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The Medical Journal of Malaysia

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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.

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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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Investigation on monosodium urate deposition in the first metatarsophalangeal joint and ankle of primary gout patients using dual-energy computed tomography

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ABSTRACT

Background: Gout is caused by deposition of monosodium urate (MSU) crystals. One of the tools of choice to identify MSU crystals is the Dual-Energy Computed Tomography (DECT). This study aims to determine MSU crystal deposition using DECT by comparing its detection in the first metatarsophalangeal joints (MTPJ) with that in the ankles, as well as to analyse the association between the crystal deposition and anthropometrics, clinical characteristics, and serum biochemical levels of a primary gout patient.

Materials and Methods: This cross-sectional study included patients (n = 94) from the Clinic Hoa Hao Medic Medical Centre in Vietnam, who were diagnosed with primary gout with pain/swelling of at least one ankle or first MTPJ. DECT of both joints was used to identify MSU. Statistical analyses were performed using the Student's t-test, Wilcoxon rank-sum, Pearson's chi-square, and Spearman's tests.

Results: Approximately 80% had MSU crystal deposition in the ankle and/or first MTPJ with no significant difference in deposition between the two joints. MSU deposition was significantly associated with disease duration (p = 0.003), flare-ups (p = 0.006), and cut-off of 6 weeks' duration (p = 0.006), bone erosion (p = 0.006), and palpable tophi (p = 0.003). There was no association between MSU deposition with age, body mass index (BMI), hypertension, serum levels of uric acid (UA), creatinine, high-sensitive C-reactive protein (hsCRP), total cholesterol (C-total), and triglyceride (TG).

Conclusions: MSU deposition occurred in both ankle and first MTP at the same rate. The deposition was associated with disease duration and flare-ups. Prevention of flare-ups seems helpful to limit MSU crystal deposition.

KEYWORDS:
ankle, Dual-Energy Computed Tomography, metatarsophalangeal joint, monosodium urate, uric acid

INTRODUCTION

Gout, which is characterised by the deposition of monosodium urate (MSU) in the synovial fluid and other tissues as a result of a chronic increase in serum uric acid (UA), is the most common form of inflammatory arthritis. The deposition of MSU crystals in-and-around the joints can lead to inflammatory reactions with clinical symptoms of swelling and pain. Microscopic identification of MSU crystals in the fluid extracted from joints is considered a gold standard in diagnosis of gout. However, this procedure involves a risk of development of complications that can cause inconvenience to patients (e.g., intra-articular infection and pain). Moreover, MSU crystals may not be detected in acute cases. In such cases, additional clinical and investigative criteria are required.[1] In asymptomatic patients, MSU crystals can be first detected by imaging techniques, such as ultrasound or Dual-Energy Computed Tomography (DECT).[2]

There are known and accepted criteria for the diagnosis of gout, in which the gout classification criteria published by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2015 is being the most commonly used criteria to diagnose this disease.[1,3,4] The usual symptoms of gout include pain, swelling, and redness of the peripheral joints, most commonly the first metatarsophalangeal (MTP) joint. In most cases, the symptoms are associated with an elevated serum UA level. Unfortunately, these presentations can also be seen in other arthropathies. Moreover, normal UA levels can occasionally be observed in some cases of acute gout. Notably, a high UA level does not necessarily lead to MSU crystal deposition.[5,6]

DECT, also known as spectral imaging, was initially designed to detect UA deposition in kidneys (i.e., kidney stones), which has been validated both by *in vitro* and *in vivo* studies. DECT has since been successfully modified for use in musculoskeletal imaging with unique applications.[7]

In a dual-source, two X-ray sources run simultaneously at two kilovolt levels (80 kV and 140 kV), with two corresponding detectors. These provide two spiral data sets that are acquired simultaneously in a single scan.[8] A specific display algorithm assigns different colours to materials of different chemical composition. This includes detection of the elementary chemical composition of urate, allowing visualisation of MSU crystal deposition.[9]

A dual-source DECT scanner enables superior spectral contrast differentiation between urate and non-urate

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depositions. Compared to conventional single-energy scans, high-resolution images with excellent material separation may be obtained using dual-source DECT without increasing the radiation dose.[10] Dual-energy imaging easily allows for the separation and characterisation of calcium, a high-molecular-weight compound, from UA, a low-molecular-weight compound, thus making DECT an important non-invasive tool in the diagnosis of gout.[7,8,11]

MATERIALS AND METHODS

Patients and Control Subjects

This cross-sectional study was performed from April 2018 to July 2019. The protocol was approved by the respective ethics committees of the Hue University of Medicine and Pharmacy, the Hue Central Hospital, and the Clinic Hoa Hao, Medic Medical Centre. All participants provided informed consent.

Ninety-four adults were diagnosed with gout based on the ACR/EULAR gout classification criteria.[1] They presented with an acute attack of pain, swelling, redness, and tenderness in their ankle joint or their first MTPJ. Their condition was confirmed by clinical evaluation, ultrasound, X-ray, and haemato-biological investigations in order to exclude other arthropathies and related diseases. Patients with known malignancy, infectious disease, undergoing immunosuppressive therapy, or having a history of ankle or foot trauma were excluded from this study. All anthropometric indices, clinical signs, and characteristics of the disease, such as flare amount, disease duration, and tophi presentation, were recorded.

Blood samples were collected, after an overnight fast of at least 12 h, for routine blood chemistry and for measurement of haemoglobin (Hb), serum UA, high-sensitive C-reactive protein (hsCRP) and serum lipoprotein cholesterol levels. Patients with a blood pressure (BP) of >140/90 mmHg and/or on anti-hypertensive medication were considered as hypertensive.[12] Anaemia was defined according to the World Health Organisation criteria.[13]

Measurements and Calculations

The ankle joint and the first MTPJ of all patients were subjected to DECT for MSU crystal detection using a Toshiba Aquilion ONE 640 (Japan).

This dual-energy CT system is equipped with two x-ray tubes allowing simultaneous acquisition at two different energy levels and creation of two different data sets that are loaded into the post processing software on a multi-technique CT workspace. An image-based two-material decomposition algorithm of the datasets is subsequently performed to separate calcium from monosodium urate, using soft tissue as the baseline. The material-specific differences in attenuation between the high- and low-tube voltage acquisitions enable easy classification of the chemical composition of scanned tissue, thus allowing accurate and specific characterisation and separation of monosodium urate (color-coded in red) from calcium (color-coded in blue). These images then were interpreted by a senior imaging diagnostic physician to identify signs of MSU crystal deposition, erosion, and soft tissue inflammation.

Statistical Analysis

Continuous variables between group comparisons were analysed using an unpaired Student's t-test or the non-parametric Wilcoxon rank-sum test, as applicable. Dichotomised variables were compared using the Pearson's chi-square test. The null hypothesis was rejected at $p < 0.05$. Data are presented as mean ± standard deviation (SD) for variables with normal distribution, or as numbers and percentages wherever appropriate. A correlation analysis using Spearman's correlation was performed for continuous variables, while Fisher's exact test was used to analyse categorical variables. Statistical analysis was performed using SPSS software 18.0 for Windows.

RESULTS

Patient Characteristics

Patients (Table I) had a mean age of 48.1 ± 10.8 years, a BMI of 24.4 ± 2.8 kg/m^2, and a disease duration of 41.8 ± 31.8 months (minimum–maximum: 1–180 months). A tophus was detected in 23.4% of the patients. The proportion of patients that were subjected to DECT of the joints was 20.2% for the ankle, 21.3% for the first MTP, and 58.5% for both joints. The average serum UA concentration was 9.0 ± 2.2 mmol/L, which was considerably higher than the serum urate level defined by the ACR/EULAR 2015 criteria (0.36 mmol/L).1 In addition, the hsCRP concentration was higher (17.9 ± 25.5 mg/L) than the normal range (≤10 mg/L).[14]

DECT Data

The results from DECT showed that 79.8% of the patients had MSU crystal deposition in at least one of the ankles or the first MTPJ (Table II). There was no significant difference in MSU crystal deposition between the two joints ($p = 0.249$) and in the amount of simultaneous MSU crystal deposition in both the joints. Among the patients with positive DECT, 62.7% showed simultaneous sedimentation in both the joints, with a significant difference compared to patients that were negative ($p < 0.001$).

The relationship between the presence of MSU crystal deposition and demographics, clinical characteristics, gout features, and biochemical levels (Table III) showed that flare-ups ($p = 0.006$), disease duration ($p = 0.003$) with cut-off at 6 weeks ($p = 0.006$), bone erosion ($p = 0.006$), and tophi presence ($p = 0.003$) were associated with a positive DECT.

DISCUSSION

DECT was validated as a tool to confirm the presence of MSU crystal deposits in the assessment of gout because of its non-invasive nature and high specificity.[2,7]

In our study, the proportion of patients that were subjected to DECT of the joints was 20.2% for the ankle, 21.3% for the first MTP, and 58.5% for both joints. A study by Bongartz et al. (2015) including 40 patients with active gout and 41 patients with other types of joint disease surveyed gout patients using DECT in one of four groups of joints – wrist, elbow, pillow, or ankle/foot.[2] In a study by Ahmad et al. with 90 patients suspected of having gout, DECT was performed on two groups of ankle joints and two lateral knees.[15]

Table I: Clinical data of patients with gout disease

Parameter		Patients with gout
No.patients		94
Age (years)		48.08±10.77
BMI (kg/m^2)		24.41±2.83
Minimum/maximum duration (months)		1/180
Number of flare-ups		7.68±4.80
Systolic blood pressure (mmHg)		107.28±20.61
Diastolic blood pressure (mmHg)		74.24±17.42
Tophi n (%)		22 (23.40)
Joint n (%)	Ankle	19 (20.21)
	First MTPJ	20 (21.27)
	Both	55 (58.51)
UA (mmol/l)		9.04±2.23
Creatinine (μmol/l)		98.65±28.62
Total cholesterol (mmol/l)		5.52±1.22
Triglyceride (mmol/l)		3.36±2.37
hsCRP (mg/l)		17.86±25.52

BMI, body mass index; DECT, Dual-Energy Computed Tomography; hsCRP, high-sensitivity C-reactive protein; MTPJ, metatarsophalangeal joint; UA, uric acid

Table II: Monosodium urate (MSU) deposition in joints

Joint	DECT				p-value
	Negative		Positive		
	n	%	n	%	
Ankle	5	26.3	14	18.7	0.249†
First MTPJ	6	31.6	14	18.7	
Both	8	42.1	47	62.7	
All	19	20.2	75	79.8	<0.001

† Fisher's exact test

DECT, Dual-Energy Computed Tomography; MTPJ, metatarsophalangeal joint

Table III: Relationship between monosodium urate (MSU) deposition, demographics, clinical characteristics and biochemical levels

Variable	DECT positive (n=75)	DECT negative (n-19)	p-value
Age (years)	49.01±10.707	44.42±10.543	0.097
BMI (kg/m2)	24.31±2.884	24.74±2.725	0.571
Flare-ups (n)	8.36±4.884	5.00±3.999	0.006
Flare-up duration, n (%)			
<6 weeks	1(1.30)	4(21.10)	0.006*†
≥6 weeks	74(98.70)	15(78.90)	
Disease duration (weeks)	188.37±145.359	84.21±64.999	0.003
Hypertension, n (%)	14(18.70)	2(10.50)	0.512
Bone erosion, n (%)	20(26.70)	0(0.0)	0.010†
Tophi, n (%)	22(23.4)	0(0.0)	0.003†
Serum UA (mmol/L)	8.93±2.268	9.47±2.091	0.349
Creatinine (μmol/L)	102.52±62.958	78.47±39.448	0.117
Total cholesterol (mmol/L)	5.43±1.243	5.89±1.100	0.138
Triglyceride (mmol/L)	3.21±2.303	3.95±2.614	0.230
hsCRP (mg/L)	19.36±27.681	11.95±12.981	0.260

* Between <6 weeks and ≥6 weeks

† Fisher's exact test

BMI, body mass index; DECT, Dual-Energy Computed Tomography; hsCRP, high-sensitivity C-reactive protein; UA, uric acid

In our study, 79.8% of the joints analysed by DECT were positive for MSU crystal deposition, with no significant differences of MSU crystal deposition rate between the two examined joints. This indicates that neither joint had a priority in MSU disposition (Table II).

Although all of the patients in the current study had different regimes for gout, they had high serum UA concentration (9.0 ± 2.2 mmol/L) and inflammatory responses were significant as indicated by hsCRP levels (Table I). It may be explained that these patients did not follow up strictly therapy for gout leading to changes in UA level and hsCRP level.

A positive correlation was observed between duration of gout and MSU deposition (p = 0.003). This association was recorded at a cut-off of 6 weeks (p = 0.006). Number of positive DECT was more at patients with 8.36 ± 4.884 of flares to those with 5.00 ± 3.999 (Table III). This result is in line with current clinical concepts that gout is characterised by deposition of MSU in synovial fluid and other tissues as a result of a long-term increase in serum UA levels.[16] Flares of gout caused by inflammatory responses are associated with the deposition of MSU in joints and periarticular tissues.[17] Therapies controlling flares should aim to decrease deposition of MSU at that sites.

Our study included 5 patients with gout <6 weeks, wherein deposition of MSU was not detected in 4 patients (80%) subjected to DECT. In patients with gout of 6 weeks or more, 81.3% had MSU crystal deposition. Our study was unable to evaluate the sensitivity and specificity of DECT in detecting MSU deposition in gout patients. However, the study by Bongartz et al. determined the sensitivity and specificity of DECT to be 0.90 (95% CI: 0.76–0.97) and 0.83 (95% CI: 0.68–0.93), respectively. A recent meta-analysis by Ogdie et al. demonstrated a pooled sensitivity of 0.87 (0.79–0.93) and specificity of 0.84 (0.75–0.90).18 It was concluded that, in fact, DECT was capable of detecting UA deposition with good sensitivity and high specificity.[11]

Our study showed no correlation between detection of MSU crystals on DECT and UA concentration. This may be due to the possible effect of treatment regimens on UA levels, and changes in the patient's clinical presentation of gout as a result. This was consistent with the results showing that DECT correlated with the presence of bone erosion markers and tophi particles (p < 0.01 for both) (Table III).

Similarly, the study of Svensson et al. on 55 patients with new or established gout, as well as the study of Dalbeth et al. on 152 gout patients treated with allopurinol also revealed an association between positive DECT with bone erosion and presence of tophi.[19,20] However, in the latter study, UA concentration was >35.69 mmol/L, which was much higher than the concentration estimated in our study.

The study by Ahmad et al. on 90 gout patients to evaluate the sensitivity and specificity of DECT for diagnosing gout compared to a composite gold standard including joint aspiration and/or the American College of Rheumatology clinico-radiographic criteria showed that DECT had a sensitivity and specificity of 82 and 89%, respectively. Compared to radiographs and non-contrast computed tomography (NCCT), the sensitivity and specificity with aspiration as a reference (n = 55) was not significantly different than the CGS. However, DECT showed a higher sensitivity of 100% (95% CI: 86–100%) and a lower specificity of 48% (95% CI: 28–68%) with aspiration alone. Thus, DECT was able to diagnose several cases of gout which would have been missed by radiographs and NCCT.[15]

Our study found no association between positive DECT and BMI, serum creatinine concentration, or serum total cholesterol (C-total) and triglyceride (TG) concentration.

Various studies have reported obesity as a risk factor for gout. A recently published meta-analysis data showed that obese people had a relative risk (RR) of 2.06–4.30 for gout, depending on each study. This analysis also showed that the association of hypertension to gout varied in terms of RR in different studies. However, there was no data regarding the association of obesity and hypertension with MSU deposition in this meta-analysis.[21] A meta-analysis of Evans et al. showed that subjects with a BMI ≥ 30 kg/m^2 had a risk of gout that was 2.14 higher than the rest of the study population.[11] However, in our study, most of the patients were not obese (BMI < 30 kg/m^2), and this index was probably negatively impacted by its association with MSU deposition in the joints.

CONCLUSION

MSU crystal deposition between the ankles and first MTPJ did not show differences in the patients analysed in the current study. The longer the duration of gout in the patients, greater was the likelihood of MSU deposition in the joints as detected by DECT. Such deposition was also related to the number of flares. Therefore, prevention from flare-ups seems one of ways to limit MSU deposition. There was no association between detection of MSU deposition and age, BMI, and serum concentrations of UA, creatinine, C-total, and TG.

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REFERENCES

1. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D. 2015 Gout classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2015; 74(10): 1789-98.
2. Bongartz T, Glazebrook KN, Kavros SJ, Murthy NS, Merry SP. Dual-energy CT for the diagnosis of gout: An accuracy and diagnostic yield study. Ann Rheum Dis 2015; 74(6): 1072-7.
3. Martin U. Diagnosis and management of gout. BMJ 2006; 332: 1315-9e.
4. Perez-Ruiz F, Dalbeth N, Bardin T. A review of uric acid, crystal deposition disease, and gout. Adv Ther 2015; 32(1): 31-41.

5. Logan JP, Morrison E, Mcgill PE. Serum uric acid in acute gout. Ann Rheum Dis 1997; 56: 696-700e.
6. Edward R, Michael D. Epidemiology of gout. Arthritis Res Ther 2010; 12(113): 1-11e.
7. Nicolaou S, Liang T, Murphy DT, Korzan JR, Ouellette H, Munk P. Dual-energy CT: A promising new technique for assessment of the musculoskeletal system. AJR Am J Roentgenol 2012; 199(5 Suppl): S78-86.
8. Nicolaou S, Yong-Hing CJ, Galea-Soler S, Hou DJ, Louis L, Munk P. Dual-energy CT as a potential new diagnostic tool in the management of gout in the acute setting. AJR Am J Roentgenol 2010; 194(4): 1072-8.
9. Ashwin R, Opetaia A, Ramanamma K, Gregory DG, Anne H, Anthony JD, et al. Lack of change in urate deposition by dual - energy computed tomography among clinically stable patients with long standing tophaceous gout: A prospective longitudinal study. Arthritis Res Ther 2013; 15(160): 1-8
10. Chou H, Chin Ty, Peh WC. Dual-energy CT in gout - A review of current concepts and applications. J Med Radiat Sci 2017; 64(1): 41-51.
11. Kiefer T, Diekhoff T, Hermann S, Stroux A, Mews J, Blobel J, et al. Single source dual-energy computed tomography in the diagnosis of gout: Diagnostic reliability in comparison to digital radiography and conventional computed tomography of the feet. Eur J Radiol 2016; 85(10): 1829-34.
12. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JLJ, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42(6): 1206-52.
13. World Health Organization (2011). Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity [cited Feb 2022]. Available from: https://apps.who.int/iris/handle/10665/85839.
14. US Food and Drug Administration. Guidance for industry and FDA staff: Criteria for assessment of C-reactive protein (CRP), high sensitivity C-reactive protein (hsCRP), and cardiac C-reactive protein (cCRP) assays [cited Feb 2022]. Available from: http://www.fda.gov/cdrh/oivd/guidance/1246.html.
15. Zohra A, Arun KG, Raju S, Ashu SB, Uma K, Sreenivas V. Dual energy computed tomography: A novel technique for diagnosis of gout. Int J Rheum Dis 2016; 19: 887–96
16. Murdoch R, Barry MJ, Choi HK, Hernandez D, Johnsen B, Labrador M, et al. Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN) common language definition of gout. RMD Open 2021; 7(2): e001623. doi: 10.1136/rmdopen-2021-001623.
17. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006; 440(7081): 237-41.
18. Ogdie A, Taylor WJ, Weatherall M, Fransen J, Jansen Tl, Neogi T, et al. Imaging modalities for the classification of gout: Systematic literature review and meta-analysis. Ann Rheum Dis 2015; 74(10): 1868-74.
19. Svensson E, Aurell Y, Jacobsson LTH, Landgren A, Sigurdardottir V, Dehlin M. Dual energy CT findings in gout with rapid kilovoltage-switching source with gemstone scintillator detector. BMC Rheumatology 2020; 4: 7. https://doi.org/10.1186/s41927-019-0104-5.
20. Dalbeth N, Nicolaou S, Baumgartner S, Hu J, Fung M, Choi HK. Presence of monosodium urate crystal deposition by dual-energy CT in patients with gout treated with allopurinol. Ann Rheum Dis 2018; 77(3): 364-70.
21. Evans PL, Prior JA, Belcher J, Mallen CD, Hay CA, Roddy E. Obesity, hypertension and diuretic use as risk factors for incident gout: A systematic review and meta-analysis of cohort studies. Arthritis Res Ther 2018; 20(1): 136. https://doi.org/10.1186/s13075-018-1612-1.

ORIGINAL ARTICLE

Endoscopic findings among geriatric patients with anaemia and chronic kidney disease at a tertiary teaching hospital in Malaysia

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ABSTRACT

Background: Older people with chronic kidney disease (CKD) may be anaemic due to various reasons, and they are vulnerable to various consequences. One of the most important causes of anaemia to be recognised in this population is gastrointestinal loss. The outcome can be improved by early detection, careful investigation, and suitable therapies. There is currently no standardised grading scale or reliable indicators to assist clinicians on handling gastrointestinal workup in elderly CKD patients who are anaemic.

Methods: A cross-sectional study of 171 people aged 60 and over who had CKD (stages 3–5), including those on Renal Replacement Therapy (RRT) and anaemia. Using oesophagogastroduodenoscopy, colonoscopy, and double balloon endoscopy, we analysed the endoscopic findings and calculated the prevalence of anaemia secondary to gastrointestinal disease. Haemoglobin, mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), mean cell haemoglobin (MCH), iron panels, and immuno-faecal occult blood test (iFOBT) were evaluated to predict the diagnostic utility of each parameter in relation to gastrointestinal disorder in the elderly CKD population.

Results: Abnormal endoscopic findings were obtained by upper and lower endoscopy in 98 individuals (57.3%). Upper endoscopy revealed the most prevalent lesions to be gastritis, gastric ulcer, and duodenal ulcer. The upper and lower endoscopies revealed a total of 14.0% malignant and pre-malignant lesions. T-test and receiver-operating characteristic (ROC) curve were performed on all haematological parameters and iron panels. Low ferritin level (less than 100 ng/mL) and combination with low transferrin saturation (less than 20%) have a significant p value less than 0.05. None of these variables had a significant area under the curve (AUC) of more than 0.75.

Conclusion: Positive endoscopic findings of anaemia are common in the older population at various stages of CKD, regardless of age, gender, or race. Malignant and pre-malignant lesions are not uncommon in older CKD patients. In the older CKD population, GI inflammation and ulceration are common lesions. Serum ferritin and TSAT levels are useful indicators of GI disorder in this population. Endoscopic evaluation as part of anaemia workup in the older people with CKD should not be ruled out.

KEYWORDS:
Anaemia ,Chronic Kidney Disease, Geriatrics, Endoscopy

INTRODUCTION

Anaemia in geriatric population is associated with a very wide range of complications, including increased risk for mortality, cardiovascular disease, cognitive dysfunction, longer hospitalisation for elective procedures and comorbid conditions, reduced bone density, and falls and fractures.[1] Anaemia is a common problem encountered by physicians in this population on a daily basis. It is a global issue that affects both developed and developing countries worldwide. World Health Organization (WHO) has defined anaemia in adults as low haemoglobin level, i.e., below 13 g/dL in men and below 12 g/dL in women.[2] Anaemia in older people has been associated with a progressive decline in their functional status, predisposing to cardiovascular complications, leading to recurrent hospitalisation, cognitive impairment, and high burden of mortality among this population.[3] Based on the WHO criteria for anaemia, the prevalence of anaemia among the geriatric population aged 65 years and above has been reported in several large studies, and these varied by age group, race, gender, and their underlying medical problems.[3-6] As the age progresses, the degree of anaemia became more salient. Older individuals were noted to have a higher prevalence of anaemia.[7] There are other predisposing factors that should also be considered in anaemia in older people, including the smoking status, their residence, physiological status, and history of multiple hospital admissions.[2,4,5]

Defining the normal haemoglobin level among geriatric population is crucial in establishing the aetiology of anaemia and in monitoring the effects of treatment and its outcome.

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Due to the increased prevalence of lower haemoglobin levels in older population, as well as increased risk of multiple co-morbidities leading to anaemia, determining the cause of anaemia can be challenging, especially in the setting of concurrent chronic kidney disease (CKD).

Anaemia in the older people with CKD is a manifestation of multi-factorial process. Deficiency of Erythropoiesis Stimulating Agent (ESA) is one of the commonest causes of anaemia in CKD, but in the older population, it is imperative that other causes of anaemia be excluded. This is especially true as the incidence of anaemia in older people with CKD is greater than that in the general geriatric population, and the rate of anaemia continues to rise with increasing age[8]. The older CKD population tends to have anaemia due to the pathophysiological changes related to CKD or to treatment-related complications. Some of the aetiological causes are easily corrected if identified early, whereas some aetiological causes are impossible to correct.

Nutritional anaemia is a common problem in older people, frequently manifesting as iron deficiency anaemia (IDA). In turn, iron deficiency anaemia occurs due to poor dietary intake and inadequate nutritional intake but both nutritional and chronic blood loss accounts for most of the IDA cases.[9] Patients with CKD demonstrate massive gastrointestinal bleeding that contributes to chronic blood loss leading to multiple complications. It is associated with high mortality rate.[10,11] However, the diagnosis of IDA can be complex, and various haematological parameters and iron panels are warranted to make a proper diagnosis. To date, there is no established scoring scheme or robust indicator to guide us as an approach for gastrointestinal workup in anaemic geriatric CKD patients.

Therefore, we evaluate the prevalence of anaemia secondary to gastrointestinal disorder in geriatric population with CKD (stages 3–5), and the associated endoscopic findings can help determine the diagnostic utility of each haematological variables in relation to gastrointestinal bleeding in the older CKD population. Later stages of CKD were chosen because these are when the kidneys have significant degree of reduced function, and stopping the progression of disease may induce a good impact on patient's life.

MATERIALS AND METHODS

This cross-sectional study was conducted in Universiti Kebangsaan Malaysia Medical Center (UKMMC) from April until December 2016. The sample size required was calculated based on specificity taken from a previous study and it came up to 350.11

$$FP + TN = \frac{z^2}{W^2} \times \frac{(SP\ (1\text{-}SP))}{0.05^2} = \frac{1.96^2 \times (0.7\ (1\text{-}0.7))}{} = 3.842 \times 84 = 322$$

$$N\ (sp) = \frac{FP + TN}{(1\text{-}P)} = 322 / 0.92 = 350$$

- Z = Z value (1.96 for 95% confidence level)
- W = accuracy = 0.05
- P = representing prevalence of anaemia attributed by CKD in elderly patients of more than 65 years (based on NHANES III)
- SP = specificity taken from a previous study.11
- TP = True positive
- FN = False negative

The purposive sampling methods recruited, however, was 171 patients, aged 60 years and above. The patients were those with established CKD including those on dialysis who had been referred from various multi-disciplinary clinics and inpatients. Patients were assessed by the gastroenterology team in UKMMC either in clinic or in inpatient settings prior to endoscopy investigations to decide on the need to undergo the procedure and the waiting time. Selected patients were also those with haemoglobin (Hb) concentration less than 12.0d/dL in women and less than 13.0g/dL in men, and they consented for endoscopic procedures . Patients with prior underlying malignancy and haematological or hepatic diseases are excluded from the study.

Patients included in the study were those with established presence of CKD (stages 3–5), who were on on regular dialysis, based on the level of kidney function (Glomerular Filtration Rate), i.e., less than 59 mL/min/1.73m^2 Endoscopic evaluation involved in this study includes oesophagogastroduodenoscopy (OGD), double balloon endoscopy (DBE), and colonoscopy. We included those with stages 3–5 CKD, who were on renal replacement therapy (RRT).

The CKD is staged according to the internationally accepted National Kidney Foundation – Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines (12). It is estimated based on the Glomerular Filtration Rate (GFR) using the Isotope Dilution Mass Spectrometry (IDMS) traceable Modification of Diet in Renal Disease (MDRD) Study Equation: $175 \times (Scr)^{-1.154} \times (Age)^{-0.203}$ x (0.742 if female) x (1.212 if black). Subjects with calculated eGFR from 30 to 59 mL/min/1.73m^2 were grouped into stage 3, eGFR between 15 to 29 mL/min/1.73m^2 into stage 4, and those with eGFR less than 15mL/min/1.73m^2 into stage 5.

The subjects were informed about the project details and provided written consent before participating in this study. The study protocol was reviewed and approved by the Research Ethics Committee of Universiti Kebangsaan Malaysia (Approval Code: FF-2016-133).

Initially, all patients completed the demographic questionnaire provided. Results of laboratory and stool assessment (iFOBT) were obtained within three months prior to the procedures. The study centre utilises immunochemical faecal occult blood testing (FIT), which had replaced the previous more cumbersome guaiac-based faecal occult blood. FIT does not require dietary restriction, and a single test is recommended. Although FIT has high sensitivity and specificity for colorectal cancer and adenomas, it has a lower sensitivity to the upper GI tract blood loss compared to the lower GI tract blood loss. This is due to the fact that blood gets reabsorbed in the small intestine, thereby potentially inducing a false negative and false sense of security when used in examination of the upper GI tract.

Blood tests include haemoglobin levels, MCV, MCHC, MCH, C-reactive protein (CRP), and iron panels – including serum iron, total iron binding capacity (TIBC), serum ferritin, and

Table I: Demographic characteristics of elderly anaemic CKD subjects

DEMOGRAPHIC DATA	n	%
Gender		
Male	97	(56.7)
Female	74	(43.3)
Race		
Malay	98	(57.3)
Chinese	57	(33.3)
Indian	12 (7.0)	
Others	4	(3.2)
CKD stages		
Stage 3	61	(35.7)
Stage 4	39	(22.8)
Stage 5	24	(14.0)
Stage 5 + dialysis	47	(27.5)
Age group (years)		
60–64	43	(25.1)
65–69	44	(25.7)
70–75	45	(26.3)
> 75	39	(22.8)

Table II: Types of anaemia in positive endoscopy

TYPE OF ANAEMIA	N (%)	TOTAL NO
Microcytic anaemia		10 (10.9)
Microcytic Hypochromic anaemia	7 (7.6)	
Microcytic Normochromic anaemia	3 (3.3)	
Normocytic anaemia		67 (72.8)
Normocytic Hypochromic anaemia	16 (17.4)	
Normocytic Normochromic anaemia	49 (53.3)	
Normocytic Hyperchromic anaemia	2 (2.2)	
Macrocytic anaemia	15 (16.3)	15 (16.3)

Table III: Characteristics of haematological and laboratory parameters between positive and negative finding groups

PARAMETER		POSITIVE ENDOSCOPY	NEGATIVE ENDOSCOPY	P VALUE
Haemoglobin level, g/dL ,	Mean, SD	7.2 ± 1.8	7.6 ± 1.5	0.428
MCV, fl	Median (IQR)	87.9 (84.6- 94.6)	86.1 (78.3-90.5)	0.191
MCHC,%	Median (IQR)	32.0 (30.9-32.9)	31.9 (30.4-33.0)	0.319
MCH, pg	Median (IQR)	28.2 (27.0-30.4)	27.8 (25.3-30.2)	0.389
Serum iron, ug/dL	Median (IQR)	8.9 (6.3-11.2)	7.75 (4.4-14.1)	0.497
TIBC	Mean, SD	37.12 ± 13.5	39.6 ± 15.3	0.460
TSAT,%,	Median (IQR)	18.4 (15.3-31.1)	18.3 (11.9-36.0)	0.218
Serum ferritin, ng/mL	Median (IQR)	419 (146-834)	315 (133-721)	0.449
TSAT				
<20%	N (%)	76 (56.7)	58 (43.3)	0.102
>20%	N (%)	16 (43.2)	21 (56.8)	
Ferritin				
< 100 ng/mL	N (%)	63 (60.0)	42 (40.0)	0.046*
>100 ng/mL	N (%)	29 (43.9)	37 (56.1)	
TSAT < 20%	N (%)	56 (60.2)	37 (39.8)	0.029*
iFOBT				
Positive	N (%)	14 (66.7)	7 (33.3)	0.082
Negative	N (%)	9 (40.9)	13 (59.1)	

Table IV: Endoscopic findings of elderly anaemic patients with CKD according to CKD staging

CKD STAGING FINDING	3 n (%)	4 n (%)	5 n (%)	5+D n (%)	TOTAL n (%)
OESOPHAGEAL LESION					
Oesophageal Ulcer	0 (0)	0 (0)	2 (1.2)	0 (0)	2 (1.2)
Oesophagitis Grade B	1 (0.6)	0 (0)	0 (0)	1 (0.6)	2 (1.2)
Oesophagitis Grade C	1 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.6)
GASTRIC LESION					
Moderate Gastritis	3 (1.8)	2 (1.2)	3 (1.8)	2 (1.2)	10 (5.8)
Severe Gastritis	1 (0.6)	1 (0.6)	1 (0.6)	3 (1.8)	6 (3.5)
F1 Gastric Ulcer	2 (1.2)	0 (0)	0 (0)	1 (0.6)	3 (1.8)
F2 Gastric Ulcer	2 (1.2)	2 (1.2)	0 (0)	3 (1.8)	7 (4.1)
F3 Gastric Ulcer	8 (4.8)	6 (3.6)	4 (2.4)	8 (4.8)	24 (14.0)
Gastric Polyp					5 (2.9)
< 1 cm	0 (0)	0 (0)	1 (0.6)	0 (0)	
> 1 cm	1(0.6)	0 (0)	1 (0.6)	2 (1.2)	
Suspicious of cancer	2 (1.2)	0 (0)	0 (0)	3 (1.8)	5 (2.9)
DUODENAL LESION					
Duodenal Polyp					4 (2.4)
< 1 cm	0 (0)	0 (0)	0 (0)	1 (0.6)	
> 1 cm	1 (0.6)	0 (0)	1 (0.6)	1 (0.6)	
Moderate Duodenitis	1 (0.6)	0 (0)	0 (0)	1 (0.6)	2 (1.2)
Severe Duodenitis	0 (0)	2 (1.2)	0 (0)	0 (0)	2 (1.2)
F1 Duodenal Ulcer	1 (0.6)	0 (0)	0 (0)	1 (0.6)	2 (1.2)
F2 Duodenal Ulcer	2 (1.2)	2 (1.2)	2 (1.2)	3 (1.8)	9 (5.3)
F3 Duodenal Ulcer	2 (1.2)	1 (0.6)	1 (0.6)	4 (2.4)	8 (4.7)
Suspicious of cancer	1 (0.6)	0 (0)	0 (0)	1 (0.6)	2 (1.2)
COLONIC LESION					
Colonic Polyp					21 (34.4)
< 1 cm	6 (9.8)	3 (4.9)	2 (3.3)	4 (6.6)	
> 1 cm	4 (6.6)	0 (0)	0 (0)	3 (4.9)	
Rectal Polyps	1 (1.6)	0 (0)	0 (0)	0 (0)	1 (1.6)
Ulcer	2 (3.3)	0 (0)	0 (0)	0 (0)	2 (3.3)
Moderate Colitis	0 (0)	1 (1.6)	0 (0)	1 (1.6)	2 (3.3)
Severe Colitis	0 (0)	1 (1.6)	0 (0)	0 (0)	1 (1.6)
Cancerous	1 (1.6)	1 (1.6)	0 (0)	0 (0)	2 (3.3)

Table V: Histopathological examination (HPE) results of polyps from the endoscopic intervention

LESION	HPE RESULT
GASTRIC POLYPS (N=5)	
< 1.0 cm (n=1)	Foveolar type adenoma with low-grade dysplasia (1 case)
> 1.0 cm (n=4)	Hyperplastic polyps (2 cases) Foveolar metaplasia (1 case) Tubular adenoma with low-grade dysplasia (1 case)
DUODENAL POLYPS (N=4)	
< 1.0 cm (n=1)	Inflammatory polyp (1 case)
> 1 cm (n=3)	Hyperplastic polyp (1 case) Tubular adenoma with low-grade dysplasia (1 case) Neuroendocrine tumour (1 case)
COLONIC POLYPS (N=22)	
< 1.0 cm (n=14)	Hyperplastic polyps (5 cases) Tubular adenoma with low-grade dysplasia (7 cases) Not biopsied – size less than 0.3 cm (2 cases)
> 1.0 cm (n=8)	Hyperplastic polyp (1 case) Tubular adenoma with low-grade dysplasia (5 cases) Tubular adenoma with high-grade dysplasia (1 case) Tubulovillous adenoma with high-grade dysplasia and intramucosal carcinoma (1 case)

TSAT, i.e., the percentage of serum iron in the TIBC. In this study, oesophagitis with erosion or ulceration involving at least 5 mm or more of the mucosal surface, moderate to severe gastritis or duodenitis, gastric or duodenal ulcer, cancerous lesion, bleeding angiodysplasia, gastric polyp of more than 1.0 cm in diameter, and polyp of less than 1.0 cm that has proven histologically as pre-malignant or malignant lesion, were considered as positive endoscopic findings related to anaemia from the OGD. The following lesions were considered as positive endoscopy findings from the colonoscopy; one or more polyps of more than 1 cm or less than 1.0 cm in diameter that has proven histologically as pre-malignant or malignant lesion, colorectal cancer, colonic ulcer, and moderate to severe colitis.

The available data were then analysed using SPSS version 23.0 software package (IBM Corporation, Armonk, NY, USA). The data are expressed as the mean with standard deviation (SD) unless otherwise indicated. Differences in continuous variables were compared using a t-test, and differences in categorical variables were compared using a chi-square test. Receiver Operating Characteristic (ROC) curve was created with endoscopic findings (negative finding versus positive finding) as the dichotomous variables and haematological variables as the continuous variables. A p value of <0.05 was considered statistically significant in this study.

RESULTS

A total of 171 patients were enrolled in this study. Table I shows the demographic characteristics of the patients. All 171 patients had undergone OGD, only one had been subjected for DBE and 61 patients were proceeded with colonoscopy. Positive upper endoscopy findings were found in 85 patients (49.7%). Eighty-six patients with normal upper endoscopies were offered for lower endoscopy procedures but only 49 patients agreed. Thirty-nine patients who did not consent for lower endoscopy was due to refusal to drink three litres of bowel preparation fluid. Out of 49 patients, positive lower endoscopy findings were found in 22 patients (12.9%). Normal finding was noted from one DBE procedure. Of the total patients, 98 patients (57.3%) had GI lesions consistent with positive endoscopy findings from upper and lower endoscopy procedures.

Characteristics of patients with positive endoscopic finding were observed. Patients who were on RRT tend to have higher prevalence of positive endoscopic finding compared to those in the negative endoscopic finding group ($p = 0.036$). Age group, gender, race, and concurrent medications did not differ between the positive and negative endoscopic findings group ($p > 0.05$). Haematological parameter, iron panels, and iFOB of the positive endoscopic finding group were further evaluated (Table II). Out of 98 patients with positive endoscopic findings, 10 patients (10.9%) have microcytic anaemia, 67 patients (72.8%) have normocytic anaemia and the rest (16.3%) manifested as macrocytic anaemia (Table IV). Haematological parameters such as haemoglobin level, MCV, MCHC, MCH, serum iron, TIBC, TSAT, serum ferritin level, and iFOB were compared between the positive and negative endoscopic group. Only ferritin level less than 100 ng/mL and a combination of ferritin level less than 100 ng/ml and TSAT less than 20% showed a significant p value ($p < 0.05$), between the positive and negative endoscopic group (Table III). A positive correlation between serum ferritin level and CRP was 0.276 with significant p value of 0.038. ROC curves were plotted for all haematological variables and laboratory parameters, with endoscopic findings (positive and negative endoscopic group) as dichotomous variables to determine the sensitivity and specificity of each variable towards GI bleeding. However, none of these variables had a significant Area Under the Curve (AUC) of more than 0.75.

For OGD, gastritis, gastric ulcer, and duodenal ulcer were the most common lesions identified (Table IV). The prevalence of oesophageal, gastric, and duodenal lesions did not differ between the patients with CKD stages 3 to 5 ($p > 0.05$). Gastritis and duodenitis were found commonly in patients with CKD stages 3 and 4. However, gastric and duodenal ulcers were detected mostly in patients with CKD stage 5 who are on RRT. None of the ulcer cases were related to *Helicobacter pylori* or positive rapid urease test.

Out of 171 CKD subjects , 22 patients (12.9%) had positive colonoscopic findings related to anaemia. Colonic polyp size of less than 1 cm was the commoner lesions seen from the colonoscopy (Table IV). The prevalence of colonic lesions did not differ between subjects in all CKD stages 3 to 5 ($p = 0.503$). All colonoscopy had good Boston Bowel Preparation Scale (BPPS) score equal or more than 5. All the identified colonic polyps were removed endoscopically, and the suspicious cancerous lesions were biopsied. Samples were sent for further histopathology examination (HPE). Only two patients declined further endoscopic intervention; however, subsequent computed tomography scans were arranged for them, which showed malignant features of intraluminal lesions at duodenum and ascending colon. A total of 8.8% of malignant and pre-malignant lesions were detected from the lower endoscopy and 5.3% from the upper endoscopy based on HPE results (Table V). Two of the biopsied samples were not representing the lesions and were re-scheduled for repeat colonoscopy. The malignant pathologies include adenocarcinoma of stomach, intramucosal carcinoma (intestinal type) of stomach, mucosa-associated lymphoid tissue (MALT) lymphoma of duodenum, adenocarcinoma of ascending colon, and one HPE reported as foveolar metaplasia of the duodenum.

DISCUSSION

Based on Malaysian Demographic Profiles 2020, the country's ethnic groups are Bumiputera (69.4%), Chinese (23.2%) and Indian (6.7%) and others (0.7%)[13] Out of these, 6.8% of the population comprised of elderly with the age of 65 years and over.[13] Our study population represented a pattern of racial distribution almost similar to Kuala Lumpur population.

We conducted a prospective study to analyse the gastrointestinal pathological characteristic in elderly patients with CKD and to determine the prevalence of anaemia secondary to GI disorder in elderly with different stages of CKD. Anaemia in elderly population is not purely a

consequence of aging and should not be regarded as such. Apart from Erythropoietin Stimulating Agent (ESA) deficiency as a classical cause of anaemia in CKD population, other confounding causes should be evaluated especially in the elderly.[14] A thorough clinical evaluation and laboratory investigations are warranted to establish the aetiology of anaemia in elderly with CKD.

The incidence of anaemia secondary to GI disorder in adults with CKD has been reported in many previous studies. It has been found to be present in 20–75% of the population.[15-18] Hwang et al. reported that 52.9% of adult CKD patients in China were found to have bleeding-related GI lesion detected on endoscopy procedure. This finding was almost similar to our findings (57.3%); however, our study population primarily included elderly age group of more than 60 years, and did not consider the type of anaemia, whether iron deficiency anaemia or the associated erythropoietin stimulating agent (ESA) deficiency. Furthermore, it is alarming that 14% of the study participants showed either benign or malignant lesions.

From this study, we had found that those who are on RRT had a significant higher risk of GI disorder related to anaemia regardless of age, gender, and race ($p = 0.036$). Similar pattern had been observed previously by Jiing-Chyuan and colleagues.[19] They compared the incidence of GI bleeding between haemodialysis, control group, and CKD population and found higher incidence of ulcer bleeding among patients receiving haemodialysis compared to those with CKD or the control group ($p < 0.05$). This has been supported by another study from Japan by Sugimoto et al.[20] They conducted a cross-sectional study looking at the incidence of gastroduodenal ulcer in patients who are undergoing haemodialysis and healthy population. Higher rates of gastroduodenal ulcer were reported in the haemodialysis group compared to the normal population (17.8% versus 7.4%).[20] However, our study did not further classify those who are on haemodialysis or peritoneal dialysis. A plausible explanation to this finding is the use of anticoagulant during haemodialysis, commonly heparin, impaired healing ulcers due to intermittent hemodynamic instability of gastrointestinal tract during dialysis and worsening of the condition with concurrent existing ulcer that is commonly observed in those with advanced CKD with multiple co-morbidities. In general, anaemia in elderly CKD is commonly observed in female aged 65 years and above especially in African Americans with advancing CKD; however, our study has failed to demonstrate that age group, gender, and race have a significant relationship in determining anaemia-related GI lesion in elderly CKD population ($p > 0.05$).[20-23]

We also evaluated the haematological parameters, iron indices, and iFOBT to predict GI disorder consistent with anaemia. Iron deficiency anaemia (IDA) is closely related to GI blood loss. The classical markers in assessing IDA are percentage of TSAT, representing the transferrin availability for iron binding and ferritin level as a marker for iron store. In our study, we demonstrated that those patients with absolute IDA (serum ferritin less than 100 ng/ml and TSAT less than 20%) ($p=0.029$) and serum ferritin level less than 100ng/ml ($p=0.046$) have significant positive endoscopic findings from the upper and lower endoscopy. Thus, these markers are useful predictors for positive endoscopic lesion relation to anaemia in elderly patients with CKD. The pro-inflammatory marker CRP indirectly increases the synthesis of ferritin. Elevated serum ferritin level neither ruled out iron deficiency anaemia nor indicated elevated of replenished iron storage in CKD population as serum ferritin level also elevated in chronic active inflammation or infection. Persistent and low-grade inflammation has been recognised as an important component in CKD that may also lead to anaemia.[24] However low level of serum ferritin level is highly distinctive for IDA in CKD population.

Anaemia due to GI loss is often manifested as microcytosis, hypochromia, and increased erythropoiesis. Therefore, the values for MCV, MCHC, and MCH are expected to be low. However, these variables failed to predict the possibilities of positive endoscopic findings in our study. Majority of our study population manifested as normocytic normochromic anaemia rather than classical microcytic hypochromic anaemia. This might be explained by multiple confounding factors in CKD population including chronic inflammation and erythropoietin deficiency that could limit the appropriate red cell changes in this population. Hence, we suggest that in any changes of haematological indices, high, normal, or low value will not be able to rule out other causes of anaemia as per normal healthy elderly population. However, none of these variables showed a significant sensitivity or specificity in determining the incidence of anaemia related GI disorder in elderly CKD population.

Many studies have been conducted on several gastrointestinal lesions occurring in CKD population including End-Stage Renal Failure (ESRF) on RRT. In our study, we focused more on elderly patients aged 60 years and over with anaemia and CKD. To our knowledge, there has not been any other publications regarding this subject. We observed that the prevalence of each lesion is higher compared to adult CKD population. The prevalence of oesophagitis was 11.4% from our study and more commonly seen in those on RRT, slightly higher compared to other previous studies by Prakash et al., Sotoudehmanesh et al., and Hwang et al., 8.8%, 5.9%, and 1.9%, respectively, which looked at the adult population with CKD.[16,23,25] Gastritis and duodenitis occur frequently in adult CKD population especially those with advancing CKD and on RRT. Hwang et al. reported that about 17.3% of the patients were found to have erosive gastritis, 7.7% had haemorrhagic gastritis with 1.9% of erosive duodenitis and haemorrhagic duodenitis from their study population.[16] In our study, the prevalence of gastritis was about 23. 9% and duodenitis in 7.7% of patients. However, it will be premature to comment on this finding as our observation was based on macroscopic evaluation rather than histological analysis. Higher prevalence has been reported by Gheissari studied in ESRF population with the incidence of gastritis in 31% and haemorrhagic duodenitis in 20% of patients.[26] However, in our study we found that the incidence of gastritis and duodenitis was higher in CKD stages 3 and 4. Early initiation of protective agent such as Proton Pump Inhibitors (PPI) and histamine-2 receptor antagonist (H2RA) in elderly age group could explain why the incidence of GI inflammations was lesser in advanced CKD group in our study.

From our data, it was demonstrated that the prevalence of gastric and duodenal ulcers was significant, in 19.9% and 11.2%, respectively. Another study of the adult CKD population also shown a similar prevalence of duodenal ulcer in 7.7% to 11.0%.[16,23,27] The possibility of chronic uraemia renders the gastric mucosal more susceptible to acid injury due to reduction in mucosal prostaglandin content, and impaired mucosal resistance to acid injury could explain that CKD patient to be more prone to have gastric ulcer.[28] However, the exact pathophysiology of the mucosal lesion in this population is still unclear. A higher incidence of acid hypersecretion due to physiological stress of chronic illnesses and haemodialysis, concurrent use of ulcerogenic medications such as Non-Steroidal Anti-Inflammatory Agents (NSAIDS), and anticoagulant or antiplatelet for multiple co-morbidities are other contributing factors that might explain the higher incidence of gastric ulcer in the elderly CKD population.

From our data, 5.3% of the gastric lesion from upper endoscopy revealed a malignant and pre-malignant state of GI disorder.

Our study also investigated the lower GI lesion that was related to anaemia. The incidence of lower GI bleeding (LGIB) increases with age and is associated with age-specific related lesions such as malignancy.[29] In general, lower GI contribute about 85% of GI bleeding in elderly compared to 10% in upper GI and 5% in small intestine.[30] There is still a lack of specific data regarding the distribution of lower GI bleeding by location in adult CKD patients. Compared to Western Europe, the commonest causes of LGIB in Asian are haemorrhoid, fissure, and malignant colorectal neoplasms followed by benign colorectal neoplasm, ulcerative colitis, infectious colitis, ischaemic colitis, and radiation colitis.29 Similar to our study, we found colonic polyps in 37.7% of our study population, and colonic polyp size less than 1 centimetre was the commonest lesion detected from the colonoscopy (26.2%). Out of these numbers, 24.6% are proven histologically as malignant and pre-malignant state of lower GI lesions. These findings strongly support the recommendation that colonoscopy should be performed routinely in elderly aged more than 60 years with anaemia with CKD. From our data, the colonic lesions did not differ between various stages of CKD ($p > 0.005$).

Our results allow us to suggest the potential utility of upper and complete lower GI endoscopy, even in selected patients older than 85 years.

LIMITATIONS

First, we did not make it to the sample size calculated in view of time constraint. Second, limited information regarding the over-the-counter medication and protective factors for peptic ulcer disease, such as the use of Proton Pump Inhibitor (PPI) and histamine-2 receptor antagonist may limit the observation and inference from this study. Third, the practical utility of the indices studied was limited as we did not measure the erythropoietin level prior to this study. Fourth, we do not have a control group to compare our data with. Fifth, the practical utility of the indices studied was limited because we include patients who were treated with iron or erythropoiesis-stimulating agents in our study. Sixth, in view of selected anaemic cohort of CKD, geriatric patients were selected; therefore, the observed results may not totally represent the whole geriatric patients with CKD. Seventh, the sample size of the study was relatively small. Eight, the inability to perform colonoscopies or lower gastrointestinal endoscopies on all patients may not represent overall lower gastrointestinal tract abnormal findings.

RECOMMENDATIONS

Exploring the history of GI symptoms pertaining to bleeding, other co-morbidities, and the concurrent use of ulcerogenic and blood thinning medications might be a useful additional predictor for anaemia-related GI lesion in elderly patients with CKD. Initial evaluation of anaemia in elderly CKD patients should include a review of complete full blood count and iron panels. A normal MCV should not completely rule out either high or low MCV causes of anaemia. Concomitant absolute IDA must always be evaluated in the face of CKD and workup thoroughly if present. Endoscopy procedures should be performed routinely in elderly with anaemia in the setting of CKD for early detection of colorectal carcinoma and to offer early intervention as required. Our results allow us to suggest the potential utility of upper and complete lower GI endoscopy, even in selected patients older than 85 years.

CONCLUSION

The positive endoscopic findings related to anaemia are highly prevalent in elderly in various stages of CKD regardless of age group, gender, and race. The malignant and pre-malignant lesions are not uncommon amongst elderly patients with CKD. The GI inflammation and ulceration are frequent lesion observed in the elderly CKD population. Serum ferritin level and TSAT are useful indicators in determining anaemia-related GI disorder in this population. Endoscopic evaluation should not be excluded as it is an integral part of anaemia workup in elderly with CKD.

REFERENCES

1. Eisenstaedt R, Penninx BW, Woodman RC. Anemia in the elderly: Current understanding and emerging concepts. Blood Rev. 2006; 20(4): 213-26.
2. Cappellini MD, Motta I. Anemia in clinical practice-definition and classification: Does hemoglobin change with aging? Seminars in hematology. 2015; 52(4): 261-9.
3. Zakai NA, French B, Arnold AM, Newman AB, Fried LF, Robbins J, et al. Hemoglobin decline, function, and mortality in the elderly: the cardiovascular health study. Am J Hematol. 2013; 88(1): 5-9.
4. Argento V, Roylance J, Skudlarska B, Dainiak N, Amoateng-Adjepong Y. Anemia prevalence in a home visit geriatric population. Journal of the American Medical Directors Association. 2008; 9(6): 422-6.
5. Chernetsky A, Sofer O, Rafael C, Ben-Israel J. Prevalence and etiology of anemia in an institutionalized geriatric population. Harefuah. 2002; 141(7): 591-4.
6. Pedersen AJ, Skjelbo E. Anemia- Prevalence and aetiology among acutely admitted geriatric patients. Ugeskrift for Laeger. 2008; 170(17): 1453-7.
7. Halawi R, Moukhadder H, Taher A. Anemia in the elderly: A consequence of aging? Expert Review of Hematology. 2017: 1-9.

8. Patel KV. Epidemiology of anemia in older adults. Semin Hematol. 2008; 45(4): 210-7
9. Rockey DC, Cello JP. Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. N Engl J Med. 1993; 329(23): 1691-5.
10. Hwang HS, Song YM, Kim EO, Koh ES, Yoon HE, Chung SJ. Decisive indicator for gastrointestinal workout in anemic patients with nondialysis chronic kidney disease. Int J Med Sci 2012; 9(8): 634-42.
11. Toke AB. GI bleeding risk in patients undergoing dialysis. Gastrointestinal Endoscopy 2010; 71(1): 50-2.
12. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US Commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation 2014; 63(5): 713-35.
13. Department of Statistics Malaysia. (2020). Population by age group. [Cited April 2022] Accessed from https://dosm.gov.my
14. Winkelmayer WC, Mitani AA, Goldstein BA, Brookhart MA, Chertow GM. Trends in Anemia Care in Older Patients Approaching End-Stage Renal Disease in the United States (1995-2010). JAMA Intern Med. 2014; 174(5): 699-707.
15. Liang CC, Wang SM, Kuo HL, Chang CT, Liu JH, Lin HH, et al. Upper gastrointestinal bleeding in patients with CKD. Clinical Journal of the American Society of Nephrology: CJASN 2014; 9(8): 1354-9.
16. Hwang HS, Song YM, Kim EO, Koh ES, Yoon HE, Chung SJ, et al. Decisive indicator for gastrointestinal workup in anemic patients with nondialysis chronic kidney disease. International Journal of Medical Sciences 2012; 9(8): 634-41.
17. Akmal M, Sawelson S, Karubian F, Gadallah M. The prevalence and significance of occult blood loss in patients with pre-dialysis advanced chronic kidney disease or receiving dialystic therapy. Clin Nephrol. 1994; 42(3): 198-2.
18. Tawfik MA. A cross-sectional study by esophagogastroduodenoscopy for occult bleeding in chronic hemodialysis patients at Tanta in Egypt. Gastrointestinal Dig Syst. 2014; 4(6): 247.
19. Luo JC, Leu HB, Huang KW, Huang CC, Hou MC, Lin HC et al. Incidence of bleeding from gastroduodenal ulcers in patients with end-stage renal disease receiving hemodialysis. CMAJ. 2011; 183(18): E1345-51.
20. Sugimoto M, Sakai K, Kita M, Imanishi J, Yamaoka Y. Prevalence of Helicobacter pylori infection in long-term hemodialysis patients. Kidney International. 2009; 75(1): 96-103.
21. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PloS One 2014; 9(1): e84943.
22. Shaheen FA, Souqiyyeh MZ, Al-Attar BA, Karkar A, Al Jazairi AM, Badawi LS, et al. Prevalence of anemia in predialysis chronic kidney disease patients. Saudi Journal of Kidney Diseases and Transplantation: An Official Publication of the Saudi Center for Organ Transplantation, Saudi Arabia 2011; 22(3): 456-63.
23. Sotoudehmanesh R, Ali Asgari A, Ansari R, Nouraie M. Endoscopic findings in end-stage renal disease. Endoscopy 2003; 35(6): 502-5.
24. Akchurin OM, Kaskel F. Update on inflammation in chronic kidney disease. Blood Purification 2015; 39(1-3): 84-92.
25. Prakash J, Agrawal BK. Upper gastrointestinal mucosal lesions in chronic renal failure. Indian Journal of Gastroenterology: Official Journal of the Indian Society of Gastroenterology 1991; 10(4): 131-2.
26. Gheissari A, Rajyaguru V, Kumashiro R, Matsumoto T. Gastrointestinal hemorrhage in end stage renal disease patients. International Surgery 1990; 75(2): 93-5.
27. Tawfik MA. A cross-sectional study by esophagogastroduodenoscopy for occult bleeding in chronic hemodialysis patients at Tanta in Egypt. Gastrointestinal Digestive System 2014; 4: 6.
28. Quintero E, Kaunitz J, Nishizaki Y, De Giorgio R, Sternini C, Guth PH. Uremia increases gastric mucosal permeability and acid back-diffusion injury in the rat. Gastroenterology 1992; 103(6): 1762-8.
29. Chait MM. Lower gastrointestinal bleeding in the elderly. World Journal of Gastrointestinal Endoscopy 2010; 2(5): 147-54.
30. Sleisenger MH, Fordtran JS. 1989. Gastrointestinal disease: pathophysiology, diagnosis, management. 4th Edition. WBSaunders, Philadelphia

ORIGINAL ARTICLE

Predictors and radiological characteristics of rheumatoid arthritis-associated interstitial lung disease in a multi-ethnic Malaysian cohort

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that is commonly associated with extra-articular manifestations. Pulmonary disease is frequently encountered, which causes serious morbidity and increases mortality. Among the pulmonary manifestations, interstitial lung disease (ILD) is the most common. We aimed to analyse the frequency and clinical characteristics of a cohort of patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD); describe the radiological features of ILD; identify predictive factors for developing ILD; and evaluate the impact of ILD on patient survival.

Materials and Methods: This retrospective study included all patients with RA who attended the rheumatology clinic of Kuala Lumpur Hospital from 2018 to 2021. RA-ILD was identified from high-resolution computed tomography (HRCT) thorax images evaluated by two thoracic radiologists. Descriptive and logistic regression analyses were conducted using SPSS version 26.0.

Results: Of the 732 patients with RA, 7.4% (54) had ILD. Univariate analysis identified Indian ethnicity, rheumatoid factor (RF) positivity, anti-cyclic citrullinated peptide antibody titre, and diabetes mellitus as risk factors for developing ILD. Multivariable logistic regression showed that RA-ILD was positively associated with female gender [Adjusted odds ratio (aOR)=3.40 (95% confidence interval (CI): 1.04, 11.17)], Indian ethnicity [aOR=2.03 (95% CI: 1.16, 3.57)], and positive RF [aOR=2.39 (95% CI: 1.18, 4.87)]. Nonspecific interstitial pneumonia (NSIP) was the predominant HRCT pattern. Majority of patients had limited disease (<20% of lung involvement) and good functional exercise capacity. There was significant improvement ($p<0.05$) in mean forced vital capacity (FVC) following treatment with immunosuppressive agents. No mortality occurred throughout the median follow-up period of 3.2 years.

Conclusion: RA patients of Indian ethnicity had an increased risk for developing ILD, suggesting that genetics play a crucial role. Other independent predictors were female gender and RF positivity. The pattern of HRCT thorax and extent of lung involvement influenced prognosis and survival of patients with RA-ILD.

KEYWORDS:
Predictors, rheumatoid arthritis, interstitial lung disease, high-resolution computed tomography, prognosis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that most frequently affects the joints. If left untreated, RA can lead to progressive joint damage leaving patients with severe functional disability and loss of physical independence. Extra-articular manifestations are not uncommon and were reported to occur in approximately 40% of RA patients.[1] These manifestations include pulmonary disease, vasculitis, rheumatoid nodules, eye conditions, and cardiovascular disease. Pulmonary disease has been described to be the most frequently encountered extra-articular manifestation. Presentations of pulmonary involvement in RA are diverse, comprising parenchymal lung disease, pleural disease, pulmonary vascular disease, and airway complications. Of the pulmonary manifestations, interstitial lung disease (ILD) is the most common.[1,2]

The reported prevalence of ILD among patients with RA is exceedingly variable, ranging from 2% to 61%.[3-8] This wide variation is largely attributed to study design, case definition, method of detection, and population diversity. Several studies have shown that only a minority of patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) are symptomatic, indicating that asymptomatic RA-ILD is more prevalent.[7-9] Studies have also described that ILD can precede the onset of RA or develop during the initial few years of RA.[7,10-12] The prevalence of RA-ILD has been reported to increase with longer duration of RA.[5,12]

To date, high-resolution computed tomography (HRCT) thorax is regarded as the most appropriate tool to diagnose ILD because it has been demonstrated to be a sensitive

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technique for evaluation and detection of ILD.[8,13] Studies have demonstrated good correlation between the radiographic pattern found on HRCT thorax and the histopathologic pattern found on surgical lung biopsy for idiopathic pulmonary fibrosis (IPF), thus obviating the need for lung biopsy.[14] Likewise, this correlation was also demonstrated in the diagnosis of usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) in patients with RA-ILD, albeit the sample sizes of these studies were small.[11,15]

The most common HRCT patterns in RA-ILD are reportedly UIP and NSIP, with UIP being the predominant pattern.[11,15] Less common patterns are organising pneumonia (OP), lymphocytic interstitial pneumonia, desquamative interstitial pneumonia, and diffuse alveolar damage.

Cardiovascular disease has been found to be the leading cause of death among RA patients.[16] This was followed by respiratory diseases, in particular, ILD.[17] Survival in patients with RA-ILD was reportedly shortened compared to patients with RA alone.[4] In addition, patients with ILD have a greater risk for developing pulmonary hypertension, which adds to the degree of morbidity.

Even though ILD is a well-recognised complication of RA, its aetiology and pathogenesis remain unclear. Numerous studies have attempted to identify the risk factors for ILD, which, to date, have not been well ascertained given conflicting and inconsistent results. In addition, several treatment modalities, in particular, methotrexate and anti-TNF (tumour necrosis factor) inhibitors, have been reported to be associated with increased risk of RA-ILD.[18,19] Regrettably, an optimal therapeutic strategy for patients with RA-ILD remains to be determined.

Our objectives were to analyse the demographic and clinical characteristics of a cohort of multi-ethnic patients with RA-ILD; describe the patterns of ILD and extent of lung involvement from HRCT thorax; identify factors associated with an increased risk for developing ILD; and evaluate the impact of ILD on patient survival.

MATERIALS AND METHODS

This retrospective study was conducted at the rheumatology clinic of Hospital Kuala Lumpur. Medical records of all patients with RA between January 2018 and June 2021 were systematically reviewed. All patients met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA.[20] Patients diagnosed with RA-ILD were identified. Those who had incomplete medical records were excluded from the study. Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia, and registration was done in accordance with the National Medical Research Register Malaysia (NMRR-19-3450-52128).

The following data were obtained: patient demographics, duration of RA, duration from onset of RA to the diagnosis of RA-ILD from HRCT thorax, and disease activity score with 28-joint counts (DAS28) for RA using C-reactive protein at the time when HRCT thorax was performed.[21] Clinical data included history of ever smoking, body mass index (BMI), hypertension, diabetes mellitus, dyslipidaemia, and coronary heart disease. Respiratory symptoms and signs included non-productive cough for at least one month, exertional dyspnoea, bibasilar fine inspiratory crepitations, modified Medical Research Council (mMRC) dyspnoea scale, and findings suggestive of pulmonary fibrosis on plain chest radiography.[22] Laboratory parameters included rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) titre.

Patients who had undergone HRCT thorax examination were scrutinised. Medical records showed that patients who had clinical indications for ILD were subjected to HRCT thorax. The indications included respiratory symptoms or signs suspicious of ILD. Scan images were retrieved and evaluated independently by two thoracic radiologists, and the final scan findings were determined by consensus. Scans that were interpreted as ILD were identified. Radiological patterns were determined based on recommendations of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society clinical practice guidelines.[23] HRCT patterns were categorised as UIP, NSIP, OP, combination of NSIP and OP (NSIP-OP), probable UIP, indeterminate for UIP, and non-idiopathic pulmonary fibrosis (non-IPF). Each lung was divided axially into three zones and scored for the percentage of lung involvement, from which an average was calculated. Based on the percentage of lung involved, disease extent was further defined as limited (<20% of lung involvement) and extensive (≥20% of lung involvement) disease.[24]

With regard to treatment for RA, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) ever received prior to and after HRCT thorax were recorded. Drug treatment ever received for RA-ILD, including dosage and duration of therapy, was documented. Forced vital capacity (FVC) measurements at baseline and after treatment for ILD were obtained. FVC value was expressed as percentage of predicted.

Statistical Analysis

Categorical variables were presented as frequencies and percentages. Normally distributed variables were presented as mean and standard deviation (SD), while non-normally distributed variables were reported as median and interquartile range (IQR).

Pearson Chi-Square test was used to analyse the significance of association between each variable and RA-ILD. Two-sided $p<0.05$ was considered statistically significant. A logistic regression model was used to produce a crude odds ratio (OR) as a measure of the associations between the development of RA-ILD and the independent variables. For the final model, a forward likelihood ratio variable selection method was used to identify significant variables. Only variables with p values of <0.25 were entered into the multivariable logistic regression model. The adjusted odds ratio (aOR), with the respective 95% confidence interval (CI), was then calculated. A p value of <0.05 was considered significant. The model fit was tested using the Hosmer–Lemeshow statistic, which was non-significant ($p>0.05$). Comparison of continuous variables was made using independent t-test for normally

distributed data; otherwise, Mann–Whitney U test was applied. Descriptive and logistic regression analyses were conducted using the IBM Statistical Package for the Social Sciences (SPSS) software for Windows, Version 26.0.

RESULTS

A total of 732 patients with RA were identified. Demographic and clinical characteristics of the whole cohort are shown in Table I. Six hundred and twenty-three (85.1%) patients were female. Female gender was predominant in both groups of RA patients with and without ILD. Mean age at onset of RA was 48.9 (SD 13.4) years and median duration of RA was 8 (IQR 8) years.

ILD was present in 7.4% (54/732) of RA patients. Among the various ethnic groups, the frequency of ILD was highest among patients of Indian ethnicity at 51.9% (28/54), followed by Malay (31.5%) and Chinese (14.8%). Forty-four (81.5%) patients with ILD had positive rheumatoid factor (RF) and 37 (71.2%) had positive ACPA. Median ACPA titre was 199 (IQR 565) IU/ml. Six (11.1%) patients had other associated connective tissue diseases: three (5.6%) had systemic lupus erythematosus, two (3.7%) had systemic sclerosis, and one (1.8%) had polymyositis. With regard to comorbidities, 24 (44.4%) had dyslipidaemia, 20 (37%) had hypertension, 19 (35.2%) had diabetes mellitus, and five (9.3%) had coronary heart disease. Mean body mass index (BMI) was 27.5 (SD 6.4) kg/m^2 (Table II).

Past or current smoking was uncommon among our cohort of RA patients, with a frequency of under 10%. Among the patients with ILD, only 3 (5.6%) patients were smokers, and they were all men. In terms of csDMARD therapy for treatment of RA, majority (80.2%) of the patients received methotrexate. The percentage of patients receiving methotrexate in the group with ILD and without ILD was significantly different ($p<0.001$), wherein methotrexate use was significantly lower in RA patients with ILD.

Table II summarises the clinical characteristics of patients with RA-ILD. Mean age at diagnosis of RA-ILD was 55.8 (SD 11.7) years. Median duration from onset of RA to the diagnosis of ILD was 3.5 (IQR 5.2) years. ILD was diagnosed in eight (14.8%) patients within the first year of onset of RA, another nine (16.7%) by the second year of disease, and a further nine (16.7%) by the third year. This indicated that ILD developed in the early phase of RA. Mean DAS28 score at the point of HRCT thorax was 3.32 (SD 1.25), which was classified as moderate disease activity.

Median follow-up period after diagnosis of RA-ILD was 3.2 (IQR 3.8) years, with the longest duration of follow-up at 12.9 years. No mortality occurred throughout the follow-up period.

In terms of respiratory symptoms among the 54 patients with ILD, 15 (27.8%) experienced non-productive cough and 14 (25.9%) had exertional dyspnoea. Bibasilar fine inspiratory crepitations were detected in 48 (88.9%) patients, and 16 (29.6%) patients had findings suggestive of pulmonary fibrosis on chest radiographs. None of the patients developed pulmonary hypertension.

With regard to HRCT pattern, NSIP was the most frequently observed ILD pattern, at 44.5% (24/54) (Table III). This was followed by probable UIP at 18.5% (10/54), UIP in 11.1% (6/54), NSIP-OP in 9.3% (5/54), and OP in 9.3% (5/54). In terms of the extent of lung involvement, majority (88.9%) of patients had limited disease (<20% lung involvement). Baseline FVC was 63.3% (SD 13.4) predicted and 54.6% (SD 15.6) predicted in the groups classified as limited disease and extensive disease, respectively. There was no statistically significant difference in baseline FVC between patients with varying disease extent.

Baseline mMRC dyspnoea scale upon the diagnosis of ILD showed that a high proportion of patients (42/49, 85.8%) had scores of 0 and 1 (Table II). Five patients were not assessed because of significant arthritis involving the lower limbs. Baseline FVC was available for 45 (83.3%) patients with ILD. All of them showed a restrictive ventilatory defect. Mean baseline value of FVC was 62.4% (SD 13.8) predicted.

Thirty (55.6%) patients received treatment for ILD, of whom 27 received prednisolone alone, two received combination therapy with prednisolone and azathioprine, and one received mycophenolate mofetil. One of the two patients who received combination therapy had concomitant polymyositis; the patient who received mycophenolate mofetil had coexisting systemic sclerosis. Mean maximal dosage of prednisolone was 33.4 mg (SD 15.6) daily, with doses ranging from 15 mg to 75 mg daily. Median duration of treatment with prednisolone was 16 (IQR 13) weeks. Among the 29 patients who received prednisolone therapy, 16 had NSIP, four had NSIP-OP, four had OP, three had probable UIP, and two had UIP. The lone patient who received mycophenolate mofetil had NSIP pattern.

Baseline FVC was available in 26 of the 30 patients who received treatment for ILD. Mean baseline FVC value was 58.1% (SD 14.0) predicted. Nineteen patients had FVC measured pre- and post-treatment. Statistical analysis showed a significant improvement in mean FVC after treatment for ILD ($p<0.05$), whereby mean FVC pre-treatment was 56.4% (SD 14.4) predicted and mean FVC post-treatment was 61.6% (13.4) predicted.

Predictive Factors for RA-ILD

Table IV depicts the univariate and multivariable logistic regression analyses taken to examine risk factors associated with the development of RA-ILD. In univariate analyses, Indian ethnicity, RF positivity, higher titres of ACPA, and diabetes mellitus were associated with the development of RA-ILD. Multivariable analysis identified female gender, Indian ethnicity, and RF positivity as independent risk factors for developing ILD. Women had a 3.4-fold greater risk for RA-ILD [aOR=3.4 (95% CI: 1.04, 11.17)] compared to men. RA patients of Indian ethnicity had a two-fold increased risk compared to other ethnic groups [aOR=2.03 (95% CI: 1.16, 3.57)], and those with RF positivity were 2.39 times more likely to be associated with RA-ILD [aOR:2.39 (95% CI:1.18, 4.87)].

