical management and antimicrobial therapy to both mother and infant. However, this requires high degree of suspicion with optimum approach and management. Although it is quite challenging to differentiate normal leucorrhoea of pregnancy with pathological vaginal discharge in pregnancy, measures should be taken to suspect and detect GAS, so that an appropriate treatment can be initiated to prevent any devastating complications during the postnatal period.

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CONSENT

Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

CONFLICT OF INTEREST

The authors state that there is no conflict of interest to declare.

REFERENCES

1. Hamilton SM, Stevens DL, and Bryant AE. Pregnancy-related group a streptococcal infections: temporal relationships between bacterial acquisition, infection onset, clinical findings, and outcome. Clin Infect Dis 2013; 57(6): 870-6.
2. Phillips C. and Walsh E. Group A streptococcal infection during pregnancy and the postpartum period. Nurs Womens Health 2020; 24(1): 13-23.
3. Mead PB and Winn WC. Vaginal-rectal colonization with group A streptococci in late pregnancy. Infect Dis Obstet Gynecol 2000; 8(5-6): 217-9.
4. Germont Z, Bidet P, Plainvert C, Bonacorsi S, Poyart C, Biran V, et al. Invasive Streptococcus pyogenes infections in< 3-month-old infants in France: clinical and laboratory features. Front Pediatr 2020; 8: 204.
5. Spaulding AB, Watson D, Dreyfus J, Heaton P, Grapentine S, Bendel-Stenzel E, et al. Epidemiology of bloodstream infections in hospitalized children in the United States, 2009–2016. Clin Infect Dis 2019; 69(6): 995-1002.
6. Miyairi I, Dominic B, John P, John B. Neonatal invasive group A streptococcal disease: case report and review of the literature. Pediatr Infect Dis J 2004; 23(2): 161-5.
7. World Health Organization, Geneva. 2015. WHO Recommendations for Prevention and Treatment of Maternal Peripartum Infections.
8. Orr K and Chien P. Sepsis in obese pregnant women. Best Pract Res Clin Obstet Gynaecol 2015; 29(3): 377-93.
9. Mason KL and Aronoff DM. Postpartum group A Streptococcus sepsis and maternal immunology. Am J Reprod Immunol 2012; 67(2): 91-100.

CASE REPORT

It is tuberculosis or melioidosis? A clinical diagnostic dilemma

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SUMMARY

Pulmonary Tuberculosis (PTB) is an endemic disease in Malaysia and continues to cause great morbidity and mortality. However, the diagnosis and treatment may pose a challenge to the attending physician since other diseases such as melioidosis can mimic tuberculosis. Hence, the final diagnosis should be done thorough history of illness, physical examination, investigations, and interpretation of findings. We present here a case of a 27-year-old man who presented at our primary care clinic with underlying diabetes mellitus whose symptoms were suggestive of PTB, and who was treated with anti-tuberculosis but later his sputum grew culture *Burkholderia pseudomallei*.

INTRODUCTION

Tuberculosis (TB) is one of the commonest infectious diseases that cause morbidity and mortality worldwide. It is caused by *Mycobacterium tuberculosis complex* and transmits via airborne droplets. In 2015, the World Health Organization (WHO) estimated around 10.4 million people were infected with TB globally.[1] In Malaysia, notified TB cases had dramatically increased from 20,666 cases per year in 2011 to 24, 220 cases per year in 2015.[1]

Patients with PTB, especially the high-risk groups usually presented with pulmonary symptoms such as chronic cough and hemoptysis with non-specific symptoms such as fever, night sweats, weight loss and dyspnoea. Those who presented with these symptoms warrant TB screening as recommended by WHO. Apart from clinical presentation, the diagnosis of TB is supported by laboratory investigations such as detection of acid-fast bacilli (AFB) on smears and cultures from the clinical sample and radiological findings of consolidation with cavitation.

Apart from pulmonary TB (PTB), melioidosis can mimic symptoms of tuberculosis clinically and radiologically. Isolation of *Burkholderia pseudomallei* from sputum culture supported by radiological findings can be considered as having pulmonary melioidosis. We present a case of a 27-year-old gentleman with underlying diabetes mellitus (DM), presented with symptoms typical of PTB with *B. pseudomallei* isolated from the sputum which had caused a dilemma in managing and raises the possible role of *B. pseudomallei* as a respiratory colonizer.

CASE PRESENTATION

A 27-year-old gentleman, a mechanic and a smoker, presented to the primary care clinic with prolonged intermittent fever for one month. The fever was worse at night and associated with chills and rigors. He also complained of productive cough with yellowish sputum for three weeks associated with reduced appetite. He had lost six kilograms of weight within two months. Despite having completed a course of antibiotic (amoxicillin-clavulanic acid), the symptoms persist. He had no history of contact with PTB.

On examination, his temperature was 38.5°C and other vital signs were stable. He was not in respiratory distress. His capillary blood glucose reading on presentation was 10.7 mmol/L. Lungs examination revealed crepitations at the left upper zone. Other physical examinations were unremarkable. A chest radiograph showed multiple cavitations with consolidation changes over the left upper zone as shown in Figure 1.

His blood results showed hemoglobin level of 10.4 g/dL, white blood count of 14.7 10^9/L (81.2% neutrophils, 8% lymphocytes) and platelet of 499 10^9/L with a raised erythrocyte sedimentation rate (ESR) of 130 mm/Hr. His renal profile showed hyponatremia (Na 129 mmol/L), hypokalemia (K 2.8 mmol/L) with normal creatinine (97 umol/L). Liver function test was also noted to be deranged with alkaline phosphatase 126 U/L, alanine transaminase 110 U/L, aspartate transaminase 76 U/L. His HbA1C level was 10.7%. However, the sputum smear samples for AFB were persistently negative.

Based on the patient's history and investigations, he was diagnosed as having smear-negative pulmonary tuberculosis with newly diagnosed diabetes mellitus. Anti-tuberculosis and insulin therapy were initiated. Serial monitoring of his serum electrolytes dramatically improved after initiation of the treatment. However, despite intensive treatment for TB for three weeks, his symptoms instead got worst which warranted admission to the hospital. He became more breathless and was still febrile. A repeat chest radiograph showed worsening of consolidation of the upper and midzone of the left lung. Diagnosis of sepsis secondary to community-acquired pneumonia with underlying PTB smear-negative was made and intravenous Ceftriaxone was started.

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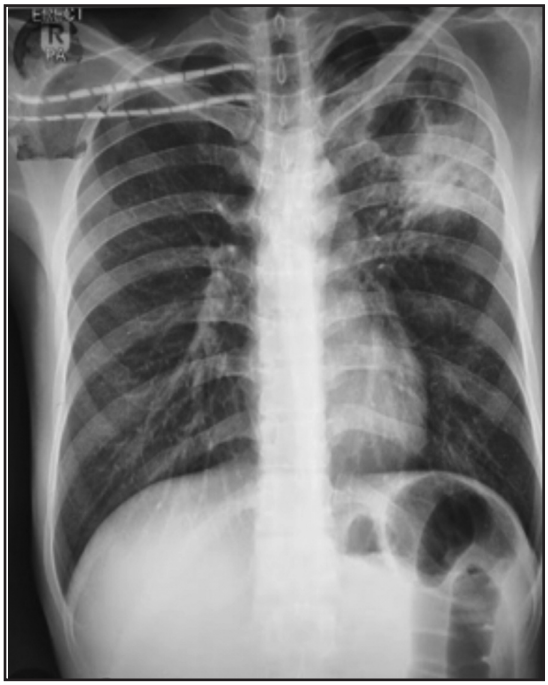

Fig. 1: Chest x-ray showing multiple cavitations with consolidation changes over the left upper zone.

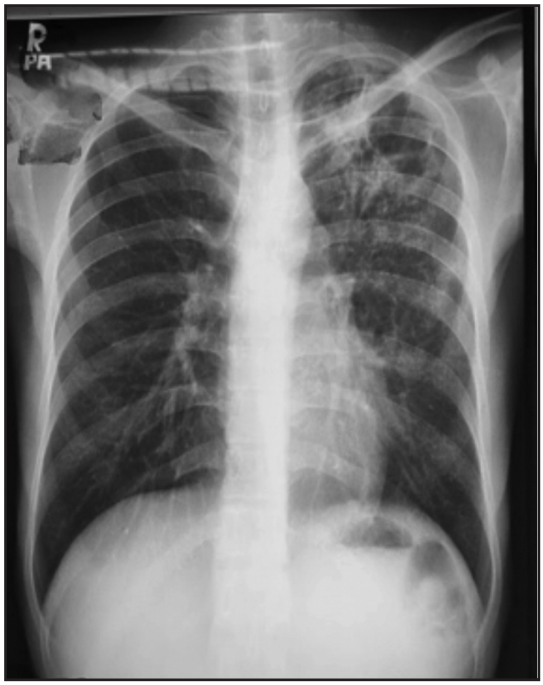

Fig. 2: Chest x-ray after completion of anti-tuberculosis therapy.

While in the ward, the sputum culture and sensitivity grew *B. pseudomallei* which was sensitive to doxycycline, imipenem, ceftazidime and amoxicillin-clavulanic acid. However, his blood culture revealed no growth of any organism. His diagnosis was then revised to pulmonary melioidosis and intravenous ceftazidime was initiated. He was subsequently referred to the respiratory physician for further management. Since his blood culture did not yield any organism of Burkholderia species and he showed excellent response to the previous antibiotic (intravenous ceftriaxone), a decision to discontinue the ceftazidime and continuation of anti-tuberculosis was made.

A week later, his symptoms improved, and he was discharged and seen in the outpatient clinic. Following discharge, he was seen biweekly in the clinic. His symptoms improved and his chest radiograph showed significant improvement as in Figure 2. His treatment was continued for six months. He responded well to treatment with resolution of symptoms, weight gaining and improved chest radiograph with no signs of disease relapse.

DISCUSSION

Melioidosis is caused by gram-negative bacilli *B. pseudomallei* and is endemic in Southeast Asia and tropical Australia. In Malaysia, the exact incidence of melioidosis is unknown, as melioidosis is not considered a notifiable disease even though many cases have been reported throughout this country. Individuals who are regularly in contact with soil and water are at high risk to get infected as it can be transmitted via percutaneous inoculation with contaminated soils or water, inhalation or ingestion. Therefore, it has been referred to as "the great mimicker" because of its similarity to other infections particularly tuberculosis.

Pulmonary melioidosis is the commonest clinical presentation of melioidosis where the patient may have features mimicking tuberculosis such as fever, productive cough, weight loss and upper lobe infiltration with or without cavitation on radiological findings as in this case. Isolation of *B. pseudomallei* from any clinical sample confirms the diagnosis of melioidosis.

However, in view that our patient had delayed response to anti-TB drugs, it has prompted the physicians to relook and revise the diagnosis especially when *B. pseudomallei* was isolated in the sputum.

Co-infection with PTB and melioidosis have been reported in some case reports.[2,3] In each of the case reports, the patient presented with clinical presentation of tuberculosis with concurrent isolation of *B. pseudomallei* from clinical culture. Both anti-TB drugs and chemotherapy for *B. pseudomallei* were commenced, making it difficult to identify whether the patient responded well either to the anti-TB drugs alone or the combination of both.

As in our case, the challenge in management was that the patient had newly diagnosed DM, had delayed response to anti-TB drugs and his clinical presentation worsened at week three of treatment. One of the commonest risk factors for melioidosis is DM, apart from renal disease, chronic alcoholic or other immunized compromised diseases.[4] Hence, a revisit on the diagnosis had to be made when *B. pseudomallei* was isolated. Furthermore, the absence of microbiological evidence of *M. tuberculosis* complex with isolation of *B. pseudomallei* infection on sputum culture made the diagnosis of melioidosis more likely.

However, since the blood culture and sensitivity results showed no growth of any organism and the patient responded well to the initial antibiotic and anti-TB drugs, thus the continuation of the current management was made. If *B. pseudomallei* had been isolated earlier, he would probably have been treated with antibiotics for melioidosis. This could lead to unnecessary exposure to antibiotics and increase the risk of antibiotic resistance. Wiersinga et al suggested that if *B. pseudomallei* is not detected in a subsequent adequate culture of specimen obtained before therapy, completion of the full course of antimicrobial therapy is generally not recommended.[5]

We postulate that *B. pseudomallei* was just a colonizer and not a true pathogen in our case, based on the clinical improvement of the patient after commencement of anti-TB drugs and response to Ceftriaxone. There are case reports that reported spontaneous recovery of melioidosis without antibiotic treatment. In one of the cases, all the patients infected with a mild form of cutaneous melioidosis had spontaneous clearance without receiving antibiotics treatment.[6] As postulated in our case, it might be possible that a lung disease with tuberculosis is considered the same phenomenon.

CONCLUSION

This case highlights the dilemma of the attending physician in diagnosing and managing between tuberculosis and melioidosis. As treatment for these two diseases is entirely different, it is crucial to differentiate between these two. It also raises the possibility of *B. pseudomallei* as a respiratory colonizer with spontaneous resolving pulmonary symptoms even though it is rare. Co-infection of melioidosis and tuberculosis should be assessed properly to make a proper treatment for both, thus avoiding unnecessarily costly prescription of broad-spectrum antibiotics and contributing to emerging of antibiotic resistance.

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CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Disease Control Division (TB/Leprosy Sector) Ministry of Health Malaysia. National Strategic Plan for Tuberculosis Control (2016-2020). KKM/BI/5000/2018. Putrajaya:Ministry of Health Malaysia; 2016.
2. Shetty AK, Boloor R, Sharma V, Bhat GH. Melioidosis and pulmonary tuberculosis co-infection in a diabetic. Ann Thorac Med 2010; 5(2): 113-5.
3. Tan SY. Tuberculosis and Melioidosis at Distinct Sites Occurring Simultaneously. Sánchez Pérez HJ, editor. Case Rep Infect Dis 2020; 2020: 9818129.
4. Tang RY, Lim SH, Lam JE, Nurasykin S, Eileen T, Chan YW. A 5-year retrospective study of melioidosis cases treated in a district specialist hospital. Med J Malaysia 2019; 74(6): 472-6.
5. Wiersinga WJ, Currie BJ, Peacock SJ. Melioidosis. N Engl J Med 2012; 367(11): 1035-44.
6. Gibney KB, Cheng AC, Currie BJ. Cutaneous Melioidosis in the Tropical Top End of Australia: A Prospective Study and Review of the Literature. Clin Infect Dis 2008; 47(5): 603-9.

Patency of permanent vascular access creation in paediatric patients with end stage renal disease

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SUMMARY

Renal transplant is the first-line therapy in paediatric patients with end-stage renal disease (ESRD). Wong HS and Goh BL reported up to 79% of 1061 paediatric patients still require long-term haemodialysis (HD).1 The lack of deceased and living donors is attributable to the poor awareness, cultural and religious grounds. Permanent vascular access (PVA) in paediatrics therefore, serves more as a long term treatment rather than a bridging therapy. We observed 5 children and an adolescent, all with previous indwelling catheters, who underwent arteriovenous fistula (AVF) creation and report the outcomes. The aim of this report is to determine the factors that influence the long-term patency of paediatric AVF. Factors such as body weight, vessel diameter, preoperative preparations, microsurgical technique and postoperative maintenance are discussed. In addition, considerations on the choice and timing of PVA is highlighted.

INTRODUCTION

In Malaysia, patients receiving dialysis increased from 15,087 in 2006 to 37,183 In 2015. Out of these 37,183 patients, 1061 were under the age of 20 were receiving renal replacement therapy (RRT). Out of these 1061 patients, 79% were on haemodialysis (HD) and only 21% received renal transplants.[1] Owing to the age of the patients at referral, size of vessels and accessibility to renal transplant, decision on the choice of vascular access is challenging. Therefore, it is important to weigh all the pros and cons of the dialysis options available, specifically the permanent vascular access (PVA), peritoneal dialysis (PD) and central venous catheter (CVC). Kidney Disease Outcomes Quality Initiative (K-DOQI) guidelines by the United States of America's National Kidney Foundation (NKF) recommends placement of permanent access in dialysis patients aged 0 to 19 years who weigh more than 20 kg and are unlikely to receive a transplant within one year. Implementation of "fistula first" has also been started for the paediatric group who require long-term HD.

In the Universiti Sains Malaysia (USM) hospital, majority of the paediatric patients are offered PD, only a minority of patients who developed complications from the ultrafiltration such as repeated infections from PD or clinically not suitable e.g., having a stoma, were offered fistula creation by the treating physician. The number of patients having new fistula creation in USM is only 5 or less each year. Even though most paediatric HD patients met the weight criteria and were expected to wait for more than one year to receive a kidney transplant for AVF upon initiation of HD, PD was chosen over AVF creation.

In this report, we look at five paediatric patients, all with pre-existing CVC and who had undergone AVF creations performed by a single surgeon. The potential factors affecting the patency rates are discussed.

CASE REPORTS

Five patients were referred. All these patients already had their HD initiated via a CVC inserted into the internal jugular vein (IJV) for temporary dialysis access with two of the patients having thrombosis from the catheterization, with a length of HD dependence ranging from 1 month to 3 years.

The weights of the patients ranged from 15 to 36kg and age between 9 and 16 years old. Four patients had RCF created and one had snuffbox AVF. Preoperatively, all patients had ultrasound assessment for the continuity and compliance of the superficial veins. All AVFs were performed with end-to-side anastomosis with interrupted monofilament sutures. No anticoagulation prophylaxis was given. Patients were seen routinely at 2 and 6 weeks postoperatively for suture removal and reassessment with ultrasound done prior to first cannulation of the fistula. Maturation of fistulas ranged from 6 weeks to 4 months.

For postoperative assessment for adolescents, the KDOQI "Rule of 6s" is used to determine the maturity of the fistula - at least 6 mm in diameter, <6 mm depth from skin and has a blood flow >600 mL/min[3] with leniency to "4s"allowed. In younger children, the fistula is considered matured with clinically strong palpable thrill and good colour Doppler signals.

Primary failure of fistula includes inadequate maturation, thrombosis, failure of first and subsequent cannulations and other complications leading to non-functional AVFs.

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Table I: Summary of patients' details and the outcomes of arteriovenous fistulas

No	Age	Sex	Weight (Kg)	Causes of ESRD	Other Comorbid	Reason of AVF creation	Mode of HD before AVF	Procedure	Time to Maturation of AVF	Early Complications	Primary or Secondary Failure	Current Condition / Fate of AVF
1	12	M	32.7	SRNS	Nil	Occlusion in CVC	Hickman catheter	Right RCF	8 weeks	Thrombosis proximal to the anastomotic site*	Secondary	Functioning well
2	9	M	15.0	Solitary kidney with reflux nephropathy	Imperforate anus (VACTERL association)	Diverting colostomy precludes PD	IJV catheter	Left RCF	6 weeks	Nil	Secondary	Thrombosed after 18 months of HD
3	10	M	30.2	SRNS	Nil	UF failure in PD	IJV catheter	Left RCF	8 weeks	Nil	N/A	Functioning well, currently in the 4th year of HD
4	12	F	18.7	SRNS	Nil	UF failure in PD	Previous 3 CVC insertions in different settings	Left RCF	4 months	Vessel calibre and flow never achieve satisfactory results	Primary	AVF was never utilised
5	16	M	36.0	SRNS	Kimura disease	long-term HD	IJV catheter	Left Snuffbox AVF	8 weeks	Nil	Secondary	Stenosed after 3 years of HD

AVF - arteriovenous fistula; SRNS - steroid resistant nephrotic syndrome; PD - peritoneal dialysis; VACTERL - vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities; HD - haemodialysis; IJV - internal jugular vein; UF - ultrafiltration; CVC - central venous catheterization; RCF - radiocephalic fistula
*Successfully salvaged with open thrombectomy

Secondary AVF failure is permanent failure after the AVF has met dialysis suitability criteria with subsequent abandonment. Out of the four RCFs and one snuffbox AVF, there was one primary failure (patient's weight: 18.7kg), three secondary failures (patients' weight: 36kg, 32.7kg, 15kg) with one salvageable by open thrombectomy and one functioning well currently in his fourth year of HD via the RCF created (patient's weight: 30.2kg). Patient with primary failure of the fistula previously had three CVCs in different settings prior to fistula creation which is significantly more when compared with the rest. One of the patients with secondary failure had Hickman catheter prior to RCF creation in which thrombus was detected proximal to the anastomotic site and salvaged with open thrombectomy. Secondary failure in the snuffbox AVF occurred at the third year of HD and require new fistula creation. Four out of five patients have nephrotic syndrome diagnosed prior to ESRD. Another patient had reflux nephropathy with underlying VACTERL syndrome (Table I).

DISCUSSION

Outcomes of PVA encompass not only the surgical techniques, but also the extensive preoperative assessments and preparations, post-operative care and maintenance. It is common to have patients with CVC inserted at the time of first consultation for AVF. CVC is beneficial for patients expected to have renal transplant in a short time or those requiring urgent dialysis. It is also recommended for children less than 10kg in weight, whose vessel caliber is expected to be small, rendering fistula creation a challenge to the surgeon. However, it is at a disadvantage in terms of catheter-related infections, thrombosis, fibrin sheath formation, catheter malfunction and short life span with medial survival of 4 to 10.6 months. Complications to central vessels also make future arteriovenous access creation difficult. Based on our case series of 5 patients, weight does not seem to be the predictor of patency, rather, the number of previous central venous catheterizations. Commonly, central venous stenosis is only apparent when AVF is established where there is increased in blood flow in the limb. Creation of AVF in paediatric patients are feasible and its long-term outcome has been evaluated in many reports.[3,4,5] A patient as small as 10kg has been described to have successful fistula creation.[3]

Preoperative preparations and proper venous mapping of the patients using colour doppler ultrasound are therefore very important in the patency rate of the PVA created. All patients with renal dysfunction should have their conditions managed as potential long-term dialysis candidates. Therefore, the aim should be to achieve maximal use from each access site. It is important to advocate the "distal before proximal" and "autogenous before prosthetic" rule in providing paediatric permanent HD access. Since all our patients had prior history of CVC insertions, the conditions of the vein must be assessed by careful preoperative clinical examination and a central venogram is mandatory. By achieving a perfect anastomosis only is not enough if the fistula created cannot be utilised for HD due to proximal thrombosis or stenosis; or inability to achieve adequate flow due to proximal venous branches that are not ligated intraoperatively. Technical victories that result in functional failures serve no purpose.

Intraoperatively, several fundamental rules should be adhered to achieve good patency. The rules for suturing are that the forceps must never grasp the intima, the adventitia is incised and not resected, high pressure clamps must be avoided and the thinnest possible needles are to be used. Vessels are only handled by the adventitia. In the literature, vessel diameters are often not specified when assessing the outcome of the fistula, instead substituted by the weight of the patients.[4] Thus, the timing for access creation should be based upon circumstances and local expertise of patients.

In Malaysia, the frequent paediatric vascular access sites are the wrist AVF, BCF, cuffed and non-cuffed catheters, artificial graft and venous graft in descending order.[1] RCF is the preferred choice in USM as the children can maintain a more comfortable position during HD, comparing to ulnar-basilic fistula and the snuffbox AVF. Comparing to BCF and BBF, RCF is chosen in order to start with a more distal access and not requiring transpositions of the vein. Study has shown that the location of AVF did not significantly affect primary or secondary patency in paediatric age group.[5]

Care and maintenance of AVF pose a challenge in the paediatric group, especially the exhaustion of vascular access in the future. Venous neointimal hyperplasia, hemodynamic and surgical stressors as well as inflammatory stimuli from dialysis needles can pose risks to AVF failures.[3,6] At the histological level, venous neointimal hyperplasia is characterized by the presence of myofibroblasts, angiogenesis and the accumulation of extracellular matrix components.[6] Buttonhole needling of HD AVF results in less complications and interventions compared to the rope-ladder technique.

ESRD itself is a prothrombotic state. An underlying diagnosis of nephrotic syndrome in these patients further constitutes a significant risk factor for thrombosis due to the increased synthesis of thrombosis-promoting factors, including factors V and VIII and fibrinogen; impaired fibrinolytic activity, attributable to decreased concentrations of both plasminogen and tissue-plasminogen activator (tPA), while at the same time the inhibitors of fibrinolysis, including plasminogen activator inhibitor-1 and α2-plasmin inhibitor, are elevated.[5] All our patients did not receive anticoagulants as we do not advocate the usage of systemic anticoagulation for vascular access surgery due to the increased incidence of bleeding and lack of benefit in primary patency.[7]

Predictors of patency of AVF in children is still a continuing study. Sisli et al. recently reported a 34.6% AVF loss over a duration of 21 months follow up in children.[5] Almási-Sperling and colleagues studied the patency rates in correlation to the maturation intervals and first access cannulation in paediatric patients.[8] Vonapanitase, which is a recombinant human type 1 pancreatic elastase that can facilitate rapid AVF dilatation and maturation by causing persistent vasodilatation, fragmenting the elastin fibres and inhibiting adventitial myofibroblast migration to the intima has been described.[9] Local application of antiproliferative agents such as coII-R, paclitaxel-coated balloons and

Vascugel, which is the cultured human aortic endothelial cells, were introduced in the attempt of maintaining patency.

Therefore, early referral for fistula creation is advised among patients who are expected to require HD in the near future to avoid complications from CVC. Preoperative preparation of vessels preservation on the decided side of upper limb is important, preference of non-dominant arm first and start distally then, work proximally. Postoperative anticoagulant should be considered in patients with diagnosis of nephrotic syndrome, which essentially is one of the major causes that leads to ESRD in paediatrics.

