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The Medical Journal of Malaysia
MJM

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Identify precisely all drugs and chemicals used, including generic name(s), dosage(s) and route(s) of administration. Do not use patients' names, initials or hospital numbers. Include numbers of observation and the statistical significance of the findings when appropriate.

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Acknowledgements:
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Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia 2020; 75(6): 613-25.
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Books and Other Monographs:
Personal Author(s)
Goodman NW, Edwards MB. 2014. Medical Writing: A Prescription for Clarity. 4 th Edition. Cambridge University Press.

Chapter in Book
McFarland D, Holland JC. Distress, adjustments, and anxiety disorders. In: Watson M, Kissane D, Editors. Management of clinical depression and anxiety. Oxford University Press; 2017: 1-22.

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Ministry of Health Malaysia. Press Release: Status of preparedness and response by the ministry of health in and event of outbreak of Ebola in Malaysia 2014 [cited Dec 2014]. Available from: http://www.moh.gov.my/english.php/database_stores/store_view_page/21/437.

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All original papers which are accepted for publication by the MJM, will be considered for the 'Best Paper Award' for the year of publication. No award will be made for any particular year if none of the submitted papers are judged to be of suitable quality.

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Original Articles

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Adverse events following immunisation of COVID-19 vaccine among health care workers in the first phase of vaccination

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ABSTRACT

Introduction: The new COVID-19 vaccine was met with worldwide overwhelming uncertainties pertaining to its safety profile, effectiveness, and potential adverse reactions when it was first introduced. This led to vaccine refusal and delay in vaccine uptake in many countries including Malaysia. The objective of this study was to determine the Adverse Events Following Immunization (AEFI) to the COVID-19 vaccine.

Materials and methods: A retrospective cross-sectional study was conducted among healthcare workers who received the COVID-19 vaccine during the first phase of immunisation from eight public primary clinics in Johor Bahru district. Data were collected between May and September 2021 using a self-administered questionnaire.

Results: A total of 240 healthcare workers participated and all of them received the Pfizer Messenger RNA vaccine. Our study found that a large majority of vaccine recipients (87.5%, n=210) experienced AEFI to COVID-19 vaccine for either the first, second, or both doses. More than 80% of them experienced more than one type of AEFI. The most common AEFI reported during the first and second dose was localised symptom such as pain at injection site (60–68%), pain on the injected arm (52–61%), and swelling at injection site (32–33%). Common systemic symptoms were fever (22–57%), myalgia (20–45%), and dizziness (24–26%). Although a large majority experienced AEFI, these reactions were mostly of mild to moderate severity (47.3–73.6%). The mean duration of AEFI onset was within 30 minutes to about 1 day (0.33–22.5 hours) of injection and lasted between 30 minutes and 2.5 days. There was no association between demographic characteristic of participants and severity of AEFI to COVID-19 vaccine. Mean duration of fever was significantly (p=0.005) longer after the second dose (34.2 hours) of vaccine compared to first (20.6 hours)

Conclusion: This study shows that a large majority of COVID-19 vaccine recipients experienced AEFI; however, these reactions were mostly of mild to moderate severity and lasted between 30 minutes and 2.5 days. A large majority experienced more than one type of AEFI. The most common AEFI was localised reactions consisting of pain and swelling at the injection site and pain on the injected arm. The most common systemic reactions were fever, myalgia, and dizziness. Duration of fever was significantly longer after the second dose.

KEYWORDS:
Adverse events, immunization, COVID-19, COVID-19 vaccines, injection site reaction

INTRODUCTION

COVID-19 became a pandemic and affected more than 120 countries, causing millions of deaths and affected the global economy.[1] Given the seriousness of the disease, many pharmaceutical companies joined the rat-race in developing a safe and effective vaccine to combat the COVID- 19 disease. In November 2020, Food and Drug Administration authorised the emergency use of the Pfizer-BioNTech COVID-19 to curb the spread of COVID-19.[2]