Table I: Demographic and clinical characteristics of a multi-ethnic cohort of 732 patients with RA

Variable	All patients with RA (n=732)	RA without ILD (n=678)	RA with ILD (n=54)	p value
Gender, n (%)				0.045*
Male	109 (14.9)	106 (15.6)	3 (5.6)	
Female	623 (85.1)	572 (84.4)	51 (94.4)	
Ethnicity, n (%)				0.062
Malay	317 (43.3)	300 (44.2)	17 (31.5)	
Chinese	147 (20.1)	139 (20.5)	8 (14.8)	
Indian	259 (35.4)	231 (34.1)	28 (51.9)	
Others	9 (1.2)	8 (1.2)	1 (1.8)	0.062
Mean age (SD), years	58.1 (13.4)	58.0 (13.5)	59.6 (11.9)	0.417
Mean age at onset of RA (SD), years	48.9 (13.4)	48.8 (13.4)	50.3 (13.0)	0.427
Median duration of RA (IQR), years	8 (8)	8 (8)	7 (7)	0.896
Rheumatoid factor positivity, n (%)	478 (66.8) (n=716)	434 (65.6)	44 (81.5)	0.017*
ACPA positivity, n (%)	433 (66.9) (n=647)	396 (66.6) (n=595)	37 (71.2) (n=52)	0.499
Median ACPA titre (IQR), U/ml	95 (338)	87 (338)	199 (565)	0.004*
Comorbidities, n (%)				
Smoking (ever)	65 (8.9)	62 (9.1)	3 (5.6)	0.465
Hypertension	268 (36.6)	248 (36.6)	20 (37.0)	0.946
Diabetes mellitus	169 (23.1)	150 (22.1)	19 (35.2)	0.028*
Dyslipidaemia	270 (36.9)	246 (36.3)	24 (44.4)	0.232
Coronary heart disease	51 (7.0)	46 (6.8)	5 (9.3)	0.414
csDMARDs, n (%)				
Methotrexate	587 (80.2)	555 (81.9)	32 (59.3)	0.000*
Sulfasalazine	408 (55.7)	378 (55.8)	30 (55.6)	0.978
Leflunomide	195 (26.6)	185 (27.3)	10 (18.5)	0.161
Hydroxychloroquine	131 (17.9)	123 (18.1)	8 (14.8)	0.539

*denotes significant p value of <0.05.
RA: rheumatoid arthritis; ILD: interstitial lung disease; SD: standard deviation; IQR: interquartile range; ACPA: anti-cyclic citrullinated peptide antibody; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs

DISCUSSION

Our data showed that the frequency of ILD in 732 multi-ethnic patients with RA was 7.4%, almost similar to that reported by Bongartz et al. where the incidence was 7.7% among 582 patients with RA.[4] We wish to highlight that the medical records of our RA patients showed that HRCT thorax was not ordered at random but directed at patients who exhibited pulmonary symptoms or clinical signs suggestive of ILD. Therefore, asymptomatic patients with ILD were inevitably precluded. As a comparison, studies where all RA patients were subjected to routine HRCT thorax showed a higher frequency of RA-ILD. Yin et al. reported 24.9% of patients with ILD, Gabbay et al. 33%, Zhang et al. 43.1%, and Chen et al. 61%.[5-8] A significant proportion of patients with RA-ILD were asymptomatic as demonstrated by Gabbay et al. (44%) and Chen et al. (55%).[7,8]

It has been widely reported that male gender, older age, smoking, and RF and ACPA positivity indicate greater risk for the development of ILD.[4,5,24,25] In our study, multivariate analyses identified female gender, Indian ethnicity, and RF positivity as predictive factors for developing ILD. The female to male ratio in our patients with RA was approximately 6:1, while the ratio for patients with RA-ILD was 17:1

Given our multi-ethnic population in Malaysia, our data revealed that the risk for developing ILD was significantly higher in patients of Indian ethnicity (p<0.05). Indian patients constituted 51.9% of the total number of patients with RA-ILD, albeit the proportion of Indian patients with RA was 35.4%. This finding is not consistent with the demographic of Malaysia wherein individuals of Indian ethnicity constitute a mere 6.8% of the population. For the information of our readers, the predominant ethnic group in Malaysia is Malay, comprising 69.6% of the population, followed by Chinese at 22.6%.[26] Of note, an earlier research conducted in Malaysia by Shahrir et al. identified Indian as the predominant (54.5%) ethnic group among patients with RA.[27] Interestingly, a research conducted in multi-ethnic South Africa also found that the majority of their patients with RA-ILD were of Indian ethnicity, comprising 72.1%, when in fact the same ethnic group constituted only 7.9% of the entire population.[28] These observations strongly suggest that ethnic Indians are more susceptible to developing RA as well as RA-ILD, indicating the impact of genetic factors.

RF and ACPA are biomarkers that are useful in the diagnosis of RA, and they have also been shown to be associated with more aggressive disease.[37] Nonetheless, the association between seropositivity for RF and ACPA in relation to RA-ILD remains controversial. Chen et al. and Ghammo et al.[8,28] failed to show any association between RF and ACPA positivity with RA-ILD, while Yin et al., Kelly et al., and Zhu et al. managed to demonstrate statistically significant positive correlation.[5,24,30] In our study, the presence of RF, but not ACPA, was strongly associated with the development of

Table II: Clinical characteristics of 54 patients with RA-ILD

Characteristics	Number (%)	Mean (SD)	Median (IQR)	Range
Age at diagnosis of RA-ILD, years		55.8 (11.7)		26.4-80.8
Duration from onset of RA to diagnosis of RA-ILD, years			3.5 (5.2)	0.17-30.5
Duration of follow-up after dx of RA-ILD, years			3.2 (3.8)	0.25-12.9
DAS28 at the time of HRCT thorax (n=50)		3.32 (1.25)		
BMI, kg/m^2 (n=53)		27.5 (6.4)		
Respiratory symptoms and signs				
Non-productive cough	15 (27.8)			
Exertional dyspnoea	14 (25.9)			
Bibasilar fine crepitations	48 (88.9)			
Features of pulmonary fibrosis on chest radiograph	16 (29.6)			
mMRC dyspnoea scale (n=49)				
Score 0	24 (49.0)			
Score 1	18 (36.8)			
Score 2	6 (12.2)			
Score 3	1 (2.0)			
Baseline FVC, % predicted (n=45)		62.4 (13.8)		
Treatment for ILD				
Prednisolone	29 (53.7)			
- Maximal dose, mg/day		33.4 (15.6)		10-75
- Duration of treatment, weeks			16 (13)	10-57
Azathioprine	2 (3.7)			
- Maximal dose, mg/day		150		
Mycophenolate mofetil	1 (1.9)			
- Maximal dose, g/day		2		
Survival status				
Alive	54 (100)			
Not alive	0 (0)			

Where n is not stated, it indicates 54 subjects.
HRCT: high-resolution computed tomography; SD: standard deviation; IQR: interquartile range; DAS 28: disease activity score for 28 joints; BMI: body mass index; mMRC: modified Medical Research Council; FVC: forced vital capacity

Table III: Radiological patterns of ILD and pulmonary function in patients with RA-ILD

		HRCT thorax	
HRCT thorax	**Patients with RA-ILD, number (%) n=54**	**Extent of lung involvement, number (%)**	
		Limited disease (<20%), n=48	**Extensive disease (≥20%), n=6**
UIP	6 (11.1)	4	2
Probable UIP	10 (18.5)	10	0
Indeterminate for UIP	2 (3.7)	2	0
NSIP	24 (44.4)	21	3
NSIP-OP	5 (9.3)	5	0
OP	5 (9.3)	4	1
Non-IPF	2 (3.7)	2	0
Pulmonary function	**Limited disease**	**Extensive disease**	**p value**
FVC (SD), % predicted	63.3 (13.4)	54.6 (15.6)	0.184

HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity

Table IV: Unadjusted and adjusted odds ratio of clinical associations for development of RA-ILD

	Unadjusted OR		Adjusted OR (aOR)	
	OR (95% CI)	p value	aOR (95% CI)	p value
Gender				
Female	3.150 (0.965, 10.280)	0.057	3.404 (1.037, 11.169)	0.043*
Ethnicity				
Indian	2.084 (1.194, 3.637)	0.010*	2.032 (1.158, 3.565)	0.013*
Age	1.009 (0.988, 1.031)	0.416	-	-
Age at onset of RA	1.009 (0.988, 1.030)	0.426	-	-
Duration of RA	0.995 (0.958, 1.034)	0.802	-	-
RF	2.312 (1.142, 4.679)	0.020*	2.394 (1.177, 4.867)	0.016*
ACPA	1.240 (0.664, 2.313)	0.500	-	-
ACPA titre	1.001 (1.000, 1.003)	0.010*	1.001 (1.000, 1.002)	0.181
Smoking, ever	0.584 (0.177, 1.927)	0.378	-	-
Hypertension	1.020 (0.574, 1.811)	0.946	-	-
Diabetes mellitus	1.911 (1.062, 3.438)	0.031*	1.653 (0.814, 3.358)	0.165
Dyslipidaemia	1.405 (0.803, 2.457)	0.233	1.233 (0.635, 2.395)	0.537
Coronary heart disease	1.402 (0.533, 3.689)	0.494		

*denotes significant p value of <0.05.
OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval; RF: rheumatoid factor; ACPA: anti-cyclic citrullinated peptide antibody

ILD. On univariate analysis, higher titres of ACPA showed a significant correlation with ILD compared to patients without ILD (199 U/ml in ILD group vs. 87 U/ml in non-ILD group, p<0.01). However, the significance of ACPA titre appeared less evident on multivariable analysis. This discrepancy may be attributed to the fact that data on ACPA were unavailable in 11.6% of patients. High titres of ACPA have been reported as risk factors for ILD from multivariate analysis.[25,31] Given these evidences, it is conceivable that higher levels of ACPA may well be predictive for the development of RA-ILD.

Several authors have found that older age and older age at onset of RA were significantly associated with the development of ILD.[4-6,8,12,25,31] Nonetheless, our cohort failed to demonstrate any correlation in terms of age of patients or age at onset of RA. In addition, there was no significant relationship between duration of RA with occurrence of RA-ILD.

The median duration from the onset of RA to the diagnosis of RA-ILD was 3.5 years. Of the 54 patients with RA-ILD, 26 (48.1%) patients were detected to have ILD within 3 years from the onset of RA, and 36 (66.7%) had ILD by 5 years. In our study, ILD presented early in the course of RA, consistent with findings in previous studies.[7,9,12]

We also examined the presence of comorbidities in relation to RA-ILD. Among the various comorbidities, only diabetes mellitus showed a significant association with RA-ILD on univariate analysis. Hypertension, dyslipidaemia, and coronary heart disease failed to demonstrate positive correlation. Ehrlich et al. have reported that patients with diabetes mellitus were at increased risk for pulmonary fibrosis, even though the exact mechanism and causal relationship have yet to be established.[32]

Smoking has been identified as an important risk factor for the development of RA in earlier epidemiological studies.[33,34] Among our patients, past or active smoking did not show significant association with RA-ILD. The correlation between smoking and risk of ILD is still debatable. Several studies demonstrated a positive association, while others did not.[5,6,9,12,25,35] Interestingly, Kronzer et al. found that among patients with RA who smoked, heavier smokers had a higher risk of developing ILD.[35] Of note, the prevalence of smoking was low among our patients, and this may have an impact on the analysis of this variable as a predictive factor for the development of ILD.

Among our RA patients who had clinical indications for HRCT thorax, findings of bibasal fine crepitations were more frequent than the presence of respiratory symptoms. This reiterated the fact that patients with RA-ILD are generally asymptomatic, unlike patients with IPF or other connective tissue diseases.[7-9] Therefore, we would like to emphasise to physicians that careful physical examination of RA patients is crucial. A greater proportion (85.7%) of our patients with RA-ILD had mMRC dyspnoea scale of 0 and 1, indicating mild disease or clinically insignificant disease. This was corroborated by the fact that 88.9% (48/54) of them had limited disease (<20% of lung involvement).

It is widely recognised that UIP is the predominant radiological pattern of ILD in patients with RA.[11,15,24,31,36] Nonetheless, this is in contrast to our data, which demonstrated that NSIP was the most frequent pattern, accounting for almost 45% of patients. Interestingly, the frequency of UIP pattern among our patients was considerably lower, at 11.1%. Our findings confirmed the observations described by Zhang et al.[6] Several authors have reported that patients with UIP pattern had poorer prognosis with worse survival when compared to patients with non-UIP patterns.[10,24,37,38]

In our study, no mortality occurred throughout the median follow-up period of 3.2 years (ranging from 0.25 to 12.9 years) after the diagnosis of RA-ILD was established. This could be explained by the low frequency of UIP among our patients, the higher proportion of patients who had limited disease on HRCT thorax, and a favourable response to immunosuppressive agents in the treatment for ILD. Data from a multi-centre study conducted by Kelly et al. found that

patients with extensive disease had an increased risk of mortality.[24] With regard to treatment for ILD, Lee et al. showed that patients with NSIP generally responded well to corticosteroids, thus improving survival.[39] To date, current recommendations on the optimal therapeutic regime for RA-ILD remains to be determined.

For the interest of our readers, mycophenolate mofetil (MMF) was prescribed to the patient with RA-ILD who had coexisting systemic sclerosis.

Methotrexate is generally considered as the first-line DMARD agent for treatment of RA. The present study confirmed that majority of our RA patients received methotrexate. However, the proportion of patients receiving methotrexate was significantly lower ($p<0.05$) in the ILD group compared to the group without ILD. It is conceivable that the reluctance to prescribe methotrexate in patients with RA-ILD stemmed from reported occurrence of methotrexate-induced lung injury in patients with RA.[18] Nevertheless, a recent systematic literature review by Fragoulis et al. reported a lack of association between methotrexate and development of ILD in RA patients.[40] This evidence should prompt us to re-consider a change in our therapeutic approach with regard to the use of methotrexate in patients with RA-ILD. Even though it is not advisable to commence methotrexate in RA patients with compromised respiratory reserve, the use of methotrexate is not an absolute contraindication in patients with pre-existing ILD who have reasonable respiratory function.

Several limitations in this study were identified. This is a retrospective, single-centre study; involvement of multiple centres may provide more meaningful results. The missing data on ACPA titres may have contributed to the negative predictive effect of ACPA titre for ILD in multivariate analysis, when in fact there was positive association on univariate analysis. The short duration of follow-up after the diagnosis of ILD was established may not have reflected the actual mortality rate associated with RA-ILD. A study with longer follow-up may be helpful in determining survival in patients with RA-ILD.

Nonetheless, there are several strong points in our study. The large sample size of RA patients allowed us to evaluate the frequency of RA-ILD more effectively. Multiple clinical and laboratory variables were analysed to determine the predictive factors for developing ILD. We categorised the disease extent to further understand the characteristics of ILD in our RA patients.

In conclusion, female gender, Indian ethnicity, and RF positivity were independent predictors for the development of RA-ILD. Higher ACPA titres and presence of diabetes mellitus were also predictive of ILD, albeit in univariate analysis. NSIP was the predominant radiological pattern on HRCT thorax, with the majority of patients having limited disease. Even though this study was not designed to compare with ILD in IPF or other connective tissue diseases, RA-ILD in our cohort appeared to be less severe with better prognosis. Finally, there remains a pressing need for collaboration in randomised controlled trials in order to generate robust evidence to determine recommendations and guidance on the optimal therapeutic approach for patients with RA-ILD.

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CONFLICTS OF INTEREST / COMPETING INTEREST

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REFERENCES

1. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: Incidence trends and risk factors over 46 years. Ann Rheum Dis 2003; 62(8): 722-7.
2. Brown KK. Rheumatoid lung disease. Proc Am Thorac Soc 2007; 4(5): 443-8.
3. Kim D, Cho SK, Choi CB, Choe JY, Chung WT, Hong SJ, et al. Impact of interstitial lung disease on mortality of patients with rheumatoid arthritis. Rheumatol Int 2017; 37(10): 1735-45.
4. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: A population-based study. Arthritis Rheum 2010; 62(6): 1583-91.
5. Yin Y, Liang D, Zhao L, Li Y, Liu W, Ren Y, et al. Anti-cyclic citrullinated peptide antibody is associated with interstitial lung disease in patients with rheumatoid arthritis. PLoS One 2014; 9(4); e92449. DOI: 10.1371/journal.pone.0092449.
6. Zhang Y, Li H, Wu N, Dong X, Zheng Y. Retrospective study of the clinical characteristics and risk factors of rheumatoid arthritis-associated interstitial lung disease. Clin Rheumatol 2017; 36(4): 817-23.
7. Gabbay E, Tarala R, Will R, Carroll G, Adler B, Cameron D, et al. Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med 1997; 156(2): 528-35.
8. Chen J, Shi YH, Wang XP, Huang H, Ascherman D. Asymptomatic preclinical rheumatoid arthritis-associated interstitial lung disease. Clin Dev Immunol 2013; 2013: 406927. DOI: 10.1155/2013/406927.
9. Gochuico BR, Avila NA, Chow CK, Novero LJ, Wu HP, Ren P, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med 2008; 168(2): 159-66.
10. Tsuchiya Y, Takayanagi N, Sugiura H, Miyahara Y, Tokunaga D, Kawabata Y, et al. Lung diseases directly associated with rheumatoid arthritis and their relationship to outcome. Eur Respir J 2011; 37(6): 1141-7.
11. Lee HK, Kim DS, Yoo B, Seo JB, Rho JY, Colby TV, et al. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest 2005; 127(6): 2019-27.
12. Koduri G, Norton S, Young A, Cox N, Davies P, Devlin J, et al. ERAS (Early Rheumatoid Arthritis Study). Rheumatology (Oxford) 2010; 49(8): 1483-9.
13. Biederer J, Schnabel A, Muhle C, Gross WL, Heller M, Reuter M. Correlation between HRCT findings, pulmonary function tests and bronchoalveolar lavage cytology in interstitial lung disease associated with rheumatoid arthritis. Eur Radiol 2004; 14(2): 272-80.
14. Hunninghake GW, Zimmerman MB, Schwartz DA, King Jr TE, Lynch J, Hegele R, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2001; 164(2): 193-6.

15. Tanaka N, Kim JS, Newell JD, Brown KK, Cool CD, Meehan R, et al. Rheumatoid arthritis-related lung diseases: CT findings. Radiology 2004; 232(1): 81-91.
16. Sihvonen S, Korpela M, Laippala P, Mustonen J, Pasternack A. Death rates and causes of death in patients with rheumatoid arthritis: A population-based study. Scand J Rheumatol 2004; 33(4): 221-7.
17. Young A, Koduri G, Batley M, Kulinskaya E, Gough A, Norton S, et al. Early Rheumatoid Arthritis Study (ERAS) group. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology (Oxford) 2007; 46(2): 350-7.
18. Kremer JM, Alarcón GS, Weinblatt ME, Kaymakcian MV, Macaluso M, Cannon GW, et al. Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis: A multicenter study with literature review. Arthritis Rheum 1997; 40(10): 1829-37.
19. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: Analysis of 122 cases. Semin Arthritis Rheum 2011; 41(2): 256-64.
20. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham 3rd CO, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62(9): 2569-81.
21. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res (Hoboken) 2012; 64(5): 640-7.
22. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988; 93(3): 580-6.
23. Raghu G, Remi-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/AAT clinical practice guideline. Am J Respir Crit Care Med 2018; 198(5): e44-e68. DOI: 10.1164/rccm.201807-1255ST.
24. Kelly CA, Saravanan V, Nisar M, Arthanari S, Woodhead FA, Price-Forbes AN, et al. British Rheumatoid Interstitial Lung (BRILL) Network. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics – a large multicentre UK study. Rheumatology (Oxford) 2014; 53(9): 1676-82.
25. Wang JX, Du CG. A retrospective study of clinical characteristics of interstitial lung disease associated with rheumatoid arthritis in Chinese patients. Med Sci Monit 2015; 21: 708-15.
26. Department of Statistics Malaysia – Current population estimates, Malaysia, 2020.
27. Shahrir M, Shahdan M, Shahid M, Sulaiman W, Mokhtar AM, Othman M, et al. Multicentre survey of rheumatoid arthritis patients from Ministry of Health rheumatology centers in Malaysia. Int J Rheum Dis 2008; 11(3): 287-92.
28. Ghammo H, Mitha M, Connolly C, Nyamande K. Rheumatoid arthritis associated interstitial lung disease in KwaZulu-Natal, South Africa: A retrospective 5-year review. Int J Respir Pulm Med 2020; 7: 132. DOI: 10.23937/2378-3516/1410132.
29. Korkmaz C, Us T, Kaşifoğlu T, Akgün Y. Anti-cyclic citrullinated peptide (CCP) antibodies in patients with long-standing rheumatoid arthritis and their relationship with extra-articular manifestations. Clin Biochem 2006; 39(10): 961-5.
30. Zhu J, Zhou Y, Chen X, Li J. A metaanalysis of the increased risk of rheumatoid arthritis-related pulmonary disease as a result of serum anticitrullinated protein antibody positivity. J Rheumatol 2014; 41(7): 1282-9.
31. Salaffi F, Carotti M, Di Carlo M, Tardella M, Giovagnoni A. High-resolution computed tomography of the lung in patients with rheumatoid arthritis: Prevalence of interstitial lung disease involvement and determinants of abnormalities. Medicine (Baltimore) 2019; 98(38): e17088. DOI: 10.1097/MD.0000000000017088.
32. Ehrlich SF, Quesenberry Jr CP, Van den Eeden SK. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. Diabetes Care 2010; 33(1): 55-60.
33. Uhlig T, Hagen KB, Kvien TK. Current tobacco smoking, formal education, and the risk of rheumatoid arthritis. J. Rheumatol 1999; 26(1): 47-54.
34. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: A meta-analysis of observational studies. Ann Rheum Dis 2010; 69(1): 70-81.
35. Kronzer VL, Huang W, Dellaripa PF, Huang S, Feathers V, Lu B, et al. Lifestyle and clinical risk factors for incident rheumatoid arthritis-associated interstitial lung disease. J Rheumatol 2021; 48(5): 656-63.
36. Solomon JJ, Chung JH, Cosgrove GP, Demoruelle MK, Fernandez-Perez ER, Fischer A, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2016; 47(2): 588-96.
37. Kim EJ, Elicker BM, Maldonado F, Webb WR, Ryu JH, Van Uden JH, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2010; 35(6): 1322-8.
38. Nieto MA, Rodriguez-Nieto MJ, Sanchez-Pernaute O, Romero-Bueno F, Leon L, Vadillo C, et al. Mortality rate in rheumatoid arthritis-related interstitial lung disease: The role of radiographic patterns. BMC Pulm Med 2021; 21: 205. DOI: 10.1186/s12890-021-01569-5.
39. Lee JY, Jin SM, Lee BJ, Chung DH, Jang BG, Park HS, et al. Treatment response and long term follow-up results of nonspecific interstitial pneumonia. J Korean Med Sci 2012; 27(6): 661-7.
40. Fragoulis GE, Conway R, Nikiphorou E. Methotrexate and interstitial lung disease: Controversies and questions. A narrative review of the literature. Rheumatology (Oxford) 2019; 58(11): 1900-6.

ORIGINAL ARTICLE

Adverse events following BNT162b2 mRNA COVID-19 vaccination among healthcare workers: A single-centre experience in Malaysia

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ABSTRACT

Introduction: The COVID-19 pandemic is a global health crisis that has resulted in a massive disease burden worldwide. Mass vaccination plays an important role in controlling the spread and severity of COVID-19 infections worldwide.

Materials and Methods: A cross-sectional study was conducted in Hospital Tuanku Ja'afar Seremban between 1 March 2021 and 4 May 2021 to describe the adverse events (AE) following BNT162b2 (Pfizer-BioNTech) vaccination. Healthcare personnel who received at least one dose of the vaccine were invited to complete an online questionnaire.

Results: Of 2282 analysed samples, AE were experienced in up to 64.5% (n=1472) of the study participants. Most AE were encountered after the second dose (56.5%, n=832). Pain at the injection site (41.5%, n=944), fever (35.1%, n=798) and lethargy (34.8%, n=792) were the most commonly reported AE. Severe AEFI were reported in a minority (2.9%, n=68). There were no documented anaphylaxis, vaccine-induced thrombosis, or myocarditis. The proportion of female recipients and recipients with a history of allergy were higher in the AE group compared to the non-AE group.

Conclusion: Our study reinforces the safety of the BNT162b2 mRNA vaccine in the local population. The main adverse events were mild, although they occurred in most patients.

KEYWORDS:
COVID-19, SARS-CoV-2, vaccines, adverse events

INTRODUCTION

The emergence of coronavirus disease 2019 (COVID-19) – caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – has led to an unprecedented global health crisis. Since the World Health Organization (WHO) declared COVID-19 a pandemic on 11th March 2020, the virus has claimed more than 5.4 million deaths worldwide.[1] The rapidly spreading pandemic has stretched healthcare systems to the limit and forced many countries to implement harsh restrictions to curb the spread of the virus.

The development of safe and effective COVID-19 vaccines brought hope to control the pandemic. Malaysia started its COVID-19 vaccination program in February 2021.[1] The vaccination program was rolled out in three phases, starting with the frontliners such as healthcare workers (HCWs), police, and military personnel as a priority group. All HCWs were offered the BNT162b2 mRNA vaccine (Comirnaty), which was the vaccine available at that time.

The swift development of effective vaccines against COVID-19 was an unprecedented scientific achievement. However, several adverse events following immunisation have been reported. Adverse events following immunisation (AEFI) can range from mild to severe, where possible local reactions include pain, swelling, and redness at the injection site. In contrast, systemic events may include fever, fatigue, headache, chills, nausea, vomiting, diarrhoea, myalgia, arthralgia, lymphadenopathy, arrhythmias, syncope, and paraesthesia.[2,3]

If poorly dealt with, the experience of AEFI can result in vaccine misconceptions and contribute to vaccine hesitancy. There have been no studies about AEFI associated with COVID-19 vaccination in the local population. Thus, we aim to evaluate the incidence and severity of AEFI associated with the BNT162b2 mRNA vaccine and identify variables associated with the development of AEFI among healthcare workers.

MATERIALS AND METHODS

We performed an online cross-sectional survey, where the target population comprised 3500 healthcare personnel working in Hospital Tuanku Ja'afar Seremban who received at least one dose of the Pfizer-BioNTech (BNT162b2) COVID-19 vaccine during the Phase 1 vaccination program from 1 March 2021 to 4 May 2021. Participants were approached and invited to join a self-administered survey via a Google

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Table I: Baseline characteristics of the study population

Baseline characteristics of patients	n (%)
Sex	
• Female	1744 (76.4)
• Male	538 (23.6)
Ethnicity	
• Malay	1898 (83.2)
• Chinese	86 (3.8)
• Indians	264 (11.6)
• Others	34 (1.5)
Professional category	
• Medical doctors	34 (1.5)
• Nurses and paramedics	1132 (49.6)
• Pharmacists	91 (4.0)
• Allied health personnel	173 (7.6)
• Supportive staff	445 (19.5)
• Administrative staff	134 (5.9)
Comorbidities*	
• None	1806 (79.1)
• Hypertension	163 (7.1)
• Bronchial asthma	123 (5.4)
• Diabetes mellitus	114 (5.0)
• Cardiac disease	40 (1.8)
• Haemato-oncological disorders	36 (1.6)
• Neurological disorders	28 (1.2)
• Immunodeficiency disorders	13 (0.6)
• Tuberculosis	10 (0.4)
• Liver disease	6 (0.3)
• Chronic kidney disease	6 (0.3)
Allergy history	
• Yes	434 (19.0)
• No	1848 (81.0)
Previous COVID-19 infection	
• Yes	114 (5.0)
• No	2168 (95.0)
Pregnancy	
• First trimester	17 (0.7)
• Second trimester	24 (1.1)
• Third trimester	16 (0.7)

* denotes that a subject may have more than one comorbidity.

Table II: Comparison of reported adverse events after both BNT162b2 vaccine injections

Reported adverse events	Cumulative, n (%)	First dose, n (%)	Second dose, n (%)	OR[a]	95% CI	p-value
Fever	1006 (44.1)	208 (9.1)	798 (35.0)	5.36	4.54–6.33	<0.01
Chills and rigors	705 (30.9)	120 (5.3)	585 (25.6)	6.21	5.05–7.63	<0.01
Lethargy	1135 (49.7)	343 (15.0)	792 (34.7)	3.00	2.60–3.47	<0.01
Pain at injection site	1468 (64.3)	524 (23.0)	944 (41.4)	2.36	2.08–2.69	<0.01
Swelling at injection site	683 (29.9)	243 (10.6)	440 (19.3)	2.00	1.69–2.37	<0.01
Headache	770 (33.7)	218 (9.6)	552 (24.2)	3.02	2.55–3.58	<0.01
Dizziness	727 (31.9)	239 (10.5)	488 (21.4)	2.33	1.97–2.75	<0.01
Myalgia and joint pain	937 (41.1)	265 (11.6)	672 (29.4)	3.18	2.72–3.72	<0.01
Vomiting	75 (3.3)	27 (1.2)	48 (2.1)	1.79	1.12–2.89	<0.05
Nausea	186 (8.2)	63 (2.8)	123 (5.4)	2.01	1.47–2.73	<0.01
Diarrhoea	64 (2.8)	15 (0.7)	49 (2.1)	3.32	1.85–5.93	<0.01
Cough	72 (3.2)	24 (1.1)	48 (2.1)	2.02	1.23–3.31	<0.01
Runny nose	117 (5.1)	38 (1.7)	79 (3.5)	2.12	1.43–3.13	<0.01
Sore throat	132 (5.8)	38 (1.7)	94 (4.1)	2.54	1.73–3.71	<0.01
Rashes	103 (4.5)	38 (1.7)	65 (2.8)	1.73	1.16–2.59	<0.01
Palpitations	172 (7.5)	62 (2.7)	110 (4.8)	1.81	1.32–2.49	<0.01
Shortness of breath	40 (1.8)	16 (0.7)	24 (1.1)	1.51	0.80–2.84	0.20
Anaphylaxis	13 (0.6)	4 (0.2)	9 (0.4)	2.25	0.69–7.33	0.16

[a]Odds ratios (OR) were calculated based on the number of adverse events following the second dose against the first dose.

Table III: Comparison of the AE and non-AE groups

	AE occurred (n = 1472)	No AE (n = 810)	p-value[†]
Mean age (SD), years	35.7 (7.2)	36.7 (8.1)	<0.01
Gender:			<0.01
Female	1181 (80.2%)	563 (69.5%)	
Male	291 (19.8%)	247 (30.5%)	
Ethnicity:			0.879
Malay	1223 (83.1%)	675 (83.3%)	
Non-Malays	249 (16.9%)	135 (16.7%)	
Comorbidities	316 (21.5%)	160 (19.8%)	0.335
History of allergies	336 (22.8%)	98 (12.1%)	<0.01
History of COVID-19	77 (5.2%)	37 (4.6%)	0.487
Pregnancy	43 (2.9%)	14 (1.7%)	0.081
First dose vaccination on left arm	1301 (88.4%)	705 (87.0%)	0.345
Second dose vaccination on left arm	1277 (86.7%)	694 (85.7%)	0.774
Premedication:			
Paracetamol	227 (15.4%)	121 (14.9%)	0.759
NSAIDS	7 (0.5%)	3 (0.4%)	0.716
Antihistamines	36 (2.4%)	13 (1.6%)	0.185
Steroids	10 (0.7%)	5 (0.6%)	0.861

[†] independent samples t-test for mean age, and chi-squared test computation for other groups.

form link. The questionnaire was composed of queries from the following domains: demographic details, baseline clinical characteristics, details on AEFI occurrences, and the clinical course after vaccination. Severe adverse events were defined as any adverse event requiring a visit to the emergency department (ED) or hospitalisation. The survey was done from June to August 2021, and 2755 responses were recorded. We removed 146 duplicate responses and further excluded 327 responses with suboptimal responses. The remaining 2282 responses were subsequently analysed.

Ethical approval for the use of an online survey form for the research in Hospital Tuanku Ja'afar Seremban was obtained from the Medical Research and Ethics Committee (MREC), and all users provided informed consent for non-commercial use of their data.

Descriptive statistics were used to analyse categorical variables collected in the study, where results were summarised and presented in frequencies and percentages. Data for continuous variables were presented as mean and standard deviation (SD). Chi-squared tests and Fisher exact tests were used to compare categorical variables as appropriate. A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 2282 participants were included in the analysis. Table I summarises the baseline characteristics of all 2282 participants in this study. More than three-quarters of the study population were female respondents (n=1744, 76.4%). By ethnicity, Malays were the majority (83.2%), followed by Indians (11.6%), Chinese (3.8%), and others (1.5%). The mean age was 36.0 years (SD 7.6). Nurses and paramedics (n=1132, 49.6%) account for almost half the subjects in the study, followed by healthcare support staff (n=445, 19.5%), medical doctors (n=307, l3.5%), and other healthcare workers from the allied-health, pharmacy, and administrative departments. Comorbidities were present in 20.9% of participants, with hypertension, bronchial asthma, and diabetes mellitus being the three most common comorbidities. A total of 434 (19.0%) participants reported a history of allergy, and 114 (5%) HCWs documented a previous COVID-19 infection. Among the female participants, 57 (2.5%) were pregnant, with the majority in a gestational age beyond the second trimester.

The study respondents were predominantly double-dose vaccine recipients, with only eight respondents (0.4%) receiving one dose. Reasons for opting out of the second dose were as follows: two respondents experienced severe AEFI following their first-dose injection, four respondents opted out due to pregnancy, whilst two other respondents did not complete vaccination due to job transfer.

In our study, AE (adverse event) was experienced in up to 64.5% (n=1472) of the study participants (Figure 1). Within this group, majority of the AE occurred after the second dose (56.5%, n = 832), while 31.6% (n=465) experienced AE with both doses. Despite the considerable number of AEs, a small number of participants (n=68, 3.0%) developed severe AE, warranting observation in the emergency department or hospitalisation. Most of the severe AEs (n=46, 67.6%) were experienced after the second dose of injection. The median duration of severe AEFI was 2 days (IQR=3). Severe AEFIs, such as life-threatening anaphylaxis, vaccine-induced thrombosis, myocarditis, or mortality, were not reported among our study participants.

The most frequently reported AEFI in this study was pain at the injection site (64.3%, n=1468), lethargy (49.7%, n=1135), and fever (44.1%, n= 1006). These AEFIs were more commonly reported after the second dose compared to the first dose, as well as other AEFIs such as chills and rigors, swelling at the injection site, headache, dizziness, myalgia and joint pain, vomiting, nausea, diarrhoea, cough, runny nose, sore throat, rashes, and palpitations (Table II).

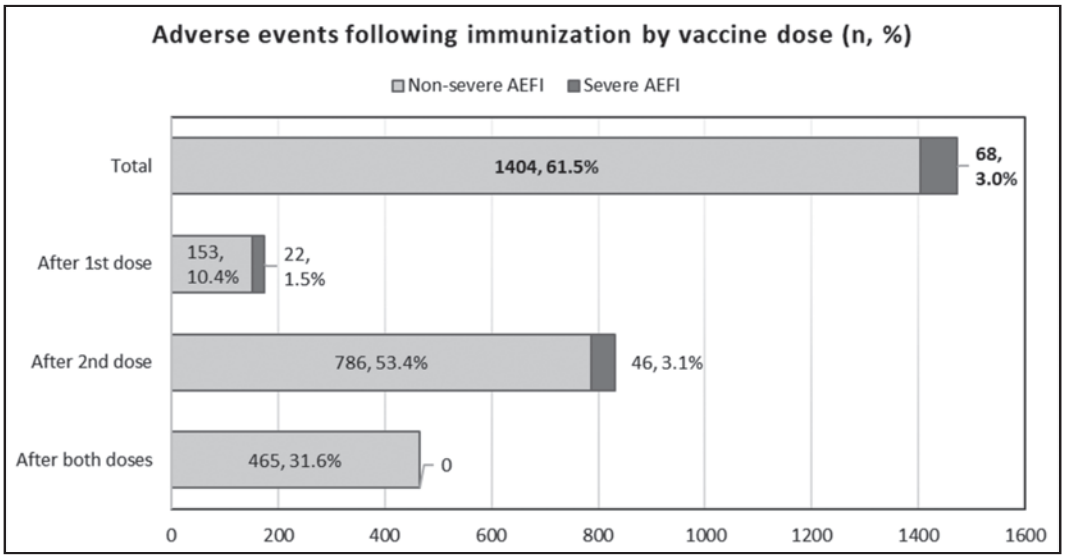

Fig. 1: Adverse events following COVID-19 vaccine immunisation.

The subjects who experienced AE were significantly younger than those who did not, with a mean age difference of 1.1 years (95% CI 0.4–1.8) (Table III). The proportion of females in the AE group (80.2%) was significantly higher than that in the non-AE group (69.5%). The site of vaccination, i.e., the left or right arm, did not affect the occurrence rates of AE during the first or second dose of vaccination. The proportion of vaccine recipients who received premedication with paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), antihistamines, or steroids did not differ significantly between both groups.

DISCUSSION

In this cross-sectional observational study, we evaluated the adverse effects following administration of BNT162b2 vaccines among healthcare workers in a tertiary, hospital-based setting. Our study showed that AEFIs following vaccination were common, but mostly mild and self-limiting. Only 3% of participants encountered severe AE requiring emergency department observation or hospitalisation. There were no documented vaccine-induced thrombotic thrombocytopenia or myocarditis among our study participants.

Our findings were consistent with previous studies documenting that AEs were more likely to occur following the second dose of BNT162b2 vaccine.[4,5] Prior studies reported that systemic AEs (such as fever, fatigue, and myalgia) were more likely to occur than local side effects (such as pain, redness, and swelling) following the second dose.[6,7] However, in our study, all local and systemic AEs were more frequently seen after the second dose. The reasons for this were unclear but could be related to a short inter-dose interval between the first and second vaccination. There are emerging data showing that a longer time interval between COVID-19 mRNA doses was associated with a reduced risk of AEFI such as myocarditis.[8]

Our results support previous findings that female recipients with a younger age were more likely to experience AEFI following the BNT162b2 vaccination.[9] Our findings of higher AEFI among females were consistent with the results of several other studies on the reactogenicity of the BNT162b2 vaccines.[6,10] The gender differences in AEFI occurrences have been previously observed with seasonal flu shots, which may be ascribed to various hormonal, genetic, and immunologic distinctions.[11]

Our study showed the AE group had a significantly higher proportion of participants with a history of allergy. This finding was also supported by Nittner et al.,[12] who reported that local and systemic reactions were more frequently seen in allergic individuals. Nevertheless, severe allergic reactions such as anaphylaxis were not seen in our study population, even among those with a prior allergy history. This could be due to the relatively rare occurrence of anaphylaxis,[13,14] which would not be captured in our study population of 2,282 people.

The proportion of those who had prior COVID-19 did not differ significantly between the AE and non-AE groups, although other studies showed an increased likelihood of developing AEFI among individuals with prior COVID-19 infections.[15–17] We did not find significant differences between those with underlying comorbidities, consistent with existing reports.[17–19] This suggests that the BNT162b2 vaccine can be safely administered to individuals with underlying comorbidities as the potential benefit outweighs the risk of developing adverse events. Our results showed no differences in the development of AEFI among pregnant mothers, consistent with the findings of several large-scale studies.[20–22]

We found no significant differences in the proportion of subjects who premedicated themselves with paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), antihistamines, or steroids in the AE and non-AE groups. This is compatible with studies demonstrating that premedication

does not prevent subsequent allergic reactions.[23,24] Instead, the use of premedication may mask acute cutaneous reactions and lead to delayed detection of severe allergic reactions.[23] There are also concerns from non-COVID-19 vaccine studies that the usage of prophylactic antipyretics may attenuate antibody responses to vaccine antigens.[25,26]

This study has several limitations. First, this is a single-centre study comprising of healthcare workers; thus, the results might not be generalisable to the greater population. Second, participation in the study was on a voluntary basis. This may lead to the possibility of bias in our results as vaccine recipients who had experienced AEFI were potentially more likely to participate in the study. Finally, at the time of study initiation, the Pfizer-BioNTech, BNT162b2 was the only vaccine available; hence, comparison with other vaccine types was not possible. Further studies involving different types of vaccines are required to allow fair comparison in terms of tolerability and effectiveness. Despite those limitations, our study provided a sufficiently broad overview of the types of AEFI, which were commonly experienced following BNT162b2 vaccination among healthcare workers.

CONCLUSION

In conclusion, local and systemic AEFIs following the BNT162b2 vaccination were commonly experienced; however, most were self-limiting. These findings could come in handy to address vaccine hesitancy caused by concerns regarding severe AEFIs associated with the COVID-19 vaccines. Our study, conducted in the context of a local population, adds to the growing amount of literature on the safety of the COVID-19 mRNA vaccines.

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CONFLICTS OF INTERESTS

The authors declare no conflict of interests.

REFERENCES

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard With Vaccination Data [Internet]. [cited 2021 May]. Available from: https://covid19.who.int/.
2. World Health Organization. Adverse events following immunization (AEFI) [Internet]. [cited 2021 Dec]. Available from: https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/aefi
3. World Health Organization. MODULE 3 – Classification of AEFIs - WHO Vaccine Safety Basics [Internet]. [cited 2021 Dec]. Available from: https://vaccine-safety-training.org/classification-of-aefis.html
4. Ossato A, Tessari R, Trabucchi C, Zuppini T, Realdon N, Marchesini F. Comparison of medium-term adverse reactions induced by the first and second dose of mRNA BNT162b2 (Comirnaty, Pfizer-BioNTech) vaccine: a post-marketing Italian study conducted between 1 January and 28 February 2021. Eur J Hosp Pharm.2021; ejhpharm-2021-002933.
5. Takeuchi M, Higa Y, Esaki A, NabeshimaY, Nakazono A. Does reactogenicity after a second injection of the BNT162b2 vaccine predict spike IgG antibody levels in healthy Japanese subjects? PLOS ONE.2021: 16(9); e0257668.
6. Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. Lancet. 2021: 21(7): 939–49.
7. Polack FP, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020; 383(27): 2603–15.
8. Buchan SA, et al. Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval. medRxiv. 2021; 2021.12.02.21267156.
9. Venkatakrishnan A, et al. Female-male differences in COVID vaccine adverse events have precedence in seasonal flu shots: a potential link to sex-associated baseline gene expression patterns. medRxiv. 2021; 2021.04.01.21254798.
10. Centers for Disease Control and Prevention. First Month of COVID-19 Vaccine Safety Monitoring — United States, December 14, 2020–January 13, 2021. Morbidity and Mortality Weekly Report. 2021; 70(8):283.
11. Klein SL, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. Trans R Soc Trop Med Hyg. 2015;109(1):9-15.
12. Nittner-Marszalska M, Rosiek-Biegus M, Kopeć A, et al. Pfizer-BioNTech COVID-19 Vaccine Tolerance in Allergic versus Non-Allergic Individuals. Vaccines (Basel). 2021;9(6):553.
13. Dages KN, Pitlick MM, Joshi AY, Park MA. Risk of allergic reaction in patients with atopic disease and recent coronavirus disease 2019 vaccination. Ann Allergy Asthma Immunol. 2021; 127(2):257-258.
14. Turner PJ, et al. COVID-19 vaccine-associated anaphylaxis: A statement of the World Allergy Organization Anaphylaxis Committee. World Allergy Organization Journal. 2021;14(2):100517.
15. Debes AK, et al. Association of Vaccine Type and Prior SARS-CoV-2 Infection With Symptoms and Antibody Measurements Following Vaccination Among Health Care Workers. JAMA Intern Med. 2021;181(12):1660–1662.
16. Colaneri, M. et al. Are people previously infected with SARS-CoV-2 likely to experience COVID-19 symptoms again after vaccination? Results from an Italian COVID-19 referral center. Hum Vaccin Immunother. 2021;1-2.
17. Joshi RK, et al. Higher incidence of reported adverse events following immunisation (AEFI) after first dose of COVID-19 vaccine among previously infected health care workers. Medical Journal, Armed Forces India. 2021; 77, S505.
18. Remlabeevi A, Mathew T, Nair GSH, Nair GLR, Alex MR. Adverse events and their association with comorbidities after first and second doses of Covishield vaccination among healthcare workers of Government owned medical colleges in Kerala. medRxiv. 2021; 2021.05.19.21257317.
19. Al Ghafri TS, Al Balushi L, Al Balushi Z, et al. Reporting at Least One Adverse Effect Post-COVID-19 Vaccination From Primary Health Care in Muscat. Cureus. 2021;13(8):e17055.
20. Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. [published correction appears in N Engl J Med. 2021 Oct 14;385(16):1536]. N Engl J Med. 2021;384(24):2273-2282.
21. National Center for Immunization & Respiratory Diseases. COVID-19 vaccine safety update. Advisory Committee on Immunization Practices (ACIP) CDC COVID-19 Vaccine Task Force Vaccine Safety Team. 2021 March.

22. Shook LL, Fallah PN, Silberman JN, Edlow AG. COVID-19 Vaccination in Pregnancy and Lactation: Current Research and Gaps in Understanding. Front Cell Infect Microbiol. 2021; 11:735394.
23. Shaker MS, Wallace DV, Golden DBK, et al. Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020;145(4):1082-1123.
24. Kim MA, et al. COVID-19 Vaccine-associated Anaphylaxis and Allergic Reactions: Consensus Statements of the KAAACI Urticaria/Angioedema/Anaphylaxis Working Group. Allergy Asthma Immunol Res. 2021;13(4):526-544.
25. Das RR, Panigrahi I, Naik SS. The effect of prophylactic antipyretic administration on post-vaccination adverse reactions and antibody response in children: a systematic review. PLoS One. 2014;9(9):e106629.
26. Hervé C, Laupèze B, Del Giudice G, Didierlaurent AM, Tavares Da Silva F. The how's and what's of vaccine reactogenicity. NPJ Vaccines. 2019;4:39.

ORIGINAL ARTICLE

The opinion of general practitioners in Malaysia on newly imposed third party health administrator policies in primary care

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ABSTRACT

Background: Third Party Health Administrators (TPA) has become an integral part in the field of funding healthcare for most parts in the world. Although they ensure access to medical care when out-of-pocket payment is required, TPAs have been found to impose unreasonable dictation in medicine prescriptions that undercuts doctors remuneration including paying very low medical consultation fees, types/methods of treatment and modalities for their policy holders. The objective of this study was to get the opinion of Malaysian doctors regarding the newly imposed policies and rates that these companies have forcibly dictated towards private primary care General Practitioners (GPs).

Materials and methods: This was a cross sectional study, conveniently sampling private GPs currently practicing in Malaysia. A self-developed online questionnaire was sent out to the members via social media with the assistance of the Malaysian Medical Association the affiliates of Federation of Private Medical Practitioners Associations of Malaysia and Medical Practitioners Coalition Association of Malaysia. Data was collected from April to July 2021. A series of 7 short questions were asked in the survey to yield a higher response rate. A population to proportion sample size was calculated and a minimum of 365 responses were required. All data collected were collated and analysed in the SPSS v21.0

Results: From a total of 7,000 GPs, 491 GPs (134.52% of intended sample size) responded to the questionnaire. The largest portion of respondents were from Selangor (21.79%). A total of 65.58% of the GPs felt that the RM 15 consultation fee dictated by the TPAs was unfair, 71.08% felt it was unfair that TPA overwrote certain investigations done or medicines given as over-treatment, 90.84% felt that TPAs had no jurisdiction to dictate the number of days of medication patients needed for chronic medical conditions, 95.52% did not agree that TPAs fix the price of each medication, 54.58% agreed that marking up medications from 5-15% of the original purchase price was fair and 68.64% agreed that they would boycott TPAs that were unreasonable with their dictation/demands.

Conclusion: GPs generally disagreed with many new policies imposed by TPAs. These new policies might hinder the screening, management and early detection of chronic non communicable diseases here in Malaysia.

KEYWORDS:
Third Party Health Administrators restrictions, General Practitioners, Malaysia

INTRODUCTION

The Malaysian healthcare system was established during colonial times and is known to have one of the best and cost effective healthcare systems in the world.[1] Today, the Malaysian healthcare system functions on a dual-tiered system: the government funded (serves 65% of the population) and the private healthcare system (serves 35% of the population).[2] The government hospitals are fully funded by the Government of Malaysia and patients pay as little as Ringgit Malaysia 1 to be able to obtain good health services (foreigners are charged in full).[2] The private healthcare system is another parallel system to that of the government healthcare system but patients (both Malaysians and foreigners) are required to either pay from their own pockets (out-of-pocket payment) or via health insurance payments/Third-Party Administrators (TPAs) appointed/selected by their employers.[2]

Both systems are divided into 3 levels- primary care (mostly health clinics), secondary and tertiary care (mostly hospital-based care). Primary care in the private settings are doctors who are either self-employed or employed under an organization mostly owned by doctors managing a chain of private health clinics.[2] They are normally termed as General Practitioners (GPs) if they are general physicians who look after basic ailments or Family Medicine Specialist if they have pursued a Masters in Primary Care (Family Medicine) or its equivalent. These doctors are required by law to have a valid practicing certificate which is renewed annually and they must work in a premise gazetted/approved by the Ministry of Health. These doctors are allowed to manage and follow up patients and dispense medications from their clinics.

Third Party Health Administrators (TPHAs) and Health Management Organisations (HMOs) are large companies or healthcare insurance companies that manage healthcare services for particular organisations. It is becoming a norm that companies/organisations appoint TPAs to manage their healthcare benefits for employees.[3] This is for both acute illnesses and chronic illnesses- but for this paper, we will focus more on chronic illnesses and comorbidities. Some companies decide to manage their own healthcare benefits

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by appointing panel clinics and they pay the doctor for services and treatment (fee for service) for their employees on a monthly basis. In this study, we refer to Third Party Administrators (TPAs) as companies managing their own healthcare benefits for employees, TPHAs or HMOs.

These TPAs generally appoint panel doctors around the country to be part of their healthcare services offered to clients- commonly known as panel-ship. As TPAs appoint GPs of their choice based on their charges on the applications sent. They have the right to revoke the GPs panel-ship should they find a reason to do (it can range from a trivial to a severe matter). TPAs constantly remind GP panels that they would look for other new GP panels to manage their healthcare needs if current panels do not comply to their fixed set of rules. As more companies are utilising TPA services, many GPs are left with little choice but to abide with sometimes unjust terms set by them. Under their new terms, there are times when GPs are left short-changed either by being underpaid or not being paid at all for certain medical treatment or procedures.[3] Among some of the new terms amended and recently implemented were- fixing of medication prices (sometimes as low as doctors' cost prices) and imposing the minimal consultation fee of RM15 (without considering if it was a long or short consultation). The TPAs claim that their fee regulation for consultation was in accordance with the last fee schedule gazetted in the 90s.[2-4]

Some TPAs went as far as dictating medical practices by specifically enforcing rules that resulted in patients only being able to receive 3 to 6 weeks of medications for chronic comorbidities- to which the patient is expected to get help from a tertiary centre (hospital) should they not respond to the prescribed medication (they are not allowed to get treatment for the same complain from the same GP due to the fact that they have not yet exhausted their prescribed medications). This is a deviation from what is normally done in primary care where doctors tend to manage early non-communicable diseases by reviewing the patients' response towards treatment for a period of 1 to 2 weeks in the beginning (depending on severity). Some TPAs (especially companies managing their own healthcare benefits) have decided to undercut the doctors by obtaining medication from pharmacies and the panel doctors are allowed only to provide a prescription for Long Term Medication (LTM) (forced dispensing separation).[3] They forced doctors to write prescriptions for policy holders and the medication is collected every 2 or 3months from an appointed pharmacy without any review of their condition(s).[3] Multiple pleas by doctors on these issues made to the TPAs went unheeded.

These newly imposed rules by TPAs have led to many unfortunate events and the GPs were caught in the middle. There were times when this new unregulated practice have seen some patients comorbid conditions deteriorating for the worse while some even experiencing side-effects (allergy reactions) of medications that were altered without the prescribing doctor's knowledge.[3] Many were also concerned with the current implications as it might affect them financially- those of the consultation fees, the fixing of the prices of drugs and unnecessary excessive medical practice controls like supressing the number of drugs doctors can provide during consultation and the number of days medications are provided for chronic conditions.

This has become worrisome as Primary Care remains and is the sole gatekeeper in the management of chronic non-communicable diseases in any country.[5] Primary care is looked upon as a bridge between the tertiary care and patient healthcare.[5] If primary care is empowered, we will see less complications of chronic diseases leading to better patient healthcare.[5] The management of these chronic comorbidities requires time and dedication of the physician to ensure that the patient receives the best of primary healthcare.[5]

Thus, the aim of this study was to obtain the opinions of GPs regarding these new dictations and financial implications imposed by the TPAs on medical practice at the GP level.

MATERIALS AND METHODS

This was a cross-sectional study conducted amongst private GPs currently practicing in Malaysia from April 2021 to July 2021. The researchers utilised a self-developed online questionnaire to GPs from professional associations (convenient sampling) to obtain the data for this study. We included only private practitioners- both general physicians and specialists who were treating patients who were under TPAs. The questionnaire was sent to potential respondents via social media with the assistance of dissemination from professional bodies like the Malaysian Medical Association, the Private Practitioners Society of Malaysia along with their subsidiaries and the Medical Practitioners Coalition Association of Malaysia. To obtain a better response rate amongst our busy colleagues, we decided to keep the questionnaire simple with a hope to yield a higher response rate. The questionnaire consisted of 7 questions. The respondents were first asked on their current location of practice (list of states were given), if they agreed with the RM 15 consultation rate offered by TPAs (Yes/No), if TPAs should be able to curb over-treatment protocols when it is acceptable to norms (Yes/No), if TPAs should dictate the number of days treatment for chronic diseases should be given (Yes/No), if TPAs should be allowed to fix the price of drugs being charged to them (Yes/No), if GPs felt that charging prices of medications with a 5-15% markup fee is acceptable (Yes/No) and if GPs were willing to participate in a boycott towards TPAs if their consultation fee was not adjusted/unreasonable dictation of demands not removed (Yes/No/Maybe). All questions were set and marked as compulsory- meaning that respondents could not proceed with submission unless they had provided an answer to all 7 questions. There was no time limit set on the questions but each GP was only allowed to answer the questionnaire once. This was done by capturing google account log in to their browsers- it served as an attendance marker for the Google forms (google enabled feature) to electronically signify that they have attempted the survey and dual participation would be denied. There were no renumerations given for answering the questionnaire. All questionnaires submitted were automatically collated in a specially designated email for the study. It was auto tabulated in an Excel spreadsheet before being imported into SPSS v21.0 for further analysis.

Sample size
There were 7,000 odd GPs registered with the Ministry of Health in Malaysia.[6] Conducting a population to proportion sample size, we utilised the Raosoft sample size calculator (available at: http://www.raosoft.com/samplesize.html) to calculate a sample size. Setting the margin of error at 5%, the confidence interval at 95%, the population size at 7,000 and the distribution at 50%- the final sample size needed for this study was 365.

Ethical approval
This study was a low-risk study conducted amongst doctors without getting any of their personal details or identifiers. The doctors were informed that participation in the study was optional and had no implications if they decided not to participate. They signified their willingness to participate in this survey by clicking on the link if they chose to participate. The researchers therefore did not see a need to apply for an ethics approval for this study.

RESULTS

The researchers sent out the invitation of the survey via social media and electronically. The total respondents were 491- this was 134.52% of the intended sample size of 365.

Demography
Most of the respondents were practicing in the state of Selangor (21.79%), followed by Pulau Pinang (17.11%), Wilayah Persektuan Kuala Lumpur (14.87%), Perak (14.26%), Sarawak (13.24%) and followed by the other states. Full description of the respondents' place of practice are listed in Table 1.

Questions concerning cost / pricing/ financing in general practice when concerning TPAs
The GPs were asked 3 questions that involved costs which TPAs newly imposed. The first was setting the consultation fee at a flat rate of RM 15- to which 65.58% of the GPs disagreed. The researchers then asked if the GPs felt that if it was alright for TPAs to be allowed to fix the prices of drugs being billed to them- to which 95.52% of GPs disagreed. From the total, 54.58% of the GPs felt that the marking up of medication prices by 5-15% was acceptable. Full details of the responses are available in Table II.

Questions concerning the practise of medicine as dictated by TPAs
The GPs were asked 3 questions regarding their opinion on the practice of medicine as being newly dictated by TPAs. The first was if GPs felt that TPAs should be allowed to curb over-treatment protocols when it was acceptable within norms- to which 71.08% disagreed. From the total, 90.84% felt that TPAs should not dictate the number of days treatment is given to patients for chronic conditions like hypertension and diabetes. When we enquired if GPs were keen to participate in the boycott should the TPAs continue making unreasonable demands/dictating the way medicine is practiced, 68.64% of them agreed to do so whilst 29.33% of them were undecided. Full details are listed in Table III.

DISCUSSION

Summary of results
From this study we found that 65.58% of doctors disagreed with the RM 15 consultation, 54.58% agreed with the 5-15% markup for drugs and 95.52% were against the fixing of medication prices by TPAs. From the grouses of dictation in medicine practice- 71.08% felt that TPAs had no right to curb overtreatment protocols, 90.84% did not agree that TPAs should dictate the number of days treatment be given for chronic illnesses and 68.64% were ready to participate in a boycott should the TPAs not repent from their current unreasonable dictations.

Discussion
TPAs must understand that primary care is getting more and more important where chronic comorbidities are managed and is looked as a bridge between the tertiary care and patient healthcare.[5] Primary care services are becoming more popular worldwide and remains the first place of presentation for many ailments the public might have before being given any medical treatment.[7] The management of chronic co-morbidities requires time and dedication of the physician to ensure that the patient receives the best of what primary healthcare can offer5. If primary care is empowered, we will see less complications of chronic diseases leading to better patient healthcare.5

The consultation fee issue is something that must be addressed urgently. The reason for this is that it was ridiculous to know that the GPs housed in private hospitals were allowed to charge a consultation fee between RM 35 to RM 125 (depending on the length and circumstances of the consultation) but GPs practicing in their own premises (not hospital based and having much more overheads) were not allowed to amend their consultation fee charges of RM 15.[3,4,8,9](6) This was due to the fact that Section 7 of the new Private Health Care Facilities and Services Act (that regulated the consultation fees for GPs practicing outside a hospital settings) was not gazetted.[9,10] This was indeed strange for doctors as they were equally qualified but paid different consultation fees solely based on the premise of practise.[9,10]

This is a cause of concern due to a few reasons. In an article published in the United States, it was reported that physicians might under-perform if they are not compensated well enough.[11] Amongst the possible reasons is that they will have to see more patients in order to earn a decent living- and this might cause them to rush in between patients.[12] Also, in a recent study done in Malaysia- it was reported that as many as 20% of the GP clinics in Malaysia would potentially close if medicine prices were controlled.[8] This is due to the fact that GPs operating from clinical premises are currently depending on these earnings to make ends meet and compensate for their meagre consultation fee. Thus, with a meagre consultation fee, the prices of medications might be affected- making them more expensive.[8]

As found in this research- controlling medication prices is something the doctors are not willing to compromise with. Controlling medicine prices might seem lucrative to the TPAs but little do they release that in the long run it will cost them more due to other newly developed chronic conditions

Table I: The place of practise of respondents answering the questionnaire

State	N (%) N=491
Selangor	107 (21.79)
Pulau Pinang	84 (17.12)
Wilayah Persektuan Kuala Lumpur	73 (14.87)
Perak	70 (14.26)
Sarawak	65 (13.24)
Johor	29 (5.91)
Sabah	17 (3.46)
Negeri Sembilan	11 (2.24)
Kedah	10 (2.04)
Pahang	9 (1.83)
Melaka	5 (1.02)
Terengganu	5 (1.02)
Perlis	2 (0.41)
Wilayah Perseketuan Putrajaya	2 (0.41)
Kelantan	1 (0.20)
Wilayah Perseketuan Labuan	1 (0.20)

Table II: Questions concerning cost/pricing/financing in General Practice when concerning TPAs

Question	N (%) N=491
Do you agree with an RM 15 consultation fee rate offered by the TPAs?	
Yes	169 (34.42)
No	322 (65.58)
Should TPAs be allowed to fix the price of drugs being charged to them?	
Yes	22 (4.48)
No	469(95.52)
Do you feel that charging prices of medication with a 5-15% markup fee is acceptable?	
Yes	268 (54.58)
No	223 (45.42)

Table III: Questions concerning the practice of medicine as being dictated by TPAs

Question	N (%) N=491
Do you think that TPAs should curb over-treatment protocols when it is within acceptable norms?	
Yes	142 (28.92)
No	349 (71.08)
Do you feel that TPAs should dictate the number of days treatment that should be given to patients (eg Chronic conditions like hypertension and diabetes)	
Yes	45 (9.16)
No	446 (90.84)
Would you join us in our quest to reprimand these TPAs or boycott those TPAs that are being unreasonable (fixing consultation fee to RM15, dictating on medications allowed and duration, fixing prices of medication etc)?	
Yes	337 (68.64)
No	10 (2.04)
Maybe	144 (29.33)

amongst their policy holders.[13] It was reported in a Malaysian study amongst the private healthcare sector, that the control of medication prices will be amongst the reasons health outcomes for patients deteriorate in the country.[8] Not only will the patients' healthcare be affected, but it will cause many private practices to potentially close (estimated 2600 from 14000 or nearly 20%) thus causing a bigger issue with healthcare access for many especially in the rural areas.[8] It might also cause many private tertiary care centres to close their primary care services and in the long run- it will cause many of them to relocate to different countries.[8] With TPAs trying to control the medication prices that doctors can charge (and some at ridiculously low prices), it can spell disaster for the healthcare of this country- in terms of complications from comorbidities, proper access to medical care for patients and long-term survival of GP practice in the country.[8]

For some time now, TPAs have been at loggerheads with the way medicine is practised.[14] In a study reviewing primary care services in the United States- it was reported that primary care facilities have been in constant disputes with third-party payer systems/TPAs especially when it comes to the type of treatment offered, the choice of investigations,

unnecessary paperwork and claims processing for simple ailments.[7] In the same paper, it was reported that 79.2% of physicians felt that TPA models were becoming more unattractive especially due to the fact of imposed over-regulations, 64.5% felt that there was a loss of clinical autonomy and 54.4% felt that there was an erosion of physician-patient relationship due to unnecessary regulations.[7] The paper also suggests that chronic conditions are not properly addressed at times because physicians are not compensated enough for their time and due to many restrictions especially when it comes to charging the TPAs.[7] In another review done in the United States, it was found that access to medical care was often restricted due to grappling healthcare centres faced with insurance companies.[14] Amongst the points of contention were the issue of costs and potential over-treatment.[14] However, the TPAs must begin to draw a line on investigations for screening and over-treatment given by the physician. The curb of over-treatment or indications/diagnosis based investigations by TPAs has been heavily debated in countries like Holland.[15] Though extensive clinical research might have been conducted on diseases with specific investigations on certain conditions, it must be understood that patients present differently and a clinical assessment/diagnosis should be the final cut-off point for doctors to perform an appropriate investigation instead of spending their time arguing with TPAs on indications of investigations.[15] For example- a case of myocardial infarction can present in many ways- some come with chest discomfort or left shoulder pain, some come with nausea and other come with gastritis symptoms.[16] More often than not, investigations like Electro Cardio Grams and blood investigations might not suggest an on-going myocardial infarction until an angiogram (Computerised Tomography or the invasive version) is performed.[16] This should be left to the doctor to decide based on his/her clinical examination, findings, experiences and at times- their hunch. The management of conditions not only requires research data but also input from clinicians, administrators and it requires a political will of financers to allow practitioners to practice medicine without being restricted by financial implications set by the TPAs.[15] As far as administration is concerned, a review done in Ghana reported that political interference towards medical practice and even to some amount of healthcare financing services can cause disruption in service treatment and quality.[17]

In order to curb over-spending on medication and treatment, it is best practitioners apply preventive medicine- to which early screening for diseases especially for non-communicable diseases becomes vital. Screening for non-communicable diseases in the United Kingdom is conducted free for those aged from forty to seventy four years of age.[18] This includes heart diseases, stroke, diabetes, kidney disease and individuals with high risk of certain cancers (ie breast cancer).[18] Though screening might be done here in Malaysia in the primary care of the government service, the waiting time is simply just too long and it might result in not detecting diseases in the nick of time. When looking at screening in Sweden- they have a healthcare system that allows for TPAs to cover for basic disease screening but a fixed price is charged to patients for the visits.[18] This is fair for all parties as it will prevent abuse by the patient, fair to the TPA as to not be over-burdened by healthcare visit costs and it is also an opportunity for TPAs to consider an increase in the consultation fees for doctors (with the savings made). In this instance- it provides a wholesome financial sense for all and it must be considered by Malaysian TPAs. After all, the Malaysian government does offer tax incentives up to RM 1,000 per year for individuals for money spent on healthcare screenings. In Germany, TPAs organise health screenings every year for individuals aged more than 35 and those attending these screenings are given a rebate on their health insurance premiums- as an incentive to cultivate the habit for chronic comorbid screening.[18] This is another way that we can foster the community to lead a healthier lifestyle and creating a reward system for doing so. Amongst ways promoted to move the healthcare systems forward is to identify the current barriers within a system and to get expert opinions for solutions.[5]

Why is screening important and not considered over-treatment? It is because non-communicable diseases are becoming the major cause of morbidity and end organ damage not to mention causing an increase in healthcare expenditure.[13,19,20] Many countries have aimed at early detection to prevent further complications from non-communicable diseases.[19,21] Among the many reasons making this possible is if there is reduction in stringent requirements or practices of investigations (ie for end organ damages) which are dictated by unreasonable terms- making primary prevention the modality of aim to prevent non-communicable diseases.[7,15,19-21]

In South East Asia, non-communicable diseases remain one of the greatest causes of mortality before the COVID-19 pandemic era.[22] Even so, we know that non-communicable diseases heavily affect the severity of the COVID-19 infection faced by patients- making a difference in severity, survival and mortality.[23] Thus, controlling non communicable diseases and preventing end-organ damage becomes even more important after COVID-19. In Malaysia- the control of our non-communicable diseases is becoming a concern.[24, 25] Not only must chronic comorbidities be handled better, but prevention is very much needed. In order for this to happen, we will need to screen more patients for chronic comorbids to pick them up in the early stages- pre hypertension, pre diabetes etc.[16,24] This can only take place if we allow physicians the freedom to investigate and conduct screening on their patients when they see fit.[26] This has to be supported by the TPAs because it will end up saving patients from chronic comorbidities and indirectly reducing the expenditure on healthcare in the long run.

In the context of Malaysia, we must get the TPAs to understand that the sustainability of healthcare includes looking after the welfare of doctors and ensuring that patient medical management is not compromised due to unreasonable dictations- including the duration of medications dispensed, the type and number of medications given to a patient. This is also another way of empowering primary care to towards creating a holistic patient care leading to a healthier Malaysia. In order to ensure that patients receive the best of healthcare services, the inclusion of certain services like physiotherapy services, weight-loss

management, cessation of smoking and newer modalities of treatment like shockwave therapy and laser therapies must find their way into primary care services covered by TPAs.[18]

For much of the recommendations to happen, we must understand that physicians have to lead change in healthcare or it might result in the loss of controlover the practice of ethical and holistic medicine with unreasonable administrative control.[11] The more physicians lead the way to reorganise healthcare, the less administrators and insurers will be driven to intervene in the practice of medicine.[11] Patients need to receive wholesome care and this requires physicians to be at liberty to practice ethical medicine without being dictated especially when it concerns the management of chronic comorbidities.[11]

Strengths, Limitation and Future research

This study would be one of the few if not the only publication on the opinion of General Practitioners based on their TPAs. In order to get more responses, the researchers collected few demographic details of the participants which might have differed according to year of practice, age etc. We also did not attempt to collect data based on different TPAs. Thus, for future research, not only should these demographic details be included, but opinion on each existing TPA can be studied to identify if GPs have different opinions based on different TPAs.

CONCLUSIONS

In conclusion, Malaysian GPs generally disagreed with many new policies imposed by the TPAs especially those that dictated unreasonable financials constraints in the practice of medicine. The GPs were also of a common opinion in agreeing that a boycott would be needed if these unreasonable demands continue to govern the way medicine is practiced towards policy holders. With Malaysia already known for having one of the best healthcare systems in the world, why are the TPAs trying to fix something which is not broken? These newly introduced TPA policies might hinder the screening, management and early detection of chronic non-communicable diseases here in Malaysia. This might cause a distress in the access to healthcare services in future and subsequently lead to an increase in the incidences of chronic diseases (ie End Stage Renal Failure, Cerebral-Vascular Accidents etc).

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REFERENCES

1. The-Daily-Star. Malaysia ranks 1st in world's best healthcare. The Daily Star. 2019.
2. Quek D, editor The Malaysian Health Care System: A Review. Intensive workshop on health systems in transition; 2014 07/05.
3. A-Concerned-Medical-Practitioner. Losing The NCD Battle With Companies Making A Quick Buck 2020 . [cited March 2022]Available from: https://codeblue.galencentre.org/2020/12/28/losing-the-ncd-battle-with-companies-making-a-quick-buck-a-concerned-medical-practitioner/.
4. Association MM. Medical Proceedures and Services Nomenclature (MPSN). In: Association MM, editor. Malaysia: Malaysian Medical Association; 2020.
5. Schoen C, Osborn R, Doty MM, Squires D, Peugh J, Applebaum S. A survey of primary care physicians in eleven countries, 2009: perspectives on care, costs, and experiences. Health Aff (Millwood). 2009;28(6):w1171-83.
6. MalaysiaKini. Medical association: 7000 GPs being sidelined by indecisive gov't2019 [cited March 2022]. Available from: https://www.malaysiakini.com/news/499961.
7. McCorry D. Direct primary care: an innovative alternative to conventional health insurance. Backgrounder. 2014;2939:1-13.
8. Zainuddin A. Medicine Price Controls May Erase RM206 Bil From Economy CodeBlue: CodeBlue; 2022 [cited March 2022] Available from: https://codeblue.galencentre.org/2022/01/28/medicine-price-controls-may-erase-rm206bil-from-economy/.
9. Lum M. GP Fees – Gazette Amended Schedule 7 - CodeBlue Codeblue- Health is a Human Right Website: Codeblue; 2019 [cited March 2022] Available from: https://codeblue.galencentre.org/2019/06/04/gp-fees-gazette-amended-schedule-7/.
10. Malaysia MoH. PRIVATE HEALTHCARE FACILITIES AND SERVICES (PRIVATE HOSPITALS AND OTHER PRIVATE HEALTHCARE FACILITIES) (AMENDMENT) ORDER 2013. In: Malaysia MoH, editor. Malaysia: Government of Malaysia; 2013. p. 174.
11. Porter ME, Teisberg EO. How physicians can change the future of health care. Jama. 2007;297(10):1103-11.
12. Atcheson SG, Brunner RL, Greenwald EJ, Rivera VG, Cox JC, Bigos SJ. Paying Doctors More: Use of Musculoskeletal Specialists and Increased Physician Pay to Decrease Workers' Compensation Costs. Journal of Occupational and Environmental Medicine. 2001;43(8).
13. Heller O, Somerville C, Suggs LS, Lachat S, Piper J, Aya Pastrana N, et al. The process of prioritization of non-communicable diseases in the global health policy arena. Health Policy Plan. 2019;34(5):370-83.
14. Schoen C, Osborn R, Squires D, Doty M, Rasmussen P, Pierson R, et al. A survey of primary care doctors in ten countries shows progress in use of health information technology, less in other areas. Health Aff (Millwood). 2012;31(12):2805-16.
15. Moes FB, Houwaart ES, Delnoij DMJ, Horstman K. "Strangers in the ER": Quality indicators and third party interference in Dutch emergency care. J Eval Clin Pract. 2019;25(3):390-7.
16. Then KL, Rankin JA, Fofonoff DA. Atypical presentation of acute myocardial infarction in 3 age groups. Heart Lung. 2001;30(4):285-93.
17. Alhassan RK, Nketiah-Amponsah E, Arhinful DK. A Review of the National Health Insurance Scheme in Ghana: What Are the Sustainability Threats and Prospects? PLoS One. 2016;11(11):e0165151.
18. Fenger M, Qaran W. New Welfare in Health Insurances? Trends in Risk-Coverage and Self-Responsibility in Four European Countries. Social Policy and Society. 2013;12(4):597-609.
19. Beaglehole R, Yach D. Globalisation and the prevention and control of non-communicable disease: the neglected chronic diseases of adults. The Lancet. 2003;362(9387):903-8.