Paediatric patients who are unlikely to receive renal transplant within one year of ESRD diagnosis should have AVF as the preferred mode of haemodialysis. It is imperative to have preoperative Doppler ultrasound and central venogram in patients with previous CVC prior AVF creation to rule out central venous obstruction. Primary and secondary patency of AVF require intricate interplay of preoperative planning, meticulous microsurgical techniques, and AVF maintenance.

CONCLUSION

High index of suspicion on the vessel patency in patients with previous CVC should be confirmed routinely with central venogram before undertaking AVF creation. Patency of AVF include all aspects of preoperative preparations, proper assessments of candidates, techniques of surgeons and postoperative care and maintenance. Cause of unfavourable results and higher risk of complications such as prior indwelling catheter can be omitted with the "fistula first" policy.

REFERENCES

1. Wong HS and Goh BL (Eds). Twenty Forth Report of the Malaysian Dialysis and Transplant 2016, Kuala Lumpur 2018
2. Vascular Access 2006 Work Group. Clinical practice guidelines for vascular access. Am J Kidney Dis 2006; 48(1): 176-247.
3. Gradman W, Lerner G, Mentser M, Rodriguez H, Kamil ES. Experience with Autogenous Arteriovenous Access for Hemodialysis in Children and Adolescents. AnnVasc Surg 2005; 19(5): 609-12.
4. Wartman S, Rosen D, Woo K, Gradman W, Weaver F, Rowe V, et al. Outcomes with arteriovenous fistulas in a paediatric population. J Vasc Surg 2014; 60(1): 170-5.
5. Sisli E, Gür A. Mid-term outcome of arteriovenous fistula in paediatric patients with end-stage renal disease: A single centre experience. Eastern J Med 2019; 24(2): 130-4.
6. Mandel-Shorer N, Tzvi-Behr S, Harvey E, Revel-Vilk S. Central venous catheter-related venous thrombosis in children with end-stage renal disease undergoing haemodialysis. Throm Res 2018; 172: 150-7.
7. Regus S, Almási-Sperling V, Lang W. Paediatric Patients Undergoing Arteriovenous Fistula Surgery without Intraoperative Heparin. J Vasc Access 2016; 17(6): 494-8.
8. Almási-Sperling V, Galiano M, Lang W, Rother U, Rascher W, Regus S, et al. Timing of first arteriovenous fistula cannulation in children on haemodialysis. Pediatr Nephrol 2016; 31(10): 1647-57.
9. Franano FN, Hance K, Bland K, Burke S. PRT-201 dilates outflow veins and improves maturation rates in a rabbit model of AVF. Nephrol Dial Transplant 2007; 22: 155-6.

Elephant attack – A rare case of survival

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SUMMARY

Conflict of human-wild elephant is not uncommon in Malaysia. Most of the human victims usually succumb to death due to internal organ injuries. Here we report a case of a woman who was the victim of an elephant attack and successfully survived to share our experience in managing this type of polytrauma.

INTRODUCTION

Conflict between human and wild elephant is not uncommon in Malaysia. The consequences range from crop damage to direct attacks on humans.[1] Most of the victims usually succumb to death due to internal organ injuries.[2] We report a case of a woman who was the victim of an elephant attacked and successfully survived to share our experience in managing this type of polytrauma.

CASE PRESENTATION

A 34-year old female veterinarian was brought to the emergency department (ED) of a district hospital in Kelantan, Malaysia after an unfortunate event while on an operation to transfer out a wild elephant that strayed out of the jungle to the plantation crops in a village. During the process of transferring, the officers from Wildlife and National Parks Department, also known as *'Perhilitan'* in Malay, lost control of the elephant after it was awakened from the initial tranquilizer dose. The elephant was estimated to be more than 30 years of age, weighing approximately 2.5 tonnes had immediately attacked the veterinarian and she was trampled two times on her chest. The veterinarian sustained pain over the entire chest, right shoulder and abdomen. She had difficulty in breathing and felt dizzy. She was able to move all four limbs but could not ambulate due to the severe pain. She had no loss of consciousness and was helped by the other *'Perhilitan'* officers. The victim was immediately taken to the hospital by the officers with a four-wheel drive vehicle and arrived at the district hospital around 30 minutes later.

On arrival to the Emergency Department of a district hospital, she was fully conscious with her airway and cervical spine were intact. However, her breathing and circulation were compromised. She was tachypnoeic with SpO_2 was 83% under room air. There were multiple bruises over the chest and abdomen with bilateral generalised anterior chest tenderness on palpation. Examination of the right lung field revealed hyper resonance on percussion and reduced air entry on auscultation. The trachea was found to have deviated to the left side. On further examination of haemodynamic status, she was in shock with a blood pressure of 60/40 mmHg and a pulse rate of 120 beats per minute. She was pale and cold peripherally with delayed capillary refill time. Her abdomen findings were generalised tender and guarded. Surgical-based teams such as surgery and orthopaedic were alerted respectively as there was no Trauma Code at the centre. The anaesthesia team was also activated to help in resuscitation.

Chest X-ray showed right pneumothorax, multiple rib fractures bilaterally, right scapular fracture, posterior wall of right acetabulum fracture and 3rd to 4th thoracic spinous process fractures. Computed tomography (CT) scan of the thorax, abdomen and pelvis showed multiple intrabdominal injuries; grade 2 liver injury, grade 2 splenic injury, grade 2 to 3 pancreatic injury and grade 3 left renal injury.

Damage control resuscitation was initiated. She was transfused with 1 Litre of normal saline and early blood products was instituted. Intravenous tranexamic acid was also administered. Other than that, a chest tube was inserted at the right lung due to haemopneumothorax. Initial discussion between the surgeons in the district hospital and tertiary centre was to continue conservative management as her condition was haemodynamically stable after the resuscitation. Day 1 post-trauma, her condition worsened. She became more tachypnoeic and required non-invasive ventilatory support. She developed acute respiratory distress syndrome (ARDS) and was intubated on day 3 post-trauma. Repeat CT scan showed complete transection of the pancreas (Figure 1). She was referred to Hospital Universiti Sains Malaysia (USM), a tertiary hospital located 70 km away from the district hospital for further surgical intervention.

At the tertiary hospital, diagnostic peritoneal lavage (DPL) was done, and 1 litre of blood was evacuated. The DPL aimed to reduce the inflammatory effect caused by the spillage of pancreatic fluid. No faecal material or bilious content visualised during the procedure. As a result, she was planned for exploratory laparotomy and distal pancreatectomy with

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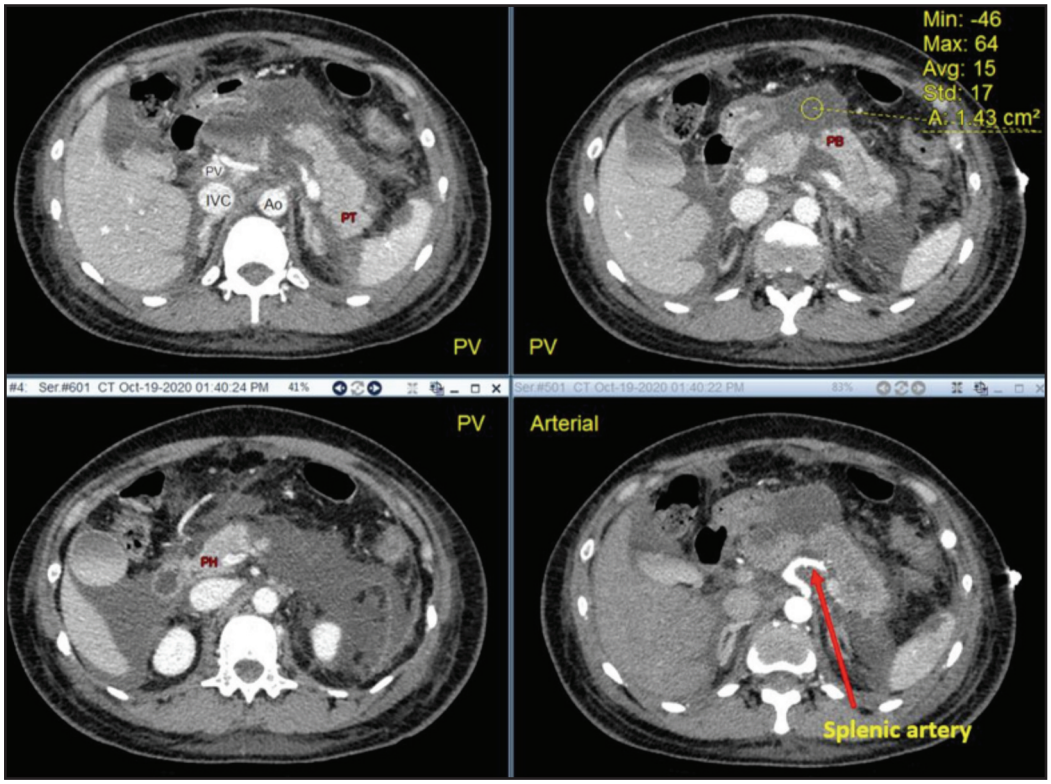

Fig. 1: CT abdomen with contrast in portovenous (PV) and arterial phases show complete transection of the pancreatic body (PB). The pancreatic head (PH) and pancreatic tail (PT) are still enhanced. There is generalised free fluid mixed with haemoperitoneum as demonstrated at the peripancreatic region (max density 64 Hounsfield unit). Splenic artery is still enhanced with no evidence of active contrast extravasation. Lacerations of the liver and spleen are partially visualised. Inferior vena cava (IVC) and aorta (Ao) are normal in size. No bowel wall thickening or pneumoperitoneum.

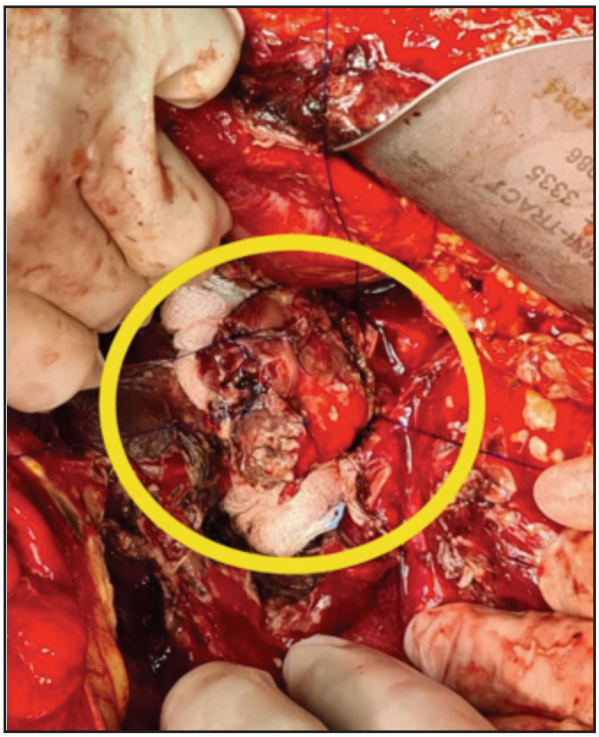

Fig. 2: Intra-operative findings of transected pancreas at the body with necrotic area.

splenic preservation. Intraoperatively, the pancreas was discovered to be transected at the body with the necrotic area and retroperitoneal haematoma (Figure 2). Post-operatively, she suffered from a surgical site infection and was administered antibiotics. She underwent slow weaning of the ventilator and was eventually extubated after 14 days of ventilation. She was discharged at one-month post-trauma with follow-up for regular wound inspection and dressing.

DISCUSSION

Human-elephant conflict occurs as a result of habitat loss due to the expansion of human settlements and agricultural activities.[3] However, most of the fatal attacks occurred outside the habitat like zoos, circuses and arenas.[4] There are 19 cases of fatal elephant attack reported, mainly in India, followed by Germany, Czech Republic and Australia.[2,4,5,6] Only one case of elephant attack survivor reported in the United States of America who underwent 30 operations during her 3 months of hospitalisation.[7]

Attributable to the extreme weight difference between humans and elephants, whose weight may go up to four tons, it potentiates to cause fatal injury and danger in relation to humans.[3] Fatal injuries can also be caused by the mechanism of trampling-stomping.[3] The main targeted area in the human are the head and torso.[6] The type of injuries varies from severe maxillofacial trauma[4], perforating lacerated tusk injury of the chest with multiple rib fractures[2],

blunt intra-abdominal trauma including bowel transection, liver and abdominal aorta lacerations as well as pelvic fractures.[3] The most common cause of death is due to haemorrhagic shock.[3]

In this particular case, the mechanism of attack by the elephant was trampling when the elephant was suddenly awakened. The veterinarian sustained blunt polytrauma, almost similar to the type of injury in other fatal cases of elephant attack. Damage control resuscitation is part of the management in this type of polytrauma, followed by conservative management. Conservative management or nonoperative management was decided after haemodynamic stability was achieved, together with findings from the imaging modalities.[8]

However, as her condition worsened and a repeat CT scan showed complete transection of the pancreas, she was referred to the Hospital USM for operative management. The decision for the operative management in blunt pancreatic injury is always difficult as only those who have pancreatic duct transection should go for the surgery. Unnecessary surgery in non-complicated pancreatic injury especially in grade 1 and 2 may result in a worse outcome of post-operative pancreatitis.[9] Unfortunately, most of the pancreatic duct transections are not easily visualised during early CT scans and in fact, patients are haemodynamically stable in the first 24 hours. As pancreatic juice spills over the retroperitoneal space, it will fill up the gap between the transection line and will be seen clearly at 72 hours as demonstrated in our patient. The spillage of the pancreatic juice at this time also increases the inflammatory response with haemorrhagic changes and the development of sequelae like acute respiratory distress syndrome and compartment syndrome. These conditions would justify the need for high morbidity surgery.[10]

CONCLUSION

Polytrauma due to elephant attack is common and the cause of death is attributed to traumatic shock. Attending physicians should always have a high index of suspicion for intraabdominal injury in the case of elephant attack even in haemodynamically stable patients as hollow organ injuries usually present late. An early intervention like damage control resuscitation and early referral for definitive treatment is vital in saving the life of the victim. The clinician should also be aware that when pancreatic injuries are managed conservatively, the clinical, radiological and laboratory parameters need to be monitored until resolution.

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CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

REFERENCES

1. Salman S, Nasharuddin O, Mohd Nawayai Y, Burhanuddin MN, Ahmad Z, Ahimsa CA. Current status of Asian elephants in Peninsular Malaysia. Gajah 2011; 35: 67-75.
2. Das SK, Chattopadhyay S. Human fatalities from wild elephant attacks - A study of fourteen cases. J Forensic Leg Med 2011; 18: 154-7.
3. Shaffer LJ, Khadka KK, Van Den Hoek J, Naithani KJ. Human-elephant conflict: A review of current management strategies and future directions. Front Ecol Evol 2019; 6: 235.
4. Hejna P, Zatopkova L, Safr M. A Fatal Elephant Attack. J Forensic Sciences 2012; 57(1): 267-9.
5. Vuletic J, Byard RW. Death due to crushing by an elephant trunk. Forensic Sci Med Pathol 2013; 9(3): 449-51.
6. Heger A, Schwarz CS, Krauskopf A, Heinze S. Fatal attack on a pedestrian by an escaped circus elephant. Forensic Sci Int 2019; 300: e1-e3.
7. Tsung AH, Allen BR. A 51-year-old woman crushed by an elephant trunk. Wilderness Environ Med 2015; 26(1): 54-8.
8. Stawicki SP. Trends in nonoperative management of traumatic injuries - A synopsis. Int J Crit Illn Inj Sci 2017; 7(1): 38-57.
9. Amal A, Hicham E, Jihane L, Khalid AT, Abdelatif L. Pancreatic transection due to blunt trauma. J Emerg Trauma Shock 2010; 3(1): 76-8.
10. Rebecca AL, Matthew AB. Traumatic Transection of the Pancreas. A Case of Delayed Presentation. JOP 2011; 12(1): 47-9.

CASE REPORT

Pediatric intrathoracic migration of ventriculoperitoneal shunt catheter post TB meningitis: A case report

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SUMMARY

Ventriculoperitoneal shunt (VPS) is a common procedure in neurosurgery for Cerebrospinal Fluid (CSF) diversion. It is associated with various complication. One of the rarer complications is migration of the shunt catheter. The incidence is higher in the paediatric population, up to 71.2% compared to adults 28.8%. We present a case of a 1 year 4 months old boy post TB meningitis with intrathoracic shunt migration 2 months after implantation of VPS.

The child presented with upward gaze palsy, on and off productive cough and fever. He had a ventriculoperitoneal shunt inserted 2 months before, when he was diagnosed and treated for TB meningitis. Radiological imaging revealed the distal catheter tip was at the right lung with pneumothorax. The shunt was removed and after confirming that there is no active infection, a new ventriculoperitoneal shunt was reinserted.

INTRODUCTION

Ventriculoperitoneal shunts (VPS) are one of the commonest surgical procedures performed in neurosurgery. Complications arising in this procedure can be divided into both mechanical and non-mechanical. Shunt migration is defined as translocation of part of or the entirety of the shunt system from the compartment where it was intended to a new compartment.[1] The most accepted theory for this is that children have a more vigorous peristaltic activity and smaller peritoneal space thus causing a relatively higher intra-abdominal pressure, predisposing them to shunt migration.[2] Displacement into the thorax can be attributed to congenital defects, erosion and perforation of the diaphragm.

We present a case of paediatric intrathoracic migration of the VPS post tuberculosis (TB) Meningitis.

CASE REPORT

A 1 year 4 months old boy with a history of post TB meningitis hydrocephalus was admitted to the Hospital Kuala Lumpur, Kuala Lumpur, Malaysia after his mother noticed that he developed an upward gaze palsy. Further history from his mother also revealed that he experienced on and off productive cough for 1 week. A VPS was inserted 2 months earlier, after he was diagnosed with TB meningitis. During the physical examination, he had bilateral upward gaze palsy, a spike of fever, and minimal crepitation over the right lower zone on chest auscultation. Otherwise, he was active. The patient had no papilledema or signs of respiratory distress, and the shunt was functioning well at bedside testing (determined by compressibility and a good refilling time of the shunt reservoir). A brain CT showed slight worsening of the hydrocephalus, probably due to suboptimal shunt drainage. In view of his cough and fever, a diagnosis of respiratory tract infection had to be ruled out, and a chest X-Ray was ordered. The chest X-ray showed the tip of his distal VPS catheter at the level of the 5th anterior rib bone (Figures 1A and 1B).

CT thorax confirmed that the distal catheter had pierced the posterior right hemidiaphragm with its tip located at the lateral segment of the right middle lobe with a small loculated pneumothorax and surrounding consolidation. The right lower lobe had collapsed (Figures 2A and 2B).

In view of the abnormal placement of the distal VPS catheter without evidence of CNS infection, we decided to externalize the VPS. The paediatric surgical team was on standby in case of any intraoperative complications. Fortunately, we were able to remove the distal catheter easily via a subcutaneous incision over the chest wall and pulling it out slowly via the subcutaneous route. The child's symptoms improved but CSF analysis from the catheter was positive for Coagulase Negative *Staphylococcus* (CONS). The VPS was removed, replaced by a temporary extraventricular drain. We did not prescribe any new antibiotics except for his regular anti-TB medications. Since the removal of the VPS, repeated CSF analyses were cleared of infection, and a left VPS was inserted one week later. He was subsequently discharged well 3 days after surgery. He remained asymptomatic during his follow-up 6 weeks later.

DISCUSSION

The incidence of shunt migration appears to be higher in the paediatric age group (71.2%) compared to adults (28.8%). Based on a literature review by Harischandra et al, common sites of migration include the bowel (35%), bladder (8%), scrotal (14%), abdominal wall (14%), intracranial/subgaleal (11%), chest/thoracic (8%), cardiac/major vessels (7%) and breast (3%).1 Obrador et al reported the first patient with a distal catheter migration into the thoracic cavity in 1977 in a 14 month-old child.3 The incidence of migration is highest in the first 6 months after surgery with a decline in incidence as time progresses.[1] However, it could occur as early as 5 days after surgery to as long as 16 years. In our patient, the migration occurred 2 months after the first VPS procedure.

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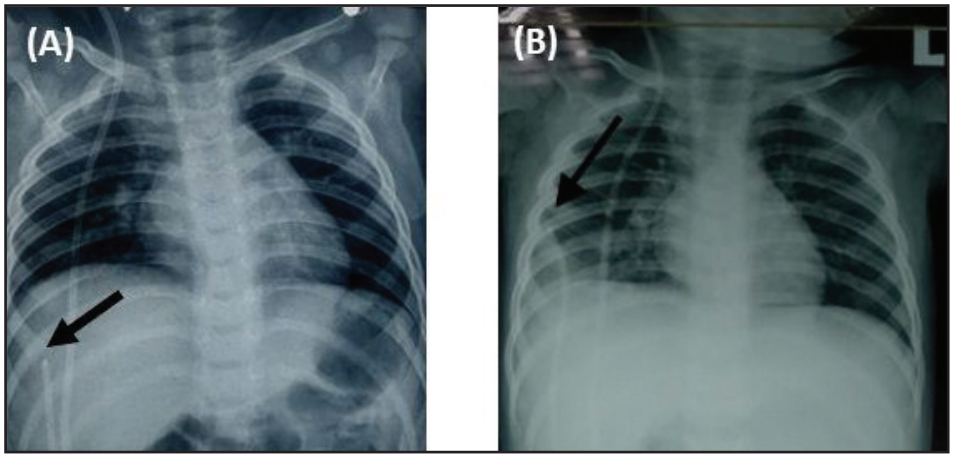

Fig. 1: Chest x-rays of the patient. (A) Chest x-ray post ventriculoperitoneal shunt insertion confirmed the location of the tip of the shunt catheter was at the right hypochondriac region in the peritoneal space. (B) Repeat chest x-ray on admission noted the migration of the catheter tip into the right hemithorax (arrow) at the level of the 5th anterior rib bone. There was no bowel herniation noted.

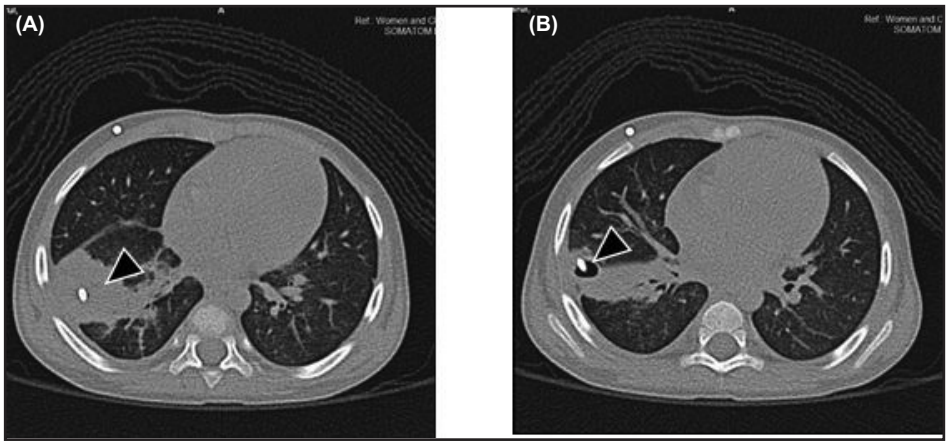

Fig. 2: CT Thorax of the patient in axial view (lung window). (A) CT Thorax scan showed a collapsed right lower lobe (arrowhead) with shunt catheter traversing through the lung parenchyma. (B) CT Thorax scan showed a small loculated pneumothorax (arrowhead) and the tip of the shunt catheter within it.

According to Taub and Lavyne intrathoracic migration of the distal catheter is divided into trans-diaphragmatic (through the diaphragm) or supra-diaphragmatic (through the chest wall).[4] Supra-diaphragmatic migration can be iatrogenic secondary to erroneous tunneling during distal shunt insertion. Trans-diaphragmatic migration has been attributed to the relative positive pressure in the abdomen compared to the negative intrathoracic pressure favoring a migration into the cavity with lower pressure.

Migration can also occur through congenital defects in the diaphragm including the foramen of Morgagni or Bochdalek and the right xipho-costal point (from where the superficial epigastric vessels enter).[5]
The presence of chronic abdominal infection or inflammation helps in adhesion of the catheter onto the diaphragm, following which a perforation takes place due to constant friction.[4] The stiffness of the catheter, inflammation, infection, an incision close to the costal margin, and the positive intra-abdominal pressure further increase the risk of perforation.6 We suggest that inflammation followed by adhesion and slow erosion through the diaphragm aided by the pressure gradient is the most likely mechanism which cause the migration in our patient as CT thorax showed no obvious diaphragm defect or no bowel loops/hernias.

Cakin H et al reported a child with Trisomy 21 where symptomatic Morgagni's hernia was brought about 5 months after a ventriculoperitoneal shunt procedure, possibly related to an increase in the intra-abdominal pressure secondary to VPS CSF drainage.[5]

Symptoms of migration inside the thoracic cavity presents predominantly as respiratory symptoms in nearly 78.8% patients, and less often as shunt dysfunction/infection in approximately 15.1% patients.[1] Presentation may also differ between intraparenchymal and intrapleural migration. Coughing and recurrent pneumonia is common in intraparenchymal migration as there is direct irritation of the airway and formation of shunt-bronchial fistula with the accumulation of CSF provides means of bacteria colonization. Pleural effusion, pneumothorax, hydrothorax

caused by an intrapleural migration may cause shortness of breath, reduced in effort tolerance and respiratory distress.[7] Our patient showed both respiratory irritation symptoms and also signs of suboptimal shunt drainage.

Imaging helps to confirm the position of the migrated shunt tip. A anterior-posterior and lateral view X-ray of the chest may be ordered to analyse the course of the distal catheter and also to look at the costovertebral angle (foramen of Bochdalek).[4] With CT scan of the chest and thorax, the role of lateral X-ray has decreased. Only 15% of thoracic cavity migration of the shunt is associated with shunt dysfunction, and so, the role of CT scan of the brain is limited, unless there are signs of hydrocephalus or raised intracranial pressure.