Immunisation has been recognized as one of the advanced preventive measures in public health.[3] If used correctly, all vaccines in the national immunisation programs are safe and effective. However, no vaccine is free from risk, and adverse reactions may occasionally occur after immunisation. Adverse events may range from mild side effects to serious reactions. These events may cause public concern about the safety of vaccines and affect vaccine acceptability.[4] An adverse event following immunisation is any untoward medical occurrence which follows immunisation and which may not necessarily have a causal relationship with the usage of the vaccine.[5]

In Malaysia, the Ministry of Health (MOH) implemented the first phase of the National COVID-19 vaccination programme in February 2021. The target was to vaccinate 25.6 million populations nationwide. This vaccination programme was carried out in three phases starting with medical and non-medical front line workers in phase one, high risk population in phase two and the rest of the population in phase three.[6]

Some of the concerns regarding the COVID-19 vaccine were pertaining to the safety, efficacy, and side effects as this was a new vaccine which was developed in a short span of time. Early studies have shown that one of the reasons for vaccine

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hesitancy, was due to concerns about the safety of COVID-19 vaccine pertaining to Adverse Events Following Immunization (AEFI).[7] Although experiences from other countries have shown that the AEFI related to the COVID-19 vaccine was low, there is a need to report and describe the vaccine experience in our local setting. Hence the aim of this study was to determine the incidence, type, severity, and factors affecting adverse events of COVID-19 vaccine among phase one recipients who were the first to receive this vaccine in Malaysia. The study also sought to determine the difference in AEFI severity between the first and the second doses of the vaccine. This data will be useful to study the local response to the vaccine and help dissipate fears regarding the side effects of COVID-19 in Malaysia.

MATERIALS AND METHODS

This is a retrospective cross-sectional study conducted among healthcare workers from eight public primary care clinics in Johor Bahru district between May and September 2021. Clinics were randomly selected using the ballot box method. Participants included doctors, pharmacist, medical assistant, dental assistants, pharmacist assistant, matron, nurse, health care assistants, medical laboratory technologist, administrative officer, ambulance driver and essential service, defence, and security personnel. Participants who were 18 years and above and completed two doses of the vaccine were approached using convenient sampling method. The main tool used in this study was a self-administered paper-based questionnaire developed from literature research.[8] An expert panel consisting of the researcher and two family medicine specialists, looked the suitability, and content validity of the questionnaire. The questionnaire was then translated forwards and backwards by two linguists to Bahasa Melayu and subjected to face validity among 20 participants from a health clinic of a similar setting. One item was suggested to be edited by the participants where the option for the initial response after the injection from "after 30 minutes" to "within 30 minutes" as some of them experienced reactions within this time frame. Some minor language adjustments were also made as suggested by the participants to facilitate an easy understanding of the questionnaire.

The questionnaire had two sections A and B. Section A contained demographic information such as age, gender, ethnicity, occupation health status of participant, such as previous history of COVID-19 infection, past medical, and drug allergy history. Participants were also asked if they had been informed regarding the possible side effects of the vaccine. The answers for this section were selected from the options provided or written in by the participants.

Section B contained 23 statements which describe the details of both the first and second vaccination such as dates, type of reaction, onset, overall perceived severity of the reaction, duration, and whether the reactions were reported, warranted treatment, required sick leave, or hospitalisation.

Severity of AEFI, was classified as mild, moderate, and severe based on participants self-report on how these events affected their daily activities. Mild adverse events were defined as events which did not interfere with their daily activity, moderate adverse events were those which interfered with their daily activity while severe adverse events were those which limited or restricted their daily activity.[5,9] For each question, participants either selected from the list of options provided or wrote in their responses.