20. Beaglehole R, Bonita R, Horton R, Adams C, Alleyne G, Asaria P, et al. Priority actions for the non-communicable disease crisis. The Lancet. 2011;377(9775):1438-47.
21. Boutayeb A, Boutayeb S. The burden of non communicable diseases in developing countries. Int J Equity Health. 2005;4(1):2.
22. Ghaffar A, Reddy KS, Singhi M. Burden of non-communicable diseases in South Asia. Bmj. 2004;328(7443):807-10.
23. Abdul Taib NA, Baha Raja D, Teo AKJ, Kamarulzaman A, William T, Arvinder-Singh H-S, et al. Characterisation of COVID-19 deaths by vaccination types and status in Malaysia between February and September 2021. Lancet Reg Health West Pac. 2022;18:100354.
24. Keng ZY, Saw YM, Thung SC, Chong WW, Albert A, Kariya T, et al. Rate of achievement of therapeutic outcomes and factors associated with control of non-communicable diseases in rural east Malaysia: implications for policy and practice. Sci Rep. 2021;11(1):3812.
25. Mok WKH, Hairi NN, Chan CMH, Mustapha FI, Saminathan TA, Low WY. The Implementation of Childhood Obesity Related Policy Interventions in Malaysia—A Non Communicable Diseases Scorecard Project. International journal of environmental research and public health. 2021;18(11):5950.
26. Daar AS, Singer PA, Persad DL, Pramming SK, Matthews DR, Beaglehole R, et al. Grand challenges in chronic non-communicable diseases. Nature. 2007;450(7169):494-6.

Malnutrition among patients admitted to the subacute geriatric ward during the COVID-19 pandemic era: A cross-sectional study in a tertiary hospital in Malaysia

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ABSTRACT

Background: Acute illness and hospitalisation detriment the nutritional status of older patients. This study aimed to describe the prevalence of malnutrition, characteristics and in-hospital outcomes associated with malnutrition, and nutritional management among patients who were admitted to the Subacute Geriatric Ward.

Methods: This is a retrospective study of older patients (age ≥ 60) who were admitted to the Subacute Geriatric Ward of Kuala Lumpur Hospital from 1 March 2021 to 31 May 2021. Malnutrition was identified using the Mini Nutritional Assessment-Short Form (MNA-SF). The in-hospital outcomes evaluated were hospital-associated complications, namely delirium, functional decline, incontinence, inpatient falls, inpatient pressure injuries, hospital-acquired infection, institutionalisation, and inpatient mortality.

Results: Seventy-three patients were included (mean age 74.7, female 58.9%), of which 28 (38.4%) and 27 (37.0%) were malnourished and at risk of malnutrition, respectively. Poorer nutritional status was associated with increased age, comorbidity burden, frailty, immobility, impaired basic activities of daily living, history of falls, cognitive impairment, incontinence, and arthritis. About 71.2% and 60.3% of patients were offered dietitian review and oral nutritional supplements, respectively. The in-hospital outcome rates were higher among malnourished patients, but the differences were not statistically significant. However, multiple hospital-associated complications were more common with poorer nutritional status (p = 0.018).

Conclusion: Hospital malnutrition is prevalent among older patients, and unidentified malnutrition is not justified due to its association with multiple adverse outcomes.

KEYWORDS:
Malnutrition; Geriatrics; Inpatients

INTRODUCTION

Malnutrition prevails with age. The complex interaction between physiological changes in aging, comorbidities, and psychosocial factors has posed challenges to maintaining good nutritional status in older adults.[1] The existing condition becomes more profound amid the Coronavirus Disease 2019 (COVID-19) pandemic due to social distancing and isolation.[2] Malnutrition can be acute or chronic, with variable degrees of severity. Associations between malnutrition and a wide range of unfavourable clinical, functional, and economic outcomes, namely prolonged hospitalisation, recurrent hospitalisation, institutionalisation, mortality, and increased healthcare cost, have been frequently reported.[3-6] Therefore, screening for malnutrition merits equal attention as other notable geriatric giants.

In Malaysia, the National Health and Morbidity Survey (NHMS) 2018 revealed that 30% of Malaysian older adults were malnourished.[7] Existing local studies on malnutrition in hospitalised older patients reported a prevalence of 21.0–34.7%, which was similar to the population-based survey.[8,9] Acute illness and hospitalisation are known to have greater detrimental effects on nutritional status among older adults.[10] Similar prevalence between those who were hospitalised and living in the community indicates that local hospital settings were not exempted from under-recognition of malnutrition.

To date, most local hospital-based studies on malnutrition had been concentrated on the description of the nutritional screening and assessment conducted. Apart from post-surgery complications,[11] limited data exist on in-hospital outcomes associated with hospital malnutrition among older patients in Malaysia. Data specific to this context may fill the information gaps and drive the implementation of policies that meet the healthcare issues of the target group. This study aimed to describe the prevalence of malnutrition, characteristics and in-hospital outcomes associated with malnutrition, and nutritional management among older patients who were admitted to the Subacute Geriatric Ward of a tertiary hospital in Malaysia.

MATERIALS AND METHODS

Study Participants and Data Collection

This is a retrospective study including patients aged 60 years and above admitted to the Subacute Geriatric Ward of Kuala Lumpur Hospital from 1 March 2021 to 31 May 2021. The

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study setting is a 22-bedded ward that uses an integrated team approach to provide the following services to older patients: (1) continued medical treatment when acute hospital care is no longer required such as titration of medication, completion of intravenous antibiotics therapy, pain management, and delirium care; (2) rehabilitation for patients who suffer from functional decline after an acute medical illness, including post-COVID rehabilitation; and (3) elective admission from the outpatient clinic for rehabilitation, treatment, or investigation. Although we do not receive direct admission from the emergency department, we manage new or changing health conditions of our existing patients, including emerging acute medical illnesses, unless they required mechanical ventilation or intensive care. We excluded patients with recurrent admission to the same subacute ward within the study period, i.e., only the first admission will be included.

Medical records were reviewed to collect data on routine clinical information of hospital admission; patient's characteristics including their demographics, residential status, and ability to perform all basic activities of daily living (ambulating, feeding, dressing, personal hygiene, continence, toileting); frailty assessed by Clinical Frailty Scale;[12] comorbidity burden expressed as age-adjusted Charlson Comorbidity Index (CCI);[13] pre-existing geriatric syndromes (cognitive impairment, previous falls, immobility, iatrogenicity/polypharmacy, incontinence); and presence of hearing/visual impairment, referring to hearing/vision loss that was identified from history and examination. The admission diagnosis was defined as the initial working diagnosis documented by the attending physician who judged that inpatient care was required, which could be to an acute hospital or a subacute unit, whichever came first.

Assessment of Nutritional Status

Mini Nutritional Assessment-Short Form (MNA-SF) was performed on admission to identify patients who were malnourished or at risk of malnutrition.[14] MNA-SF, which consists of anthropometry data, general status, dietary habits, self-perceived health, and nutrition states, is a validated nutritional assessment tool in older patients, including elderly acute medical patients and the local older population.[15-17] It categorises patients to be malnourished, at risk of malnutrition, and normal if they score 0–7, 8–11, 12–14, respectively.[14] It is done by the clinician in charge during admission to the ward, and it is usually performed in conjunction with comprehensive geriatric assessment (CGA). CGA is defined as a multidimensional interdisciplinary diagnostic process focused on determining a frail older person's medical, psychological, and functional capability to develop a coordinated and integrated plan for treatment and long-term follow-up.[18] The components of CGA are shown in Figure 1. Existing literature had demonstrated the efficacy of performing CGA on admission in reducing mortality and care home discharge at 3–12 months of follow-up.[19]

Nutritional Management and In-Hospital Outcomes

The nutritional management report included dietitian review, prescription of oral nutritional supplements (ONS), and multivitamins. Decisions on nutritional management were dependent on the clinician's judgement and dietitian review. The in-hospital outcomes investigated were hospital-associated complications (delirium, functional decline, new onset of incontinence, inpatient falls, inpatient pressure injuries),[20] hospital-acquired infection, institutionalisation, and inpatient mortality.

Statistical Analysis

Analyses were performed using SPSS version 26. Continuous data were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) depending on their distribution. Categorical data were expressed as frequencies and percentages. Multiple hospital-associated complications referred to the development of two or more of the following complications: delirium, functional decline, new onset of incontinence, inpatient falls, inpatient pressure injury, and hospital-acquired infection. Associations between categorical variables were assessed using Pearson's chi-squared test, while the associations between continuous variables were assessed using the one-way ANOVA test or Kruskal-Wallis test depending on the distribution. The significance level of all the statistical tests was set at $p<0.05$. Analyses were only performed on available data.

Ethics Statement

This study was conducted following the ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. The research protocol was approved by the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (NMRR ID: NMRR-21-655-59132- IIR).

RESULTS

During the 3-month study period, 94 patients were admitted to the Subacute Geriatric Ward of Kuala Lumpur Hospital. After excluding patients who were aged below 60 (n=19) and recurrent admission (n=2), 73 patients were included in the analysis. The mean age was 74.4 (7.6). Majority were women (43/73, 58.9%). Patient baseline characteristics are shown in Table I. Twenty-eight (38.4%) and 27 (37.0%) patients were identified to be malnourished and at risk of malnutrition, respectively. The mean MNA-SF score was 8.6 (3.9).

COVID-19 pneumonia (21/73, 28.8%) was the commonest admission diagnosis followed by other infections, falls or fractures, and neurological disorders (Table I). A lower rate of malnutrition was reported among patients admitted for COVID-19 pneumonia. There was no association between worsening nutritional status with other admission diagnoses (Table 1).

The nutritional management of patients with different nutritional statuses during hospitalisation is shown in Figure 2. Majority were reviewed by dietitians (52; 71.2%) and given ONS prescriptions (44; 60.3%). Prescription of multivitamins (21; 28.8%) was less common. Two out of 28 malnourished patients and 8/27 patients at risk of malnutrition did not receive any of the specified nutritional management. All patients who had dysphagia and required enteral tube feeding during their hospitalisation (17; 23.3%) were reviewed by dietitians. There was no difference in the rate of malnutrition between patients who had dysphagia and those who did not (38.5% versus 38.3%). Three patients had been on enteral tube feeding before admission, and they were all malnourished.

Table I: Characteristics of patients who were admitted to the Subacute Geriatric Ward

	All (N=73) n(%)	Normal (N=18) n(%)	At risk of malnutrition (N=27)	Malnourished (N=28) n(%)	p
Age(year)[a]	74.7±7.6	68.6±5.8	76.5±7.1	77.0±7.2	<0.001
Female	43(58.9)	10(55.6)	15(55.6)	18(64.3)	0.762
Ethnicity					
Malay	23(31.5)	5(27.8)	8(29.6)	10(35.7)	
Chinese	34(46.6)	9(50.0)	14(51.9)	11(39.3)	
Indian	15(20.5)	3(16.7)	5(18.5)	7(25.0)	
Others	1(1.4)	1(5.6)	0	0	
Nursing Home Resident	6(8.2)	0	4(14.8)	2(7.1)	-
BADL independent	47(64.4)	18(100.0)	19(70.4)	10(35.7)	<0.001
Ambulation					<0.001
Independent	34(46.6)	17(94.4)	10(37.0)	7(25.0)	
Walking stick/frame	18(24.7)	1(5.6)	10(37.0)	7(25.0)	
Chair or bedbound	21(28.8)	0	7(25.9)	14(50.0)	
Geriatric Syndromes					
Previous falls	40(54.8)	5(27.8)	18(66.7)	17(60.7)	0.027
Cognitive impairment	30(41.1)	1(5.6)	11(40.7)	18(64.3)	<0.001
Incontinence	19(26.0)	2(11.1)	5(18.5)	12(42.9)	0.030
Immobility	18(24.7)	0	5(18.5)	13(46.4)	0.001
Iatrogenicity/polypharmacy	12(16.4)	1(5.6)	(14.8)	7(25.0)	-
Comorbidities					
Hypertension	60(82.2)	11(61.1)	26(96.3)	23(82.1)	-
Diabetes mellitus	54(74.0)	12(66.7)	20(74.1)	22(78.6)	0.668
Stroke	28(38.4)	5(27.8)	14(51.9)	9(32.1)	0.184
Ischaemic heart disease	22(30.1)	6(33.3)	8(29.6)	8(28.6)	0.940
Arthritis	21(28.8)	1(5.6)	12(44.4)	8(28.6)	0.019
Dementia	18(24.7)	0	10(37.0)	8(28.6)	0.015
Chronic kidney disease	17(23.3)	2(11.1)	8(29.6)	7(25.0)	0.342
Congestive cardiac failure	10(13.7)	3(16.7)	4(14.8)	3(10.7)	-
Depression	8(11.0)	1(5.6)	2(7.4)	5(17.9)	-
Malignancy	5(6.8)	2(11.5)	1(3.7)	2(7.1)	
Charlson Comorbidity Index[b]	6.0(4.0 —7.0)	4.0(3.0 —5.0)	7.0(4.0 —8.0)	6.0(4.0 —8.0)	0.001
Clinical Frailty Scale[b]	5.0(4.0 —6.0)	4.0(3.0 —4.0)	6.0(4.0 —6.0)	6.0(5.0 —7.0)	<0.001
Visual impairment	28(38.4)	4(22.2)	12(44.4)	12(42.9)	0.266
Hearing impairment	7(9.6)	2(11.1)	2(7.4)	3(10.7)	-
Admission Diagnosis					
COVID-19 pneumonia	21(28.8)	11(61.1)	5(18.5)	5(17.9)	0.002
Other infections	16(21.9)	2(11.1)	7(25.9)	7(25.0)	0.441
Falls or fracture	10(13.7)	1(5.6)	3(11.1)	6(21.4)	-
Neurological disorders	10(13.7)	1(5.6)	6(22.2)	3(10.7)	-
Cardiac events	6(8.2)	1(5.6)	3(11.1)	2(7.1)	-
Gastrointestinal bleeding	5(6.8)	1(5.6)	1(3.7)	3(10.7)	-
Others	5(6.8)	1(5.6)	2(7.4)	2(7.1)	-
Length of stay[b]	17.0(11.5 —26.5)	20.0(13.0 —27.3)	20.0(6.0 —34.0)	17.0(11.0 —24.8)	0.754

BADL, Basic activities of daily living
[a]Mean(SD)
[b]Median(IQR)
p-values obtained using the one-way ANOVA test, Pearson's chi-squares test, and Kruskal-Wallis test
Other infections: Non-COVID-19 pneumonia, urinary tract infections, skin and soft tissue infections
Neurological disorders: Ischaemic stroke, intracerebral haemorrhage, seizure, and dementia
Cardiac events: Acute coronary syndrome, acute heart failure, and arrhythmia
Others: Haematological disorders, endocrine emergencies, and electrolyte imbalance

The median (IQR) length of stay was 17.0 (11.5–26.5) days. The frequencies and rates of in-hospital outcomes are shown in Table II. Functional decline was the commonest hospital-associated complication followed by hospital-acquired infections and delirium (Table II). Forty-four (60.3%) patients had developed multiple hospital-associated complications, and the percentage of hospital-associated complications per patient is shown in Figure 3. The mortality rate was 13.7% (Table II). Despite the lack of association with individual outcomes, a higher rate of multiple hospital-associated complications was observed as nutritional status deteriorated (Table II). Total number of hospital-associated complications was not demonstrated to be increased with worsened malnourished state (Table II).

DISCUSSION

This is the first study looking at in-hospital outcomes of older patients with malnutrition in Malaysia. Three-quarters were either malnourished or at risk of malnutrition. Various associating factors of malnutrition were identified, namely increased age, inability to perform basic activities of daily

Table II: In-hospital outcomes of patients who were admitted to the Subacute Geriatric Ward

	All (N=73) n(%)	Normal (N=18) n(%)	At risk of malnutrition (N=27) n(%)	Malnourished (N=28) n(%)	p
Hospital-Associated Complications					
Functional decline	49(67.1)	11(61.1)	16(59.3)	22(78.6)	0.257
Hospital-acquired infection	36(49.3)	6(33.3)	14(51.9)	16(57.1)	0.273
Delirium	30(41.1)	4(22.2)	13(48.1)	13(46.4)	0.171
Inpatient pressure injury	20(27.4)	4(22.2)	10(37.0)	6(21.4)	0.367
New onset of incontinence	19(26.0)	3(16.7)	9(33.3)	7(25.0)	0.453
Inpatient falls	2(2.7)	0	1(3.7)	1(3.6)	-
Number of hospital-associated complications[a]	2.0(1.0 —3.0)	1.0(0 —2.0)	2.0(0 —3.0)	2(1.0 —4.0)	0.158
Multiple hospital-associated complications	44(60.3)	6(33.3)	17(63.0)	21(75.0)	0.018
Institutionalisation	8(11.0)	1(5.6)	4(14.8)	3(10.7)	-
Mortality	10(13.7)	1(5.6)	4(14.8)	5(17.9)	-

p-values obtained using Pearson's chi-squares test and Kruskal-Wallis test
[a]Median(IQR)
Multiple hospital-associated complications: development of two or more of the following complications: delirium, functional decline, new onset of incontinence, inpatient falls, inpatient pressure injury, and hospital-acquired infection.

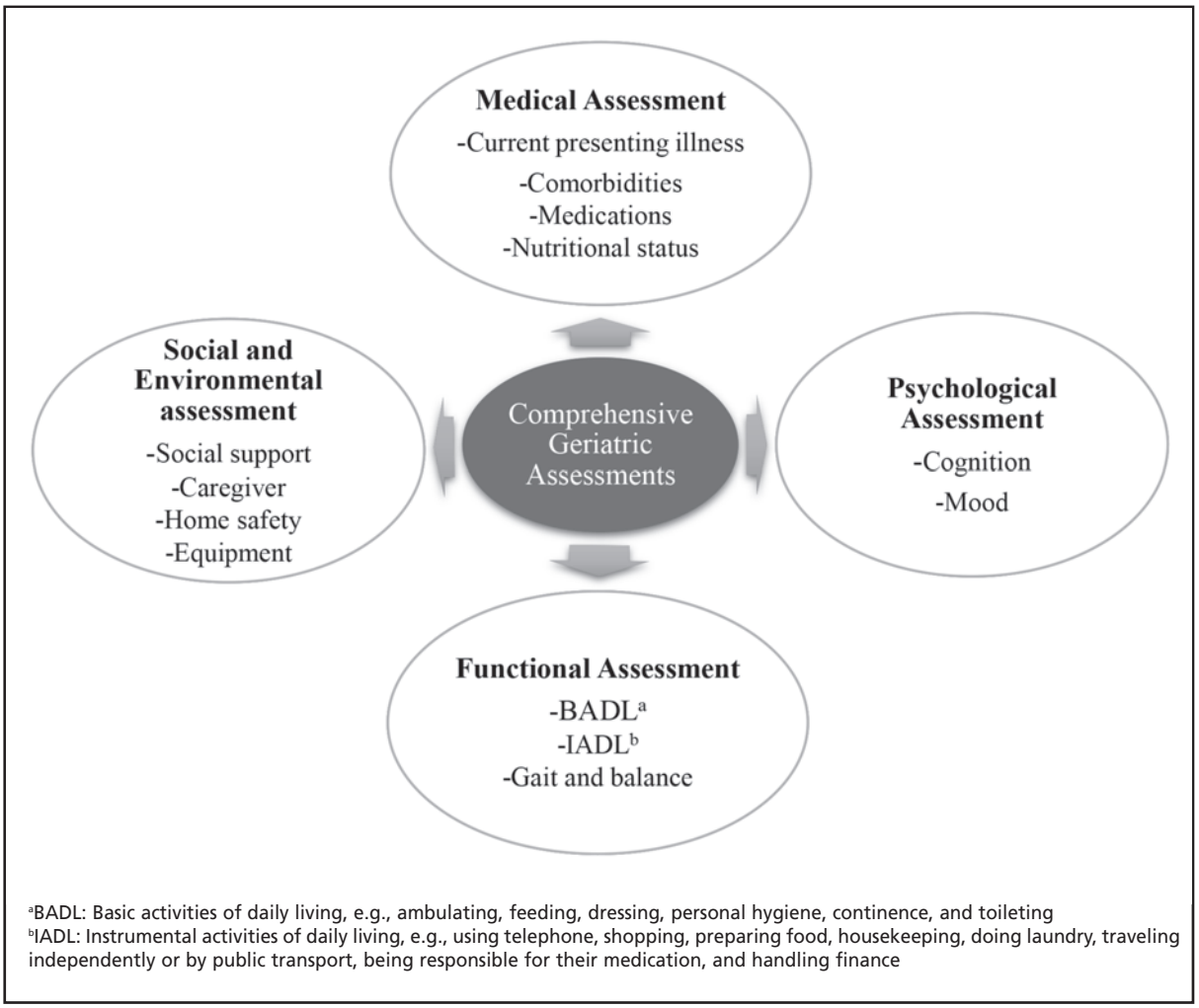

Fig. 1: Components of comprehensive geriatric assessments.

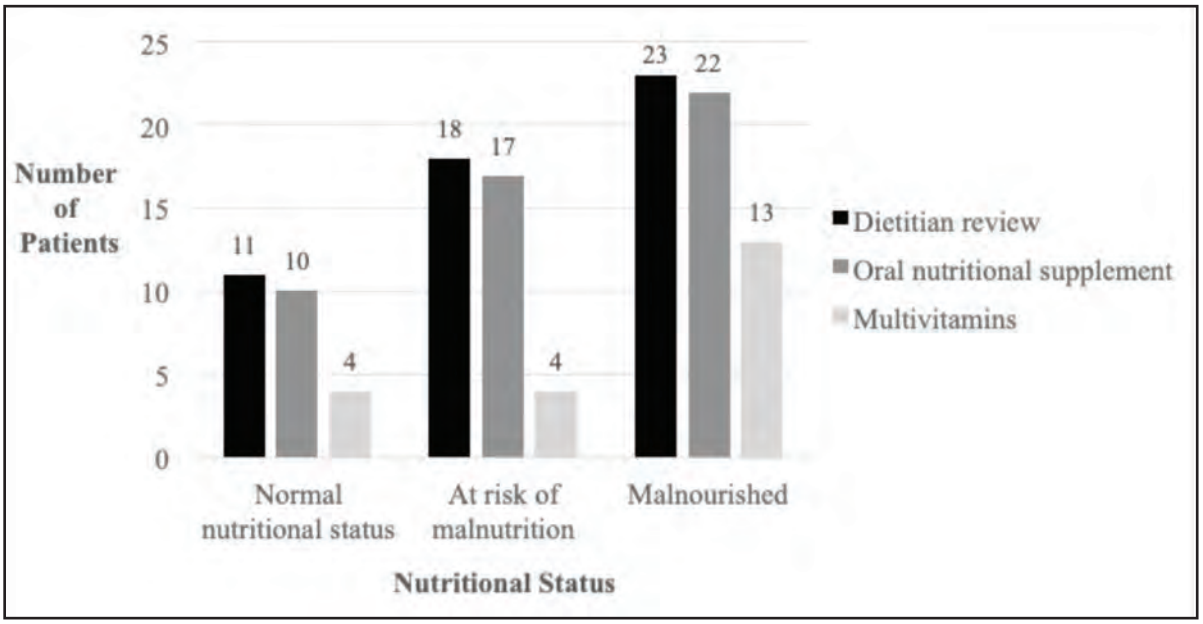

Fig. 2: Nutritional management provided according to nutritional status. N = 73. Normal nutritional status, n=18; At risk of malnutrition, n=27; Malnourished, n=28.

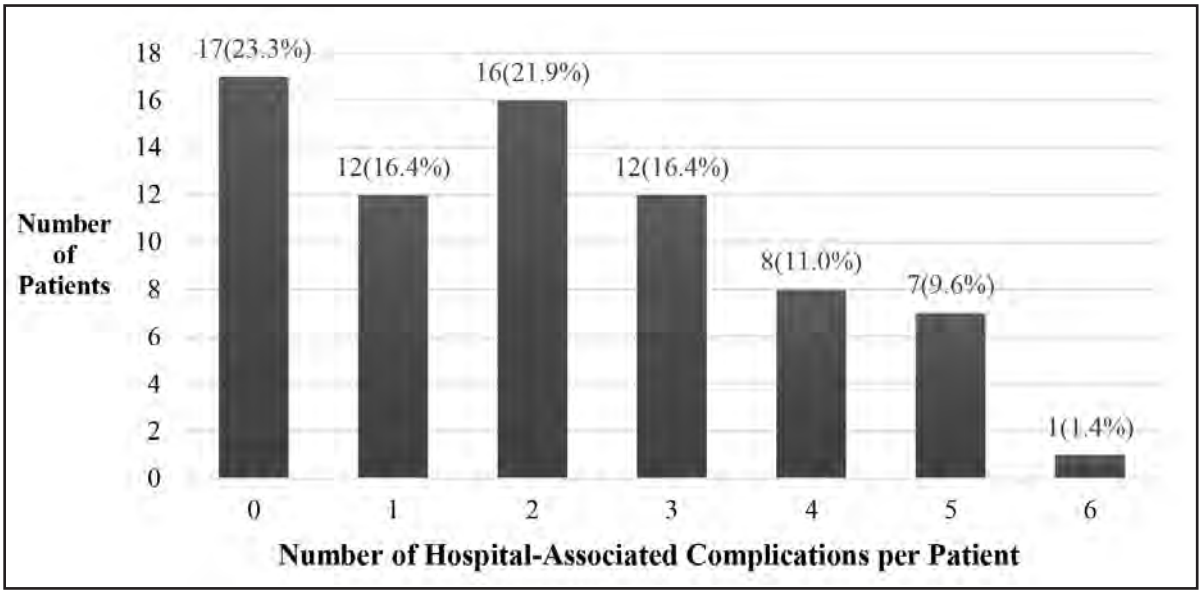

Fig. 3: Number of hospital-associated complications (delirium, functional decline, new onset of incontinence, inpatient falls, inpatient pressure injuries, and hospital-acquired infection) per patient.

living (BADL), immobility, cognitive impairment, comorbidity burden, and frailty. Its association with multiple hospital-associated complications was not unanticipated as a large majority of malnourished older patients were frail.

The reported prevalence of malnutrition was higher than prior local studies. This could be contributed by the discrepancy in patient characteristics as the patient admitted to the Subacute Geriatric Ward were more likely to have pre-existing geriatric syndromes compared to those admitted to the general medical ward. Our findings of associations between age[21,22] and pre-existing geriatric syndrome[23] with malnutrition were consistent with existing literature. Length of stay was not included as an adverse outcome as it could be determined by rehabilitation progress in the study setting. The finding of a higher rate of complications among malnourished patients without statistically significant association could be contributed by a small number of participants. Nevertheless, similar findings had been reported in an earlier study.[24] Loss of protein, which is a common feature of malnutrition, renders older adults to be immunocompromised and sarcopenic, which in turn leads to delayed recovery, increased susceptivity to infection, instability, and immobility.[25] These detrimental effects of

malnutrition could have driven the development of hospital-associated complications. Although this study was unable to establish a causal link between malnutrition and hospital-associated complications, the MNA-SF assessment on admission might have reduced the likelihood that malnutrition was induced by complications during hospitalisation.

MNA is the most widely used screening tool and a shorter form of the MNA (MNA-SF) is designed exclusively for older patients.[26] It is a simple validated tool for assessing nutritional status among older acute medical patients.[16] Although there were concerns about its accuracy and reliability among patients who could not complete the questions themselves, particularly those who were cognitively impaired,[27] this can be overcome by acquiring collateral history from their family members or caregivers to complete the questions,[28] and this has been a common practice in the study setting. As MNA-SF was conducted on admission, the impact of dysphagia on nutritional status may not be imminent, especially because most patients did not have dysphagia before admission. This could explain our finding that a similar rate of malnutrition was found between patients with and without dysphagia. Regrettably, there were patients with malnutrition who did not receive any of the specified nutritional management. The explanations discussed included a recent dietitian's review before admission and a brief hospital stay. However, the precise reasons were unknown, and the clinician's oversight could not be excluded.

This study was limited by the small sample size and was a single-centre retrospective study. We could not rule out selection bias as the admission to the Subacute Geriatric Ward was determined based on bed availability and the clinician's judgment on the benefit or suitability of admission. Socioeconomic factors were not investigated in this study, and they had been comprehensively discussed in a large local community study.[29] The accuracy of data was dependent on clinicians' documentation as data were extracted from hospital medical records. Outcomes studied here, such as delirium and functional decline, may lack standardisations. The amount of data that could be extracted was limited to what had been recorded. We did not capture details on the nutritional management, such as frequency of dietitian reviews, compliance to dietary advice, and the types of oral nutritional supplements. Limited by the study design, we could not conclude the efficacy of nutritional management on patient outcomes. Instead, long-term outcomes such as readmission rate and 3- or 6-month mortality should be evaluated.

The optimal management strategy of malnutrition is characterised by an individualised nutritional care plan that involves screening and detailed assessment, multidisciplinary teamwork, and patient-centred care.[30] Nevertheless, assessment of malnutrition is not a mandatory process in Malaysian government hospitals. The management reported in this study (dietitian review, prescription of oral nutritional supplements, and oral multivitamins) should not be regarded as the sole management of malnutrition. The affordability of oral nutritional supplements limits their use, especially after discharge from the hospital. Access to oral multivitamins is not a concern in many Malaysian government hospitals and subsequently becomes a common practice that lacks support from evidence. Injudicious use results not only in extra pill counts but also in unfavourable effects. Efforts should be given to addressing oral care, drug–drug interaction, or polypharmacy in addition to treating acute medical issues. Patients' preferences and cultural backgrounds should not be neglected in formulating dietary plans, especially in this multiracial and multicultural nation. As malnutrition is a multifactorial condition, service improvement projects on adherence to active identification of various factors of malnutrition merit consideration in the future. Barriers exist due to scarce resources in sustaining care delivered to tackle both personal and organisational factors contributing to malnutrition in hospitalised patients, which requires a multidisciplinary effort. In addition to an increased number of referrals to dietitians, re-evaluation of nutritional status and intervention are often required in vulnerable older patients with dynamic clinical conditions. We need a sufficient number of dietitians to meet these requirements, which is currently lacking in our service. Prioritising those who are malnourished or at risk of malnutrition as they are more prone to complications could be a sensible short-term strategy till more resources are available. This can be facilitated by the clinician's commitment to nutritional assessment upon admission and preferably periodic assessment during the hospital stay. Future research should be directed to the reassessment of nutritional status.

CONCLUSION

Hospital malnutrition is prevalent among older patients in Malaysia. Unidentified malnutrition is not justified as it subjects older patients to multiple adverse outcomes. Management of malnutrition is a crucial element of geriatric care. The implementation of the Malaysian Diagnosis Related Group (DRG) case-mix system as a funding and reimbursement tool could only resolve the obstacles in sustaining nutritional care plans in hospital settings, provided that prompt and accurate documentation of malnutrition and its associated complications are in place. This study's findings will serve as the foundation for the change in the delivery of nutritional care to hospitalised older patients.

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CONFLICTS OF INTEREST DISCLOSURES

The researchers claim no conflicts of interest.

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REFERENCES

1. Leslie W, Hankey C. Aging, nutritional status and health. Healthcare (Basel, Switzerland) 2015; 3(3): 648-58.
2. Lekamwasam R, Lekamwasam S. Effects of COVID-19 pandemic on health and wellbeing of older people: A comprehensive review. Ann Geriatr Med Res 2020; 24(3): 166-72.
3. Rasheed S, Woods RT. Malnutrition and associated clinical outcomes in hospitalized patients aged 60 and older: An observational study in rural Wales. J Nutr Gerontol Geriatr 2013; 32(1): 71-80.
4. Ruiz AJ, Buitrago G, Rodríguez N, Gómez G, Sulo S, Gómez C et al. Clinical and economic outcomes associated with malnutrition in hospitalized patients. Clin Nutr 2019; 38(3): 1310-6.
5. Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. Clin Nutr 2003; 22(3): 235-9.
6. Lim SL, Ong KC, Chan YH, Loke WC, Ferguson M, Daniels L. Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality. Clin Nutr 2012; 31(3): 345-50.
7. Institutes of Public Health Ministry of Health Malaysia. National Health and Morbidity Survey (NHMS) 2018: Key Findings from the Elderly Health Survey; 2019 [cited March 2021]. Available from: http://iku.moh.gov.my/images/IKU/Document/REPORT/NHMS2018/ReportNHMS2018.pdf.
8. Sakinah H, Tan SL. Validity of a local nutritional screening tool in hospitalized Malaysian elderly patients. Health Environ J 2012; 3(3): 59-65.
9. Tan SL, Harith S, Abdullah H, Yusuf WN. Re-evaluation of malnutrition risk screening tool-hospital (MRST-H) for geriatric patients: A multicentre study in Peninsular Malaysia. Sains Malaysiana 2016; 45(9): 1311-7.
10. Krumholz HM. Post-hospital syndrome–an acquired, transient condition of generalized risk. N Engl J Med 2013; 368: 100-2.
11. Latiff NSMA, Ahmad N, Islahudin F. Complications associated with malnutrition in elective surgical patients in a Malaysian setting. Trop J Pharm Res 2016; 15: 1321-5.
12. Rockwood K, Theou O. Using the clinical frailty scale in allocating scarce health care resources. Can Geriatr J 2020; 23(3): 210-5.
13. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994; 47(11): 1245-51.
14. Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T et al. Validation of the Mini Nutritional Assessment Short-Form (MNA-SF): A practical tool for identification of nutritional status. J Nutr Health Aging 2009; 13(9): 782-8.
15. Rubenstein LZ, Harker JO, Salvà A, Guigoz Y, Vellas B. Screening for undernutrition in geriatric practice: Developing the Short-Form Mini-Nutritional Assessment (MNA-SF). J Gerontol A Biol Sci Med Sci 2001; 56(6): M366-72.
16. Ranhoff AH, Gjøen AU, Mowé M. Screening for malnutrition in elderly acute medical patients: The usefulness of MNA-SF. J Nutr Health Aging 2005; 9(4): 221-5.
17. Suzana S Jr, Siti Saifa H. Validation of nutritional screening tools against anthropometric and functional assessments among elderly people in Selangor. Malays J Nutr 2007; 13(1): 29-44.
18. Rubenstein LZ, Stuck AE, Siu AL, Wieland D. Impact of geriatric evaluation and management programs on defined outcomes: Overview of the evidence. J Am Geriatr Soc 1991; 39: 8S-16S.
19. Ellis G, Gardner M, Tsiachristas A, et al. Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane Database Syst Rev 2017; 9(9): CD006211.
20. Mudge AM, McRae P, Hubbard RE, et al. Hospital-associated complications of older people: A proposed multicomponent outcome for acute care. J Am Geriatr Soc 2019; 67(2): 352-6.
21. Damayanthi HDWT, Moy FM, Abdullah KL, Dharmaratne SD. Prevalence of malnutrition and associated factors among community-dwelling older persons in Sri Lanka: A cross-sectional study. BMC Geriatr 2018; 18(1): 199.
22. Orlandoni P, Venturini C, Jukic Peladic N, Costantini A, Di Rosa M, Cola C et al. Malnutrition upon hospital admission in geriatric patients: Why assess it? Front Nutr 2017; 4: 50.
23. Saka B, Kaya O, Ozturk GB, Erten N, Karan MA. Malnutrition in the elderly and its relationship with other geriatric syndromes. Clin Nutr 2010; 29(6): 745-8.
24. Dominguez R. Burden of malnutrition in a tertiary care hospital in Baguio City. SAGE Open 2013; 3. doi: 10.1177/2158244013504936.
25. Volkert D, Beck AM, Cederholm T, Cereda E, Cruz-Jentoft A, Goisser S et al. Management of malnutrition in older patients – current approaches, evidence and open questions. J Clin Med 2019; 8(7): 974.
26. Morley JE. Assessment of malnutrition in older persons: A focus on the mini nutritional assessment. J Nutr Health Aging 2011; 15(2): 87-90.
27. Poulia KA, Yannakoulia M, Karageorgou D, Gamaletsou M, Panagiotakos DB, Sipsas NV et al. Evaluation of the efficacy of six nutritional screening tools to predict malnutrition in the elderly. Clin Nutr 2012; 31(3): 378-85.
28. Orsitto G. The mini-nutritional assessment and cognitive impairment in older people. In: Martin CR, Preedy V, Editors. Diet and nutrition in dementia and cognitive decline. Elsevier Inc; 2015: 1174-85.
29. Ahmad MH, Salleh R, Cheong SM, Pardi M, Che Abdul Rahim N, Shahri N et al. Malnutrition among the elderly in Malaysia and its associated factors: Findings from the National Health and Morbidity Survey 2018. J Nutr Metab 2021: 6639935.
30. Avelino-Silva T, Jaluul O. Malnutrition in hospitalized older patients: Management strategies to improve patient care and clinical outcomes. Int. J. Gerontol 2017; 11(2): 56-61.

ORIGINAL ARTICLE

Brain evoked response audiometry recording from the mastoid and earlobe electrodes in normal-hearing children

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ABSTRACT

Background: Electrode placement plays an important role in Brain Evoked Response Audiometry (BERA) recording. It is important to measure wave latency and amplitude accurately in determining hearing level. Young children usually have limited mastoid area, and in certain condition, it is often difficult to place the vibrator and electrodes coinciding on the mastoid. Therefore, earlobe electrode is considered as an alternative placement. Purpose: The aim was to correlate the wave V latency and amplitude on the mastoid and earlobe electrodes in BERA recording.

Materials and methods: Our study was a cross-sectional study conducted at Cipto Mangunkusumo Hospital, Jakarta, Indonesia, between November 2020 and November 2021. Our subjects were infants and young children with normal hearing who underwent BERA examination. Electrodes were used to record BERA, and the electrodes were placed over the earlobes and mastoid area. Clicks at 20, 40, and 60 dB and tone burst at 500 Hz were used as stimuli for both ears.

Result: Fifty subjects (100 ears) were included in the study. Our statistical analysis showed that there was a strong correlation between wave V latencies from mastoid and earlobe electrode. Moderate correlation was also found in wave V amplitude between both electrodes.

Conclusion: Our study has demonstrated that placing electrodes on the earlobe area is reliable, particularly in certain condition when placing the electrodes on the mastoid area is not possible.

KEYWORDS:
Brain Evoked Response Audiometry, Wave latency, Electrode placement, Mastoid, Earlobe

INTRODUCTION

Hearing is one of the sensory functions that is essential to daily life. Hearing loss will cause limited communication skills and hinder the process of growth and development, especially in infants. An examination to evaluate peripheral hearing thresholds using Brain Evoked Response Audiometry (BERA) was introduced in 1970 by Jewett. BERA examination is a technique for measuring the activity response of the auditory nerves starting from the cochlea to the brain stem. It causes changes in electrical potential after a sound stimulation is given, through either air or bone.[1,2] Auditory Evoked Potential (AEP) is classified based on latency, anatomical generator, and its relationship with the origin of the stimulus, which is endogenous or exogenous.[3]

BERA examination is used for both screening and diagnostics among infants. AEP is an electrical potential evoked in the brain due to sound stimulation, which can be recorded by placing electrodes on the surface of the scalp. In general, the electrodes are placed both on the mastoid and vertex. Waves I, III, and V are usually detected in BERA examinations for infants. Wave I amplitude is usually found greater in infants than in adults. In addition to amplitude, an assessment of wave latency is also carried out, which includes absolute, inter-wave, and inter-ear latencies. Absolute latency and inter-peak interval are the most widely, clinically used assessment. Within the normal hearing threshold, wave V can be easily identified to the lowest intensity; therefore, it can be used to estimate peripheral hearing threshold.[1] Compared to other parameters, wave V latencies are the most important to be analysed, especially their correlation with age, sex, and amount of hearing loss.[4]

The length of the latency is influenced by several factors including the placement of the surface electrodes. The placement of electrodes must consider several factors, namely: (1) how to prepare the skin for electrode placement, (2) types of electrodes available for recording auditory evoked responses, (3) electrode sites or locations, (4) customary labels used to describe electrode sites, (5) electrode terminology such as non-inverting versus inverting, and (6) electrode combinations or arrays.[2]

The absolute latency is influenced by several factors including the placement of the surface electrodes. It is recommended that surface electrodes should be placed on the scalp, and generally, the electrodes are placed on the mastoid area. The area is recommended for electrode placement since it is easy to clean and hairless.[5] The scalp hair should be oil-free. The patient's hair, therefore, should be washed using shampoo on the day of examination.6 The non-inverting electrode is placed over the vertex of the head, and the inverting electrode is placed over the earlobe or mastoid prominence. Electrodes that are placed over the mastoid process or earlobe should be symmetrical.[7]

Young children usually have limited mastoid area; therefore, it is often difficult to perform examination when we need to evaluate the bone conduction threshold due to the position of

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the bone vibrator and electrodes coinciding on the mastoid. Electrode placement on the earlobe was considered as an alternative to electrode placement on the mastoid. Therefore, we aim to study the correlation between mean latency and amplitude on earlobe electrodes and mastoid electrodes in normal-hearing children.

MATERIALS AND METHODS

Our study was a cross-sectional study, which was conducted between November 2020 and January 2021. Our subjects were infants and children with normal hearing who had been confirmed with BERA at Cipto Mangunkusumo Hospital. Our inclusion criteria were term infants (0 to 1 years old with normal gestational age of 37–42 weeks) and young children aged 1 to 5 years with normal peripheral hearing threshold (20 dB). Patients who did not complete BERA examination under any circumstances such as restlessness and uncooperativeness during the procedure were excluded from this study. The subjects were examined using headlamp, otoscope, nasal speculum, and tongue spatula. Furthermore, inter-acoustic tympanometry, Biologic Navigator Pro OAE, and BERA were also used in this study.

Subjects with normal results of tympanogram and OAE (Oto Acoustic Emission) were further evaluated using BERA examination. Infants underwent BERA examination without sedation, while young children were given sedation (chloralhydrate 50 mg/kg BW). Electrodes were placed on both the mastoid and vertex after the skin was cleaned using abrasive electrode prep gel. The same preparation was also made on the earlobe by cleaning and removing the accessories such as earrings.

Furthermore, electrode discs were filled with conduction paste and were attached to the vertex and mastoid area of both ears. The parameters used were rarefaction polarity in click stimuli and alternating polarity in tone burst stimuli. The stimulus rate was 27.7/second. The recording was done at an intensity of 60, 40, and 20 dB for both ears. The 80-dB intensity was not performed considering the normal hearing threshold of the subjects. When the wave V was detected at 20 dB (normal peripheral hearing threshold), an additional recording was performed by moving the electrodes from the mastoid to the earlobes, and we used the same parameters. The absolute latency and amplitude of wave V were then recorded, which served as inputs to our data. The results of the examination were then analysed using SPSS version 26.0.

RESULTS

Fifty subjects (32 males and 18 females) participated in the study (Table I). Their age was between 2 and 60 months (median age = 24.82 months). In total, 100 ears were included and analysed to evaluate data distribution. Statistical analysis demonstrated that wave latency and amplitude in all subjects had a normal distribution. In Tables II-IV, we present data of wave V latency and amplitude of both electrode placements, i.e., on the mastoid and earlobe area. An example of BERA wave from the earlobe electrode and mastoid electrode is presented in Figure 1. The statistical analysis showed that wave V latency of electrode placement on the mastoid and earlobe with click stimuli at 60, 40, and 20 dB had a strong to very strong correlation with R values ranging between 0.800 and 0.944 (p=0.00). Meanwhile, with an alternating stimulus of tone burst at 500 Hz, the wave latency of 60, 40, and 20 dB had also shown a moderate to strong correlation between both recordings with an R-value

Table I: Subject characteristics

	0–24 months	24–60 months	Total (subjects)
Gender			
Male	15	17	32
Female	12	6	18
Total (subjects)	27	23	50

Table II: Correlation between wave V obtained from electrodes placed over mastoid and earlobe area at 60-dB intensity

	Latency Mean (±SD)	R	p	Amplitude Mean (SD)	R	p
Right Ear ME (Click)	5.85 (0.4)	0.944**	0.000	0.09 (0.05)	0.517**	0.000
Right Ear LE (Click)	5.93 (0.37)			0.10 (0.04)		
Left Ear ME (Click)	5.85 (0.38)	0.800**	0.000	0.11 (0.07)	0.508**	0.000
Left Ear LE (Click)	5.96 (0.41)			0.11 (0.07)		
Right Ear ME (Tone Burst 500 Hz)	8.09 (0.76)	0.913**	0.000	0.16 (0.08)	0.598**	0.000
Right Ear LE (Tone Burst 500 Hz)	8.23 (0.68)			0.20 (0.09)		
Left Ear ME (Tone Burst 500 Hz)	8.05 (0.72)	0.896**	0.000	0.22 (0.11)	0.716**	0.000
Left Ear LE (Tone Burst 500 Hz)	8.24 (0.69)			0.23 (0.08)		

**Pearson Correlation Test
ME: Mastoid Electrode
LE: Earlobe Electrode

Table III: Correlation between wave V obtained from electrodes on the earlobe and the mastoid area at 40-dB intensity

	Latency Mean (±SD)	R	p	Amplitude Mean (SD)	R	p
Right Ear ME (Click)	6.43 (0.38)	0.842**	0.000	0.09 (0.05)	0.700**	0.000
Right Ear LE (Click)	6.52 (0.38)			0.07 (0.04)		
Left Ear ME (Click)	6.44 (0.37)	0.903**	0.000	0.08 (0.04)	0.467**	0.000
Left Ear LE (Click)	6.54 (0.39)			0.08 (0.04)		
Right Ear ME (Tone Burst 500 Hz)	9.64 (0.91)	0.588**	0.000	0.13 (0.06)	0.585**	0.000
Right Ear LE (Tone Burst 500 Hz)	9.81 (0.97)			0.13 (0.05)		
Left Ear ME (Tone Burst 500 Hz)	9.60 (0.9)	0.688**	0.000	0.16 (0.07)	0.618**	0.000
Left Ear LE (Tone Burst 500 Hz)	9.76 (0.81)			0.17 (0.07)		

**Pearson Correlation Test
ME: Mastoid Electrode

Table IV: Correlation between wave V obtained from electrodes on the mastoid and earlobe area at 20-dB intensity

	Latency Mean (SD)	R	p	Amplitude Mean (SD)	R	p
Right Ear ME (Click)	7.27 (0.41)	0.845**	0.000	0.06 (0.04)	0.644**	0.000
Right Ear LE (Click)	7.42 (0.45)			0.07 (0.05)		
Left Ear ME (Click)	7.30 (0.35)	0.881**	0.000	0.06 (0.04)	0.551**	0.000
Left Ear LE (Click)	7.43 (0.42)			0.08 (0.13)		
Right Ear ME (Tone Burst 500 Hz)	11.84 (0.79)	0.632**	0.000	0.10 (0.06)	0.789**	0.000
Right Ear LE (Tone Burst 500 Hz)	12.17 (0.78)			0.10 (0.06)		
Left Ear ME (Tone Burst 500 Hz)	11.91 (0.82)	0.649**	0.000	0.11 (0.6)	0.679**	0.000
Left Ear LE (Tone Burst 500 Hz)	12.1 (0.81)			0.11 (0.08)		

**Pearson Correlation Test
ME: Mastoid Electrode
LE: Earlobe Electrode

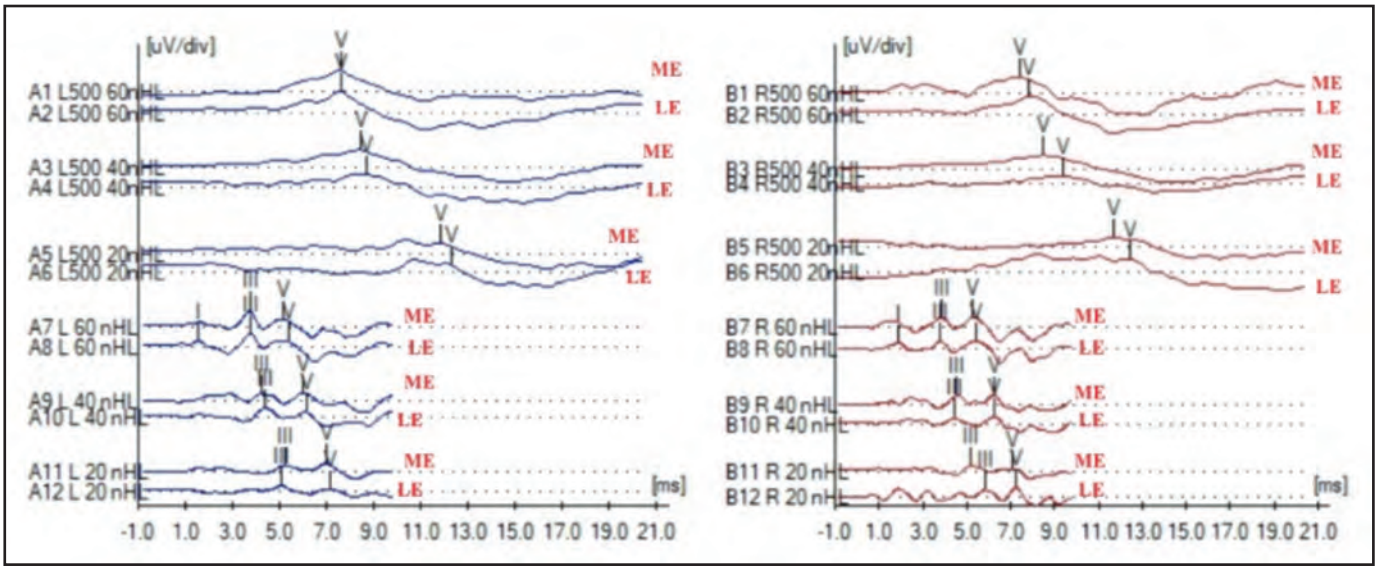

Fig. 1: Left and right ear BERA wave from the mastoid electrode (ME) and earlobe electrode (LE).

between 0.588 and 0.913 (p=0.00). The amplitude of wave V in both mastoid and earlobe electrode placement showed moderate correlation with R-values between 0.467 and 0.789 (p=0.00).

DISCUSSION

In our study, the BERA examinations were carried out twice for each subject by placing the electrode disc on the mastoid and the earlobe area in children. Our study collected the data that could be used as a reference for normal hearing children's wave latency when using electrodes placed on the earlobe. Assessment of wave latency and amplitude was performed for both recordings, and a strong to very strong correlation was found especially in click stimuli in intensities of 20, 40, and 60 dB. Such correlation showed that BERA wave recording with electrode placement on the earlobe is reliable even in children. Other study in adult patient found that the earlobe and mastoid are close enough to the potential generator or the cochlea for resulting latencies within normal limit.[8] Our study result was consistent with previous literature; however, the wave latency obtained from the lobe electrode is slightly longer than the mastoid electrode. This should be noted by the examiner, but this is negligible because the range is still within the normal limit.

Previous experimental recordings have shown that the amplitudes of cochlear and auditory nerve potentials become smaller as the distance between the physiological generators and recording site increases.[9] Wave V amplitude may slightly reduce with earlobe placement.[2] Our finding is also consistent with this literature and shows moderate wave V amplitude correlation between mastoid and earlobe electrode.

There are several advantages with electrode placement on the earlobe area such as the absence of muscle contraction, making distance between the electrode and the bone vibrator; thus, reducing electrical artifacts in bone conduction BERA recording. The placement of electrodes on the earlobe could also be beneficial in some cases, particularly when it is not possible to place the electrode on the mastoid area. However, one of the disadvantages is the possibility of electrode migration due to soft and flexible anatomy of the earlobe. This condition can be avoided by securing the earlobe electrode with tape. In the case of microtia/anotia, in which the earlobe is too small/missing, the electrode can be placed on the skin tag.[2]

Some research reports have suggested another option for electrode placement such as ear canal electrode. However, despite their advantages and disadvantages, the ear canal electrode size can still be too large for infants' ears, and there is a possibility that the electrode could dislodge or move. Atcherson et al.[3] found that there was no statistical advantage of ear canal electrodes for wave I enhancement compared to the earlobe or mastoid electrode placement.

There are some limitations in our study as we did not separate the subjects based on gender when conducting the analysis. Most of our subjects are males who tend to have longer latencies than females because of the comparable head size, while gender is one of the influencing factors that should be considered when evaluating BERA absolute latency.[10-12]

CONCLUSION

Our study has demonstrated that there is a strong correlation between wave V latency obtained from mastoid and earlobe electrode. Therefore, placing electrodes on the earlobes area is reliable, particularly in certain condition when placing the electrodes on the mastoid area is not possible.

ETHICAL AND CONSENT

Our study has received approval from the Ethics Committee (Faculty of Medicine Universitas Indonesia Protocol number 20-07-0840) and research permission from Cipto Mangunkusumo General Hospital. Informed consent has also been obtained from the patients' parents before the initiation of the study.

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REFERENCES

1. Hood LJ. Clinical Applications of the Auditory Brainstem Response. San Diego: Singular Publishing Group, Inc.; 1998.
2. Hall JW. eHandbook of Auditory Evoked Responses Amazon Digital Services; 2015.
3. Atcherson SR, Stoody TM. Auditory Electrophysiology: A Clinical Guide. New York Stuttgart: Thieme Medical Publishers Inc.; 2012.
4. Singh V, Agrawal U, Chaudhary AK, Ranjan M. Study of variation and latency of wave V of brain stem evoked response audiometry in North Central India. Indian J Otolaryngol Head Neck Surg 2019; 71(Suppl 2): 1408-11. doi:10.1007/s12070-018-1484-3.
5. Ray B, Raman S, Sen S, Sharma M, Ghosh KC, Saha AM. A study of brainstem auditory evoked responses in normal human subjects and normal variations as a function of stimulus and subject characteristics. Int J Res Med Sci 2016; 4 (9).
6. Atcherson RA, Lim TJ, Moore PC, Minaya CP. Comparison of auditory brainstem response peak measures using earlobe, mastoid, and custom ear canal reference electrodes. Audiology Research 2012; 2(1): e3.
7. Thiagaraja B. Brain stem evoked response audiometry. A review. Otolaryngology Online Journal 2012; 5(1).
8. Terlildsen K, Osterhammel P. The influence of reference electrode position on recordings of the auditory brainstem responses. Ear and Hearing 1981; 2: 9-14.
9. Coats AC. On electrocochleographic electrode design. J Acoust Soc Am 1974; 56: 708-11.
10. Dzulkarnain AA, Tengku Zam Zam TZH, Azed Z, Zuri MI, Sulaiman NH. Effects of electrode position on tone-burst-evoked auditory brainstem responses (ABR) in humans. Middle-East Journal of Scientific Research 2014; 21(8): 1180-7.
11. Jerger J, Hall J. Effects of age and sex on auditory brainstem response. Archives Otolaryngology 1980; 106: 387-91.
12. Trune DR, Mitchell C, Phillips DS. The relative importance of head size, gender and age on the auditory brainstem response. Hearing Research 1988; 32: 165-74.

ORIGINAL ARTICLE

Characteristics and quality of life in pemphigus patients

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ABSTRACT

Introduction: Pemphigus is an autoimmune blistering disease affecting the skin and mucus membranes. It is a debilitating skin condition with painful bullae and erosions, which may limit the patient's daily activities. Therefore, measuring the quality of life (QoL) from the perspective of physical, functional, social, and emotional well-being is important to address the disease burden. This study aims to review the demography and assess the impact of disease on QoL in pemphigus patients at the Department of Dermatology, Hospital Melaka.

Materials and methods: This is a single-centre, cross-sectional study on the characteristics and QoL among the pemphigus patients at the Department of Dermatology, Melaka General Hospital, from August 2020 to July 2021. Patients' information was collected, and each patient was assessed objectively on the disease severity physically using the Pemphigus Disease Area Index (PDAI) scoring system. The disease severity was then assessed subjectively, in which each participant was given three questionnaires to answer, namely the Dermatology Life Quality Index (DLQI), Visual Analogue Scale (VAS) for pain and itch, and Autoimmune Bullous Disease Quality of Life (ABQOL).

Results: There were a total of 30 pemphigus patients (13 males, 17 females), with an average age of 54.0 ± 13.6 years. Our study population had low median PDAI score (2.0 ± 4.0) with low median DLQI (3.0 ± 8.0) and ABQOL (11.0 ± 12.0). The median VAS scores for pain (1.0 ± 2.0) and itch (2.0 ± 3.0) were also low. Patients with tertiary educational qualification reported higher median DLQI (10.0 ± 12.0, p = 0.016) and ABQOL (21.0 ± 23.0, p = 0.026). Significant correlation was neither observed between PDAI and DLQI scores nor observed between PDAI and ABQOL scores. The DLQI and ABQOL scores were not affected by gender, age, ethnicity, and duration of illness.

Conclusion: Most of the patients in our study cohort had low DLQI and ABQOL scores, with mild clinical severity, as evidenced by low PDAI and VAS scores for both pain and itch. Disease severity had no correlation with QoL in our study. However, educational level showed significant influence on the QoL.

KEYWORDS:
Pemphigus, quality of life, characteristics, demography

INTRODUCTION

The word 'pemphigus' is derived from the Greek word pemphix meaning blister or bubble. Pemphigus is an autoimmune intraepithelial blistering disease affecting the skin and mucous membranes and potentially life threatening. It is mediated by circulating autoantibodies directed against antigens on the keratinocyte cell surfaces, causing loss of adhesion between keratinocytes and subsequently giving rise to blister formation and painful erosions on the skin and mucous membrane. The two major subtypes are pemphigus vulgaris (PV) and pemphigus foliaceous (PF). PV accounts for approximately 70% of pemphigus cases.[1] It is also considered the most severe form of the disease. Other subtypes of the pemphigus group are paraneoplastic pemphigus, drug-induced pemphigus, and Ig A pemphigus.

Pemphigus usually occurs in adults, with an average age of 40–60 years for PV and nonendemic PF. However, it may occur at any age. In some countries of the Middle East and Brazil, disease onset is earlier. A Brazilian study estimated that 17.7% of cases occur before the age of 30 years.[2] The incidence of PV worldwide varies from 0.1 to 0.5 cases per 100,000 population per year. In most countries, PV is more prevalent than PF. For example, PV accounts for 73% of cases of pemphigus in France. In Japan, the ratio of PV to PF is 2:1.[3] The male to female ratio for PV and PF appears to be equivalent or close to equivalent. However, there are studies showing imbalance in the gender distribution. Male to female PF patient ratio is 1:4 in Tunisia and 19:1 in an endemic location in Colombia.[4-5]

Pemphigus can be debilitating, particularly if the affected areas are of high visibility. Bullae and erosions secondary to the rupture of bullae may be painful and therefore limit the patient's daily activities, especially during the active stage. Based on the consensus statement by the International Pemphigus Committee in 2008, complete remission is defined as the absence of new or established lesions for at least 2 months, whereas partial remission is defined as the presence of transient new lesions that heal within 1 week.[6]

This severe debilitating disease has strong negative impact on the patients, both physically and psychosocially. Measuring the quality of life (QoL) is important in assessing the disease burden. The QoL encompasses the physical, functional, social, and emotional well-being of a person.[7] The World Health Organization (WHO) defines QoL as individuals' perception of their position in life in the context of the culture

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and value systems in which they live, and in relation to their goals, expectations, standards, and concerns.[8] Contributing factors to QoL include physical discomfort, time spent on treatment, staining of sheets, clothes with skin scales or blood, and the visible nature of skin diseases, which often brings negative reactions from the public, leading to low self-esteem.[9]

Several studies have been done worldwide on QoL in pemphigus patients. A study done in Korea revealed that pemphigus significantly impaired the QoL and significantly correlated with clinical severity.[7] An Egyptian study, as well as a local study at Selayang Hospital, Malaysia, showed that pemphigus decreased the patients' QoL.[10-11] The median PDAI score for Selayang cohort done in 2015 was 4 and median ABQOL score was 20.[11] To date, there are not many studies done on the QoL in pemphigus patients in Malaysia. The aim of this study was to review the demography and assess the impact of disease on QoL in pemphigus patients who were under the follow-up at the Department of Dermatology in Hospital Melaka. We expected to see the correlation of disease severity with the QoL in this study. Patients' satisfaction is crucial in pemphigus disease management. Clinicians evaluate patient clinically, but patients view their own disease in different manner. Better understanding of patients' needs and improving the QoL will lead to better management of the disease.[10]

MATERIALS AND METHODS

This was a cross-sectional study of pemphigus patients conducted at the Department of Dermatology, Melaka General Hospital, in which patients were observed at a single time point during the course of the disease. Universal sampling method was adopted, in which all pemphigus patients attending Dermatology clinic, Melaka General Hospital, from August 2020 to July 2021, were included. Inclusion criteria were patients who were 18 years old and above; who were diagnosed to have pemphigus clinically, confirmed with skin biopsy histopathology and direct immunofluorescence study; who were able to provide written informed consent; who could understand either English language or Bahasa Malaysia. Patients who were deemed mentally incapable of giving consent and patients with other concurrent dermatoses were excluded from this study.

The demographic data and disease profile of the participants were collected. Pemphigus severity was evaluated by two investigators, one dermatologist and one dermatology trainee, using the Pemphigus Disease Area Index (PDAI) score. Both the investigators discussed and decided on the PDAI score during the assessment. This aimed to reduce the inter-rater variability. The PDAI scoring system was developed by the International Pemphigus Committee. It has three components relating to the skin, scalp, and mucous membranes. Skin and mucous membranes were further subdivided into 12 anatomical sites, while scalp to four quadrants. Each site was reviewed, and a score was assigned according to the number of erosions, blisters, or new erythema. The total activity score for PDAI ranges from 0 to 250. The scores of PDAI were classified into mild (0–8), moderate (9–24), and severe (≥25).[12] PDAI had the highest validity and is recommended for use in pemphigus vulgaris.[13] This scoring system is recognised to be more reproducible than the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS).[7]

Each participant was given three questionnaires: the Dermatology Life Quality Index (DLQI), Autoimmune Bullous Disease Quality of Life (ABQOL), Visual Analogue Scale (VAS) for pain and itch. Patients were assessed using different questionnaires to ensure consistency in their responses. We expected the ABQOL to be correlated highly with the DLQI, as reported in a previous study.[14] In the event, if we found the answers provided by the participants in the questionnaires were not consistent, we would reassess the understanding of the language again, as it was one of the inclusion criteria. However, this did not happen. The other reason of using both DLQI and ABQOL is to compare with other studies, as certain studies used DLQI, such as the Korean study, while some used ABQOL, such as the study done in Selayang Hospital.[7,11]

DLQI is a skin-specific QoL assessment tool. The questionnaire in DLQI evaluates patient from different aspects, which include symptoms and feelings, daily activities, leisure, work or school, personal relationships, and treatment. The maximum DLQI score is 30, and the minimum score is 0. ABQOL questionnaire was developed by an Australian group and has been validated.[15] It is a reliable tool in measuring the impact of autoimmune bullous disease on QoL, in terms of pain, itch, clothes changes, healing, showering, pain in the oral cavity, gingival bleeding, food avoidance, embarrassment, depression, anxiety, friend and family, sexual activity, relationship, social life, work or study, and discrimination. The ABQOL score ranges from 0 to 51. For both DLQI and ABQOL, higher score reflects greater impairment in the patient's QoL. We implemented both English version as well as the validated Bahasa Malaysia version of the DLQI and ABQOL in this study.

Visual Analogue Scale (VAS) for pain and itch assessment is a psychometric response scale to measure subjective pain and itch perception. The validated VAS is a 10-cm line with number 0 (no pain or no itch) to number 10 (extremely painful or worst imaginable itch). Patient was asked to indicate his/her perceived pain or itch by marking the score on the scale. Pain and itch were assessed in ABQOL, from the aspects of frequency: never, occasionally, sometimes, or all the time. Meanwhile, VAS assessed the intensity of pain and itch.

DLQI and ABQOL were analysed against variables, such as gender, age group, ethnicity, educational level, pemphigus subtypes, comorbidities, employment, marital status, disease severity (mild if PDAI ≤ 8, moderate or severe if PDAI > 8), disease duration (<6 months or ≥6 months), disease activity (active; partial remission; complete remission), and treatment with corticosteroid only or with adjuvant immunosuppressant. Data were analysed using SPSS statistics software version 23.0. Categorical variables were described using frequencies and percentages. Numerical variables were described using mean ± standard deviation or median ± interquartile range. Correlation between

Table I: Effects of gender, age group, ethnicity, educational level, pemphigus subtypes, disease duration, comorbidities, PDAI, treatment, employment, and marital status on DLQI and ABQOL

Variables (n)	DLQI		ABQOL	
	Median ± IQR	p-value	Median ± IQR	p-value
Gender				
Male (13)	3.0 ± 12	0.145	12.0 ± 11	0.257
Female (17)	2.0 ± 8		8.0 ± 14	
Age				
≤55 years old (14)	3.0 ± 8	0.834	13.0 ± 15	0.269
>55 years old (16)	2.0 ± 9		7.0 ± 12	
Ethnicity				
Malay (22)	3.5 ± 9	0.266*	11.5 ± 15	0.410*
Chinese (5)	1.0 ± 6		11.0 ± 9	
Indian (2)	6.0 ± 0		24.5 ± 0	
Portuguese (1)	0.0 ± 0		9.0 ± 0	
Education				
Primary/Secondary (21)	1.0 ± 6	0.016	9.0 ± 10	0.026
Tertiary (9)	10.0 ± 12		21.0 ± 23	
Pemphigus subtypes				
P. vulgaris (20)	1.5 ± 4	0.152*	11.0 ± 10	0.804*
P. foliaceous (9)	8.0 ± 15		16.0 ± 17	
P. erythematosus (1)	7.0 ± 0		8.0 ± 0	
PDAI				
≤8 (26)	2.5 ± 7	0.295	11.0 ± 12	0.691
>8 (4)	7.5 ± 7		11.5 ± 24	
Comorbidities				
With (28)	2.5 ± 8	0.502	11.0 ± 14	0.405
Without (2)	5.5 ± 0		15.5 ± 0	
Treatment				
CS only (3)	3.0 ± 0	0.780	15.0 ± 0	0.835
CS with adjuvant Immunosuppressant (27)	3.0 ± 9		11.0 ± 15	
Employment				
Working (11)	4.0 ± 6	0.778	14.0 ± 12	0.262
Unemployed/Retired (19)	3.0 ± 9		8.0 ± 12	
Disease activity				
Active disease (11)	5.0 ± 7	0.187*	11.0 ± 9	0.449*
Partial remission (15)	2.0 ± 10		15.0 ± 17	
Complete remission (4)	1.0 ± 3		8.0 ± 9	
Disease duration				
<6 months (3)	4.0 ± 0	0.862	7.0 ± 0	0.467
≥6 months (27)	3.0 ± 7		11.0 ± 11	
Marital status				
Single/Divorce/Widow/Widower (7)	3.0 ± 7	0.767	12.0 ± 23	0.712
Married (23)	3.0 ± 9		11.0 ± 11	

p-values generated using Mann–Whitney test, except for * generated using Kruskal–Wallis test
CS = Corticosteroid

categorical and numerical variables was analysed using Mann–Whitney test and Kruskal–Wallis test, while correlation between two numerical variables was analysed using Spearman correlation. Statistical significance was taken at $p<0.05$

RESULTS

There were a total of 30 pemphigus patients (13 males, 17 females), with an average age of 54.0 ± 13.6 years, presented to the Department of Dermatology, Hospital Melaka, from August 2020 to July 2021. Majority of patients were Malays (22/73.3%), followed by Chinese (5/16.7%), Indians (2/6.7%), and 1 Portuguese. This is consistent with the racial distribution in Melaka, Malaysia. Twenty patients had pemphigus vulgaris (PV), while nine patients had pemphigus foliaceous (PF) and one patient had pemphigus erythematosus. The ratio of PV to PF was almost 2:1. There were 10 pemphigus patients presented with mucocutaneous involvement, 16 with cutaneous involvement only, and 4 with mucosal involvement only. Oral cavity was the commonest site of mucosal involvement.

The mainstay of treatment for pemphigus patients is systemic corticosteroids. All 30 patients in our study received either intravenous hydrocortisone or oral prednisolone. Twenty-seven of them had adjuvant immunosuppressant (Table I). Azathioprine is the commonest steroid sparing immunosuppressant, which was used in pemphigus patients in our study. The demography and clinical characteristics of the study population are summarised in Table II.

Overall, our study population had low PDAI score (2.0 ± 4.0) with low DLQI (3.0 ± 8.0) and ABQOL (11.0 ± 12.0). The VAS scores for pain (1.0 ± 2.0) and itch (2.0 ± 3.0) were also low. We observed significant difference in the DLQI and ABQOL scores among patients with different educational levels. Those patients who have tertiary educational qualification

Table II: Characteristics of the study population, n = 30

Patient characteristics	Mean ± SD or n (%)
Age (years)	54.0 ± 13.6
Gender	
Male	13 (43.3)
Female	17 (56.7)
Ethnicity	
Malay	22 (73.3)
Chinese	5 (16.7)
Indian	2 (6.7)
Portuguese	1 (3.3)
Subtype	
Pemphigus vulgaris	20 (66.7)
Pemphigus foliaceous	9 (30.0)
Pemphigus erythematosus	1 (3.3)
Site of disease involvement	
Cutaneous only	16 (53.3)
Mucocutaneous	10 (33.3)
Mucosal only	4 (13.3)
Mucosal involvement	
Oral/lips	9 (30.0)
Ear, nose, throat	7 (23.3)
Genital	2 (6.7)
Conjunctival	0 (0.0)
Treatment modalities	
Corticosteroid	30 (100.0)
Azathioprine	26 (86.7)
Intravenous immunoglobulin	11 (36.7)
Methotrexate	6 (20.0)
Rituximab	4 (13.3)
Cyclophosphamide	3 (10.0)

Table III: Pemphigus Disease Area Index (PDAI), Dermatology Life Quality Index (DLQI), Visual Analogue Scale (VAS) for pain and itch, and Autoimmune Bullous Disease Quality of Life (ABQOL) scores

Variables	Median ± IQR
PDAI	2.0 ± 4.0
DLQI	3.0 ± 8.0
VAS pain	1.0 ± 2.0
VAS itch	2.0 ± 3.0
ABQOL	11.0 ± 12.0

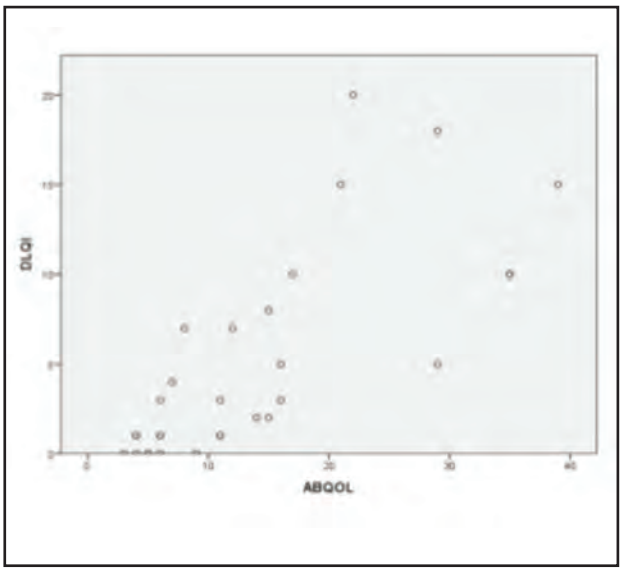

Fig. 1: Correlation between DLQI and ABQOL generated using Spearman correlation.