The management of shunt migration depends on the presence or absence of shunt dysfunction and/or infection. In patients with shunt infection, exteriorization of the catheter and treatment with antibiotics is suggested. A direct shunt replacement or revision can be done if there is no evidence of shunt infection on CSF tapping or thoracocentesis(if CSF hydrothorax is present).[1,4] This could be done by reopening the abdominal wound, retrieving the distal end of the peritoneal catheter, and reinserting it in the peritoneal cavity. There is no need to inspect the inferior surface of the diaphragm for a perforation, as this would require a larger incision.

In patients with associated defects in the diaphragm on imaging, a diaphragmatic repair may need to be carried out prior to shunt replacement; or the shunt may have to be converted to a VA shunt.[6] Karapolat et al from thoracic surgery suggested that adherences for catheter to omentum and intraperitoneal soft tissue must be kept in mind when removing the distal shunt and the catheter should not be pulled extensively as to prevent breakage. In cases of adhered catheter where transdiaphragmatic removal is difficult, a thoracotomy maybe needed to remove the shunt entirely.[8]

To date, there has not been any report that links intrathoracic shunt migration to a history of TB meningitis. Naik et al reported a case of complete intracranial migration of VPS in a child 12 months after the insertion of VPS following TB meningitis.[9] In patients with a history of TB meningitis, it is possible that the distal absorption might be reduced in view of high CSF protein content. We hypothesize that a failure of absorption or slower peritoneal absorption of CSF can lead to a relative positive pressure in the abdomen which promotes migration to a space with lower pressure. However, a study done by Tyagi et al concluded that there is no increase in the statistically significant in the complication rate of VP shunt in TB Meningitis patients versus non infective patients.[10]

CONCLUSION

Thoracic complications of VPS are rare but can potentially be serious. Our patient presented post TB Meningitis with intrathoracic migration and associated pneumothorax. With ventriculoperitoneal shunting, it is important to keep in mind the possibility of intrathoracic migration especially if patients present with respiratory symptoms. Further study may be needed to determine the association between TB, infective and non-infective nature associated with shunt migration.

CONFLICT OF INTERESTS

The author declare that they have no conflict of interest.

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REFERENCES

1. Harischandra LS, Sharma A, Chatterjee S. Shunt. Migration in ventriculoperitoneal shunting: A comprehensive review of literature. Neurol India 2019; 67(1): 85-99.
2. Ezzat AAM, Soliman MAR, Hasanain AA, Thabit MA, Elshitany H, Kandel H, et al. Migration of the Distal Catheter of Ventriculoperitoneal Shunts in Pediatric Age Group: Case Series. World Neurosurg 2018; 119: e131-7.
3. Obrador S, Villarejo F. Hydrothorax: Unusual complication of ventriculoperitoneal shunts. Acta Neurochir (Wien) 1977; 39: 167-72.
4. Taub E, Lavyne MH. Thoracic complications of ventriculoperitoneal shunts: Case report and review of the literature. Neurosurgery 1994; 34: 181-3; discussion 183-4.
5. Cakin H, Kaplan M, Ozturk S, Kazez A. Intrathoracic migration of ventriculoperitoneal shunt through the Morgagni's hernia in case with Down syndrome: A rare shunt complication. Neurol India 2013; 61: 552.
6. Leyon JJ, Kaliaperumal C, Flynn PA, Gray WJ, Kelly MG, Choudhari KA. Broncho-pleural fistula due to trans-diaphragmatic migration of the distal end of ventriculo-peritoneal shunt. Clin Neurol Neurosurg 2008; 110: 276-78.
7. Katsevman GA, Harron R, Bhatia S. Shunt-Bronchial Fistula with Coughing Up and Swallowing of Cerebrospinal Fluid: Rare Complication of Ventriculopleural Shunt. World Neurosurg X. 2019; 5: 100065.
8. Karapolat S, Onen A, Sanli A. Intrathoracic migration of ventriculoperitoneal shunt: a case report. Cases J 2008; 1(1): 42.
9. Naik V, Phalak M, Chandra PS. Total intracranial shunt migration. Journal of neurosciences in rural practice, 2013; 4(1): 95-6.
10. Tyagi et al. Outcome analysis of ventriculoperitoneal shunt procedures in hydrocephalus due to tubercular meningitis and non-infective cases. International Journal of Contemporary Pediatrics 2016. 10.18203/2349-3291.ijcp20162788.

Complete resolution of constrictive pericarditis after coronary bypass surgery

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SUMMARY

Classical constrictive pericarditis (CP) is an unusual and rare complication after coronary artery bypass grafting. It can be transient, progressive or fixed form of cardiac constriction. However recently recognized transient variant of constrictive pericarditis can be managed with medical therapy, though other progressive and irreversible forms may require pericardiectomy. We describe a 65-year-old male patient who developed a classical but a very early transient CP, just within two weeks as a result of post cardiac injury syndrome after coronary bypass surgery. The patient had a complete recovery following medical treatment.

INTRODUCTION

Constrictive pericarditis (CP) after coronary bypass surgery is a rare clinical condition which may appear early or late. The classical form of CP after cardiac surgery is usually progressive and irreversible, requiring pericardial stripping.[1] However, in some patients CP may resolve spontaneously or with medical treatment.[2,3,4]

CASE REPORT

A 65-year-old man with a long-standing history of diabetes, hypertension, and hyperlipidemia presented with unstable angina was referred for an early coronary artery bypass grafting (CABG) after diagnosing having a critical left main stem and triple vessel disease. A conventional CABG was performed under cardiopulmonary bypass. The postoperative course was uneventful and he was discharged well on post-operative day 6. However, 4 days later, the patient was re-admitted with complaints of fever, exertional dyspnoea and generalized oedema. Physical examination revealed elevated jugular venous pressure, generalized peripheral oedema, including ascites and mild hepatomegaly. The blood test findings were within normal limits except for an elevated C-reactive protein (3.1 mg/dL). Blood, urine and sputum cultures were negative. The chest radiograph showed a mild to moderate bilateral pleural effusion. (Figure 1). An echocardiography revealed a thickened pericardium and an abnormal interventricular septal movement. Pulse wave Doppler study showed significant mitral inflow velocity variation with respiration and exaggerated expiratory diastolic flow reversal in hepatic vein (Figure 1). These findings were not seen at the time of discharge earlier. These findings were highly suggestive of acute CP following CABG as part of the post-cardiac injury syndrome (PCIS). The patient was then treated with aspirin, non-steroidal anti-inflammatory drugs (NSAIDS) (celecoxib), anti-heart failure drugs including diuretics (Furosemide and Spironolactone), beta-blocker (Bisoprolol) and angiotensin converting enzyme (ACE) inhibitor (Ramipiril). As the patient could not tolerate colchicine after 2 days, we switched to steroid treatment. Prednisolone therapy (0.5 mg/kg/day) was started too, continued for 10 days, and progressively tapered over two weeks. The patient felt better and the generalized oedema disappeared. The chest radiograph and repeated echocardiography showed improvements.

The patient was discharged well on post-operative day 20. At the 3rd month of follow-up, the patient was asymptomatic. The chest radiograph showed complete resolution of pleural and pericardial effusion. The echocardiography examination revealed thinner pericardium, normalized mitral inflow velocity with respiration and expiratory diastolic flow reversal in the hepatic vein (Figure 2).

DISCUSSION

CP can be defined as a spectrum of diseases resulting from thickened, rigid and fused pericardial membranes that impair ventricular filling, leading to venous congestion and reduced cardiac output.[2,3] Common causes of CP are previous cardiac surgery, thoracic radiation, uremia, previous myocardial infarction, infection and idiopathic disease.[2,3] CP was thought to be irreversible but some have reported resolution of a transient form without surgical intervention.[3,4] Transient CP is an increasingly recognized sub-type and was first described back in 1987 by Sagrista-Sauleda et al, when a small group of subjects with CP demonstrated spontaneous and permanent resolution on serial echocardiograms.[1] Hence, it was suggested that there are several types of CP. These include classic chronic, sub-acute, transient and occult CP, all of which have their own characteristic natural history. The European Society of Cardiology has formally recognized it as a variant of CP in their updated guidelines for the management of pericardial diseases.[5]

About 17% of patients develop constrictive physiology on

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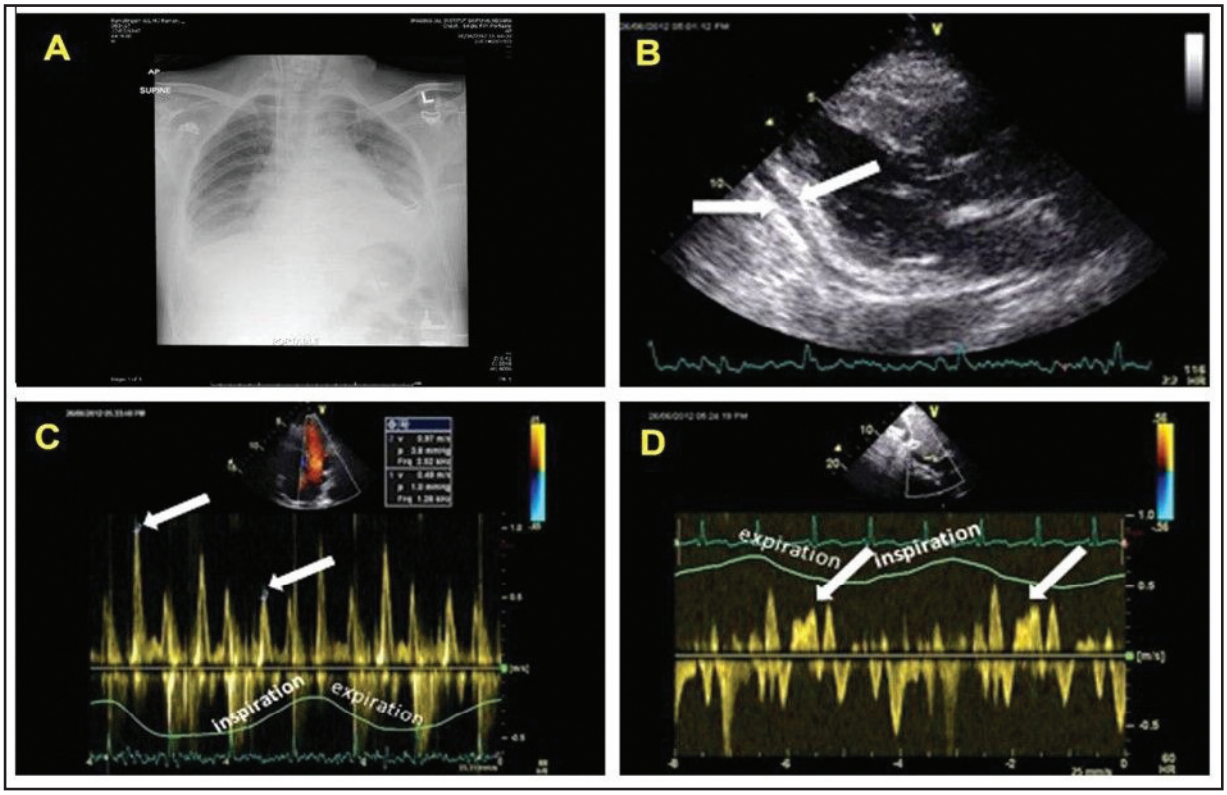

Fig. 1: Initial diagnosis: A) Chest radiograph revealed bilateral pleural effusions. B) 2D echocardiography showed thickened pericardium (white arrows). C) Pulse wave Doppler study illustrated significant mitral inflow velocity variations with respiration (white arrows). D) Pulse wave Doppler study showed exaggerated expiratory diastolic flow reversal in hepatic vein (white arrows).

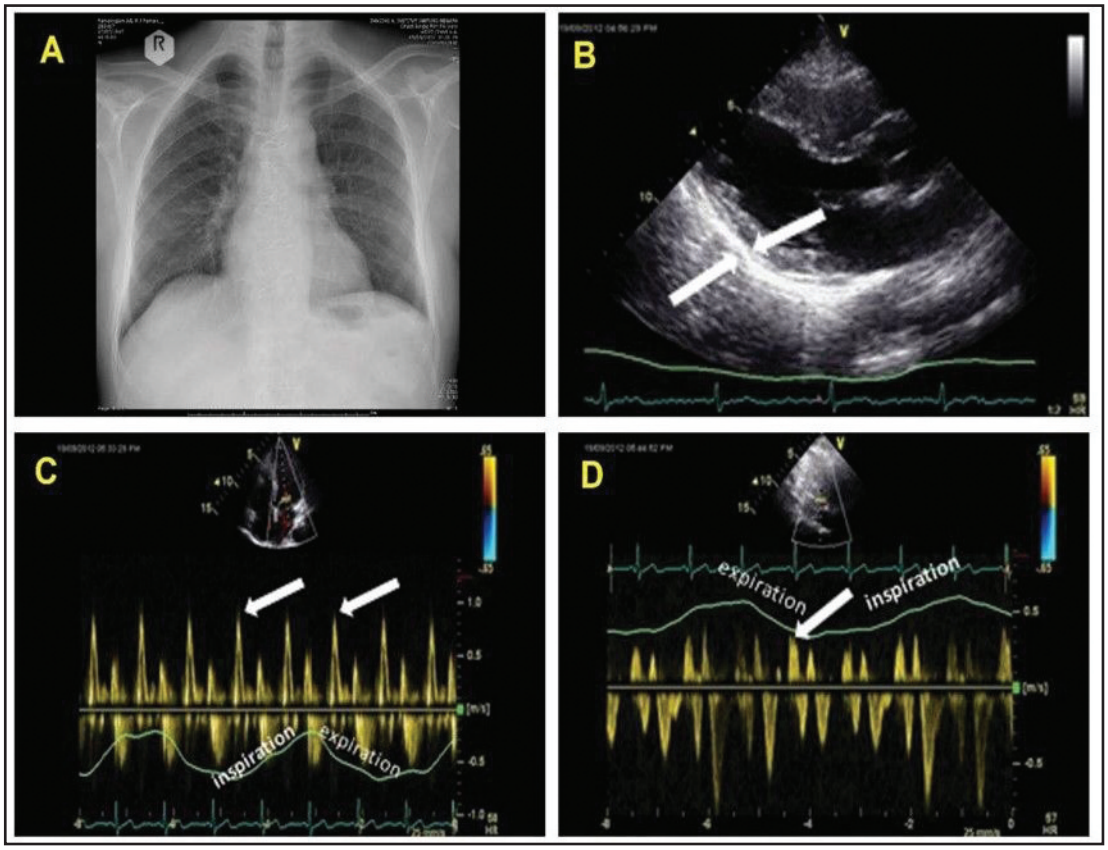

Fig. 2: Ten weeks after completion of treatment: A) Chest radiograph revealed complete resolution of the pleural effusions. B) 2D echocardiography showed normalised pericardium (white arrows). C) Pulse wave Doppler study illustrated normalised mitral inflow velocity variations with respiration (white arrows). D) Pulse wave Doppler study showed significantly reduced expiratory diastolic flow reversal in hepatic vein (white arrow).

postoperative echocardiography after open heart surgery but typical CP following coronary bypass surgery is a rare phenomenon with occurrence rate of 0.2 ~ 0.3%.[2,3] The interval between surgery and development of symptoms varies from 1 to 204 months. The common features are dyspnoea (81%), chest pain (34%), and fatigue (29%); peripheral edema (90%) and elevated jugular venous pressure (86%).

The precise mechanism of CP after cardiac surgery remains unknown. Many reported that CABG is a traumatic procedure with intraoperative irritation to the pericardium by the physical manipulation of surgeons and later continuous violent friction between the pericardium and the beating heart leading to PCIS.[2,3,4] Eui Im et al. suggested that post-operative pericardial effusion and normal left ventricular ejection fraction were predictors of constrictive after CABG.[3]

Our patient showed acute form of CP which appeared very early, just less than 2 weeks after the CABG, which has not reported before. We decided to treat this symptomatic patient medically. Unfortunately, our patient could not tolerate colchicine which is the first line of treatment in acute pericarditis with effusion.[5] Corticosteroids has been effective in reversing pericardial constriction only in some cases when it is given within the first 6 weeks of the surgery.[5]

CONCLUSION

Acute transient constrictive pericarditis after CABG can be treated successfully with medical therapy resulting in complete resolution.

CONFLICT OF INTERESTS

None to declare.

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REFERENCES

1. Sagrista-Sauleda J, Permanyer-Miralda G, Candell-Rierra J, Angel J, Soler-Soler J. Transient cardiac constriction: an unrecognized pattern of evolution in effusive Gaafare acute idiopathic pericarditis. Am J Cardiol 1987; 59(9): 961- 6.
2. Haley JH, Tajik AJ, Danielson GK, Schaff HV, Mulvagh SL, Oh JK. Transient constrictive pericarditis; causes and natural history. J Am Coll Cardiol 2004; 43(2): 271- 5.
3. Im E, Shim CY, Hong GR, Yoo KJ, Youn YN, Chang BC, et al. The Incidence and Clinical Outcome of Constrictive Physiology after Coronary Artery Bypass Graft Surgery. J Am Coll Cardiol 2013; 61(20): 2110-2.
4. Maeda K, Saito S, Toda T, Ueno T, Kuratani T, Sawa Y. Transient constrictive pericarditis following cardiac surgery. Ann Thorac Cardiovasc Surg 2014; 20 Suppl: 897-900.
5. Adler Y, Charron P, Imazio M, Badano L, Baron-Esquivias G, Bogaert L, et al. ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2015; 36(42): 2921- 64.

CASE REPORT

Acute necrotizing encephalopathy in a child secondary to dengue fever: A case report

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SUMMARY

Dengue fever (DF) is an important public health problem, and it is now endemic in more than 100 countries worldwide. Dengue associated neurological complication is estimated to be affecting 0.5 to 6.2% of patients. Even though this is rare, neurological manifestation of DF is an increasingly recognized entity in recent years due to significant mortality and morbidity reported/seen. Reported central nervous system manifestations due to dengue include encephalitis, encephalopathy, myelitis, myositis, acute disseminated encephalomyelitis, Guillain-Barré syndrome, stroke and etc. We report here a case of acute necrotizing encephalopathy secondary to DF in a previously healthy 12-year-old girl.

INTRODUCTION

Dengue fever (DF) is an arthropod-borne disease caused by dengue virus. Dengue virus is a single-stranded RNA virus belonging to the family of *Flaviviridae*, transmitted by Aedes mosquitoes. Worldwide, the incidence of DF has increased dramatically in recent decades. World Health Organisation estimates around 390 million dengue infections per year, of which around 96 million manifests clinically with any disease severity.[1] Thus far reported neurological manifestations of dengue include encephalitis, encephalopathy, Guillain-Barre Syndrome and encephalomyelitis. We report here a case of acute necrotizing encephalopathy in a child secondary to DF.

CASE REPORT

A previously healthy 12-year-old girl presented to Hospital Lahad Datu, Sabah, Malaysia with fever for 4 days with vomiting and epigastric pain. There was no headache or altered sensorium. On arrival at the hospital, she was restless. Her Glasgow Coma Scale (GCS) was E4V4M6. Her peripheries were cold with capillary refilling time of 3 seconds and reduced pulse volume. Her blood pressure was 85/37mmHg, pulse rate was 173 beats per minute and temperature was 40C. Her dengue NS-1 antigen was positive, dengue IgM and IgG were negative. She was treated as severe dengue in decompensated shock.

Her initial full blood count showed hemoglobin of 12.5g/dl, TWBC of $2.4x10^9$/L, platelet of $97x10^9$/L and hematocrit of 38%. Her renal function and liver function tests were normal. Her lactate dehydrogenase (LDH) was 1031U/ml. She was treated with fluid resuscitation with close monitoring in intensive care unit (ICU). Upon ICU admission, she became encephalopathic and not obeying command. Five hours later, she developed three episodes of generalized tonic-clonic seizures, each lasted 1-2 minutes. Her GCS deteriorated to E4V1M5. Neurological examinations showed brisk reflexes with normal plantar responses. She also has bulbar weakness which she required a nasogastric tube. A loading dose of intravenous phenytoin was administered for seizure control. An urgent computed tomography (CT) scan of the brain (day 5 of illness) showed bithalamic hypodensities extending to the posterior limbs of internal capsule (Figure 1). Lumbar puncture was not done due to severe thrombocytopenia.

Subsequently, her neurological deficits did not improve despite in recovery phase where she still has persistent bulbar weakness. A magnetic resonance imaging (MRI) of her brain (day 19 of illness) was performed, which revealed corresponding bithalamic high signal on T2 weighted images with no evidence of restricted diffusion. Post contrasted images showed enhancing lesions with an incomplete ring configuration at the right high frontal lobe (Figure 1). Overall, MRI brain features were highly suggestive of Acute Necrotizing Encephalopathy of Childhood (ANEC). The patient was then treated with intravenous methylprednisolone 750mg daily for 5days, followed by intravenous immunoglobulin for 5 days. She did not have any recurrence of seizure after that and did not require additional anti-epileptics. Her serum dengue polymerase chain reaction was positive for DEN3. She had excellent neurological recovery with resolution of the brain lesions on follow up MRI brain done 3 months later (Figure 2). Her neurological deficits completely resolved on clinic follow up.

DISCUSSION

The exact neuropathogenesis of neurological manifestations of dengue is still poorly understood. Host and virus factors play essential roles. Isolation of dengue virus and specific

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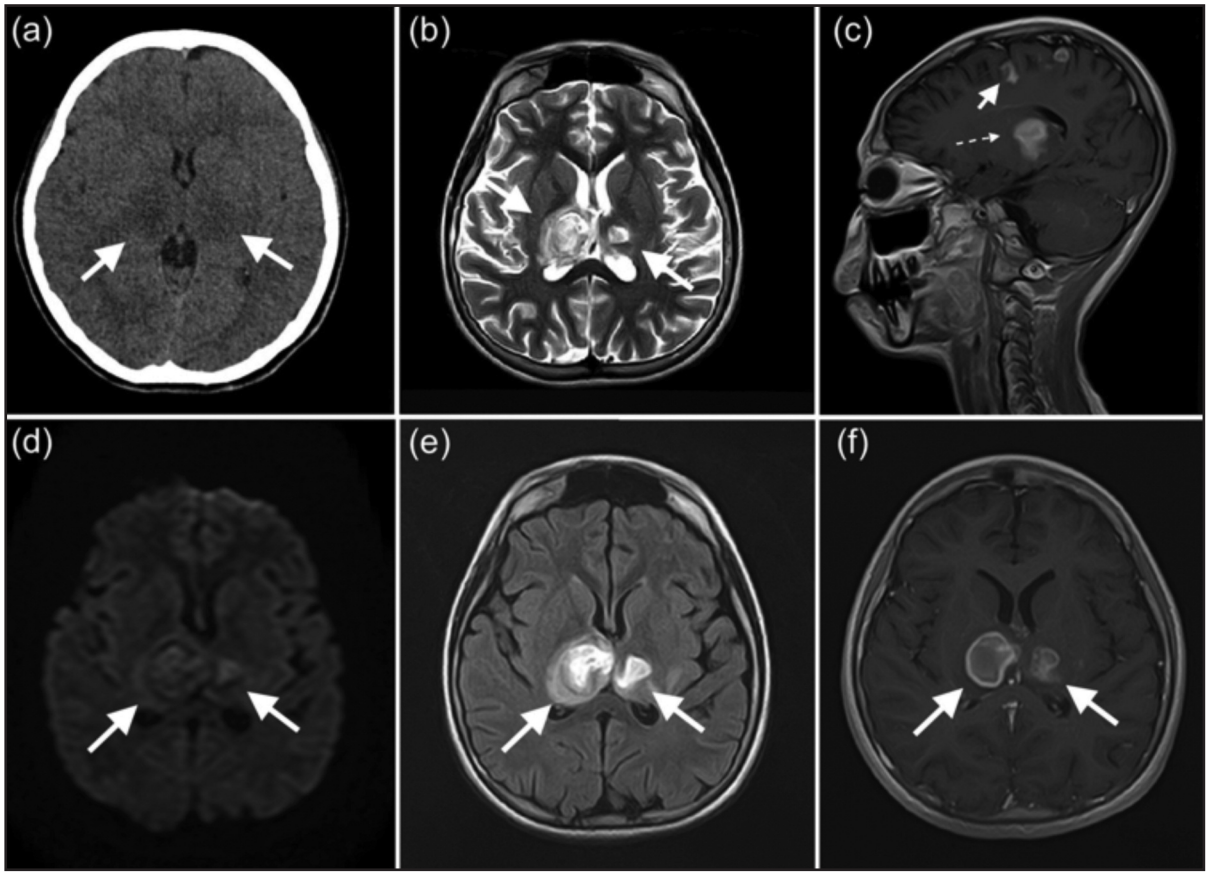

Fig. 1: Selected MR and CT images acquired prior to treatment. (a) Axial unenhanced CT brain shows ill-defined bithalamic hypodensities extending to the posterior limbs of internal capsule. (b) Axial T2 weighted MR brain images shows bithalamic high signal. (c) Post-gadolinium T1 weighted MR images demonstate rim-enhancing lesions at the grey-white matter junction of the right frontal lobe. One of the lesions demonstrates an incomplete ring configuration (white arrow). (d) Diffusion weighted MR image shows absence of restricted diffusion. (e)FLAIR MR brain images shows bithalamic high signal.(f) Post-gadolinium T1 weighted MR images demonstate rim-enhancing lesions at thalamus.

antibodies in cerebrospinal fluid have shown that the virus is capable of invasion of the CNS.[2] In general, neurological manifestation of dengue can be classified as (1) direct neurotropic effect of virus (2) systemic or metabolic complication of dengue and (3) post-infection complications. All in all, we believe that neurological complications are likely to occur as a result of complex interactions of the above mechanisms. Associated systemic metabolic abnormalities, abnormalities of vascular permeability, cytokine storms can all contribute to the neurological complications of dengue.[3]

In our patient, the clinical suspicion of dengue encephalitis was raised when she became encephalopathic and developed seizures. CT brain of our patient showed ill-defined hypodensities at bilateral thalami suggesting a fulminant inflammatory process involving the deep grey matter. The bilateral thalamic high signal on MRI, was suggestive of ongoing necrosis. The lack of restricted diffusion ruled out intra-axial abscess formation and the attenuated, hypodense signal on plain CT ruled out bithalamic haemorrhages. Critically, the presence of the enhancing incomplete ring lesions at the high frontal lobe demonstrated that underlying process was demyelination. Correlating with clinical history, these findings are consistent with Acute Necrotizing Encephalopathy of Childhood (ANEC).