Sample size was calculated using Open Epi programme calculator based on previous reported AEFI prevalence of 0.2% using the formula n = [DEFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1) + p*(1-p)] taking 95% confidence level and 20% added for incomplete response requiring a total of 238 participants.[8,10]

This study was approved by Universiti Kebangsaan Malaysia Research Ethics Committee and Institute of Medical Research Ethics Committee. This project was registered with the National Medical Research Registration (NMRR-21-1025-59179). Data were analysed using SPSS version 27 descriptive statistics and associations using Chi-square test and T-test (Mann–Whitney U test)

RESULTS

A total of 240 health front-line workers agreed to participate in this study. The median age of participants was 32 years with the youngest being 24 and the oldest being 55 years of age. Majority were females (87.5%, n=201), worked as nurses (32.1%, n=77) and belonged to the Malay ethnic group (77.1%, n=185). All participants received the Pfizer Messenger RNA vaccine for the first and second dose, while only one participant received Sinovac for the second as he developed anaphylaxis with the first dose of Pfizer mRNA vaccine. Most (80.3%, n=191) of them did not have any previous history of drug allergy and did not have any underlying medical conditions (86.1%, n=205). Almost all participants (98.8%, n=237) received information regarding possible vaccine-related adverse reaction prior to vaccination.

The overall incidence of AEFI (for either first or second dose) of COVID-19 vaccine was 87.5 % (n=210) meaning the majority who received the vaccine experienced some form of AEFI. Majority (> 80%) of the vaccine recipients also reported more than one type of AEFI. The most common AEFIs reported during the first and second dose were pain at injection site (60–68%), pain on the injected arm (52–61%), and fever (57%). The AEFIs experienced for the first and second doses of the COVID-19 vaccine were almost similar. Only three participants required hospital admission, out of which one was due to anaphylactic shock. But all three had a complete recovery and were discharged well (Table I).

Although a large majority of participants experienced AEFI to COVID-19 vaccine, these reactions were mostly reported as mild (47.3–73.6%), did not require sick leave (94.8%) or hospital admission (98.2%). About 60% took self-medication after the second dose of vaccine. Only 13.5 to 23.0% reported severe reaction. Only half of the participants (53.4%, n=93) reported the AEFIs at the MySejahtera Application (Table II).

The mean duration for onset for AEFI to COVID-19 vaccine ranged from, within 30 minutes of injection to about 1 day (0.33 to 22.5 hours) and lasted between 30 minutes and 2.5

Table I: Frequency and type of AEFI for 1st and second doses of COVID-19 vaccine

Types of AEFI reported			
1st dose		2nd dose	
AEFI	% (n)	AEFI	% (n)
Pain at injection site	68.9 (120)	Pain at injection site	60.0 (104)
Pain on the entire arm	60.9 (107)	Fever	57.2 (99)
Swelling at injection site	33.7 (59)	Pain on the entire arm	52.3 (91)
Dizziness	24.0 (42)	Myalgia	44.8 (78)
Fever	22.2 (39)	Chills	39.1 (68)
Myalgia	19.4 (34)	Swelling at injection site	32.2 (56)
Chills	16.0 (28)	Arthralgia	30.1 (52)
Headache	14.2 (25)	Headache	27.0 (47)
Arthralgia	12.0 (21)	Dizziness	25.7 (44)
Nausea	10.3 (18)	Nausea	9.7 (17)
Vomiting	1.7 (3)	Vomiting	4.0 (7)
Rashes	1.1 (2)	Diarrhoea	1.1 (2)
Fainted	0.5 (1)	Rashes	0.6 (1)
Anaphylactic shock	0.5 (1)	Fainted	0 (0)
Diarrhoea	0 (0)	Anaphylactic shock	0 (0)
Others	4.5 (8)	Others	6.9 (12)

Table II: Severity and reporting of AEFI to COVID-19 vaccine

1st Dose	% (n)	2nd Dose	% (n)
Severity level (self-reported)		**Severity level (self-reported)**	
Mild	73.6 (126)	Mild	47.3 (78)
Moderate	12.9 (22)	Moderate	29.7 (49)
Severe	13.5 (23)	Severe	23.0 (38)
Took self-medication for AEFI		**Took self-medication for AEFI**	
Yes	37.8 (65)	Yes	60.2 (103)
No	62.2 (107)	No	39.8 (68)
Took sick leave for AEFI		**Took sick leave for AEFI**	
Yes	5.2 (9)	Yes	15.8 (27)
No	94.8 (163)	No	84.2 (144)
AEFI requiring hospital admission		**AEFI requiring hospital admission**	
Yes	1.8 (3)	Yes	0.6 (1)
No	98.2 (167)	No	99.4 (170)
Reporting of AEFI (to doctor/ MySejahtera)		**Reporting of AEFI (to doctor/ MySejahtera)**	
Yes	53.4 (93)	Yes	60.2 (103)
No	46.6 (81)	No	39.8 (68)