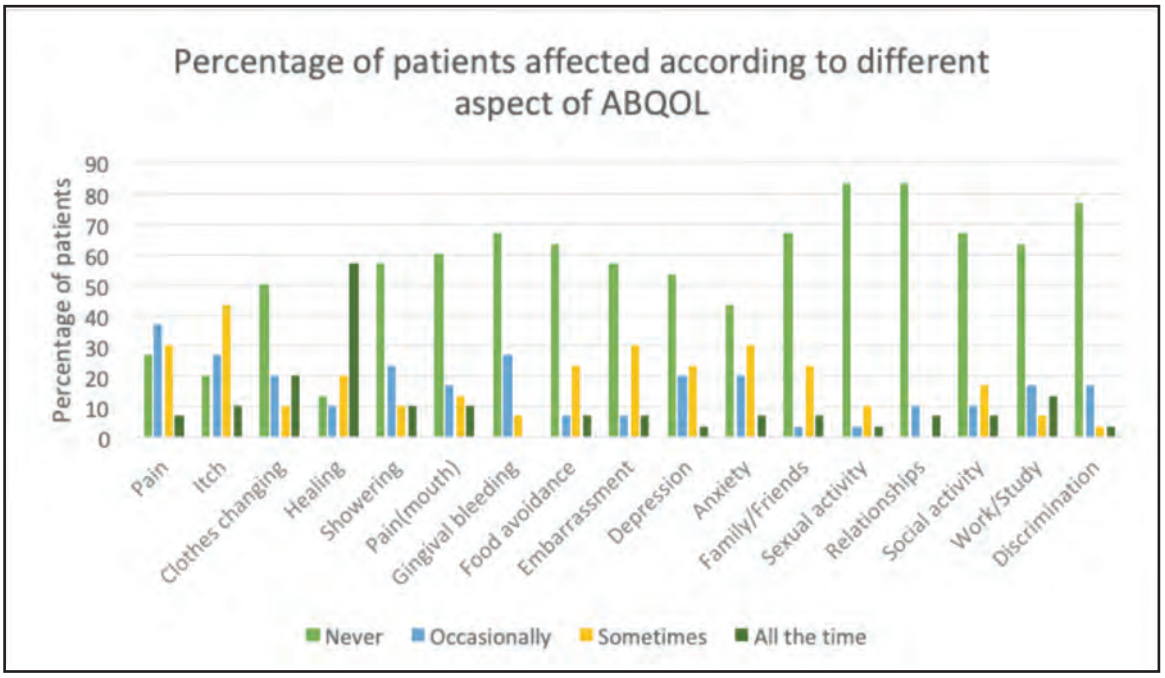

Fig. 2: Percentage of affected patients according to different aspects of ABQOL.

tend to report higher DLQI (10.0 ± 12.0, p = 0.016) and ABQOL (21.0 ± 23.0, p = 0.026) compared to the group of patients who have either primary or secondary education level (Table I).

There were no significant differences in the DLQI and ABQOL scores among patients with differences in gender, age, ethnicity, pemphigus subtypes, disease severity, disease activity, duration of illness, and marital and employment status. This study revealed that there was no significant difference in QoL between patients with or without comorbidities. In addition, the use of adjuvant immunosuppressive agents did not significantly affect the QoL of pemphigus patient in our study cohort. We noticed that the working group of pemphigus patients reported higher DLQI and ABQOL, compared to the unemployed or retired group. However, this was not statistically significant.

DLQI was found to correlate positively with ABQOL (r = 0.84, p < 0.001) in our study (Figure 1). There was no correlation observed between disease severity and QoL in our study cohort, as there was neither significant correlation between PDAI and DLQI scores (r = 0.24, p = 0.202) nor PDAI and ABQOL scores (r = 0.18, p = 0.355).

Majority of the patients were affected by the symptoms of pain (73.3%) and itch (80.0%), occasionally, sometimes, or all the time. However, the median VAS scores for pain (1.0 ± 2.0) and itch (2.0 ± 3.0) were low (Table III). Fifty percent of patients encountered difficulty in changing clothes and 43.4% in showering. About one-third of patients (36.7%) were unable to enjoy food, 33.3% had gingival bleed, and 40.0% experienced mouth pain. From the psychosocial aspects, 43.0% of the patients felt embarrassed, 46.7% were depressed, and 56.7% were anxious about their condition. One-third of the patients (33.3%) claimed their social life was affected, and 36.7% had difficulty in carrying out their work or study. However, only small number of patients (16.7%) reported relationship and sexual difficulties (Figure 2).

DISCUSSION

In general, most of our study population had mild disease, with low PDAI scores. The results may be different if this was done in the group with more patients of moderate and severe disease. Pemphigus patients often presented with highly active disease for a short period of time, and they were treated with corticosteroid, which is effective and fast-acting, to control the disease. Most of the patients in our cohort had their disease controlled by the time they were enrolled in our study. Twenty-seven patients (90%) had disease duration of 6 months or more during data collection. There were 26 patients (86.7%) presented with PDAI scores of 8 or less. Disease duration of less than 6 months had clinical stages of baseline and flare, where clinical states were expected to be most severe. According to a local study done in Hospital Sultanah Aminah, Johor Bahru, only 5.2% were in severe stages, amongst patients with disease duration of more than 6 months.[14] Therefore, our finding may be different if we collect the data at the peak of the disease activity for each patient. As reported in a Singapore study, oral cavity was the commonest site of mucosal involvement in our study cohort.[16]

There were various studies that reported average DLQI score of 10 in pemphigus patients.[7,17-18] However, our study cohort showed low DLQI scores in general, with the median score of 3. This can be attributed to the mild disease during presentation. ABQOL was found to correlate positively with the DLQI (r = 0.837, p < 0.001) in our study, which is similar to that reported in a previous study.[14] Overall, our study population had lower ABQOL scores, with median of 11, compared to median ABQOL score of 20 in Selayang study.[11]

Again, this can be attributed to the mild disease severity during the study. Since most of our study population had the disease for 6 months or more, they have better coping and adaptation abilities to their condition following sufficient understanding of the clinical implications of the disease. This may lead to low scores in both DLQI and ABQOL.

A Korean study showed that the DLQI score strongly correlated with the clinical severity of the disease ($r = 0.71$, $p < 0.0001$), while a local study in Malaysia reported moderate correlation between ABQOL and PDAI ($r = 0.47$, $p < 0.001$).[7,14] However, a Polish study found poor correlation between ABQOL and disease severity ($r = 0.38$).[19] Our study showed no correlation between disease severity and both ABQOL and DLQI.

Furthermore, QoL could be affected by other factors such as patient demographic characteristics. This study analysed other factors that may influence the DLQI and ABQOL scores. Interestingly, we found that educational level was one of the factors that had significant effect on the QoL. Patients who had lower educational level tend to report lower score in DLQI as well as ABQOL, and vice versa. This could be accounted by the fact that patients with lower educational level tend to endure, accept, and adapt to the presence of illnesses, while higher levels of educational attainment were associated with better self-assessed health and physical functioning. The higher educated group reported a greater sense of control over their health.[20]

Even though there was no significant difference in DLQI and ABQOL in terms of employment status, we noticed that the working group of patients reported higher DLQI and ABQOL scores. This was consistent with a previous study, which reported that disturbance in work performances negatively affected QoL.[21] An Egyptian study revealed a significant increase in DLQI scores in pemphigus patients who was single compared to married patients.[10] However, in our study, these two groups of patients had almost the same median scores for both DLQI and ABQOL.

In terms of ABQOL, sexual activity (83.3%), interpersonal relationships (83.3%), and discrimination at workplace or school (76.7%) were the three highest aspects with the score of zero reported. This was similar with the study done in Hospital Sultanah Aminah, Johor Bahru, Malaysia. Since sexual issue is not comfortably discussed as well as due to the preservation of public appearance in the local culture, these questions had lower scores.[14]

LIMITATION

This study is limited by its cross-sectional design at a single time point during the course of the disease and small sample size.

CONCLUSION

There were 30 pemphigus patients presented to Melaka General Hospital from August 2020 to July 2021. Most of them had low DLQI and ABQOL scores with mild clinical severity, as evidenced by low PDAI and low VAS scores for both pain and itch. Disease severity had no correlation with QoL in our study. However, the educational level showed significant influence on the QoL.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

REFERENCES

1. Vanessa Ngan, StaffWriter, 2003. Updated by DermNet NZ Editor-in-Chief, Adjunct Prof. Amanda Oakley, Dermatologist, January 2019. [cited Jan 2022] Available from: https://dermnetnz.org/topics/pemphigus-vulgaris.
2. Celere BS, Vernal S, Brochado MJF, Segura-Munoz SI, Roselino AM. Geographical foci and epidemiological changes of pemphigus vulgaris in four decades in Southeastern Brazil. Int J Dermatol 2017; 56: 1494-6.
3. Adriana Maria Porro, Camila Arai Seque, Maria Carolina Corsi Ferreira, Milvia Maria Simoes e Silva Enokihara. Pemphigus vulgaris. An Bras Dermatol 2019 May-Jun; 94(3): 264-78.
4. Bastuji-Garin S, Souissi R, Blum L, Turki H, Nouira R, Jomaa B, et al. Comparative epidemiology of pemphigus in Tunisia and France: Unusual incidence of pemphigus foliaceus in young Tunisian women. J Invest Dermatol 1995 Feb; 104(2): 302-5.
5. Abreu-Velez AM, Hashimoto T, Bollag WB, Tobon Arroyave S, Abreu-Velez CE, Londono ML, et al. A unique form of endemic pemphigus in northern Colombia. J Am Acad Dermatol 2003; 49(4): 599.
6. Murrell DF, Dick S, Ahmed AR, Sirois D, Zillikens D, Werth VP, et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. Journal of the American Academy of Dermatology 2008 June; 58(6): 1043-6.
7. Jae Yong Sung, Mi Ryung Roh, Soo-Chan Kim. Quality of life assessment in Korean patients with pemphigus. Ann Dermatol 2015; 27(5): 492-8.
8. WHOQOL: Measuring Quality of Life [cited Jan 2022]. Available from: https://www.who.int/tools/whoqol.
9. Pemphigus and Quality of Life [cited Jan 2022]. Available from: https://plasticsurgerykey.com/pemphigus-and-quality-of-life/.
10. Morsy H, Abdel-Motaleb AA, Soliman AMA. Quality-of-life assessment in pemphigus vulgaris in Upper Egypt using the Dermatology Life Quality Index and SF-36 questionnaires. Egyptian Journal of Dermatology and Venereology 2016; 36: 1-3.
11. Ng HW, Khairul SMA, Ng FY, Rohna R, Yue YC, Ang WS, et al. Quality of Life in Pemphigus Vulgaris patients in Selayang Hospital. E-poster 17 [cited Jan 2022]. Available from: http://www.dermatology.org.my/pdf/eposters%2017.pdf.
12. Shimizu T, Takebayashi T, Sato Y, Niizeki H, Aoyama Y, Kitajima Y, et al. Grading criteria for disease severity by pemphigus disease area index. The Journal of Dermatology 2014; 41: 96973.
13. Rahbar Z, Daneshpazhooh M, Mirshams-Shahshahani M, Nafiseh Esmaili N, Heidari K, Aghazadeh N, et al. Pemphigus disease activity measurements. Pemphigus disease area index, autoimmune bullous skin disorder intensity score, and pemphigus vulgaris activity score. JAMA Dermatol 2014; 150(3): 266-72.
14. Yap EWY, Tey KE, Supramaniam P, Murrell D, Choon SE. Validation of the Malay version of Autoimmune Bullous Disease Quality of Life (ABQOL) questionnaire. Malaysian Journal of Dermatology 2020; 44: 2-8.
15. Sebaratnam DF, Hanna AM, Chee SN, Frew JW, Venugopal SS, Daniel BS, et al. Development of a quality-of-life instrument for

autoimmune bullous disease: The Autoimmune Bullous Disease Quality of Life questionnaire. JAMA Dermatol 2013; 149: 1186-91.
16. Valencia L, Tay YK, Teo R. Pemphigus: A Singapore perspective. Malaysian Journal of Dermatology 2016 Dec; 37: 28-34.
17. Mayrshofer F, Hertl M. Significant decrease in quality of life in patients with pemphigus vulgaris. Results from the German Bullous Skin Disease (BSD) Study Group. J Disch Dermatol Ges 2005; 3: 431-5.
18. Ghodsi SZ, Chams-Davatchi C, Daneshpazhooh M, Valikhani M, Esmaili N. Quality of life and psychological status of patients with pemphigus vulgaris using Dermatology Life Quality Index and General Health Questionnaires. J Dermatol 2012; 39: 141-4.
19. Kalinska-Bienias A, Jakubowska B, Kowalewski C, Murrell DF, Wozniak K. Measuring of quality of life in autoimmune blistering disorders in Poland. Validation of disease-specific Autoimmune Bullous Disease Quality of Life (ABQOL) and the Treatment Autoimmune Bullous Disease Quality of Life (TABQOL) questionnaires. Adv in Medical Sciences 2017; 62: 92-6.
20. Ross CE, Wu CL. The links between education and health. American Sociological Review 1995; 60: 719-45.
21. Heelan K, Hitzig SL, Knowles S, Drucker AM, Mittmann N, Walsh S, et al. Loss of work productivity and quality of life in patients with autoimmune bullous dermatoses. J Cutan Med Surg 2015; 19: 546-54.

Predictors of Clinical Outcomes in Acute Appendicitis: A Retrospective Study

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ABSTRACT

Introduction: Acute appendicitis is one of the most common causes of intra-abdominal emergency surgery worldwide. This study was conducted to contribute to global databases by presenting data from our institution, which consist of multi-racial population. We aimed to evaluate the presentation, diagnosis, and management of acute appendicitis and post-operative outcome in our institution and evaluate the risks factors associated with severe complications and prolonged length of stay (LOS).

Materials and Methods: We performed a retrospective analysis using multivariate regression analysis of all patients who underwent appendectomy (2009–2014) in our institution. The primary outcomes included demographics, presentation, and perioperative management, and the secondary outcomes included risk factors associated with prolonged LOS.

Results: Of the 1185 patients, the mean age was 36.4 years, and 940 (79.3%) were male. Majority (98.1%) of patients were ASA (American Society of Anaesthesiologists) 1 or 2. Most of them (83.9%) were from the four racial subgroups (Chinese, Malay, Bangladeshi, and Indian). There was no racial variation in the diagnosis and presentation of disease. The mean duration of symptoms was 1.8 days. The history was commonly a localised or migratory abdominal pain associated with anorexia, nausea, vomiting, and fever. The commonest physical findings were right-sided abdominal tenderness associated with rebound and guarding. About 42.9% of the patients underwent pre-operative CT scan to establish the diagnosis of appendicitis prior to surgery, whilst 57.1% underwent surgery on clinical diagnosis and blood investigation (NWR and CRP). An open appendectomy was performed in 13.2% of the patients. The conversion rate of laparoscopic appendectomy was 4.9% (n = 50). The mean length of hospital stay was 3.6 days. On multivariate Cox regression, patients of Burmese and Thai descent were independently associated with a prolonged LOS. The post-operative morbidity was 5.5%. The 30-day readmission rate was 2.4%. There was no mortality in our study.

Discussion: Our study showed that pre-operative diagnosis of acute appendicitis can be made accurately by classical clinical presentation or by imaging. Independent risk factors associated with increased LOS included increased age, male gender, prolonged duration of symptoms pre-admission, fever, generalised tenderness, and prolonged operative time. The effect of race on LOS has been observed in the literature for other surgical procedures. The prolonged LOS found in Burmese and Thai patients contribute to the possibility of intrinsic racial differences in the post-surgery recovery. However, the numbers are small and therefore prone to type I error. Compared to the open approach, the use of laparoscopic appendectomy was associated with shorter LOS. This has similar outcomes to those reported in the literature.

Conclusion: The identification of risks factors could help surgical team to predict the clinical outcomes and develop risk reduction strategy in post-operative care of these patients.

KEYWORDS:
Predictors of clinical outcomes in acute appendicitis

INTRODUCTION

Acute appendicitis is one of the most common causes of acute abdomen, with a lifetime risk of 8%.[1] Worldwide, acute appendicitis is associated with higher healthcare costs. If left untreated, this may result in the perforation of the appendix with a localised abscess or generalised peritonitis, with ensuing morbidities and mortality.[2] In the United States, hospitalisations attributed to acute appendicitis cost $3 billion dollars per year.[3] In low- to middle-income countries, appendicitis is a common and treatable condition but often carries a high fatality rate in the absence of safe and essential surgical care.[4]

Although the diagnosis of acute appendicitis may be clinically aided by scoring system, the increasing use of modern imaging (such as ultrasound, computed tomography (CT) scan, and magnetic resonance imaging (MRI)) is observed in the developed countries. Its management has evolved from open appendectomy to the use of minimally invasive surgery and non-operative management (by antibiotics). In recent times, even the effect of the COVID-19 pandemic on the clinical course of appendicitis has been studied.[1]

Singapore is a multi-racial city state of 5.7 million people.[5] The 2021 Population Census indicated a local citizen population of three predominant racial groups (Chinese,

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Malays, and Indians), and a 30% foreign population drawn from neighbouring countries, which includes Thais, Burmese, Bangladeshis, Subcontinental Indians, and Mainland Chinese. This study was conducted to contribute to global databases by presenting data from our institution, which consist of multi-racial south Asian population. We aimed to evaluate the presentation, diagnosis, and management of acute appendicitis and post-operative outcome in our institution and evaluate the risks factors associated with severe complications and prolonged length of stay (LOS).

MATERIALS AND METHODS

A retrospective analysis of all patients who underwent surgery for acute appendicitis from September 2009 to November 2014 at a single institution (Alexandra Hospital) was conducted. The study protocol (DSRB Reference: 2015/00313) was assessed and approved by the Ethics Committee of the National Healthcare Group (NHG) Institutional Review Board (IRB). All patients received same level of care at the point of admission regardless of demographics, immigration status, and insurance status. Demographic data included the patient's race, age, and gender. Race was divided into Chinese, Malay, Indian, Thai, Burmese, and Bangladeshi. Persons falling into categories outside of these main groups were collectively termed 'Others', as there were insufficient numbers per race to form groups for meaningful statistical analysis. Comorbidities were recorded. Patients were also scored based on their American Society of Anaesthesia (ASA) status.

The patient's duration of symptoms was recorded in days. The patient's symptom of abdominal pain was divided into five groups: classical migratory pain from midline to right iliac fossa (RIF), localised pain at the RIF, generalised pain, periumbilical pain, and atypical pain. Patients who had atypical pain had abdominal pain that did not conform to any of the other four groups. The patient's symptoms of fever, nausea, diarrhoea, vomiting, anorexia, and dysuria were also recorded. The patient's sign of abdominal tenderness was also divided into five groups: right-sided tenderness, generalised tenderness, suprapubic tenderness, absence of tenderness, and atypical tenderness. Patients who had atypical tenderness had abdominal tenderness that did not conform to any of the other four groups. In addition, the presence of rebound tenderness, localised guarding and a palpable mass were also recorded. Two biochemical investigations were recorded: the neutrophil to WBC ratio (NWR) and C-reactive protein (CRP) levels. Whether a computed tomography (CT) scan was performed was also recorded. In our institution, all CT scans are performed with IV contrast unless contraindicated.

All patients in our institution with a suspected clinical diagnosis (or confirmed by imaging) of acute appendicitis will be offered surgery (with laparoscopic approach preferred). The decision to perform open appendectomy (or laparotomy) was up to the discretion of the surgical team. All residents were trained and encouraged to perform laparoscopy where possible. Open surgery was done in cases where patients were unstable and septic, where adhesion would be encountered (e.g., previous history of laparotomy), or where laparoscopic skills were not available. Patients who opted for antibiotics and underwent surgery (delayed appendectomy) and those with chronic appendicitis were excluded from the study. Therefore, operative parameters were the approach to surgery: open, laparoscopic, and laparoscopic converted to open surgery. All operating theatres dedicated to general surgery are equipped with laparoscopic stack system and laparoscopic instruments throughout the day and night. All patients received a single dose of broad-spectrum antibiotics intravenously at induction. The continuation of antibiotics beyond surgery was determined by the presence of sepsis and Mannheim Peritonitis Index, which may take up to seven days (orally or intravenously). The duration of surgery was recorded in minutes. The time of surgery was categorised into '08:00–16:59', '17:00–23:59', and '00:00–07:59' to represent office hours, after office hours, and overnight procedures, respectively.

The Mannheim Peritonitis Index (MPI) was also scored following laparotomy.[6] This index uses eight parameters of different weights to generate a composite score that predicts for mortality. The raw score on addition of the eight parameters is presented.

Outcome measures, which were relevant to our analysis, included the presence of surgical site infection (SSI), organ space infection (OSI), pneumonia, ileus, acute myocardial infarction (AMI), cerebrovascular accident (CVA), deep venous thrombosis (DVT), and pulmonary embolism (PE). Ileus was defined as failure to progress to normal diet on day 3 post-operation if the patient was still inpatient. Clavien-Dindo Classification for complications was calculated for each patient.[7] The patient's total LOS and 30-day readmission rates were also recorded. At the time of discharge, all patients were given a copy of medical discharge summary, medication, and instructions to return to the emergency department of our hospital in the event of deterioration and a return clinic appointment 2–6 weeks after surgery.

Statistical analysis

Continuous variables were expressed as means with standard deviation (SD), while categorical and ordinal variables were expressed as counts with percentages. Continuous variables were analysed with Kruskal-Wallis H test, while categorical and ordinal variables were analysed with χ^2 test.

Variables relating to demographics, presentation of appendicitis, and operative factors were considered for further analysis. Clavien-Dindo Classification scores were divided into none or mild complications (0–II) and severe complications (III–V). Univariate and multivariate logistic regression analyses were used to identify independent risk factors for worse outcomes following surgery based on Clavien-Dindo Classification. In addition, univariate and multivariate Cox regression analyses were used to identify independent factors for shorter LOS. In both these analyses, univariate values ($p < 0.10$) were included in multivariate regression analysis. Multiple collinearities were also verified using the variance inflation factor, and none of the multiple regressions were noted to be collinear (VIF<5). *P*-values of <0.05 were considered statistically significant. Statistical

analysis was performed using Stata version 14.2 (StataCorp LP, College Station, Texas, USA).

RESULTS

From September 2009 to November 2014, a total of 1185 patients underwent appendectomy at our institution. Most patients were young (mean age +/- SD= 36.4 ± 15.8 years), male (n= 940, 79.3%), healthy (98.1%, ASA 1 or 2), and of four racial subgroups (Chinese, Malay, Bangladeshi, and Indian; 83.9%).

The mean duration of symptoms was 1.8 +/- 1.5 days(+/- SD). The history was commonly a localised or migratory abdominal pain associated with anorexia, nausea, vomiting, diarrhoea, and fever. The commonest physical findings were right-sided abdominal tenderness associated with rebound and guarding.

Demographics and clinical presentation of our entire population are shown in Table I.

A diagnosis of appendicitis was established in 42.9% (n= 508) of the patients after CT scan of the abdomen and pelvis prior to surgery. Decision for surgery was made on the remaining 57.1% on clinical diagnosis and blood investigation (neutrophil–white blood cell ratio and C-reactive protein).

Majority of the appendectomy (82.0%; n = 972) was performed between office hours (08:00 hr to 17:00 hr) and up to 12 at midnight. Most patients (n = 1029, 86.8%) underwent laparoscopic appendectomy with a conversion rate of 4.9% (n = 50); the remaining 13.2% underwent open surgery up-front. The mean duration of operation was 94.3 ± 79.7 minutes (mean +/- SD).

The mean LOS was 3.6 (± 6.0 days, SD). The post-operative morbidity was 5.5%, (n = 65) with ileus as the commonest complication, followed by surgical site infection, organ space infection, pneumonia, and acute myocardial infarction. Serious complications (Clavien-Dindo Classification Grades III–IV) were reported in 19 patients (1.6%). The 30-day readmission rate was 2.4% (n = 29). There was no mortality in our study.

Management and treatment outcome of our patients with acute appendicitis are shown in Table II.

Risk factors for severe complications

A total of 19 patients (1.6%) suffered from severe complications. Variables input into univariate logistic regression were race, age, gender, ASA status, comorbidities, duration of symptoms, symptoms on presentation, signs on examination, NWR and CRP values, timing of surgery, approach of surgery, and duration of surgery. Variables with $p < 0.100$ were included in multivariate analysis. This included race, age, gender, all comorbidities, duration of symptoms, presence of fever and diarrhoea, and laparoscopic approach. CRP was excluded although it was statistically significant on univariate analysis as less than 25% of patients had a recorded CRP value. The proportion of patients who underwent laparoscopic conversion was noted to be statistically significant on univariate analysis but was excluded as this subset was entirely from the laparoscopic group and would have been collinear. Following multivariate analysis, only age (OR1.04/year, p=0.026, 95% CI 1.01–1.08) was an independent risk factor for severe outcomes. Compared to the open approach, the use of laparoscopic approach (OR 0.30, p=0.025, 95% CI 0.10–0.86) was an independent negative risk factor for severe outcomes. Data are not shown.

Risk factors for prolonged length of stay

Variables input into univariate Cox regression were race, age, gender, ASA status, comorbidities, duration of symptoms, symptoms on presentation, signs on examination, NWR and CRP values, timing of surgery, approach of surgery, and duration of surgery. Variables with p<0.100 were included in multivariate analysis. This included race, age, gender, ASA status, all comorbidities, duration of symptoms, distribution of abdominal pain, presence of fever or diarrhoea, distribution of abdominal tenderness, presence of rebound or abdominal mass, timing of surgery, approach of surgery, and duration of surgery. CRP and laparoscopic conversion were not included due to the reasons mentioned in the previous section. Following multivariate analysis, patients who were Burmese (HR1.56, p = 0.010, 95% CI 1.11–2.22) and Thai (HR1.52, p=0.019, 95% CI 1.08–2.17) were associated with an increased risk of prolonged hospital stay. In addition, age (HR1.01/year, p<0.0001, 95% CI 1.01–1.02), male gender (HR1.20, p=0.033, 95% CI 1.01–1.41), longer duration of symptoms (HR1.14/day, p<0.0001, 95% CI 1.09–1.18), presentation with fever (HR1.25, p=0.01, 95% CI 1.10–1.43), generalised abdominal tenderness (HR1.52, p=0.014, 95% CI 1.09–2.08), atypical abdominal tenderness (HR1.47, p=0.011, 95% CI 1.09–1.96), and prolonged duration of surgery (HR1.01/min, p<0.0001, 95% CI 1.01–1.01) were independent risk factors for prolonged LOS. We also noted that surgery performed after office hours (HR0.78, p<0.0001, 95% CI 0.69–0.90) and surgery performed overnight (HR0.77, p=0.003, 95% CI 0.65–0.92) were associated with a statistically significant reduction in the LOS.

A detailed analysis of univariate and multivariate regression is shown in Table III.

Analysis by race

There was a statistically significant difference in mean age at presentation between races in our study cohort (p=0.0001). Mean age of Indians was 29.3 (SD 8.2) years, while Chinese was 39.4 (SD 16.1) years, representing the youngest and oldest mean ages, respectively. There was also a statistically significant difference in gender amongst the various racial groups (p<0.0001). Mean duration of symptoms was shortest amongst Thais (1.7 days, SD 1.2) and longest amongst Malays (2.2 days, SD 1.9) (p=0.0353). A statistically significant difference in the utilisation of CT scans was also noted, with more than half of Chinese and Malay patients undergoing a CT scan (p<0.0001). Operative approach and conversion rate did not yield a statistically significant difference between racial groups, although there was a statistically significant difference in the duration of surgery, with Chinese, Malays, and Thais being much longer than their counterparts from other races (p<0.0001). We observed

Table I: Demographic characteristics of study population

Characteristics	Value
Age, mean ± SD	36.4 ± 15.8
Gender: Male N (%)	940 (79.3)
Race, N (%)	
Chinese	397 (33.5)
Malay	111 (9.4)
Indian	278 (23.4)
Bangladeshi	208 (17.6)
Burmese	40 (3.4)
Thai	37 (3.1)
Others	114 (9.6)
ASA, N (%)	
1 and 2	1162 (98.1)
3 and 4	23 (1.9)
Comorbidities, N (%)	
Ischaemic heart disease	9 (0.8)
Hypertension	71 (6.0)
Diabetes mellitus	39 (3.3)
Chronic obstructive pulmonary disease	1 (0.1)
Chronic kidney disease	3 (0.3)
Cancer	4 (0.3)
Duration of symptoms, mean ± SD (days)	1.8 ± 1.5
Abdominal pain, N (%)	
Migratory	320 (27.0)
Localised	565 (47.7)
Generalised	81 (6.8)
Periumbilical	87 (7.3)
Atypical	113 (9.5)
Other symptoms, N (%)	
Fever	409 (34.5)
Nausea	323 (27.3)
Vomiting	524 (44.2)
Anorexia	192 (16.2)
Diarrhoea	134 (11.3)
Dysuria	38 (3.2)
Abdominal tenderness, N (%)	
Right-sided	1013 (85.5)
Generalised	44 (3.7)
Suprapubic	22 (1.9)
Atypical	57 (4.8)
None	43 (3.6)
Other signs, N (%)	
Rebound	458 (38.6)
Guarding	413 (34.9)
Mass	14 (1.2)

SD, standard deviation
N, number
ASA, American Society of Anesthesiologists

higher MPI scores in Chinese and Malays and lower scores amongst Burmese and Bangladeshis. LOS was longest amongst Burmese at 5.0 (SD 10.9) days and shortest in Bangladeshis (2.6 days, SD 4.5) (p=0.0001). Readmission rates were similar amongst races. Five percentage (n=2) of Burmese patients suffered from complications of Clavien-Dindo Class III and above, whilst no patients amongst Thai and Bangladeshi groups suffered such severe complications (p=0.024). However, these numbers are small.

DISCUSSION

Our study population was predominantly young healthy male who presented with a relatively short duration of symptoms. The clinical presentation and physical findings were classical of acute appendicitis as reported in the literature.[8] There was no racial variation in the diagnosis and presentation of disease.

In our series, 42.9% underwent pre-operative CT scan and the decision to operate after a clinical diagnosis of acute appendicitis and blood investigation were common (57.1%). In contrast to the national audit in the Netherlands, nearly all patients underwent pre-operative imaging,[9] and in a prospective multicentre observational study across 44 countries worldwide, the use of imaging (US, CT, or both) was reported in 70% (with 30% CT scan, 70% US) of the patients.[10] In the United States, the Surgical Care and Outcomes Assessment programme (SCOAP) in Washington State demonstrates that 86% of patients underwent pre-operative imaging (of whom, 91% CT).[11] This can be explained by our younger study population, and the CT scan was increasingly performed only in patients who were older with higher ASA to rule out other pathologies that are more prevalent in the elderly.

Table II: Management and treatment outcome of patients with acute appendicitis

Variables	Value
Investigations	
Blood test, mean ± SD	
Neutrophil–white blood cell ratio (NWR)	0.81 ± 0.11
C-reactive protein (CRP)	102 ± 137
Imaging	
Computed tomography scan (CT scan), N (%)	508 (42.9)
Surgical approach, N (%)	
Open appendectomy	156 (13.2)
Laparoscopic appendectomy	1029 (86.8)
Laparoscopic appendectomy converted to open appendectomy	50 (4.9)
Duration of surgery, mean ± SD (minutes)	94.3 ± 79.7
Open appendectomy	89.6 ± 15.6
Laparoscopic appendectomy	96.4 ± 30.8
Time of surgery, N (%)	
08:00–16:59	448 (37.8)
17:00–23:59	524 (44.2)
00:00–07:59	213 (18.0)
Mannheim's Peritoneal Index Score (MPI), mean ± SD	7.5 ± 6.0
Outcomes, N (%)	
Surgical site infection (SSI)	21 (1.7)
Organ space infection (OSI)	9 (0.8)
Ileus	32 (2.7)
Pneumonia	2 (0.2)
Acute myocardial infarction	1 (0.1)
Clavien-Dindo Classification, N (%)	
Grades 0–II	1166 (98.4)
Grades III–IV	19 (1.6)
Length of stay, mean ± SD (days)	3.6 ± 6.8
30-day readmission, N (%)	29 (2.4)
Malignancy on histology, N (%)	7 (0.6)
Pathology including non-appendicitis and negative appendectomy, N (%)	99 (8.4)

SD, standard deviation
N, number

Our management of acute appendicitis was a laparoscopy-first approach as it has been shown to confer protective effect against severe complications such as less pain, lower incidence of SSI, decreased LOS, earlier return to work, and overall cost.[12] A national audit in the Netherlands showed that laparoscopy was predominant in 75% of appendectomy,[9] and in our series, 86.8% of the population. In a prospective multicentre observational study across 44 countries worldwide, more than half the cases were performed laparoscopically (51.7%), while 42.2% had open appendectomy.[10] This indicates that our practice in the adoption of laparoscopy for acute appendicitis is comparable to the West.

The risks factors associated with prolonged LOS following appendectomy were analysed in our study. These included increased age, male gender, prolonged duration of symptoms prior to hospitalisation, patients symptomatic with fever, patients with generalised tenderness, and prolonged operative time. Increasing age appeared to be an independent risk factor for complication after appendectomy. This is supported by the study using the NSQIP database where age was found to be associated with the increased risk of post-operative sepsis.[13] Laparoscopic approach was associated with shorter LOS. A laparoscopic appendectomy appeared to confer protective effect against severe complications. This is consistent with studies demonstrating clear advantages in terms of less pain, lower incidence of SSI, decreased LOS, earlier return to work, and overall costs.[12]

The effect of race on LOS has been observed in the literature for other surgical procedures. In elective colorectal surgeries, it was observed that Black patients had longer post-operative stays even in the absence of post-operative complications.[14] Similarly, Schneider et al.[15] demonstrated that race was an independent risk factor for prolonged LOS following pancreaticoduodenectomy even after adjusting for other differences prior to surgery. In our study, multivariate Cox regression analysis showed that patients of Burmese and Thai descent were independently associated with a prolonged LOS. In addition, the mean MPI scores for Burmese and Thais were lower than other racial groups such as the Chinese and Malays. These findings contribute to the possibility of intrinsic racial differences in the post-surgery recovery. However, the numbers are small and therefore prone to type I error.

The limitation of our study was its retrospective nature and the lack of socioeconomic data in our analysis of our patient demographics. Nonetheless, our large-scale study with multi-racial south Asian population may provide sufficient power and robustness to determine the independent risk factors even when considering multiple variables.

Table III: Univariate and multivariate Cox regression analyses of variables on the length of hospital stay of patients with appendicitis

	Univariate analysis			Multivariate analysis		
Variables	**HR**	**p-value**	**95% CI**	**HR**	**p-value**	**95% CI**
Race						
Chinese	1			1		
Malay	0.95	0.633	0.77–1.18	0.98	0.847	0.79–1.22
Indian	0.75	<0.0001	0.65–0.87	1.16	0.091	0.98–1.39
Bangladeshi	0.76	0.002	0.65–0.91	1.16	0.108	0.97–1.41
Burmese	1.08	0.673	0.77–1.49	1.56	0.010	1.11–2.22
Thai	1.19	0.302	0.85–1.67	1.52	0.019	1.08–2.17
Others	1.10	0.365	0.89–1.35	1.43	0.002	1.14–1.79
Age	1.02	<0.0001	1.01–1.02	1.01	<0.0001	1.01–1.02
Male	1.32	<0.0001	1.15–1.52	1.20	0.033	1.01–1.41
ASA status						
1 and 2	1			1		
3 and 4	2.70	<0.0001	1.79–4.17	1.37	0.219	0.83–2.27
Comorbidities						
IHD	2.04	0.036	1.05–3.85	0.65	0.235	0.31–1.33
DM	2.27	<0.0001	1.67–3.13	1.22	0.332	0.82–1.79
HTN	2.17	<0.0001	1.69–2.78	1.09	0.599	0.79–1.52
CKD	6.67	0.008	1.64–25.0	2.44	0.245	0.54–11.1
Duration of symptoms	1.18	<0.0001	1.12–1.22	1.14	<0.0001	1.09–1.18
Abdominal pain						
Migratory	1			1		
Localised	1.04	0.528	0.91–1.20	0.98	0.805	0.85–1.14
Generalised	1.56	<0.0001	1.25–1.96	1.20	0.124	0.95–1.54
Periumbilical	1.22	0.088	0.97–1.54	1.08	0.578	0.84–1.37
Atypical	1.49	<0.0001	1.20–1.85	1.11	0.379	0.88–1.41
Other symptoms						
Fever	1.30	<0.0001	1.15–1.45	1.25	0.010	1.10–1.43
Nausea	0.94	0.392	0.83–1.08			
Vomiting	0.91	0.114	0.81–1.02			
Anorexia	0.98	0.776	0.84–1.14			
Diarrhoea	1.35	0.001	1.14–1.64	1.05	0.641	0.86–1.27
Dysuria	0.95	0.788	0.69–1.32			
Abdominal tenderness						
Right-sided	1			1		
Generalised	1.69	0.001	1.25–2.32	1.52	0.014	1.09–2.08
Suprapubic	1.67	0.001	1.23–2.27	1.37	0.125	0.53–2.08
None	1.61	0.017	1.09–2.38	1.12	0.514	0.79–1.59
Atypical	1.47	0.005	1.12–1.92	1.47	0.011	1.09–1.96
Other signs						
Rebound	0.89	0.041	0.79–1.00	1.04	0.948	0.88–1.13
Guarding	1.01	0.851	0.90–1.14			
Mass	1.92	0.015	1.14–3.33	0.88	0.654	0.51–1.52
Investigations, mean ± SD						
NWR	1.00	0.355	1.00–1.01			
CRP	1.00	<0.0001	1.00–1.01			
Approach						
Laparoscopic	0.71	<0.0001	0.60–0.84	0.66	<0.0001	0.56–0.79
Converted	2.17	<0.0001	1.61–2.86			
Duration of surgery	1.01	<0.0001	1.01–1.01	1.01	<0.0001	1.01–1.01

HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; IHD, ischaemic heart disease; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; SD, standard deviation; NWR, neutrophil–white blood cell ratio; CRP, C-reactive protein

CONCLUSION

In our institution, the surgical management of acute appendicitis is driven by pre-operative imaging and laparoscopic approach, with low conversion rate, morbidity, and readmission rate. Risks factors associated with severe complications and prolonged LOS may potentially provide targets for risk reduction strategies in quality-improvement program to reduce complications, LOS or readmission. The impact of shortening every person's LOS by one day will have large impact and free up hospital beds for other more complex procedures.

REFERENCES

1. Stewart B, Khanduri P, McCord C, M Ohene-Yeboah, S Uranues, F Vega Rivera, et al. Global disease burden of conditions requiring emergency surgery. Br J Surg 2014; 101(1): e9-22.
2. Teng TZJ, Thong XR, Lau KY, S Balasubramaniam, V Shelat. Acute appendicitis–advances and controversies. World J Gastrointest Surg 2021 Nov 27; 13(11): 1293-314.
3. Davies GM, Dasbach EJ, Teutsch S. The burden of appendicitis-related hospitalizations in the United States in 1997. Surg Infect (Larchmt) 2004; 5(2): 160-5.
4. Meara JG, Leather AJM, Hagander L, Alkire BC, Alonso N, Ameh EA, et al. Global Surgery 2030: Evidence and solutions for achieving health, welfare, and economic development. Lancet 2015; 386(9993): 569-624.
5. Available from: https://www.singstat.gov.sg/find-data/search-by-theme/population/population-and-population-structure/latest-data
6. Linder MM, Wacha H, Feldmann U, Wesch G, Streifensand RA, Gundlach E. The Mannheim peritonitis index. An instrument for the intraoperative prognosis of peritonitis. Chirurg 1987; 58(2): 84-92.
7. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: Five-year experience. Ann Surg 2009; 250(2): 187-96.
8. Humes DJ, Simpson J. Acute appendicitis. BMJ 2006 Sep 9; 333(7567): 530-4.
9. van Rossem CC, Bolmers MDM, Schreinemacher MHF, van Geloven AAW, Bemelman WA, et al. Prospective nationwide outcome audit of surgery for suspected acute appendicitis. Br J Surg 2016; 103(1): 144-51.
10. Sartelli M, Baiocchi GL, Di Saverio S, Ferrara F, Labricciosa FM, Ansaloni L, et al. Prospective observational study on acute appendicitis worldwide (POSAW). World J Emerg Surg 2018; 13: 19.
11. Collaborative SCOAP, Cuschieri J, Florence M, Flum DR, Jurkovich GJ, Lin P, et al. Negative appendectomy and imaging accuracy in the Washington State Surgical Care and Outcomes Assessment Program. Ann Surg 2008; 248(4): 557-63.
12. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World J Emerg Surg 2020; 15(1): 27.
13. Ninh A, Wood K, Bui AH, Leitman IM.. Risk factors and outcomes for sepsis after appendectomy in adults. Surg Infect (Larchmt) 2019; 20(8): 601-6.
14. Giglia MD, DeRussy A, Moris MS, Richman JS, Hawn MT, Vickers SM, et al. Racial disparities in length-of-stay persist even with no postoperative complications. J Surg Res 2017; 214: 14-22.
15. Schneider EB, Calkins KL, Weiss MJ, Herman JM, Wolfgang CI, Makary MA, et al. Race-based differences in length of stay among patients undergoing pancreatoduodenectomy. Surgery 2014; 156(3): 528-37.

ORIGINAL ARTICLE

Comparison of the COVID-19 mortality occurring in hospitals and those brought in dead within Malaysia

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ABSTRACT

Background: Measuring the success of the control of COVID-19 in any country includes a review of the mortality especially to compare the deaths of those dying in hospitals and those brought in dead (BID). The objective of this study was to compare the death groups with the demographic factors that influenced the type of death.

Methods: This was a case-control study (1:1 ratio) looking at COVID-19 secondary public data from March 2020 to February 2021. Data such as the basic demographic data and comorbidities were analysed descriptively and then using a binary-logistic regression analysis to compare the independent variables against the outcome of BID. From the database, 120 cases were included as BID (4 excluded due to insufficient information) and 120 patients from the 1006 who passed away in hospital were randomly selected as comparators. The data was analysed in SPSS v21.0.

Results: The mean age for the BID was 59.59 (SD: 18.74), with more males (70.8%) than females (29.2%), of which 61.7% were Malaysians, 46.7% from the state of Sabah, and 64.2% having at least one co-morbidity (50% of them had hypertension). A univariate binary logistic regression analysis yielded factors such as age, nationality, and presence of any co-morbidities that are favourable to be included into the multivariate analysis. From the final analysis, the only factor that distinguished the BID from those dying in the hospital was being a foreigner (AOR: 4.32 [95%CI: 2.02–9.24], p<0.001).

Conclusions: This concluded that foreigners in Malaysia were likely to die from COVID-19 outside of the hospital compared to Malaysians. Amongst the reasons that needed to be addressed were cost, accessibility issues regarding medical care, and the testing policies in Malaysia.

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KEYWORDS:
COVID-19, BID, foreigner deaths, pandemic

INTRODUCTION

In 2019, the Hubei province in China had reported several cases characterised by pneumonia and respiratory failure caused by a fatal unknown virus. This was later successfully isolated and termed the novel coronavirus and later dubbed as SARS-CoV-2.[1] The virus originates from the coronaviruses of the Coronaviridae family in the Nidovirales order and is known to have a single-stranded RNA.[2] Being from the list of coronaviruses, there has been much debate and controversy about the origins of the virus – it is now accepted that the virus originated as a zoonotic virus that found its way into infecting humans (human-to-human) through droplet spread.[2] Since that discovery, the virus has mutated multiple times causing different variants. Though the spread and mitigation of the virus remains the same, the transmissibility and infectiousness of each variant differs, with the Omicron (B.1.1.529), Delta (B.1.617.2), and Beta (B.1.351) strains dubbed collectively as the variants of concern.[3,4] COVID-19 can affect the infected population with several severities, from being asymptomatic to having full-blown respiratory failure needing ventilation.[5] The ultimate acute complications that are faced include ventilator -related medical issues and death.[5] Deaths however can occur in two instances: one that occurs in hospitals after all medical interventions/diagnostics have been done and the other occurring before the patient can be given medical attention, largely termed as 'brought in dead' (BID), and this sometimes is used interchangeably with the term 'dead on arrival'.[6,7] Part of the issues in some countries, especially very early on in the pandemic, were the number of BID that occurred perhaps due to COVID-19.[6]

Malaysia, a country situated in the region of South East Asia with a population of 32 million consisting of Malays, Chinese, Indians, Indigenous population, and foreigners, is a country that has also been affected by COVID-19. The first documented case of COVID-19 in Malaysia was recorded on 25 January 2020 that was traced back to three Chinese mainland national citizens who were infected whilst being in Singapore.[8] The first Malaysian to have had contracted COVID-19 happened on 4 February 2020 who had claimed to have contracted it from Singapore.[8]

Malaysia has already seen five waves of COVID-19 cases with the biggest coming with the Delta and Omicron variants. The deaths however differed in both waves due to the presence of better vaccination rates during the Omicron phase. Until the time of the data collection period (28 February 2021), the country had seen 300,752 cases with the recovery being at 273,417 (90.91%), 6.2 million tests performed and 1,130 deaths already witnessed (case fatality rate: 0.38%).[9] From these 1,130 deaths, they were broadly categorised into two categories: those dying after receiving treatment and those who were BID and were found to have had COVID-19 after being tested (post-mortem).

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Malaysia since has setup a specific COVID-19 surveillance and management system. There is a specific mode of reporting especially for testing, positive case reporting, and analytics – all of which are centralised to the federal government system officially runned, maintained, and handled by the Ministry of Health Malaysia. Their daily public communication from this central repository comes in two different ways, either through the sharing from the official health portal concerning COVID-19 (available at http://covid-19.moh.gov.my/) or from the Director General of Health's official website (available at: https://kpkesihatan.com/) that is updated daily. All numbers that were reported have been on a 24-hour basis (from 12 pm the previous day to 12 pm on the day of reporting). Until the time of publication for the stipulated time period, both resources have reported the same statistical numbers and they tally.

After the emergence of COVID-19 in Malaysia, Malaysia beefed up its capacity to handle COVID-19 cases in multiple stages. At the point of preparation of this manuscript in 2021, Malaysia had 63 hospitals to treat COVID-19 throughout the country, which includes 6,755 beds and 543 ICU beds.[10,11] These are specifically reserved for those diagnosed with COVID-19 at Tier 3, 4, and 5. These numbers exclude the numerous quarantine centres across states in Malaysia (some even potentially capable to house 10,000) for those that were tested positive for COVID-19 but were suffering from Tier 1 or 2 stages of the disease. At present, Malaysia is practicing a home-quarantine policy if someone tests positive (Tier 1/2) unless the house/living situation is deemed inappropriate by the authorities, to which they are then quarantined in the government quarantine centres. Those that are having COVID from Tier 3 onwards are required to be admitted into a designated COVID-19 hospital for treatment. Deaths are dealt accordingly as how deaths were reported within the hospitals, but for COVID-19, a special report has to be sent to the central repository for documentation. From this pandemic, there have been cases that patients were BID, and when they were tested, they tested positive for COVID-19 and were included in the daily reporting to the central repository.

There were very few publications at the time of authorship regarding the BID due to COVID-19.[6] A study reported that 72.5% of the COVID-19 deaths in the Zambian community were found to have been BID.[6] Amongst the reasons cited for this was the question of the health seeking behaviour in their local population.[6] Some of the reasons that BID was deemed important was for the country to know if their mitigation of the COVID-19 pandemic in terms of testing, contact tracing, and public health measures was effective. It is important to study the BID as it reflects if enough was being done to contain the virus within any nation. Another study comparing the deaths which analysed the data based on BID by age in the United States was done- it reported that the range was from 9.8% to 38.9%.[12]

The aim of this study was to compare the deaths including demographic factors that influenced them with deaths that occurred outside the hospital and within the hospitals in Malaysia.

MATERIALS AND METHODS

Methodology

This study was a case-control study (1:1 ratio between the BID and hospitalised deaths) that was conducted using secondary publicly made available data on COVID-19 in Malaysia. Data from the pandemic starting on 17 March 2020 until 28 February 2021 were taken into account for this study. The reason the time line was started on 17 March 2020 despite the pandemic being reported since 24 January 2020 was simply because that the researcher decided to obtain data from the first recorded death in Malaysia, which occurred on 17 March 2020.

Data such as age, gender, the nationality, the place where the death occurred (by state), and the presence of co-morbidities were made readily available as granular data on a day-to-day basis. The researcher collated the data by accessing the data pages of each day on the stipulated dates to obtain the data. All data collected were entered into Microsoft Excel for tabulation before being exported into SPSS v21.0 for statistical analysis.

Selection of data and authenticity

Data were obtained from the following sources:

1. The Director General's website (https://kpkesihatan.com/)
2. The Official Malaysian Health Ministry Portal for COVID-19 information (http://covid-19.moh.gov.my/terkini)

Data on the stipulated dates were obtained on a day-to-day basis (as per reported by the above websites). Data of the daily deaths were made available in detail by source 1, whilst general clumped data details (e.g., daily total deaths) were made available from source 2. Data consisted of patients who had been admitted and died due to COVID-19 or those who were BID and were later diagnosed (post-mortem) to have had died from COVID-19 causes. Patients included were both Malaysians and foreigners who availed from medical facilities within Malaysia (both government and private healthcare facilities). BID was identified within the daily report as entries worded with '*Jenazah dibawa ke Hospital …*', which directly translated from Bahasa Melayu (native Malaysian language) to English as 'Corpse brought to Hospital …' within the column that identifies the place of where the post-mortem was conducted.

The author presumed that the date the death was reported as the day of death and the case number assigned to COVID-19 patient (case number assigned were numbers in sequence following the total cumulative cases Malaysia has seen) was used to determine the day of admission when comparing to the correspondence of the cumulative cases. Data entered were cross-checked by two other independent individuals to see if there were any discrepancies. Any discrepancies were rectified and corrected before analysis.

Data selection and randomisation

From 17 March 2020 till 28 February 2021, the author recorded 124 (10.97%) cases of BID and 1006 (89.03%) deaths of those passed away in hospital (total 1130) due to COVID-19. From the total of 124, the author excluded 4 BID cases as they were backdated (date of death not reported), they had died outside the country, or the information shared on the

official reporting portals (sources 1 and 2) were incomplete. After the exclusion, a total of 120 (96.77%) of the 124 were included into the final analysis.

The author then randomly selected 120 patients (accounting for 10.62% of the total 1130 deaths) who had died in the hospital settings due to COVID-19. From the 1006 patients who died in hospital during the stipulated time, the author assigned an individual number to each patient following the sequence of deaths according to the date of death. The author then used the EpiCalc 2000 (v1.01) to select 120 random numbers from the possible 1006 to be included in the study as a comparator. These selected numbers were inspected, and all the initial selected 120 numbers were included as comparators after affirming that the data of these patients were complete. The data was selected and included in a Microsoft Excel file containing the BID cases previously entered. Once the data was cleaned and standardised, it was imported into SPSS v21.0 for the final analysis.

Ethics approval

Ethics approval was obtained from the National Medical Research Registry and the Malaysian Research Ethics Committee (NMRR-21-962-60004). There were no identifiers as data obtained and used were secondary data already anonymised by the provider.

Mode of analysis

Data were analysed and provided as numbers/percentages (for categorical data) and mean/median with standard deviation/inter-quartile range for continuous variables. The continuous variables that were normally distributed (each skewness was between -1/+1 and Kurtosis between -3/+3) were reported as mean (standard deviation). The variables that were not normally distributed were reported as median (inter-quartile range). For the logistic regression, *p* values ≤0.3 for the univariate regression were considered significant and included for the multivariate analysis. For the multivariate analysis and all other statistical tests (other than the univariate analysis), *p* values of <0.05 was considered statistically significant. To see if both groups were homogenous, we used the presence of comorbidities as a comparative baseline. This was done because during the time of data collection, the ministry had always suggested that the presence of comorbidities made a difference between recovering from COVID-19 or succumbing to it.[13]

RESULTS

Demography

The demographic characteristics of the people who were BID and those who were randomly selected that died in hospital are listed in Table I. The comparative baseline of having comorbidities was done via a chi-square, which showed no statistical significance between the two groups (p=0.06), thus making the groups comparable (the breakdown of each comorbidity compared was also not significant at p=0.68). The mean age for the BID group was 59.59 (SD: 18.74) years and for those who died in hospitals was 64.33 (16.00) years. In both groups, there were more males than females. There were also more Malaysians than foreigners (p<0.001) and many deaths happening in the state of Sabah (p=0.04), all of which when compared were statistically significant. Most of the co-morbidities present were similar, with hypertension being the most common (50.0% in the BID group and 55.8% in the hospital group), followed by diabetes (29.2% in the BID group and 48.3% in the hospital group) and chronic kidney disease (12.5% in the BID group and 23.3% in the hospital group).

A statistical analysis was also conducted to see if the demographics varied between the two groups. Conducting an independent t-test analysis yielded a statistically significant difference (p=0.03), which showed that the two groups were indeed different from each other, with the BID being more prone to die at an early age from COVID-19 compared to those who died in hospitals. There was also a significant difference amongst the nationalities of those who passed away. A chi-square test showed that there was a statistically significant difference amongst the nationalities (p<0.001). This was because there was a larger proportion of foreigners who were BID compared to those who died in the hospital. The median time from the time of admission to the time of death amongst those who passed away in hospitals was 5 days (IQR: 12.25).

Advance analysis

Binary logistic regression analysis comparing the BID patients with the patients who died in hospital

Goodness-of-fit model

The researcher decided to perform a binary logistic regression analysis to compare the basic demographic variables when comparing the outcome of being BID or patients dying in hospitals. The researchers first ran a 'goodness-of-fit' Hosmer and Lemeshow modelling for the data, which yielded only the categorical variables with p= 0.76 and a goodness of fit amounting to 67.9%. The researcher also ran the goodness of fit via the Nagelkerke R^2, which yielded 20.7% or 79.3% fit. All variables were left in the original categorical form except for the age variable that was analysed as a continuous variable.

Univariate analysis

The researcher then proceeded with a univariate analysis, which was conducted to compare variables such as age, gender, nationality, states where the death occurred, and co-morbidities (all of which underwent an interaction check and there were no interactions with the data). The outcome was the comparison of the BID (numerator) with the patients dying in hospital (denominator). The univariate analysis conducted used the variables that yielded a p≤0.3 to be included for the multivariate analysis. From the univariate analysis, it was found that age (OR: 0.98, 95% CI: 0.97–0.99), gender (male having the OR: 1.51, 95% CI: 0.88–2.58), nationality (foreigners having an OR of 5.12, 95% CI: 2.58–10.13), those without any co-morbidities (OR 1.92, 95% CI: 1.09–3.40), those with co-morbidities including hypertension (OR: 1.40, 95%CI: 0.84–2.32), diabetes mellitus (OR: 2.27, 95%CI: 1.33–3.87), chronic kidney disease (OR: 2.13, 95%CI: 1.07–4.23), ischemic heart disease (OR: 2.47, 95%CI: 1.07–5.67), chronic lung disease (OR: 2.42, 95%CI: 0.61–9.57), and those who are immunocompromised or with some oncological disorders (OR: 4.10, 95%CI: 0.45–37.26)

Table I: Demographic details of those who were brought in dead (BID) and those who died in hospital, and a statistical comparison between the two groups

Variables	BID n (%) N= 120	Died in hospital n (%) N= 120	p value
Age*	59.59 (18.74)	64.33 (16.00)	0.03
Gender			
Male	85 (70.8)	74 (61.7)	0.13
Female	35 (29.2)	46 (39.3)	
Nationality			
Malaysian	74 (61.7)	107 (89.2)	<0.001
Foreigner	46 (38.3)	13 (10.8)	
States where deaths occurred			
Sabah	56 (46.7)	39 (32.5)	0.04
Selangor	29 (24.2)	37 (30.8)	
Kuala Lumpur	12 (10.0)	10 (8.3)	
Sarawak	5 (4.2)	5 (4.2)	
Perak	4 (3.3)	3 (2.5)	
Labuan	3 (2.5)	0	
Pahang	3 (2.5)	2 (1.7)	
Johor	2 (1.7)	15 (12.5)	
Melaka	2 (1.7)	0	
Negeri Sembilan	2 (1.7)	2 (1.7)	
Penang	2 (1.7)	3 (2.5)	
Kedah	0	1 (0.8)	
Kelantan	0	2 (1.7)	
Putrajaya	0	1 (0.8)	
Co-morbidity			
Yes	77 (64.2)	93 (77.5)	0.06
No	42 (35.0)	27 (22.5)	
NA	1 (0.8)	0	
Hypertension	60 (50.0)	67 (55.8)	0.68
Diabetes mellitus	35 (29.2)	58 (48.3)	
Chronic kidney disease	15 (12.5)	28 (23.3)	
Dyslipidaemia	12 (10.0)	16 (13.3)	
Stroke	11 (9.2)	14 (11.7)	
Ischemic heart disease	9 (7.5)	20 (16.7)	
Obesity	7 (5.8)	7 (5.8)	
Asthma	5 (4.2)	5 (4.2)	
Gout	5 (4.2)	6 (5.0)	
Bronchiectasis	2 (1.7)	0	
Chronic lung disease	2 (1.7)	7 (5.8)	
Anaemia	1 (0.8)	1 (0.8)	
Autoimmune diseases	1 (0.8)	2 (1.7)	
Immunocompromised/oncology	1 (0.8)	4 (3.3)	
Chronic liver disease	0	1 (0.8)	
Thyroid disorder	0	1 (0.8)	
Average time from admission to death**		5 (12.25)	

*reported as Mean (SD) **reported as Median (IQR)

were factors that had a p value of less than 0.3 and were included into the multivariate analysis. The *p* values of ≤0.3 were only for the purpose of including them into the multivariate analysis (any comparison without the multivariate analysis, significance should be considered at $p<0.05$).

Multivariate analysis

The significant variables in the univariate analysis ($p<0.3$) were included in the multivariate analysis to identify the variables that had an effect on those who were BID when compared to those who died in the hospital. The value of significance in the multivariate analysis was considered at $p<0.05$. From the final analysis, we found that the nationality was the main variable that had an effect on the patient being BID compared to those who died in hospital. Foreigners had an adjusted odds ratio of 4.32 times (95%CI: 2.02–9.24) more likely to be BID instead of dying in hospitals when compared to Malaysians. This also yielded a significant *p* value at $p<0.001$. The other factors yielded no statistically significant difference, though it must be mentioned that having ischemic heart disease ($p=0.06$, OR: 2.42, 95%CI: 0.96–6.10), having diabetes mellitus ($p=0.09$, OR: 1.79, 95%CI: 0.91–3.53), and being the male gender ($p=0.09$, OR: 1.68, 95%CI: 0.93–3.05) were factors that were rather close to a statistically significant difference. Complete details are available in Table II.

Table II: The odds ratio (OR) and the multivariate analysis of adjusted odds ratio (AOR) for the binary logistic regression performed

Variables	Univariate analysis OR (95% CI)	p value	Multivariate analysis AOR (95% CI)	p value
Age	0.98 (0.97–0.99)	0.04	0.99 (0.97–1.01)	0.25
Gender				
Male	1.51 (0.88–2.58)	0.13	1.68 (0.93–3.05)	0.09
Female	Ref		Ref	
Nationality				
Malaysian	Ref	<0.001	Ref	<0.001
Foreigner	5.12 (2.58–10.13)		4.32 (2.02–9.24)	
States where deaths occurred				
Selangor	Ref	0.55		
Sabah	1.83 (0.97–3.46)			
Kuala Lumpur	1.53 (0.58–4.04)			
Sarawak	1.28 (0.34–4.83)			
Perak	1.70 (0.35–8.21)			
Labuan	>1000			
Pahang	1.91 (0.30–12.22)			
Johor	0.17 (0.04–0.80)			
Melaka	>1000			
Negeri Sembilan	1.28 (0.17–9.61)			
Penang	0.85 (0.13–5.43)			
Kelantan	-			
Kedah	-			
Putrajaya	-			
Co-morbidity				
Yes	Ref		Ref	
No	1.92 (1.09–3.40)	0.02	0.87 (0.35–2.18)	0.77
Hypertension	1.40 (0.84–2.32)	0.20	0.66 (0.30–1.43)	0.29
Diabetes mellitus	2.27 (1.33–3.87)	0.03	1.79 (0.91–3.53)	0.09
Chronic kidney disease	2.13 (1.07–4.23)	0.03	1.37 (0.62–3.01)	0.43
Dyslipidaemia	1.39 (0.63–3.07)	0.42	-	-
Stroke	1.31 (0.57–3.01)	0.53	-	-
Ischemic heart disease	2.47 (1.07–5.67)	0.03	2.42 (0.96–6.10)	0.06
Obesity	1.00 (0.34–2.94)	0.99	-	-
Asthma	1.00 (0.28–3.55)	0.99	-	-
Gout	1.21 (0.36–4.08)	0.76	-	-
Bronchiectasis	0	0.99	-	-
Chronic lung disease	2.42 (0.61–9.57)	0.21	2.65 (0.59–11.87)	0.20
Anaemia	1.00 (0.06–16.17)	0.99	-	-
Autoimmune diseases	2.02 (0.18–22.55)	0.57	-	-
Immunocompromised/oncology	4.10 (0.45–37.26)	0.21	2.82 (0.28–28.15)	0.38
Chronic liver disease	>1000	0.99	-	-
Thyroid disorder	>1000	0.99	-	-

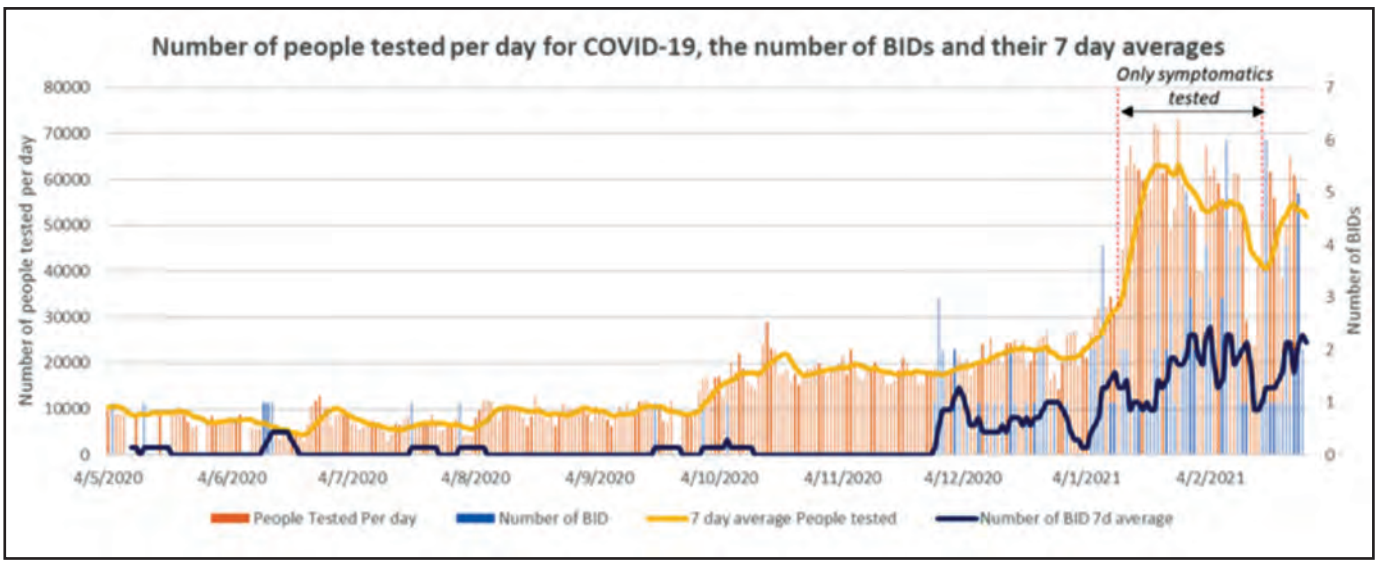

Fig. 1: The number of people tested and being BID per day and their respective seven-day averages with respect to COVID-19.

Summary of Findings

Foreigners were 4.32 times (95% CI: 2.02–9.24) more likely to die by being BID than dying in hospitals compared to Malaysians. In this study, the multivariate binary logistic regression showed that being a foreigner was the only factor that determined if a COVID-19 patient was to be BID or die in hospital (p<0.001).

DISCUSSION

From this study, it was found that the only factor that determined if a COVID-19 patient was BID or died in hospital was the fact of nationality. This has given a rise to the healthcare of foreign workers in Malaysia– a topic that has always been a debate in Malaysia.

The literature search revealed that there were only two papers published on BID concerning COVID-19 in Zambia and another in the United States. The Zambian paper reported that as high as 72.5% of the COVID-19 deaths were occurring within the community and were likely to be BID, which was much higher than the 10.97% cases that were BID in Malaysia.[6] The Zambian study implied that not only were BID a concern for public health safety of the people, but they made contact tracing of COVID-19 much more difficult.[6] Amongst the reasons cited for a potential cause of the BID was the poor "healthcare seeking behaviour" among the population, a lack of knowledge about COVID-19 and its severity along with the reported high proportion of recoveries, perception of illness, stigma associated with the disease, and medication being readily made available over the counter.[6,14] The U.S. study showed that the range of BID were 9.8%–38.9%.[12] They also found that the younger age group were likely to be BID compared to the older group.[12]

Although there has been limited literature published about BID with regards to COVID-19, there were a few papers published on different subject matters with relation to BID. From a paper published in 2016 concerning maternal deaths, amongst the reasons cited for BID reported were that 56.25% of patients were guilty of a delay in seeking proper medical attention.[15] Data for the exact reasons for the BID due to COVID-19 in Malaysia were not made available in the current study. In another paper, where BID were assessed in a state in India, it was reported that many BID were due to the fact of unexpected deaths especially in the 21- to 30-year-old age group, which however was attributed to physical factors like motor vehicle accidents and social activities.[16] In the current study, the mean age group of the BID differed at 59.59 (SD: 18.74) compared to the study done in India. The study in Zambia did not report any age groups that were BID due to COVID-19.[6]

In this current research, the researcher found that foreigners were prone to be BID compared to Malaysians. Some of the possible reasons were explored. In a qualitative paper published in 2019 regarding foreign worker's healthcare in Malaysia, it was reported that healthcare services in Malaysia (private or public) has become rather inaccessible to migrant workers.[17] Some of the factors that have been identified were complex access barriers that were mainly related to matters beyond the control of the healthcare sector – including financial constraints, legality issues concerning documentation, language barriers, discrimination/ xenophobia, and employer-related barriers.[17] Amongst the things that were suggested in the paper to overcome these barriers was to ensure that the government has a compulsory healthcare worker insurance cover so that foreign workers are able to attain healthcare services especially in the times of emergency.[17] In another paper published in 2020 by the same author, it was reported that migrant health policies at destination countries (China and Malaysia) were predominantly protectionist, concerned with the transmission of communicable diseases (such as tuberculosis and blood-borne diseases) and diseases that might burden the health systems.[18] Another point of concern was there were reports of instances where migrant workers intending to renew their permits failed their medical examination and ended up overstaying as undocumented workers.[18] This, in a way, has caused them to refrain from getting medical attention during the time of illness to avoid being deported, thus causing them to present to healthcare facilities at a delayed and at dire stages.[18]

Another reason for delayed medical care attention towards foreign workers was due to the fact that foreigners were liable to higher payments when seeking medical care in the public healthcare sector.[19,20] Due to high costs that are incurred in the public sector, the foreigners are more likely to seek private healthcare services especially in primary care.[20,21] There was also a disparity of healthcare access based on the place of stay of these foreign workers.[21] As it is known in Malaysia, there was a delay in allowing the private healthcare services to screen for COVID-19, not forgetting the constant voicing of the private sector mentioning that they were not prepared to receive/treat COVID-19 patients.[22] All of these might have contributed to foreigners being BID.

Another possible reason that foreigners might be prone to BID is due to the fact that they might not be well-educated on COVID-19 symptoms. A study done in Malaysia showed that Malaysians had good knowledge, attitude, and practice when it came to COVID-19 but this study excluded foreigners.[23] However, from a report written in 2020, it can be summarised that the understanding of COVID-19 especially an explanation in the native language of foreigners is vital to disseminate vital public information for prevention.[24]

In this research, we report that many patients that were BID were younger than those dying in hospitals. This possibly throws doubt to the concept of some theories that might consider younger patients to be less risky in succumbing to COVID-19. However, it must be also considered that the presences of co-morbidities might be an influencing factor that determines whether the COVID-19 infection could to be severe or not.[25] In our latest published National Health and Morbidity Survey of 2019, it was reported that many co-morbidities (that were linked to COVID-19 severity) were rather hidden within the community especially diabetes and hypertension (both individually, nearly half of the national prevalence especially among young adults remain silent and unknown).[26] Additionally, the fact that the prevalence of obesity is high in Malaysia could also be a contributing factor to these deaths,[27] which could also be another factor why

many of the young patients in this study were found to have been BID. This however, can only be coupled with the applied methods of active case detection.

In a debate article published in 2020 in the United States, there was a discussion suggesting if COVID-19 management should see a change in the management/admission according to the patients' age.[28] Although there was much debate about fairness and recovery rates, it did show that the concept of admission and the prognosis for recovery is highly debatable. However, in the study conducted in the United States looking at BID, the younger age group had seen higher mortality rates compared to the older age groups.[12] Being younger might might be a contributing factor, owing to the reason that younger people might not show symptoms till the later stages.[12] In this study, we saw that although age was not a predictor to determine if a patient was to be BID or die in hospital, upon comparing, the BID group was indeed statistically significantly younger when compared to those dying in the hospital group. This might give rise to the discussion within the paper that was published in United States on whether the admission and management of patients be done based on tier severity rather than having the confounder of age selection.