ANEC, is a very specific subtype of encephalopathy which has a distinct clinical, radiological and pathological feature. It was first reported by Mizuguchi et al., where it usually affects the young and previously healthy children.[4] The exact etiology of ANEC remains unclear. Infection by influenza virus, herpes simplex virus, mycoplasma, swine flu, respiratory syncytial virus have all been associated.[5,6] It is believed that the virus can trigger the formation of cytokines, hypercytokinemia and subsequently cytokine storm, which eventually lead to the clinical syndrome of ANEC and multi-organ failure.[6] Clinically, ANEC is characterized by rapid neurological decline, encephalopathy, seizure, coma and neurological deficits.

In general, the optimal treatment for ANEC is unknown. Management of ANEC is mainly supportive with ventilation and antiepileptics.[7] Treatment with antiviral, methylprednisolone, intravenous immunoglobin (IVIG), plasmapheresis, antithrombin III and therapeutic hypothermia have been reported. Additionally, immunotherapy with methylprednisolone and IVIG have all been tried with variable degree of success. Our patient was treated with methylprednisolone and IVIG. She showed good clinical improvement with brain lesions resolving observed on follow-up imaging study.

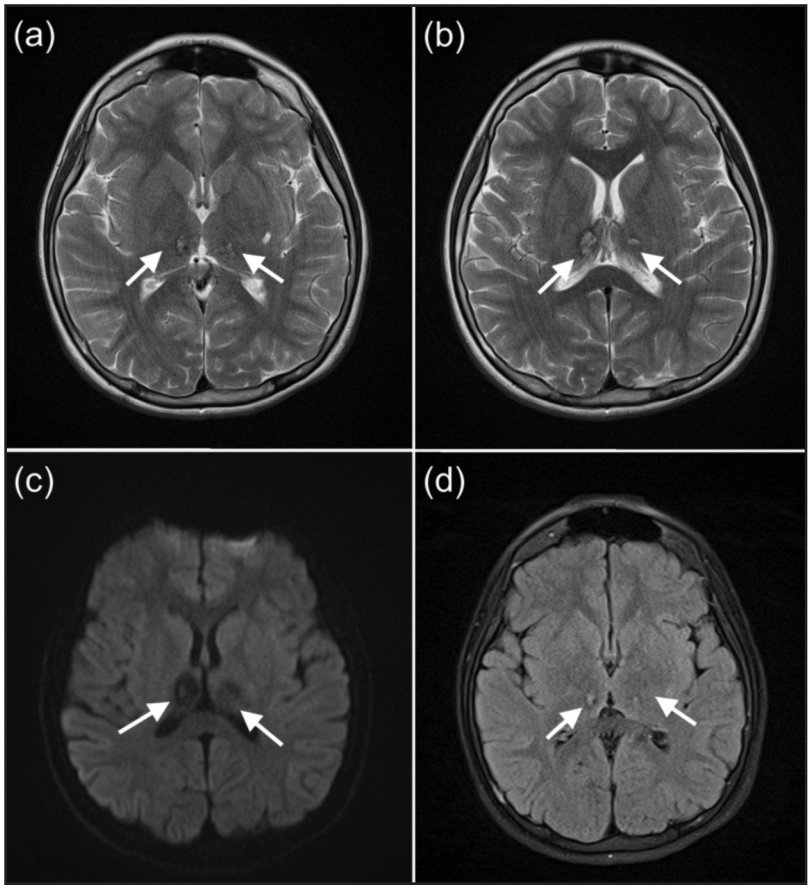

Fig. 2: Brain MRI images of the patient that were acquired at 3 months after treatment. (a&b)

CONCLUSION

In conclusion, neurological manifestation of dengue, though rare, are diverse in presentation. ANEC is a rare neurological complication of DF. High clinical suspicion is needed for early diagnosis as ANEC progresses rapidly and any delay in management will potentially lead to profound neurologic morbidity. Methylprednisolone and IVIG are helpful drugs that can be used to treat this condition.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

INFORMED CONSENT

Written informed consent was obtained from the patient's mother for publication of this manuscript.

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REFERENCES

1. World Health Organization. Dengue and severe dengue: Fact sheet, Updated 13 September 2018. https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue.
2. Sudhir U, Anil Kumar T, Gupta B, Punith K. Dengue Meningoencephalitis. J Indian Acad Clin Med 2010; 11(2): 141-3.
3. Madhavi C, Kejriwal GS, Giridhar GG. Role of Neuro-Imaging in Dengue Encephalitis. Int J Med Health Res 2010; 11(2): 141-3.
4. Mizuguchi M. Acute necrotizing encephalopathy of childhood: a novel form of acute encephalopathy prevalent in Japan and Taiwan. Brain Dev 1997; 19(2): 81-92.
5. Yadav S, Das CJ, Kumar V, Lodha R. Acute Necrotizing Encephalopathy. Indian J Pediatr 2010; 77: 307-9.
6. Fong CY, Saw MT, Li L, Lim WK, Ong LC, Gan CS. Malaysian outcome of acute necrotising encephalopathy of childhood. Brain Dev 2021; 43(4): 538-47.
7. Abbas Q, Jafri SK, Ishaque S, Jamil MT. Acute necrotizing encephalopathy of childhood secondary to dengue infection: A case report from Pakistan. J Pediatr Neurosci 2017; 12: 165-7.

Vitamin C deficiency in a picky eater child

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SUMMARY

Vitamin C deficiency or scurvy is an uncommon condition that occurs in poorly developed countries or in refugee camps. Nonetheless, in countries where food is readily available, like Malaysia, occasionally there are cases of vitamin C deficiency reported. Although it was primarily reported in children with special needs or learning disability, scurvy is encountered in children with normal development, among the severe picky eaters. We present here case of a nine-year-old picky-eating boy with scurvy. The development of scurvy in this child took several years, especially after he became a very selective eater at the age of five. The child had displayed limping when walking with knee-joint pain before he came to a primary hospital. However, his condition was not diagnosed promptly and progressively worsened until he was unable to walk. Thus, it is crucial to recognize scurvy in children who limps and are severe picky eaters.

INTRODUCTION

Human body does not synthesize and store vitamin C and consequently it depends on exogenous contribution for the requirement. Additionally, Vitamin C in the body depletes rapidly if the oral intake is inadequate.[1,2] The minimal daily requirement of vitamin C depends on the age and children, between the ages of one and fifteen, their requirement increases from 20mg to 85mg per day.[3]

The clinical manifestation of Vitamin C deficiency is scurvy, and symptoms usually begin after one to three months of absence of vitamin C in the diet.[4] Initial symptoms include fatigue, malaise, and inflamed gums.[2,4] If vitamin C deficiency persists, collagen synthesis will be impaired, weakening connective tissues, causing rupture of capillaries, joint pain, poor wound healing, and corkscrew hairs.[2,4] Other signs of scurvy include depression, swollen and bleeding gums, and loosening or even fall of teeth. Iron deficiency anaemia may develop because of significant blood loss due to bleeding and decreased non-heme iron absorption.[2] Children may also experience severe lower limb pain related to sub periosteal bleeding.[1,5]

One of the risk factors of vitamin C deficiency is picky eating. Picky eating is not an uncommon behaviour among children.[6] However, it becomes a disorder if this affects growth and development of children resulting in including micronutrient deficiency. Picky eating disorder forms part of a spectrum of feeding difficulties characterized by the refusal of children to eat familiar foods or try new foods and having strong food preferences.[7] There is no single universally accepted definition of picky eating and the method of assessment of this condition. This discrepencies made it difficult to estimate the prevalence.[6] We present a nine-year-old boy who developed scurvy due to being a severe picky eater over several years.

CASE REPORT

MA, a 9-year-old boy was born full-term via caesarian section due to maternal hypertension with a birth weight of 3.3kg. During infancy, he was on formula milk and was weaned at six-month-old with a blended diet consisting of a mixture of vegetables, rice, and fruits. However, when he was about two to three years old, he started to dislike vegetables, fruits, and many other protein sources other than eggs. At the age of five to seven years old, he became very selective of the food he ate. His breakfast mainly consisted of carbohydrates with a malt chocolate drink. In school, he ate plain fried noodles with no vegetables. His lunch consisted of rice with fried eggs and soy sauce; he usually lunch upon returning from school before rushing to a religious school. He ate rice with fried egg and soy sauce or potato-filling curry puff for an afternoon snack. Dinner also consisted mainly of carbohydrates with eggs and soy sauce which he usually ate in front of television. He refused to try any new food. He took very little fruits and vegetables since he was seven years old. His weight and height are both at the 3rd percentiles as charted in the growth chart. However, his developmental milestones were appropriate for his age.

He is the first of two siblings and lives with his extended family. His five-year-old sister was not a picky eater and had average growth pattern. His father did odd jobs in a rubber plantation while his mother was a housewife. At nine years old, he was taken to a primary health clinic for left knee pain and complaint of limping for a week. The left knee pain worsened when he walked and climbed stairs. He had no history of fever or fall and trauma. He was referred to the orthopaedic team at a district hospital and was treated symptomatically as the diagnosis was uncertain. The doctor applied skin traction on him for one day before discharging him with a back-slab the following day. The back-slab was removed a week later, and he continued with physiotherapy. However, his condition worsened, and he had difficulties walking finally requiring a wheelchair to mobilize. He went

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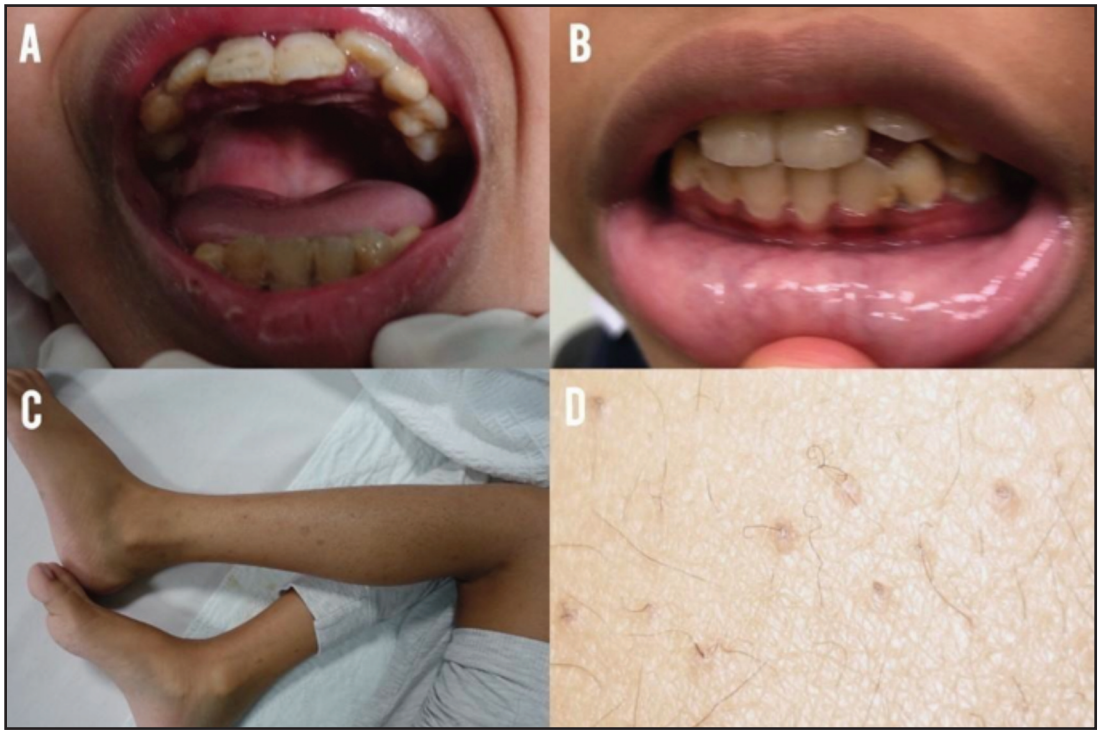

Fig. 1: (A) Gingival swelling on admission. (B) Improving gingival swelling post-one-month treatment. (C) Bruises over both ankles. (D) Follicular purpura and corkscrew hairs.

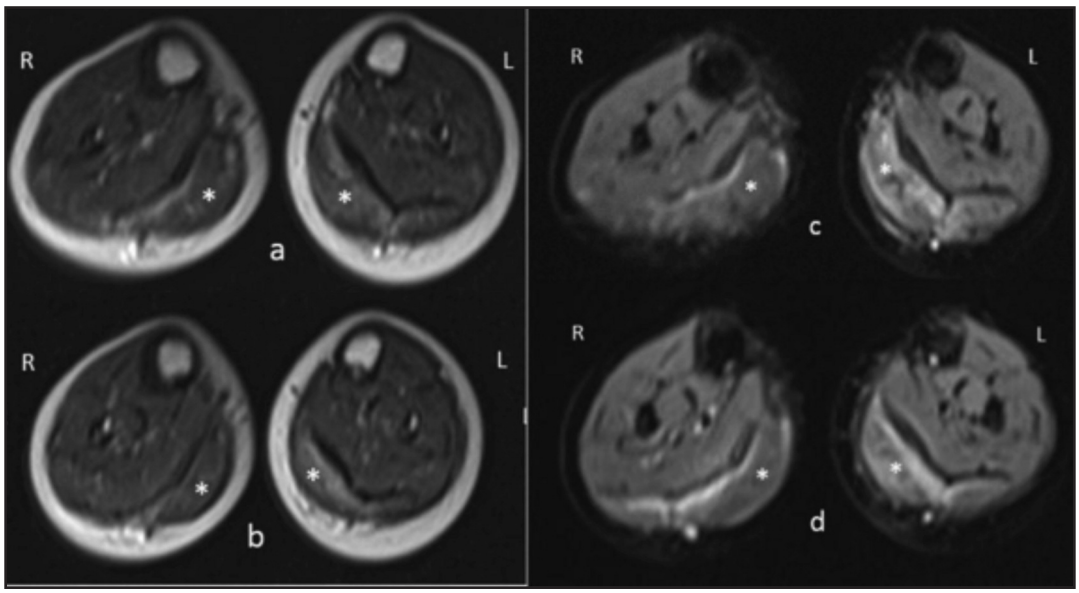

Fig. 2: MRI (Magnetic Resonance Imaging) of both the lower limbs. a & b – axial T2 weighted, c & d – axial T1 fat-suppressed images showing a subtle increased signal within the gastrocnemius muscles (asterisks) most pronounced on the left side. No enhancement observed post IV gadolinium.

to a private hospital and was referred for further management.

On examination, he was alert, conscious, but very fretful. He did not like to be touched or examined. He was pale, but there was no cyanosis or jaundice. He could not walk and laid down with both lower limbs flexed. His weight was 18.2kg (below 3rd percentile), and his height was 122cm (at 3rd percentile). His oral hygiene was poor, with plenty of caries. The gingiva was swollen and bleed easily (Figure 1A and 1B). He had muscle wasting on both hamstrings with bruises at both ankles (Figure 1C) and follicular purpura with corkscrew hairs over his legs (Figure 1D).

The muscle power, tone and reflex of both upper limbs were normal. However, power in both lower limbs was MRC grade

IV (Medical Research Council). His bilateral knee flexion and extension were restricted, ranging between 120°- 130° due to stiffness and tenderness of the calf muscles. The tone and reflex of both lower limbs were normal with no clonus, and the Babinski sign was negative. There was no spine deformity, and examination his other systems was unremarkable. At this point, a provisional diagnosis of Juvenile Idiopathic Arthritis was made.

The full blood picture showed hypochromic microcytic anaemia. Serum iron was 4.7 µmol/L, and total iron-binding capacity (TIBC) was 56.7 µmol/L. C-reactive protein and creatine kinase were not raised while the erythrocyte sedimentation rate was 78 mm/hour. Serum liver function and renal function tests were normal. Serum calcium was 2.29 µmol/L while serum magnesium was 0.97 µmol/L and serum phosphate was 1.8 µmol/L. Radiographs of both the knees and lower limbs were normal. Magnetic Resonance Imaging (Figure 2) of the lower limbs revealed a very subtle high signal of the gastrocnemius muscles (left > right side), which may suggest a mild inflammatory myositis. The long bones were normal, and there were no appearances to suggest periosteal bleeding.

Due to the limited intake of Vitamin C in the diet, supported with clinical findings of follicular purpura, corkscrew hair, swollen and easily bleed gum, and intolerable to movement and physical contact, a laboratory testing for Vitamin C level was carried out. The vitamin C level was found to be low at <0.1mg/dL. Thus, a diagnosis of scurvy was confirmed and treatment with daily oral vitamin C 300 mg was commenced. He was also referred to dieticians for dietary advice and modification. He was also started on syrup multivitamin and syrup iron and underwent limb physiotherapy.

After a week of vitamin C, his clinical condition improved, and pain became more bearable with both knees having a full range of movement and tolerating a more aggressive physiotherapy. On day ten of vitamin C, he started to bear weight and practiced walking. He was discharged with a vitamin C supplement of 300 mg daily after four weeks whereby, he was able to walk, though with some limping. After two months of vitamin C, he could walk and run and back to his usual cheerful self. His weight increased from 17kg to 19.05 kg within two months. He is currently eating chicken, but still refuses fish, and he eats blended vegetables mixed with fried rice or noodles. He occasionally drinks fruit juices and cordial drinks.

DISCUSSION

Scurvy is a disease that is still common in underdeveloped countries. However, in countries where food is readily available or considered developed, scurvy exists almost exclusively in children with autism, developmental and behavioural issues, food malabsorption, iron overload, and swallowing disorders.[1] Conversely, rarely it manifests in normal developmental with severe picky-eating children, as in our patient. Our patient showed selective-eating behavior at preschool age and it worsened till he began to totally refuse food enriched with vitamin C. During this period, signs and symptoms of scurvy started to appear. In the early age, the food was chosen by the parents and thus, the patient still consumed adequate vitamin C. However, as he grew older and became more independent, he started to become extremely selective to consume only the food that he likes and tolerated. This progressively change of worsening food-selectiveness is characteristic of a certain group of picky eater children.

The diagnosis of scurvy in the patient was suspected after the characteristic physical finding of scurvy was recognised. The radiological investigations were not very helpful in our patient as the findings were non-specific. The expected skeletal radiograph findings in scurvy include subperiosteal hematoma, transverse metaphyseal lines of decrease intensity (scurvy line), metaphyseal beak-like excrescences, sub epiphyseal infraction, and Wimberger's sign of scurvy (circular calcification surrounding the osteoporotic epiphyseal center of ossification).[5] The confirmatory vitamin C level was finally performed by the treating doctor, driven by the clinical features of the patient. The clinical findings also influenced the initiation of vitamin C treatment prior to receiving the laboratory results. Golriz et. al. identified 32 children with vitamin C deficiency treated in a children's hospital in Texas in over five years.[4] Almost all of the children with established vitamin C deficiency suffered acute and subacute illnesses. Among these cases, 60% of the children had underlying chronic transfusion, related to iron overload including thalassemia and sickle cell anaemia, 12% had developmental disorder, while another 10% were bone marrow transplant recipients on chemotherapy. Only one of these children had Vitamin C deficiency attributable to being neglected.[4] Harknett et al. reported a case series of 18 children with scurvy. Only one of the cases was a boy with no developmental problem and a picky eater.[8] Occasionally, there are isolated case reports of scurvy in normal developmental children.[1]

Our case illustrates the importance of preventing and managing picky eating behavior properly. Management of children with picky eating behaviour requires commitment from the whole family member.[9] Some of the strategies include distraction avoidance (e.g. gadget and toys), a regular feeding interval of between three and four hours with no snacks in between, and maintaining a happy and pleasant environment throughout the feeding session.[9] The food served should be appropriate in amount and texture according to the developmental age with limited mealtime of 20 to 30 minutes. Parents should also encourage self-feeding by providing personal feeding utensils, allowing an age-appropriate level of messiness, and systematically introducing new food.[9] In summary, parents and caretakers should ensure that children under their care have a healthy and balanced diet, along with good dietary habits to prevent vitamin C deficiency and scurvy.

CONCLUSION

Vitamin C deficiency in children is still being reported even in Malaysia. Unfortunately, because of infrequency of reports, clinician may still overlook it particularly if the occurrence is not recognized. It needs to be recognized in children who are picky eaters having the relevant clinical findings and can be prevented if adequate vitamin C is taken as per requirement.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

CONSENT

Written informed consent was obtained from the patient for publication of this manuscript.

REFERENCES

1. Nastro A, Rosenwasser N, Daniels SP, Magnani J, Endo Y, Hampton E, et al. Scurvy due to selective diet in a seemingly healthy 4-year-old boy. Pediatrics 2019; 144(3): e20183824.
2. Hosen Z, Bipasha SA, Kamal S, Rafique S, Islam B, Fatema K. Dietary supplementation of citrus limon L. (lemon) and evaluation of its role to prevent and cure of vitamin C deficiency diseases. Int J Food Sci Nutr 2020; 9(1): 1.
3. German Nutrition Society (DGE). New Reference Values for Vitamin C Intake. Ann Nutr Metab 2015: 67(1): 13-20.
4. Golriz F, Donnelly LF, Devaraj S, Krishnamurthy R. Modern American scurvy - experience with vitamin C deficiency at a large children's hospital. Pediatric Radiol 2017; 47(2): 214-20.
5. Miraj F, Abdullah A. Scurvy: Forgotten diagnosis, but still exist. Int J Surg Case Rep 2020; 68: 263-6.
6. Taylor CM, Emmett PM. Picky eating in children: causes and consequences. Proc Nutr Soc 2019; 78(2): 161-9.
7. Thompson C, Cummins S, Brown T, Kyle R. What does it mean to be a 'picky eater'? A qualitative study of food related identities and practices. Appetite 2015; 84: 235-9.
8. Harknett KM, Hussain SK, Rogers MK, Patel NC. Scurvy mimicking osteomyelitis: case report and review of the literature. Clin Pediatr (Phila) 2014; 53(10): 995-9.
9. Yang HR. How to approach feeding difficulties in young children. Korean J Pediatr 2017; 60(12): 379-84.

A case of lupus nephritis flare-up in severe COVID-19 infection

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SUMMARY

The novel Coronavirus disease 2019 (COVID-19) had rapidly spread and became a worldwide pandemic since its detection in Wuhan, China. The disease has caused significant morbidity and mortality, particularly among patients with comorbidities. The current treatment involves supportive management alongside antiviral therapy and immunosuppressant therapy in severely affected patients. We describe a case of a patient with underlying lupus nephritis (LN) who presented with severe COVID-19 infection and concomitant LN flare with acute kidney injury (AKI). The patient was treated with antiviral therapy, Favipiravir, considering his risk of developing severe COVID-19 infection. As the patients would usually have AKI alongside LN flare, we administered initial steroid therapy at a lower dose (Methylprednisolone 50mg daily) and oral hydroxychloroquine despite the initial concerns on immunosuppressant usage in COVID-19 infections. Although our patient recovered relatively well from COVID-19 infection, he continued to have positive reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharyngeal swab for COVID-19 up to 29 days of illness. His kidney function stabilised despite having persistent nephrotic range proteinuria. Hence, the attending team decided to pulse the patient with a high dose steroid (IV Methylprednisolone 250mg OD for three days) after two weeks of illness despite the persistent positive swab. The patient's condition continued to improve, and this case illustrates an approach in treating COVID-19 with concomitant active immune-mediated glomerulonephritis. We find that it is safe to institute high dose immunosuppressant in recovered COVID-19 patients two weeks after the illness.

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected more than 2 million people since its discovery in December 2019. The disease is associated with significant mortality and morbidity, especially among critically ill patients. Acute kidney injury (AKI) is common in COVID-19 patients, and around 20% of COVID-19 critical care admission require renal replacement therapy.[1] There is a lack of evidence on the optimal treatment in immune-mediated kidney disease in COVID-19 due to its novelty and limited data available. We describe a case of symptomatic COVID-19 infection with concomitant relapse of lupus nephritis (LN) presenting with AKI. In this case, we highlight the difficulty in initiating immunosuppression treatment for LN in symptomatic COVID-19 infection.

CASE REPORT

A 30-year-old Indian immigrant with a background history of LN presented with a three-day history of fever, cough with exertional dyspnoea, vomiting and diarrhoea. He developed multiple pustular skin lesions on his upper and lower limbs five days before admission. He denied any history of hair loss or Raynaud's phenomenon and no history of nephrotoxic drug exposure. In the last three months, he had defaulted his immunosuppressive medications (prednisolone and mycophenolate mofetil).

He looked lethargic and dehydrated with hypotension (76/49mmHg) and had tachycardia (120 beats/minute) on admission. His blood pressure responded to normal saline resuscitation and improved to 105/71mmHg. He was febrile (39.2° Celsius) with good oxygen saturation on room air. His right elbow was swollen and warm with pus discharge. There was also presence of multiple minor ulcerated wounds on bilateral feet and buttocks (Figure 1 A, B). He also had pitting oedema of bilateral legs. There were no oral ulcer, malar rash, or lymphadenopathy. The rest of the examination was unremarkable.