Table III: Onset and duration of AEFI to COVID-19 vaccine in mean hours for 1st and 2nd dose

AEFI	Onset of AEFI (in mean hours)				Duration of AEFI (in mean hours)			
	1st dose	2nd dose	t statistics *(df)*	*p* value	1st dose	2nd dose	t statistics *(df)*	*p* value
Pain at injection site	17.7	18.2	-0.47 (71)	0.963	48.2	49.7	-0.103 (60)	0.918
Swelling	20.3	21.1	0.52 (39)	0.605	52.9	52.6	0.686 (32)	0.498
Dizziness	12.0	9.2	1.8 (20)	0.081	17.3	23.4	-0.682 (20)	0.503
Fever	20.6	20.4	-0.66 (23)	0.515	20.6	34.2	-3.1 (2.2)	0.005
Myalgia	19.5	21.5	1.59 (15)	0.132	38.4	50.3	-1.699 (15)	0.110
Chills	19.1	18	-1.7 (12)	0.116	21.1	26.5	-0.99 (33)	0.338
Headache	15.7	11.8	-0.01 (7)	0.991	35.1	15.2	1.022 (4)	0.365
Arthralgia	18.3	21.1	-0.18 (7)	0.991	41.3	56.3	-1.17 (8)	0.276
Nausea	12.8	14.7	-1.19 (5)	0.286	33.4	24.6	0.364 (5)	0.730
Vomiting	13.0	17.2	-	-	16.2	24.2	-	-
Rashes	168.0				732			
Fainted	1.0				0.5			
Anaphylactic shock	0.33				24			
Pain on arm injected arm	19.6	22.5	1.8 (51)	0.075	46.9	52.9	-0.910 (51)	0.367

Table IV: Association between demographic factors and AEFI to COVID-19 vaccine

Demographic data	AEFIs (dose 1 + dose 2)		Test	*p* value
	Yes % (n)	No % (n)		
Age group				
< 40 years	87.9 (182)	12.1(25)	c^2	
≥40years	84.8 (28)	15.2(5)	0.246	0.577
Gender				
Male	20 (6)	80 (24)	c^2	
Female	88.6 (186)	11.4 (24)	1.763	0.232
Ethnic group				
Malay	88.6 (164)	11.4(21)	c^2	
Non-Malay	83.6 (46)	16.4 (9)	0.974	0.324
Previous COVID-19 infection				
Yes	80 (16)	20 (4)	c^2	
No	88.6 (194)	11.4 (25)	1.267	0.279
Previous allergy (any)				
Yes	85.1 (40)	14.9 (7)	c^2	
No	88.5 (169)	11.5 (22)	0.385	0.535
Medical problems (any)				
Yes	81.8 (27)	18.2 (6)	c^2	
No	88.8 (182)	11.2 (23)	1.288	0.256

Table V: Association between demographic factors and severity of AEFI to COVID-19 vaccine