Amongst the ways that could have been employed to rampantly reduce the number of COVID-19 cases and deaths in any country at a point of high deaths, especially the BID, is the mass and rapid testing.[29] The reason for this is the turn-over time from test results to mitigation. During the early days, the antibody testing was used; however, since we have known that it was not as sensitive and specific, the reverse transcriptase polymerase chain reaction (RT-PCR) test was used in hospitals for better reliability.[29] However, we know that the RT-PCR can take a few days (1–3 days) to be processed and for a result to be made available.[30] Therefore, with the invention and accurate sensitivity/specificity of some brands of the rapid test kits-antigen (RTK-Ag including the saliva tests done correctly), it was a better alternative than the antibody tests that were used earlier.[30] With this, countries will be able to mitigate with faster decision-making in isolating and contact tracing close contacts within 1–3 hours compared to 1–3 days with RT-PCR.[30,31] When a person is diagnosed early, many of the other mitigation processes like contact tracing, early initiation of treatment, and early isolation can not only help with the detection of other cases, but it will also assist to isolate the case from becoming a potential source of spread to other individuals. This is even more so amongst infected individuals who are asymptomatic. The report received in Malaysia via the Ministry of Health in July 2020 showed that about 70% of the COVID-19 patients in the country were asymptomatic.[32] Figure 1 lists the number of people tested per day in Malaysia since May 2020. As we approached the new year in 2021, Malaysia received a new circular issued (13 January 2021) by the Ministry of Health stating that only symptomatic close contacts would be tested.[33] This was later retracted on 17 February 2021.[34] However, we can see from the graph that the number of cases increased tremendously during that period and so did the 7-day BID average baseline. This might be due to the fact that many positive cases were perhaps not screened and because of not being bounded by the law to quarantine, many would have been in contact with the community, thus causing further spread of the virus within. This might be especially true after Malaysia was seen to have many workplace clusters during the pandemic.[35] With the way testings were conducted from 13 January 2021, it might be indicative in the rise in the BID as patients might have been infected and not known until they reached a critical state of infection that caused them to succumb before medical intervention was possible. Amongst the possibilities is happy hypoxemia that affects younger individuals.[36] This, however, was a time before mass vaccination was done in the country.

STRENGTHS

- Until the time of submission, the researchers are unaware of any other publications in Malaysia comparing the BID patients with those who died in hospitals.
- This study used data from official government sources that verified the deaths of COVID-19 before being made public.

LIMITATIONS

- The assumption of date of deaths and admissions might have a discrepancy of one day as the reporting in Malaysia has a cut-off point of 12 pm daily. The subsequent deaths on the day will be taken into account only the next day.
- Data was entered manually by the author after reviewing the data posted on official sources. The author had allotted two individuals to examine the data entered for accuracy. However, due to manual data entry, there might be random errors (though dataset was inspected multiple times by different individuals).
- All data was obtained from the official source of COVID-19 information in Malaysia. Any discrepancy that was made by the source will be reflected in the dataset.

CONCLUSIONS

Foreigners were four times more likely to be BID due to COVID-19 compared to Malaysians. The mitigation of the pandemic highly depends on the number of deaths a country deals with. With a high number of foreigners being BID, consideration on their access to medical care needs, accessibility, costing, and mass testing might need to be considered to ensure that COVID-19 cases are picked up early for mitigation purposes. The BID at that time might also be more likely linked to the COVID-19 'testing policy' choice adopted by governments, especially those involving the testing of asymptomatic individuals who were close contacts.

DECLARATIONS

• *Ethics approval and consent to participate*

Data in this study were obtained from a public domain data source. No individuals were approached for this study. Consent therefore was not applicable.

• *Consent for publication*

Publication consent was obtained from the Director General of Health. The author would like to thank the Director

General of Health for approving the publication of this study.

• *Availability of data and materials*

Data tabulated in the Excel sheet will be made available to researchers upon request from the author.

• *Competing interests*

The author declares no competing interest in this study.

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• *Authors' contributions*

As the only author, Arvinder-Singh HS collected the data, compiled the data, performed the analysis, and wrote the final manuscript.

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REFERENCES

1. Ferrer R. COVID-19 pandemic: The greatest challenge in the history of critical care. Medicina Intensiva 2020; 44(6): 323-4.
2. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res 2020; 24 (1): 91-8.
3. Kumar V, Singh J, Hasnain SE, Sundar D. Possible link between higher transmissibility of B.1.617 and B.1.1.7 variants of SARS-CoV-2 and increased structural stability of its spike protein and hACE2 affinity. bioRxiv 2021: 2021.04.29.441933 [pre-publication].
4. Du X, Tang H, Gao L, Wu Z, Meng F, Yan R, et al. Omicron adopts a different strategy from Delta and other variants to adapt to host. Signal Transduct Target Ther 2022; 7(1): 45.
5. Lai CC, Liu YH, Wang CY, Wang YH, Hsueh SC, Yen MY, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. J Microbiol Immunol Infect 2020; 53(3): 404-12.
6. Chileshe M, Mulenga D, Mfune RL, Nyirenda TH, Mwanza J, Mukanga B, et al. Increased number of brought-in-dead cases with COVID-19: Is it due to poor health-seeking behaviour among the Zambian population? The Pan African Medical Journal 2020; 37 (136): 1-4
7. Simpson MA. Brought in dead. OMEGA – Journal of Death and Dying 1976; 7(3): 243-8.
8. Elengoe A. COVID-19 outbreak in Malaysia. Osong Public Health Res Perspect 2020; 11(3): 93-100.
9. Malaysia MoH. Jumlah Keseluruhan Taburan Kes COVID-19 Di Malaysia (Sehingga 28 Februari 2021, 12 tengah hari National CPRC, MOH; 2021) [cited March 2022]. Accessed from: http://covid-19.moh.gov.my/terkini/2021/feb/situasi-terkini-covid-19-di-malaysia-28022021:
10. CodeBlue. Covid-19 Deaths, ICU, Ventilated, Active Cases Rise in Growing Outbreak. CodeBlue. 2021 [cited March 2022] Accessed from: https://codeblue.galencentre.org/2021/05/03/covid-19-deaths-icu-ventilated-active-cases-rise-in-growing-outbreak/ .
11. Su-Lyn B. Half of Malaysia's Covid-19 Cases Now Symptomatic: Adham. : CodeBlue. 2021. [cited March 2022] Accessed from: https://codeblue.galencentre.org/2021/05/10/half-of-malaysias-covid-19-cases-now-symptomatic-adham/
12. Pathak EB, Garcia RB, Menard JM, Salemi JL. Out-of-hospital COVID-19 deaths: Consequences for quality of medical care and accuracy of cause of death coding. Am J Public Health 2021; 111(S2): S101-6.
13. Ismail SNA, Abdul Halim Zaki I, Noordin ZM, Md Hussin NS, Ming LC, Zulkifly HH. Clinical characteristics and risk factors for mortality in patients with COVID-19: A retrospective nationwide study in Malaysia. Proceedings of Singapore Healthcare 2022: 20101058221085743; 0(0):1-8.
14. Chew CC, Lim XJ, Chang CT, Rajan P, Nasir N, Low WY. Experiences of social stigma among patients tested positive for COVID-19 and their family members: A qualitative study. BMC Public Health 2021; 21(1): 1623.
15. Kumar A, Agrawal N. Brought in dead: An avoidable delay in maternal deaths. The Journal of Obstetrics and Gynecology of India 2016; 66(1): 60-6.
16. Bansal AK, Patel A, Mittal P, Bhoot R, Merchant S, Patel P. Pattern of spot death cases brought to VS General Hospital, Ahmedabad: A retrospective study. JIAFM 2013; 35(2): 131.
17. Loganathan T, Rui D, Ng CW, Pocock NS. Breaking down the barriers: Understanding migrant workers' access to healthcare in Malaysia. PLoS One 2019; 14(7): e0218669.
18. Loganathan T, Rui D, Pocock NS. Healthcare for migrant workers in destination countries: A comparative qualitative study of China and Malaysia. BMJ Open 2020; 10(12): e039800.
19. Loganathan T, Chan ZX, Pocock NS. Healthcare financing and social protection policies for migrant workers in Malaysia. PLoS One 2020; 15(12): e0243629.
20. Noh NA, Wahab HA, Bakar Ah SH, Islam MR. Public health services for foreign workers in Malaysia. Soc Work Public Health 2016; 31(5): 419-30.
21. Sohrabi M, Osman AF, Tumin M. Why workers do not use health care services in public clinics-a case of non-citizens in Malaysia. International Journal on Recent Trends in Business and Tourism (IJRTBT) 2019; 3(1): 1-7.
22. Bernama. Private hospitals unable to accept more Covid-19 patients. Malaysian Reserve. 2021. [cited March 2022] Accessed from : https://themalaysianreserve.com/2021/04/29/private-hospitals-unable-to-accept-more-covid-19-patients/
23. Chang CT, Lee M, Lee JCY, Lee NCT, Ng TY, Shafie AA, et al. Public KAP towards COVID-19 and antibiotics resistance: A Malaysian survey of knowledge and awareness. International Journal of Environmental Research and Public Health 2021; 18(8): 3964.
24. Guadagno L. Migrants and the COVID-19 pandemic an initial analysis. Geneva, Switzerland International Organization for Migration, 2020.25 [cited March 2022] Accessed from: https://publications.iom.int/system/files/pdf/mrs-60.pdf .
25. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med 2020; 2(8): 1069–1076
26. (NIH) NIoH. Key Findings – National Health and Morbidity Survey 2019. Non-communicable diseases, healthcare demand, and health literacy. Malaysia: 2019 [cited March 2022]. Accessed from: https://iptk.moh.gov.my/images/technical_report/2020/4_Infographic_Booklet_NHMS_2019_-_English.pdf .

27. Hamer M, Gale CR, Kivimaki M, Batty GD. Overweight, obesity, and risk of hospitalization for COVID-19: A community-based cohort study of adults in the United Kingdom. Proc Natl Acad Sci U S A 2020; 117(35): 21011-3.
28. Archard D, Caplan A. Is it wrong to prioritise younger patients with Covid-19? BMJ 2020; 369: m1509.
29. Abdullah JM, Wan Ismail WFN, Mohamad I, Ab Razak A, Harun A, Musa KI, et al. A critical appraisal of COVID-19 in Malaysia and Beyond. Malays J Med Sci 2020; 27(2): 1-9.
30. Smyrlaki I, Ekman M, Lentini A, Rufino de Sousa N, Papanicolaou N, Vondracek M, et al. Massive and rapid COVID-19 testing is feasible by extraction-free SARS-CoV-2 RT-PCR. Nat Commun 2020; 11(1): 4812.
31. Khoo ML, D'Souza BA, Hamzah R, See KKS, Chin JW, Ramadass S, et al. A Sustainable Approach to COVID-19 Testing -Forging a Public-Private-People Healthcare Initiative. Advances in Clinical and Medical Research 2021; 2(1):1-8.
32. Online TS. Covid-19: 70% of cases in Malaysia were asymptomatic, says Health DG. Star Newspaper 2020 [cited March 2022] Accessed from: https://www.thestar.com.my/news/nation/2020/07/08/covid-19-70-of-cases-in-malaysia-were-asymptomatic-says-health-dg.
33. Su-Lyn B. MOH: Home Quarantine Close Contacts, Test Only Those with Symptoms. CodeBlue. 2021 [cited March 2022] Accessed from: https://codeblue.galencentre.org/2021/01/14/moh-home-quarantine-close-contacts-test-only-those-with-symptoms/ .
34. Su-Lyn B. MOH Aims Below 500 Daily Covid Cases, Now Testing All Close Contacts. CodeBlue. 2021 [cited March 2022] Accessed from: https://codeblue.galencentre.org/2021/02/23/moh-aims-below-500-daily-covid-cases-now-testing-all-close-contacts/ .
35. Nationalist AC. Where Are Covid-19 Clusters Found in Malaysia? CodeBlue. 2021 [cited March 2022] Accessed from: https://codeblue.galencentre.org/2021/04/07/where-are-covid-19-clusters-found-in-malaysia/ .
36. Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of 'happy' hypoxemia in COVID-19. Respir Res 2020; 21(1): 198.

Does knowledge and attitude of healthcare professionals working in critical care areas affect their willingness to offer the option of organ donation? Results of a tertiary hospital survey

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ABSTRACT

Introduction: Organ donation (OD) rates in Malaysia have remained suboptimal for decades. Healthcare professionals (HCPs) working in critical care areas are responsible for diagnosing brain death (BD) and initiating the OD process. Impact of their knowledge and attitudes on willingness to offer the option of OD to families of potential donors is unknown.

Methods: Knowledge and attitudes about BD, OD, and organ transplantation (OT) of critical care HCPs in a Malaysian transplant centre were studied using a validated questionnaire. Responses were analysed using multivariable analysis with willingness to offer the option of OD to families of potential donors as dependent variable.

Results: Age (p = 0.04), profession (doctors > nurses, p < 0.001), religion (Buddhists > others, p = 0.013) [but not ethnicity], higher knowledge scores for Brain Death Test, Brain Death Knowledge, Organ Donation and Transplantation, and overall knowledge score (p < 0.001) were associated with greater odds of offering OD to families. Belief in the reliable diagnosis of BD, confidence in explaining BD, and belief that OD will not affect religious services were significantly associated with willingness to offer OD, while HCPs who were willing to personally donate organs had greatest odds (p < 0.001). Other factors that significantly influenced HCPs' willingness to offer included their perception about families' willingness to donate, body disfigurement, and confidence in OT.

Conclusions: Overall, HCPs had highly positive attitudes. However, potential barriers in offering OD to families were identified. Proven interventions from international experience could help address these issues and likely improve OD rates in Malaysia.

KEYWORDS:
Brain Death; Tissue and Organ Procurement; Transplantation; Critical Care; Health Personnel

INTRODUCTION

Although the first successful renal transplant in Malaysia was performed in 1975, transplantation rates in this country have remained low over the last four decades. In 2020, the deceased organ donation (DOD) in Malaysia was only 0.9 per million population (pmp), compared to 38.03 and 18.68 pmp in the United States and United Kingdom, respectively. In Southeast Asia, Singapore and Thailand achieved DOD rates of 2.03 and 4.51 pmp respectively, in the same year.[1] With over 20,044 patients on the transplant waiting list (personal Correspondence, National Transplant Resource Centre), the gap between supply and demand of organs in Malaysia has reached a critical point, where many are likely to die before they receive a transplant.

Suboptimal DOD in Malaysia has been suggested as a determinant of low transplantation rates.[2] Previous studies have shown that cultural-religious-ethnic beliefs and attitudes, a lack of awareness of DOD in the general population, and inadequate trust in the medical system are associated with the low organ donation (OD) rates.[3-8] The Malaysian Ministry of Health in collaboration with the Malaysian Islamic Development Department released a joint statement declaring the permissibility of OD and transplantation, consolidating the Islamic position in this field.[9] In addition, Malaysia follows an 'opt-in' OD policy (explicit consent needed).[10] Failure of healthcare professionals (HCPs) to identify donors, obtain their consent, and procure organs may be another contributory factor for low DOD rates.[11-13]

Brain death (BD) is defined as the irreversible loss of brain function and is recognised legally as death. Globally, the diagnosis of BD is based on strict fulfilment of all the components of the diagnostic criteria based on the mandatory preconditions, exclusions, and the recommended bedside neurological tests. In special circumstances, ancillary tests may be used to confirm the diagnosis. Consistent with the international consensus, the Malaysian Consensus Statement on Brain Death 2003 was published jointly by the

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Ministry of Health, Academy of Medicine of Malaysia, and the Malaysian Society of Neurosciences, outlining the details of the procedures and technical instructions. Related Malaysian Medical Council guidelines were issued in 2006.[14-17]

Early identification of potential donors by diagnosing BD is crucial in initiating the OD process. HCPs working in critical care areas are the first to come in contact with such donors.[18] They are responsible for facilitating BD declaration when suspected, commencing discussions regarding OD with families and referring potential donors.[19] The donor conversion rate in Malaysia (percentage of organ procurements actually performed on potential donors) was only 9.46% in 2019 (presentation by Dr H Haron, 20th May 2020, unreferenced).[20] This has been attributed to failure to conduct brain death tests (BDT),[2] which may be a consequence of HCPs having poor knowledge about BD and BDT and negative attitudes towards handling the OD process.[3] It was reported that HCPs were reluctant to offer OD to families as they believed that families may not accept the diagnosis of BD.[2,5] Therefore HCPs working in critical care areas require the knowledge and skills to approach families at a time of grief.[3,11,12,21] Previous studies have focused on factors influencing family consent rates[22,23] and strategies to initiate discussions with families about OD.[24-26] Few have studied the impact of knowledge and attitudes of HCPs working in critical care areas in Malaysia. In this study, we explored the association of the knowledge and attitudes related to BD, OD, and organ transplantation (OT) of HCPs working in critical care areas with their willingness to offer the option of OD to families of potential donors.

MATERIALS AND METHODS

The study was registered with the National Medical Research Register (NMRR-14-1790-23450 S5 R0) and was approved by the Hospital Kuala Lumpur Clinical Research Centre, Malaysian Research Ethics Committee (MREC) and the Perdana University Institutional Review Board (PUIRB-HR0090).

A cross-sectional survey was conducted amongst HCPs working in selected critical care areas of a tertiary referral hospital in Malaysia according to the recommendations from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[27] HCPs at or above the rank of Medical Officer or Registered Nurse working in General ICU, Neurosurgical ICU, Emergency Department, and Neurology Ward were included in this study. The study tool, derived from existing literature[16,28-33] and investigators' clinical experience, was subjected to face and content validation and has been described in related publications.[34,35]

In brief, it contained 51 items including demographics (10 items) and questions on knowledge (25 items) and attitudes (16 items) related to BD, OD, and OT (Supplement 1). HCPs were categorised as willing to offer the option of OD if they had responded 'Probably Yes' or 'Definitely Yes' to the question: 'Would you offer the option of organ donation to the family of a brain dead patient once brain death has been confirmed?'. The responses for knowledge and attitudes were dichotomised into 'correct/incorrect' and 'Yes and No/Unsure', respectively. Each 'correct' and 'incorrect' answer for the knowledge questions was given a score of one and zero, respectively, with a maximum possible score of 25. Respondents who answered 'Unsure' to attitude questions were regarded as being doubtful towards BD, OD, or OT, hence were taken as negative responses. Responses submitted with less than 33 of 41 items in the BD, OD, and OT section answered (less than 80% completed) were excluded from the statistical analysis.

Descriptive statistics were computed for demographics and knowledge of the respondents. Pearson's chi-square tests were performed to assess whether associations between demographics and various attitudes were statistically significant. Pairwise correlation was assessed using Kendall's tau-b and Spearman's rho. All analyses were done taking HCPs' willingness to offer the option of OD to the families of potential organ donors as the dependent variable. Univariable logistic regression analysis was performed for all independent variables. For categorical variables, the odds ratios were computed relative to the reference group identified in the tables. Statistical tests used were two-tailed, and p-values <0.05 were considered significant. Multivariable regression analyses were done separately for different clusters of independent variables, including sociodemographic, knowledge, attitudes, and religious beliefs. To develop the most parsimonious multivariable regression model, only variables that were significant in univariable analysis were included in multivariable analyses. When analysing the sociodemographic variables, ethnicity was selected over religion. Our clinical and community experience in Malaysia indicates that communication channels between HCPs and potential donors are more effective and efficient along the lines of ethnicity, given the overarching socio-cultural and language homogeneity within ethnic groups.

RESULTS

Socio-Demographics

Of the 565 eligible staff, 420 available during the recruitment period were contacted. Seven HCPs declined to participate and one incomplete submission was excluded from the analysis, leaving a total eligible population response rate of 72.9% (412/565). The demographics of this cohort of HCPs and their willingness to donate organs themselves were reported previously.[34,35] In brief, the mean age of respondents was 29.4 years, with females being the majority (77.2%). Participants included 249 nurses (60.4%) and 163 doctors (39.6%). Most of the respondents were Malays (n=293, 71.1%) followed by Indians (n = 60, 14.6%), Chinese (n =50, 12.1%), and others (n = 9, 2.2%, Table I).

Out of 412 respondents, 411 answered the question on willingness to offer the option of OD, of which 312 (75.9%) expressed their willingness to offer. The proportion of willingness to offer the option of OD according to different sociodemographic characteristics is detailed in Table I.

In univariable logistic regression analysis, age, gender, ethnicity, and profession were significantly associated with willingness to offer. Since religion was highly correlated with ethnicity in Malaysia (all Malays are Muslims, Kendall's tau-

b = 0.951), position was correlated with profession (Kendall's tau-b = 0.874), and gender was correlated with profession (most of the nurses are females, Kendall's tau-b = 0.471); religion, position, and gender were excluded from the multivariable logistic regression model. In the multivariable model including age, profession, and ethnicity, only age and profession remained significantly associated with willingness to offer, while ethnicity became non-significant. Every one-year increase in age reflected 1.06 greater odds of offering OD to families (aOR = 1.06; 95% CI 1.00–1.11; p = 0.047, Table I).

Association with Beliefs

After adjusting for attitude towards religious services in multivariable logistic regression analysis, compared with Muslims, all other religious groups were more willing to offer the option of OD (range of ORs: 2.00–6.35), although this association was significant only for Buddhists and Hindus (Table II).

Most HCPs (74.0%) believed that their religion permitted OD (Table II). There was no significant correlation between this belief and willingness to offer the option of OD (p = 0.286). HCPs who believed that OD will not affect religious services had greater odds of offering OD. After adjusting for religion, HCPs who believed that OD will not affect religious services were more likely to offer OD compared with those who believed otherwise (aOR 2.70; 95% CI 1.68–4.34; p < 0.001).

Association with Knowledge and Profession

Of the three knowledge scores, BDT sub score had the strongest association with willingness to offer, followed by BD knowledge and ODT knowledge subscores. Knowledge and profession were computed in a single multivariable logistic regression. Every point increase in the overall knowledge score was associated with 1.14 times greater odds of offering the option of OD (Table III). Doctors were more likely to offer compared to nurses. The association between doctors and willingness to offer, compared with nurses, remained significant in the multivariable regression model (aOR = 12.10; 95% CI 4.64–31.56; p<0.001, Table III).

Association with Attitudes

HCPs who believed in BD, who were convinced that doctors could reliably diagnose BD, and who were confident in explaining BD were more likely to offer the option of OD compared with those who did not possess these attitudes. These variables were included in a single multivariable logistic regression model with willingness to offer the option of OD as the dependent variable. Being convinced that doctors could reliably diagnose BD (aOR = 2.34; 95% CI 1.13–4.82; p = 0.022) and confidence in explaining BD (aOR = 5.04; 95% CI 3.01–8.43; p<0.001) remained significant, while the attitude of being convinced of BD became non-significant (aOR = 1.22; 95% CI 0.59–2.49; p = 0.592). Confidence in explaining BD had the strongest association among all BD attitudes (Table IV).

Of seven OD attitudes tested, (Table V) five attitudes, which were significant in univariable logistic regression, were included in the same multivariable logistic regression model. Attitudes towards willingness to personally donate (aOR = 14.35; 95% CI 5.08–40.56; p<0.001) and the belief that OD will not cause body disfigurement (aOR = 3.63; 95% CI 1.63–8.09; p = 0.002) remained significant with willingness to offer OD.

In the multivariable logistic regression model including three attitudes addressing confidence in OT (Table VI), belief that OT was a good form of treatment had the strongest association to offer the option of OD (aOR =2.49; 95% CI 1.44–4.31; p = 0.001), followed by the belief that transplantation had high success rates when performed by trained staff (aOR = 2.30; 95% CI 1.37–3.86; p = 0.002) and willingness to accept an organ for transplantation themselves, if indicated (aOR 1.84; 95% CI 1.10–3.08; p = 0.020).

DISCUSSION

To our knowledge, this is the first study in Malaysia, exploring the knowledge and attitudes of critical care HCPs towards OD and OT and their intention to offer the option of OD to families of potential donors. Overall, this cohort had mostly positive attitudes towards BD, OD, and OT; ethnicity was not a negative predictor.

HCPs who believed that OD would not affect any religious services after death were more likely to report their willingness to offer OD. HCPs may presume that families will not consent for OD due to concerns about potential delays in completing religious rituals. However, the OD process can be planned and completed without affecting religious services and facilitated by a faith representative in the multidisciplinary team (MDT).[24,26,36,37] In a multi-faith country like Malaysia, it is important to ensure that HCPs hold no preconceptions about the religious beliefs of the donor family. All potential donor families must be approached.

Compared with nurses, doctors were found to be more likely to offer the option of OD, even after adjusting for knowledge. In many countries, the ODT process has evolved into a MDT effort where bedside nurses work collaboratively with doctors and play an important role in suspecting BD and leading discussions with families.[18,24,38] The 'Specialist Nurse for Organ Donation' and 'Donor Coordinator Nurses' are examples of nursing roles successfully integrated into OD programmes.[18,38,39] OD protocol in Malaysia seems to underutilise nursing resources and could benefit from better empowerment and integration of nurses into the OD MDTs.

HCPs with suboptimal knowledge about BD and BDT are likely to have difficulties in initiating the OD process.[13,26] BD is underdiagnosed in Malaysia, with far less cases referred for OD than expected for the number of ICU deaths.[40,41] HCPs should complete confirmatory tests for BD irrespective of the families' intention to donate and ensure that all BDs are diagnosed and reported. Families are more likely to consent if they accept the diagnosis of BD before discussing OD.[22,24]

HCPs' positive attitudes towards donating their own organs correlated strongly with their willingness to offer OD. However, those who perceived that OD may result in body disfigurement were less likely to offer. There is a paucity of literature about HCPs' perceptions regarding body

Table I: Association between socio-demographics of HCPs and willingness to offer the option of organ donation to families of potential organ donors

	Respondents		Willingness to Offer*							
	Individuals	Percentages	Yes (312)	No/Unsure (99)	Univariable Analysis			Multivariable Analysis††		
	(n)	(%)	n (%)	n (%)	cOR†	95% CI§	p-Value	aOR‡	95% CI§	p-Value
Socio-demographics										
Gender										
Male	94	22.8	86 (91.5)	8 (8.5)	4.33	(2.02–9.30)	< 0.001			
Female	318	77.2	226 (71.3)	91 (28.7)	1	-	-			
Profession										
Doctor	163	39.6	156 (95.7)	7 (4.3)	13.14	(5.91–29.25)	< 0.001	7.90	3.33–18.79	< 0.001
Nurse	249	60.4	156 (62.9)	92 (37.1)	1	-	-	1	-	-
Position										
Consultant	12	2.9	11 (91.7)	1 (8.3)	6.76	(0.86–53.26)	0.070			
Specialist	30	7.4	29 (96.7)	1 (3.3)	17.81	(2.38–133.15)	0.005			
Medical Officer	123	30.1	118 (95.9)	5 (4.1)	14.50	(5.70–36.90)	< 0.001			
Matron¶	1	0.2	1 (100)	0 (0)	-	-	-			
Sister	15	3.7	12 (80.0)	3 (20.0)	2.46	(0.67–8.96)	0.173			
Registered Nurse	227	55.6	140 (61.9)	86 (38.1)	1	-	-			
No answer	4		1	3						
Ethnicity										
Malay	293	71.1	204 (69.9)	88 (30.1)	1	-	-	1	-	-
Chinese	50	12.1	48 (96.0)	2 (4.0)	10.35	(2.46–43.54)	0.001	3.18	0.69–14.66	0.136
Indian	60	14.6	54 (90.0)	6 (10.0)	3.88	(1.61–9.36)	0.003	2.13	0.83–5.48	0.109
Others	9	2.2	6 (66.7)	3 (33.3)	0.86	(0.21–3.53)	0.837	0.46	0.09–2.31	0.349
	Mean (SD)‖				OR	95% CI	p-Value	OR	95% CI	p-Value
Age **	29.4 (6.082)				1.15	(1.08–1.22)	< 0.001	1.06	(1.00–1.11)	0.047

*One participant did not respond to the question on willingness to offer, total = 411.
†cOR, crude odds ratio.
‡aOR, adjusted odds ratio.
§95% CI, 95% confidence interval.
‖SD, Standard deviation.
¶Matron was excluded in logistic regression analyses due to its extremely small sample size; four respondents did not respond to the item on Position.
**All values represent number of respondents except those for age, which represents mean age (standard deviation).
††Multivariable regression analysis was done for Profession and Ethnicity. Gender and Position are highly correlated variables to profession, hence were not included in the analyses.

Table II: Association between religious belief and willingness to offer the option of organ donation to families of potential donors

	Willingness to Offer*							
	Yes	No/Unsure	Univariable Analysis			Multivariable Analysis‡		
	n (%)	n (%)	cOR†	95% CI§	p-Value	aOR‡	95% CI§	p-Value
Religion (n=408)								
Muslim	207 (70.2)	88 (29.8)	1	-	-	1	-	-
Buddhist	33 (94.3)	2 (5.7)	7.01	(1.65–29.87)	0.008	6.35	(1.48–27.35)	0.013
Christian	22 (84.6)	4 (15.4)	2.34	(0.78–6.98)	0.128	2.00	(0.66–6.10)	0.221
Hindu	39 (90.7)	4 (9.3)	4.15	(1.44–11.95)	0.008	4.12	(1.41–12.04)	0.010
Others	8 (88.9)	1 (11.1)	3.40	(0.42–27.60)	0.252	2.91	(0.35–24.28)	0.323
No answer	3	0						
Religious belief does not object to deceased donor organ donation‖								
Yes	235 (77.3)	69 (22.7)	1.32	(0.79–2.18)	0.286	-	-	-
No/Unsure	75 (72.1)	29 (27.9)	1	-	-			
No answer	2	1						
Organ donation will not affect any religious services performed after death								
Yes	215 (83.3)	43 (16.7)	2.92	(1.83–4.64)	< 0.001	2.70	(1.68–4.34)	< 0.001
No/Unsure	96 (63.2)	56 (36.8)	1	-	-			
No answer	1	0						

*One participant did not respond to the question on willingness to offer, total = 411.
†cOR, crude odds ratio.
‡aOR, adjusted odds ratio.
§95% CI, 95% confidence interval.
‖Belief that religion does not object to deceased donor organ donation was not included in the multivariable regression model as it was found to be not significantly associated with willingness to approach.

Table III: Association between profession, knowledge,* and willingness to offer the option of organ donation to families of potential organ donors

	Willingness to Offer†					
	Univariable Analysis			Multivariable Analysis**		
	cOR§	95% CI‖	p-Value	aOR¶	95% CI‖	p-Value
Brain Death Tests (BDT) Score‡	1.79	(1.38–2.31)	< 0.001	-	-	-
Brain Death Knowledge (BDK) Score	1.36	(1.23–1.50)	< 0.001	-	-	-
Organ Donation and Transplantation (ODT) Knowledge Score	1.28	(1.12–1.46)	< 0.001	-	-	-
Overall Knowledge Score*	1.25	(1.16–1.35)	< 0.001	1.14	(1.05–1.24)	0.002
Profession						
Doctors	13.14	(5.91–29.25)	< 0.001	12.10	(4.64–31.56)	< 0.001
Nurses	1			1		

*Maximum score for overall knowledge based on correct responses was 25, including 5 for BDT, 10 for BD knowledge, and 10 for ODT knowledge.
†One participant did not respond to the question on willingness to offer, total = 411.
‡BDT scores are a subcategory of BDK scores.
§cOR, crude odds ratio.
‖95% CI, 95% confidence interval.
¶aOR, adjusted odds ratio.
**Multivariable logistic regression analysis was performed for willingness to offer with Overall Knowledge Scores and Profession as independent variables in the model. BDT, BDK, and ODT scores are a subset of overall knowledge scores, hence were not included in the model.

Table IV: Association between brain death attitudes and willingness to offer the option of organ donation to families of potential organ donors

	Willingness to Offer*							
	Yes (312)	No/Unsure (99)	Univariable Analysis			Multivariable Analysis		
	n (%)	n (%)	cOR[†]	95% CI[§]	p-Value	aOR[‡]	95% CI[§]	p-Value
How convinced are you of the existence of a clinical state called brain death?								
Yes	264 (81.5)	60 (18.5)	2.98	(1.61–5.50)	< 0.001	1.22	0.59–2.49	0.592
No/Unsure	47 (54.7)	39 (45.3)	1	-	-	1	-	-
No answer	1	0						
Do you feel confident to explain what brain death is to a patient's family member?								
Yes	237 (81.7)	53 (18.3)	3.23	(1.71–6.11)	< 0.001	2.34	1.13–4.82	0.022
No/Unsure	75 (62.0)	46 (38.0)	1	-	-	1	-	-
In your opinion, can doctors reliably diagnose brain death?								
Yes	249 (82.2)	54 (17.8)	5.87	(3.61–9.55)	< 0.001	5.04	3.02–8.43	< 0.001
No/Unsure	63 (58.3)	45 (41.7)	1	-	-	1	-	

*One participant did not respond to the question on willingness to offer, total = 411.
[†]cOR, crude odds ratio.
[‡]aOR, adjusted odds ratio.
[§]95% CI, 95% confidence interval.

Table V: Association between organ donation attitudes and willingness to offer the option of organ donation to families of potential organ donors

	Willingness to Offer*							
	Yes	No/Unsure	Univariable Analysis			Multivariable Analysis‖		
	n (%)	n (%)	cOR†	95% CI§	p-Value	aOR‡	95% CI§	p-Value
Organ Donation Attitudes								
Do you have an organ donation card?								
Yes	97 (88.2)	13 (11.8)	2.81	(1.49–5.30)	0.001	1.39	(0.59–3.240)	0.449
No/Unsure	202 (72.7)	76 (27.3)	1	-	-	-		
No answer	13	10						
Do you feel that in the interest of society at large, you will donate your own organs after death for the purpose of transplanting into others in need?								
Yes	243 (87.1)	36 (12.9)	6.15	(3.767–10.055)	< 0.001	14.35	(5.08–40.56)	< 0.001
No/Unsure	68 (52.3)	62 (47.7)	-	-	-			
No answer	1	1						
If you are willing to donate your organs, is your family aware about your decision to donate your own organs after death for the purpose of transplantation?								
Yes	160 (87.4)	23 (12.6)	2.609	(1.423–4.781)	0.002	1.71	(0.81–3.62)	0.16
No/Unsure	80 (72.7)	30 (27.3)	1	-	-			
No answer	72	46						
Disfigurement will not occur to the deceased donor's body during or after the process of donation.								
Yes	151 (82.1)	33 (17.9)	1.899	(1.183-3.050)	0.008	0.28	(0.12 –0.61)	0.002
No/Unsure	159 (70.7)	66 (29.3)	1	-	-	-		
No answer	2	0						
In your opinion, will families consent to have their relative's organs donated after brain death has been confirmed?								
Yes	167 (82.3)	36 (17.7)	2.02	(1.27–3.21)	0.003	1.75	(0.85–3.61)	0.132
No/Unsure	145 (69.7)	63 (30.3)	1	-	-	-		
If a patient has pledged to donate their organs without their families' consent, families do not have the right to refuse donation after the patient's death.								
Yes	100 (80.0)	25 (20.0)	1.38	(0.825-2.300)	0.221	-	-	-
No/Unsure	212 (74.4)	73 (25.6)	1	-	-			
No answer	0	1						
Deceased organ donation rates are low in this country. Do you think this is because of a lack of counselling to families of patients who are certified brain dead?								
Yes 272 (77.3)	80 (22.7)	1.656	(0.907-3.025)	0.101	-	-	-	
No/Unsure	39 (67.2)	19 (32.8)	1	-	-			
No answer	1	0						

*One participant did not respond to the question on willingness to offer, total = 411.
†cOR, crude odds ratio.
‡aOR, adjusted odds ratio.
§95% CI, 95% confidence interval.
‖All attitudes with statistically significant cOR were analysed in a multivariable logistic regression model. Attitudes that were not significantly associated with willingness to offer were excluded from the model.

Table VI: Association between confidence in transplantation and willingness to offer the option of organ donation to families of potential organ donors

	Willingness to Offer*							
	Yes (312)	No/Unsure (99)	Univariable Analysis			Multivariable Analysis		
	n (%)	n (%)	cOR†	95% CI§	p-Value	aOR‡	95% CI§	p-Value
Do you believe that organ transplantation, when indicated, is a good form of treatment for patients with end-stage organ disease?								
Yes	264 (81.5)	60 (18.5)	3.65	(2.20–6.07)	< 0.001	2.49	1.44–4.31	0.001
No/Unsure	47 (54.7)	39 (45.3)	1	-	-	1	-	-
No answer	1	0						
Would you accept a deceased donor organ for transplantation if you had end-stage organ failure?								
Yes	237 (81.7)	53 (18.3)	2.74	(1.71–4.40)	< 0.001	1.84	1.10–3.08	0.020
No/Unsure	75 (62.0)	46 (38.0)	1	-	-	1	-	-
In your opinion, is the success rate of transplantation high when performed by trained personnel?								
Yes	249 (82.2)	54 (17.8)	3.29	(2.03–5.34)	< 0.001	2.30	1.37–3.86	0.002
No/Unsure	63 (58.3)	45 (41.7)	1	-	-	1	-	

*One participant did not respond to the question on willingness to offer, total = 411.
†cOR, crude odds ratio.
‡aOR, adjusted odds ratio.
§95% CI, 95% confidence interval.

disfigurement and its implications in this setting, which needs to be explored.

A majority of the HCPs believed that the families had the right to refuse OD even if their loved ones had pledged to donate their organs and also perceived the lack of adequate family counselling as the cause of low DOD rates. However, these beliefs were not significantly associated with their willingness to offer. Traditionally, Malaysia has large, closely knit families, which often come together at the time of grief and offer support. When offered the option of OD, there could be conflicting opinions if multiple decision-makers are involved.[42] Several countries have issued legally binding guidance on next of kin hierarchy to facilitate collaborative decision-making for OD.[38,43,44] Additionally, routine 'opt-out' OD policy (which presumes that everyone consents to donating their organs unless they explicitly register their choice not to donate) has been implemented in other countries. Although the pros and cons of such a policy have been debated,[45] it is likely to help increase the willingness of HCPs to offer OD in the Malaysian context. These policies would give clarity and confidence to HCPs in providing targeted counselling to relevant family members and offering them the option of OD. Applicability of such strategies in the Malaysian setting should be explored.

HCPs with positive attitudes towards OT, especially those who believed in the success of OT when performed by trained staff, were most likely to offer OD. Amongst other factors, a successful transplantation programme requires a critical number of transplants to be undertaken each year. Currently, HCPs in Malaysia involved in OD and OT continue to fulfil other responsibilities. Having dedicated transplantation teams will help increase OT numbers and HCPs' experience and expertise in this field. This will not only help further improve the OT outcomes and increase the HCPs' and general public's confidence in the process but also benefit the growing number of patients on the OT waiting list.

LIMITATIONS AND FUTURE DIRECTION

This is a single-centre study; therefore, generalisation of our findings should be done with caution. Exploring the experiences and expectations of the families of potential donors may help identify other interventions to increase HCPs' willingness to offer the option of OD. The degree to which the expressed willingness of HCPs to offer OD translates into actual practice needs to be assessed.

CONCLUSION AND RECOMMENDATIONS

In this study, we observed a high overall willingness of HCPs to offer OD to potential donor families. Age, profession, religious beliefs, higher knowledge scores, and certain positive attitudes were significantly associated with higher willingness to offer. However, several modifiable factors that negatively influenced this willingness were also identified.

Mandating completion of BDT and reporting all BDs, empowering and integrating nurses into OD MDTs, formulating legal definition of the next of kin responsible for OD, including faith representatives in OD MDTs, and establishing dedicated transplantation teams and targeted training for HCPs are some examples of possible interventions identified from successful international experience. Applicability of these strategies in the Malaysian context may be considered to increase HCPs' willingness to offer OD and improve the overall OD rates in Malaysia.

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REFERENCES

1. Glanville AR, Stephan A, Avsec D, Ashikari J, Gunderson S, Garcia VD. International Registry in Organ Donation and Transplantation (IRODaT) Final Numbers 2020 Internet. 2020. Available from: https://www.irodat.org/.
2. Hooi L, Yasmin ML. 11th Report of National Transplant Registry Malaysian Internet. 2017. Available from: http://www.mst.org.my/ntrsite/donwload/report2014/11thNTR_Report2014_Full.pdf.
3. Rozaidi SW, Sukro J, Dan A. The health care professional's attitudes towards brain death and cadaveric organ transplantation: The influence of cadaveric donor and transplantation programs a Malaysian survey. Med J Malaysia 2000; 55(4): 478-85.
4. Loch A, Hilmi IN, Mazam Z, Pillay Y, Choon DSK. Differences in attitude towards cadaveric organ donation: Observations in a multiracial Malaysian society. Hong Kong J Emerg Med 2010; 17(3): 236-43.
5. Abidin ZLZ, Ming WT, Loch A, Hilmi I, Hautmann O. Are health professionals responsible for the shortage of organs from deceased donors in Malaysia? Transpl Int 2013; 26(2): 187-94.
6. Wong LP. Knowledge, attitudes, practices and behaviors regarding deceased organ donation and transplantation in Malaysia's multi-ethnic society: A baseline study. Clin Transplant 2011; 25(1): 22-32.
7. Wong LP. Factors limiting deceased organ donation: Focus groups' perspective from culturally diverse community. Transplant Proc Internet 2010; 42(5): 1439-44. Available from: http://dx.doi.org/10.1016/j.transproceed.2009.11.053.
8. Tumin M, Noh A, Jajri I, Chong CS, Manikam R, Abdullah N. Factors that hinder organ donation: Religio-cultural or lack of information and trust. Exp Clin Transplant 2013; 11(3): 207-10.
9. Ministry of Health Malaysia. Organ transplantation from the Islamic perspective Internet. 2011. Available from: www.moh.gov.my.
10. Rosenblum AM, Horvat LD, Siminoff LA, Prakash V, Beitel J, Garg AX. The authority of next-of-kin in explicit and presumed consent systems for deceased organ donation: An analysis of 54 nations. Nephrol Dial Transplant 2012; 27(6): 2533-46.
11. Floden A, Kelvered M, Frid I, Backman L. Causes why organ donation was not carried out despite the deceased being positive to donation. Transplant Proc 2006; 38(8): 2619-21.
12. Paterson B, Rigg K, Murphy P, Aubrey P, Cooke M, Rudge C. The role of emergency medicine in organ donation. 2010; 1-22.

13. Cohen J, Ami S Ben, Ashkenazi T, Singer P. Attitude of health care professionals to brain death: Influence on the organ donation process. Clin Transplant 2008; 22(2): 211-5.
14. Russell JA, Epstein LG, Greer DM, Kirschen M, Rubin MA, Lewis A. Brain death, the determination of brain death, and member guidance for brain death accommodation requests. Neurology 2019; 92(5): 228-32.
15. Greer DM, Shemie SD, Lewis A, Torrance S, Varelas P, Goldenberg FD, et al. Determination of brain death/death by neurologic criteria: The world brain death project. JAMA – J Am Med Assoc 2020; 324(11): 1078-97.
16. Jusoh MR, Delilkan A, Tan CT, Abdul Khalid R, Azman Ali R, Ong LC, et al. Consensus statement on brain death Internet. 2003 cited 4 Apr 2022; 24. Available from: https://www.moh.gov.my/moh/resources/auto download images/589d78f8e0101.pdf.
17. Abdul Kadir AH, Delilkan A, Isa MN, Jusoh MR, Raja Jallaludin RM, Jegasothy R, et al. Brain death Internet. 2006 cited 4 Apr 2022; 20. Available from: https://mmc.gov.my/wp-content/uploads/2019/11/Brain-Death.pdf.
18. Organ Donation and the Emergency Department Strategy Group, NHS Blood and Transplant. Organ donation and the emergency department: A strategy for implementation of best practice. 2019; Available from: https://bts.org.uk/wp-content/uploads/2018/01/ed-strategy-final-nov-2016.pdf.
19. Dominguez-Gil B, Delmonico FL, Shaheen FAM, Matesanz R, O'Connor K, Minina M, et al. The critical pathway for deceased donation: reportable uniformity in the approach to deceased donation. Transpl Int 2011; 24(4): 373-8.
20. Haron H. Organ Donor Conversion Rate in 2019 – Personal Communication. 20 May 2020;
21. Rudge C, Matesanz R, Delmonico FL, Chapman J. International practices of organ donation. Br J Anaesth 2012; 108(Suppl. 1): 48-55.
22. Siminoff LA. Factors influencing families' consent for donation of solid organs for transplantation. Jama Internet 2001; 286(1): 71. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.286.1.71.
23. Adanir T, Erdogan I, Hunerli G, Unveren G, Dasci H, Cetin HY, et al. The effect of psychological support for the relatives of intensive care unit patients on cadaveric organ donation rate. Transplant Proc Internet 2014; 46(10): 3249-52. Available from: http://dx.doi.org/10.1016/j.transproceed.2014.05.086.
24. Shemie SD, Robertson A, Beitel J, Chandler J, Ferre E, Evans J, et al. End-of-life conversations with families of potential donors: Leading practices in offering the opportunity for organ donation. Transplantation Internet 2017; 101(5): S17-26. Available from: http://insights.ovid.com/crossref?an=00007890-201705001-00002.
25. Care I, Clinical S, Hospital R. Effect of "collaborative requesting" on consent rate for organ donation: Randomised controlled trial (ACRE trial). Bmj Internet 2009; 339(7726): 899. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.b3911.
26. Chandler JA, Connors M, Holland G, Shemie SD. "Effective" requesting: A scooping review of the literature on asking families to consent to organ and tissue donation. Transplantation Internet 2017; 101(5): S1-16. Available from: http://insights.ovid.com/crossref?an=00007890-201705001-00001.
27. Elm E Von, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement : Guidelines for reporting observational studies. BMJ 2007; 1453-7.
28. Alsaied O, Bener A, Al-Mosalamani Y NB. Knowledge and attitudes of health care professionals toward organ donation and transplantation. Saudi J Kidney Dis Transplant Internet 2012; 23(1): 158-61. Available from: http://www.sjkdt.org/text.asp?2012/23/6/1304/103585.
29. Saleem T, Ishaque S, Habib N, Hussain SS, Jawed A, Khan AA, et al. Knowledge, attitudes and practices survey on organ donation among a selected adult population of Pakistan. BMC Med Ethics 2009; 10(1): 1-12.
30. Kim JR (Theresa), Fisher MJ, Elliott D. Undergraduate nursing students' knowledge and attitudes towards organ donation in Korea: Implications for education. Nurse Educ Today 2006; 26(6): 465-74.
31. Sobnach V, Kahn D, John T, Chandauka T, Adams KG, Sobnach S. A survey of medical students on their attitudes towards face transplantation. Int J Surg Internet 2014; 12(1): 45-50. Available from: http://dx.doi.org/10.1016/j.ijsu.2013.10.014.
32. Ki JC, Tong KK, Lew TWK. A survey of brain death certification – An impetus for standardisation and improvement. Ann Acad Med Singapore 2007; 36(12): 987-94.
33. Wijdicks E, Varelas P, Gronseth G, Greer D. Evidence-based guideline update: Determining brain death in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010; 74(23): 1911-8.
34. Oo WL, Ong JS, Foong JW, Hossain MM, Baskaran ND, Haron H, et al. Knowledge and attitudes of healthcare professionals and the impact on willingness to donate organs: A tertiary hospital survey. Singapore Med J 2020; 61(3): 154-61.
35. Foong JW, Sheng OJ, Loon OW, Hossain MM, Baskaran ND, Haron H, et al. Demographics of healthcare professionals' knowledge and attitude toward deceased organ donation: Survey of critical care areas in a tertiary hospital. Med J Malaysia 2019; 74(2): 109-15.
36. Tumin M, Ariffin RNR, Satar NM, Abdullah N, Wan Md Adnan WAH, Ismail AZ, et al. Organ donation among Malaysian muslims: The role of mosques. Ann Transplant 2015; 20: 206-10.
37. Department of Health and Social Care. The new approach to organ and tissue donation in England Internet. 2018. Available from: www.nationalarchives.gov.uk/doc/open-government-licence/.
38. UK Donation Ethics Committee. Involving the family in deceased organ donation Internet. London: 2016. Available from: http://www.aomrc.org.uk/wp-content/uploads/2016/07/Involving_family_deceased_organ_donation_0416-2.pdf.
39. National Institute for Health and Clinical Excellence. Organ donation for transplantation – Improving donor identification and consent rates for deceased organ donation. NICE Pathways Internet 2011;(December): 101. Available from: http://pathways.nice.org.uk/pathways/organ-donation-for-transplantation#path=view:/pathways/organ-donation-for-transplantation/organ-donation-for-transplantation-overview.xml&content=view-index.
40. Sulaiman O, Hooi LS. Chapter 8, Thirteenth Report of the National Transplant Registry Internet. Kuala Lumpur: 2016. Available from: http://www.mst.org.my/ntrSite/.
41. Chen TP, Teo SM, Tan JCK, Koh SN, Ambalavanar N, Tan SY. Cadaveric organ donation at University Hospital Kuala Lumpur. Transplant Proc 2000; 32(7): 1809-10.
42. Schreiber J. Politics, Piety, and Biomedicine: The Malaysian Transplant Venture Internet. Verlag, Bielefeld: Transcript Independent Academic Publishing; 2017. Available from: https://books.google.com.my/books?id=OImsDgAAQBAJ.
43. Organ and Tissue Authority. Best practice guideline for offering organ and tissue donation in Australia Internet. 2017. Available from: www.donatelife.gov.au.
44. Childress JF, Domnitz S, Liverman CT. Opportunities for organ donor intervention research: Saving lives by improving the quality and quantity of organs for transplantation. Internet. Washington (DC): National Academies Press (US); 2017. Available from: https://doi.org/10.17226/24884.
45. Becker F, Roberts KJ, De Nadal M, Zink M, Stiegler P, Pemberger S, et al. Optimizing organ donation: Expert opinion from Austria, Germany, Spain and the U.K. Ann Transplant 2020; 25: 1-16.

Acinetobacter baumannii: An overview of emerging multidrug-resistant pathogen

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ABSTRACT

The emergence of infections caused by *Acinetobacter baumannii*, a multidrug-resistant bacterium, has been a concern worldwide. This bacterium is an important hospital-acquired pathogen that causes several diseases, including ventilator-associated pneumonia, bloodstream infections, and meningitis. This study aimed to determine antibiotic-resistant mechanisms in the pathogenesis of *A. baumannii* and the alternative treatment strategies against it. The combined actions of the outer membrane protein A, formation of a biofilm on biotic and abiotic surfaces, phospholipases C and D, metal homeostatic system, lipopolysaccharides, and verotoxins are relevant for virulence and pathogenesis. *A. baumannii* resists to a broad-spectrum antibiotics by its mechanisms of resistance, such as β-lactamases, efflux pump, aminoglycoside modifying enzymes, permeability changes, and alternation of targets. In an attempt to overcome the resistance mechanisms, plant-derived compounds and a combination of the antibiotics and the plant phytocompounds have been focused. Nanoparticles synthesised with the plant extract have been studied extensively. Furthermore, we projected modern methods, including multi-omics analysis, to study insight into mechanisms of actions of antibiotics. The information suggested that the potential antibiotic mechanisms of *A. baumannii* could lead to an alternative treatment against *A. baumannii* infections.

KEYWORDS:
Acinetobacter baumannii, Multidrug resistance, Hospital-acquired infection, Advance diagnostic, Nanoparticles, and Plant-derived compounds

1. Introduction

Acinetobacter baumannii has been a human pathogen with increasing importance, since it causes a high number of infections and the occurrence of multidrug-resistant (MDR) strains. *Acinetobacter spp.* are characterised by being aerobic, non-fermentative, non-mobile, non-fastidious, catalase-positive, oxidative-negative, and Gram-negative coccobacilli.[1] This bacterium was first described in 1911, and having been isolated from the soil, it has been given several designations such as *Micrococcus calcoaceticus, Achromobacter, Alcaligenes, Bacterium anitratum, Moraxella glucidolytica, Neisseria winogradsky, Alcaligenes haemolysans, Mima polymorpha, and Moraxella lwoffii*.[2] Over the past few decades, the nomenclature of the genus Acinetobacter has been changed, and then, in 1974, it was described in Bergey's Manual of Systematic Bacteriology, with one species only: *Acinetobacter calcoaceticus*.[3] The complex *A. calcoaceticus-baumannii* includes four genospecies: genospecies 1, *A. calcoaceticus*; genospecies 2, *A. baumannii*; genospecies 3, *A. pittii*; and genospecies 13TU, *A. nosocomialis*. *A. baumannii* is the most important species in clinical settings due to nosocomial infections that are associated with the highest mortality rate.[4-5] Habitat-wise, since they are ubiquitous, they are found everywhere, especially in wet/moist environments like ponds, waste water, water treatment plants, and soil/mud.[6] The environmental reservoirs like food and various types of livestock have served as an important source for resistance elements making their way from multiple environmental sources into the human population and changing into clinically relevant strains, often harbouring antibiotic resistance mechanisms, namely extended-spectrum-lactamases (ESBLs) and metallo-beta lactamases (MBL).[6-7] Usually, it is resistant to complete decolourisation and can deceive as Gram-positive cocci. It does not produce urease, indole, cytochrome oxidase, and citrate; however, it produces catalase enzyme. *A. baumannii* is able to grow at 44°C, as the only bacterium of this genus to grow on the commonly used media in the laboratory.[8]

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Once considered of low virulent activity, it has literally taken over most of the commonly used drugs and has made them impotent, and there has been a significant interest in this organism over the past few decades.[4,9-10] It have been called 'Iraqibacter' as they have been isolated from individuals serving in the war in Iraq and Afghanistan.[10] The bacteria have rapidly spread across the globe in many hospital settings, especially the intensive care units (ICUs), where it account for 20% of infections worldwide.[11] Today, Acinetobacter infections have spread rapidly across the globe in the community. It can survive and thrive in diverse conditions of pH and temperature, in dry and moist conditions, and on surgical tools, ventilators, catheters, and respirometers.[12-13] As a result, they cause hospital- and community-acquired infections like meningitis, bloodstream infections, endocarditis, and wound and soft tissue infections.[1,11,14] The WHO stated that one of the most resistant ESKAPE organisms *(Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, A. baumannii, Pseudomonas aeruginosa, and Enterobacter species)* escaping the action of antibacterial drugs was *A. baumannii* and classified it as a top priority critical pathogen for antibiotic research and development.[15-16] They can form biofilms on several abiotic surfaces that may account for their perseverance in the hospital environment, increasing the possibility of causing healthcare-associated infections and outbreaks.[17-18] There are unknown virulence and resistance mechanisms developed by *A. baumannii* against the drugs counting with β-lactamase, low-porin expressions, lipopolysaccharides (LPS), alteration of target cells by mutations, iron-chelating systems, and capsular polysaccharides.[1,19,20] Another significant factor that contributed to its spread was the failure to accurately diagnose this organism due to the similarities between species. Misidentification on several occasions by phenotypic and chemotaxonomic methods underrated the role of *A. baumannii* as a cause of nosocomial infection. In addition, the presence of a hospital environment fully supported a selective pressure for cloning of resistant properties of some antibiotics. The ability of *A. baumannii* to incorporate exogenous DNA, through horizontal genetic transfer (HGT), is one of the factors responsible for the multidrug resistance phenotype observed in severalty of clinical strains worldwide.[21-22] With the advent of molecular techniques, such as mass spectrometry, ribotyping, multilocus sequence typing (MLST), RNA spacer fingerprinting, amplified fragment length polymorphism analysis, pulsed-field gel electrophoresis (PFGE), and matrix-assisted laser desorption ionisation time-of-flight (MALDI-TOF), identification of several virulence factors have been made easier.[23-24]

This review article aims to focus on the virulence factors of *A. baumannii*, its pathogenesis, antimicrobial resistance, advanced technology for identification, and alternative treatment strategies, which provide information for the development and discovery of new antibiotics and for the determination of essential effective combination treatment to combat multidrug resistant infections.

2. Search Strategy

We searched full-text research and review articles on *Acinetobacter baumannii* through PubMed (Medline) databases and Google Scholar, published in English in the last 20 years, using the following keywords: *'Acinetobacter baumannii'*, 'epidemiology', 'pathogenesis', 'antibiotic resistance', 'multi-omic study', '*in vitro* studies' 'virulence', and 'treatment'. Exclusion criteria included irrelevant studies on *A. baumannii* (Figure 1).

3. Epidemiology

The epidemiology of *A. baumannii* infection is broad, which includes infections associated with hospital outbreaks, wars, natural disasters, and the community in tropical climates. Several previous research studies focused on the mechanisms of occurrence of MDR *A. baumannii* infection all around the globe, including Europe, North America, South America, China, Taiwan, Hongkong, Japan, Korea, and other parts of Asia and the Middle East.[25]

The outbreaks are commonly seen in critical care and burn units, with mechanically ventilated patients.[25] An international report in ICUs showed that *Acinetobacter* infection rate was 19.2% in Asia, 17.1% in Eastern Europe, 14.8% in Africa, 13.8% in Central and South America, 5.6% in Western Europe, 4.4% in Oceania, and 3.7% in North America.[11] It was found to be 15% in HIV-positive patients in South Africa and 13% in critical burn care units in Canada.[26,27] Community-acquired pneumonia has been reported in the tropical climatic regions, mainly in Asia and Australia, during warm and humid months.[25] *A. baumannii* was once also coined as 'Iraqbacter' because of its outbreak within military treatment facilities in Iraq war.[28] UK and US military also detected an abundant number of multidrug-resistant *A. baumannii calcoaceticus* complex in military individuals injured during Iraq and Afghanistan war.[4] *A. baumannii* was the most frequent isolated organism (32.5%) from the combat casualties in Iraq and Afghanistan battle victims with open tibia fractures.[29] *A. baumannii* can cause outbreaks since it is highly resistant to antimicrobials and can overcome desiccation.[30] It is noted that the ability of *A. baumannii* to form a biofilm is one of the major virulence factors to a large number of its clinical isolates.[31]

The outbreaks of *Acinetobacter* have been attributed to source contamination, particularly contaminated respiratory and mechanical ventilators, and the cross-infection by the contaminated hands of healthcare workers caring for colonised or infected patients.[32-33] The several risk factors associated with colonisation or infection by multidrug-resistant (MDR) *A. baumannii* are prior exposure to long-term antimicrobial therapy, mechanical ventilation, duration of hospital stay, the severity of disease, current surgery, and other invasive processes.[34]

During 2016, the National Healthcare Safety Network (NHSN) of the United States reviewed the commonest drug-resistant organism involved in healthcare-associated infections where the *Acinetobacter* accounted for the following proportions among the most common Gram-negative isolates: ventilator-associated pneumonia (12.8%), central line-associated bloodstream infection (8.8%), catheter-associated UTIs (1.3%), and surgical site infection (1.3).[35] According to the prevalence study of infections in 2009, EPIC II (Extended Prevalence of Infection in Intensive Care) classified *A. baumannii* as the fifth most common pathogen in

ICU in 75 countries.[11] Furthermore, as reported by the international surveillance program (2009–2011), *A. baumannii* was the seventh most common pathogen isolated from ICU patients in the USA and European hospitals and ranked the eighth and seventh from non-ICU patients in the USA and European hospitals, respectively.[36] The report of drug resistance in the USA (2011) showed that 63% of *Acinetobacter* spp. infections were caused by multi-drug resistance strains.[37] The global rate of MDR *A. baumannii* was increased from 23% in 2004 to 63% in 2014.[38] In the USA and Europe, from 2009–2011, the colistin-resistant *A. baumannii* was around 5% and 3%, respectively, whereas the worldwide prevalence of *A. baumannii* resistant to colistin and polymyxins B was only 0.9% and 0.8%, respectively.[36,39]

4. Pathogenesis

4.1. Virulence factors

The single virulence factors of *A. baumannii* are not clearly defined, and the joint action of multiple factors leads to the pathogenesis by adherence, biofilm formation, invasion, serum resistance, *in vivo* survival, and killing of host cells.[40] Biofilm formation is one of the important factors that enhance its adherence to biotic and abiotic surfaces, including those of host tissues and medical devices.[41] The production of biofilm-associated protein (BAP) gene is correlated to the formation and maturation of biofilms.[42] The BAP enhances adherence to epithelial cells, and the inhibition of its production can control *A. baumannii* infection.[43] The metallic homeostatic system, which is required for colonisation in different tissues is well defined in *A. baumannii*; among these, iron uptake system and zinc acquisition system play an important role in virulence.[44-45] Another factor is that the K1 capsular polysaccharide prevents *A. baumannii* from phagocytosis by macrophages and facilitates its multiplication in fluid from human ascites and serum.[46] Several other proteins, such as Omp38, RecA protein, phospholipases C, and phospholipases D, are estimated as probable virulence factors in *A. baumannii* as they lead to apoptosis of host cells, increase survival as a response to heat shock and desiccation, and enhance survival in human serum and epithelial cells invasion.[47-48] Significantly, the other factors related to epithelial cells apoptosis caused by targeting the bacterial mitochondria is the outer membrane protein 'A', which is most abundantly present in *A. baumannii*.[49] Once the *A. baumannii* enters the bloodstream, the lipopolysaccharides, an important component of cell envelop, may cause septic shock. *A. baumannii* also produces two antigenic types of verotoxins, vtx-1 and vtx-2, which enhance virulence by targeting the cell ribosome machinery and inhibiting protein synthesis.[25,50]

5. Clinical Relevance

A. baumannii can lead to several human infections, including ventilator-associated pneumonia, bacteraemia, septicaemia, urinary tract infection, surgical site wound infection, and meningitis.[30] The mortality rate ranging from 7.8% to 43 % was seen in *A. baumannii* infections with higher levels in ICUs patients. Studies on morbidity reported that *Acinetobacter pneumonia* increases patients' stay in ICU for several days.[51]

5.1. Hospital-associated pneumonia

Acinetobacter pneumonia is observed predominantly in ICU patients who are under mechanical ventilation, and however, sometimes it is not easy to distinguish between airway colonisation from true pneumonia. *A. baumannii* is the second commonest pathogen among Gram-negative bacteria causing hospital-associated pneumonia.[52] The hospital-associated pneumonia caused by *A. baumannii* was around 3–5%, with a death rate of 30–75% being reported.[53]

5.2. Community-associated pneumonia

Community-associated *Acinetobacter* pneumonia shows sudden onset, which progresses rapidly, causing respiratory failure and hemodynamic instability, though the infection is rare.[54-55] It has been reported in people who consume alcohol or in patients with chronic obstructive pulmonary disease from tropical areas of Asia and Australia during monsoon.[4,56]

5.3. Bloodstream infections

The vascular catheters and respiratory tract are the commonest sources for *A. baumannii* bacteraemia, and the origin remains unknown in about 21–70% cases.[57,58] About 1.5–2.4 % of the patients acquired infections nosocomially.[57,59] The mortality rate of *A. baumannii* septicemia ranged 34–43.4% in critical care units and 16.3% in other units of the hospital.[7,60] *A. baumannii* bloodstream infections are associated with various risk factors, including prolonged hospital and ICU stay, mechanical ventilation, surgery and other invasive procedures, wounds, burns, use of broad-spectrum antibiotics, and immunosuppression.[57-58,61-62]

5.4. Urinary tract infection

A. baumannii urinary tract infection is infrequent and accounts for only 1.6% cases.[4] The setting of indwelling urinary catheters usually causes the colonisation of the urinary tract, leading to nosocomial urinary tract infections.[57]

5.5. Meningitis

Meningitis followed by neurosurgery induced by multidrug-resistant *A. baumannii* is a relevant issue.[63] One study showed that about 2.1% of cases of meningitis post-craniotomy were caused by *Acinetobacter*.[64] The certain risk factor associated with it includes surgery involving the brain and spinal cord, cerebrospinal fluid leakage, prior antibiotic treatment, and intracranial hemorrhage.[65] Studies have shown that the mortality rate was about 20–30% and the survivors being left with severe neurologic deficits.[4,66]

5.6. Skin, soft tissue, and bone infection

The soft tissue infection progressing to osteomyelitis caused by contaminated surgical and traumatic wounds is seen in the case of *A. baumannii* infections.[67] It rarely causes other skin infections such as cellulitis, folliculitis, skin abscesses, and necrotising fasciitis.[68-71] The wound and soft tissue infections caused by multidrug-resistant *A. baumannii* are mainly recognised after war injuries. Among different isolated organisms, *A. baumannii* accounted for 32% of the war victims of combat casualties in Iraq and Afghanistan war.[72]

5.7. Other infections

Acinetobacter eye infection is mainly seen in contact lens wearers, which may lead to corneal ulcers, endophthalmitis, periorbital cellulitis, and traumatic infection.[73-77] Some rarely

reported cases of *A. baumannii* infection are endocarditis, nosocomial sinusitis, and peritonitis.[78-80]

6. Laboratory Identification of *A. baumannii*

6.1. Conventional and molecular methods

A. baumannii is a pleomorphic coccobacillus bacterium that is 0.9–1.6 × 1.5–2.5 µm in size, which becomes spherical in the stationary phase of growth.[81] It is a strict aerobe, Gram-negative, non-lactose fermenter, glucose oxidiser, catalase-positive, and oxidase-negative, which grows at 44^{0}C, but practically these properties cannot confidently specify *A. baumannii* and could be easily misinterpreted with the other clinically relevant *Acinetobacter* species. The overnight colony morphology of *A. baumannii* on sheep blood agar at 37℃ is light grey, circular, convex, entire, translucent, shiny, mucoid, and non-pigmented.

Automated methods like analytical profile index (API) kits, VITEK 2 system, and matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI TOF MS) are currently used for the identification of different species.[82] The 16S ribosomal DNA sequence comparison, amplified fragment length polymorphism (AFLP), and amplified 16S ribosomal DNA restriction analysis (ARDRA) are also used to identify *Acinetobacter* species in comparison with restriction enzyme-digested DNA fragment pattern on a gel.[83] Amplification of *recA* and *bla*$_{OXA-51}$-like gene using Real-time PCR is also used for identification of *A. baumannii*. At present, phylogenetic trees of *rpoB* gene or 7 housekeeping genes from multilocus sequence typing (MLST) are an indeed more reliable way to discriminate between species within *Acb*-complex that includes six species: *A. calcoaceticus, A. baumannii, A. pittii, A. nosocomialis, A. seifertii,* and *A. dijkshoorniae*, as well as NIPH 542 and NIPH 817 that have no scientific names.[83-84]

6.2. Advance technology

6.2.1. Detection of *Acinetobacter baumannii* by nanoparticles

A. baumannii infections can cause serious damage to patients if not treated in a timely manner. Therefore, it is relevant to implement rapid analytical methods to detect *A. baumannii* to control its spread. DNA-based techniques as conventional methods have been employed for the identification of *A. baumannii*.[85-86] However, these methods are complicated and require well-trained personnel. Currently, nanoparticle-based diagnostic procedures, such as fluorescence technique, colorimetric assays along with gold nanoparticles, and fluorescence nanoprobes, are used for detection of *A. baumannii*.[87-90] As a result of the attraction and ease-of-functionalisation of magnetic nanoparticles, they are used very often to trap bacteria from complex clinical specimens, and those bacteria trapped by functional magnetic nanoparticles may be readily identified using MALDI-TOF mass spectrometry.[91-93]

Yi-Ling et al. reported on Fe_3O_4 and Al_2O_3 magnetic nanoparticles against *A. baumannii*, with values of M3237 and 54149, respectively.[94] The bacteria trapped by functional nanoparticles were characterised using MALDI-TOF mass spectrometry, and the specificity and sensitivity of these nanoprobes against particular *A. baumannii* strains were evaluated.[95] Similarly, Khalil et al. developed a nano-gold assay, which can colorimetrically identify and differentiate *A. baumannii* from other Gram-negative bacteria.[88] Chan et al. reported that the gold nanoclusters encapsulated with lysozyme in the presence of red photo-luminescence act as affinity probes to attract and accumulate infectious bacteria such as *A. baumannii, Enterococcus faecalis,* and *Staphylococcus aureus*.[94] Chan et al. reported that MALDI-MS coupled with principal component analysis could identify bacteria in the conjugates. A fluorometric assay is used to demonstrate *A. baumannii* in the blood specimen using Zr-MOFs with methods such as functional coating for magnetic Fe_3O_4 nanoparticles to offer surface modification and as a carrier to fluorescein to create fluorescence indicators.[89,95]

6.2.2. Multi-omics analysis of *A. baumannii*

Infections caused by *A. baumannii* are a crucial cause of morbidity and mortality in hospital settings, and *A. baumannii* resists a wide spectrum of antibiotics used to treat the infections. Therefore, many researchers have focused on studying insight into the mechanisms of actions of the drugs against the pathogen.[96-97] Multi-omics analysis, including proteomic, genomic, and transcriptomic analyses, is a powerful tool to shed light on the key expression of genes, metabolites, and proteins in the different metabolic pathways, as shown in Table I. The method has been used to study the expression of genes and metabolites in exposure to antibiotics and nutrient-limited conditions.