The patient underwent the reverse transcriptase-polymerase chain reaction (RT-PCR) test through the nasopharyngeal swab because of positive COVID-19 contact history. He was tested positive with an initial Cycle Threshold (Ct) value of 26. His blood investigations revealed AKI with hyperkalaemia (Table I). However, there was no metabolic acidosis on blood gas analysis. Initial full blood count showed hypochromic microcytic anaemia with haemoglobin of 10.2g/dL, a raised white cell count of 37.8 x 10^9 (predominantly neutrophilia), absolute lymphocyte count of 1.2. Serum procalcitonin and C-reactive protein were 10.5ng/L and 33.8mg/dl, respectively. No evidence of haemolysis on peripheral blood film and serum lactate dehydrogenase and bilirubin levels were normal.

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Table I: Summary of blood investigations during three admissions

Admission	1st					2nd	3rd
Day of Illness	Day 4	Day 6	Day 11	Day 13	Day 17	Day 23	Day 29
Urea (mmol/L)	25	23	21	12	10	10	8
Creatinine (umol/L)	321	194	126	65	69	76	73
Urine PCI (g/mmol creatinine)	0.14		0.63	0.60	-	0.43	0.58
Albumin (g/dL)	13	11	13	15	17	18	15
Antinuclear antibody (titre)	1/320						
Anti-dsDNA	Positive						
C3 (mg/dl)	30						
C4 (mg/dl)	5						
WBC (x 109)	37.8			13	9.4	7.4	8.6
C-reactive protein (mg/dl)	33.8			0.1	-		8.4
Procalcitonin (ng/L) [Normal value: <0.05 ng/L]	10.5			3.0	-		
Cycle threshold (Ct) value for RT-PCR	26					27	25

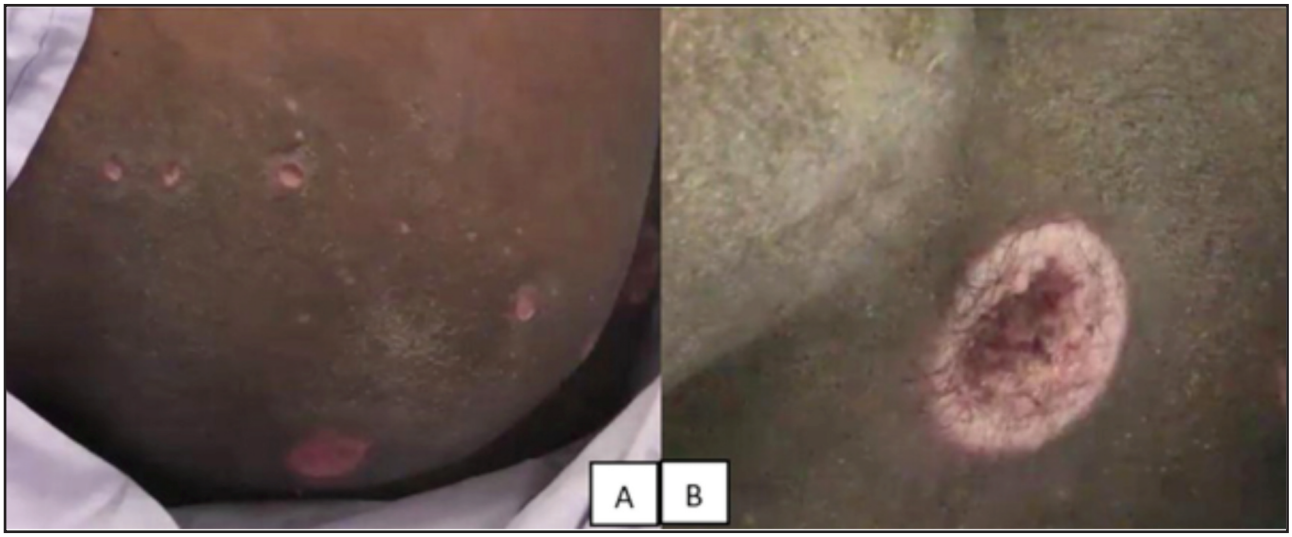

Fig. 1: (A) multiple ulcerated lesions on buttock, and (B) ulcerated lesion with suppurative based on the left gluteal region.

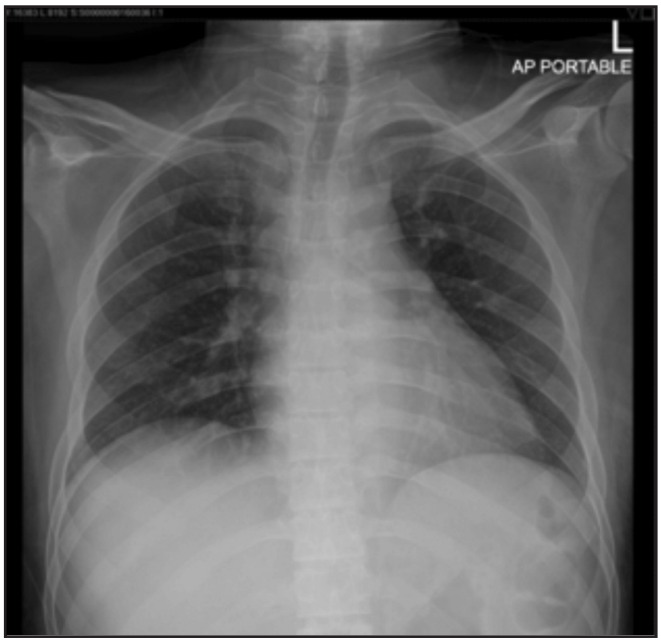

Fig. 2: Chest radiograph during admission did not reveal any abnormalities.

Further investigations showed hypocomplementemia with a high titre of anti-dsDNA suggestive of a lupus flare. The initial urine protein creatinine index (PCI) result was 0.14 g/mmol creatinine, but it rose to nephrotic range later. His chest radiograph at admission was normal (Figure 2) but the computed tomography scan of the chest revealed ground glass opacities at the periphery of the lower zone of the right lung (Figure 3). Additionally, there was no intra-articular collection or deep-seated abscess found on ultrasound at the region of the elbow. Skin biopsy results confirmed the presence of abscess without evidence of vasculitis. The skin biopsy culture and the blood culture were both negative.

The patient was treated for COVID-19 infection with concurrent sepsis, LN flare and AKI. Due to the concerns of COVID-19 deterioration, he was started on the new antiviral agent, favipiravir, with a loading dose of 1600mg twice daily followed by 600mg twice daily for four days. Intravenous cefazolin was also commenced. Despite the initial concern on initiating steroid in active COVID-19 infection, the managing team decided to control his lupus flare with a lower dose of steroid (intravenous methylprednisolone 50mg once daily) throughout hospitalisation in addition to oral hydroxychloroquine 200mg once daily. Venous thromboembolism prophylaxis was also given because of a

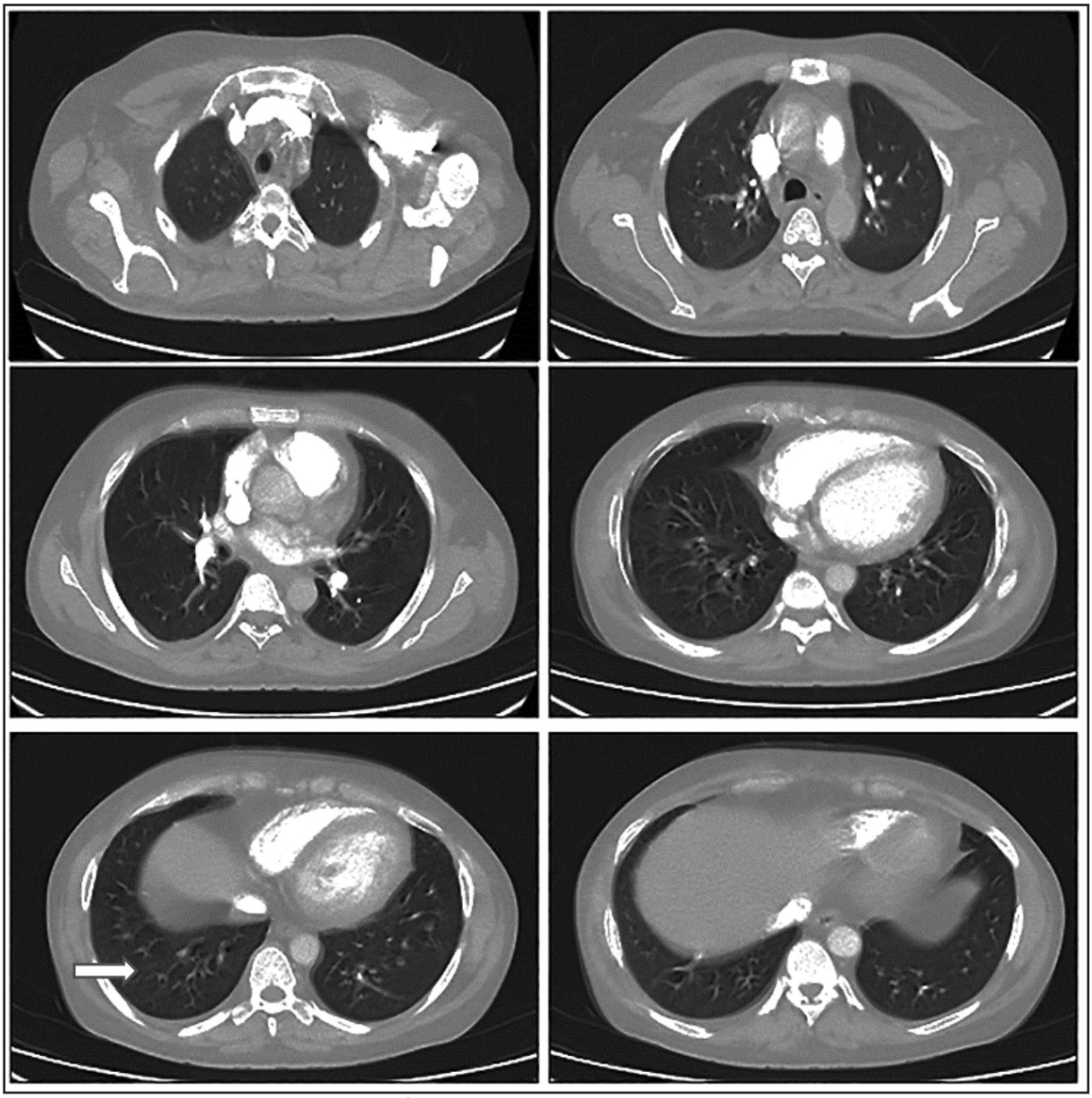

Fig. 3: Contrast-enhanced computed tomography of the chest showed ground glass opacities at the right lower zone involving the lung periphery (white arrow).

high D-dimer of 6.91ug/ml and marked hypoalbuminemia (serum albumin 13g/l). The patient was nursed in the critical care ward, and his general condition improved during the hospitalisation. He remained afebrile and did not need an increase in oxygen requirement. His kidney function improved, and septic parameters normalised on day 10 of hospitalisation (Table I). Perindopril 4mg once daily was started after renal function normalised. He was discharged after 18 days of hospitalisation with oral prednisolone 30mg daily and was scheduled for an outpatient nephrology clinic follow up.

However, the patient was readmitted two days later due to worsening pedal oedema. He had no further respiratory symptoms, and repeated chest radiograph did not show any worsening pneumonia. Despite a stable kidney function, his biochemical parameters revealed a persistent nephrotic syndrome. Although his repeat nasopharyngeal swab for RT-PCR test was still positive for COVID-19, the disease was considered inactive due to the absence of symptoms and signs of deterioration. Therefore, the decision was made to induce his LN into remission with IV Methylprednisolone 250mg daily for three days, followed by oral prednisolone of 0.5mg/kg along with mycophenolate mofetil. He was discharged after his fluid overload stabilised.

Unfortunately, he required the third admission due to lower limb cellulitis, requiring one week of intravenous antibiotics in which he had a good recovery. His RT-PCR remained positive on the 29 days since the first illness, but there was no respiratory symptoms progression. The Ct value for his recurrent admission was of similar value, 27 and 25 for his

second and third admission, respectively. His kidney function remained stable, but urine PCI was persistently in the nephrotic range with a slow improvement of serum albumin. Due to immigration rules, the patient was discharged to his home country after the completion of antibiotics.

DISCUSSION

There is limited evidence on the treatment of COVID-19 with concomitant immune-mediated kidney disease relapse. Numerous routine therapeutics and diagnostic procedures are being reconsidered as unsuitable during the active COVID-19 infection based on expert opinions and guidelines. We approached this case by prioritising the treatment of COVID-19 and, at the same time, instituting immunosuppression at a reduced dose. We also modified our diagnostic strategy to limit the spread of the disease.

The usage of antiviral treatment in COVID-19 was drawn from experience in managing the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) pandemic. We treated our patient with the antiviral favipiravir for the COVID-19 infection even before it was widely used as a standard treatment for COVID-19. Treatment that includes favipiravir has been shown to shorten the median length of viral clearance compared to lopinavir/ritonavir and was also associated with faster viral clearance. The drug's side-effect profile also seems acceptable.[2] Favipiravir has since been incorporated into Malaysia's COVID-19 management guideline, but caution was given to its usage in patients with AKI due to its renal excretion. Although favipiravir and its active metabolite concentration were high in patients with mild to moderate renal impairment, the range is expected to be safe.[3] Neither renal dose adjustment nor renal adverse effect was mentioned in the literature, and patient with lower glomerular filtration rate (GFR <20ml/min) was excluded from clinical trials.[4] Our case showed no worsening of kidney function or side effects while on favipiravir despite the AKI.

Hydrating the patient and administering antibiotics has helped improve the patient's kidney function, suggesting an element of pre-renal causes of AKI. Predisposing factors like hypovolaemia and sepsis are among the commonest contributory factors to AKI in COVID-19 apart from cardiovascular comorbidity. Interestingly, autopsy studies have identified SARS-COV-2 particles in the patient's kidney that could suggest renal tropism.[1] These may support biopsy's role in delineating the AKI cause, but without current proven treatment of COVID-19, such invasive procedure will not alter disease management, which is mainly supportive. In our case, the result of kidney biopsy may indicate the LN activity, but such indication for biopsy is not preferred during active COVID-19 infection unless it is essential. Although the causes of AKI in our patient were multifactorial, the nephrotic range proteinuria, hypoalbuminaemia, hypocomplementemia and high titre of ANA pointed towards LN flare. Hence, as the patient's kidney function recovered, we deferred the biopsy and treated the patient empirically for LN relapse.

Before RECOVERY trial, the use of steroids in COVID-19 patients was highly debated as the suppression of cellular immunity was thought to have contributed to a poor outcome for COVID-19 infections. The usage of steroids in the recent novel coronavirus infections, i.e., MERS and SARS, has caused delayed virus clearance, and many results pointed towards harm. However, early small studies in severely ill COVID-19 patients showed positive outcome with the use of steroids.[5] It was confirmed later in a large randomised controlled trial, RECOVERY, which has significantly changed the practice in treating COVID-19.6 The use of dexamethasone at a dose of 6mg daily has proven to reduce mortality in COVID-19 patients who require respiratory supplementation.

Our patient was at risk of developing end-stage kidney disease due to his active LN without any immunosuppression; hence we decided to treat him with IV Methylprednisolone at 50mg daily for the renal indication. Steroid administration has become the standard of treatment for COVID-19 patients with hypoxia, where low dose dexamethasone or methylprednisolone are routinely given. However, in immune-mediated kidney disease with concomitant COVID-19 infection, many guidelines emphasised individualised immunosuppressive treatment for both steroid and other modalities and suggested a lower dose of steroids during active infection.[7] Instead of administering high dose steroid pulses, we gave intravenous methylprednisolone at a lower dose equivalent to prednisolone 1mg/kg/d. The mycophenolate mofetil was discontinued due to active COVID-19 and sepsis.

Among patients with simultaneous COVID-19 infection and active immune-mediated glomerulonephritis, the optimal timing of immunosuppression intensification is unknown, especially among patient with concurrent sepsis. The dose of steroid in inducing remission in LN is much higher than the dose administered for COVID-19 infection, and the consequence of such dose on virus clearance is unknown, especially if administered early when the viral burden is high. In our case, we initiated pulse intravenous methylprednisolone (250mg/d for three days) during his second admission, 20 days after his COVID-19 illness. His RT-PCR remained positive with a Ct value of 27 but active COVID-19 infection cannot be proven without a viral culture. Ct values that are generated by qualitative PCR assays are affected by multiple factors and does not reliably correspond to viral load. The Centre for Disease Control and Prevention (CDC) suggested discontinuation of isolation after ten days for mild COVID-19 infection and up to 20 days for severe infection, suggesting a complete recovery and possible arbitrary non-infectious state.[8] The difficulties in determining the clearance of infection will ultimately rely on the overall patient's clinical assessment as performing viral culture is labour-intensive and not easily available. Ct value may be of help, but its limitation needs to be recognized.

One study has shown that the median duration of virus shedding was eight days from symptoms onset. The probability of detecting the virus in culture dropped below 5% after 15.2 days of post-onset of symptoms suggesting low viral burden, especially in patients with symptoms

resolution.[9] Hence, we believe that initiating high dose immunosuppression after two weeks of illness will be safe in recovered COVID-19 patients. We believe that the initiation of mycophenolate mofetil for consolidative treatment after the steroid pulse is also appropriate due to its oral route delivery, hence reducing contact with health service compared to cyclophosphamide that requires parenteral treatment and a more intense immunosuppressive agent.

CONCLUSION

In managing LN relapse with AKI in COVID-19 patients, it is important to concentrate on any reversible cause of the kidney injury and prioritise managing the COVID-19 before treating the LN. Initiation of steroid has now been proven to be helpful in oxygen dependent active COVID-19 infection and the benefit may also extend to patients with concomitant immune-mediated kidney disease. Additionally, treatment with high dose immunosuppressive treatment after 14 days of COVID-19 illness is acceptable in lupus nephritis flare-up.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med 2020; 8(7): 738-42.
2. Agrawal U, Raju R, Udwadia ZF. Favipiravir: A new and emerging antiviral option in COVID-19. Med J Armed Forces India 2020; 76(4): 370-6.
3. Pharmacologic Treatment of COVID-19: What Nephrologists Need to Know - Mass General Advances in Motion [Internet] [cited May 17, 2021]. Available from: https://advances.massgeneral.org/research-and-innovation/article.aspx?id=1224
4. Izzedine H, Jhaveri KD, Perazella MA. COVID-19 therapeutic options for patients with kidney disease. Kidney Int 2020; 97(6): 1297-8.
5. Wang Y, Jiang W, He Q, Wang C, Wang B, Zhou P, et al. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. Sig Transduct Target Ther 2020; 57(5)
6. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Eng J Med 2021; 384(8): 693-704.
7. Anders H-J, Bruchfeld A, Fernandez Juarez GM, Floege J, Goumenos D, Turkmen K, et al. Recommendations for the management of patients with immune-mediated kidney disease during the severe acute respiratory syndrome coronavirus 2 pandemic. Nephrol Dial Transplant 2020; 35(6): 920-5.
8. Interim Guidance on Duration of Isolation and Precautions for Adults with COVID-19 | CDC [Internet] [cited Feb 23, 2021]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html#print
9. Kampen JJA van, Vijver DAMC van de, Fraaij PLA, Haagmans BL, Lamers MM, Okba N, et al. Duration and key determinants of infectious virus shedding in hospitalized patients with coronavirus disease-2019 (COVID-19). Nat Commun 2021; 12: 267.

CASE REPORT

A challenging road to diagnosing transthyretin cardiac amyloidosis and using technetium-99m pyrophosphate bone scintigraphy in nuclear cardiology - A case report

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SUMMARY

Cardiac amyloidosis (CA) is a rare form of protein deposition disease, leading to restrictive cardiomyopathy that often presents with signs and symptoms of unexplained heart failure with preserved ejection fraction (HFpEF). There are two main subtypes of CA, namely light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR), which are conventionally confirmed by endomyocardial biopsy (EMB). The prognosis and treatment of the subtypes differ extensively, making it crucial to distinguish between the two. Although echocardiography (ECHO) and cardiac magnetic resonance imaging (CMR) are useful to aid in the diagnosis, they are unable to differentiate between the subtypes. Advantageously, the transthyretin cardiac amyloidosis (ATTR-CA) subtype can be diagnosed based on nuclear medicine bone scintigraphy imaging using Technetium-labelled bone-seeking radiotracers. We report a case of a previously well, elderly gentleman who presented with acute heart failure symptoms, whereby ECHO findings were suspicious for CA. Technetium-99m pyrophosphate (^{99m}Tc-PYP) bone scintigraphy performed with complementary single photon emission computed tomography/computed tomography (SPECT/CT) at three hours post-injection revealed radiotracer uptake in the myocardium that was higher than the skeletal bone uptake. This corresponded to Perugini score of 3 along with an increased heart to contralateral lung ratio (H:CL) of 1.69. The bone scintigraphy findings together with his symptoms, ECHO, CMR, and laboratory results enabled the diagnosis of ATTR-CA to be made. In summary, bone scintigraphy offers a reliable and non-invasive method for the diagnosis of ATTR-CA. We also highlight the diagnostic pitfalls and recommendations in reporting bone scintigraphy for the indication of typing cardiac amyloidosis.

INTRODUCTION

Cardiac amyloidosis (CA) is a rare condition that occurs when there is deposition of misfolded proteins that bind together to form amyloid fibrils in the myocardium.[1] CA is a part of a localised or systemic deposition of amyloid proteins that manifests as a rapidly progressive infiltrative, restrictive cardiomyopathy, which eventually leads to cardiac failure. CA can be further divided into light chain amyloidosis (AL) and the transthyretin amyloidosis (ATTR) subtypes. The cardiac amyloidosis of the ATTR subtype (ATTR-CA) if left untreated, can lead to death within 3-5 years from diagnosis, whereas the AL subtypes has a poorer prognosis with life expectancy of less than 6 months due to its direct toxicity to the cardiomyocytes.[2] The ATTR-CA can be further divided into the i) hereditary or familial autosomal dominant mutant type (ATTRm), whereas the age-related protein misfolding that occurs in the elderly above 65 years old, which was previously termed as senile CA, is known as the ii) wild type ATTR (ATTRwt).[1,2] The CA subtypes all eventually lead to heart failure with preserved ejection fracture (HFpEF), and patients often present with progressive fatigue, reduced effort tolerance, shortness of breath on exertion, and peripheral oedema.[3] In light of emerging treatment for ATTR-CA such as the FDA approved drug Tagamidis, which is a TTR protein stabilizer, there is a pressing need to distinguish between the two subtypes of CA.[4]

The gold standard for diagnosing CA is by performing endomyocardial biopsy (EMB). This procedure is invasive and carries a low but consequential risk of cardiac perforation.[5] Congo red dye viewed under polarized light or sulphated Alcian blue dye used to stain the biopsied specimen will give an apple-green birefringent appearance that is confirmatory for amyloidosis.[1] Currently, EMB is reserved for equivocal cases having discordant clinical and imaging findings. This is because there is a growing body of evidence regarding the role of i) transthoracic echocardiography (ECHO) with or without cardiac magnetic resonance imaging (CMR) having features suspicious of CA, in combination of results from ii) serum and urine electrophoresis (SEP and UEP, respectively) and immunofixation to detect light chain immunoglobulins pointing to a diagnosis of AL as well as iii) serum light chain assays to detect the presence of clonal plasma cells, together with iv) bone scintigraphy using Technetium-labelled bone-seeking radiotracers, for making the diagnosis and detecting the type of CA, which can obviate the need to perform EMB.[6] The elevation of cardiac enzymes and HF biomarkers, such as Troponin T and N-terminal prohormone of brain natriuretic

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peptide (NT-proBNP) that are highly disproportionate to the degree of severity of HF symptoms may also point to a suspicion of ATTR-CA. Hence, the contemporary diagnosis of ATTR-CA is made from a high clinical index of suspicion based on the age of the patients, the presence of congestive heart failure and unexplained left ventricular wall thickening, the absence of light chain proteins on SEP and UEP, and a positive Technetium-labelled bone scintigraphy. Technetium-labelled bone scintigraphy, particularly using Technetium-99m pyrophosphate (^{99m}Tc-PYP) can aid in the non-invasive diagnosis of cardiac ATTR. This technique, used for a relatively rare condition, requires proper training for accurate interpretation and is not without pitfalls and limitations.

We report a rare case of an elderly Malay gentleman with acute heart failure and unexplained left ventricular hypertrophy, who had benefited from a bone scintigraphy at our nuclear medicine department at Institut Kanser Negara, Malaysia. Based on our imaging findings, we were able to make an early diagnosis of ATTR-CA. To the best of our knowledge, this is the first report in Malaysia that highlights the diagnostic pitfalls and recommendations in reporting bone scintigraphy for the indication of typing ATTR-CA.