Participant Character	AEFI severity 1st dose		Test	*p* value	AEFI severity 2nd dose		Test	*p* value
	Mild & Moderate % (n)	Severe % (n)			Mild & Moderate % (n)	Severe % (n)		
Age group								
< 40 years	87.2 (130)	12.8 (19)	c^2		77.4 (113)	22.6 (33)	c^2	
≥40years	81.8 (18)	18.2 (4)	0.486	0.486	73.7 (14)	26.3 (5)	0.131	0.718
Gender								
Male	83.3 (15)	16.7 (3)	c^2		73.3 (11)	26.7 (4)	c^2	
Female	86.9 (133)	13.1 (20)	0.179	0.672	77.3 (116)	22.7 (34)	0.123	0.726
Ethnic group								
Malay	87.1 (115)	12.9 (17)	c^2	0.695	76.2 (99)	23.8 (31)	c^2	
Non-Malay	84.6 (33)	15.4 (6)	0.162		80 (28)	20 (7)	0.230	0.631
Previous COVID-19 infection								
Yes	90.9 (10)	9.1 (1)	c^2		83.3 (10)	16.7 (2)	c^2	
No	86.3 (138)	13.8 (22)	0.192	0.661	76.5 (117)	23.5 (36)	0.296	0.587
Previous allergy (any)								
Yes	87.5 (28)	12.5 (4)	c^2		68.8 (22)	31.3 (10)	c^2	0.227
No	86.3 (120)	13.7 (19)	0.031	0.861	78.8 (104)	21.2 (28)	1.458	
Medical problems (any)								
Yes	84.25 (16)	15.8 (3)	c^2		66.7 (12)	33.3 (6)	c^2	
No	86.8% (131)	13.2% (20)	0.093	0.76	78.1% (114)	21.9% (32)	1.173	0.279

days (30 min to 56 hours). Pain at the injection site which was the most common AEFI, was usually experienced after 17–18 hours of injection and lasted for about 2 days. There was no significant difference in the onset of the AEFI between the first and second doses but the duration of fever experienced after the second dose was significantly longer (p=0.005)(Table III).

There was no association between demographic characteristic of participants and AEFI to COVID-19 vaccine (Table IV).

Analysis for association between demographic characteristic of participants and severity of AEFI to COVID-19 vaccine also showed no significance (Table V).

DISCUSSION

There has been much apprehension and hesitation for the COVID-19 vaccination acceptance as it is a new vaccine and was developed over a short period of time to fight the pandemic. Hence, there is much emphasis on monitoring the efficacy and possible AEFIs related to the COVID-19 vaccines. Our study found that a large majority (87.5 %) of recipients developed AEFI to the COVID-19 vaccine (Pfizer BioNTech) and most (>80%) of them experienced more than one type of reaction. This was similar to the findings from a metanalysis which showed that adverse events related to the COVID-19 vaccines ranged between 21 and 90% with higher percentage of reactions with mRNA vaccines. In Malaysia, almost 25,000 adverse events related to the COVID-19 vaccine were reported by The National Pharmaceutical Regulatory Agency (NPRA) by the end of January 2022.[11]

This study found that the most common (50–70%) AEFI to the Pfizer mRNA COVID-19 vaccine were localised symptoms such as pain at injection site, pain on the injected arm, and swelling at injection site. Similarly, a study in Ontario found that the most common reported adverse events were allergic skin reaction and injection site pain or swelling, 31.6% and 21.2%, respectively.[12] These findings are also similar to the common AEFIs recorded by CDC (Centres for Disease control and Prevention) and NPRA which are pain at injection site and muscle ache.[11,13] Pain at the injection site was also the most common reaction followed by headache and fatigue reported worldwide.[14] The common adverse event reported for Pfizer-BioNTech COVID-19 vaccine were injection site pain, swelling and redness, tiredness, headache, muscle pain, chills, joint pain, fever, nausea, feeling unwell, and lymphadenopathy.[13,15] However, the localised symptoms experienced by our study participants were not associated with recipient characteristics. There is inconsistency in the available literature pertaining to the relationship between the adverse events experienced and participant characteristics. The CDC reported that younger recipients (age 18–55 years) experienced pain more frequently compared to older participants (>55 years) for both first and the second dose of vaccine.[13] However, a study in Indonesia found that age, gender, previous COVID-19 infection, previous allergy, and past medical history did not affect AEFI occurrence whether the participants were vaccinated with either Pfizer-BioNTech, Sinovac, or Oxford–AstraZeneca vaccine (Covishield).[16]

The most common systemic adverse events of the vaccine reported in our study was fever, dizziness, and myalgia for both first and second dose vaccine. These systemic adverse events also did not show any association with recipient characteristics. The common systemic adverse events recorded by CDC to this vaccine were fatigue, headache, and new or worsened generalised muscle pain which was more among the younger age group and after the second dose.[13] Common systemic adverse events reported in Malaysia by the NPRA were fever, headache, and Immunisation Stress-Related Response (ISRR).[11] ISSR is a response to the stress that individuals may feel regarding getting an injection which includes vasovagal reaction, fainting, hyperventilation, or non-epileptic seizures. These reactions were previously known as "AEFI arising from anxiety about the immunisation").[17]