In a study on proteomic analysis, Tiwari and team reported that the excess production of membrane proteins like ferric-acinetobactin, ferrienterochelin, ferric siderophore, and FhuE receptors were detected under iron-limited conditions.[98] Besides, the interaction between FhuE receptor and siderophores was synthesised by *A. baumannii* as well as other bacteria in iron acquirement. Depending upon the immune status established by the host, the interaction between the siderophores and the corresponding receptors favours iron sequestration and bacterial survival. It has been concluded that the target-FhuE receptor inhibits siderophore-mediated iron acquirement in *A. baumannii*.[98] It has been reported that a total of 65 unique periplasmic proteins of the pathogen were identified underexposure and un-exposure to imipenem; among these, the eight types of proteins were associated with protein fate in relation to antibiotic resistance, energy metabolism, and oxidative stress (Figure 2).[99] In antibiotic resistance, four proteins were detected, which include GES-11, the carbapenemases OXA-23, the cephalosporinase AmpC, and the RND-type efflux pump AdeT. In protection against oxidative stress, ABUW_2868 encoding a heat shock protein was possibly found to be associated under upregulated imipenem-exposed bacteria.[99]

A combination of drugs is a powerful treatment to cure the infection caused by *A. baumannii*. A synergistic effect of colistin in combination with sulbactam against the organism has been reported. The combination was carried out by colistin through agitation of the levels of fatty acid and phospholipid at 1 hour. The biosynthesis of the bacterial cell wall was perturbed when *A. baumannii* was treated with sulbactam alone and the combination over 24 hours. Using metabolic analysis, expression of uridine diphosphate-N-

Table I: Multi-omics analysis of *Acinetobacter baumannii*

Type of Omics	Result	Reference
Proteomic	- It was found that the outer membrane vesicles of antibiotic-sensitive strain consisted of 8 antibiotic resistance-conferring proteins. In contrarily, the vesicles of multidrug-resistant stain comprised 24 proteins of antibiotic resistance.	96
Proteomic	- It was shown that Type II secretion system secretome provides an advantage of the colonization to the pathogen multi-drug resistant strain rather than the reference strain used for biofilm formation.	97
Proteomic	- The over-expression of four membrane proteins including ferric-acinetobactin, ferrienterochelin, ferric siderophore, and Fhu-E receptors were detected under iron-limited conditions. - The interaction between FhuE receptor and siderophores was produced by *A. baumannii* as well as other bacteria in iron acquirement. - Under nutritional immunity established by the host, The interaction between the receptor and siderophores helps in iron sequestration and survival of *A. baumannii*. - FhuE receptor, as a target, was shown to inhibiting siderophore-mediated iron acquirement in *A. baumannii*.	98
Proteomic	- A total of 65 unique periplasmic proteins were identified underexposure and un-exposure to imipenem. - There are eight proteins involved in protein fate and response to antibiotic-resistance, energy metabolism, and oxidative stress. - In antibiotic-resistance, four proteins were detected which include GES-11, the carbapenemases OXA-23, the cephalosporinaseAmpC, and the RND-type efflux pump AdeT. - In protection against oxidative stress, ABUW_2868 encoding a heat shock protein was likely found to be involved under upregulated in imipenem-exposed bacteria.	99
Metabolomic	- A synergistic effect of colistin in combination with sulbactam against *A. baumannii* has been reported. - The combination was carried out by colistin through agitation of the levels of fatty acid and phospholipid at 1 h. - The biosynthesis of the bacterial cell wall was perturbed when *A. baumannii* was treated with sulbactam alone and the combination over 24 hrs. - Expression of uridine diphosphate-N-acetylglucosamine and uridine diphosphate-N-acetylmuramate involved in amino sugar metabolism were decreased when the pathogen was treated with the drug combination.	100
Metabolomic	- A synergistic effect of colistin in combination with doripenem against *A. baumannii* has been reported. - Perturbation of glycerophospholipids and fatty acids by colistin resulted in the disruption of A. baumannii outer membrane and cell wall. - Doripenem alone suppressed the expression of peptidoglycan biosynthesis metabolites at 4 h. - The combination of the drugs suppressed the expression of D-sedoheptulose 7-phosphate (nucleotid metabolism) and D-ribose 5-phosphate (pentose phosphate pathway).	101
Transcriptomic	- The upregulation of genes associated with transposable elements was detected when the bacteria were treated with antibiotic including amikacin, imipenem, and meropenem. - In pan-drug resistant *z*strains, overexpression of amino acid metabolism and membrane transporters has been reported. - Antibiotic resistance genes were up-regulated in both antibiotic-resistant and -sensitive strains of *A. baumannii*.	102
Transcriptomic	- Under tigecycline pressure, upregulation of efflux pumps including RND transporter permease subunit, EmrAB, MacB, and Tet resistance operon was detected in antibiotic-resistant *A. baumannii*, when compared with the sensitive strain. - Genes related to benzene-containing compound metabolic process, translation, ribosomal structure, and biogenesis were found to be overexpress in the resistant strain treated with tigecycline.	103
Transcriptomic and proteomic	- Upregulation of ribosomal proteins and resistance pumps including MFS, RND, MATE, and ABC transporters were observed in *A. baumannii* treated with eravacycline. - In outer membrane vesicle, overexpression of ribosomal proteins, toluene tolerance protein, siderophore receptor, and peptidases was detected in multidrug-resistant *A. baumannii*.	104 \

Table II: Antimicrobial activity of plant-derived compounds against *Acinetobacter baumannii*

Product/Plant species	Examination procedure	Antibacterial activity	Reference
Norwogonin/*Scutellaria baicalensis*	MIC_{90} determination	MIC_{90} = 128 µg/mL	129
Terchebulin/*Terminalia chebula*	MIC_{90} determination	MIC_{90} = 500 µg/mL	129
Ellagic acid/*Terminalia chebula*	MIC_{90} determination	67% inhibition at 250 µg/mL	129
Chebulagic acid/*Terminalia chebula*	MIC_{90} determination	60.39% inhibition at 62.5 µg/mL and 88% inhibition at 1,000 µg/mL	129
Chebulinic acid/*Terminalia chebula*	MIC_{90} determination	65% inhibition at 62.5 µg/mL	129
Corilagin/*Terminalia chebula*	MIC_{90} determination	56% inhibition at 15.625 µg/ml and 83% inhibition at 1,000 µg/mL	129
Norwogonin/ *Scutellaria baicalensis*	Time-kill analysis	Complete growth inhibition at 2 ×MIC (256 µg/mL) after 24 h	129
Ellagic acid	Inhibition zone measurement	Increased inhibition zone of aminocoumarins (novobiocin, chlorobiocin, and coumermycin), tetracycline, rifampicin, andfusidic acid by 4 to >8 mm	130
Tannic acid	Inhibition zone measurement	Increased inhibition zone of aminocoumarins (novobiocin, chlorobiocin, and coumermycin), tetracycline, rifampicin, and fusidic acid by 4 to >8 mm	130
Ellagic acid	MIC determination	2- to 4-fold reduction in MICs of novobiocin, chlorobiocin, coumermycin, fusidic acid, and rifampicin	130
Tannic acid	MIC determination	2- to 4-fold reduction in MICs of novobiocin, chlorobiocin, coumermycin, rifampicin, and tetracycline	130
(–)-epigallocatechin-3-gallate/ *Camellia sinesis*	Inhibition zone measurement	IZ = up to 7 mm	131
(–)-epigallocatechin-3-gallate/ *Camellia sinesis*	MIC determination	MIC_{50} = 0.312 µg/mL MIC_{90} = 0.625 µg/mL	131
(–)-epigallocatechin-3-gallate/ *Camellia sinesis*	Chequerboard assay	The synergistic effect at a concentration of 0.039 µg/µL in combination with 0.625% µg/µL concentration of mafenide acetate (Sulfamylon)	131
(–)-epigallocatechin-3-gallate/ *Camellia sinesis*	Time-kill analysis	3-log reduction in CFU/ml at 2 ×MIC after 5 h	131
Oleanolic acid	MIC determination	MIC = 512 µg/mL A 4-fold reduction in MICs of both aminoglycosides gentamicin and kanamycin	132
Oleanolic acid	Chequerboard assay	Synergistic effect in combination with both gentamicin and kanamycin, with FICI values of 0.375 and 0.313, respectively	132
Oleanolic acid	Time-kill analysis	Bactericidal effect at < 1/16 MIC (64 µg/mL) in combination with gentamicin at 1/16 MIC (0.13 µg/mL) concentration	132
Cinnamon natural oil	MIC determination	MIC = 0.125-1 mg/mL	133
Clove natural oil	MIC determination	MIC = 0.125-1 mg/mL	133
Thyme natural oil		MIC determination MIC = 0.25-1 mg/mL	133
Tea tree natural oil	MIC determination	MIC = 0.25-2 mg/mL	133
Lavander natural oil	MIC determination	MIC = 0.25-3 mg/mL	133
(-) Terpinen-4-ol	MID determination	MID = 130.61 mg/L	134
Carvacrol	MID determination	MID = 4.88 mg/L	134
Carvacrol	MID determination	MID = 3.89-48.8 mg/L	134
Tea tree oil (NanoTTO)/ *Melaleuca alternifolia*	MIC determination	MIC = 3.52 mg TTO/mL	141
Oregano essential oil/ *Origanum vulgare*	MIC and MBC determination	MIC = 0.298 mg/Ml MBC = 0.298 mg/mL	142
Oregano essential oil/ *Origanum vulgare*	Chequerboard assay	Additive antibacterial effect at concentration of 0.149 mg/mL in combination with 15.62 µM concentration of Bio-AgNP, with FICI values of 0.62	142

Bio-AgNP: Biological silver nanoparticles, FICI: Fractional inhibitory concentration index, IZ: Inhibition zone, MBC: MIC: Minimum bactericidal concentration, Minimum inhibitory concentration, MID: Minimum inhibitory dose

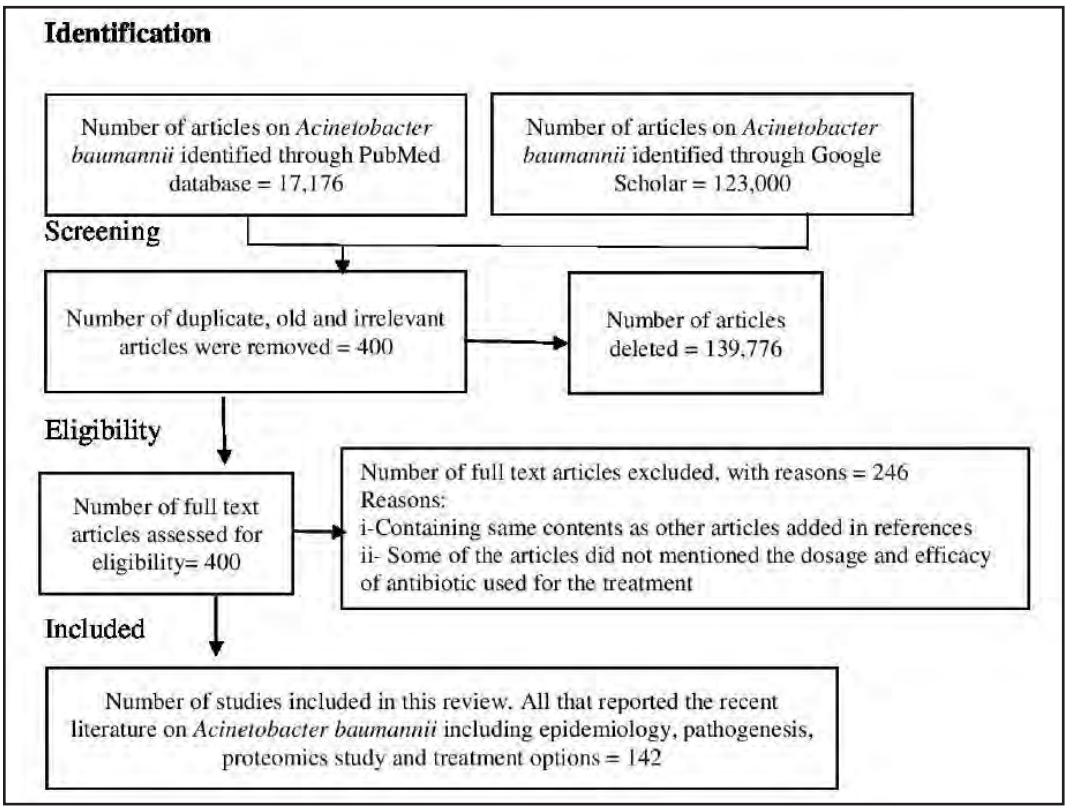

Fig. 1: The overall flowchart of phases used to identify published articles included in this review.

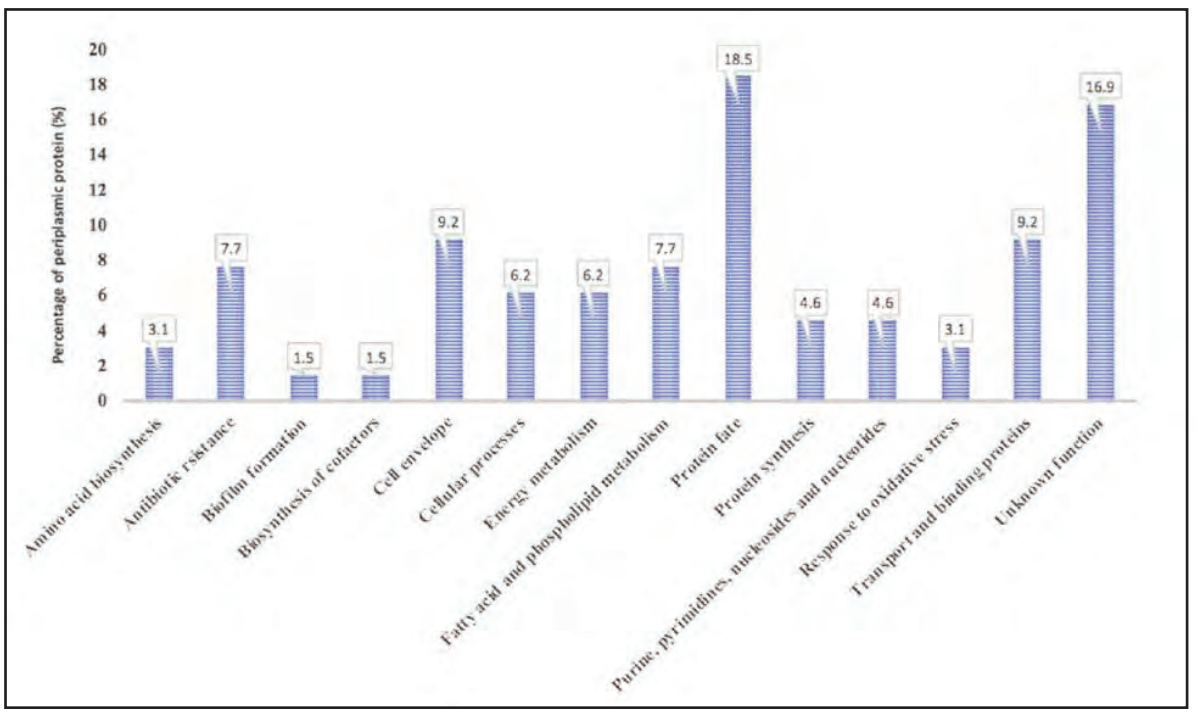

Fig. 2: Periplasmic proteins identified in MDR *A. baumannii* strain AB7075 cultured in the presence and absence of imipenem.

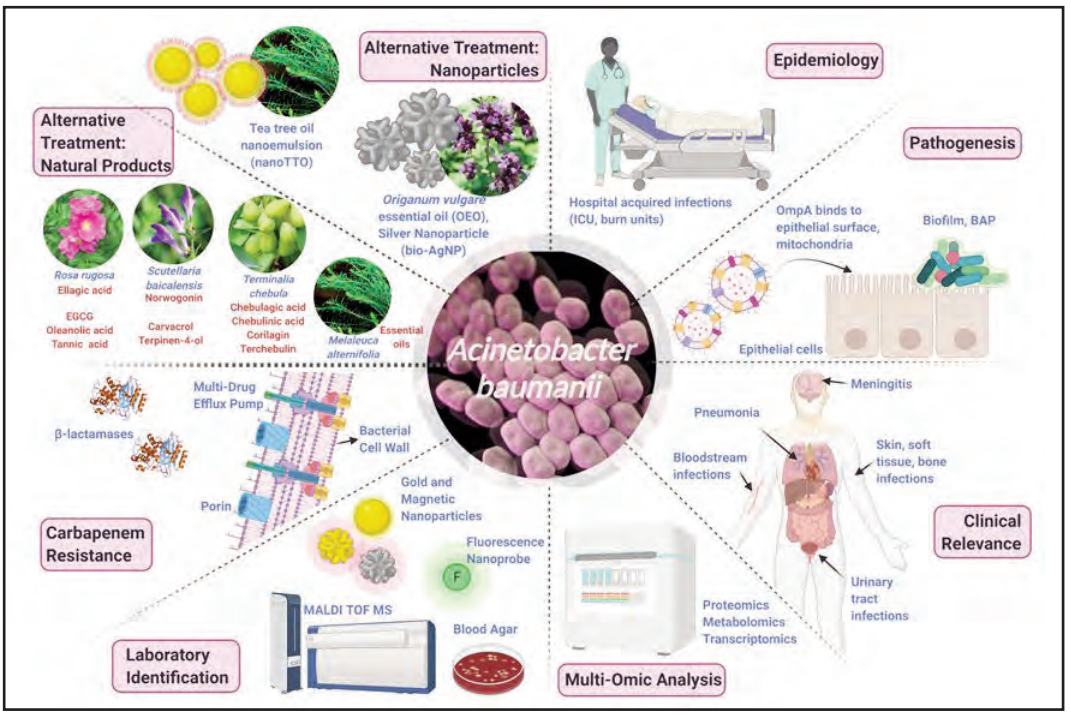

Fig. 3: Overview of *A. baumannii*.

acetylglucosamine and uridine diphosphate-N-acetylmuramate involved in amino sugar metabolism was decreased when the pathogen was treated with the drug combination.[100] Maifiah and the team reported the synergistic effects of colistin in combination with doripenem against *A. baumannii*.[101] The perturbation of glycerophospholipids and fatty acids by colistin resulted in the disruption of *A. baumannii* outer membrane and cell wall. Doripenem alone suppressed the expression of peptidoglycan biosynthesis metabolites at 4 hours. The combination of the drugs suppressed the expression of D-sedoheptulose 7-phosphate (nucleotid metabolism) and D-ribose 5-phosphate (pentose phosphate pathway).[101]

Study on transcriptomic analysis, Qin and team reported that upregulation of genes associated with transposable elements was detected when the bacteria were treated with antibiotics, including amikacin, imipenem, and meropenem.[102] In pan-drug resistant *A. baumannii* strains, overexpression of amino acid metabolism and membrane transporters has been reported. Antibiotic resistance genes were upregulated in both antibiotic-resistant and sensitive strains of *A. baumannii*.[102] Under tigecycline pressure, upregulation of efflux pumps, including RND transporter permease subunit, EmrAB, MacB, and Tet resistance operon, was detected in antibiotic-resistant *A. baumannii*, compared with the sensitive strain. Genes linked to the metabolism of benzene-containing compounds, translation, ribosomal structure, and biogenesis were found to be overexpressed in the resistant strain treated with tigecycline.[103] Integration of transcriptomic and proteomic analysis is a powerful tool to clarify the key expression of genes and proteins in the organism. Kesavan and team reported that the upregulation of ribosomal proteins and resistance pumps, including MFS, RND, MATE, and ABC transporters, was observed in *A. baumannii* treated with eravacycline. In the outer membrane vesicle, overexpression of ribosomal proteins, toluene tolerance proteins, siderophore receptors, and peptidases was detected in multidrug-resistant *A. baumannii*.[104]

In summary, multi-omics analysis, including proteomic, genomic, and transcriptomic analyses, is a powerful tool to shed light on the key expression of genes, metabolites, and proteins in the different metabolic pathways. The analysis can be used to identify the antibacterial mode of action and the expression of the resistance mechanism of the drug against *A. baumannii*.

7. Treatment

It is well known that carbapenems are the drug of choice against the infection caused by multidrug-resistant *A. baumannii*. For *A. baumannii* resistant to carbapenem, tigecycline and colistin are used.[30] The global emergence of MDR, XDR, and PDR *A. baumannii* and the paucity of newer antimicrobial compounds are a major challenge for the healthcare industries.[105] For PDR *A. baumannii*, combination therapies like carbapenem+ampicillin/sulbactam, carbapenem+colistin, colistin+rifampicin+sulbactam, and tigecycline+rifampicin+ampicillin have been used worldwide. The combination therapies are costly, and their toxicity and adverse effects are strong.[106]

7.1. Carbapenem resistance in *A. baumannii*

Currently, most strains of *A. baumannii* are highly resistant to broad-spectrum antibiotics used clinically. Several resistance mechanisms targeting different antibiotic classes are observed in *A. baumannii*, such as production of β-lactamases, efflux pumps, aminoglycoside-modifying enzymes, permeability defects, and target sites alteration.[107] Mostly these mechanisms target the different antibiotic classes; however, various mechanisms can also support the resistance to a single antibiotic class. The chief β-lactamases resistance

mechanism involving carbapenem-hydrolysing property is due to the presence of class Docxcillinase and class B metallo-β-lactamases (MBLs). In addition, the loss or mutation of CarO porins and alteration of penicillin-binding proteins also favour carbapenem resistance.[108-109] The dissemination of multidrug resistance determinants in *A. baumannii* is strongly due to plasmid conjugation and acquisition of transposons, which leads to mobilisation of a bunch of drug resistance genes to several antibiotic class.[110] Furthermore, the presence of insertion sequences also multiplies the antibiotic-resistant strains.[111]

The leading source of carbapenem resistance in *A. baumannii* is due to the presence of class D (OXA) oxacillinase, a type of beta lactamase, which occurs naturally in *A. baumannii* (OXA51/66 group). In most strains, the oxacillinase, OXA-51-like genes are expressed poorly, having less influence on susceptibility pattern to all beta-lactam antibiotics, including carbapenems. The expression and influence of these genes are also facilitated by the presence of insertion sequence ISAba1, when present upstream to the structural gene, further leading to the development of carbapenem resistance in *A. baumannii*.[112] Based on sequence homology, OXA carbapenemases are further grouped into the various clusters: OXA-23-like (includes OXA-27 and OXA-49), OXA-(24)-40-like (includes OXA-25, OXA-26, and OXA-40), and OXA-58.[113] The OXA-23-like genes, which are most commonly seen in *A. baumannii*, are mediated through both chromosome and plasmid. The OXA-23-like genes in *A. baumannii* have been frequently observed since 1985, including the strains obtained from outbreaks in the UK, Asia, and South America. This strain exists in one multi-resistant clone, which is prevalent in the UK and identified as OXA 23 clone-1.[114] Another oxacillinase group of resistance genes, OXA-24-like, which are also chromosomal or plasmid mediated, are less prevalent compared to OXA-23-like genes, with data mainly restricted to European countries and the United States.[115] The expression of other genes like ambler class B metallo-beta lactamases (MBLs), such as IMP, VIM, and SIM-1, was also observed in *A. baumannii*. The expression of these genes also confers a high level of resistance to most of the beta lactams, including carbapenems, but excluding aztreonam.[116]

7.2. Drug metabolism

Carbapenem-resistant *A. baumannii* strains are considered as a pathogen for causing life-threatening infections since no alternative therapy is available. Though the mechanisms leading to antibiotic resistance in *A. baumannii* have been studied extensively, the general response to keep the viability of bacteria under antimicrobial exposure needs more investigation.[117] A study based on periplasmic protein of MDR *A. baumannii* strain AB7075 cultured in the presence and absence of imipenem reported that besides carbapenems, the periplasmic space also displays various other proteins with essential functions of the cell. In both types of culture conditions, a total of 65 periplasmic proteins were detected by proteomic approach, and out of this, eight proteins were associated with protein fate, resistance to antibiotics, energy breakdown, and reaction to oxidative stress. Among these proteins, some gene products like ABUW_1746 and ABUW_2363 presented the tetratricopeptide repeat motif, which mediates the protein–protein interactions. These proteins expressed by the genes can regulate definite proteins and help to adapt well in altered environmental situations. The heat shock proteins coded by ABUW_2868 genes are possibly associated with defence against oxidative damage, which is seen upregulated in bacteria exposed to imipenem. Scribano et al. evidenced the first report on the content of the periplasmic proteins of a multidrug-resistant *A. baumannii* strain and its susceptibility to imipenem, pointing towards the probable new targets to develop substitute antibiotics.[99] The new antibacterial molecules can be designed with the knowledge of IMP upregulated proteins and their molecular functions, and it has been concluded that MDR *A. baumannii* on stressful exposure to IMP adapts various strategies to successfully cope with it.

ß-Lactamases, coded chromosomally, plays an important role in finding alternative and efficient therapy for treatment against multidrug-resistant *Acinetobacter* spp. The occurrence of chromosome-mediated ß-lactamases, like class C *Acinetobacter*-derived cephalosporinases and class D oxacillinases, and also the existence of plasmid-encoded class A ß-lactamases represent a therapeutic challenge in *Acinetobacter* spp. The newly permitted ß-lactamase inhibitors such as avibactam and vaborbactam represent a range of gap in inhibition against OXA like ß-lactamase. The new, sensibly designed, diazabicyclooctenone inhibitor ETX2514 adequately targets against all, class A, C, and D ß-lactamases.[118] Barnes et al. showed that the sulbactam-ETX2514 combination has an extensive inhibitory range to target class D, A, and C ß-lactamases and also promising treatment options against infections induced by MDR *Acinetobacter* spp.[119] For instance, curcumin in combination with blue light is an effective photodynamic treatment (PDT), exerting antimicrobial operation. In one of the studies, Chang et al. explored the probable underlying mechanism to examine the protein carbonylation in response to the bactericidal action in the presence of oxidative stress when *A. baumannii* resistant to imipenem was subjected to blue light assisted curcumin a shotgun proteomics approach has been implemented and afterwards, the bacterial proteins were extracted, 2,4-dinitrophenylhydrazine (DNPH) derivatised, and trypsin were digested.[118] On searching the customised database, the carbonylated proteins were documented, and the analysis of the peptides was conducted using LC-nano ESI ion trap mass spectrometry. After utilising the investigation of gene ontology, annotation and the STRING protein association network for the 70 identified proteins, the commonest was the protein related to the membrane, translation, and oxidative stress response. Various proteins, which are associated in interpretation of *A. baumannii*, were described to be carbonylated targets. These proteins incorporate the lengthening factor Tu and P, two ribosomal proteins, and ribosome discharging factor. A maximum number of these interpretation-associated proteins in bacteria has been documented in past studies based on the exploration of the target macromolecules in microorganisms under oxidative pressure.[118]

Several micronutrients are required for the survival of *A. baumannii* inside the host. Among these micronutrients, the bio-availability of iron is limited by the nutritional immunity

created by the host, and because of this, *A. baumannii* needs to develop a mechanism to uptake iron while causing infections. Research by Tiwari et al.[98] attempted to recognise membrane proteins associated with the iron sequestration process of *A. baumannii* with the use of two-dimensional electrophoresis and liquid chromatography with tandem mass. The distinguished iron-directed layer protein (IRMP) of *A. baumannii* was utilised during communication studies with various siderophores, and inhibitor against *A. baumannii* was also designed focusing on this IRMP212. The four membrane proteins were overexpressed in the membrane proteomic results, which include FhuE receptor, ferric-acinetobactin receptor, ferrienterochelin receptor, and ferric siderophore receptor, under iron-constrained condition. Iron-managed layer proteins like FhuE receptor cause the bacteria to oblige during difficult situations inside the host. A great association has been observed between the siderophores produced by *A. baumannii* and the FhuE receptor. Similar results also demonstrated that FhuE receptor has an association with siderophores delivered by bacteria other than *A. baumannii*. This connection between the FhuE receptor and siderophores supports iron sequestration and bacterial survival under a nutritionally invulnerable environment. Therefore, it gets basic to locate a possible FhuE receptor–inhibitor through which the survival of *A. baumannii* within the host is suppressed. In-silico screening and molecular mechanics studies recognised ZINC03794794 and ZINC01530652 as major structure inhibitors against the FhuE receptor of *A. baumannii*. The structured inhibitors are tentatively approved for their bactericidal action against *A. baumannii*. Thus, a structured inhibitor affects the iron uptake mechanism of *Acinetobacter*, and therefore, it might be favourable in the prevention of infections caused by *A. baumannii* by constraining nutrient accessibility. Additionally, a study involving an animal model is to be performed further to explore the utilisation of FhuE receptor inhibitor and to validate its function.[98]

8. Alternative strategies for MDR *A. baumannii*

With rising antibiotic resistance and treatment difficulties, many studies have focused on alternative drugs and phytomedicine.[120] Combined actions of antibiotics and active components of plant extracts have been studied mostly as an alternative strategy.[121] Many studies stated that the synergistic action of plant active components and the antibiotics could play a role to combat drug resistance and increase bacterial susceptibility.[122] Along with the screening of herbal compounds, a nanomaterial-based approach has been tried to find susceptible alternative agents to MDR *A. baumannii*.[123] The nanoparticles having low molecular weight were potentially effective against most bacteria causing human infections.[124] Silver nanoparticles have shown antimicrobial activity against a wide array of microbes, including *A. baumannii*, probably caused by their several bactericidal mechanisms.[125] The effectiveness of synergistic action of nanoparticles and plant active components against bacterial inhibition was seen high compared to its independent action.[126] The study also demonstrated a synergistic effect of imipenem and silver nanoparticles against *A. baumannii* planktonic cells as well as biofilms.[127]

8.1. Use of natural products and nanoparticles

Many plant active compounds (Table II) are being used worldwide as traditional remedies against several antibiotic-resistant bacteria, including carbapenem-resistant *A. baumannii*.[128] For example, flavones, tannins, and phenolic compounds are demonstrated to have inhibitory activity against *Acinetobacter*. Miyasaki et al. reported that six compounds, including ellagic acid extracted from *Rosa* sp., norwogonin extracted from *Scutellaria baicalensis*, and chebulagic acid, chebulinic acid, corilagin, and terchebulin extracted from *Terminalia chebula*, had the maximum antimicrobial effect against *A. baumannii in vitro*.[129] Norwogonin (5,6,7-trihydroxyflavone) from *Scutellaria baicalensis* was identified as the most potent compound with a minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of 128 µg/mL and 256 µg/mL, respectively, against clinical isolates of *A. baumannii*. Other herbal compounds, including ellagic acid (67% inhibition at 250 µg/mL), chebulinic acid (65% inhibition at 62.5 µg/mL), chebulagic acid (60.39% and 88% inhibition at 62.5 µg/mL and 1,000 µg/mL, respectively), and corilagin (56% and 83% inhibition at 15.625 µg/mL and 1,000 µg/mL, respectively) exhibited lower antimicrobial activity. Furthermore, several plant-derived phenolic compounds are reported in the medical literature to increase the strength of synthetic antibiotics against *A. baumannii*. For instance, the *in vitro* activity of several antibiotics, including novobiocin, coumermycin, chlorobiocin, rifampicin, and fusidic acid, has been increased against MDR *A. baumannii* in the presence of ellagic and tannic acids.[130] Synergy was also observed between the epigallocatechin-3-gallate (EGCG), a purified polyphenol from green tea leaves, and topical mafenide acetate (Sulfamylon) against a clinical isolate of MDR *A. baumannii in vitro*.[131] Another study showed that the MIC of aminoglycosides (e.g., gentamicin and kanamycin) in combination with oleanolic acid (a pentacyclic triterpenoid compound) decreased to one-fourth of the MIC alone in *A. baumannii*. Moreover, the fractional inhibitory concentration index (FICI) values of both aminoglycosides in combination with oleanolic acid were indicative of synergism.[132] In contrast, Miyasaki et al. observed no synergy effect between anti-Gram-negative antibiotics and norwogonin.[129]

Interest in the inspection of antimicrobial properties of aromatic plant extracts has grown, particularly essential oils (also known as volatile oils).[132] One study found that cinnamon, thyme, lavender, clove, and tea tree essential oils had very powerful activity against *A. baumannii* with MIC values from 0.125 to 1 mg/mL, followed by lemon and orange oils with MIC value > 2 mg/mL.[133] The antibacterial activities of 15 essential oil compounds against hospital-associated pathogens, including clinical isolates of multidrug-resistant *A. baumannii* were reported, and among carvacrol and terpinen-4-ol, the latter had broad antimicrobial spectrum affecting all five pathogenic species, ESBL-*Klebsiella pneumoniae*, ESBL-*Escherichia coli*, MDR *A. baumannii*, ATCC Methicillin-resistant *Staphylococcus aureus* (MRSA), and *Pseudomonas aeruginosa*. In particular, carvacrol showed strong activity, such as very low MIDs for MDR *A. baumannii* (4.88 mg/L) and MRSA (24.4 mg/L) compared to other bacterial species tested, representing an important molecule against infection, especially for *A. baumannii* resistant to carbapenem.[134]

Nanoparticles have received great attention in recent years to combat antimicrobial resistance in microbial pathogens.[135] Several types of nanoparticles, such as silver, gold, zinc, chitosan, platinum, iron, copper, and carbon nanotubes, have been evaluated for their antimicrobial activity in combination with essential oils.[136-140] One study assessed the antimicrobial activity of tree tea oil nanoemulsion (nanoTTO) against different microbial pathogens associated with pneumonia, including *A. baumannii*.[141] The nanoTTOs showed strong antibacterial effects in *A. baumannii* ATCC19606 with the MIC of 3.52 mg TTO/mL. Furthermore, this nanoemulsion notably decreased the lung injury of pneumonia induced by *A. baumannii* in the rat model, indicating its relatively high in vivo anti-*A. baumannii* effect, which is vital for the treatment of bacterial pneumonia. In another study, *Origanum vulgare* essential oil (OEO) and the biologically synthesised silver nanoparticle (bio-AgNP) showed a bactericidal effect in low concentration against all bacterial strains resistant to multi-drugs tested, with MBC values of 0.298 mg/mL and 125 µM, respectively, for multidrug-resistant to carbapenem-resistant *A. baumannii* isolate.[142]

Besides, the combination of OEO and bio-AgNP resulted in significantly lower MICs compared to individual treatment, where the two compounds together led to additive antibacterial activity against *A. baumannii*. Taken together, the promising results of synergistic and additive interactions are a milestone that facilitates the combination of nanoparticles and antimicrobial compounds derived from plants as antimicrobial agents to be applied in certain industries (e.g., cosmetics, food, and pharmaceuticals) and healthcare facilities for the control and treatment of various infections or disinfection of hospitals to combat pathogens resistant to several multi-drugs, particularly *A. baumannii*.

The synergistic action of nanoparticles and antibiotics could be a promising treatment option to combat bacterial resistance in future. Moreover, nanoparticles have the property to deliver antibiotics to the infected cells and also decrease the dose and toxicity of antibiotics.[143] The synergistic bactericidal action of antibiotics and silver nanoparticles at low concentrations against different bacteria including *A. baumannii* has been reported.[144] Though the plant extract and metal-based nanoparticles, alone or in synergy with antibiotics, have shown their bactericidal activity against *A. baumannii* and other bacteria *in vitro*, to confirm this as a novel treatment against various bacterial infections, without causing severe damage to the human cells, there should be a randomised control study. The nanomaterial causes huge cell damage *in vitro*, which is not suitable for direct application to human cells without proper dosage recommendation based on clinical trials. The appropriate and effective dosage that is suitable for use in human infections needs to be studied thoroughly, and more clinical trials are needed before the application of nanoparticle-based treatment in patients.

9. Conclusion

The clinical significance of *A. baumannii* in the past one and half decades has been increased by its isolation in ICU patients causing several infections, high morbidity, and mortality, its resistant-acquiring mechanisms, and its emergence as a prominent nosocomial pathogen challenging the current antibiotic era. To combat dissemination of this MDR bug, strict hospital aseptic procedures and appropriate antimicrobial stewardship policies are highly recommended. The prompt diagnosis of *A. baumannii* infections to overcome serious damage to the patients is a sole priority. The MALDI-TOF mass spectrometry and nanoparticle-based diagnostic procedures involving fluorescence technique, colorimetric assays, and fluorescence nanoprobes are used as advanced diagnostic tools. The antibiotics and phytochemicals in combination or synergy with silver or gold nanoparticles showed a promising result to overcome this MDR challenge in future with further intensive research (Figure 3).

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REFERENCES

1. Lin MF, Lan CY. Antimicrobial resistance in *Acinetobacter baumannii*: From bench to bedside. World J Clin Cases 2014; 2(12): 787-814.
2. Henriksen SD. Moraxella, Acinetobacter, and the mimeae. Bacteriol Rev 1973; 37(4): 522-61.
3. Rossau R, Van LA, Gillis M, De-Ley J. Taxonomy of Moraxellaceae fam. Nov., a new bacterial family to accommodate the genera Moraxella, Acinetobacter, and Psychrobacter and related organisms. Int J System Bacteriol 1991; 41(2): 310-19.
4. Peleg AY, SeifertH, Paterson DL. *Acinetobacter baumannii*: Emergence of a successful pathogen. Clin Microbiol Rev 2008; 21(3): 538-82.
5. Chuang YC, Sheng WH, Li SY, Lin YC, Wang JT, Chen YC, et al. Influence of genospecies of *Acinetobacter baumannii* complex on clinical outcomes of patients with *Acinetobacter bacteremia*. Clin Infect Dis 2011; 52(3): 352-60.
6. Al Atrouni A, Joly-Guillou ML, Hamze M, Kempf M. Reservoirs of non-*Acinetobacter baumannii* species. Front Microbiol 2016; 7: 49.
7. Zhang WJ, Lu Z, Schwarz S, Zhang RM, Wang XM, Si W, et al. Complete sequence of the bla(NDM-1)-carrying plasmid pNDM-AB from *Acinetobacter baumannii* of food animal origin. J Antimicrob Chemother 2013; 68(7): 1681-2.
8. Bouvet PJ, Grimont PA. Identification and biotyping of clinical isolates of Acinetobacter. Annales de l'Institut Pasteur/Microbiologie 1987; 138(5): 569-78.
9. Spellberg B, Bonomo RA. The deadly impact of extreme drug resistance in *Acinetobacter baumannii*. Crit Care Med 2014; 42(5): 1289-91.

10. Scott P, Deye G, Srinivasan A, Murray C, Moran K, Hulten E, et al. An outbreak of multidrug-resistant *Acinetobacter baumannii*-calcoaceticus complex infection in the US military health care system associated with military operations in Iraq. Clin Infect Dis 2007; 44(12): 1577-84.
11. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302(21): 2323-9.
12. Tiwari V, Moganty RR. Conformational stability of OXA-51 beta-lactamase explains its role in carbapenem resistance of *Acinetobacter baumannii*. J Biomol Struct Dyn 2014; 32(9): 1406-20.
13. Bravo Z, Orruno M, Parada C, Kaberdin VR, Barcina I, Arana I. The long-term survival of *Acinetobacter baumannii* ATCC 19606(T) under nutrient-deprived conditions does not require the entry into the viable but non-culturable state. Arch Microbiol 2016; 198(5): 399-407.
14. Su CH, Wang JT, Hsiung CA, Chien LJ, Chi CL, Yu HT, et al. Increase of carbapenem-resistant *Acinetobacter baumannii* infection in acute care hospitals in Taiwan: Association with hospital antimicrobial usage. PloS One 2012; 7: e37788.
15. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis.2009; 48(1): 1-12.
16. World Health Organization, Geneva. 2017. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. News release by the WHO.
17. Tomaras AP, Dorsey CW, Edelmann RE, Actis LA. Attachment to and biofilm formation on abiotic surfaces by *Acinetobacter baumannii*: Involvement of a novel chaperone–usher pili assembly system. Microbiol 2003; 149(pt 12): 3473–84.
18. Jawad A, Seifert H, Snelling AM, Heritage J, Hawkey PM. Survival of *Acinetobacter baumannii* on dry surfaces: Comparison of outbreak and sporadic isolates. J Clin Microbiol 1998; 36(7): 1938–41.
19. Santella G, Docquier JD, Gutkind G, Rossolini GM, Radice M. Purification and biochemical characterization of IMP-13 metallo-beta-lactamase. Antimicrob Agents Chemother2011; 55(1), 399-401.
20. McConnell MJ, Actis L, Pachon J. *Acinetobacter baumannii*: Human infections, factors contributing to pathogenesis and animal models. FEMS Microbiol Rev 2013; 37(2): 130-55.
21. Roca I, Espinal P, Vila-Farres X, Vila J. The *Acinetobacter baumannii* oxymoron: Commensal hospital dweller turned pan-drug-resistant menace. Front Microbiol 2012; 3: 148.
22. Ramirez MS, Merkier AK, Quiroga MP, Centron D. *Acinetobacter baumannii* is able to gain and maintain a plasmid harbouring In35 found in Enterobacteriaceae isolates from Argentina. Curr Microbiol 2012; 64(3): 211-3.
23. Higgins PG, Perez-Llarena FJ, Zander E, Fernandez A, Bou G, Seifert H. OXA-235, a novel class D β-lactamase involved in resistance to carbapenems in *Acinetobacter baumannii*. Antimicrob Agents Chemother 2013; 57(5): 2121-6.
24. Li XM, Choi JA, Choi IS, Kook JK, Chang YH, Park G, et al. Development and evaluation of species-specific PCR for detection of nine Acinetobacter species. Ann Clin Lab Sci 2016; 46(3): 270-8.
25. Kanafani AZ, Kanj SS, 2014. Ministry of Health, Kingdome of Saudi Arabia. http://www.updates.com/contents/ XXXcinetobacter-infection-treatment-and –prevention.
26. Ntusi NB, Badri M, Khalfey H, Whitelaw A, Oliver S, Piercy J, et al. ICU-associated *Acinetobacter baumannii* colonisation/infection in a high HIV prevalence resource-poor setting. PloS One2012; 7(12): e52452.
27. Simor AE, Lee M, Vearncombe M, Paul LJ, Barry C, Gomez M, et al. An outbreak due to multirésistant *Acinetobacter baumannii* in burn unit: Risk factors for acquisition and management. Infect Control Hosp Epidemiol 2002; 23(5): 261-67.
28. Centers for Disease Control and Prevention. *Acinetobacter baumannii* infections among patients at military medical facilities treating injured U.S. service members, 2002-2004. MMWR Morb Mortal Wkly Rep 2004; 53(45): 1063-6.
29. Falagas ME, Vardakas KZ, Kapaskelis A, Triarides NA, Roussos NS. Tetracyclines for multidrug-resistant *Acinetobacter baumannii* infections. Int J Microb Agents 2015; 45(5): 455-60.
30. Fournier PE, Richet H, Weinstein RA. The epidemiology and control of *Acinetobacter baumanniiin* health care facilities. Clin Infect Dis 2006; 42(5): 692-9.
31. Longo F, Vuotto C, Donelli G. Biofilm formation in *Acinetobacter baumannii*. New Microbiol 2014; 37(2): 119-27.
32. Huang YC, Su LH, Wu TL, Leu HS, Hsieh WS, Chang TM, et al. Outbreak of *Acinetobacter baumannii* bacteremia in a neonatal intensive care unit: Clinical implications and genotyping analysis. Pediatr Infect Dis J 2002; 21(12): 1105-9.
33. Hartstein AI, Rashad AL, Liebler JM, Actis LA, Freeman J, Rourke JW, et al. Multiple intensive care unit outbreak of *Acinetobacter calcoaceticus* subspecies anitratus respiratory infection and colonization associated with contaminated, reusable ventilator circuits and resuscitation bags. Am J Med 1988; 85(5): 624-31.
34. Shamsizadeh Z, Nikaeen M, Esfahani BN, Mirhoseini SH, Hatamzadeh M, Hassanzadeh A. Detection of antibiotic resistant *Acinetobacter baumannii* in various hospital environments: Potential sources for transmission of Acinetobacter infections. Environ Health Prev Med 2017; 22(1): 44.
35. Weiner LM, Webb AK, Limbago B, Dudeck MA, Patel J, Kallen AJ, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: Summary of data reported to the national healthcare safety network at the Centers for Disease Control and Prevention, 2011-2014. Infect Control Hosp Epidemiol 2016; 37(11): 1288-301.
36. Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of gram negative organism isolated from patients hospitalized in intensive care units in United States and European hospitals (2009-2011). Diagn Microbial Infect Dis 2014; 78(4): 443-8.
37. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. [Report] Atlanta, Georgia: U.S. Department of Health and Human Services, CDC; 2013 [cited 31 May 2018]. Accessed from: https://www.cdc.gov/drugresistance/ threat-report-2013/pdf/ar-threats-2013-508.pdf.
38. Giammanco A, Cala C, Fasciana T, Dowzicky MJ. Global assessment of the activity of tigecycline against multidrug-resistant Gram-negative pathogens between 2004 and 2014 as part of the Tigecycline Evaluation and Surveillance Trial. M Sphere 2017; 2(1): e00310-16.
39. Gales AC, Jones RN, Sader HS. Contemporary activity of colistin and polymyxins B against a worldwide collection of Gram-negative pathogens: Results from the SENTRY Antimircobial Surveillance Program (2006-2009). J Antimicrob Chemother 2011; 66(9): 2070-4.
40. Lee CR, Lee JH, Park KS, Park KS, Bae IK, Kim YB, et al. Biology of *Acinetobacter baumannii*: Pathogenesis, antibiotic resistance mechanisms, and prospective treatment options. Front Cell Infect Microbiol 2017; 7: 55.
41. Gaddy JA, Actis LA. Regulation of *Acinetobacter baumannii* biofilm formation. Future Microbiol 2009; 4(3): 273-8.
42. Tomaras AP, Flagler MJ, Dorsey CW, Gaddy JA, Actis LA. Characterization of a two-component regulatory system from *Acinetobacter baumannii* that controls biofilm formation and cellular morphology. Microbiol 2008; 154(pt 11): 3398-409.
43. Fattahian Y, Rasooli I, Mousavi-Gargari SL, Rahbar MR, Astaneh SDA, Amani J, et al. Protection against *Acinetobacter baumannii* infection via its functional deprivation of biofilm associated protein (Bap). Microb Pathog 2011; 51(6): 402-6.
44. Eijkelkamp BA, Hassan KA, Paulsen IT, Brown MH. Investigation of the human pathogen *Acinetobacter baumannii* under iron limiting conditions. BMC Genom 2011; 12: 126.

45. Hood MI, Mortensen BL, Moore JL, Zhang Y, Kehl-Fie TE, Sugitani N, et al. Identification of an *Acinetobacter baumannii* zinc acquisition system that facilitates resistance to calprotectin-mediated zinc sequestration. PloS Pathog 2012; 8: e1003068.
46. Russo TA, Luke NR, Beanan JM, Olson R, Sauberan SL, MacDonald U, et al. The K1 capsular polysaccharide of *Acinetobacter baumannii* strain 307-0294 is a major virulence factor. Infect Immun 2010; 78(9): 3993-4000.
47. Choi CH, Lee EY, Lee YC, Park TI, Kim JH, Hyun SH, et al. Outer membrane protein 38 of *Acinetobacter baumannii* localizes to the mitochondria and induces apoptosis of epithelial cells. Cell Microbiol 2005; 7(8): 1127-38.
48. Jacobs AC, Hood I, Boyd KL, Olson PD, Morrison JM, Carson S, et al. Inactivation of phospholipase D diminishes *Acinetobacter baumannii* pathogenesis. Infect Immun 2010; 78(5): 1952-62.
49. Choi CH, Hyun SH, Lee JY, Lee JS, Lee YS, Kim SA, et al. *Acinetobacter baumannii* outer membrane protein A targets the nucleus and induces cytotoxicity. Cell Microbiol 2008; 10(2): 309-19.
50. Lambert T, Gerbaud G, Galimand M, Courvalin P. Characterization of *Acinetobacter haemolyticus* aac (6')-Ig geneencoding an aminoglycoside 6'-N-acetyltransferase which modifies amikacin. Antimicrob Agents Chemother 1993; 37(10): 2093-100.
51. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: A cohort study evaluating attributable mortality and hospital stay. Am J Med 1993; 94(3): 281-8.
52. Luna CM, Aruj PK. Nosocomial Acinetobacter pneumonia. Respirol 2007; 12(6): 787-91
53. Doughari HJ, Ndakidemi PA, Human IS, Benade S. Theecology, biology and pathogenesis of Acinetobacter spp.: An overview. Microbes Environ 2011; 26(2): 101-12.
54. Leung WS, Chu CM, Tsang KY, Lo FH, Lo KF, Ho PL. Fulminant community-acquired *Acinetobacter baumannii* pneumonia as a distinct clinical syndrome. Chest 2006; 129(1): 102.
55. Chen MZ, Hsueh PR, Lee LN, Yu CJ, Yang PC, Luh KT. Severe community-acquired pneumonia due to *Acinetobacter baumannii*. Chest 2001; 120(4): 1072-7.
56. Whitman TJ, Qasba SS, Timpone JG, Babel BS, Kasper MR, English JF, et al. Occupational transmission of *Acinetobacter baumannii* from a United States serviceman wounded in Iraq to a health careworker. Clin Infect Dis 2008; 47(4): 439-43.
57. Gaynes R, Edwards JR. National nosocomial infections surveillance system. Overview of nosocomial infections caused by gram-negative bacilli. Clin Infect Dis 2005; 41(6): 848-54.
58. Cisneros JM, Rodríguez-Baño J. Nosocomial bacteremia due to *Acinetobacter baumannii*: Epidemiology, clinical features and treatment. Clin Microbiol Infect 2002; 8(11): 687-93.
59. Wisplinghoff H, Edmond MB, Pfaller MA, Jones RN, Wenzel RP, Seifert H. Nosocomial bloodstream infections caused by Acinetobacter species in United States hospitals: Clinical features, molecular epidemiology, and antimicrobial susceptibility. Clin Infect Dis 2000; 31(3): 690-7.
60. Garnacho-Montero J, Amaya-Villar R, Ferra´ndiz-Millo´n C, Díaz-Martín A, López-Sánchez JM, Gutiérrez-Pizarraya A. Optimum treatment strategies for carbapenem-resistant *Acinetobacter baumannii* bacteremia. Expert Rev Anti Infect Ther 2015; 13(6): 769-77.
61. Gerner-Smidt P. The epidemiology of *Acinetobacter calcoaceticus*: Biotype and resistance-pattern of 328 strains consecutively isolated from clinical specimens. Acta Pathol Microbiol Scand Ser B Microbiol 1987; 95(1): 5-11
62. Cisneros JM, Reyes MJ, Pachón J, Becerril B, Caballero FJ, García-Garmendía JL, et al. Bacteremia due to *Acinetobacter baumannii*: Epidemiology, clinical findings, and prognostic features. Clin Infect Dis 1996; 22(6): 1026-32.
63. Basri R, Zueter AR, Mohamed Z, Alam MK, Norsa'adah B, Hasan SA, et al. Burden of bacterial meningitis: A retrospective review on laboratory parameters and factors associated with death in meningitis, Kelantan Malaysia. Nagoya J Med Sci 2015; 77(1-2): 59-68.
64. Rodríguez GA, Maradona JA, Asensi V, Cartón JA, Perez F, Blanco A, et al. Postsurgical meningitis caused by *Acinetobacter baumannii*: Study of 22 cases and review of the literature. Rev Clin Esp 2001; 201(9): 497-500.
65. Korinek AM, Baugnon T, Golmard JL, Effenterre RV, Coriat P, Puybasset L. Risk factors for adult nosocomial meningitis after craniotomy: Role of antibiotic prophylaxis. Neurosurg 2008; 62(2): 532-9.
66. Wroblewska MM, Dijkshoorn L, Marchel H, Barselaar-Van-Dan M, Swoboda-Kopec E, Broek-Van-Den PJ, et al. Outbreak of nosocomial meningitis caused by *Acinetobacter baumannii* in neurosurgical patients. J Hosp Infect 2004; 57(4): 300-7.
67. Davis KA, Moran KA, McAllister CK, Gray PJ. Multidrug-resistant Acinetobacter extremity infections in soldiers. Emerg Infect Dis 2005; 11(8): 1218.
68. Chiang WC, Su CP, Hsu CY, Chen SY, Chen YC, Chang SC, et al. Community-acquired bacteremic cellulitis caused by *Acinetobacter baumannii*. J Formos Med Assoc 2003; 102(9): 650-2.
69. Bachmeyer C, Landgraf N, Cordier F, Lemaitre P, Blum L. *Acinetobacter baumannii* folliculitis in a patient with AIDS. Clin Exp Dermatol 2005; 30(3): 256-8.
70. Ng G, Sharma BK, Fox GF. Acinetobacter skin abscess in a neonate. J Perinatol 2004; 24(8): 526-7.
71. Adler BL, Krausz A, Friedman AJ. *Acinetobacter baumannii* emerging as a multidrug-resistant skin and soft-tissue pathogen: parallels to methicillin-resistant Staphylococcus aureus. JAMA Dermatol 2014; 150(8): 905-6.
72. Sheppard FR, Keiser P, Craft DW, Gage F, Robson M, Brown TS, et al. The majority of US combat casualty soft-tissue wounds are not infected or colonized upon arrival or during treatment at a continental US military medical facility. Am J Surg 2010; 200(4): 489-95.
73. Corrigan KM, Harmis NY, Willcox MD. Association of Acinetobacter species with contact lens-induced adverse responses. Cornea 2001; 20(5): 463-6.
74. Wang AG, Wu CC, Liu JH. Bacterial corneal ulcer: A multivariate study. Ophthalmol 1998; 212(2): 126-32.
75. Gopal L, Ramaswamy AA, Madhavan HN, Saswade M, Battu RR. Postoperative endophthalmitis caused by sequestered *Acinetobacter calcoaceticus*. Am J Ophthalmol 2000; 129(3): 388-90.
76. Miller J. Acinetobacter as a causative agent in preseptal cellulitis. J Optom 2005; 76(3): 176-80.
77. Mark DB, Gaynon MW. Trauma-induced endophthalmitis caused by *Acinetobacter anitratus*. Br J Ophthalmol 1983; 67(2): 124-6.
78. Fang G, Keys TF, Gentry LO, Harris AA, Rivera N, Getz K, et al. Prosthetic valve endocarditis resulting from nosocomial bacteremia. A prospective, multicenter study. Ann Intern Med 1993; 119(7): 560-7.
79. Bert F, Lambert-Zechovsky N. Sinusitis in mechanically ventilated patients and its role in the pathogenesis of nosocomial pneumonia. Eur J Clin Microbiol Infect Dis 1996; 15(7): 533-44.
80. Dandecha P, Sangthawan P. Peritonitis in acute peritoneal dialysis in a university hospital. J Med Assoc Thai 2002; 85(4): 477-81.
81. Bouvet PJM, Grimont PAD. Taxonomy of genus Acinetobacter with recognition of Acinetobacter baumannii sp. Nov., *Acinetobacter haemolyticus* sp. Nov., *Acinetobacter johnsonii* sp. Nov., and *Acinetobacter junii* sp. Nov. and emended descriptions of *Acinetobacter calcoaceticus* and *Acinetobacter lowffii*. Int J SystEvolMicrobiol 1986; 36(2): 228-40.
82. Kim YJ, Kim SH, Park HG, Park HG, Park D, Song SA, et al. MALDI-TOF MS is more accurate than VITEK II ANC card and API Rapid ID 32: A system for the identification of Clostridium species. Anaerobe 2016; 40: 73-5.
83. Dijkshoorn L, Nemec A, Seifert H. An increasing threat in hospitals: Multidrug-resistant *Acinetobacter baumannii*. Nat Rev Microbiol 2007; 5(12): 939-51.

84. Cosgaya C, Mari-Almirall M, Van-Assche A, Fernández-OrthD, Mosqueda N, TelliM, et al. Acinetobacter dijkshoorniae sp. Nov., a member of the *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex mainly recovered from clinical samples in different countries. Int J SystEvol Microbiol 2016; 66(10): 4105-11.
85. Olive DM, Bean P. Principles and applications of methods for DNA-based typing of microbial organisms. J Clinic Microbiol 1999; 37(6): 1661-9.
86. Ma X, Song L, Zhou N, Xia Y, Wang Z. A novel aptasensor for the colorimetric detection of *S. typhimurium* based on gold nanoparticles. Int J Food Microbiol 2017; 245: 1-5.
87. Lai HZ, Wang SG, Wu CY, Chen YC. Detection of *Staphylococcus aureus* by functional gold nanoparticle-based affinity surface-assisted laser desorption/ionization mass spectrometry. Anal Chem 2015; 87(4): 2114-20.
88. Khalil MAF, Azzazy HME, Attia AS, Hashem AGM. A sensitive colorimetric assay for identification of *Acinetobacter Baumannii* using unmodified gold nanoparticles. J Appl Microbiol 2014; 117(2): 465-71.
89. Chan PH, Chen YC. Human serum albumin stabilized gold nanoclusters as selective luminescent probes for *Staphylococcus aureus* and methicillin-resistant Staphylococcus aureus. Anal Chem 2012; 84(21): 8952-56.
90. Liu JC, Tsai PJ, Lee YC, Chen YC. Affinity capture of uropathogenic *Escherichia coli* using pigeon ovalbumin-bound Fe3O4@Al2O3 magnetic nanoparticles. Anal Chem 2008; 80(14): 5425-32.
91. Kuo FY, Lin WL, Chen YC. Affinity capture using peptide-functionalized magnetic nanoparticles to target *Staphylococcus aureus*. Nanoscale 2016; 8(17): 9217-25.
92. Ho YP, Reddy PM. Advances in mass spectrometry for the identification of pathogens. Mass Spectrom Rev 2011; 30(6): 1203-24.
93. Bai YL, Mahmud MSA, Selvaprakash K, Lin NT, Chen YC. Tail fiber protein-immobilized magnetic nanoparticle-based affinity approaches for detection of *Acinetobacter baumannii*. Anal Chem 2019; 91(15): 10335-42.
94. Chan PH, Wong SY, Lin SH, Chen YC. Lysozyme-encapsulated gold nanocluster-based affinity massspectrometry for pathogenic bacteria. Rapid Commun Mass Spectrom 2013; 27(19): 2143-8.
95. Shuangshuang Y, Guo Y, Fan J, Yang Y, Zuo C, Bai S, et al. A fluorometric assay for rapid enrichment and determination of bacteria by using zirconium-metal organic frameworks as both capture surface and signal amplification tag. Mikrochim Acta 2020; 187(3): 188.
96. Agarwal B, Karthikeyan R, Gayathri P. Proteomics: Studies on the mechanism of multi-drug resistance of *Acinetobacter baumannii* by proteomic analysis of the outer membrane vesicles of the bacterium. BBA-Proteins Proteom 2019; 10(1): 1-15.
97. Elhosseiny NM, Elhezawy NB, Attia AS. Comparative proteomics analyses of *Acinetobacter baumannii* strains ATCC 17978 and AB5075 reveal the differential role of type II secretion system secretomes in lung colonization and ciprofloxacin resistance. Microb Pathog 2019; 128: 20-7.
98. Tiwari V, Rajeswari MR, Tiwari M. Proteomic analysis of iron-regulated membrane proteins identify FhuE receptor as a target to inhibit siderophore-mediated iron acquisition in *Acinetobacter baumannii*. Int J Biol Macromol 2019; 125: 1156-67.
99. Scribano D, Marzano V, Mortera SL, Sarshar M, Vernocchi P, Zagaglia C, et al. Insights into the periplasmic proteins of *Acinetobacter baumannii* AB5075 and the impact of imipenem exposure: A proteomic approach. Int J Mol Sci 2019; 20(14): 3451.
100. Han ML, Liu X, Velkov T, Lin YW, Zhu Y, Creek DJ, et al. Comparative metabolomics reveals key pathways associated with the synergistic killing of colistin and sulbactam combination against multidrug-resistant *Acinetobacter baumannii*. Front Pharmacol 2019; 10: 754.
101. Maifiah MHM, Creek DJ, Nation RL, Forrest A, Tsuji BT, Velkov T, et al. Untargeted metabolomics analysis reveals key pathways responsible for the synergistic killing of colistin and doripenem combination against *Acinetobacter baumannii*. Sci Rep 2017; 7: 45527.
102. Qin H, Lo NWS, Loo JFC, Lin X, Yim AKY, Tsui SKW, et al. Comparative transcriptomics of multidrug-resistant *Acinetobacter baumannii* in response to antibiotic treatments. Sci Rep 2018; 8(1): 3515.
103. Cheng J, Kesavan DK, Vasudevan A, Cai W, Wang H, Su Z, et al. Genome and transcriptome analysis of *A. baumannii*'s 'Transient' increase in drug resistance under tigecycline pressure. J Glob Antomicrob Re 2020; 22: 219-25.
104. Kesavan DK, Aparna V, Wu L, Chen J, Su Z, Wang S, et al. Integrative analysis of outer membrane vesicles proteomics and whole-cell transcriptome analysis of eravacycline induced *Acinetobacter baumannii* strains. BMC Microbiol 2020; 20(1): 31.
105. Giamarellou H, Antoniadou A, Kanellakopoulou K. *Acinetobacter baumannii*: A universal threat to public health? Int J Antimicrob Agents 2008; 32(2): 106-19.
106. Falagas ME, Blizniotis IA, Siempos II. Attributable mortality of *Acinetobacter baumannii* infections in critically ill patients: A systematic review of matched cohort and case-control studies. Crit Care 2006; 10(2): 48.
107. Gordon NC, Wareham DW. Multidrug-resistant *Acinetobacter baumannii*: Mechanisms of virulence and resistance. Int J Antimicrob Agents 2010; 35(3): 219-26.
108. Perez F, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. Global challenge of multidrug-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 2007; 51(10): 3471-84.
109. Poirel L, Nordmann P. Carbapenem resistance in *Acinetobacter baumannii*: Mechanisms and epidemiology. Clin Microbiol Infect 2006; 12(9): 826-36.
110. Esterly J, Richardson CL, Eltoukhy NS, Qi C, Scheetz MH. Genetic mechanisms of antimicrobial resistance of *Acinetobacter baumannii*. Ann Pharmacother 2011; 45(2): 218-28.
111. Turton JF, Ward ME, Woodford N, Kaufmann ME, Pike R, Livermore DM, et al. The role of ISAba1 in expression of OXA carbapenemase genes in *Acinetobacter baumannii*. FEMS Microbiol Lett 2006; 258(1): 72-7.
112. Rice LB. Challenges in identifying new antimicrobial agents effective for treating infections with *Acinetobacter baumannii* and Pseudomonas aeruginosa. Clin Infect Dis 2006; 43(2): 100-5.
113. Poirel L, Pitout JD, Nordmann P. Carbapenemases: Molecular diversity and clinical consequences. Future Microbiol 2007; 2(5): 501-12.
114. Coelho JM, Turton JF, Kaufmann ME, Glover J, Woodford N, Warner M, et al. Occurrence of carbapenem-resistant *Acinetobacter baumannii* clones at multiple hospitals in London and Southeast England. J Clin Microbiol 2006; 44(10): 3623-7.
115. Suárez CJ, Lolans K, Villegas MV, Quinn JP. Mechanisms of resistance to beta-lactams in some common Gram-negative bacteria causing nosocomial infections. Expert Rev Anti Infect Ther 2005; 3(6): 915-22.
116. Maragakis LL, Perl TM. *Acinetobacter baumannii*: Epidemiology, antimicrobial resistance, and treatment options. Clin Infect Dis. 2008; 46(8): 1254-63.
117. Galata V, Laczny CC, Backes C, Hemmrich-Stanisak G, Schmolke S, Franke A, et al. Integrating culture-based antibiotic resistance profiles with whole-genome sequencing data for 11,087 clinical isolates. GPB 2019; 17(2): 169-82.
118. Chang KC, Cheng YY, Lai MJ, Hu A. Identification of carbonylated proteins in a bactericidal process induced by curcumin with blue light irradiation on imipenem-resistant *Acinetobacter baumannii*. Rapid Commun. Mass Spectrom 2020; 34(1): e8548.
119. Barnes MD, Kumar V, Bethel CR, Moussa SH, O'Donnell J, Rutter JD, et al. Targeting multidrug-resistant Acinetobacter spp.: Sulbactam and the diazabicyclooctenone β-lactamase inhibitor ETX2514 as a novel therapeutic agent. mBio 2019; 10(2): e00159-19.

120. Intorasoot A, Chornchoem P, Sookkhee S, Intorasoot S. Bactericidal activity of herbal volatile oil extracts against multidrug-resistant *Acinetobacter baumannii*. J Intercult Ethnopharmacol 20171; 6(2): 218-22.
121. Phatthalung PN, Chusri S, Voravuthikunchai SP. Thai ethnomedicinal plants as resistant modifying agents for combating *Acinetobacter baumannii* infections. BMC Complement Altern Med 2012; 56.
122. Hemaiswarya S, Kruthiventi AK, Doble M. Synergism between natural products and antibiotics against infectious diseases. Phytomed 2008; 15(8): 639-52.
123. Tiwari V, Roy R, Tiwari M. Antimicrobial active herbal compounds against Acinetobacter baumannii and other pathogens. Front Microbiol 2015; 6: 618.
124. Ito H, Ura A, Oyamada Y, Tanitame A, Yoshida H, Yamada S, et al. A4-aminofurazan derivative A 189- inhibits assembly of bacterial cell division protein FtsZ in vitro and in vivo. Microbiol Immunol 2015; 50(10): 759-64.
125. Losasso C, Belluco S, Cibin V, Zavagnin P, Micetic I, Gallocchio F, et al. Antibacterial activity of silver nanoparticles: Sensitivity of different Salmonella serovars. Front Microbiol 2014; 5: 227.
126. Ali K, Ahmed B, Dwivedi S, Saquib Q, Al-khedhairy A, Musarrat J. Microwave accelerated green synthesis of stable silver nanoparticles with *Eucalyptus globulus* leaf extract and their antibacterial and antibiofilm activity on clinical isolates. PloS One 2015; 10(7): eo131178.
127. Hendiani S, Abdi-Ali A, Mohammadi P, Kharrazi S. Synthesis of silver nanoparticles and its synergistic effects in combination with imipenem and two biocides against biofilm producing Acinetobacter baumannii. Nanomed J 2015; 2(3): 291-8.
128. Chusri S, Villanueva I, Voravuthikunchai SP, Davies J. Enhancing antibiotic activity: A strategy to control Acinetobacter infections. J Antimicrob Chemothe 2009; 64(6): 1203-11.
129. Miyasaki Y, Rabenstein JD, Rhea J, Crouch ML, Mocek UM, Kittell PE, et al. Isolation and characterization of antimicrobial compounds in plant extracts against multidrug-resistant Acinetobacter baumannii. PloS One 2013; 8(4): e61594.
130. Osterburg A, Gardner J, Hyon SH, Neely A, Babcock G. Highly antibiotic-resistant *Acinetobacter baumannii* clinical isolates are killed by the green tea polyphenol (–)-epigallocatechin-3-gallate (EGCG). Clin Microbiol Infect 2009; 15(4): 341-6.
131. Shin B, Park W. Synergistic effect of oleanolic acid on aminoglycoside antibiotics against *Acinetobacter baumannii*. PloS One 2015; 10(9): e0137751.
132. Reichling J, Schnitzler P, Suschke U, Saller R. Essential oils of aromatic plants with antibacterial, antifungal, antiviral, and cytotoxic properties–an overview. Complement Med Res 2009; 16(2): 79-90.
133. Sonbol F, El-Banna T, Abd El-Aziz A, Gouda N. Antimicrobial susceptibility of some natural oils against Acinetobacter species. J Clin Chem Lab Med 2017; 1(1): 1-9.
134. Alanís-Garza BA, Bocanegra-Ibarias P, Waksman-de-Torres N, Salazar-Aranda R, Mendoza-Olazaran S, Perez-Lopez LA, et al. Antimicrobial activity of essential oils-derived volatile compounds against several nosocomial pathogens including representative multidrug-resistant A. baumannii clinical isolates. J Essent Oil Res 2018; 30(5): 341-6.
135. Rai M, Paralikar P, Jogee P, Agarkar G, Ingle AP, Derita M, et al. Synergistic antimicrobial potential of essential oils in combination with nanoparticles: emerging trends and future perspectives. Int J Pharm 2017; 519(1-2): 67-78.
136. Merino N, Berdejo D, Bento R, Salman H, Lanz M, Maggiet F, et al. Antimicrobial efficacy of *Thymbracapitata* (L.) Cav. essential oil loaded in self-assembled zein nanoparticles in combination with heat. Ind Crops Prod 2019; 133(2): 98-104.
137. Rai M, Yadav A, Gade A. Silver nanoparticles as a new generation of antimicrobials. Biotechnol Adv 2009; 27(1): 76-83.
138. Schmitt J, Hajiw S, Lecchi A, Degrouard J, Salonen A, Imperor-Clerc M, et al. Formation of superlattices of gold nanoparticles using Ostwald ripening in emulsions: Transition from fcc to bcc structure. J Phys Chem B2016 Jun 30; 120(25): 5759-66.
139. Gortzi O, Lalas S, Chinou I, Tsaknis J. Reevaluation of antimicrobial and antioxidant activity of Thymus spp. extracts before and after encapsulation in liposomes. J Food Protect 2006; 69(12): 2998-3005.
140. Liolios CC, Gortzi O, Lalas S, Tsaknis J, Chinou I. Liposomal incorporation of carvacrol and thymol isolated from the essential oil of Origanumdictamnus L. and in vitro antimicrobial activity. Food Chem 2009; 112(1): 77-83.
141. Li M, Zhu L, Liu B, Du L, Jia X, Han L, et al. Tea tree oil nanoemulsions for inhalation therapies of bacterial and fungal pneumonia. Colloids Surf B Biointerfaces 2016; 141: 408-16.
142. Scandorieiro S, Camargo LC, Lancheros CA, Yamada-Ogatta SF, Nakamura CV, Admilton Oliveira AG, et al. Synergistic and additive effect of oregano essential oil and biological silver nanoparticles against multidrug-resistant bacterial strains. Front Microbiol 2016; 7: 760.
143. Hemeg HA. Nanomaterials for alternative antibacterial therapy. Int J Nanomed 2017; 12: 8211-25.
144. Scandorieiro S, De Camargo LC, Lancheros CA, Yamada-Ogatta SF, Nakamura CV, De Oliveira AG, et al. Synergistic and additive effect of oregano essential oil and biological silver nanoparticles against multidrug-resistant bacterial strains. Front Microbiol 2016; 7: 760.

SHORT COMMUNICATION

Post–cardiac surgery outcomes following COVID-19 infection in unvaccinated patients

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SUMMARY

The provision of cardiac surgery services nationwide has been affected by the COVID-19 pandemic. We noticed a high COVID-19 mortality rate in unvaccinated patients who were diagnosed with COVID-19 after recent cardiac surgery. All the patients were tested negative for COVID-19 before surgery. We conducted a review of our hospital data and reported our findings. We identified 15 patients and reported 7 deaths (46.7%). All the patients died from COVID-19 or its complications. We recommend that cardiac centres actively promote vaccination before cardiac surgery and also enhance infection control measures to prevent nosocomial infections.

INTRODUCTION

Cardiac surgery is a resource intensive service due to the high utilisation of ICU (intensive care unit) beds. COVID-19 infection post–cardiac surgery appears to have an increased mortality, up to 43% in small case series in other countries.[1-3] This article aims to describe the clinical outcomes of patients who were infected with COVID-19 after cardiac surgery in Malaysia.

METHODS

This was a cross-sectional study conducted at Institut Jantung Negara (National Heart Institute) from October 2020 till July 2021. We included all adults who were diagnosed with COVID-19 after surgery. Our cohort of patients were mostly unvaccinated as the national vaccination rate in July 2021 was 8%.[4]

This cohort included patients having a positive test during the after surgery within the same admission, or patients testing positive for COVID-19 following discharge within six weeks after surgery. Patients in the latter group were admitted to another hospital for COVID-19 treatment. Records were collected by reviewing medical records and phone calls

The methodology is described in Figure 1.

Table I: Demographics of patients with Covid-19 post–cardiac surgery

Variables, n=15		n (%)
Age	<50	1 (6.67)
	51–59	4 (26.7)
	60–69	6 (40)
	≥70	4 (26.7)
Gender, male		11 (73.4)
Chronic renal disease		11 (73.4)
Previous renal transplant		1 (6.67)
Obesity (BMI > 25)		4 (26.7)
Euroscore II	<2	5 (33.3)
	2–4	8 (53.3)
	≥4	2 (13.3)
Ejection fraction	≤50	9 (60)
	>50	6 (40)
Type of operation	CABG only	9 (60)
	Valve only	2 (13.3)
	Surgery on aorta	2 (13.3)
	CABG + valve	1 (6.65)
	CABG + septal myomectomy	1 (6.65)
Urgent operation		3 (20)
Days between surgery and Covid-19	<5	2 (13.3)
diagnosis	5–10	5 (33.3)
	11–20	6 (40)
	>20	2 (13.3)
Source of infection	Another patient	5 (33.3)
	Family member	2 (13.3)
	Community	4 (26.6)
	Unsure	4 (26.6)

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Table II: In-hospital events of patients with Covid-19 post–cardiac surgery

In-hospital events (n=12)		n (%)
ICU admission		7 (58.3)
Intubation		2 (16.6)
Non-invasive ventilation		4 (33.3)
Deaths		7 (46.7)
Mode of death	ARDS	2 (16.6)
	Pulmonary embolism	1 (8.3)
	Septic shock	1 (8.3)
	Unclassified	3 (20)

ARDS: Acute respiratory distress syndrome. Mode of death was unclassified for three patients who died in rural hospitals.