CASE REPORT

An 81-year-old Malay gentleman was diagnosed with acute decompensated congestive heart failure (HF) at Institut Kanser Negara, Malaysia. He presented with reduced effort tolerance, shortness of breath on exertion, and bilateral upper and lower limbs oedema, for one month duration. He denied angina symptoms and his overall performance was categorized as NYHA Class II-III. The patient was an ex-chronic smoker (25 pack years) with no other underlying medical conditions. His blood pressure was within the normal range and cardiovascular system examination did not reveal any murmur. Plain radiograph of the chest showed evidence of left-sided pleural effusion and an apparent cardiomegaly. Electrocardiography (ECG) showed atrial arrhythmia with variable atrioventricular (AV) dissociation and broad QRS complexes suggestive of intraventricular conduction defect and bi-fascicular block. There was also low voltage ECG as evidenced by peak-to-peak QRS complex of <5 mm in the limb leads. There was, however, no evidence of acute ischaemic changes on ECG. ECHO revealed speckled, heterogeneously echogenic ('starry-sky' appearance) and thickened right and left ventricular walls, as well as dilated atria, with associated left-sided pleural effusion (Figure 1a). Tissue Doppler imaging (TDI) over the mitral annulus region demonstrated diastolic dysfunction as evidenced by restrictive filling pattern (Figure 1b). Reduced medial and lateral velocities were noted at this region, 0.02 cm/s and 0.03 cm/s, respectively (normal range early diastolic mitral tissue Doppler velocity is > 0.06 cm/s). The ejection fraction was relatively preserved i.e., 65%. In view of his elderly age, and ECHO features of HFpEF that was unexplained due to a lack of comorbid illness, the patient was suspected to have an infiltrative type of cardiomyopathy such as CA. A coronary angiogram done for this patient excluded the likelihood of atherosclerotic coronary artery disease. Biomarkers for cardiac ischaemia and heart failure were also investigated. The high-specificity Troponin T level was 78 mmol/L (normal range: < 14 mmol/L), and the NT-proBNP level was 2400 pg/mL (normal range: <450 pg/mL for age 75 years and above). Concurrently, serum and urine samples were sent for SEP and UEP, as well as serum assay for free light chain proteins, which all returned as negative. Thus, this made the diagnosis of AL type of CA unlikely.

Subsequently, CMR was performed for further assessment of infiltrative cardiac disease. Standard cine images using the steady state free precession cine sequence in (a) horizontal long axis, (b) vertical long axis and (c) short axis (SA) views that revealed thickened LV and RV myocardial walls (white arrows), bilateral atria dilatation, and a small left-sided pleural effusion (red star) (Figure 1 c, d, e). Then T1-mapping using the shortened Modified Look-Locker Inversion Recovery (shMOLLI) technique was performed. Axial T1 scouts in a single breath hold using double inversion recovery were performed to generate the dark blood sequence. The T1 maps of the basal, midventricular, and apical SA slices were performed at rest. Viability study using gadolinium contrast was done to look for late gadolinium enhancement (LGE) pattern, which is indicative of cardiac myocardial infiltration or ischemia, i.e., myocardial scarring. There was evidence of LGE at several foci of the myocardium in a subendocardial and transmural distribution (Figure 1 g). The T1-mapping revealed thickened LV myocardium and increased extracellular volume (ECV) (Figure 1 g). Furthermore, on the time inversion T1 scout images, there were foci of 'reverse nulling' pattern noted in the myocardium, i.e., the presence of low signal intensity nulling patterns that occurred before the onset of the dark blood pool, which was characteristic of CA (Figure 1 g).

Following these conventional cardiac imaging findings, the patient was referred to our nuclear medicine department for differentiation of the subtypes of CA, as there was a high index of clinical suspicion of the diagnosis of ATTR-CA. Bone scintigraphy was performed using ^{99m}Tc-PYP, based on the recommended protocol by Dorbala et al..[1] Planar imaging of the thorax in anterior, posterior, left anterior oblique (LAO) and left lateral views were performed at one hour post injection (p.i) using a ^{99m}Tc-PYP radiotracer dose of 15.67 mCi. The same static views were then repeated three hours p.i. A complementary single photon emission computed tomography/computed tomography (SPECT/CT) of the thorax was also performed to increase the accuracy of anatomical localization of the heart. Planar anterior and posterior views of the whole-body were also performed at 3 hours p.i.

At one-hour p.i. imaging, the planar images were reviewed. There was an abnormally increased radiotracer uptake at the lateral aspect of the left hemithorax in the region of the heart (H). Then a circular-shaped region of interest (ROI) was placed over the (H) region with similar ROI placed at the contralateral lung (CL) to yield the heart to contralateral lung (H:CL) ratio. The H:CL ratio was 1.69 (normal ratio is expected to be <1.5) (Figure 2 a). which gave a quantitative assessment that was highly indicative of ATTR-CA. Moreover, the whole-body scan at three hours p.i demonstrated that there was scoliosis noted in thoracolumbar spine along with

Table I: Multimodal imaging characteristics for making the diagnosis of cardiac amyloidosis

Imaging Modality	Echocardiography	CMR	^{99m}Tc-labelled bone scan
Characteristic features	• increased RV and LV wall thickness • heterogeneous echogenicity / speckled appearance of myocardium ('starry sky' appearance) • reduced LV cavity size • TDI: reduced myocardial relaxation velocities at the mitral annulus • Impaired global longitudinal strain (LS) showing reduced global strain with sparing of the apex ('cherry on top' appearance on the Bull's eye plot) or Apical/ mid-basal LS ratio that is > 1.0 • Increased LV filling pressure leading to atrial dilatation • small pericardial effusion • left-sided pleural effusion	• increased RV and LV wall thickness (≥12mm) • presence of septal thicknening (occurs in approx. 80% of ATTR-CA) • thickened valves • bi-atrial dilatation • 'reverse nulling' pattern of the myocardium on T1 mapping scout images • LGE of the myocardium in a subendocardial, transmural or diffuse pattern • small pericardial effusion • left-sided pleural effusion	• 1-hour planar scan having H:CL ratio of >1.5 (qualitative assessment) • 3-hour planar scan having Perugini Grade 2 or 3 cardiac uptake (semi-quantitative assessment)
Advantages	• relatively cost-effective investigation • does not involve ionizing radiation	• excellent soft tissue resolution of the myocardium • does not involve ionizing radiation • able to provide significant imaging findings to increase the likelihood of diagnosing CA	• able to distinguish between AL and ATTR-CA subtypes with a high degree of confidence • can be repeated for follow-up cases in order to quantitatively assess the response to treatment • able to provide significant imaging findings to increase the likelihood of diagnosing CA
Disadvantages	• operator dependant • unable to confirm the diagnosis or distinguish between AL and ATTR-CA	• relatively expensive and time-consuming investigation • requires highly trained experts for interpretation • unable to distinguish between AL and ATTR-CA subtypes with high degree of confidence	• involves a relatively small dose of ionizing radiation • may give falsely positive results if interpreted by inexperienced personnel who is unaware of the criteria that increased the pre-test likelihood for diagnosing ATTR-CA

Table II: Recommendations for interpreting and reporting Technetium-labelled bone scans in diagnosing ATTR-CA

No.	Points for concern	Recommendation
1.	Physicians may refer for a Technetium-labelled bone scan without performing other conventional imaging first or without performing biochemical tests to exclude the presence of light chain immunoglobulins	Put in place system prompts in the hospital medical information system when ordering a Technetium-labelled bone scan, to include serum and urine protein electrophoresis and clonal plasma cell analysis
2.	Wrong timing and wrong placement of ROI to measure the H:CL ratio, which may give a falsely positive or falsely negative result for diagnosis of ATTR-CA	To perform the H:CL ratio measurement during the 1-hour scan, which can confidently identify a value of > 1.5 to be diagnostic of ATTR-CA*. A SPECT/CT can also be performed to ensure the correct localization of the heart and avoid diagnostic pitfall.
3.	Wrong timing and wrong interpretation of radiotracer retention in the heart using the Perugini grading system, which may give a falsely positive result for diagnosis of ATTR-CA	To perform the semi-quantitative assessment at 3-hours to ensure adequate biodistribution of the of the blood pool tracer uptake. A SPECT/CT can also be performed to ensure the correct localization of the heart and avoid diagnostic pitfall.
4.	Referring clinicians and patients are not aware of how to proceed after receiving a Technetium-labelled bone scan report that is positive for the diagnosis of ATTR-CA*.	Reports of Technetium-labelled bone scans are required to include a recommendation for performing genetic testing when a positive scan is reported. This will enable the differentiation of ATTRwt from ATTRm. Those having ATTRm will require further family genetic counselling and an option for testing of other immediate family members because of its hereditary nature.

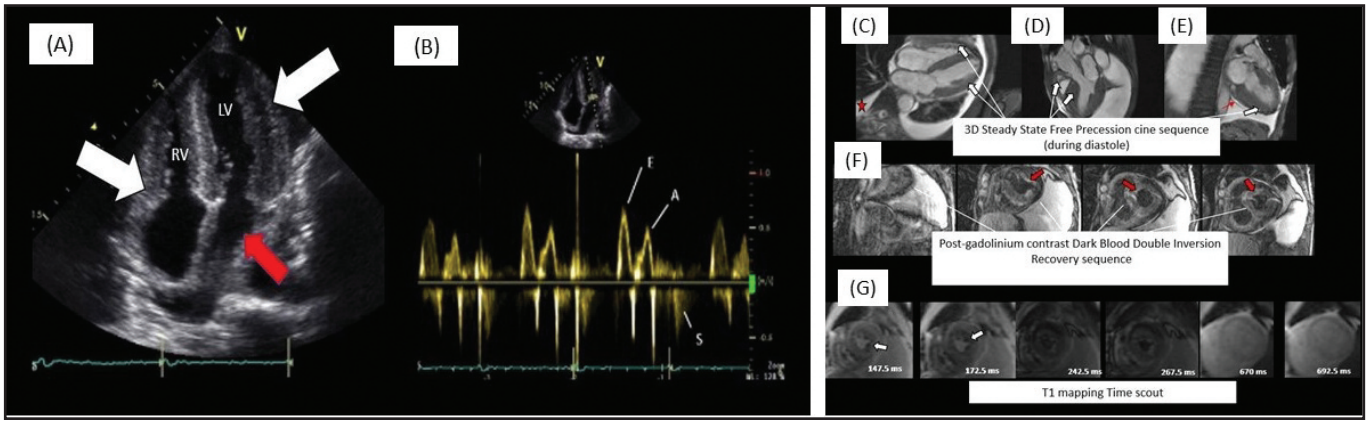

Fig. 1: Echocardiography and MRI images of the patient. (a) Echocardiography showed the 4-chamber view having thickened left ventricular (LV) and right ventricular (RV) walls (white arrow). There is also presence of dilated left atrium (red arrow). (b) Tissue Doppler imaging (TDI) demonstrated low myocardial relaxation velocities at the mitral annulus. (c,d,e) Cardiac magnetic resonance spectroscopy (CMR) of the 3D Steady State Free Precession cine sequence in the horizontal long axis, short axis, and vertical long axis views demonstrated thickened LV, RV and septal walls (white arrows). There is also a small pericardial effusion (thin red arrow) and left-sided pleural effusion (red star). (f) CMR in the post-gadolinium contrast dark blood double inversion recovery sequence demonstrated late gadolinium enhancement (LGE) in subendocardial, and transmural patterns (red arrow). (g) T1 mapping time scout identified the 'reverse nulling' pattern of the myocardium, whereby there was low signal nulling of the myocardial tissue (white arrows) that occurred before the nulling of the dark blood pool signal that is indicative of cardiac amyloidosis.

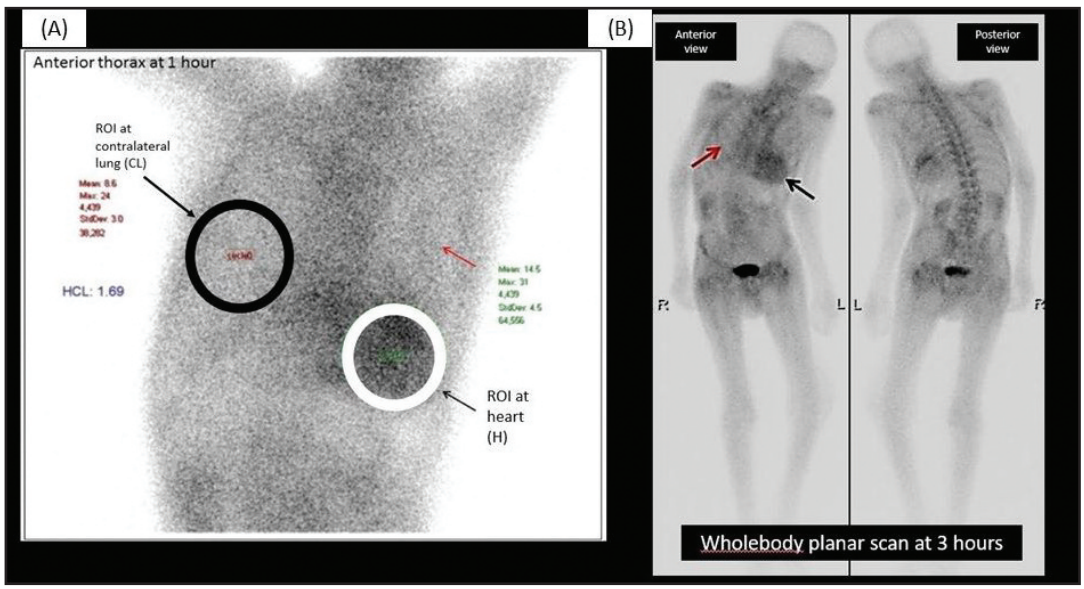

Fig. 2: (a) ^{99m}Tc-labelled bone scintigraphy with the anterior planar view of the thorax at 1-hour demonstrated increased radiotracer uptake at the region of the heart with H:CL lung ratio of 1.69, indicative of ATTR-CA within the given clinical context. (b) Anterior and posterior views of the wholebody bone scintigraphy scan demonstrated increased tracer uptake at the region of the heart (black arrow) with associated apparent attenuation of the skeletal bone uptake (red arrow), which was consistent with a Perugini Grade 3 scoring.

some mild degenerative changes of the joints, however there were no abnormal foci of radiotracer uptake in the bones. There was moderately increased diffuse tracer uptake in the (H) (thin black arrow), which was comparatively higher than the uptake seen on adjacent ribs and bones (thin red arrow) (Figure 2 b). This semi-quantitative assessment method using a visual scoring based on the Perugini grading system was used to compare the intensity of cardiac uptake with the skeletal uptake on planar images.2 Since the heart uptake was higher than the bones, hence a Perugini grade 3 scoring was given, which was consistent with a diagnosis of ATTR-CA.

Consequently, based on the overall picture of clinical restrictive cardiomyopathy, HFpEF, typical cardiac ECHO and CMR findings, biochemical laboratory tests that were negative for plasma-cell dyscrasia, as well as positive bone scintigraphy findings, a diagnosis of ATTR-CA was conclusively made. In view of the patient's old age and poor

performance status, conservative and supportive management were proposed. The family was counselled regarding the prognosis of the disease and the need for genetic testing to further identify the subtypes of ATTR-CA, i.e., ATTRwt or ATTRm.

DISCUSSION

ATTR-CA is a rare condition but is likely underdiagnosed due to the non-specific presentations that cause delays in performing the pertinent investigations. ATTRwt has been mostly detected in Caucasians and the ATTRm is prevalent among those of African American descent.[2] Thus, its detection in a Malaysian of Malay descent is very rare. Nevertheless, as this condition is likely to be underdiagnosed, there should be a high index of suspicion to further investigate elderly patients who present with sudden, unexplained HFpEF. Furthermore, this condition is frequently associated with a preceding history of carpal tunnel syndrome or lumbar spinal stenosis.[2] Thus, a thorough past medical and surgical history should be sought when investigating such patients.

Currently, there is great advancement in the expertise of nuclear cardiology to aid in the diagnosis and characterization of ATTR-CA. Apart from being a non-invasive investigation, is also relatively inexpensive to perform, with the ability to distinguish AL subtype of CA from the ATTR-CA subtype. Bone-seeking agents such as ^{99m}Tc-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), pyrophosphate(PYP), and methylene diphosphonates (MDP) have be shown to be taken up by the myocardium in patients with the ATTR-CA subtype.1 It has been postulated that the preferential binding of ^{99m}Tc-PYP to ATTR-CA is similar to those of ^{99m}Tc-MDP and ^{99m}Tc-HDP, which are more commonly available in Malaysia, may be attributed to the fact that TTR fibrils in the myocardium have higher calcium content.[7] This may be due to altered calcium metabolism that occurs due to the oxidative damage to the myocytes triggered by the abnormal deposition of the TTR fibrils.[3] Nevertheless, there may be 22-30% of cases that may have a mildly false positive bone scintigraphy result in cases of AL subtype of cardiac amyloidosis.

Hence, a diagnostic algorithm has been developed to improve the accuracy for detecting ATTR-CA using bone scintigraphy. These include using a semi-quantitative Perugini grading system of Grade 2 or 3 radiotracer uptake at post 3 hours imaging to indicate a positive scan, and together with a H:CL ratio of > 1.5 in the one-hour planar imaging to be diagnostic of ATTR-CA, provided that the clinical history, and ECHO with or without CMR findings suspicious of CA (Table I), together with laboratory tests to exclude AL have been performed.[6,7] The Perugini grading system is an assessment of the cardiac uptake on planar bone scintigraphy imaging, which can be visually score by comparing the intensity of the heart uptake with the adjacent ribs. This grading system can be evaluated as Grade 0: no cardiac uptake and normal bone uptake; Grade 1: cardiac uptake that is less intense than the bone signal, Grade 2: cardiac uptake with intensity similar to bone; and Grade 3: cardiac uptake that in higher than bone with relatively attenuated or absent bone signal.[8] Grade 0 corresponded to a negative predictive value (NPV) of 87% and Grade 3 corresponded to a positive predictive value (PPV) of 96% for ^{99m}Tc-PYP positivity.[8] The H:CL ratio of > 1.5 introduced by Bokhari et al., reported that this quantitative score along with diffuse intense myocardial radiotracer retention had a sensitivity and specificity of 97% and 100%, respectively with area under the curve (AUC) 0.992, for identifying ATTR-CA.[9] A meta-analysis of six bone scintigraphy studies involving 529 patients by Treglia et al., stated that bone scintigraphy had a sensitivity of 92.2% (95% CI: 89-95%), specificity of 95.4% (95% CI: 77-99%) for making the diagnosis of ATTR-CA, given that the relevant pre-scan criteria had been fulfilled.[10]

The limitations of bone scintigraphy for diagnosing ATTR-CA increases when only one method of assessment is used, e.g., only the Perugini grading system or the H:CL ratio alone. False positive results can be reported due to erroneous detecting of cardiac radiotracer uptake at an earlier scan times that in actual fact represents increased blood pool activity, or detecting of radiotracer uptake in adjacent rib fractures or the presence of aortic or mitral calcifications mistaken for cardiac myocardial tissue uptake.[4] Furthermore, the presence of acute or subacute myocardial infarction, hydroxychloroquine toxicity, and low cardiac output are among the causes of abnormal radiotracer uptake reported in the heart region on planar bone scintigraphy.[4] In particular the wrong placement of ROI or anatomical localization of the heart can be corrected by performing a targeted SPECT/CT scan at the thoracic region (Table II).

Another nuclear medicine radiotracer that can have a positive uptake in cardiac amyloidosis is ^{123}I meta-iodobenzylguanidine (MIBG). It cannot be used to conclusively diagnosed CA, however, as it can be positive in other types of conditions such as Parkinson's disease. Additionally, positron emission tomography (PET) radiotracers such as C11-PiB, F18-florbetapir and F18-florbetaben have been recently studied for the utility of diagnosing CA because they have high affinity and specificity to β-amyloid protein.[6] However, the limitation of these radiotracers cannot conclusively differentiate between ATTR-CA and AL subtype of CA.[6]

CONCLUSION

Technetium-labelled bone scintigraphy can be confidently used for the non-invasive diagnosis and subtyping of ATTR-CA (provided that there are supportive imaging findings from ECHO or CMR, and biochemical results that exclude the likelihood of AL). Clinical expertise is required to exclude the potential pitfalls and limitations in reporting the scans, to make it feasible for clinicians to forego invasive EMB when diagnosing ATTR-CA.

ACKNOWLEDGMENT

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DECLARATIONS

The authors declare no potential conflicts of interest with respect to the case report, authorship, and publication of this article.

CONSENT

Patient described in the above case report has given his written consent for the description of case, utilization of scan images and publication of this case report.

REFERENCES

1. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 1 of 2—evidence base and standardized methods of imaging. J Nucl Cardiol 2019; 26(6): 2065-123.
2. Brunjes DL, Castano A, Clemons A, Rubin J, Maurer MS. Transthyretin Cardiac Amyloidosis in Older Americans. J Card Fail 2016; 22(12): 996-1003.
3. Mankad AK, Shah KB. Transthyretin Cardiac Amyloidosis. Curr Cardiol Rep 2017; 19(10): 97.
4. Gerber J, Miller EJ. Optimal interpretation of Tc99m PYP in 2020: Avoiding the million-dollar mistake. J Nuc Cardio 2021; 28(2): 503-6.
5. Chen W, Ton V-K, Dilsizian V. Clinical Phenotyping of Transthyretin Cardiac Amyloidosis with Bone-Seeking Radiotracers in Heart Failure with Preserved Ejection Fraction. Curr Cardiol Rep 2018; 20(4): 23.
6. Dorbala S, Cuddy S, Falk RH. How to Image Cardiac Amyloidosis. JACC Cardiovasc Imaging 2020; 13(6): 1368-83.
7. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation 2016; 133(24): 2404-12.
8. Marume K, Takashio S, Nishi M, Hirakawa K, Yamamoto M, Hanatani S, et al. Combination of Commonly Examined Parameters Is a Useful Predictor of Positive Labeled Pyrophosphate Scintigraphy Findings in Elderly Patients With Suspected Transthyretin Cardiac Amyloidosis. Circulation 2019; 83(8): 1698-708.
9. Bokhari S, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Im 2013; 6(2): 195-201.
10. Treglia G, Glaudemans AWJM, Bertagna F, Hazenberg BPC, Erba PA, Giubbini R, et al. Diagnostic accuracy of bone scintigraphy in the assessment of cardiac transthyretin-related amyloidosis: a bivariate meta-analysis. Eur J Nuc Med Mol Im 2018; 45(11): 1945-55.

CASE REPORT

Luc's abscess in Down syndrome – A case report

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SUMMARY

Luc's abscess is an exceedingly rare complication of otitis media, where the middle ear infection spreads extra-temporally causing a subperiosteal collection under the temporalis muscle. It is known as a benign complication of otitis media as it is thought not to involve the mastoid bone in comparison to other types of extratemporal abscesses related to otitis media. We describe a challenging case of a 19-year-old male with Down syndrome diagnosed with Luc's abscess involving the mastoid bone. A high-resolution computed tomography scan is important to determine the extent of the abscess, with or without mastoid involvement, and the presence of complications. These findings will then help to determine the surgical options. Drainage of abscesses is a simple, initial, and conservative approach but less effective compared to mastoidectomy. 'Mastoid-sparing' approach should only be considered if there is complete resolution after a simple drainage and antibiotic treatment.

INTRODUCTION

Otitis media (OM) is a very common entity in childhood and is usually self-limiting and rarely progress to complications due to advancement in modern antibiotics.[1] However, complications are on the rise due to growing antibiotic resistance and increasing number of immunocompromised patients leading to significant morbidity and mortality.[1] The incidence rate in developed countries range from 1.2 to 3.8 per 100,000 persons.[2] Complications of OM are well known to be categorized into extracranial and intracranial complications. Subperiosteal abscesses are rare extracranial and extratemporal complications of OM and are defined by location. *Bezold's* abscess is located deep to sternocleidomastoid muscle, while *Citelli's* abscess is situated in digastric triangle. For Luc's abscess, the infection is located deep to the temporalis muscle.[3] Due to its rarity, complications maybe missed due to lack of experience of clinicians who treat this disease.

Luc's abscess is different from other types of subperiosteal abscess as infection can spread from the middle ear through an anatomical pathway in the ear canal without erosion of the cortical bone. This was the description by Henri Luc in which subperiosteal temporal abscess is due to otitic origin without intraosseous destruction.[4] However, our case below was not in accordance with this theory as there was involvement of the mastoid bone.

CASE REPORT

A 19-year-old man with Down syndrome presented with intermittent right otorrhea for 1 month duration which was purulent in nature, and it was associated with ear itchiness. The history was solely dependent from the mother who is the caretaker. She claimed he never had any history of ear discharge prior to the current presentation and the ear discharge resolved after completing 1-week course of oral Augmentin. However, 2 weeks post-treatment, he started to develop right temporal swelling, which increased progressively in size spreading to the post-auricular region then to right cheek region associated with right mucopurulent ear discharge. The swelling was also painful. His mother denied that the patient had fever, symptoms of rhinitis, headache, or history of trauma.

On examination, there was a diffuse swelling at the right temporal, superior half of post-auricular and zygomatic region which were tense, tender, and erythematous (Figure 1) pushing the right pinna anteriorly. The right cheek and lower eyelid also had mild edema. Otoendoscopy showed an edematous right external ear canal (EAC) with prominent sagging from superior wall without visualization of the tympanic membrane. The left EAC was narrow and dry with an intact tympanic membrane. In addition, the facial nerve function was intact bilaterally, and other nose, throat, and neck examinations were unremarkable.

Laboratory analysis revealed increased C-reactive protein (CRP: 47.0 mg/L; normal<10.0) and slight leukocytosis (12.89 K/uL). Pure tone audiogram as a baseline hearing level demonstrated a moderate to severe hearing loss on the right side and a mild hearing loss on the left side with a type B tympanogram bilaterally.