Comparing other COVID-19 vaccines, such as the inactivated virus, Sinovac life sciences Co, the localised symptom such as pain at the injection site was also the most common localised AEFI. While the most common systemic AEFI with this vaccine was malaise.[16] AEFI due to another widely used vaccine, the Oxford–AstraZeneca recombinant vaccine, Covishield, affecting about 50% of recipients with majority (37%) experiencing localised symptoms of swelling and pain at the injection site and fever (25%) as the main systemic symptoms.[18] Among the more serious AEFIs, anaphylaxis is a life-threatening response that requires emergency treatment. Fortunately, only one recipient in our study developed anaphylaxis with the first dose and was given Sinovac vaccine (inactivated virus) for the second dose. Although rare, continued monitoring of the anaphylaxis AEFI due to Pfizer-BioNTech COVID-19 is essential for further research and development.[10]

Although a large majority of vaccinated individuals in our study experienced some type of AEFI, most of these reactions were reported as mild (47.3–73.6%) to moderate (12.9–29.7%) hence not requiring sick leave, hospital admission, or causing severe limitation of activity. Similarly, other studies looking at the COVID-19 mRNA vaccine also showed that that most of the local or systemic adverse reactions were non-severe with about only 2–22% of cases being severe.[12,19,20,21] Most of the recipients of the Oxford–AstraZeneca vaccine (Covishield) in a study from Bangladesh also reported mild to moderate severity of the AEFI.[18] Similarly, in Ontario, 99.0% of AEFI reported were non-serious.[12]

The mean duration for onset for AEFI to COVID-19 vaccine in our study, ranged within 30 minutes and about 1 day (0.33–22.5 hours) and reactions mostly lasted between 30 minutes and 2.5 days. Pain at the injection site, which was the most common AEFI was commonly experienced after 12 hours of receiving the vaccine and lasted for about 2.5 days. The median time of local reaction onset recorded by CDC was from the day of vaccine receipt, up to 2 days and lasted between 1 and 2 days.[13] Another study by Chen et al. also found a similar presentation.[19] The median interval for symptom onset of non-anaphylactic adverse reactions for the Pfizer-BioNTech COVID-19 vaccine in an earlier local study was similar to our findings.[10] Shimabukuro et al. found that the median interval for anaphylactic reaction was 13 minutes.[22] Our study also found that the mean duration of fever experienced after the second dose vaccine was significantly longer compared to the first dose. In general, the severity of AEFI to vaccines is anticipated to be more with the second dose; however, these reactions may be unpredictable. This is because there are multiple factors affecting AEFIs due to the complex immune system activation which gets triggered when the vaccine is instituted into the system.[23]

LIMITATIONS

This study was based on self-reported adverse reaction to the vaccine hence other possible causes for the symptoms could not be verified. Recall bias cannot be excluded, as data were collected between 2 weeks after the first dose up to the following 5 months during which the participants received their second dose. Most vaccine recipients probably anticipated to experience AEFI as almost all (98.8%, n=237) of them received information regarding possible vaccine-related adverse events. This heightened awareness could have influenced the self-reported symptoms related to ISRR. Convenience method of sampling could have contributed to selection bias; hence the findings may not be generalisable.

CONCLUSION

This study shows high rates (87.5%) of AEFI with the COVID-19 mRNA vaccine (Pfizer-BioNTech) and the majority of recipients experienced more than one reaction. However, it is reassuring that most of these reactions were reported as mild to moderate severity. A large majority of these reactions

started within 1 day of the injection and were transient, lasting between 30 minutes and about 2.5 days. Pain at injection site, pain on the injected arm, and swelling at injection site were the most common localised symptoms while fever, myalgia, and dizziness were the most common systemic symptoms. Duration of fever was significantly longer after the second dose of vaccine compared to the first.