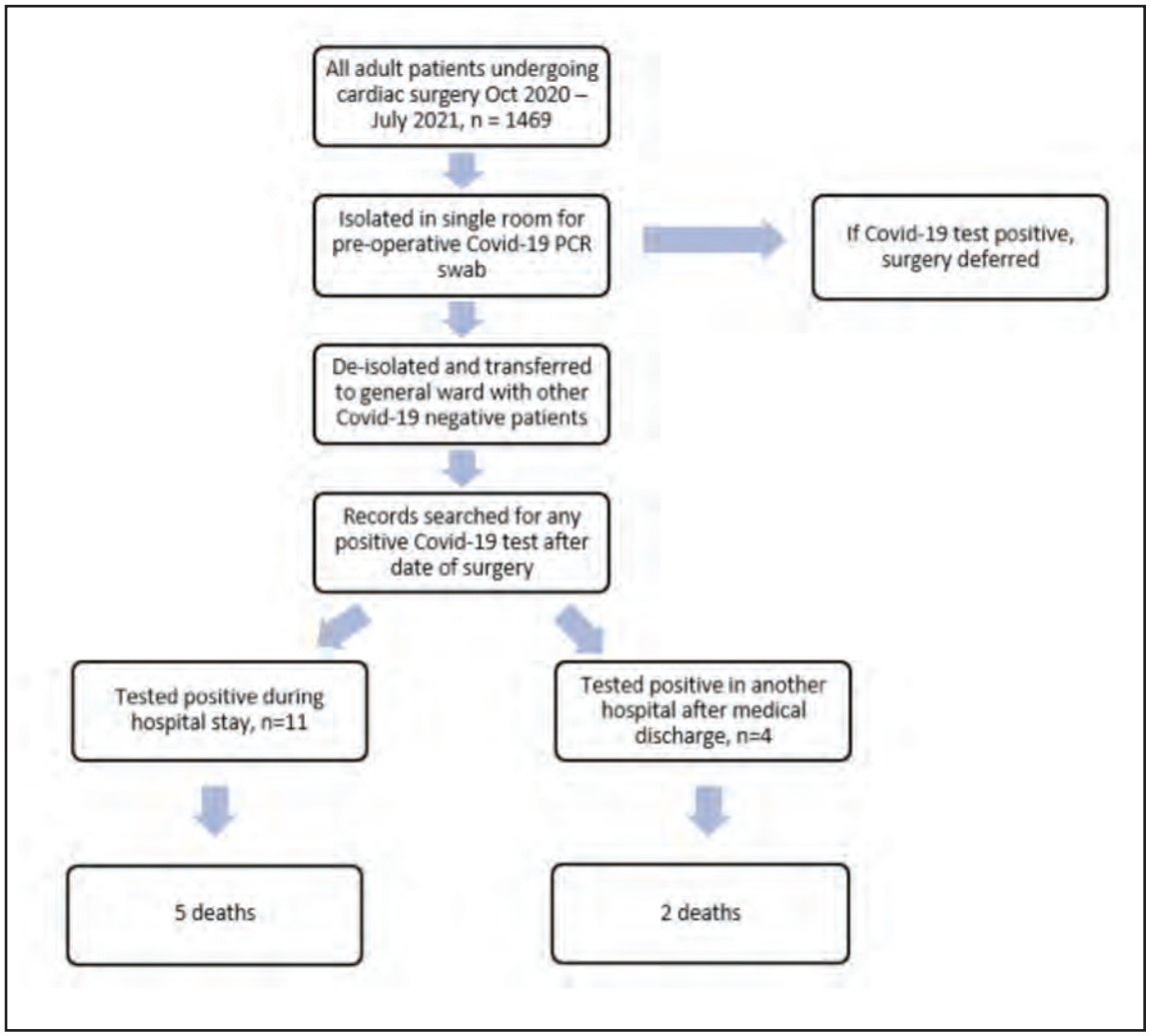

Fig. 1: Methodology.

RESULTS

We identified 15 patients who fulfilled our inclusion criteria. The demographic details are described in Table I.

The patient outcomes are described in Table II.
We identified 10 cases of nosocomial infection in our group, out of the 1469 patients who underwent surgery. The total nosocomial infection rate was 0.61%.

We found two early infections that occurred within the first 2 days after heart surgery. Both patients were clinically asymptomatic but the repeat COVID-19 swab was taken due to contact tracing. This may have been due to a false negative pre-operative COVID-19 swab during the window period.

DISCUSSION

Despite the COVID-19 pandemic, cardiac surgery services need to be continued. Cardiac surgery is life saving, and patients can have good long-term outcomes with successful surgery.

In our group of patients, the overall mortality rate was very high, i.e., at 46.7%, compared to the national 7-day average mortality of ≤2.1% during the same time period.[5] These mortality figures are comparable to a similar-sized cohort in the UK, which had a mortality rate of 37.1%.[2] In each of the cases within our cohort, the comorbidities of patients who died and survived were similar.

The risk of nosocomial infection appears to be low[6] in our hospital, allowing the majority of patients to receive adequate and timely treatment for their heart disease. However, each case of nosocomial infection substantially increases the cost of healthcare. Within our hospital, there have been multiple anecdotal cases of patients who have died from heart disease as a result of postponing cardiac surgery due to COVID-19 quarantine.

Some of the limitations of this study are the potential for recall bias from patients who died in rural hospitals. Genetic testing for variants of COVID-19 was not done due to resource constraints. The antiviral and immunomodulatory treatments were also not standardised.

On top of the COVID-19 PCR testing before surgery, our hospital has started rapid antigen testing on the night before surgery to reduce the false negative rate.

CONCLUSION

Due to the high mortality risk of COVID-19 after cardiac surgery in unvaccinated adults, we recommend that patients are vaccinated before surgery.[7,8] Additional resource allocation for infection control should also be considered for cardiac centres to manage this high-risk group. We also recommend regular auditing and review of hospital and national infection control policies. A good balance needs to be made as an overzealous infection control policy can harm patients by delaying treatment for heart disease. Further studies need to be done to compare the protective effects of vaccination on this cohort of patients.

REFERENCES

1. Yates MT, Balmforth D, Lopez-Marco A, Uppal R, Oo AY. Outcomes of patients diagnosed with COVID-19 in the early postoperative period following cardiac surgery. Interact Cardiovasc Thorac Surg 2020; 31: 483-5.. DOI: 10.1093/icvts/ivaa143.
2. Sanders J, Akowuah E, Cooper J, Kirmani BH, Kanani M, Acharya M, et al. Cardiac surgery outcome during the COVID-19 pandemic: A retrospective review of the early experience in nine UK centres. Journal of Cardiothoracic Surgery 2021; 16: 43. DOI: 10.1186/s13019-021-01424-y.
3. Rhee C, Baker M, Vaidya V, Tucker R, Resnick A, Morris CA, et al. Incidence of nosocomial COVID-19 in patients hospitalized at a large US academic medical center. JAMA Network Open 2020; 3(9): e2020498. DOI: 10.1001/jamanetworkopen.2020.20498.
4. Malay Mail. Dr Adham: 8pc of Malaysian population fully vaccinated against Covid-19 2021 [cited April 2022]. Available from: https://www.malaymail.com/news/malaysia/2021/07/05/dr-adham-8pc-of-malaysian-population-fully-vaccinated-against-covid-19/1987303.
5. Ministry of Health. COVID-19 deaths in Malaysia 2021 [cited April 2022]. Available from: https://covidnow.moh.gov.my/deaths/.
6. Limper U, Defosse J, Schildgen O, Wappler F. Perioperative risk evaluation in patients scheduled for elective surgery in close relation to their SARS-CoV-2 vaccination. British Journal of Anaesthesia 2021; 126: e225-6. DOI: 10.1016/j.bja.2021.03.007.
7. Ridwan K, DeVarennes B, Tchervenkov C, Shum-Tim D, Cecere R, Lachapelle K. Postoperative nosocomial COVID 19 infection in cardiac surgery: An uncommon event with high mortality. CJC Open 2021; 3(10): 1217-20DOI: 10.1016/j.cjco.2021.05.017.
8. Royal College of Surgeons of England. Vaccinated patients guidance 2021 [cited October 2021]. Available from: https://www.rcseng.ac.uk/coronavirus/vaccinated-patients-guidance/.

Evaluation and management of abnormal uterine bleeding

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SUMMARY

Abnormal uterine bleeding (AUB) is one of the commonest complaints of women in reproductive age and non-gravid state that brings them to the attention of the primary care doctor or the gynaecologist. Anovulation without any medical illness or pelvic pathology seems to be the common cause. Bleeding due to a wide variation in pathology both inside and outside the reproductive tract can be termed as anovulatory bleeding. Therefore, it is mandatory to elicit a focused menstrual history and appropriate evaluation followed by a pelvic examination. This includes a vaginal speculum examination to differentiate anovulatory bleeding from other causes of bleeding. In contrast, Heavy menstrual bleeding (HMB) is referred to as an ovulatory bleeding exceeding 8 days duration and is often caused by uterine fibroids or adenomyosis, a copper IUD or coagulation disorders. PALM-COEIN classification is a system designed by the Federation Internationale de Gynaecologie et d'Obstetrique to define the precise underlying causes of AUB. Aetiology of AUB can be classified as the following acronym "PALM-COEIN": Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic and Not yet classified. AUB describes a range of symptoms, such as HMB, inter-menstrual bleeding (IMB) and a combination of both heavy and prolonged menstrual bleeding (MB). Dysfunctional uterine bleeding (DUB) and menorrhagia are now better described as AUB. Newborn girls sometimes spot for a few days after birth, due to placental oestrogenic stimulation of the endometrium in utero.

KEYWORDS:
Abnormal uterine bleeding, Historical views of menstruation, Female genital tract pathology, Bleeding disorders (thrombophilia), Pharmacological treatment, Minimally invasive surgical procedures

INTRODUCTION

Abnormal uterine bleeding (AUB), a frequent reason for outpatient and emergency department visits in reproductive-aged, non-gravid women, may substantially affect a woman's physical, social, and mental quality of life. Evaluation and management of AUB incurs high healthcare costs. This predicament may affect 10–30% of women of reproductive age group.[1,2] All clinicians in the field, therefore need to be alert about the causes and keep a well-organised and prudent approach to formulate the management plan.
Formally AUB describes a range of symptoms, such as HMB, IMB, and combination of both heavy and prolonged menstrual bleeding. Menstrual disorders previously portrayed as DUB and menorrhagia are now better described as AUB.[3]

Bleeding due to a wide variation of pathology both inside and outside the reproductive tract can be mimicked as an anovulatory bleeding. Therefore, it is mandatory to elicit a focused menstrual history appropriate for AUB followed by a pelvic examination that includes a vaginal speculum examination, to differentiate anovulatory bleeding from other causes of bleeding. In contrast, HMB is referred to ovulatory bleeding exceeding 8 days duration and is often caused by uterine fibroids, adenomyosis, a copper intrauterine device (IUD), or coagulation disorders. Newborn girls sometimes spot for a few days after birth, due to placental oestrogenic stimulation of the endometrium in utero.

There is no agreement on a structured, universal approach to the diagnosis of AUB with the aide memoires PALM-COEIN as shown in Fig. 1. Once malignancy and pelvic pathology have been ruled out, medical treatment is an effective first-line therapeutic option, with surgery including endometrial ablation or hysterectomy, offered when medical management failed to resolve symptoms and fertility is no longer desired. The acronym PALM-COEIN denotes Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not yet classified as defined by the Federation of Internationale de Gynaecologie et d'Obstetrique.[4]

Learning Objectives:

1. To understand the causes of AUB and its management in non-pregnant, pre-menopausal women.
2. To be able to evaluate various relevant investigations required to evaluate AUB.
3. To recognise the differential diagnosis of AUB in various phases of reproduction.
4. To be aware of both medical and surgical therapies including the newer hysteroscopic and non-hysteroscopic ablative techniques, taking into cognizance the morbidity and mortality

Not Yet Classified:

This group is poorly defined, inadequately studied, and rare. They include arteriovenous malformations, myometrial hypertrophy, and uterine isthmocele secondary to previous caesarean section residual scar defects. Imaging with TVUS and MRI[3] will be able to recognise these defects.

FIGO defines normal uterine bleeding as approximately 37–41 ml of blood loss over the first 5–7 days of the menstrual cycle, FIGO also defines HMB as 100–130 ml of blood loss, over a varying number of days throughout the whole cycle but often within the first 10 days resulting in anaemia.[5] AUB

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can have a significant impact on women's quality of family perspectives and poses embarrassment, because of soiling outer garments with blood.[1] Also, AUB can be as consequences of infections, uterine fibroids, polyps, adenomyosis, or endometriosis. Newborn girls sometimes spot for a few days after birth due to placental oestrogenic stimulation of the endometrium in utero.

The term DUB is synonymous with anovulatory bleeding, in the absence of pregnancy or any obvious pelvic pathology. In anovulatory menstruation, the follicles grow without any selection of a dominant follicle. The oestrogen is secreted in increasing amount. The net effect is unopposed secretion of oestrogen leading to fragile endometrial growth without proper stromal support. When the oestrogen level falls, there is asynchronous shedding of the endometrium resulting in heavy or prolonged and irregular bleeding. The term *menorrhagia* spells out as regular, heavy, or prolonged bleeding. In clinical practice, a wide variety of terms are used to denote this pattern of bleeding.

Historical Views of Menstruation

Throughout early recorded history, many superstitious beliefs have surrounded menstruation, and women were isolated and prevented from handling food. Many considered menstruating women were impure, unclean, and subjected to segregation with special rituals. They were prohibited and shunned at holy places and social functions. These practices were prevalent in rural and remote areas in India and Nepal and other third world countries decades ago.[6,7] Attitudes and ideas about this aspect of female physiology have changed dramatically. The scientific progress in recent years has revealed the dynamic relationships between the pituitary and gonadal hormones and the cyclic pattern of the normal reproductive process. In Malaysia, there are no anecdotal records of such segregation practices.

Recognising these cultural sensitivities, healthcare providers need to be familiar with the existing cultural and social views and attitudes towards menstrual disorders and provide medically appropriate therapies for their menstrual disturbances.

Despite sophistication and modernisation in lifestyle, negative attitudes towards menstruation do persist in modern times in many countries.[8]

Clinical evaluation of AUB

A careful and detailed history of the presenting illness, menstrual health, sexual and contraceptive details inclusive of past obstetric performance, drug history and allergies, family and social history are pertinent. This is followed by a general examination including vital signs, cardio-respiratory assessment, breast examination followed by abdominal and pelvic examination inclusive of speculum and bimanual examination. Requesting relevant laboratory and imaging tests is done when indicated.

Bimanual examination elicits the size and contour of the uterus. An enlarged or lobular uterus suggests leiomyomas or adenomyosis. Cervical or adnexal tenderness is suggestive of *pelvic inflammatory disease* (PID). The presence of hyperandrogenic features, for example, acne, hirsutism, and basal metabolic index (BMI) >25 kg/m^2, suggests polycystic ovarian syndrome (PCOS), whereas galactorrhoea demonstrates possibility of a pituitary hyperprolactinaemia and hypothyroidism.

On the other hand, intermenstrual bleeding IMB may be caused by an endometrial polyp, endometritis, or an IUD, whilst postcoital bleeding suggests presence of cervical disease (cervicitis, polyp, or malignancy as in Fig II). Anticoagulant use can cause HMB whilst medications that may induce hyper-prolactinaemia (e.g., risperidone or haloperidol) can cause AUB. Pregnancy test is prudent in women younger than 55 years. Laboratory testing should include cervical cytology, human papillomavirus along with *Chlamydia trachomatis*, *Neisseria gonorrhoea* and *Trichomonas vaginalis* using nucleic acid amplification testing on vaginal swabs for patients younger than 25 years or when there is vaginal discharge, pelvic pain, new or multiple sexual partners with cervical motion or adnexal tenderness. A complete full blood count (FBC) and serum ferritin levels should be taken from women with HMB because of the risk of iron depletion resulting in an iron deficiency anaemia. Leucocytosis is pathognomonic of PID or postpartum endometritis. Assessment of thyroid and prolactin concentrations is vital. Von Willebrand disease (VWB) is the most common inherited bleeding abnormality affecting women. In adolescent girls, a heavy bleeding pattern since menarche is suspicious. The possibility of *coagulopathy* also should be kept in mind especially in adolescents whose menstrual history is short and not yet well defined. Besides, in adolescents, genital trauma, sexual abuse, cervicitis relating to sexually transmitting infections *(Chlamydia trachomatis)*, and foreign bodies (e.g., retained tampons merit special consideration).

Certain medications can predispose to AUB, by interfering with haemostasis, resulting in menorrhagia by disrupting the hypothalamic-pituitary-ovarian (HPO) axis. Drugs associated with AUB include hormonal contraception, anticonvulsants, anticoagulants, and psychopharmacologic medications. Some common herbs have oestrogenic activity (e.g., ginseng)

Systemic illnesses may predispose to anovulation or coagulation abnormalities; examples include diabetes mellitus, systemic lupus erythematosus, malignancies, and myelodysplasias. Chronic renal disease is associated with both ovulatory and platelet dysfunction. Liver disease too can affect oestrogen metabolism and predispose to anovulation.

The reality of a post-tubal ligation syndrome of menstrual abnormalities has been debated for some time now.[9] The popular theory is that extensive tubal electrocoagulation adversely affects ovarian blood supply and steroidogenesis. This syndrome is seen frequently many years after sterilisation particularly electrocautery but not with rings and clips.

Imaging the transvaginal route is useful in the evaluation of patients with AUB. Imaging is also useful in suspected PCOS and polyps or leiomyoma in the endometrial cavity. Abdominal ultrasound is appropriate in virginal patients and others in whom a vaginal ultrasound is inappropriate.

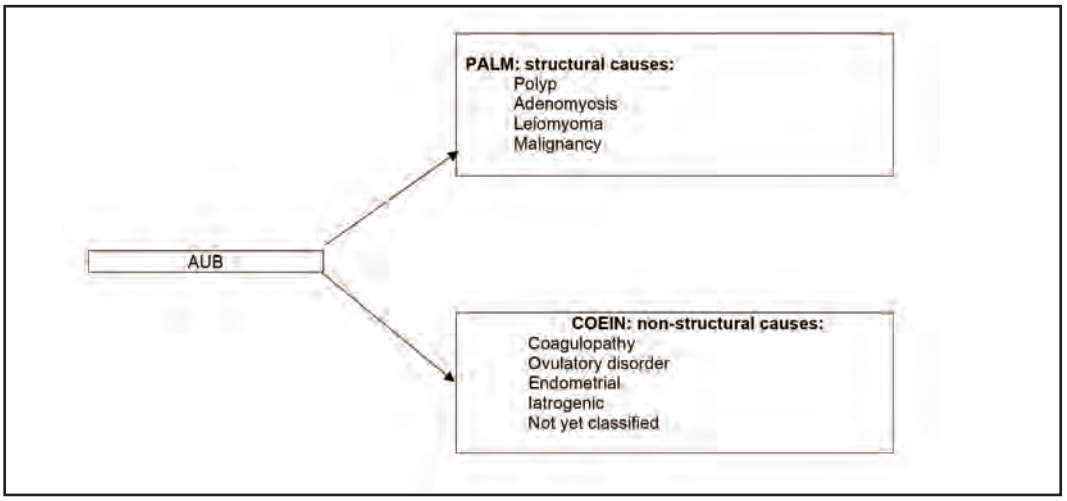

Fig. 1: FIGO AUB System II PALM COEIN (2011)
(Source: British Medical Bulletin 2017, 123: 103-114)

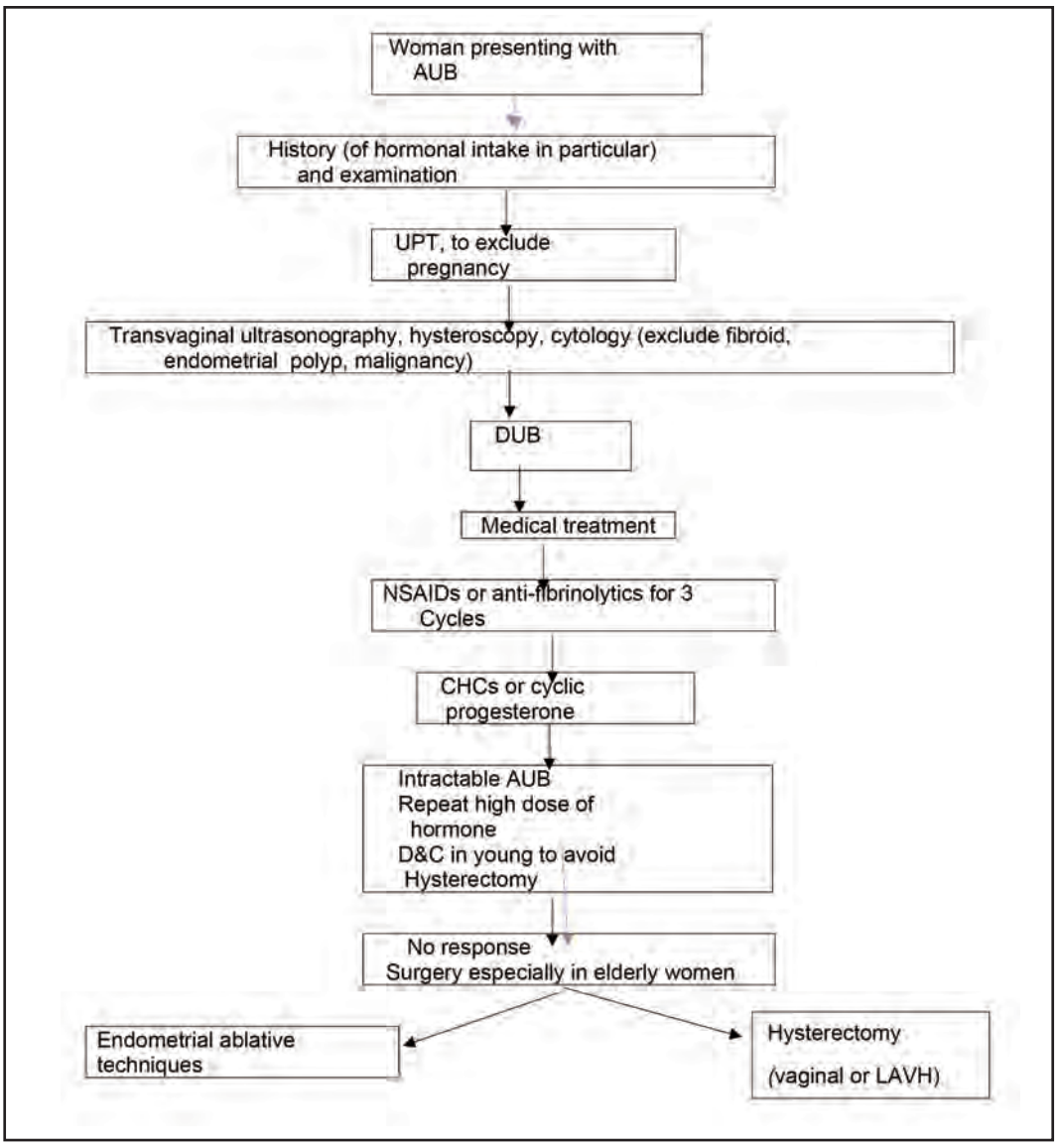

Fig. 2: Algorithm in the clinical evaluation of patient presenting with AUB.

Table I: Laboratory evaluation

Laboratory evaluation	Specific Laboratory Tests
Initial laboratory testing	• Full blood count (FBC) • Blood group and cross match • Pregnancy test • Well-timed serum progesterone
Initial laboratory evaluation for disorders of haemostasis	• Partial thromboplastin time • Prothrombin time (PT) • Activated partial thromboplastin time (aPTT) • Fibrinogen
Initial testing for Von Willebrand disease	• Von Willebrand factor activity (optional) • Factor VIII level (optional)
Other laboratory tests to consider	• Thyroid-stimulating hormone (TSH) • Serum iron/ferritin • Total iron-binding capacity (TIBC) • Liver function tests (LFTs) (optional) • Renal function tests (RFTs) for those with suspected renal disease (optional) • Chlamydia trachomatis N. Gonorrhoea • Wet prep for Trichomonas vaginalis
Ultrasonography as primary diagnostic tool	• Early pregnancy features • Small ovarian cysts
Saline infusion sonography (SIS)(optional) Magnetic resonance imaging (MRI) if ultrasonography information is inadequate (optional)	• Leiomyoma/adenomyosis • Endometrial thickness
Hysteroscopy and endometrial biopsy	• Small polyps • Submucous fibroids • Endometrial hyperplasia • Endometrial carcinoma

Table II: Medical Treatment

Hormonal

- Combined hormonal contraceptives (CHCs)
- Progestins
- Levonorgestrel impregnated intrauterine system (LNG-IUS)
  (Suitable to patients <35 years, non-smokers, no comorbid complications, migraine, and history of VTE)

Non-Hormonal

- Prostaglandin synthetase inhibitors (PGSI)
- Anti-fibrinolytic agents – Tranexamic acid
- Reducers of platelet fragility – Ethamsylate
  (Suitable for women >35 years with hypertension, diabetes)

Others

- Danazol (17-α-ethinyl testosterone)
- GnRH agonists
- Selective oestrogen receptor modulations (SERMs)
- Epsilon amino caproic acid
- Gestrinone (19-Norsteroid derivative)
- Interleukin II
- Vasopressin analogues
- Desmopressin (dDAVP) analogues
  (Suitable in women with HMB in women with Von Willebrand disease, beginning treatment with onset of menstruation)

Other second-line imaging tests are computed tomography (CT) and magnetic resonance imaging (MRI) in exceptional cases. Alternatively, hysteroscopy may facilitate targeted biopsy, resection of intracavitary pathology or both. Endometrial sampling is performed after exclusion of pregnancy in patients with AUB. Biopsy facilitates to exclude endometrial hyperplasia or cancer.

Case study I

Ms. T, an 18-year-old college student came to the primary health centre HMB lasting 6–7 days interfering with her lifestyle. Menstrual history showed she had this problem since her first period at 12. Never been on any hormonal medications. She has history of excessive bleed during dental scaling and few occasions of epistaxis, and both conditions resolved spontaneously. She is not sexually active. There was mild pallor and pelvic ultrasonography was unremarkable. Her vital signs were normal. There were few ecchymosis spots on her abdomen and forearms.

Questions:

1. What could be the possible causes of this problem?
2. List two tests that may confirm her diagnosis.
3. How do you manage and follow-up this case?

Answers:

1. Anovulation and effect of unopposed oestrogen stimulation leading to endometrial hyperplasia
2. i. Pelvic ultrasonography to check endometrial thickening
   ii. Full blood count/evaluation of disorders of haemostasis, e.g., PT and aPTT
3. Progestins for three cycles, prostaglandin synthetase inhibitors (PGSI), rarely surgical interventions at this age

Pathophysiology

The menstrual cycle is an organised string of endocrine signals that gives the menstrual cycle the regularity, predictability, and reliability. The cycles become irregular around extremes of reproductive age (menarche and menopause) mainly due to anovulation and inadequate follicular development.[10] This is due to disturbance in the hypothalamus-pituitary-ovarian (HPO) axis, a phenomenon seen commonly in PCOS and extremes of reproductive age groups as shown in Table I. The term DUB refers to anovulatory bleeding in the absence of pregnancy or any demonstrable pelvic pathology or coagulation disorders.[11]

In ovulatory DUB, the bleeding is regular but heavy with 90% of the bleeding is greater in the first three days.[12] The HPO axis is not involved. Here, the gonadotrophin and steroid hormone profiles are similar as in normal menstrual cycles. The decline in oestrogen and progesterone levels in the late secretary phase leads to disintegration, followed by re-epithelialisation of the functional layer of the endometrium. The main defect appears in the process of vasoconstriction and haemostasis.

HMB refers to ovulatory (cyclic) bleeding exceeding 8 days' duration or heavy enough to soak a pad or tampon more than every 2 hours and during peak flow, large clots are passed and interfere with daily activities of life.[13] About 1 in 20 women aged 10–49 years will consult their primary care physicians. HMB is often caused by uterine fibroids or adenomyosis but may also be caused by a copper intrauterine device (IUD) or coagulation disorders.

The differential diagnosis of AUB includes problems associated with pregnancy, infection, vaginal and cervical abnormalities, benign and malignant uterine neoplasms, coagulopathies, endocrine disorders, trauma, and foreign bodies inserted into the lower genital tract, systemic diseases leading to vaginal bleeding as seen in Table I. The causes may vary with age. In premenarchial girls, foreign bodies, trauma, and infection are more prevalent as in Table I. In post menarche adolescents, anovulatory bleeding, coagulopathies, infections, and pregnancy complications are common. In suspected cases of a coagulopathy, history of heavy menstrual bleeding from menarche, after dental procedures, epistaxis, frequent gum bleeding, skin bruises, and a family history of bleeding symptoms are noted. During the reproduction years, anovulation, hormonal contraception, complications of pregnancy, infection, endocrine disorders, cervical lesions, and fibroids are frequent. In perimenopausal women, anovulation, uterine neoplasia, and endometrial hyperplasia are the principal causative factors. In postmenopausal women, vaginal/endometrial atrophy, and HRT prescriptions are the chief causes.

Laboratory Evaluation

Laboratory tests can be very helpful but not always necessary. A urine pregnancy test quickly excludes the possibility of an early pregnancy abnormal bleeding. A complete FBC excludes anaemia and thrombocytopenia which is useful in women who complaints abnormal bleeding.

A complete Serum progesterone level exceeding 3 ng/ml during the luteal phase between days 22 and 24 of the cycle can help diagnose ovulation. If the menstrual pattern is erratic or poorly documented, then conventional basal body temperature (BBT) measurement may be employed. Endometrial sampling is only reserved for women beyond 40 years or when suspected of endometrial hyperplasia or cancer.

In women who are sexually active, tests for *chlamydia* and *gonorrhoea* and a wet preparation for trichomonas infection merit consideration, particularly in those with evidence of cervicitis/vaginitis. Cervical cultures and a cervical smear are appropriate for the presence of sexually transmitted diseases or cervical dysplasia. In adolescent girls who present heavy menstruation since menarche or a family history, it may be prudent to do coagulation screening. In addition to VWB disease, other factor deficiencies, platelet function abnormalities, screening should also include both PT and aPTT as in Table I. The former demonstrates abnormalities of the extrinsic and common pathway, whilst the latter is the intrinsic and common pathway. With proven abnormalities, consultation with a haematologist is pertinent. Renal and liver function tests are done when there is a suspicion of the particular-organ involvement.

Imaging techniques could shed light on anatomical abnormalities such as fibroids and endometrial polyps. Transvaginal may throw light on the precise size and location of fibroids or may explain bleeding due to other causes.[14] Saline infusion sonography identifies intracavitary lesions such as endometrial polyps or submucous myomas with high accuracy. CT scans and MRIs are done in more obscure cases. MRI can reliably define uterine anatomy, distinguishing between adenomyosis and leiomyomas. The risk of cancer is remote in women who are either perimenopause, or post-menopause with an endometrial thickness less than 5 mm but clinically present with abnormal bleeding.[15] Endometrial hyperplasia and cancer are more commonly detected in older than in younger women. The duration of exposure to unopposed oestrogen stimulation is the most critical risk factor. Endometrial biopsy is almost mandatory.

Hysteroscopy plays a very decisive role in those with intrauterine pathology that requires biopsy or excision. Modern hysteroscopes with an outer diameter of 2–3 mm permit both diagnostic and therapeutic procedures at an office setting.[16]

Case study II

Mrs. R.K., a 36-year-old lady with 2 living children 8 and 10, went to the outpatient clinic in a district hospital for excessive per vaginal bleeding during every cycle using 8–10 pads per day with clots for the past one year. She was on barrier contraception between her 2 children but nil presently.

Her vital signs were normal with pallor. Cardiorespiratory systems were normal. Abdominal palpation showed a firm 16-week size central mass below the umbilicus, soft in consistency, no nodularity, mobile side to side and non-tender and could not feel the lower border. A trans-abdominal ultrasonography revealed a bulky mass measuring 15 x 8 x 5 cm. A pelvic examination confirmed a normal cervix, the size and consistency of the uterine mass with normal adnexa.

Questions:

1. What is the probable diagnosis and why?
2. What further investigations would complement your diagnosis?
3. How would you manage this case?

Answers:

1. Submucous fibroid/adenomyosis presenting with a firm central mass of 16-week size
2. Imaging techniques: pelvic ultrasonography, CT scan, and MRI (optional)
3. Expectant management if one desires further childbearing: myomectomy, endometrial ablation, uterine artery embolisation, otherwise opt for hysterectomy

Medical Treatment

Although AUB can often be managed medically on an outpatient basis as in Table II, discussion pertaining to contraceptive needs, desire for future pregnancies, medical comorbidities, patient preferences, and desire for endometrial ablation or hysterectomy is well discussed. Improving access to care will require multi-level approaches that involve local socio-cultural needs and improved healthcare facilities.

Combined hormonal contraceptives (CHCs)

CHCs reduce the MBL and result in a consistent menstrual cycle interval.[17] The reported MBL or Pictorial blood assessment chart (PBAC) score range from 32–36% at 3 months and 35–68% in 12 months.[18] CHCs could be prescribed for 3 weeks followed by a pill-free week to facilitate withdrawal bleed or be given as hormone free interval to induce amenorrhoea in 80–100% of women.

Rare side effects of CHCs are breast tenderness and mood changes. The contraindications for use of CHCs are for women more than 35 years, who smoke, have hypertension, cardio-vascular disease, migraine, breast cancer, or history of VTE.

Progestin Therapy:

Synthetic progestogens have been used in the treatment of menorrhagia for over 30 years. The drug dosage and the duration of use will influence the effect on the endometrium and consequent pattern of bleeding. Progestins are the mainstay of treatment for anovulatory bleeding. This is commenced after organic pathology is excluded. In oligomenorrhoeic anovulatory patients, an orderly organised withdrawal bleeding can be worked out. Cyclic oral progestins, medroxyprogesterone acetate (MPA) 5–10 mg for 10–12 days each month. MPA inhibits FSH release from the anterior pituitary and prevents ovulation. When the endometrium is either normal or increased in thickness, the regime is continued for 3 weeks and 10 days thereafter, decreased to once a day for 7–10 days.[19]

The progesterone impregnated intrauterine device: relating to 20 µg of levonorgestrel per day has proven to be successful in reducing menstrual blood loss.[20] Progestogens may be safely used for long-term treatment of DUB.

Modern low dose CHCs can be safely prescribed for most young women, provided they do not have any contraindications. The CHC is used frequently for the treatment of menorrhagia. The efficacy has been confirmed objectively.[21] CHCs are unpopular for treatment of menorrhagia, particularly in women over 35 years of age over concerns of thromboembolic diseases.

Non-hormonal medical therapy

Suitable for women beyond 35 years, smokers with comorbid complications and history of VTE.

Iron therapy

Intravenous iron like iron sucrose is given 200 mg intravenous in 200 ml of normal saline over 30 min, thrice a week. Side effects: mainly gastro-intestinal. Contraindications: known hypersensitivity to intravenous iron. Precautions: asthma, eczema, and other atopic allergies.[22]

Prostaglandin Synthetase Inhibitors (PGSIs)

Use of inhibitors of COX enzymes had been shown to reduce MBL implicating impairment of prostaglandin pathways in the aetiology of excessive menstrual bleeding. NSAIDs reduce MBL by (10–51%) inhibiting endometrial prostaglandin synthesis. The endometrium is a rich source of PGE_2 and $PGF_{2\alpha}$. Reductions in MBL in proven menorrhagia range from 22% to 46%.[23,24]

Anti-Fibrinolytic Agents

The endometrium possesses an active fibrinolytic system. Tranexamic acid is an inhibitor of fibrinolysis, is used frequently as first-line therapy in the United Kingdom , despite of a number of trials showed only 50% reduction in MBL.[25,26] It decreases endometrial plasminogen activator activity. Side effects were minimal with no discontinuation on account of adverse drug reactions. A third of women experience gastrointestinal side effects with 3–6 grams daily. As 90% of MBL in the first 3 days of flow, dose-related side effects can be minimised by limiting the number of treatment days to the first 3 or 4 days of the period.

Other Medical Therapies

Danazol is a synthetic androgen (17-α-ethinyl testosterone) with anti-oestrogenic and anti-progestogen activities, leading to endometrial atrophy and reduced blood loss. A high incidence of androgenic side effects such as weight gain, muscle cramps, and skin rashes have limited its treatment option. When prescribed at more than 400 mg daily, as a treatment option for women with gynaecological diseases, it is mainly used as a second-line therapy, especially as a short-term, pre-surgical procedures.[27]

Gonadotrophin-Releasing Hormone Agonists (GnRHa)

GnRH agonists achieve short-term relief from a bleeding problem and has been used as a pre-operative adjunct in women awaiting myomectomy or endometrial ablation or definitive surgery (hysterectomy) for AUB. The resultant shrinkage of myomas and thinning of endometrium promotes less bleeding intra-operatively.[28]

The analogues control menstrual loss by pituitary down regulation and subsequent inhibition of cyclical ovarian activity. Ovarian suppression and amenorrhoea with associated hypo-oestrogenic-state and endometrial atrophy leads to hot flushes, vaginal dryness, and bone mineral depletion. Add-back therapy with oestrogen may alleviate the problem.

The Levonorgestrel-releasing Intrauterine System (LNG-IUS, Mirena®)

Progestogen can be delivered directly to the endometrium using a hormonal intrauterine device. The operation compliance and carry with them additional contraceptive benefits. Potential modes of action of progesterone and progestogen-releasing devices are a reduction of endometrial prostaglandin synthesis and endometrial fibrinolytic activity.[29] The reservoir contains 52 mg of LNG mixed with polydimethylsiloxane and release 20 µg of LNG per day. It is contraindicated in pregnancy and unexplained vaginal bleeding.

Desmopressin (dDAVP)

A synthetic analogue, Desmopressin is used to treat AUB in women with coagulation disorders especially those with VWD. It has been shown to reduce median PBAC score by 24–42% during two cycles of treatment.[30]

Ethamsylate is a haemostatic agent used to treat HMB given at 500 mg 4 times daily during days of menstruation, it reduces MBL by 25% of women during 3 cycles.[31]

Other options include haemostatic agents, SERMs, epsilon aminocaproic acid, gestrinone (19-Norsteroid derivative) and interleukin II.

Case study: III

Madam M, 48-years-old lady with 3 living children age ranging 18–12, delivered normally, was never on any form of contraception. She was amenorrhoeic for 8 months followed by per vaginal spotting and frank bleeding past 6 months. She had gone to see her family physician. She is not a hypertensive or diabetic.

Her BMI was 26, BP 120/70 mm Hg, looked tired and weak. Abdominal examination was unremarkable, pelvic examination showed a pale vaginal mucosa, normal cervix, and bulky uterus, with no adnexal masses. A transvaginal scan essentially showed normal uterus with an endometrial thickening of 11 mm. Her doctor referred her to see the gynaecologist at a tertiary centre.

Questions:

1. What is your provisional and differential diagnosis?
2. What investigations would you perform for the thickened endometrium?
3. What will be your further management of this patient?

Answers:

1. Small polyps, submucous fibroids, endometrial hyperplasia, endometrial carcinoma.
2. Endometrial sampling is performed after exclusion of pregnancy. Biopsy facilitates to exclude endometrial hyperplasia or cancer.
3. Further management depends on investigation results: In view of the age group, surgical extirpation of uterus is more plausible.

Surgical considerations

Surgery is seldom indicated in young women with menstrual disturbances. Hysterectomy, the traditional surgical treatment of menorrhagia, is only suitable for women who have no further wish to conceive. The operation itself is not without risk. Concerns about the "invasiveness" of hysterectomy have led to the development of minimal access approaches including endometrial resection and ablation both as inpatient and as outpatient treatment modality.[32]

Uterine artery embolisation (UAE) is an alternative for uterine fibroids in cases where pregnancy is still desired. Both the uterine arteries are blocked with particles injected through a catheter inserted into them via the femoral artery. This procedure causes shrinkage of the fibroids. UAE is performed by an interventional radiologist. Embolisation may be an appropriate treatment for larger fibroids where the risks from surgery are higher.[33]

Current minimal Access Techniques

Hysteroscopy and visually directed endometrial sampling have replaced blind curettage for the diagnosis of endometrial disease. The development of minimal access techniques has made it possible to therapeutic destruction of endometrium in situ as a day-care operation. The earliest techniques ablated endometrium with ND: YAG LASER,

(hysteroscopic first generation).34 The second-generation of endometrial ablation devices are technically simpler to perform, less invasive, designed to ablate the full thickness of endometrium by application of heat, cold, or microwave. The aim of these new procedures is to remove only the endometrium and leave the myometrium intact. Generally, the technique of endometrial ablation is divided into two groups: Hysteroscopic and Non-Hysteroscopic procedures.

A. Hysteroscopic (First-Generation Devices).
- Transcervical resection of endometrium (TCRE)
- Rollerball endometrial ablation (Endometrial "Rollerball" Electrocoagulation)
- LASER ablation (Nd YAG LASER)

B. Non-Hysteroscopic (Second-Generation Devices) Hot liquid balloons
- Thermal balloon endometrial ablation: Cavaterm, ThermaChoice

Thermablate
- Microwave endometrial ablation (MEA)
- Bipolar radiofrequency induced thermal endometrial ablation (RITEA)

COMPLICATIONS

Both hysteroscopic and non-hysteroscopic techniques for endometrial ablation appear to offer good patient satisfaction and symptom relief. Endometrial ablation generally is more effective when the endometrium is relatively thin.

Complications associated with hysteroscopic techniques primarily involve those resulting from unrecognised uterine perforation and injury to the bladder and bowel and from fluid and electrolyte disturbance relating to excessive absorption of distention media.[35] Fluid overload can result in hyponatremia and pulmonary oedema.[36]

Non-hysteroscopic methods of endometrial ablation requires less technical skill and operative time.

CONCLUSION

Gynaecological health has historically remained a taboo subject, yet this stigmatisation, has meant that many women today are not able to talk about issues such as menstruation. This has resulted in many women normalising symptoms or "suffering in silence". AUB is a disabling condition compelling many women to seek medical help. The literature is replete with drugs recommended for the treatment of menorrhagia throughout the ages. There are a limited number of studies that have explored women's experiences in accessing care for AUB. Improving access to care will require multi-level approaches that include consideration of local socio-cultural needs with improved training for primary healthcare providers.

In addition, consequent to failure of medical therapy, an increasing number of surgical procedures have developed. Although hysterectomy is associated with increasing patient satisfaction, it is beset with unprecedented morbidity and mortality. The last two decades have witnessed development of less invasive minimal access techniques that conserve the uterus facilitating shorter in-patient care and faster recovery. Training in hysteroscopic surgery, knowledge about the indications, contraindications, and limitations are essential prerequisites to ensure the safety and sound care of the patients. Adolescent menstrual disorders are relatively commonly handled by primary care physicians, in many instances reassurance is all that is required. Otherwise, those presenting with protracted bleeding require referral to tertiary centres for further assessment of rare haematological, endocrine, or structural abnormalities.

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None declared

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Not applicable

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REFERENCES

1. Liu Z, Doan QV, Blumenthal P, Dubois RW. A systemic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding. Value Health 2007; 10(3): 183-94.
2. Shaplay M, Jordan K, Croft PR. An epidemiological survey of symptoms of menstrual loss in the community. Br J Gen Pract 2004 May; 54(502): 359-63.
3. Munro MG, Critchley HO, Fraser IS. Committee FMD. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int J Gynaecol Obstet 2018 Dec; 143(3): 393-408.
4. Munro M, Critchley HO, Broder MS, Fraser IS. FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet 2011 Apr; 113(1): 3-13.
5. Fraser IS, Critchley HO, Broader M, Munro MG. The FIGO recommendations on terminologies and definitions for and abnormal uterine bleeding. Semin Reprod Med 2011; 29(5): 383-90.
6. Joseph S. Women and Sabarimala: The science behind restrictions. Notion Press, 1st ed., Nov 2019.
7. Thapa S, Aro AR. 'Menstruation means impurity': multilevel interventions are needed to break the menstrual taboo in Nepal. BMC Womens Health. 2021 ;21(1):84.
8. Delfin Tan, Rohana H, Fraser IS. Cultural aspects and mythologies surrounding menstruation and abnormal uterine bleeding. Best Pract Res Clin Obstet Gynaecol 2017; 40: 121-133.
9. Cattanach J. Oestrogen deficiency after tubal ligation. Lancet 1985; 1(8433): 847-9.
10. Euling SY, Herman-Giddens ME, Lee PA, Selevan SG, Juul A, Sorenson et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: Panel findings. Pediatrics 2008 Feb; 121 Suppl 3: S172-91.
11. Fritz MA, Speroff L Abnormal uterine bleeding 2012. In Clinical Gynecologic Endocrinology and Infertility. 8th ed. Wolters Kluwer, Lippincott Williams & Wilkins: 591-619.
12. Haynes PJ, Anderson ABM, Turnbull AC. 1979, Patterns of menstrual blood loss in menorrhagia. Research and Clinical Forums I: 73-78.

13. Kaunitz AM. Abnormal Uterine Bleeding in Reproductive-Age Women. JAMA 2019 Jun 4; 321(21): 2126-7.
14. Dubinsky T, Abu-Gazzeh, Stroehlein K. Role of transvaginal sonography and endometrial biopsy in the evaluation of dysfunctional uterine bleeding in premenopausal women. J Clin Ultrasound 1998; 280: 1510.
15. de Vries LD, Dijkhuizen FB, Mol BW, Brolmann HA, Moret E, Heintz AP. Comparison of transvaginal sonography, saline infusion sonography, and hysteroscopy in premenopausal women with abnormal uterine bleeding. J Clin Ultrasound 2000 Jun; 28(5): 217-23.
16. Lindheim SR, Kavic S, Shulman SV, Saucer MV. Operative hysteroscopy in the office setting. J Am Assoc Gynecol Laparoscopists 2000 Feb; 7(1): 65-9.
17. Fraser IS, Kovacs GT. The efficacy of non-contraceptive uses for hormonal contraceptives. Med J Aust 2003 Jun 16; 178(12): 621-3.
18. Bitzer G, Heikinhermo O, Nelson AL, Lalif-Asina J, Fraser IS. Medical management of heavy menstrual bleeding: A comprehensive review of the literature. Obstet Gynecol Surv 2015 Feb; 70(2): 115-30
19. Aksu F, Madazli R, Budak E, Cepni I. High-dose medroxyprogesterone acetate for the treatment of dysfunctional uterine bleeding in 24 adolescents. Aust N Z J Obstet Gynaecol 1997 May; 37(2): 228-31.
20. Cohen BJB, Gibor Y. 'Metabolic and endocrine effects of medicated intra-uterine device'. In Benagiano G, Diczfalusy E (eds.) Endocrine mechanism in fertility regulation. New York: Raven Press, 71-124.
21. Nilsson CM, Solyell L. 'Clinical studies on oral contraceptives-a randomized, double blind, crossover study of four different preparations'. Acta Obstetrica Gynecologica Scand 1967: 1-31.
22. Fergusson RJ, Lethaby A, Shepperd S, Farquher C, . Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. Cochrane Database Systemic Review 2013 Nov 29; CD000329.
23. Fraser IS, Pearce C, Shearman RP, Elliot PM, Mcllveen J, Markham R, . Efficacy of mefenamic acid in patients with a complaint of menorrhagia. Obstet Gynecol 1981 Nov; 58(5): 543-51.
24. Hall P, Malachlan N, Thorn N, Nudd MWE, Taylor CG, Garrioch DM .l. Control of menorrhagia by the cyclo-oxygenase inhibitors naproxen sodium and mefenamic acid. Br J Obstet Gynaecol 1987 Jun; 94(6): 554-8.
25. Coulter A, Kelland J, Peto V, Rees MC. Treating menorrhagia in primary care. An overview of drug trials and a survey of prescribing practice. Int J Technol Assess Health Care Summer 1995; 11(3): 456-71.
26. Milsom I, Anderson ABM, Andersch B, Rybo G. A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. Am J Obstet Gynecol 1991 Mar; 164(3): 879-83.
27. Chimbira TH, Anderson ABM, Naish N, Turnbull AC. Reduction of menstrual blood loss by danazol in unexplained menorrhagia: Lack of effect of placebo. Br J Obstet Gynaecol 1980 Dec; 87(12): 1152-8.
28. Sowter MC, Lethaby A, Singla AA. Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. Cochrane Database System Reviews 2002; (3): CD001124.
29. Cameron IT, Leask R, Kelly RW, Baird DT. The effects of danazol, mefenamic acid, norethisterone and a progesterone-impregnated coil on endometrial prostaglandin concentrations in women with menorrhagia. Prostaglandins 1987 Jul; 34(1): 99-110.
30. Kouides PA, Byaras VR, Philips CS, Stein SF, Heit JA, Lukes AS, et al. Multisite management study of menorrhagia with abnormal laboratory haemostasis: A prospective crossover study of intranasal desmopressin and oral tranexamic acid. Br J Haematol 2009 Apr; 145(2): 212-20.
31. Harrison RF, Cambell S. A double-blind trial of ethamsylate in the treatment of primary and intrauterine-device menorrhagia. Lancet 1976 Aug 7; 2(7980): 283-5.
32. Anderson JK, Rybo G. Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia. Br J Obstet Gynaecol 1990 Aug; 97(8): 690-4.
33. Lower AM. Laparoscopic myomectomy. In Progress in Obstetrics and Gynaecology Studd J (ed), 2003; Churchill Livingstone, 15: 381-88.
34. Goldrath M, Fuller TA, Segal S. Laser photovaporization of endometrium for the treatment of menorrhagia. Am J Obstet Gynecol 1981 May 1; 140(1): 14-9.
35. Downes E, O'Donovan P. Microwave endometrial ablation in the management of menorrhagia: Current status Curr Opin Obstet Gynecol 2000 Aug; 12(4): 293-6.
36. Magos AL, Lockwood GH, Baumann R.Absorption of irrigating solution during transcervical resection of endometrium. Br Med J 1990. 300: 1079.

Multiple Choice Questions:

1. Abnormal uterine bleeding (AUB) encompasses cyclic and non-cyclic bleeding.
   A. Anovulatory bleeding is the most common type of non-cyclic uterine bleeding.
   B. Menorrhagia is defined as excessive cyclical uterine bleeding more than 100 ml or above.
   C. In many women, the underlying cause is still unknown.
   D. Polyp, adenomyosis. and coagulopathy are some of the possible causes of AUB.
   E. Treatment mainly involves surgical procedures.

2. Dysfunctional uterine bleeding (DUB)
   A. It is an excessive, prolonged, or erratic endometrial bleeding with no organic, general, or local lesions.
   B. DUB is common in all age groups during the reproductive phase.
   C. It is due to abnormalities of the hypothalamus-pituitary-ovary-endometrial axis.
   D. Gestagen therapy (progestogen) is one of the medical forms of therapy.
   E. Minimal access techniques have no role as alternative therapies.

3. AUB in a 48-year-old woman came with an endometrial biopsy, whose histopathological examination (HPE) revealed as 'endometrial hyperplasia', and she came for counselling.
   A. The knowledge of pathogenesis and type of 'endometrial hyperplasia' is irrelevant in advising modality of further treatment.
   B. Role of informed consent is disregarded.
   C. First- and second-generation ablative techniques as day-care procedures is advised.
   D. Endometrial hyperplasia without atypia could be treated with progestins/medroxyprogesterone acetate (MPA)/LNG-IUS.
   E. Reconsideration for hysterectomy in the presence of persistent or non-regressive symptoms is advisable.

4. AUB in adolescent girls
   A. Anovulation and oestrogen excess secondary to a lack of maturation of the negative feedback in the hypothalamus-pituitary axis.
   B. Coagulation defects is the cause in up to 20% mainly due to ITP and Von Willebrand's disease.
   C. The possibility of a pregnancy must be ruled out.
   D. Thyroid dysfunctions must be excluded.
   E. Close follow-up, iron supplementation, and reassurance are adequate in many instances.

5 Endometrial hyperplasia
   A. In anovulatory type of DUB, the histological changes are described as 'cystic glandular hyperplasia'.
   B. Cystic glandular hyperplasia can be treated by endometrial resection and ablation.
   C. Simple endometrial and adenomatous hyperplasia without atypia are usually precursors of endometrial malignancy.
   D. Cytologic atypia or atypical adenomatous hyperplasia are best treated by hysterectomy.
   E. Dilatation and curettage can be employed when the histological features are unknown.

The eyes that saw the kidneys

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SUMMARY

Renal involvement in sarcoidosis is very uncommon and often diagnosed through renal biopsy. It is a chronic and multisystem disease with unknown aetiology and can affect all organs of the body with strong predilection to the lungs. Although glucocorticoids are effective in the treatment of sarcoidosis, the mainstay of management includes supportive hydration and prevention of nephrotoxins. We report a case of a young man who was admitted with an ocular and renal impairment secondary to sarcoidosis.

INTRODUCTION

Sarcoidosis is a rare multisystem disease caused by noncaseating granulomas with highly variable course. Its aetiology remained unknown and renal involvement is uncommon. We present a case of a 32-year-old male patient admitted with ocular symptoms and renal impairment secondary to sarcoidosis.

CASE REPORT

A 32-year-old Indian man was referred to the Ophthalmology clinic for eye assessment with a complaint of incidental finding of left eye small whitish spots. There was no history of recent eye redness, photophobia, blurring of vision, floaters, or trauma. On examination, his visual acuity was 6/9 with glasses bilaterally. Anterior segment examination showed old mutton-fat pigmented keratic precipitates with anterior chamber cells of 1+ and presence of pigmented anterior vitreous cells of 1+ bilaterally. Fundus examination revealed bilateral hyperaemic discs and periphlebitis around the optic disc with candle wax dripping appearance. There was one focal small choroiditis seen at the peripheral fundus of right eye superiorly. Optical coherence tomography revealed no evidence of cystoid macular oedema. Unfortunately, he had not consented for fundus flurescein angiography for further evaluation.

Further questioning revealed that he had history of frothy urine three months prior to presentation. His blood investigations in Ophthalmology clinic showed normal range of complete blood count, liver function test, erythrocyte sedimentation rate, and C-reactive protein. His Mantoux test result was 0 mm. He was started on topical corticosteroids by the Ophthalmologist in view of good visual acuity with no macula oedema. Renal profile however showed raised serum creatinine 156 µmol/L, and he was referred to the Nephrology clinic for further evaluation.

On review in Nephrology clinic, he denied any constitutional symptoms of weight loss, night sweats, altered bowel habit, joint pain, alopecia, and oral ulcerations. He denied taking any regular medications or supplements. His family history was not significant for any renal disease. He is the fourth of six siblings, and he worked as a painter. He was a non-smoker and denied indulging in any high-risk behaviour. Clinical examination was unremarkable.

Further investigation revealed that serum creatinine rose to 180 µmol/L, which later peaked at 206 µmol/L and mild hypercalcaemia (serum calcium 2.61 mmol/L). Other blood investigations were not significant: phosphate level of 0.87 mmol/L, alkaline phosphatase 68 U/L, hepatitis B, C and human immunodeficiency virus screening negative, intact parathyroid hormone not elevated, serum antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) negative, and serum and urinary paraproteins not detected. Urinalysis revealed urine protein 1+ and blood trace, and urine protein creatinine index (PCI) was mildly elevated at 0.06 g/mmol Cr. His 24-hour urine calcium was elevated at 17.7 mmol/day (normal range 2.5–8.0 mmol/day). Ultrasound of his kidneys showed normal kidney size with no obstructive uropathy. His chest radiograph showed normal heart size with no perihilar lymphadenopathy. A baseline spimometry also showed normal lung function capacity. Serum angitensin-converting enzyme (ACE) was elevated at 124 U/L (normal range 16–85 U/L).

Renal biopsy was performed and showed granulomatous inflammation with tubulointerstitial nephritis and no morphological features of glomerulonephritis. Immunofluorescence stains were inconclusive but the Ziehl-Nelson stain was negative. A diagnosis of systemic sarcoidosis with ocular and renal involvement was made.

He was started on prednisolone at a dose of 20 mg (0.5 mg/kg/day) and later discharged with outpatient follow-up. He remained asymptomatic with no other organ involvement. However, his renal function did not normalised despite being treated with prednisolone for six months. At 16 months after initial presentation, his creatinine rose to 173 µmol/L but there was no proteinuria. It was decided for a repeat course of prednisolone, but starting dose was 1 mg/kg/day. His renal function improved within a month, and the prednisolone was tapered rapidly within two months. The latest outpatient review at 20 months after initial presentation showed a stable renal function (creatinine 121 µmol/L and urinary protein-creatinine ratio of 7 mg/mmol). His uveitis remained stable with no worsening of vision.

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Table I: Treatment Algorithm for Sarcoidosis

First line:
Glucocorticoids:
Oral prednisolone 0.5–1.0 mg/kg/day
Taper dose by 5 mg per week after 4 weeks (unless no clinical improvement)
Duration of treatment: 6–12 months
Consider IV Methylprednisolone 500–1000 mg/day for 3 days followed by oral prednisolone 1 mg/kg/day (in those with major organ involvement)
Second line:
Steroid-sparing agents:
Azathioprine 2 mg/kg/day (maximum 200 mg/day)
Methotrexate 10–20 mg/week (to be supplemented with folic acid)
Mycophenolate mofetil 1000 mg BD
*Taper glucocorticoid dose by 5 mg weekly until 5–10 mg daily
Third line:
Tumour necrosis factor – alpha inhibitor:
Infliximab 3–5 mg/kg at weeks 0, 2, 6 and every 6–8 weeks thereafter

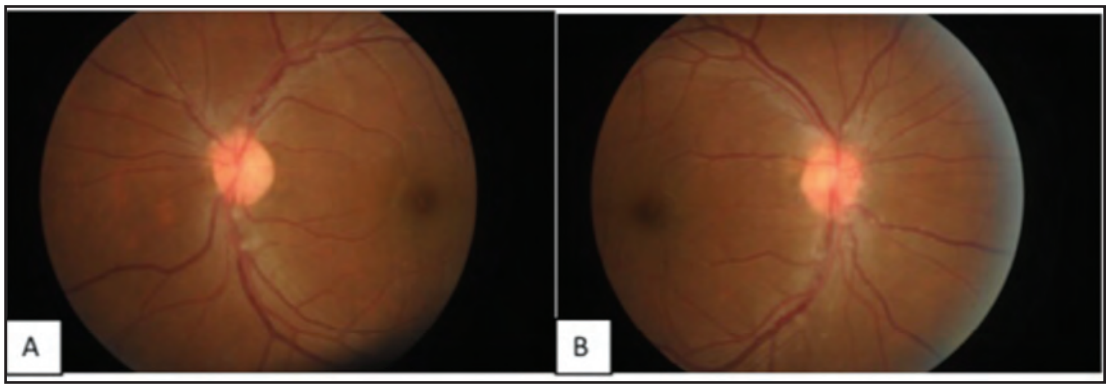

Fig. 1: Fundal image
Bilateral hyperemic optic disc with segmental area of periphlebitis in the (A) left and (B) right eye.

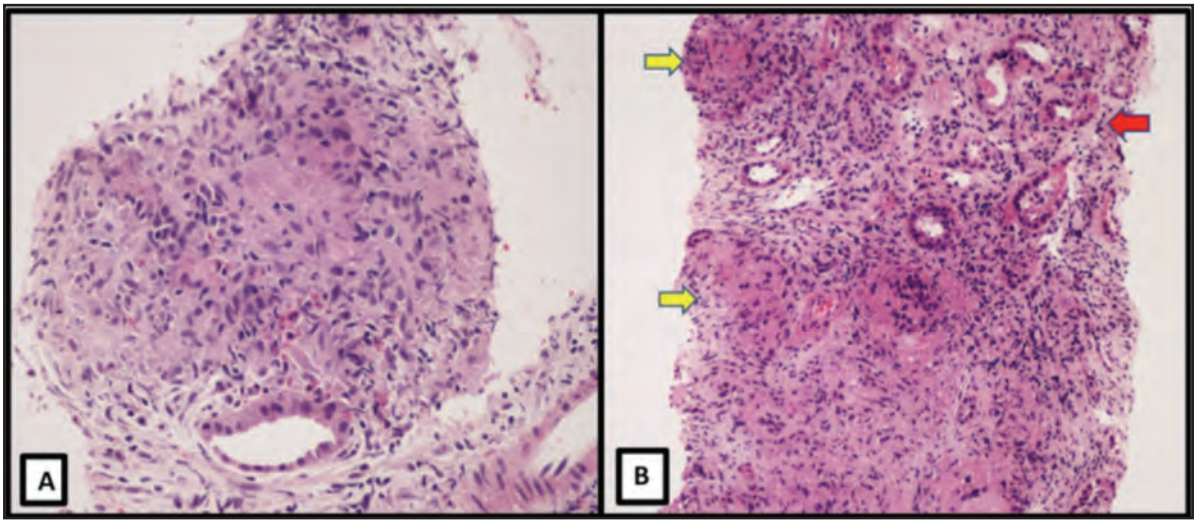

Fig. 2: Light microscopy of kidney biopsy specimen
There are numerous nodules seen in renal cortical tissue, which mainly comprised of epithelioid histiocytic granulomata (yellow arrow) in (B) with some interstitial inflammation. Renal tubules are readily seen (red arrow). In (A), the granuloma is composed of aggregates of epithelioid histiocytes admixed with multinucleated giant cells and scattered lymphocytes. No definite necrosis is seen. (A) Hematoxylin-eosin stain (H&E; original magnification, x200) and (B) H&E (original magnification, x100).

DISCUSSION

The incidence of sarcoidosis varies according to geographical regions and is affected by gender and race. It is very uncommon in Malaysia but patients of Indian race appeared to be more susceptible to sarcoidosis compared to other ethnicities.[1] Because of its heterogeneity of multiorgan involvement, many cases remained undiagnosed. It is believed that the disease is now much more prevalent with higher mortality rates than previously reported.[2] Although majority had benign self-limiting course of disease, up to a third of the patients will develop chronic disease leading to significant organ failure. Sarcoidosis appears more common in young adults.[3]

The diagnosis of sarcoidosis is not standardised and often by exclusion. Three major criteria needed to aid the diagnosis include a compatible clinical presentation, the finding of non-necrotising granulomatous inflammation on tissue biopsy, and exclusion of alternative causes of granulomatous disease.[3] Diagnosing sarcoidosis is often a challenge due to the many clinical and radiological similarities it shared with tuberculosis, a highly prevalent chronic granulomatous disease in Malaysia.[1] Sarcoidosis involving both renal and eye disease is extremely rare. We believe this is the first case reported in our country.

Renal sarcoidosis has a wide spectrum of clinical manifestations ranging from asymptomatic state to progressive and relapsing disease. The most typical form of renal sarcoidosis is the granulomatous interstitial nephritis, followed by secondary glomerulonephritis such as IgA nephropathy and membranous nephropathy. Impaired calcium homeostasis, occured as a result of abnormal vitamin D production due to over-expression of 1-alpha-hydroxylase, often lead to nephrolithiasis and nephrocalcinosis. In addition, calcium precipitates may obstruct both the proximal and distal tubules and cause acute tubular necrosis. Amyloidosis is a rare manifestation of renal sarcoidosis.[4,5]

Urinary abnormalities are not specific as seen in our case. One should remember that bland urine sample does not exclude renal involvement. Serum angiotensin-converting enzyme is also not specific to sarcoidosis as it can be elevated in other granulomatous disorders and even in end-stage kidney disease of varying causes. Nonetheless, it can still be useful as a marker of disease severity and to assess treatment response.[5]

Histopathological evaluation is often required to establish the diagnosis. A typical sarcoidosis granuloma has well-formed, concentrically arranged layer of immune cells, most prominent being the central core of macrophage aggregates and multinucleated giant cells, and often non-necrotic. Again, one should remember that absence of such renal biopsy findings does not exclude the the diagnosis as lesions can be focal and missed on biopsy.[3,5]

In 2017, the International Workshop on Ocular Sarcoidosis (IWOS) published a revised criteria for diagnosing ocular sarcoidosis. This criteria was based on seven clinical signs and eight systemic investigation results, and other causes of granulomatous uveitis must be ruled out.[6] In this case, our patient had three ocular clinical signs: mutton-fat keratic precipitates, segmental periphlebitis with candle wax dripping and bilateral involvement, and fulfilled two systemic investigation in suspected ocular sarcoidosis, which was negative tuberculin test and elevated serum ACE. In terms of ocular management, his initial treatment was topical corticosteroids as there was significant anterior chamber inflammation with no cystoid macula oedema formation. Subsequent treatment with oral corticosteroid was indicated after confirming the diagnosis of renal sarcoidosis, and his eye manifestations of hyperaemic disc and periphlebitis were resolved.[7]

Although there is no strong evidence from randomised controlled trials, management of renal sarcoidosis has been largely focussed on optimising hydration to treat hypercalcaemia and hypercalciuria as well as using corticosteroids in treating interstitial nephritis. Intravenous saline hydration is often the first initial therapy in these patients as hypercalcaemia often leads to dehydration. Concomitant loop diuretics will help enhance urinary calcium excretion. Use of thiazide diuretics should be avoided in these patients. Glucocorticoids are used to reduce calcium absorption by inhibiting the activity of 1-alpha hydroxylase. Dose and duration of treatment remain unestablished, but many recommended initiation dose of 0.5–1.0 mg/kg/day. Other preventive measures include low dietary calcium and vitamin D intake and limiting exposure to sunlight.[5]

Glucocorticoids, namely prednisolone, remain the most effective treatment for interstitial nephritis. However, other immunosuppressive drugs such as methotrexate, azathioprine, and mycophenolate mofetil are also used as steroid-sparing agents or in patients who have failure or contraindications to glucocorticoids. The evidence for these agents is limited to case series only. Tumour necrosis factor (TNF) alpha inhibitor such as infliximab has been used in several case studies in treatment of steroid-resistant sarcoidosis. TNF is thought to be responsible in granuloma formation, and therefore, its inhibition is postulated to be helpful in these resistant cases.[5] Another biologic agent of interest is adalimumab, but more data on its efficacy are required. Refer to Table I for comparison of agents.

Although majority of patients undergo disease remission, it is not uncommon that some patients progress to end-stage kidney disease. These patients are commonly elderly and have failed to respond to first-line treatment, or they have multiorgan involvement. Another poor prognostic factor is presence of kidney scarring at presentation. Morbidy from chronic sarcoidosis can also be substantial, and this is often more prominent in those with lower socioeconomic status.[8,9]

CONCLUSIONS

Sarcoidosis with renal and ocular involvement is rare. Renal biopsy, in this case, is vital to establish the diagnosis and initiate prompt treatment. Management via multidisciplinary approach is of paramount importance.

ACKNOWLEDGEMENTS

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REFERENCES

1. Liam CK, Menon A. Sarcoidosis: A review of cases seen at the University Hospital, Kuala Lumpur. Singapore Med J 1993; 34: 153-6.
2. Fidler LM, Balter M, Fisher JH, To T, Stanbrook MB, Gershon A. Epidemiology and health outcomes of sarcoidosis in a universal healthcare population: A cohort study. Eur Respir J 2019; 54: 1900444 [https://doi.org/10.1183/13993003.00444-2019].
3. Crouser ED, Maeir LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis: An official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 2020; 201(8): e26-e51.
4. Bergner R, Löffler C. Renal sarcoidosis: Approach to diagnosis and management. Curr Opin Pulm Med 2018; 24(5): 513-20.
5. Hinderson I, Van Laecke S, Wauters A, Donck J. Treatment of renal sarcoidosis: Is there a guideline? Overview of the different treatment options. Nephrol Dial Transplant 2014; 29: 1841-7.
6. Mochizuki M, Smith JR, Takase H, Kaburaki T, Acharya NR, Rao NA, et al. Revised criteria of International Workshop on Ocular Sarcoidosis (IWOS) for the diagnosis of ocular sarcoidosis. Br J Ophthalmol 2019; 103(10): 1418-22.
7. Takase H, Acharya NR, Babu K, Bodaghi B, Khairallah M, McCluskey PJ, et al. Recommendations for the management of ocular sarcoidosis from the International Workshop on Ocular Sarcoidosis. Br J Ophthalmol 2021; 105: 1515-9.
8. Gerke AK. Morbidity and mortality in sarcoidosis. Curr Opin Pulm Med 2014; 20(5): 472-8.
9. Papalia T, Greco R, Mollica A, Bonofiglio R. Acute renal failure in sarcoidosis: A review of the literature. Arch Clin Nephrol 2016; 2(1): 011-6.

A case report of acquired Haemophilia A: A rare medical emergency

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SUMMARY

Acquired Haemophilia A (AHA) is a rare potentially life-threatening bleeding disorder caused by the presence of autoantibodies against coagulation factors. It is usually characterised by severe spontaneous haemorrhage, which can lead to high morbidity and mortality. The diagnosis is often challenging. Treatment requires vigilant and accurate laboratory investigations, control of bleeding episodes, and eradication of inhibitors using bypassing agents and/or immunosuppressive agents. Hereby, we present a case report of unusual bleeding episodes with isolated raised activated partial thromboplastin time (APTT).

INTRODUCTION

Acquired haemophilia A (AHA) is a rare but serious autoimmune bleeding disorder caused by the spontaneous formation of autoantibodies directed against plasma coagulation factors, i.e. factor VIII (FVIII). The condition is usually idiopathic but is commonly associated with autoimmune diseases, pregnancy, malignancy, infections, and dermatological conditions.[1] Genetic and environmental factors, along with the immune response in elderly individuals, are thought to lead to breakdown in immune tolerance, causing development of autoantibodies against FVIII.[2]

AHA has reported an incidence of 1.5 cases per million persons per year, which increases with increasing age and is primarily seen in patients aged 60 to 80 years. There is neither any hereditary pattern nor gender preponderance. Mortality rate is 8–22%.[3] Majority of the cases affect the adult population unlike congenital haemophilia. Median age at presentation is 60–67 years. Two peaks in AHA incidence are typically observed: one associated with pregnancy and another with older age (>60 years).[4]

Patients typically present with spontaneous bleeding or even asymptomatic with an isolated prolonged activated partial thromboplastin time (APTT) due to acquired FVIII deficiency. The bleeding phenotype of AHA is variable, ranging from life-threatening bleeds to mild or no bleeding. Subcutaneous hematomas are characteristic of AHA and can be the first sign of the disease. An isolated prolonged APTT is almost pathognomonic to AHA. Neutralising antibodies (inhibitors) are detected using the Nijmegen-modified Bethesda assay. A prolonged APTT should never be ignored prior to invasive procedures.[4]

The main goal of therapy is to control acute bleeding and prevent injury, whereas the mainstay of treatment is bypassing agents, including recombinant activated factor VII (rFVIIa), activated prothrombin complex concentrate (APCC), or recombinant porcine FVIII (rpFVIII) in bleeding patients.

AHA represents a clinical challenge, as lack of familiarity of AHA can result in delayed diagnosis and/or inadequate treatment, contributing to high mortality and morbidity rates. Hence, we report a case report of an elderly with AHA with an underlying skin condition.

CASE REPORT

This is a 75-year-old gentleman with underlying hypertension, chronic kidney disease stage 4 (stable), bilateral knee osteoarthritis, gouty arthritis, and plaque psoriasis (in remission), presented to outpatient clinic with progressive and spontaneous bruises with mild swelling over the medial aspect of bilateral forearm for the past 2 weeks. Prior to the presentation, he experienced dactylitis and tenderness of the small joints of the fingers for the past 1 month. He also had recent flare up of the skin psoriasis in the past 2 month, which resolved after topical application of steroid cream and emollients. Otherwise, there is no evidence of septic arthritis nor clinical features of tophaceous gout.

He visited family physician and was given intramuscular Diclofenac for pain relief; however, the pain was partially relieved and progressive worsening bruises spread to medial aspect of thigh, left flank, and medial aspect of bilateral forearm. Clinically, it showed haematoma and ecchymosis over the flank (Figure 1), medial thigh, right forearm, and left medial arm.

His previous medications included T. Furosemide 40 mg daily, T. Amlodipine 10 mg daily, T. Calcium Carbonate 500 mg twice daily, T. Rocaltriol 0.25 µg every other day, and T. Allopurinol 150 mg daily. He had no history of spontaneous bleeding, malignancy or blood disorder, and blood transfusion. He denied taking over the counter medications, steroids, non-steroidal anti-inflammatory drugs (NSAID), or traditional herbs.