High resolution computed tomography (HRCT) of the temporal bone revealed a hypodense collection in the right temporal region measuring 6.1 cm (AP) x 1.7 cm (W) x 4.7 cm (CC) with ring enhancement pattern (Figure 2). Both mastoid cavities were sclerotic with soft tissue density in both middle ear cavities. There was erosion of the right mastoid cortex, right incus, stapes, scutum, right tegmen tympani and lateral wall of tympanic part of the facial nerve. Subsequently, the patient underwent examination under anaesthesia, incision, and drainage of the right temporal abscess through Wilde's post aural incision in which 20cc of pus was drained and sent for cultures and acid-fast bacilli (AFB) smear. The right EAC was cleansed and packed with

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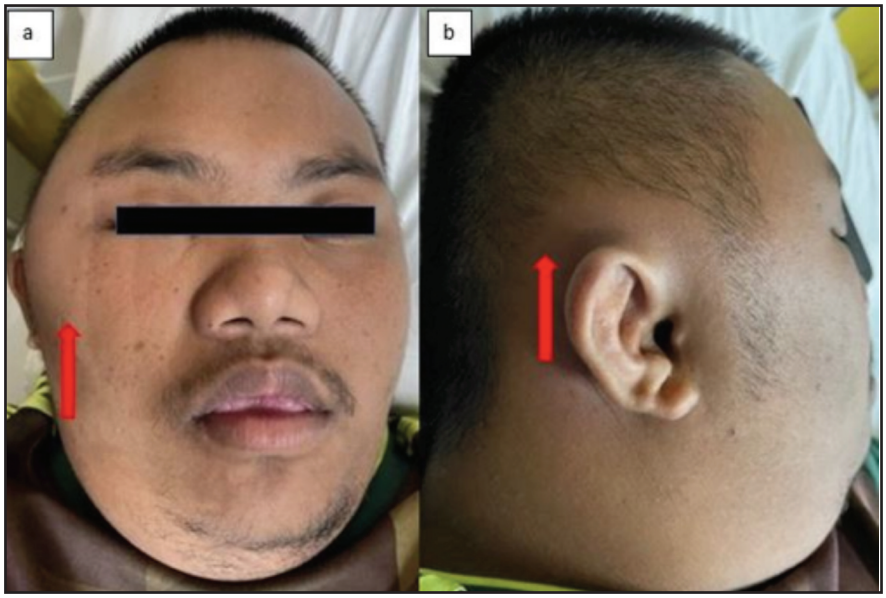

Fig. 1: (a) The right temporal swelling extended anteriorly to right zygoma and lower eye lid (red arrow) and (b) posteriorly to post auricular region (red arrow).

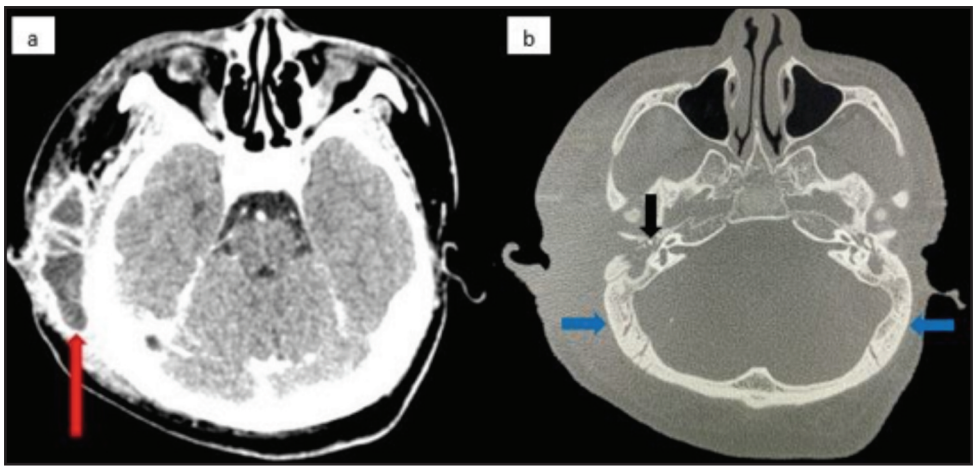

Fig. 2: (a) Heterogenous collection in the right temporal region with ring enhancement in axial soft tissue setting (red arrow). (b) Bilateral sclerotic mastoid air cells (blue arrow) with soft tissue density and erosion of right ossicles (black arrow).

otowick soaked with anti-microbial solutions. Excessive bleeding was encountered intraoperative which made visualization and removal of disease in mastoid and middle ear difficult. Hence, combined approach tympanoplasty (CAT) which was the definitive plan to address the condition of the mastoid and middle ear was planned later after the swelling and oedema subsides. He was initially started on empirical broad spectrum intravenous antibiotics and was later changed to Piperacillin-tazobactam 4.5g tds for one week according to cultures sensitivity which grew *Pseudomonas aeruginosa* and *Streptococcus viridans*. He was discharged after 3 weeks of admission with oral Ampicillin-sulbactam 375mg BD for one week after marked improvement of the temporal swelling and a healing post auricular wound. During subsequent follow up, the patient was well and asymptomatic, however, the parent refused further surgical intervention. This patient is still under our close monitoring and follow up.

DISCUSSION

Henri Luc in 1913 first described the subperiosteal temporal abscess related to OM without involvement of the mastoid bone. He suggested the possible route of bacterial spread is from the submucosa of the middle ear through the notch of Rivinus, deep auricular artery branches towards the subperiosteal area.[4] Therefore, Luc believed mastoidectomy is not needed as there were absence of clinical signs of mastoiditis such as post auricular swelling and persistent otorrhea. This theory was also supported by Weiss et al in 2010.[5] However, our case differs from the original report by Luc, as the abscess developed as a complication of mastoiditis with erosion of its cortex.

Luc's theory has been brought into question by an increasing number of cases for both children and adults presented with a subperiosteal abscess underneath the temporal muscle with concurrent mastoiditis. This has been proven by a systematic

review on the clinical features and managements of Luc's abscess based on case reports collected from 1989 to 2018, with a total of 21 patients (17 children and 4 adults).[6] It reported that almost all patients (95.2%) except one showed signs of mastoiditis in computed tomography (CT) scan,[6] hence not in accordance with Luc's theory.

The commonest presenting symptoms of Luc's abscess were otalgia and swelling at zygomatic region followed by fever and malaise especially in children.[6] The site of swelling may involve multiple sites such as the preauricular, temporal, cheek, eyelids, and mastoid area in descending order of frequency.[6] Our patient presented with otalgia and temporozygomatic swelling without fever. Diagnosing Luc's abscess could be a challenge especially in our case as the patient was a poor historian. Signs and symptoms could be masked or misjudged by clinicians in view of his underlying Down syndrome. Thus, clinical diagnosis can only be relied on the physical examination and imaging techniques in a mentally challenged patient. Furthermore, Luc's abscess could easily be misdiagnosed as orbital complications of acute rhinosinusitis. This is due to frequent association of zygomatic, eyelid and cheek swelling with rhinitis symptoms.[6] Mastoid swelling with anterior displacement of pinna usually developed few days after preauricular swelling.[6] Fortunately, otalgia being the commonest symptoms could pinpoint to the otic origin to aid our diagnosis. Only 14% of cases are associated with cholesteatoma.[6] Risk factors for developing Luc's abscess are drug users and diabetic individuals, but the majority of cases are without risk factors, similar to our case.[6] Our patient could have been a case of undiagnosed chronic inactive OM evidenced by the sclerotic mastoid air cells. Furthermore, Down syndrome patients has been proven to have an intrinsic defect of their immune system leading to higher frequency of infections and complications.[7]

HRCT Temporal bone is the imaging of choice, and we recommend this being done promptly. This is to exclude intracranial and extracranial complications, confirming diagnosis, disease extension, and status of the mastoid. HRCT scan could aid the decision making of either doing mastoidectomy or local drainage only. In the event of coalescent mastoiditis or cortical erosion of mastoid, cortical mastoidectomy is recommended especially in children after 48 hours of intravenous empirical antibiotics without signs of improvement.[8] Interestingly, our case showed a sclerotic mastoid bilaterally with soft tissue density within both middle ear which suggest poor aeration and ventilation for a long period, thus the risk of developing complications is higher. Right mastoid cortex was eroded making a direct connection with the temporal area possibly due to the virulence of the bacterium isolated.

Treating Luc's abscess is best managed by surgical approach. Abscess drainage together with myringotomy (with or without grommet insertion) and cortical mastoidectomy was the favored surgery in Luc's abscess.[6] On the other hand, it is of utmost important to cover suspected Luc's abscess patients empirically with wide spectrum intravenous antibiotics without waiting for culture and sensitivity tests. Our case was managed with incision and drainage of abscess without myringotomy as the ear canal was edematous which obscured the tympanic membrane. CAT was purposely planned in a different setting to allow complete resolution of temporal swelling before definitive operation addressing the mastoid and middle ear. Decision to perform mastoidectomy is usually guided by pre-operative CT scan. Finally, not doing mastoidectomy or 'mastoid sparing' approach should only be considered if the mastoid was spared, and complete improvement was seen after a simple drainage and antibiotic treatment. Drainage of abscesses is a simple, initial, and conservative approach but less effective compared to mastoidectomy.[9]

CONCLUSION

Luc's abscess is a rare complication of otitis media, and often associated with mastoiditis. Diagnosis is challenging due to the delay signs of suppurative mastoiditis. Thus, HRCT scan should be the investigation of choice to obtain definitive diagnosis and identify associated mastoiditis and rule out possibility of intracranial complications. HRCT findings will help in the decision of performing mastoidectomy in uncertain cases. Cortical mastoidectomy is proven to be more effective than abscess drainage especially in non-responding cases and paediatric group.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Van Den Aardweg MT, Rovers MM, de Ru JA, Albers FW, Schilder AG. A systematic review of diagnostic criteria for acute mastoiditis in children. Otol Neurotol 2008; 29(6): 751-7.
2. Van Zuijlen DA, Schilder AG, VAN BALEN FA, Hoes AW. National differences in incidence of acute mastoiditis: relationship to prescribing patterns of antibiotics for acute otitis media?. Pediatr Infect Dis J 2001; 20(2): 140-4.
3. Spiegel JH, Lustig LR, Lee KC, Murr AH, Schindler RA. Contemporary presentation and management of a spectrum of mastoid abscesses. Laryngoscope 1998; 108(6): 822-8.
4. Luc H. The sub-periosteal temporal abscess of otic origin without intra-osseous suppuration. Laryngoscope 1913; 23(10): 999-1003.
5. Weiss I, Marom T, Goldfarb A, Roth Y. Luc's abscess: the return of an old fellow. Otol Neurotol 2010; 31(5): 776-9.
6. Fernandez IJ, Crocetta FM, Pelligra I, Burgio L, Dematte M. Clinical features and management of Luc's abscess: case report and systematic review of the literature. Auris Nasus Larynx 2020; 47(2): 173-80.
7. Kusters MA, Verstegen RH, Gemen EF, de Vries E. Intrinsic defect of the immune system in children with Down syndrome: a review. Clin Exper Immunol 2009; 156(2): 189-93.
8. Marom T, Roth Y, Boaz M, Shushan S, Oron Y, Goldfarb A, et al. Acute mastoiditis in children: necessity and timing of imaging. Pediatr Infect Dis J 2016; 35(1): 30-4.
9. Psarommatis I, Giannakopoulos P, Theodorou E, Voudouris C, Carabinos C, Tsakanikos M. Mastoid subperiosteal abscess in children: drainage or mastoidectomy?. J Laryng Otol 2012; 126(12): 1204.

Columella necrosis in a child secondary to nasal continuous positive airway pressure during neonatal period

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SUMMARY

The advent of continuous positive airway pressure ventilation as a mode of treatment for respiratory distress syndrome for premature infants has increased the risk of nasal injuries such as pressure necrosis. We describe a case of a 24-week infant who received CPAP ventilation as a mode of ventilatory support for respiratory distress syndrome and the complication of pressure necrosis of the columella. There are many factors that predispose an infant receiving CPAP ventilation to nasal injury. Many strategies can be employed to reduce the incidence of nasal injuries such as the use of nasal barrier dressings, the use of nasal high flow oxygen (nHF) cannula instead of CPAP ventilation, and the use of nasal masks instead of nasal prongs for CPAP ventilation delivery. The treatment of pressure necrosis can be either medical or surgical. The use of ointments or growth sprays can be used in cases of skin breakdown. Surgical reconstruction can be offered in cases of nasal deformity.

INTRODUCTION

Continuous positive airway pressure (CPAP) is an efficacious mode of ventilation for respiratory distress syndrome. Since its first report in 1971 as a form of treatment of severely ill infants with idiopathic respiratory distress syndrome, there has been an increase in the usage of nasal CPAP ventilation.[1] Over the last 40 years it is considered the "gold standard" form of non-invasive respiratory support to treat preterm infants. However, the prolonged use of CPAP as non-invasive ventilation has increased the risk of pressure necrosis of the nose.[2,3] The prevention of nasal injuries in very low birth weight and very preterm infants can be difficult despite highly skilled nursing.[3] We report a case of severe cosmetic sequelae of such injury.

CASE REPORT

A 24-week female infant weighing 680grams, required assisted ventilation immediately after birth due to respiratory distress syndrome. The infant was born at a private hospital and required neonatal intensive care unit (NICU) admission and treatment. Her ventilation ranged from intubation, CPAP ventilation, and finally nasal prongs. She was also treated for retinopathy of prematurity and necrotizing enterocolitis. After a 3 month stay in the hospital, the infant was discharged with a weight of 2.1 kilograms. However, upon discharge parents noted a deformity of their child's columella. The treatment instituted was only dressings over the raw columella skin, with no surgical debridement required. Hence, a diagnosis of columella necrosis was made.

At the age of 3 years, the patient presented to Department of Otorhinolaryngology, University Malaya Medical Centre for cosmetic reconstruction. Upon examination, it was noted that there was a columella defect, giving the impression of a single nasal aperture (Fig. 1). The nasal tip, philtrum and ala were preserved (Fig. 2). Anterior rhinoscopy evaluation confirmed that the nasal septum as well as both nares were intact. A flexible nasopharyngoscopy was performed which showed no abnormalities of the nasal septum, inferior and middle turbinates, as well as the postnasal space. A referral was made to our plastic surgery colleagues for columella reconstruction. The surgery was planned to be conducted when the child became older.

DISCUSSION

The most prevalent form of ventilatory support in newborns is CPAP ventilation with nasal prongs.[2] However, due to the wide usage of CPAP ventilation with nasal prongs, many forms of nasal injuries occur in newborns. In preterm infants, it is vital that the skin and mucosal membranes are intact to protect against infection (cellulitis, vestibulitis, nosocomial bacterial infections), discomfort, and nasal deformities (nasal tip deviation, nostril asymmetry, columella necrosis).[3] Buettiker et al. have classified nasal injuries based on their severity into three grades: mild (Grade I), moderate (Grade II), and severe (Grade III). The Grade I injury encompasses persistent redness or nasal hyperemia with intact skin, whereas Grade II injury patients have partial skin loss, superficial ulcers, and bleeding. Grade III injuries encompasses full-thickness skin loss and columella necrosis.[3,4] A study by Fischer et al. reported nasal injury in 42.5% of infants receiving CPAP ventilation.[5] The majority of the nasal injuries were Grade I (88.3%), Grade II (11%) and Grade III (0.7%).[5] The mechanism of injury is principally due to the pressure caused by ill-fitting, inappropriate sizing, and positioning of the binasal prongs.[3] The two main predictive factors for skin damage are the number of days on CPAP ventilation with nasal prongs and the gestational age.[3]

The onset of nasal injury to the columella can be seen as early as 18 hours or 2 to 3 days after initiation of CPAP.[3] In terms of gestational age, nasal injury is most common before 30 weeks of gestation due to the poorly defined epidermal

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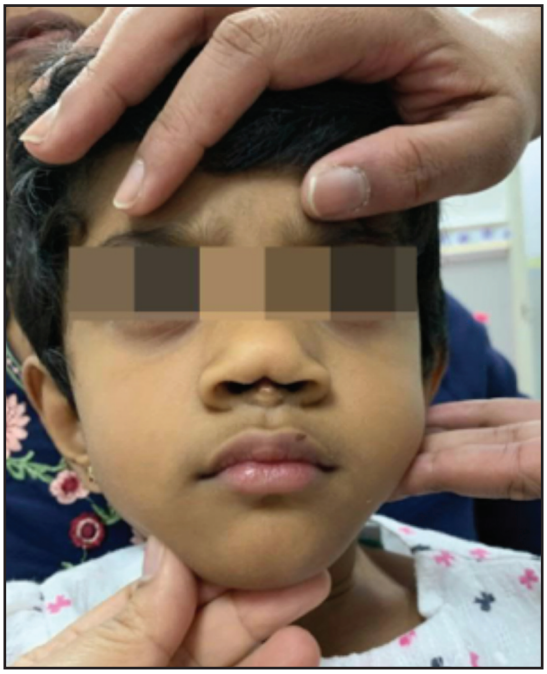

Fig. 1: Columella necrosis giving the appearance of a single nasal aperture.

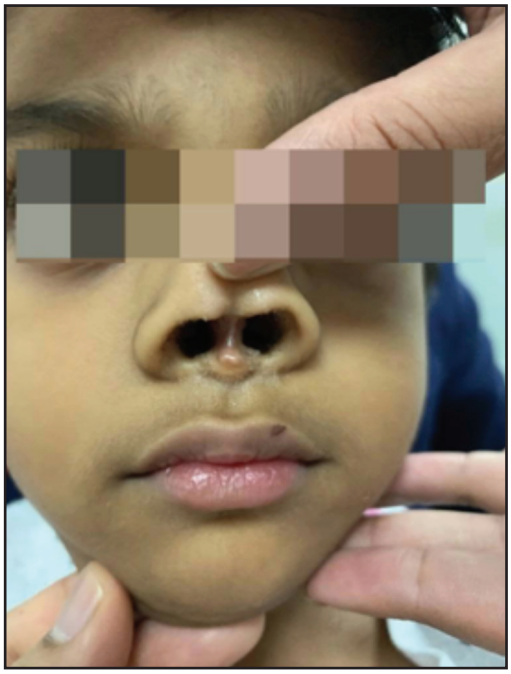

Fig. 2: Columella necrosis with intact nasal septum.

skin layers and stratum corneum.[3] The key to prevention is pressure relief. Identifying a nasal prong that is appropriately sized is of paramount importance. Nasal prongs that are too large tend to cause nasal flaring whereas nasal prongs that are too small may damage the internal nares due to excessive movement.[2] This is especially difficult in very preterm or low birth weight infants despite highly skilled nursing care.[3] Hence, nursing staff in the NICU should be educated, trained and privileged in CPAP ventilation nursing care. A review by Naha et al. reported a higher risk of nasal injury in newborns cared for by non-privileged nurses (66%) as opposed to privileged nurses (11%).[6]

Many strategies can be employed to reduce the frequency of nasal injury in newborns receiving CPAP ventilation. A review by Imbulana et al., reported three main preventive strategies: the use of a nasal barrier dressing, the use of nasal high flow oxygen (nHF) cannula instead of CPAP ventilation, and the use of nasal masks instead of nasal prongs for CPAP ventilation delivery.[3] The incidence of nasal injuries has been reduced by the usage of barrier dressings like silicone gel sheeting or hydrocolloid dressings placed like a mustache.[3] The ideal dressing has not been identified.[3] A study by Collins et al. compared two nasal dressings; a hydrocolloid material (Cannulaide) which was placed on the nose and upper lip and a Velcro-coated hydrocolloid dressing (Sticky Whiskers) placed on the upper lip of 132 preterm infants born at less than 32 weeks gestation. The preterm infants received either nasal high flow cannula or CPAP ventilation. There was no significant difference in nasal injury score between both types of dressings.[7] Nasal injury rates are reduced with the use of (nHF) cannula compared to CPAP ventilation. However, in preterm neonates with moderate and severe lung disease, CPAP ventilation is still preferred.[3] Nasal mask usage has been suggested instead of binasal prongs. However, compared to the nasal mask, short binasal prongs are favored for oxygen delivery and popular CPAP ventilation configuration.[3] Nasal injuries between both devices vary as noted by a study done by Yong et al.[8] The nasal mask patients suffered more from crusting, narrowing of nasal passages, excoriation of the nasal septum, and redness at the base of the nasal septum. Whereas patients who used nasal prongs had bleeding, narrowing of nasal passages, and injury to the medial aspect of the nostril.[8]

Another strategy for prevention is to alternate use of nasal prongs and face mask every 4 to 6 hours.[5] This strategy is especially useful for infants weighing less than 1500grams, or if an infant presents with mild to moderate nasal injuries.[3] For the treatment of nasal skin breakdown: epidermal growth sprays, hirudoid cream, and mupirocin ointment have been suggested.[3,5] A checklist should be employed by nursing staff, which should include a regular skin assessment and positioning of binasal prongs or nasal masks. The use of a barrier dressing or ointment should be instituted in cases of skin breakdown.

Common sequelae of nasal injuries include nasal deformities persisting beyond the neonatal period. These nasal injuries are nasal tip deformities, nostril asymmetry, columella injury, nasal septal injury, and nasal obstruction.[3] These deformities may be both cosmetic and/ or functional, often requiring corrective surgery in later years. Systemic complications to newborns due to nasal injury could be sepsis secondary to gram-negative bacteria due to damage to the skin and mucosa. Graham et al. reported a correlation between CPAP ventilation and gram-negative sepsis in a case-controlled series.[9]

Among the treatment methods that can be offered is columella reconstruction surgery. Columella reconstruction can be done by either oral maxillofacial surgeons or plastic surgeons. One surgical method that can be used is the modified Cronin technique. This is based on the surgical principle to increase columella length whereby tissue from the nasal sill and the anterior nasal floor is rotated superiorly. The common challenge of columella reconstruction is due to its shape, limited vascularity as well as skin coverage.[10]

CONCLUSION

Columella necrosis can occur due to pressure from the nasal prongs used for positive pressure ventilation. Hence, early identification and prevention are important to avoid columella necrosis as this leads to cosmetic disfigurement and requires corrective surgery. Thus, awareness, education, and proper training of nursing staff in charge of neonates receiving CPAP ventilation is vitally important.

REFERENCES

1. Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. N Engl J Med 1971; 284 (24): 1333-40.
2. do Nascimento RM, Ferreira AL, Coutinho AC, Santos Veríssimo RC. The frequency of nasal injury in newborns due to the use of continuous positive airway pressure with prongs. Rev Lat Am Enfermagem 2009; 17(4): 489-94.
3. Imbulana DI, Manley BJ, Dawson JA, Davis PG, Owen LS. Nasal injury in preterm infants receiving non- invasive respiratory support: a systematic review. Arch Dis Child Fetal Neonatal Ed 2018; 103(1): F29-35.
4. Buettiker V, Hug MI, Baenziger O, Meyer C, Frey B. Advantages and disadvantages of different nasal CPAP systems in newborns. Intensive Care Med 2004; 30(5): 926-30.
5. Fischer C, Bertelle V, Hohlfeld J, Forcada-Guex M, Stadelmann-Diaw C, Tolsa JF. Nasal trauma due to continuous positive airway pressure in neonates. Arch Dis Child Fetal Neonatal Ed 2010; 95(6): F447-51.
6. Naha N, Pournami F, Prabhakar J, Jain N. Nasal Injury with Continuous Positive Airway Pressure: Need for "Privileging" Nursing Staff. Indian J Pediatr 2019; 86(7): 595-8.
7. Collins CL, Holberton JR, Barfield C, Davis PG. A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. J Pediatr 2013; 162 (5): 949-54.e1
8. Yong SC, Chen SJ, Boo NY. Incidence of nasal trauma associated with nasal prong versus nasal mask during continuous positive airway pressure treatment in very low birthweight infants: a randomised control study. Arch Dis Child Fetal Neonatal Ed 2005; 90(6): F480-3.
9. Graham PL 3rd, Begg MD, Larson E, Della-Latta P, Allen A, Saiman L. Risk factors for late onset gram- negative sepsis in low-birth-weight infants hospitalized in the neonatal intensive care unit. Pediatr Infect Dis J 2006; 25(2): 113-7.
10. Jayaratne YS, Zwahlen RA, Htun SY, Bütow KW. Columella pressure necrosis: a method of surgical reconstruction and its long-term outcome. BMJ Case Rep 2014; 2014: bcr2013203132

CASE REPORT

Massive penile lipogranuloma following olive oil injections

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SUMMARY

Penile self-injections are performed with the purpose of increasing the size of the penis. Commonly, mineral oils or mineral oil-like substances are used for this purpose. However, there are very few publications describing on the complications from vegetable oil injections especially olive oil. Following the injection, the resulting deformity of the male genitalia is described as penile paraffinomas lipogranuloma of the penis. We would like to report a case of penis augmentation by a 50-year-old gentleman using olive oil injections that caused a massive, severely deformed of the penis and scrotum. Surgical excision and reconstruction was done. The patient was discharged after five days post-operatively, with full graft take.

Injecting any oily substances into the human body is hazardous. The differential diagnosis of nodules following injections should be kept in mind and in doubtful cases, biopsy should be done. Regular follow-up is essential to prevent the further inflammatory event. Safe and legal procedures should be implemented for penile enlargement so as to avoid self-injections and in the prevention of such debilitating problems.

INTRODUCTION

Penile self-injections are performed with the purpose of increasing the size of the penis. Commonly, mineral oils or mineral oil-like substances are used for this purpose. However, there are very few publications describing on the complications resulting from vegetable oil injections especially olive oil. Following the injection, the resulting deformity of the male genitalia is described as penile paraffinomas lipogranuloma of the penis. We would like to report a case of penis augmentation by using olive oil injections causing massive, severely deformed of the penis and scrotum.