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This study was self-funded, and we declare no conflicts of interest.

ETHICAL APPROVAL

The ethical approval was obtained from Medical Research & Ethics Committee's (MREC), Ministry of Health Malaysia, and Research Ethics Committee of Universiti Kebangsaan Malaysia

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Psychological impact amongst patients with COVID-19 in Perak state

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ABSTRACT

Introduction: Psychological distress had been documented since the beginning of the COVID-19 outbreak in 2019. The aim of the study is to describe the psychological impact among those who were hospitalized for COVID-19 infection within 6 months after being discharged from the hospital. The psychological impact in this study is defined as depression, anxiety, and stress.

Materials and methods: This was a cross-sectional study conducted from July 2020 till August 2021 in a regional state hospital, north of Malaysia. All patients requiring hospitalization for COVID-19 were approached within the first 2 weeks after admission to administer the Depression, Anxiety and Stress Scale – 21 Items (DASS-21) scale. Follow-up phone calls were made within 3 months of discharged to enquire about the DASS-21 items as well as the Impact of Event Scale-Revised (IES-R) scale items. Participants above the age of 18 and technology savvy to answer an online questionnaire were recruited for the study. We excluded participants with a known history of psychotic disorder from the study. We utilised the DASS-21 to screen for depression, anxiety, and stress, as well as the IES-R to identify symptoms of post-traumatic stress disorder. Participants could answer the questionnaires in either English or Bahasa Malaysia. For comparison of two categorical data, a chi-square was applied. A univariate analysis was first conducted and all variables with a p ≤0.3 was then entered into the multivariate analysis for the final output. Other than the univariate analysis, all other *p* values <0.05 were considered to be statistically significant. All data collected were tabulated and analysed in the SPSS v21.0 system.

Results: A total of 306 out of 696 COVID-19 patients responded. The mean age for the participants was 31.69 (SD:11.19) years old. From the total, 54.2% were ladies, 78.8% were Malay, 50.7% were unmarried, 55.2% had higher education, and 67.6% were employed at the time of the survey. We found 20.5% of the participants were depressed, 38.9% had moderate anxiety, and 17.3% were stressed. From the total, 31.7% of the participants were deemed to have had some symptoms of post-traumatic stress disorder (PTSD) ranging from mild to severe. From the final multivariate analysis, it was found that depression (*p*=0.02) had a 2.78 times likeliness of having PTSD, anxiety (*p*<0.001) had a 3.35 times likeliness of having PTSD and stressed patients (*p*=0.02) 2.86 times likeliness of having PTSD when compared to those without PTSD.

Conclusion: Patients reported to suffer from symptoms of PTSD and might benefit from psychological interventions to mitigate the impact in the long run.

KEYWORDS:
COVID-19, mental health, anxiety, depression, stress, PTSD

INTRODUCTION

The World Health Organization (WHO) declared COVID-19 as a Public Health Emergency of International Concern on 30 January 2020 and a pandemic on 11 March 2020 when the life-threatening coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly from China to more than 222 countries and territories since December 2019.[1] Over time, there are also emerging new variants which have been observed to be more infectious, contagious, and more likely to cause breakthroughs or even re-infections to those who have been vaccinated or have been infected previously. Till now, Malaysia has reported a total of 2,754,513 local cases (as of 31 December 2021), with recovered 2,677,406 patients and 31,462 deaths due to COVID-19 infections.[2] In the state of Perak, a total of 128,864 (as of 31 December 2021) patients were diagnosed with COVID-19 infection with 108,396 recovered and 1,393 deaths (http://COVID-19.moh.gov.my/).[3] Patients with Category 3 and above were admitted to COVID-19 hospitals within the state of Perak, whilst those with mild or no symptoms were quarantined at home.