The initial blood investigations are as follows: Haemoglobin (Hb) 11.0 g/dL, WBC 6.6 x 10^9/L, Plt 178 x 10^9 /L, HCT 34.5%, INR 0.97, Prothrombin time (PT) 13.0 s, Partial

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Table I: Blood investigations

Haemoglobin	11.0	6.7	Reticulocytes	2.8%
White blood cells	6.6	16.8	LDL	238
Platelet	178	228	D-Dimers	0.2
Haematocrit	34.5%	20.3	ANA	Negative
Prothrombin time	13.0s	12.5	CEA	3.9
Partial Thromboplastin Time	70.7s (high)	48.0 (high)	CA 19-9	9.5
INR	0.97	0.92	AFP	<1.7
Urea	8.5	18.7		
Creatinine	149.4	250	Lupus anticoagulant	Negative
Sodium	140	138	Anti-cardiolipin	Negative
Potassium	3.8	4.2	Anti-beta-2 glycoprotein 1 antibodies	Negative
Chloride	101	101		

PTT mixing study	**Full blood pictures**
APTT mixing	42s	Reactive leucocytosis. No evidence of haemolysis.
Rosner index	12.3%	
APTT mixing (2 hour) 53.5s (high)	
Rosner index(2 hour) 29.5% (high)	
Factor VIII	3% (low)
Factor IX	104%(normal)
Factor VIII inhibitor	5.8 BU

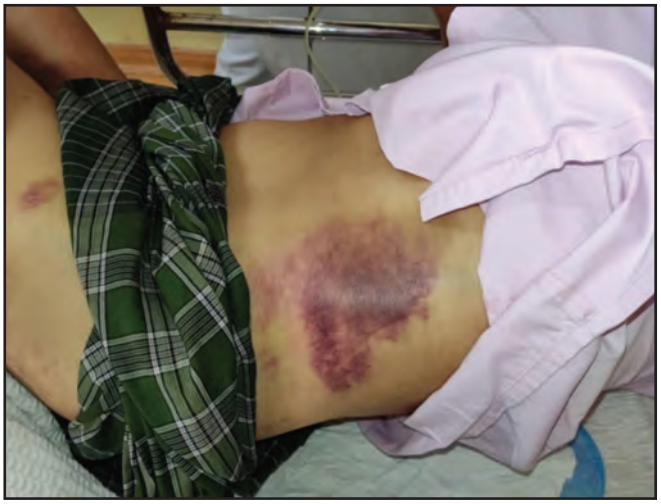


Fig. 1: Haematoma and ecchymosis over left flank.

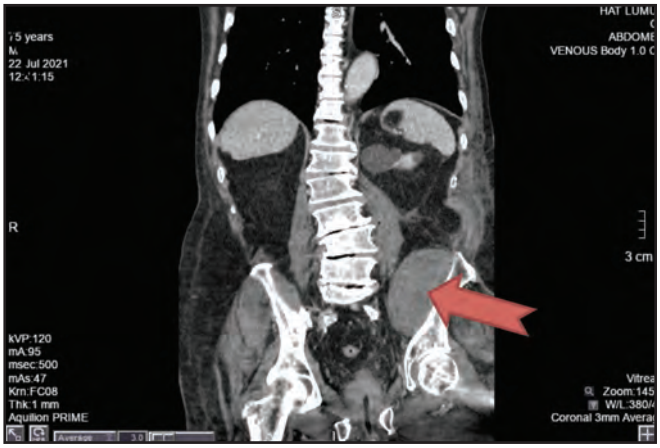


Fig. 2: Haematoma of the left Iliac muscle.

Thromboplastin Time (PTT) 70.7 s, Urea 8.5 mmol/L, Creatinine 149.4 µmol/L, Na 140 mmol/L, Potassium K 3.8 mmol/L, Chloride 101 mmol/L.

We repeated laboratory workup and noticed that Hb dropped abruptly from baseline 11.0 g/dL to 6.7, HCT 34.5% to 20.3%, leucocytosis WBC raised to 16.8 x 10^9, and Urea raised from 8.5 to 18.7 mmol/L. Notably, isolated raised PTT 48.0 s, PT 12.5 s, INR 0.92.

A PTT mixing study was immediately performed, which showed isolated raised APTT was not corrected. Rosner index was more than 15%. Low factor VIII was 3%. Bethesda assay revealed factor VIII inhibitor of 5.8 Bethesda Unit (BU). Features are consistent with Acquired Haemophilia A (AHA) (Table I).

Other relevant investigations include Full Blood Pictures showing no evidence of haemolysis, Reticulocytes 2.8%, LDH 238, D-dimers 0.2 (negative). TFT was normal. Infective screening was non-reactive. ANA was negative. Tumour markers CEA 3.9 IU/ml, CA 19-9 9.5 IU/ml, AFP <1.7 IU/ml. Thrombophilia screening showed that Lupus Anticoagulant (LA) antibodies, anti-cardiolipin antibodies, and anti-beta-2-glycoprotein 1 antibodies were all negative.

Urgent CT abdomen and pelvis with contrast showed enlarged left iliacus muscle due to acute intramuscular haematoma measuring 4.5 (AP) x 5.6(W) x 10.4(H) cm at its anterior aspect (Figure 2); enlarged left quadratus lumborum muscle due to subacute intramuscular haematoma measuring 1.6 (AP) x 2.6 (W) x 2.5 (H) cm at its anterior aspect; and enlarged left external oblique muscle due to

subacute intramuscular haematoma measuring 1.1 (AP) x 6.0(W) x 3.8 (H) cm over the left 10th intercostal space laterally. No free fluid was found. Abdominal aorta and its main branches are patent with no thrombosis. No extraluminal contrast extravasation on arterial phase nor pooling of contrast on portal venous and delayed phase was observed to suggest internal abdominal bleeding.

We ruled out any source of infection that could lead to sepsis causing Disseminated Intravascular Coagulation (DIC). There is no sign and symptoms of sepsis and afebrile. CRP was not raised. Fibrinogen degradation product was not significantly elevated, and D-dimers was negative. We checked any medications that could induce ecchymosis or purpura including steroids, NSAIDs, and anticoagulants such as warfarin. However, other than the intramuscular injection of Diclofenac for pain relief for his joint pain, the patient denied taking any medications.

TREATMENT

The patient was admitted for close observation of any worsening signs of bleeding. Our first priority is haemostatic treatment. We aimed at preventing further iatrogenic causes of bleeding in the ward and control of acute bleeding. Venepuncture only be taken by experienced medical officers and as indicated. Blood pressure cuff measured only as often as when deemed clinically relevant to prevent worsening of ecchymosis. We applied cold compression over the haematoma sites.

The patient was started intravascular Tranexamic acid 500mg three times a day and intravascular Hydrocortisone 100 mg three times a day, completed for 1 week. We also transfused 5-pint packed cells, 4 unit of Fresh Frozen Plasma (FFP), and 2 unit of Cryoprecipitates. After diagnosis, AHA is confirmed, and he was started immunosuppressant IV Cyclophosphomide 150 mg daily for 1 week. He was closely monitored for any signs of worsening bleeding. During the hospitalisation, he has no clinical evidence of worsening ecchymosis and haematoma. The bruises over bilateral upper limb were reducing in size and non-tender. Hb was static (Hb 9.7–10.8) after transfusion, and platelet count was within normal range (250– 290). aPTT was not worsening, ranging 48.3–50, PT 13–13.7, INR 0.98–1.03. Total protein 58.ALP 80 AST 23. Total bilirubin 22. He was discharged well after 10 days of hospitalisation.

During the follow-up at the clinic, he has neither new bruises nor bleeding. There are residual bruises over left thigh, but not increasing in size, and not limiting his range of motion.

DISCUSSION

The above case presentation showed sign of haemorrhage with typical isolated prolonged aPTT, which can be missed at a clinical setting. Prevalence and occurrence rates in Malaysia are still unknown. However, there are three reports found in the literature describing the same disease from 1995 till recent 2015.[3,5,6]

No exact aetiology could explain the condition, approximately half of patients with AHA have concomitant disorders, most often other autoimmune disorders or malignancy. Some literature revealed there is a relationship between genetic and environmental factors, which might lead to failure in immune tolerance and cause development of autoantibodies against FVIII. Some human leukocyte antigen (HLA) class II alleles and single-nucleotide polymorphisms of the cytotoxic T lymphocyte antigen 4 (CTLA-4) have been observed in a higher frequency in AHA.[2,7] In this case presentation, we can correlate the patient's recent flare-up of plaque psoriasis, which is an autoimmune condition that could possibly contribute to AHA.

AHA is frequently confused with other life-threatening conditions (e.g., disseminated intravascular coagulation) and typically occurs in an elderly population, thus can lead to severe morbidity and even mortality before it is correctly diagnosed. Estimates of the mortality associated with acquired haemophilia range from 8% to 22%, with most haemorrhagic deaths occurring within a few weeks of presentation.[8] If left untreated, bleeding was the cause of death in 9% of the cohort and remained a risk until the inhibitor had been eradicated.[9]

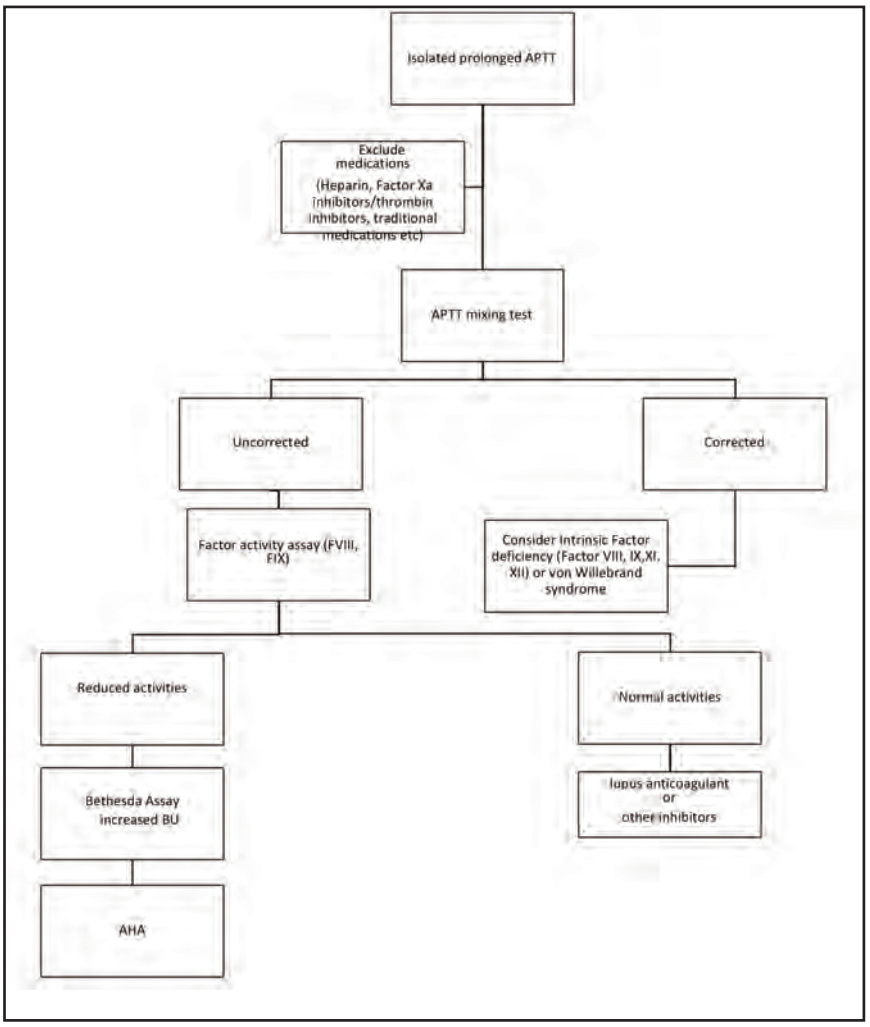
Typically, patients with AHA present with acute or recent bleeding symptoms, without a previous bleeding history, with laboratory investigation showing an isolated prolonged APTT. The bleeding pattern is characterised with subcutaneous bleeds being most common (observed in 80% of patients), followed by muscle, gastrointestinal, genitourinary, and retroperitoneal bleeds. Hemarthrosis, which is the hallmark of Congenital Haemophilia, is much less common in AHA.[4]

Coagulation factor deficiencies or coagulation factor inhibitors, including autoantibodies, LA, or pharmacological anticoagulants, may result in prolonged APTT. To distinguish a factor deficiency from the presence of an inhibitory substance, diagnostic aPTT mixing test is indicated. The diagnostic algorithm is shown in Table II.

In aPTT mixing test, varying amounts of patient plasma and pooled normal plasma are mixed, and the aPTT was measured. After mixing, measurement of the aPTT should be performed not only immediately but also after incubation at 37ºC for one to two hours. The second measurement is necessary to detect factor VIII inhibitors with slow reaction kinetics. Correction of the prolonged aPTT suggests a factor deficiency or VWD, while persistent prolongation of the aPTT indicates the presence of an inhibitor. The mixing test will establish whether an inhibitor is present but will not identify the inhibitor's specificity.

The Bethesda assay both establishes the diagnosis of a factor VIII inhibitor and quantifies the antibody titre. The Bethesda assay was developed to detect and quantify FVIII alloantibodies and thus useful in detecting FVIII inhibitors in AHA. A serial dilutions of patient plasma are incubated with pooled normal plasma at 37ºC for two hours; factor VIII activity is then measured using a clotting assay as one would in a patient with hereditary factor VIII deficiency. The

Table II: Blood investigations



reciprocal dilution of patient plasma that results in 50% factor VIII activity is defined as one Bethesda unit (BU). The stronger the inhibitor, the greater the dilution required to allow for factor VIII activity.

The first priority of management is to control acute bleeds and to prevent injury in the measure of limited iatrogenic cause of bleeding injury, haemostatic therapy, tranexamic acid, and blood transfusion if indicated. The second goal of treatment would be to reduce or to eliminate the inhibitor using bypassing agents, for example, APCC (FEIBA) or recombinant activated factor VII (NovoSeven).4 Corticosteroid therapy with prednisolone or prednisone 1 mg/kg/day PO for 4–6 weeks was suggested in the 2009 international AHA recommendations. In the Society for Thrombosis and Haemostasis Research e.V. study, it is recommended that patients not responding to steroids after 3 weeks were escalated to second-line therapy with cyclophosphamide, and later rituximab.[4]

In this case study, the bypassing agents such as APCC (FEIBA) or NovoSeven were not given due to the high-cost consideration. Despite this, the patient started corticosteroid therapy combined with cyclophosphamide and achieved recovery and remission as clinical outcomes.

The prognosis of patients with AHA depends on the patient's response to immunosuppression therapy. A meta-analysis of 249 patients with AHA found that three factors had an independent impact on overall survival and disease-free survival: related conditions (malignancy vs postpartum), complete remission status, and age at diagnosis (<65 y vs. ≥65 y).[10] Survival was greatest in patients with postpartum inhibitors, in those who achieved complete remission, and in those who were younger than 65 years.

Generally, there is variable consensus on management guidelines on management of AHA. Large, multinational collaborative randomised controlled trials are required for better assessment of treatment regimes in these patients with a rare, but devastating disorder. We hope this case report could shed some light on understanding of AHA.

REFERENCES

1. Kessler CM, Knöbl P. Acquired haemophilia: An overview for clinical practice. Eur J Haematol 2015; 95: 36-44.
2. Pavlova A, Diaz-Lacava A, Zeitler H, Satoguina J, Niemann B, Krause M, et al. Increased frequency of the CTLA-4 49 A/G polymorphism in patients with acquired haemophilia A compared to healthy controls. Haemophilia 2008; 14(2): 355-60.
3. Lee CP, Bahariah Bt Khalid B. A case series of acquired haemophilia in a Malaysian hospital: Unpredictably rare medical emergency. Oxford Med Case Reports 2015 Oct 1; 2015(10): 330-2.
4. Tiede A, Collins P, Knoebl P, Teitel J, Kessler C, Shima M, et al. International recommendations on the diagnosis hemophilia and a treatment of acquired. Haematologica 2020; 105: 1791-801.
5. Teh A, Leong KW, Bosco JJ, Koong PL, Jayaranee S. Acquired Haemophilia- A Therapeutic Challenge. Med J Malaysia Vol 50 No. 2 June 1995
6. Kyaw TZ, Jayaranee S, Bee PC, Chin EFM. Edinsel faktör VIII inhibitörleri: Üç olgu. Turkish J Hematol 2013; 30(1): 76-80.
7. Mulliez SMN, Vantilborgh A, Devreese KMJ. Acquired hemophilia: A case report and review of the literature. International Journal of Laboratory Hematology. Blackwell Publishing Ltd.; 2014; 36: 398-407.
8. Ma AD, Carrizosa D. Acquired factor VIII inhibitors: Pathophysiology and treatment. Hematology Am Soc Hematol Educ Program 2006; 432-7.
9. Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J, Makris M, et al. Acquired hemophilia A in the United Kingdom: A 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' organisation. Blood 2007; 109(5): 1870-7.
10. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: Review and meta-analysis focused on therapy and prognostic factors Br J Haematol 2003; 121(1): 21-35.

CASE REPORT

Acute pericarditis as a clinical manifestation in COVID-19 infection in a district hospital setting

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SUMMARY

The global outbreak of coronavirus disease 2019(COVID-19) pandemic has heavily impacted the health service, leading to increased mortality and morbidity. Although known to manifest primarily as a respiratory illness, there are reports of cardiac involvement as extrapulmonary manifestation. We are reporting a case of pericarditis in a young patient who presented with only cardiac symptoms in COVID-19. He was admitted to the hospital for observation and treated with oral colchicine and oral ibuprofen. His conditions improved and subsequently discharged well. Acute pericarditis can present as part of the COVID-19 extrapulmonary spectrum. Therefore, it is important and challenging for clinicians to recognise the atypical presentations of COVID-19 to reduce morbidity and mortality.

INTRODUCTION

COVID-19 is an illness caused by the SARS-CoV-2 virus, which has immensely burdened the public healthcare. It has been linked to a variety of disease manifestation including pulmonary and extrapulmonary.Myocarditis and pericarditis have been reported amongst the extrapulmonary manifestations of COVID-19 infection.[1] Higher incidences of thromboembolic events, leading to coronary thrombosis in COVID-19 infections, were reported compared to pericarditis and myocarditis, which may manifest at any stage of the disease. Therefore, it serves as a challenge for clinicians to diagnose and monitor the disease progression. In some cases, pericardiocentesis is often required due to pericardial effusion.[1] We next describe a case of acute pericarditis as a result of COVID-19 infection.

CASE REPORT

A 21-year-old man was admitted in early March 2021 with a chief complaint of severe chest pain for four days, associated with shortness of breath and diaphoresis. The chest pain was described as pleuritic in nature (pain score of 7/10), aggravated by lying down and deep inspiration, and slightly relieved by sitting upright. He has a body mass index (BMI) of 27 kg/m^2, working as an operator at a tofu factory with no known medical illness or surgeries prior to admission. He was not vaccinated against COVID-19. He denied any food or drug allergies. In addition, there was no family history of cardiac disease or sudden deaths. He is an active cigarette smoker with 7-pack-year exposure. He denied any high-risk behaviour such as illicit drug use.

He was hemodynamically stable (blood pressure of 106/62 mmHg; pulse rate of 96 beats/min; oxygen saturation 98% under room air; febrile with a body temperature of 38°C). Examination revealed that there were no signs of acute cardiac failure and no added heart sounds nor pericardial rub .

ECG showed saddle-shaped ST segment elevation at lead I, II, AVL, V2–V6 and PR segment depression in inferior leads with PR segment elevation in lead aVR (Figure1). Nasopharyngeal swab for RT-PCR SARS-CoV-2 came back as positive, and he was thereafter managed and monitored in the COVID-19 ward. The chest radiograph was normal (Figure 2).

Serum biochemistry showed raised troponin I of 0.1 ng/ml (normal range < 0.02 ng/ml), creatinine kinase of 760 U/L (Normal range 26 U/L–174 U/L), and inflammatory markers (white blood cell count 19600/mm^3, C-reactive protein 305.4 mg/L, ferritin level 635.1 ug/L). Echocardiogram revealed good left ventricular function with ejection fraction of 64% with no pericardial effusion, and all chamber sizes were normal. Infective screening, coagulation profile, and kidney and liver function tests were normal. However, blood samples for viral panel to look for other causative viral causes were not done due to limitation of resources in district hospital setting.

The case was consulted with the cardiologist on-call at a tertiary hospital, following which an impression of acute pericarditis secondary to COVID-19 infection was made, based on the clinical, ECG, and laboratory findings. Treatment was initiated for this patient with oral colchicine 0.5 mg thrice a day and oral ibuprofen 400 mg thrice a day.

He was discharged well on day 14 of illness with a follow-up appointment to the cardiology unit in a tertiary centre. Prior to which, repeated ECG showed sinus rhythm with resolution of ST segments, CRP level of 1.1 mg/L, and a normal creatinine kinase level of 105 U/L. Serial troponin-I level was not performed in this case in view of limited resources in our district hospital setting.

DISCUSSION

COVID-19 infection has led to various clinical pathologies relating to the cardiovascular system. There are various reports on COVID-19–related cardiac injuries that have

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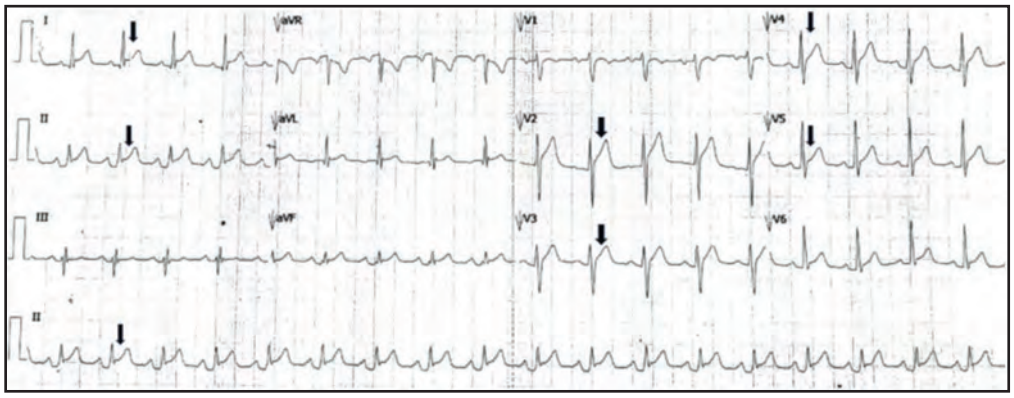

Fig. 1: ECG with ST segment elevation and PR depression.

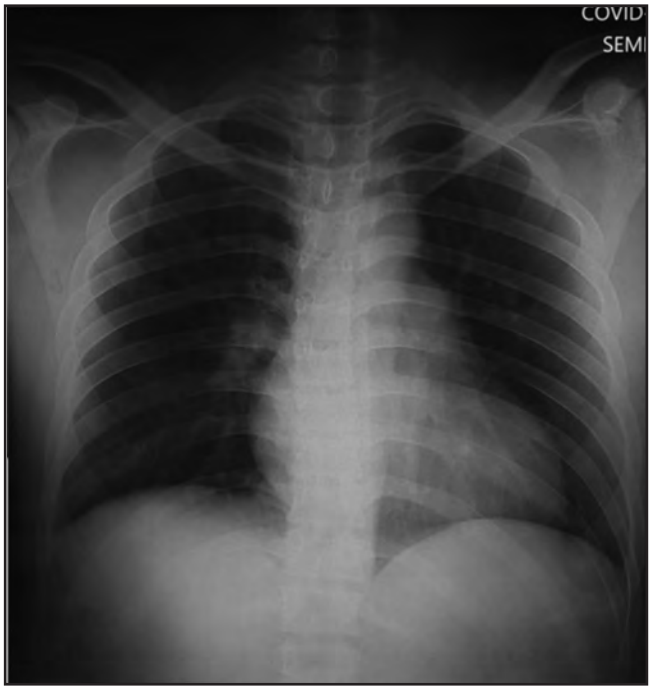

Fig. 2: Chest X-ray showed clear lung field.

caused an increase in the mortality rate.[2] The actual mechanism is unknown. However, it is believed to be related to the raised inflammatory markers during the cytokine storm that has caused worsening of heart function and cardiac injury.

Acute pericarditis is the most common disease of the pericardium where inflammation of the pericardium is frequently painful and causes fluid to enter the pericardial space. The exact aetiologies are highly variable, commonly seen in viral infections, including coxsackie, enterovirus, herpes simplex, cytomegalovirus, H1N1, respiratory syncytial virus, parvovirus B19, influenza, varicella, HIV, rubella, echovirus, and hepatitis B and C.[3] In this report, it was believed that the patient suffered from acute pericarditis secondary to SARS-CoV-2 (viral infection). Pericardiocentesis served as the gold standard to determine the underlying cause but was not performed in this case due to negative findings from the echocardiogram.

The patient complained of severe pericarditis chest pain, and the ECG revealed widespread ST elevation. Furthermore, inflammatory markers such as CRP, troponin I, ferritin, and WBC were elevated. This patient met two of the four criteria that led to the diagnosis of acute pericarditis.[4] The diagnosis of pericarditis was based on the clinical findings, ECG, and ECHO. Myocarditis frequently manifests as heart failure symptoms, an ECG with dysrhythmias, or an ECHO with hypokinesia. This patient has none. According to studies, 30–50% of patients with acute pericarditis have elevated cardiac troponin I.[5,6] Troponin I was tested with the Quidel Triage Troponin I fluorescence immunoassay, which has a minimum sensitivity of 95%. This patient has a high troponin level (0.1 ng/ml), whereas the normal range is 0.0–0.02 ng/ml. A large pericardial effusion, tamponade, fever > 38°C, subacute onset, and failure to respond to aspirin or NSAIDs are all poor prognostic factors.[4] A study conducted by Imazio et al.[7] showed that pericardial effusion was reported as high as 60% in patients with acute pericarditis. In

this case, he did not have any of the risk factors for poor prognosis and recovered gradually with no complications.

Further imaging such as CTCA and cardiac MRI may offer additional information regarding pericardial thickening, quantify systolic function, myocardial inflammation, and small effusions. As a district hospital with resource limitations, such imaging is not available to enable better understanding of the disease progression or prognostication in this patient.

Acute pericarditis is usually self-limiting, although it may recur. Treatment usually includes the use of non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and treating the underlying causative disease. At the beginning of the COVID-19 pandemic, there was a concern regarding the use of NSAIDs in COVID-19 patients. It is believed that NSAIDs may increase disease severity in patients with COVID-19. Various studies have been conducted and dismissed this idea.[8,9] Colchicine is an anti-inflammatory drug that is used to treat a variety of conditions, including gout, recurrent pericarditis, and familial Mediterranean fever. The use of colchicine in COVID-19 has been controversial. The COLCORONA and RECOVERY trials did not demonstrate any benefit in the colchicine arm, whereas the GRECCO-19 trial showed that colchicine reduced the primary clinical endpoint of deterioration in clinical status from baseline.[10] As for this patient, he was treated with both colchicine and ibuprofen for 1 week. His condition improved in the ward, and he was discharged home.

CONCLUSION

Acute pericarditis can be a clinical presentation of COVID-19 patients. Our understanding of the COVID-19 disease spectrum is limited, and pericarditis may be underdiagnosed in most cases. Therefore, this case report emphasises the importance of recognising the atypical presentation of COVID-19 so that the patient can be treated promptly to reduce morbidity and mortality.

REFERENCES

1. Jassim ZS, Smitha AK, Ashfaq AP. Myocarditis and pericarditis in patients with COVID-19. Heart Views 2020 Jul-Sep; 21(3): 209-14.
2. Shi s,Qin M, Shen B,Cai Y, Liu T, Yang F et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardio 2020;5.
3. Kytö V, Sipilä J, Rautava P. Clinical profile and influences on outcomes in patients hospitalized for acute pericarditis. Circulation 2014; 130: 1601-6.
4. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. European Heart Journal 2015 Nov 7; 36(42): 2921-64.
5. Lange RA, Hillis LD. Clinical practice: Acute pericarditis. N Engl J Med 2005; 352(11): 1163.
6. E Bonnefoy , P Godon, G Kirkorian, M Fatemi, P Chevalier, P Touboul. Serum cardiac troponin I and ST-segment elevation in patients with acute pericarditis. Eur Heart J 2000; 21(10): 832-6.
7. Imazio M, Demichelis B, Parrini I, Giuggia M, Cecchi E, Gaschino G, et al. Day-hospital treatment of acute pericarditis: A management program for outpatient therapy. Journal of the American College of Cardiology 2004; 43(6): 1042-6.
8. Drake TM, Fairfield CJ, Pius R, Knight SR, Norman L, Girvan M, et al. Non-steroidal anti-inflammatory drug use and outcomes of COVID-19 in the ISARIC Clinical Characterisation Protocol UK cohort: A matched, prospective cohort study. Lancet Rheumatol 2021 (3).
9. Chandan JS, Zemedikun DT, Thayakaran R, Byne N, Dhalla S, Acosta-Mena D, et al. Non-steroidal antiinflammatory drugs and susceptibility to COVID-19. Arthritis Rheumatol 2021(73).
10. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health [cited Aug 2021]. Available from: http://www.covid19treatmentguidelines.nih.gov.

Tree-in-Bud Opacities: Not only tuberculosis

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SUMMARY

We report a clinical case of mentally challenged young gentleman who was repeatedly hospitalized for respiratory symptoms. Contrast-enhanced CT (computed tomography) thorax revealed tree-in-bud (TIB) opacities. Provisional diagnosis of pulmonary tuberculosis was made and was referred to the respiratory team. However, after listening to patient's voice and reviewing the images on CT thorax, the diagnosis was confirmed as aspiration bronchiolitis.

INTRODUCTION

Tree-in-bud (TIB) opacities are a subset of centrilobular nodules. TIB opacities typically show branching configurations from secondary pulmonary lobules with sparing of subpleural lungs on CT thorax. CT finding of centrilobular nodules with TIB opacities was first described in pulmonary tuberculosis and is considered highly predictive of pulmonary tuberculosis for patients with intermediate-to-high incidence of tuberculosis in their country of origin. Later, it was found that this feature can be present in other medical conditions. This case highlights the necessity of correlation with clinical features and radiological findings to reach a diagnosis.

CASE REPORT

A 20-year-old mentally challenged Chinese gentleman presented with complaints of fever and productive cough for 5 days, associated with exertional dyspnoea and pleuritic chest pain to our emergency department. On assessment, he was febrile and mildly tachypnoeic. Supplemental oxygen of 2l/min via nasal prongs was needed to relieve his hypoxia. Crackles were present over his left lower zone on auscultation, more pronounced posteriorly. Neurological examination was normal.

His blood investigations showed evidence of infection and type 1 respiratory failure (Table I). His chest radiograph showed nodular consolidation changes bilaterally over both lower zones (Fig. 1a). He was admitted and treated for community-acquired pneumonia. A course of IV Augmentin was prescribed, and he was discharged well 5 days later. In this admission, bacterial culture from sputum and blood had no growth. A week later, he was readmitted with similar complaints. Chest radiograph showed worsening consolidation (Fig. 1b). A contrast-enhanced CT thorax (Fig. 2a and 2b) was performed, which reported the presence of centrilobular nodules with TIB appearance in multiple lobes, especially at both lower lobes. Based on this CT finding, the respiratory team was consulted for a high suspicion of pulmonary tuberculosis and consideration for empirical treatment. On our first encounter with the patient, we noted that he had a breathy, weak voice. This arose concern for vocal cord palsy, and an immediate referral to our otorhinolaryngology (ORL) team was made. Direct laryngoscopy demonstrated bilateral vocal cord palsy with no other associated abnormalities. Microbiological workup grew ESBL Klebsiella pneumoniae from sputum. Workup for tuberculosis, including sputum for GeneXpert MTB/RIF Ultra, was negative. Further contrast enhanced CT of brain, neck, and abdomen showed no anomalies. A final diagnosis of aspiration bronchiolitis secondary to idiopathic bilateral vocal cord palsy was made.

He was referred to the dietitian for dietitian advice and the speech therapist for voice therapy. His condition responded well with IV Ertapenem. Clinically, his fever settled and oxygenation improved. A repeat chest radiograph before discharge showed gradual resolution of consolidation changes (Fig. 1c). During follow-up after 3 months of second admission, his vocal cord palsy remained unchanged.

DISCUSSION

TIB opacities were initially described in and considered highly predictive for pulmonary tuberculosis.[1] However, it is not pathognomonic and has a wide range of differentials. Nevertheless, in regions with intermediate-to-high incidence of tuberculosis, it commonly rings alarm bells with regard to tuberculosis.

In a study done in Hong Kong, it seems that most common aetiology of TIB is infection, in particular, mycobacterial infection. The next most common is non-bacterial bronchiectasis and bronchiolitis.[2] However, in Western countries, apart from infection, the next common cause is aspiration. Other aetiologies of TIB opacities include inhalation injury, congenital disorders, immunological disorders, connective tissue diseases, and peripheral vascular diseases. Therefore, when interpreting TIB opacities on CT, we should consider the other associated clinical presentations and radiological features.[3] Anatomical distribution of TIB on CT, presence of bronchiectasis, presence of cavities, presence of ground glass opacity or consolidation, and lymphadenopathies may provide us additional important radio imaging clues for us to identify the cause.

In this case, two elements alerted us to an alternate possibility. First, the quality of the patient's voice typified

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Table I: Selected blood investigations during the first admission

	Normal range	Value on admission
FBC		
WBC (10^9/l)	4.0–11.0	18.6
Hb (g/dl)	13.0–18.0	10.9
Platelet (10^9/l)	150–400	377
CRP (mg/l)	<5	102.1
ABG on room air		
pH	7.35–7.45	7.33
PO_2 (mmHg)	80.0–100.0	78.0
PCO_2 (mmHg)	35.0–45.0	55.7
HCO_3 (mmol/l)	21.0–25.0	29.6

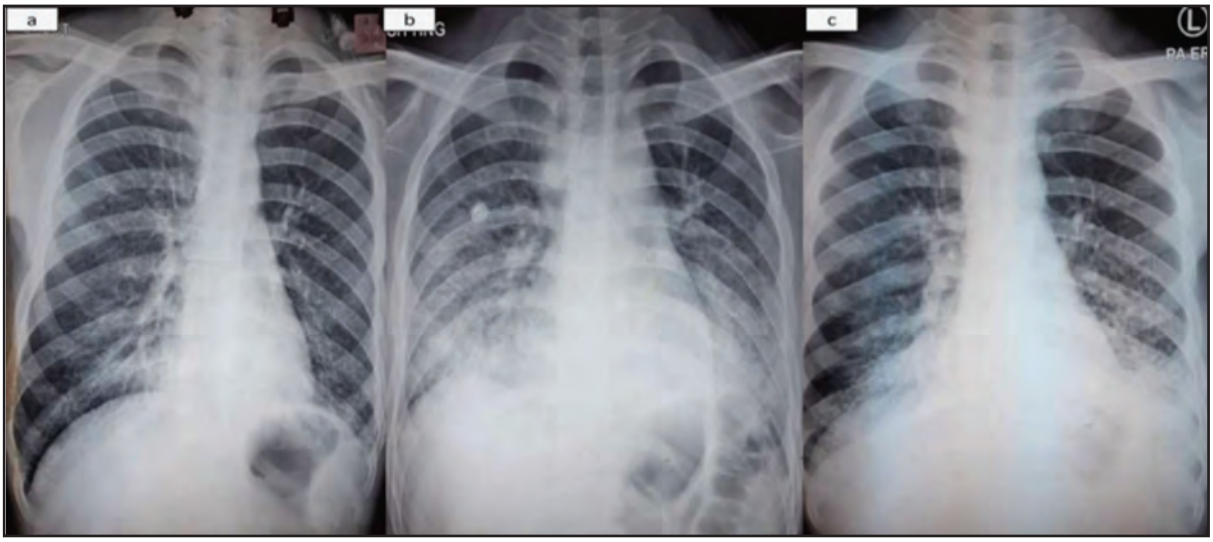

Fig. 1: Serial chest radiographs. a) During the first admission, bilateral lower zone nodular consolidation changes. b) During the second admission, consolidation worsens. c) After 2 weeks of treatment during the second admission, consolidation has improved.

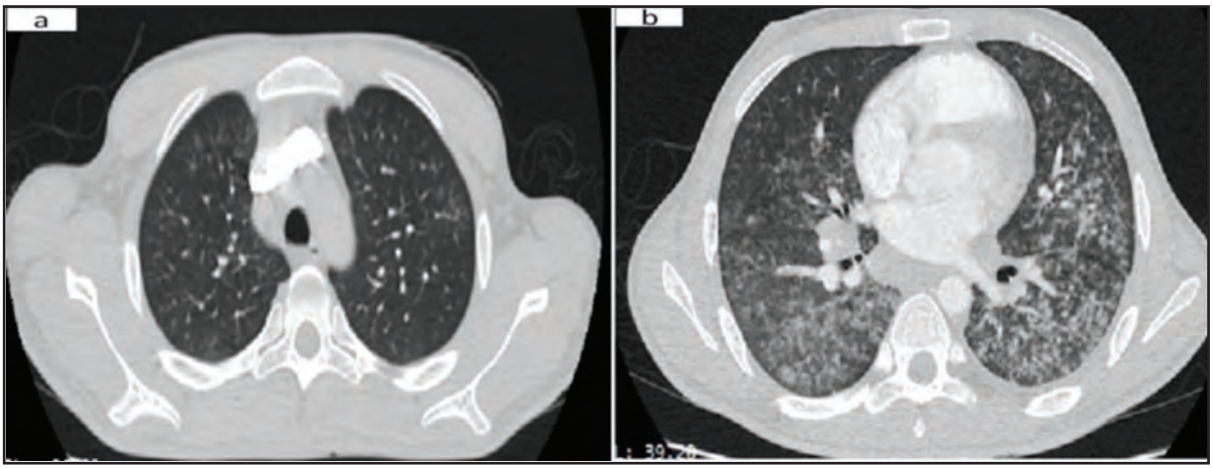

Fig. 2: Contrast-enhanced CT thorax showing centrilobular nodules with TIB opacities, especially at lower lobes. a) A slice of upper lobes. b) A slice of lower lobes.

vocal cord paresis. The second clue was the basal distribution of the CT abnormalities, intimating the likelihood of aspiration. Tying in both these hints led us to the clinical diagnosis of aspiration bronchiolitis. However, in other interstitial lung diseases, histology examination via biopsy may be helpful to confirm the diagnoses, because the histological features of aspiration bronchiolitis are less specific. Therefore, the diagnosis of aspiration bronchiolitis is often made on clinical ground.

Recurrent aspiration is the main cause of aspiration bronchiolitis. Common symptoms are cough, dyspnoea, and fever. Predisposing factors include impaired swallowing, impaired conscious level, impaired cough reflex, and gastric reflux. In our patient, the unprotected upper airway during swallowing would have led to repetitive aspirations resulting in the clinical presentation. In contrast, patients with pulmonary tuberculosis usually present with chronic cough and constitutional symptoms.

The CT thorax appearance in this case was consistent with aspiration bronchiolitis given the distribution of the abnormalities. The key features of this entity are ground glass opacities and centrilobular nodules with TIB configuration.[4] Anatomically, aspiration bronchiolitis classically involves the basal segments of lower lobes in those patients who aspirate in erect position and mainly the posterior segment of the upper lobes and the superior segment of the lower lobes for those in recumbent position. TIB opacities are typically found predominantly in upper lobes and superior segments of lower lobes for pulmonary tuberculosis.

The mainstays of management of aspiration bronchiolitis are to treat the aspiration pneumonia, to prevent further aspiration, and to address the underlying cause. For aspiration pneumonia, bacterial cultures should be obtained. Microaspiration or macroapiration from the content of oral cavity is the usual culprit. This means antibiotics that have effect on both aerobic and anaerobic organisms should be started empirically and altered after reviewing culture and sensitivity. This explains the choices of antibiotics during the first and second admission.

Current evidence does not support the use of prophylactic antibiotics to prevent further aspiration.[5] However, adjustment of the thickness of food, size of intake, and drinking water during and after meal to clear the secretion are some of the steps to be considered.[6] Other measures would include posturing during meals, practicing swallowing, and vocalising and introducing a feeding tube, especially for those who have no positive progression in their diseases or who have worsening nutritional status.[7] These measures are applicable, although most evidences are modest and from paediatric age group's studies.

In this case, ORL team decided to treat the bilateral idiopathic vocal cord palsy conservatively with voice therapy while keeping a watchful eye for another episode of aspiration as most of the young patients with short presentations recover spontaneously, although some may advocate a more definite aggressive approach. Presence of severe upper airway obstruction will require urgent tracheostomy or even laryngectomy. Patients who do not improve after 12 months have poor recovery.[8] Definite treatment would include injection laryngoplasty and vocal cord medialisation.[9] Substantial numbers of patients with vocal cord palsy may develop malignant aetiologies later, and therefore, long-term follow-up is desirable.[8,10]

CONCLUSION

TIB opacities on CT are not uncommon and are not solely caused by pulmonary tuberculosis. Combination of clinical features and radiological findings is the key to make an accurate diagnosis. Multidisciplinary management is important to achieve the best outcome.

REFERENCES

1. Im J, Itoh H, Shim Y, Lee J, Ahn J, Han M, et al. Pulmonary tuberculosis: CT findings – early active disease and sequential change with antituberculous therapy. Radiology 1993; 186(3): 653-60.
2. Wan AYH, Shum JSF, Kwan WH, Cheng CS. Tree-in-bud nodules in Asian population. Hong Kong J Radiol 2011; 14(3): 161-6.
3. Miller WT, Panosian JS. Causes and imaging patterns of tree-in-bud opacities. Chest 2013; 144(6): 1883-92.
4. Cardasis JJ, MacMahon H, Husain AN. The spectrum of lung disease due to chronic occult aspiration. Ann Am Thorac Soc 2014; 11(6): 890-7.
5. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. Am J Respir Crit Care Med 2019; 200(7): E45-67.
6. Loeb MB, Becker M, Eady A, Walker-Dilks C. Interventions to prevent aspiration pneumonia in older adults: A systematic review. J Am Geriatr Soc 2003; 51(7): 1018-22.
7. Duncan DR, Larson K, Davidson K, May K, Rahbar R, Rosen RL. Feeding interventions are associated with improved outcomes in children with laryngeal penetration. J Pediatr Gastroenterol Nutr 2019; 68(2): 218-24.
8. Willatt DJ, Stell PM. The prognosis and management of idiopathic vocal cord paralysis. Clin Otolaryngol Allied Sci 1989; 14(3): 247-50.
9. Dunya G, Orb QT, Smith ME, Marie JP. A review of treatment of bilateral vocal fold movement impairment. Curr Otorhinolaryngol Rep 2021; 9(1): 7-15.
10. Rubin F, Villeneuve A, Alciato L, Slaïm L, Bonfils P, Laccourreye O. Idiopathic unilateral vocal-fold paralysis in the adult. Eur Ann Otorhinolaryngol Head Neck Dis 2018; 135(3): 171-4.

CASE REPORT

The curious case of missing heartbeats

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SUMMARY

Paroxysmal atrioventricular block (AVB) is a poorly defined and easily missed bradyarrhythmia, which can potentially lead to sudden cardiac death. It is under-recognised due to its abrupt onset and unpredictability. We describe a case that had paroxysmal AVB post-coronary angioplasty and highlight the mechanism as well as the management of this rare condition.

CASE REPORT

An 83-year-old man with hypertension and hyperlipidaemia, who underwent coronary artery bypass surgery 8 years ago, presented with a 1-day history of chest pain. He was treated for non-ST elevation myocardial infarction (NSTEMI) with a peak serum troponin I value of 1437 ng/dL. His 12-lead electrocardiogram (ECG) on admission showed sinus rhythm with evidence of ST-depressions on leads II, III, and aVF (Figure 1a). He was started on continuous cardiac monitoring in the ward. He received aspirin and clopidogrel prior to procedure. He then underwent coronary angiogram, which showed native left main and triple vessel disease with a patent left internal mammary artery graft to the left anterior descending artery and occluded saphenous venous graft (SVG) to the right coronary artery. His SVG to the first obtuse marginal branch (OM1) was patent with evidence of severe stenosis beyond anastomosis. He received balloon angioplasty to the OM1 beyond the SVG anastomosis with reduction in stenosis from 99% to less than 40% and normal coronary flow. There was resolution of ST-depression on his 12-lead ECG post coronary intervention (Figure 1b). He was continued on telemetry post-angioplasty. On day 2 post-angioplasty, his telemetry strips showed an initial sinus rhythm with wide QRS complexes followed by an episode of ventricular standstill lasting 5.6 seconds (Figure 1c). The patient was not on any beta blockers or calcium channel blockers.

The patient was haemodynamically stable and asymptomatic. He was transferred to the high dependency ward for closer monitoring. A temporary transvenous pacing wire was inserted in view of potential recurrent serious bradyarrhythmia, and baseline pacing rate was set at 60 beats per min. There were no further ventricular standstill episodes. His transthoracic echocardiogram showed left ventricular ejection fraction of 35% with regional wall motion abnormalities consistent with multivessel disease and mild-to-moderate mitral regurgitation. A transvenous dual chamber implantable cardioverter-defibrillator (ICD) was implanted for management of bradyarrhythmia in view of the potential need for pacing (bifascicular block and paroxysmal AVB) and for primary prevention against sudden cardiac death on day 5 of admission. He was discharged well 3 weeks later after rehabilitation.

DISCUSSION

Paroxysmal AVB is an uncommon cause of syncope and is often missed to be diagnosed due to its acute onset and unpredictability. It was first described by Sachs and Traynor in 1933,[1] subsequently by Coumel et al.[2] in 1972, demonstrating two cases of paroxysmal AVB precipitated by a premature atrial complex. It is defined by Rosenbaum et al.[3] as an unexpected complete AVB in a patient with delayed ventricular escape but otherwise with normal 1:1 AV-conduction. However, there is no clear consensus on the definition of paroxysmal AVB at present. Patients often present with syncope or presyncope, unlike in our patient, where it was incidentally noticed via continuous cardiac monitoring. It is an ominous cardiac rhythm that may lead to sudden cardiac death as there may be no suggestion of underlying AV conduction disease between culprit episodes.

The prevalence of paroxysmal AVB is not well established in the medical literature and is likely underreported due its unpredictability and abrupt onset. In a prospective study of 52 patients with incomplete or complete RBBB (right bundle branch block) who had syncope and a negative electrophysiology study (EPS), implantable loop recorders showed development of complete heart block in 13 (25%), but only 5 (10%) had complete heart block triggered by a premature beat and were attributable to paroxysmal AVB.[4] Evidence of distal conduction disease is often present and includes underlying RBBB, LBBB (left bundle branch block), and intra-ventricular conduction defect in descending order. However, in up to one-third of the patients, the baseline ECG may be normal.[5]

There are a few mechanisms that can explain paroxysmal AVB, namely vagally mediated, intrinsic, and idiopathic causes. An intrinsic paroxysmal AVB occurs when there is a phase 4 bradycardia-dependent block, which results when a supraventricular or ventricular impulse reaches a diseased His-Purkinje system (HPS) during phase 4 of the action potential when sodium channels are inactive. This leads to ventricular asystole as subsequent impulses are unable to depolarise the diseased tissue. This AVB persists until another premature atrial or ventricular beat captures the HPS prior to phase 4 depolarisation to restore normal conduction. Our patient developed a RBBB and LAFB post-NSTEMI likely due

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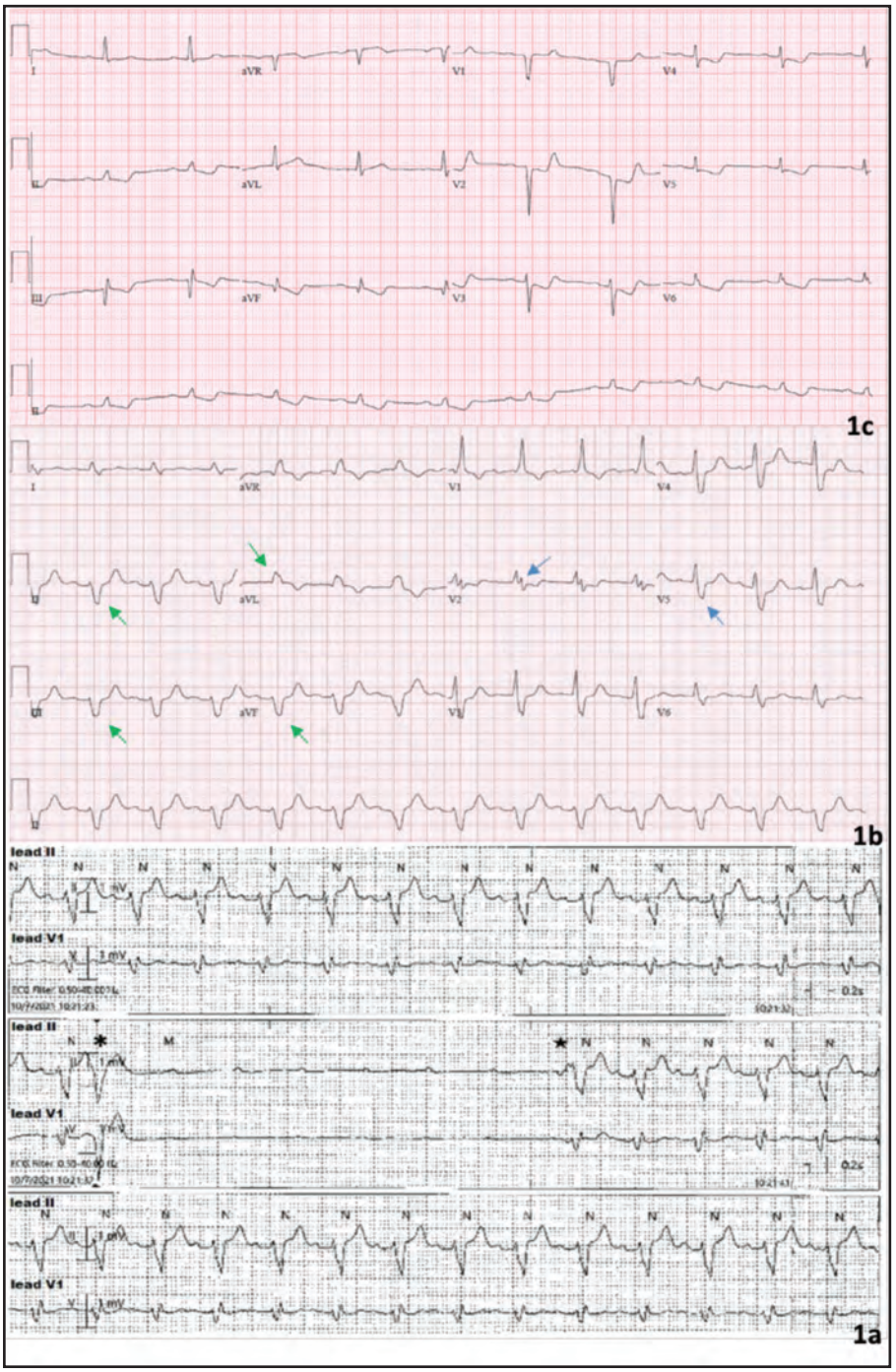

Fig. 1a: A 12-lead ECG on admission, showing sinus rhythm with down-sloping ST-depressions in leads V2–V6 and II, III, and aVF.

Fig. 1b: A 12-lead ECG post-angioplasty, showing baseline sinus rhythm with right bundle branch block (RBBB) (blue arrows) as evidenced by the following features:
1) QRS duration >120 ms
2) RSR' pattern in leads V1 and V2
3) S wave in leads I and V5–V6
The figure also shows left anterior fascicular block (LAFB) (green arrows) as demonstrated by
1) Left axis deviation
2) rS complexes in leads II, III, and aVF
3) Prolonged R wave peak time in aVL > 45 ms
ST-depression resolution was also found in the patient's ECG.

Fig. 1c: Telemetry strip post-angioplasty captured in the ward
The figure shows an initial sinus rhythm with widened QRS complexes. This was followed by a ventricular premature beat (*) with a left bundle branch block (LBBB) morphology that led to an episode of ventricular standstill lasting 5.6 seconds. A non-sinus premature atrial impulse with a negative P wave in lead II (star) restored subsequent AV conduction. This is highly suggestive of paroxysmal atrioventricular block (AVB).

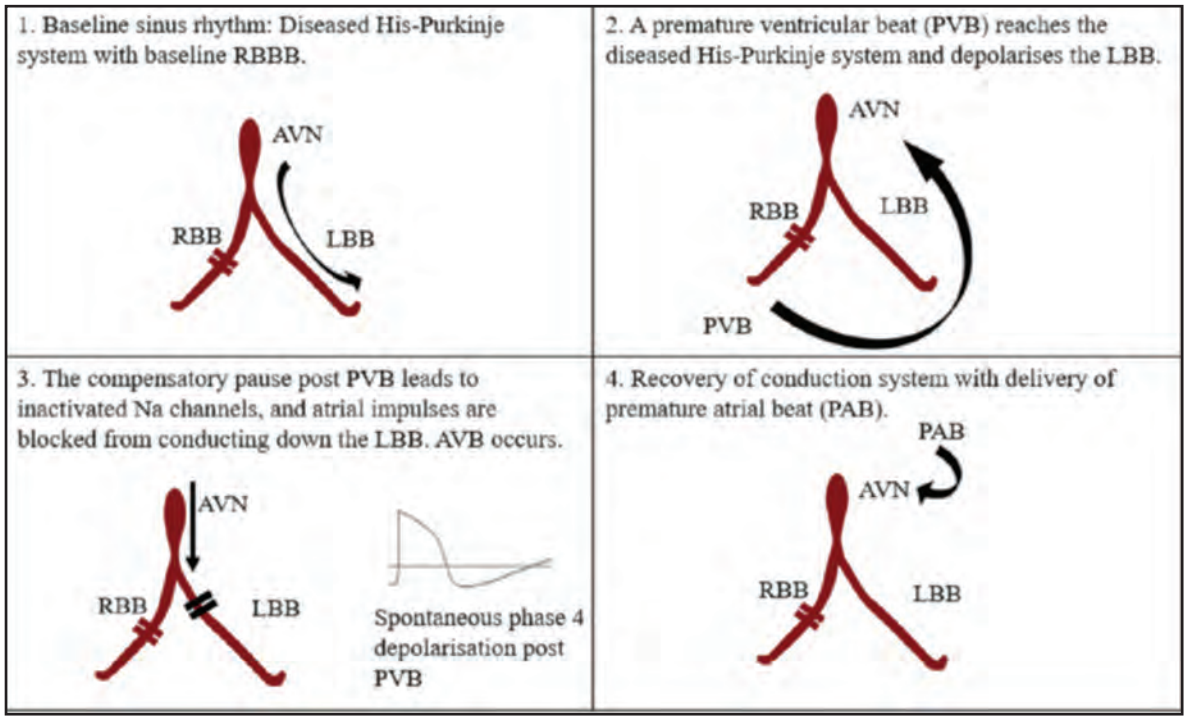

Fig. 2: A schematic diagram showing mechanism of paroxysmal AVB in our patient with baseline RBBB ECG, initiated by a premature ventricular beat leading to spontaneous phase 4 depolarisation of left bundle branch with period of ventricular asystole ensues until restoration of conduction system by a premature atrial beat. RBBB: right bundle branch block; RBB: right bundle branch; LBB: left bundle branch; AVN: atrioventricular node; PVB: premature ventricular beat; PAB: premature atrial beat.

to ischaemia and infarct, with evidence of phase 4 bradycardia-dependent block occurring over the left bundle branch (LBB), leading to a period of ventricular asystole as subsequent atrial impulses are unable to conduct down the LBB (Figure 2). The conduction system was subsequently restored by a premature atrial beat.

It is important to differentiate between paroxysmal AVB and vagally mediated AVB because the latter shows a benign prognosis with no benefit in prophylactic pacemaker implantation.[6] It may not always be possible to differentiate the two entities, but there are some clues on the ECG that allow us to lean towards either diagnosis. Paroxysmal AVB is usually initiated by a premature atrial or ventricular beat, followed by a pause or tachycardia leading to suppression of AV conduction. In vagally mediated AVB, there is gradual slowing with P-P and P-R prolongation prior to AVB or sinus arrest. One can also look at the clinical history to see if there is any suggestion of high vagal tone, which would be more suggestive of vagally mediated AVB. In paroxysmal AVB, there is usually sudden development of AVB and symptoms.

Prompt recognition of paroxysmal AVB is essential because of its potential to lead to sudden cardiac death, which can be prevented by permanent pacemaker implantation. A possible exception to a pacemaker implantation is when paroxysmal AVB occurs in the acute setting with a reversible process such as ischaemia in acute coronary syndrome.[7] However, there are no studies to provide evidence that paroxysmal AVB related to ischaemic events will not recur. In our patient, the episode of paroxysmal AVB occurred 3 days post-myocardial infarction and after revascularisation. Although he was asymptomatic during that episode, decision was made for implantation of dual chamber ICD for prevention of future arrhythmic events after shared decision-making between the patient and medical team. Decision was made for ICD implantation rather than a cardiac resynchronisation therapy device as the patient was unlikely to be pacemaker dependent.

CONCLUSION

Paroxysmal AVB is a rare bradyarrhythmia, whose diagnosis may be easily missed due to its unpredictability and occurrence even in patients with baseline normal 1:1 AV conduction. Prolonged continuous cardiac monitoring may be useful to detect paroxysmal AVB in patients with syncope, especially in those with underlying bundle branch blocks or structural heart disease.

REFERENCES

1. Sachs A, Traynor RL. Paroxysmal complete auriculo-ventricular heart-block: A case report. Am Heart J 1933; 9: 267-71.
2. Coumel P, Fabiato A, Waynberger M, Motte G, Slama R, Bouvrain Y Bradycardia-dependent atrio-ventricular block: Report of two cases of A-V block elicited by premature beats. J Electrocardiol 1971; 4: 168-77.
3. Rosenbaum MB, Elizari MV, Levi RJ, Nau GJ. Paroxysmal atrioventricular block related to hypopolarization and spontaneous diastolic depolarization. Chest 1973; 63: 678-88.
4. Brignole M, Menozzi C, Moya A, Garcia-Civera R, Mont L, Alvarez M et al. Mechanism of syncope in patients with bundle branch block and negative electrophysiological test. Circulation 2001; 104: 2045-50.

5. Lee S, Wellens HJ, Josephson ME. Paroxysmal AV block. Heart Rhythm 2009; 6: 1229-34.
6. Connolly SJ, Sheldon R, Thorpe KE, Roberts RS, Ellenbogen KA, Wilkoff BL et al. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope. Second Vasovagal Pacemaker Study (VPS II): A randomized trial. JAMA 2003; 289: 2224-9.
7. Bortone A, Albenque JP, Marijon E, Donzeau JP. Complete atrioventricular block and asystole in a patient with an inferior acute myocardial infarction: What is the mechanism? Heart Rhythm 2008; 5: 1077-9.

CASE REPORT

Pontine stroke: a rare mimicker of Bell's palsy

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SUMMARY

Pontine infarct is a rare but clinically significant cause of an isolated facial nerve palsy. Prompt diagnosis with the use of magnetic resonance imaging (MRI) allows early initiation of treatment for such patients. We report a 62-year-old gentleman with diabetes, hypertension, and gout, presenting with lower motor neuron facial nerve palsy. This report highlights that isolated facial nerve palsy is not always associated with Bell's palsy, which remains the commonest cause of facial nerve paralysis. A thorough neurological examination and good clinical correlation with the patient's history and physical findings, coupled with the use of facial nerve anatomical knowledge and early employment of MRI, are imperative in clinching the diagnosis.

INTRODUCTION

Stroke carries significant morbidity and mortality. Brainstem stroke, commonly located at the pons, accounts for 10% of all ischemic strokes.[1] While pontine stroke is a rare but significant cause of an isolated facial nerve paralysis, it should not be easily dismissed and misdiagnosed as Bell's palsy. A strong clinical acumen and correlation with a patient's history and neurological examination allows a clinician to determine the precise aetiology of the facial palsy. Accurate and timely diagnosis with the use of MRI is instrumental in the management of an acute ischemic stroke to ensure good clinical outcomes in patients. In this report, we describe a rare presentation of pontine infarct with unilateral facial palsy and report the limitations of CT scan and MRI, emphasising on early detection of pontine stroke via MRI.

CASE REPORT

Our patient is a 62-year-old Malay gentleman with diabetes, hypertension, and gout. He presented to us with a sudden onset of right facial asymmetry, which was associated with slurring of speech, giddiness, blurring of vision, and mild right-sided weakness for 2 days in duration.

On examination, he was conscious and noted to have dysarthria. His blood pressure was recorded at 192/119 mmHg. Heart rate was 84 beats per minute, regular in rhythm. Neurological examination showed an obvious loss of right forehead creases, inability to close the right eye, loss of right nasolabial fold, and drooping of the right angle of mouth (Figure 1). All other cranial nerves were intact. Motor examination showed a mild right-sided weakness over the upper and lower limbs, with a power of 4/5, which quickly resolved the next day. Sensation was intact, and there were no cerebellar signs. There was no carotid bruit. His NIHSS score was 4.

ECG (electrocardiogram)showed sinus rhythm. His blood parameters, including full blood count and renal profile, were normal. Lipid profile showed a raised LDL level of 3.9 mmol/L and a fasting glucose level of 7.2 mmol/L. Computed tomography (CT) imaging of the brain did not reveal any abnormality. An initial differential diagnosis of Bell's palsy was considered. However, putting together his acute presenting symptoms, hypertension, and a normal CT brain finding, we proceeded to perform an MRI scan of the brain. It confirmed a small acute central pontine infarct with non-specific small foci of hyperintense signal at bilateral frontal lobes, representing small vessel disease or old lacunar infarct (Figure 2). Magnetic resonance angiography (MRA) was normal.

A final diagnosis of isolated facial nerve palsy secondary to acute pontine infarct was made. He was started on aspirin and clopidogrel as well as atorvastatin. Subsequently, he was discharged well with residual facial asymmetry and a complete resolution of his right-sided weakness. A repeat brain MRI performed a week later showed no worsening of the infarct.

DISCUSSION

A complete facial paralysis in the setting of stroke is a rare presenting symptom. With an annual incidence of approximately 15–30 in 100,000, Bell's palsy is the most common cause of complete facial palsy, accounting for 72% of cases, while pontine infarct contributes around 1% of such cases.[1,2] Bell's palsy is mostly idiopathic in nature, affecting individuals between ages 15 and 45, and its symptoms generally resolve within six months. It is a diagnosis of exclusion.[2] Strokes with facial involvement usually involve a unilateral lower facial palsy, often accompanied with symptoms such as hemiplegia, slurred speech, and other central symptoms. Risk factors for stroke include advanced age, hypertension, diabetes, dyslipidaemia, smoking, and cardiovascular diseases.[3] Therefore, isolated facial nerve palsy is not always synonymous with Bell's palsy. It is imperative to differentiate between the two as management and clinical approach differ for both.

In addition to having a strong clinical index of suspicion, good application of neuroanatomical knowledge and correlation of the patient's signs and symptoms enable us to deduce the location of the infarct. A clinical-radiological

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Fig. 1: Loss of right forehead creases upon raising eyebrows and loss of right nasolabial fold.

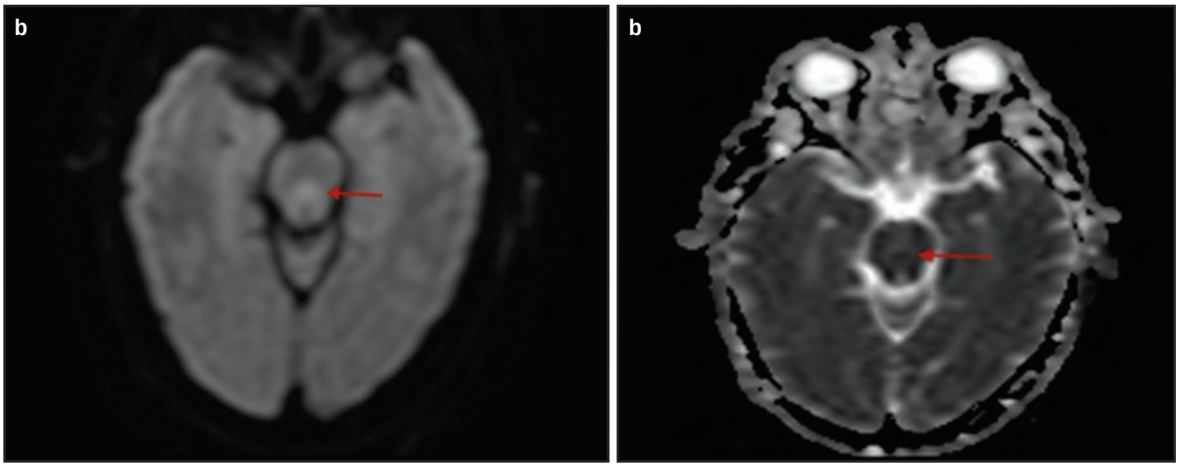

Fig. 2 a&b : DWI/ADC sequence showing small foci of Hyperintense signal/restricted diffusion at the central pontine.

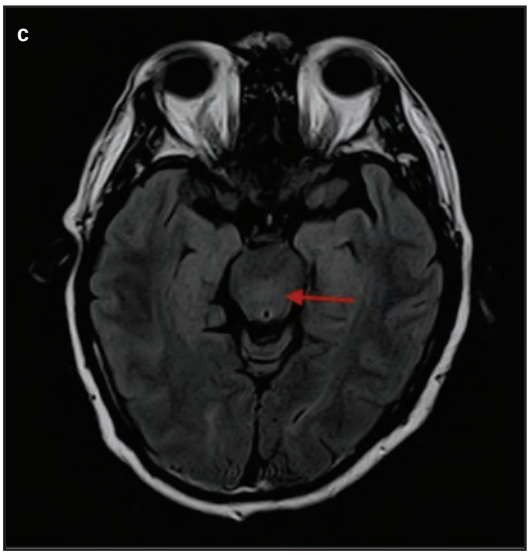

Fig. 2c : Axial FLAIR sequence depicting the similar hyperintense focus at the central pontine.

correlation study of pontine base infarct syndromes published in the American Heart Association (AHA) journal by Kim JS et al. classified pontine syndromes into pure motor hemiparesis, sensorimotor stroke, ataxic hemiparesis, and dysarthria-clumsy hand syndromes according to its clinical presentation.[4] Variants of dysarthria-clumsy hand syndrome include dysarthria-facial paresis, which was similar to that reported in our patient. The study concluded that large lesions involving the paramedian caudal or middle pons correlated with severe hemiparesis (PMH), whereas lesions of similar size located in the paramedian rostral pons tended to produce dysarthria-clumsy hand syndrome. Out of the 37 patients studied, only 2 patients with similar clinical presentation to our patient (dysarthria, facial paresis, and mild hemiparesis) had a central, small pontine infarct.[4] To the best of our knowledge, there have been no reported cases of central pontine infarct presenting as such just yet; most of which were reported to have a dorsal pontine infarct instead. This suggests that not all pontine infarcts manifest in a typical pontine syndrome presentation.

An additional challenge in diagnosing a pontine stroke in a presentation that mimics Bell's palsy is the availability of diagnostic imaging facilities. CT is the most widely used diagnostic imaging tool in most centres due to its availability and rapid acquisition time. It is accurate in distinguishing vascular and non-vascular lesions as well as differentiating infarcts from haemorrhages. This allows time-critical decision-making with regard to treatment such as in patients who are considered potential candidates for thrombolysis.[5] However, small infarcts are less likely to be visible than large ones on CT imaging, especially those involving the posterior circulation and the brainstem.[6] Recent studies have shown that MRI is more sensitive in identifying ischemic lesions in an acute ischemic stroke setting, even in a clinical presentation of minor stroke or transient ischemic attack (TIA).[7] Infarcts can be detected via MRI using sequences such as fluid-attenuated inversion recovery (FLAIR) or diffusion-weighted imaging (DWI). Of all techniques, DWI has the greatest sensitivity. It provides the earliest information about the physiology of the infarct and enables further classification of stroke. DWI also accurately monitors the evolution of the ischemic core over time, which is crucial in the selection of patients for endovascular treatment.[8] Some drawbacks include limited access, longer scan duration, and longer screening time for contraindications. In centres where MRI service is available, these should not be a major obstacle.[5] These advantages of MRI over CT support the early use of MRI as an imaging modality in an acute stroke protocol especially when clinical diagnosis is a challenge.

An additional diagnostic challenge here is the presence of mild ipsilateral hemiparesis in this patient given that most pontine syndromes manifest with contralateral hemiparesis. This could possibly be explained by the MRI findings of a small vessel disease or an old lacunar infarct. It is not uncommon in clinical practice for patients to not notice or report clinical symptoms of a minor stroke until it is detected incidentally on MRI findings much later during a hospital admission. Our history taking is very much dependent on the patient's medical literacy. From a psychological point of view, potentially life-threatening or life-altering events would be remembered more vividly and reported more accurately compared to less complex events, thus giving rise to the discrepancy in the patient's reported neurological symptoms as opposed to the expected neurological outcome in a pontine stroke.[9]

CONCLUSION

Isolated facial nerve palsy resulting from pontine stroke is a rare mimicker of Bell's palsy. Ultimately, Bell's palsy remains a diagnosis of exclusion. Clinicians must remain vigilant in such clinical presentations especially in the setting of elderly patients with cardiovascular risk factors. This case highlights the importance of thorough neurological examination and good clinical correlation with patient's symptoms and radiological evidence. Evidently in this case, the early use of MRI enables rapid detection and localisation of the stroke lesion, which is crucial in reducing morbidity and mortality.

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CONFLICT OF INTEREST

The authors have no conflict of interest with respect to this case report.

PATIENT'S CONSENT

The patient gave his consent for the use of his photograph and the publication of this case report.

REFERENCES

1. de Mendivil AO, Alcalá-Galiano A, Ochoa M, Salvador E, Millán JM. Brainstem stroke: Anatomy, clinical and radiological findings. Semin Ultrasound CT MR 2013; 34: 131-41.
2. Holland NJ, Weiner GM. Recent developments in Bell's palsy. BMJ 2004; 329: 553-7.
3. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ et al. Executive summary: Heart disease and stroke statistics – 2014 update. A Report from the American Heart Association Circulation 2014; 129: 399-410.
4. Kim JS, Lee JH, Im JH, Lee MC. Syndromes of pontine base infarction. A clinical-radiological correlation study. Stroke 1995; 26: 950-5.
5. Provost C, Soudant M, Legrand L, Hassen W, Xie Y, Soize S, et al. Magnetic resonance imaging and computed tomography before treatment in acute ischemic stroke, effect of workflow and functional outcome. Stroke 2019; 50: 659-64.
6. Bryan RN, Levy LM, Whitlow WD, Killian JM, Preziosi TJ, Rosario JA. Diagnosis of acute cerebral infarction: Comparison of CT and MR imaging. AJNR Am J Neuroradiol 1991; 12(4): 611-20.
7. Moreau F, Asdaghi N, Modi J, Goyal M, Coutts SB. Magnetic resonance imaging versus computed tomography in transient ischemic attack and minor stroke: The more you see the more you know. Cerebrovasc Dis Extra 2013 Jan-Dec; 3(1): 130-6.
8. Okorie CK, Ogbole GI, Owolabi MO, Ogun O, Adeyinka A, Ogunniyi A. Role of diffusion-weighted imaging in acute stroke management using low-field magnetic resonance imaging in resource limited setting. West Afr J Radiol 2015 Jul-Dec; 22(2): 61-6.
9. Curcio N, Wilmoth K, LoBue C, Cullum CM. Reliability of medical history reporting in older adults with and without cognitive impairment. J Central Nervous System Disease 2019; 11: 1-9.

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