CASE REPORT

A 50-year-old gentleman was given subcutaneous olive oil injections into his penile shaft by some unknown personnel. It was done in 1 session with an unknown amount and was given in a non-sterile environment. After 3 months of the injection, the penis began to swell, deform, and harden. Over this time, the penile shafts gradually became deformed, swollen, and hard. He was able to achieve an erection, however, the erection and sexual intercourse became painful at one year after the injection. He started to seek for treatments after 1 year of the injection. Physical examinations showed that the penile shaft was massively swollen and disfigured, measuring 7cm x 10cm with irregular semi-mobile masses extending into the scrotum. The overlying skin was diffusely dark with no cutaneous ulceration. After a full history taking and physical examination, followed by patient counselling, the decision was made to proceed with a surgical excision of the mass and penile reconstruction. Full skin excision was required in this patient because the granulomas were extensive; involving subcutaneous tissue of the penile shaft with extension into the overlying penile skin. The fibrotic skin and subcutaneous tissue were circumferentially excised from the corona distally to the scrotum proximally down to the level of Buck's fascia. Thick split skin grafts, harvested from the inner thigh, was used to cover the bare penile shaft. The patient was discharged after five days post-operatively, with full graft take. At the outpatient review, one month postoperatively the wound was well healed. Histopathological examination showed multiple lipid vacuoles occupying almost the entire pieces of skin tissue with surrounding numerous granulomas but with no malignant cells seen, consistent with a diagnosis of lipogranuloma.

DISCUSSION

There are many publications about granuloma formation and other tissue reactions following mineral oil injections for body augmentation but there are very few publications describing complications from vegetable oil injections, especially olive oil. Granuloma formations after intramuscular injections using sesame seed oil[1] and oleomas due to sunflower oil injections[2] in bodybuilders have been previously reported.

Olive oil has been reported to be used together with other augmentation solutions such as industrial-grade silicone or paraffin for breast augmentation before the 1960's when medical-grade silicon was not yet available. Olive oil contains phenol that acts as a sclerosing agent, thus the purpose of using olive oil in breast augmentation at that time was to cause a sclerosis reaction in the breasts, to contain the liquid silicone or paraffin, and to hopefully prevent it from migrating through the breast tissue to other sites. Nevertheless, the adverse effects of the injected liquid were very similar to those of paraffin and industrial-grade silicon. These included the following adverse effects: migration of silicone to other parts of the body, inflammation, discoloration, and the formation of granulomas, ulceration, and fistulae formation. To the best of our knowledge, there are no reports describing lipogranuloma due to olive oil as a

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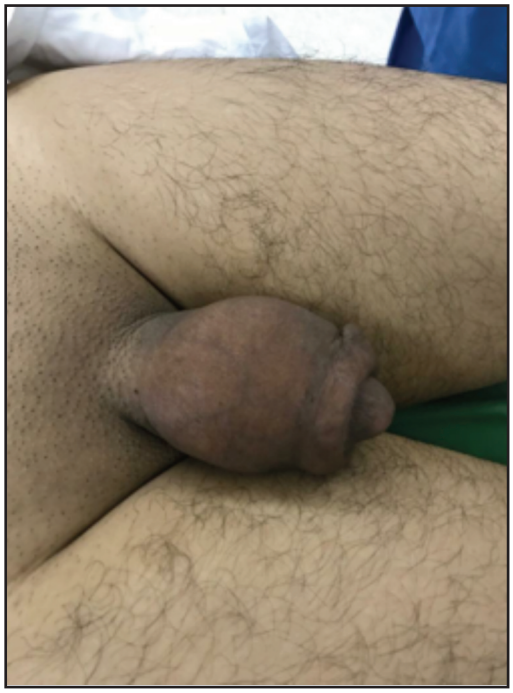

Fig. 1: Massively swollen penis measuring 7cm x 10cm with irregular semi-mobile masses extending into the scrotum.

Fig. 2: Post-operative Day 14 photo demonstrates the end results after excision of the lipogranoloma and closure with Split-thickness Skin Graft.

single agent for body augmentation. There is also no study reporting factors that can influence the amount or size of lipogranuloma which develops from olive oil is as the same as the foreign-body reaction from the administration of mineral or other vegetable oils, involving macrophages that react to the foreign material by surrounding it and forming giant multinucleated cells.[3] However, in comparison with clinical presentation, inflammatory reactions and histopathological findings in our patient are similar with other mineral oil. Olive oil has been shown to cause lipogranulomas not only on the subcutaneous injection site but also appeared on the capsular or serosal surface of the abdominal organs in a study using rodents when injected subcutaneously. The olive oil may have reached the peritoneal cavity from the subcutaneous tissue passively via the lymphatic vessels or actively after engulfment by antigen-presenting cells via the lymphatic or blood vessels.[3] However, whether olive oil can cause a massive reaction surrounding the injection site or not, remains unknown.

The diagnosis is however challenging if the patient does not reveal the information and misdiagnosis of malignancy that may happen. Some studies have shown that magnetic resonance imaging (MRI) to be effective in diagnosing paraffinomas aside from biopsy and this depends on the time interval before its presentation.[4] Various methods of treatment from conservative management such as steroid injection and hot water baths to radical surgical management like excision with skin grafting repair are available. A complete surgical excision of the nodule is the definitive treatment in order to prevent recurrence. Antibiotics and topical and or systemic steroids can be used for the medical treatment of primary sclerosing lipogranuloma, however success has never been reported for treatment of foreign body induced lipogranuloma. Surgery is the best treatment for penile lipogranuloma for both primary and foreign body induced. Granulomatous skin needs complete excision. Common options for wound closure are scrotal skin flap, Cecil's inlay operation, and a Split thickness Skin Graft (SSG).[5] The most successful management technique for a denuded penis is penile split-thickness skin grafts which demonstrates a good graft survival 5 and are able to achieve full erection with normal sexual intercourse after the surgery.[5]

CONCLUSION

Injecting any oily substances into the human body is hazardous. The differential diagnosis of nodules following injections should be kept in mind and in doubtful cases, biopsy should be done. Regular follow-up is essential to prevent the further inflammatory event. Safe and legal procedures should be implemented for penile enlargement so as to avoid self-injections and in the prevention of such debilitating problems.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

INFORMED CONSENT

Written informed consent was obtained from the patient for the publication of this article.

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REFERENCES

1. Darsow U, Bruckbauer H, Worret WI, Hofmann H, Ring J. Subcutaneous oleomas induced by self-injection of sesame seed oil for muscle augmentation. J Am Acad Dermatol 2000; 42: 292-4.
2. Sarıca Ö, Kayhan A, Demirkürek HC, İğdem AA. Subcutaneous Oleomas Following Sunflower Oil Injection: A Novel Case and Review of Literature. J Breast Health 2016; 12(3): 141-4.
3. Ramot Y, Ben-Eliahu S, Kagan L, Ezov N, Nyska A. Subcutaneous and intraperitoneal lipogranulomas following subcutaneous injection of olive oil in Sprague-Dawley rats. Toxicol Pathol 2009; 37(7): 882-6.
4. Cormio L, Di Fino G, Scavone C, et al. Magnetic resonance imaging of penile paraffinoma: case report. BMC Med Imaging 2014; 14:39.
5. Inn FX, Imran FH, Ali MF, Ih R, Z Z. Penile augmentation with resultant foreign material granuloma and sequalae. Malays J Med Sci 2012; 19(4): 81-3.

Renal sympathetic denervation in the treatment of resistant hypertension

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SUMMARY

Hypertension is a significant cardiovascular risk factor. Although the mainstay of treatment remains medication, there are a number of patients with resistant hypertension who have elevated blood pressure despite multiple medications. Failure to achieve adequately controlled blood pressures despite medications put these patients at risk of target organ damage and significant morbidity from hypertension. The renal denervation procedure involves the application of radiofrequency energy or ultrasound at the renal arteries to modulate afferent and efferent sympathetic renal activity. This treatment potentially can improve blood pressure control in patients who have resistant hypertension despite medication. This article presents two case reports of successful treatment of resistant hypertension using radiofrequency renal sympathetic denervation (RDN) at a private medical centre using the latest Spyral catheter. We also reviewed the latest RDN trials to give some insights into this procedure.

INTRODUCTION

Hypertension is a significant cardiovascular risk factor that is implicated in coronary artery disease and stroke. Only about half of patients with hypertension are adequately controlled on medical therapy and about a quarter of patients may develop severe or resistant hypertension. Resistant hypertension is defined as failure to achieve target blood pressure (BP) of < 140/90 mmHg while on full doses of an appropriate three-drug regimen that includes a diuretic.

Renal sympathetic denervation (RDN) was first used to treat resistant hypertension by modulating renal sympathetic nerve activity using radiofrequency ablation. Renal sympathetic efferent nerves activate the renin – angiotensin – aldosterone system, subsequently leading to a decrease renal blood flow, a decrease in urinary excretion of salt and water. By decreasing efferent sympathetic nerve activity, RDN can lower BP. This article presents two case reports of successful treatment of resistant hypertension using the latest Spyral catheter and we reviewed the latest RDN trials.

CASE REPORT

A 44-year-old man presented to an ophthalmologist at our centre, Subang Jaya Medical Centre, Malaysia for visual disturbance, diagnosed with right eye retinal artery occlusion and was found to have elevated blood pressure. The patient was referred to a cardiologist at our centre for further management. The patient had no other medical history and was not on medication. His BP was 200/120 mmHg on initial consultation. He was started on amlodipine 10mg od, valsartan 160mg od, hydrochlorothiazide 25mg od.

After 4 weeks of treatment with medication, the patient still had an elevated office BP of 170/100 mmHg and hence, was admitted for further investigation. Investigations were performed to assess for target organ damage from hypertension and to rule out secondary causes of hypertension. Renal function was normal, creatinine was 84 umol/l with estimated glomerular filtration rate (eGFR) of >59 ml/min/1.73 m^2. Other normal results included Renin 10.1 (5.3-99 mU/L), Aldosterone 402 (103-1197 pmol/l), 24-hour urine Noradrenaline 214 (71-505 nmol/24 hr), urine Adrenaline 20 (9-122 nmol/24 hr), urine Dopamine 530 (0-3237 nmol/24 hr). Abdominal CT angiography showed no evidence of coarctation of aorta, renal artery stenosis and no adrenal masses. Echocardiography showed concentric left ventricular hypertrophy, with normal systolic function and no significant valve abnormalities. MRA of the brain showed, on diffusion weighted imaging, a few hyperintense foci in right corona radiata and left centrum semiovale, representing likely subacute infarction.

Despite treatment with the 3 hypertension medications and medication compliance monitored during hospital admission, 24-hour Ambulatory BP monitoring (ABPM) still showed severe systolic and diastolic hypertension and a non-dipper pattern (overall average: 171/105 mmHg). The patient was offered an option for further 4th medication or RDN procedure. He opted for RDN and consented for it.

The RDN procedure was performed under general anesthesia. After gaining vascular access via the right femoral artery, renal artery angiography was performed. Intravenous heparin was administered. Following catheterization and using the RDC guide catheter, a Symplicity® Spyral catheter (Medtronic, USA) was connected to a radiofrequency generator and inserted into each renal artery sequentially. The procedure was planned by identifying renal artery branches with sizes between 3 mm to 8 mm. Multiple applications of radiofrequency energy for up to 60s each were performed with 25 points ablated in the right and 28 points ablated in the left renal artery branches. There were no post-procedural complications, and the patient was discharged well with the continuation of the three hypertension medications.

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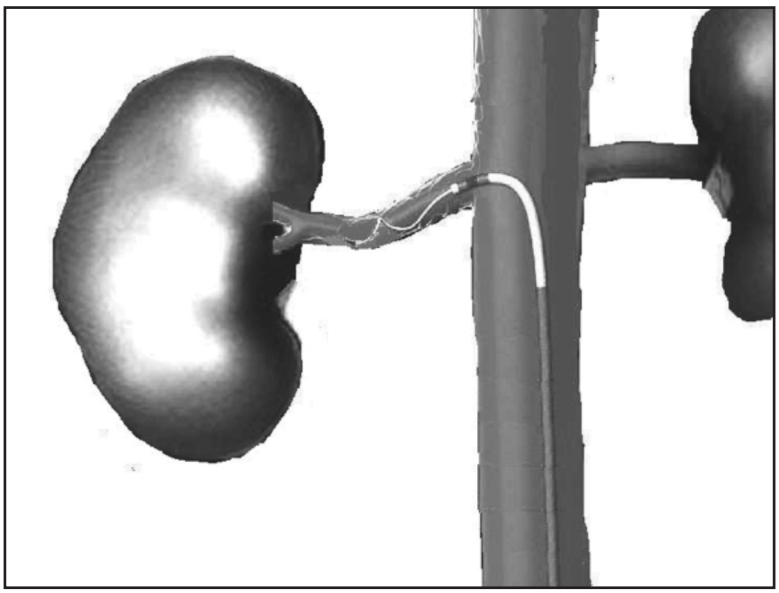

Fig. 1: The Spyral catheter used for renal sympathetic denervation.

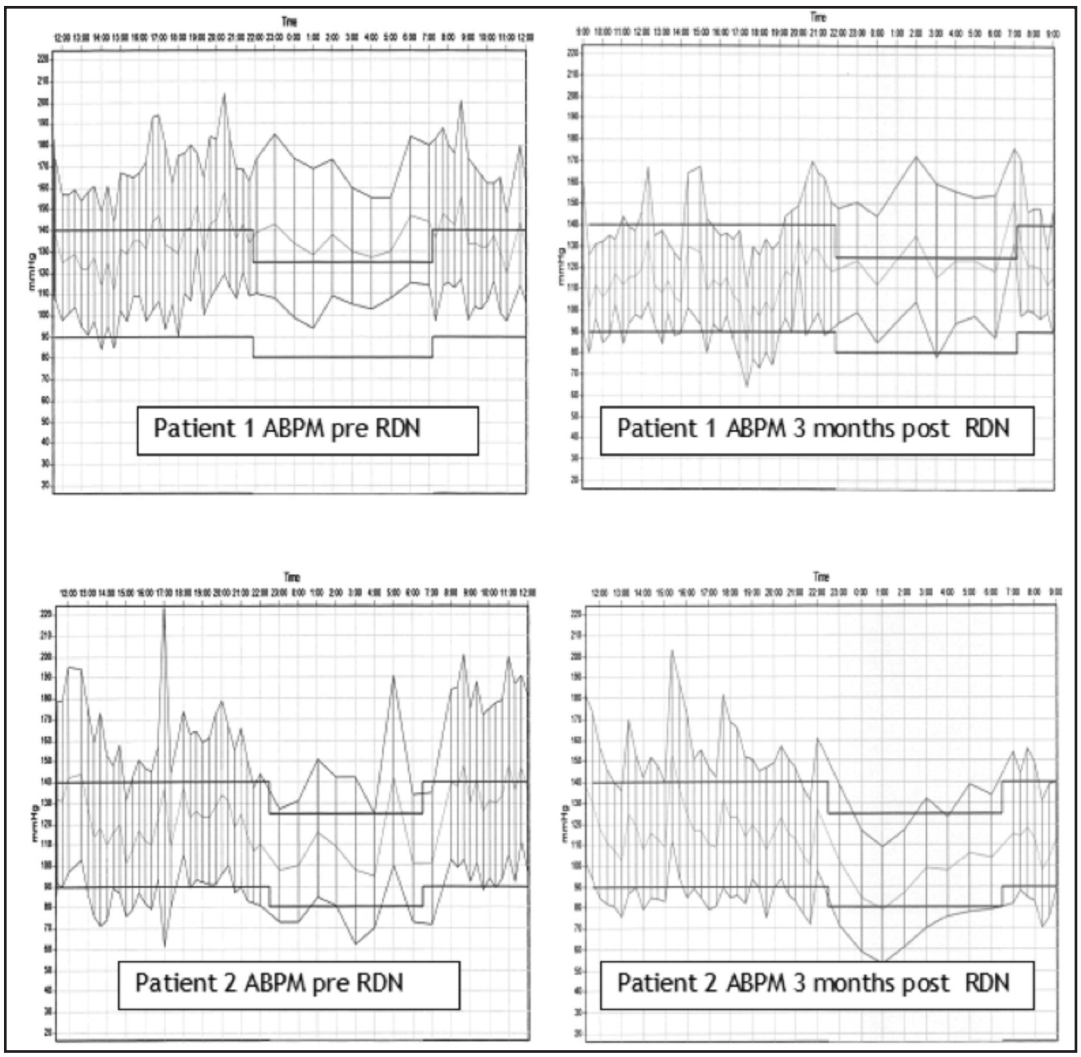

Fig. 2: Both patients demonstrated a significant reduction of BP with 24-hour ABPM at pre RDN procedure (left) and 3 months post procedure (right). For Patient 1 the mean BP decrease was 26/13 mmHg. For Patient 2 the mean BP decrease was 16/5 mmHg.

At one month follow up, renal function showed no significant deterioration with eGFR of >59 ml/min/1.73 m^2. There was sustained reduction of BP when 24-hour ABPM was repeat at 3 months (Figure 2). His 24-hour ABPM at 3 months after the procedure showed an average BP of 145/92 mmHg; (mean systolic and diastolic BP). At 3 months, the mean BP decrease was 26/13 mmHg (systolic and mean diastolic BP decrease). Further follow up for BP and renal imaging is planned.

CASE REPORT 2

A 69-year-old man, presented to the emergency department at our centre with symptoms of headache and lethargy. He had previous medical history of hypertension and diabetes mellitus. He was already on 5 hypertensive medications for more than a year, amlodipine 10mg od, co-aprovel (irbesartan/hydrochlorothiazide) 300 / 12.5mg od, bisoprolol 5mg od, physiotens 0.4 mg od. His BP was 180/100 mmHg on initial consultation.

He was admitted to the medical ward at our centre. Investigations were performed to rule out secondary causes of hypertension. Renal function was normal with creatinine 85 umol/l and estimated glomerular filtration rate (eGFR) of >59 ml/min/1.73 m^2. Other normal results included Renin 39.1(5.3-99 mU/L), Aldosterone 713 (103-1197 pmol/l), 24-hour urine Noradrenaline 340 (71-505 nmol/24 hr), urine Adrenaline 30 (9-122 nmol/24 hr), urine Dopamine 1636 (0-3237 nmol/24 hr). Abdominal CT angiography showed no evidence of coarctation of aorta, renal artery stenosis and no adrenal masses. Echocardiography showed normal left ventricular systolic function and no significant valve abnormalities.

Despite treatment with the five hypertension medications and medication compliance monitored during hospital admission, 24-hour ABPM still showed severe systolic and diastolic hypertension (overall average: 165/88 mmHg).

The patient agreed for the RDN procedure, he chose to have heavy sedation rather than general anesthesia during the procedure. Intravenous heparin was administered for the procedure. Following femoral arterial catheterization and using the RDC guide catheter, a Symplicity® Spyral catheter (Medtronic, USA) was inserted into each renal artery, connected to a radiofrequency generator. The procedure was planned by identifying renal artery branches with sizes between 3 mm to 8 mm. Multiple applications of radiofrequency energy for up to 60s each were performed with 24 points ablated in the right renal artery branches and 29 points ablated in the left renal artery branches. There were no post-procedural complications, and the patient was discharged well with the continuation of his hypertension medications.

At one month follow up, renal function showed no significant deterioration with eGFR of >59 ml/min/1.73 m^2. Follow up with the patient on the same doses of five BP medications showed office BP reduction and the patient felt symptomatically improved. There was BP reduction when 24-hour ABPM was repeated at 3 months (Figure 2). His 24-hour ABPM at 3 months after the procedure was overall average 149/83 mmHg. At 3 months, the mean BP decrease was 16/5 mmHg (systolic and mean diastolic BP decrease). Further follow-up for BP and renal imaging was planned.

DISCUSSION

These two cases illustrate the successful renal denervation treatment of resistant hypertension. Although the mainstay for the majority of hypertensive patients is still medication, there are a small proportion of patients who have persistent elevated blood pressure despite multiple medications for whom RDN may be helpful.

The first-generation radiofrequency ablation (RFA) system (Symplicity Flex; Medtronic, Minneapolis, Minnesota) used for RDN was a catheter with single electrode. The early study (SIMPLICITY HTN-1 study) using this studied 45 patients who underwent RDN treatment. The study demonstrated significant reduction in office systolic BP of 26 mmHg in the RDN group compared to 12 mmHg in the control group at 6 months.[1] The Symplicity HTN-2 trial,[2] a multicenter randomized controlled trial also showed success in lowering BP in hypertensive patients with ≥ 3 antihypertensive drugs. RDN was performed using the Simplicity Flex catheter. The study found that the mean office BP at 6 months dropped by 32 mmHg ($p < 0.001$) in the RDN group (n = 52) compared to BP drop of 12 mmHg in the control group (n = 54).

The Symplicity HTN-3 was a multicentre single blinded trial which randomised 535 patients on ≥3 antihypertensive medications to either RDN using Symplicity Flex or sham control.[3] After 6 months following RDN treatment, there was a mean decrease in office systolic BP of 14.1 mm Hg in the RDN group (n = 364) compared to a decrease of 11.7 mm Hg in the control group (n = 171). Since both RDN and sham controlled groups showed significant decreases in the blood pressure, this raised doubt as to the genuine effectiveness of the RDN treatment.

Since the publication of SYMPLICITY HTN-3 trial, further advances have been made in the technology for RDN. One such system, the Spyral catheter (Simplicity Spyral; Medtronic, Minneapolis, Minnesota) was designed as a 4-electrode system which for more effective ablation. The SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED, were proof of concept studies for the Spyral catheter.[4,5] The SPYRAL HTN-OFF MED showed that at 3 months following RDN, there was significant reduction in both office and 24-hour ambulatory BP from baseline in the treatment group (-10/-5.3 mmHg and -5.5/-4.8 mmHg) compared to the sham control group. Significant BP reduction in the RDN arm was also reported in the SPYRAL HTN-ON MED study at 6 months (-9.0/-6.0 mmHg for 24-hr ambulatory BP).

Several other randomized controlled trials have used RFA in renal denervation with variable results. The simplicity HTN-Japan trial included RDN (n=22) and control (n=19) subjects.[6] The 6-month office SBP change was -16.6 ± 18.5 mmHg for RDN subjects ($P<0.001$) and -7.9 ± 21.0 mmHg for control subjects ($P=0.117$). The French DENER-HTN trial[7] on patients with resistant hypertension found a mean change of systolic blood pressure at 6 months –15·8 mm Hg (95% CI –19·7 to

–11·9) in the renal denervation group and –9·9 mm Hg (95% CI –13·6 to –6·2) in the control group. A trial carried out in Denmark, the ReSet trial, randomized resistant hypertension patients to RDN (n=36) or a Sham procedure (n=33).[8] This trial however, found no significant differences when comparing RDN to a sham procedure at 6 months [–6.1 ±18.9 mmHg (RDN) vs. –4.3±15.1mmHg (SHAM)].

Apart from RFA as described above, catheter-based ablation of renal nerves has also been shown to be effective using ultrasound (Paradise ultrasound system; ReCor Medical, Palo Alto, California). The RADIANCE-HTN SOLO studied catheter-based ultrasound in patients who were not on antihypertensive medications.[9] The decrease in daytime ambulatory systolic BP from baseline to 2 months was greater in the RSDN group (8.5 mmHg, *n* = 74) when compared to the sham group (2.2 mmHg, n = 72). Two additional RCTs with ultrasound-based ablation systems are ongoing.[10] The RADIANCE-HTN TRIO trial is being conducted in the United States and Europe. The REQUIRE study is being conducted in Japan and Korea. Both trials aim to evaluate the safety and efficacy of the ultrasound RDN system in patients with uncontrolled hypertension.

Although there are positive results from SPYRAL HTN-OFF MED, RADIANCE SOLO, and SPYRAL HTN-ON MED trials, several limitations and unknown issues remain. Since RDN was performed in a small number of selected patients and follow-up was only up to 6 months, it is not clear whether the BP lowering effects can be sustained in the long-term. However, past trials have laid down lessons such that future trials are likely to be blinded, involve ambulatory blood pressure monitoring and have longer follow up periods.

CONCLUSION

There is progressively increasing evidence for RDN as an option for effective treatment in resistant hypertension. RDN could potentially reduce the morbidity and mortality risks associated with resistant hypertension in Malaysia.

CONFLICT OF INTEREST

None to declare.

CONSENT

Patients described in the above case reports have given written informed consent for the use of the data and publication of this article.

REFERENCES

1. SYMPLICITY HTN-1 Investigators. Catheter- based renal sympathetic denervation for resistant HTN: durability of blood pressure reduction out to 24 months. Hypertension 2011; 57: 911-7.
2. SYMPLICITY HTN-1 Investigators. Renal sympathetic denervation in patients with treatment-resistant HTN (the SYMPLICITY HTN-2 trial): a randomised controlled trial. Lancet 2010; 376: 1903-9.
3. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med 2014; 370: 1393-401.
4. Kandzari DE, Bohm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet 2018; 391: 2346–55.
5. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRALHTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet 2017; 390:2160–70.
6. Kario K, Ogawa H, Okumura K, Okura T, Saito S, Ueno T, et al. SYMPLICITY HTN-Japan first randomized controlled trial of catheter-based renal denervation in Asian patients. Circ J 2015; 79: 1222-9.
7. Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multi- centre, open-label, randomised controlled trial. Lancet 2015; 385: 1957-65.
8. Mathiassen ON, Vase H, Bech JN, Christensen KL, Buus NH, Schroeder AP, et al. Renal denervation in treatment-resistant essential HTN. A randomized, SHAM-controlled, double-blinded 24-hr blood pressure-based trial. J Hypertens 2016; 34: 1639-47.
9. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, et al. Endovascular ultrasound renal denervation to treat HTN (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham- controlled trial. Lancet 2018; 391: 2335-45.
10. Mauri L, Kario K, Basile J, Daemen J, Davies J, Kirtane AJ, et al. A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: The RADIANCE-HTN and REQUIRE clinical study designs. Am Heart J 2018; 198: 115-29.

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