The COVID-19 pandemic has been found to be associated with psychological distress and symptoms of mental illness.[4] Implementation of movement control orders to control the spread of virus had a profound impact on people's daily activities. People are forced to live in isolation, leading to changes in their daily lives, loss of jobs, financial difficulties, and grief over death of loved ones. Similarly, the psychological impact of being infected with COVID-19 itself has also affected the mental health and well-being of many. The majority of the published research focused on the psychological response during the COVID-19 outbreak among healthcare workers,[5] the general public [6] and the vulnerable groups like elderly people, pregnant mothers, underlying medical condition, children, and migrants. There is more evidence of post-traumatic stress symptoms following COVID-19 infection. Online surveys conducted by Sun et al[7] found the prevalence of post-traumatic stress symptoms (PTSS) 1 month after the COVID-19 outbreak was 4.6% and

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7% reported in China's hardest-hit areas.[8] A recent review among the 236 379 survivors of COVID-19 found the estimated incidence of a neurological or psychiatric diagnosis in the following 6 months was 33.62% (95% CI 33.17-34.7) with 17.39% (95% CI 17.04-17.74) fulfilled the diagnosis of anxiety disorder.[9] However, studies on mental health of hospitalized patients with COVID-19 after being discharged from the hospital, particularly on post-traumatic stress disorders (PTSDs) are still scarce.

Psychological factors, particularly among those who were hospitalized for COVID-19, such as fear of their illness progression, disability, and even stigma are valuable information to mitigate the impact of mental health in longer terms. Thus, it is vital to investigate the related factors of depression, anxiety, stress, and even PTSD (within 6 months) and delayed onset PTSD (6 months after exposure of an event) among patients infected with COVID-19. Evidence has shown that the initial phase of the pandemic, prevalence of significant post-traumatic stress symptoms in the patients discharged from the quarantine facilities was at a staggeringly high 96.2%.[10]

The objective of this study was to understand the psychological impact through evaluation on COVID-19 patients who were hospitalized in the state hospital of Hospital Raja Permaisuri Bainun, Ipoh.

The study defines psychological impact as depression, anxiety, and stress.

The findings may assist in providing a holistic intervention, including psychological intervention, in improving the physical and mental health of the patients during the COVID-19 pandemic. It may also enable policymakers and mental health care providers to tailor the needs of the survivors.

MATERIALS AND METHODS

Study design

This is a cross-sectional study which was conducted over 13 months from July 2020 till August 2021 in the northern regional state hospital, Hospital Raja Permaisuri Bainun Ipoh, Perak. All patients who required hospitalization for COVID-19 and subsequently discharged were approached for the study. The study was approved by the Malaysia medical research and ethics committees on the 9 July 2020 with NMRR-20-1053-54983.

Participants were informed about the research through telephone when they were contacted by the Mental Health Psychosocial and Support team from the Department of Psychiatry and Mental Health of the hospital for psychological first aid within the first 2 weeks after their admission (DASS-21 scale items were used). Follow-up phone calls were made within 3 months of discharge to enquire about the DASS-21 items as well as the Impact of Event Scale-Revised (IES-R) scale items. To be eligible, participants had to be 18 years or above and were literate to answer online questions in either language, i.e., Bahasa Malaysia and English. The questions took approximately 10 minutes to complete. Participants who had a recent diagnosis of psychotic disorder 4 weeks prior to recruitment were excluded from the study and was confirmed through electronic medical record.

Study tool

The DASS-21 and Impact of Event Scale were used. DASS-21 Item is a self-report scale designed to measure the emotional states of depression, anxiety, and stress. Each score will provide a mild, moderate, or severe result. It consists of three 7-item subscales: anxiety (items 2, 4, 7, 9, 15, 19, and 20), stress (1, 6, 8, 11, 12, 14, and 18), and depression (items 3, 5, 10, 13, 16, 17, and 21). Subjects are asked to use 4-point severity/frequency scales ranging from 0 (Did not apply to me at all) to 3 (Applied to me very much, or most of the time) to rate the extent to which they have experienced each state over the past 1 week. Scores for Depression, Anxiety, and Stress are calculated by summing the scores for the relevant items. The subscales scores can be allocated on one of five levels of severity, for depression, normal (0–9), mild (10–13), moderate (14–20), severe (21–27), and extremely severe (28+); for anxiety, normal (0–7), mild (8–9), moderate (10–14), severe (15–19), and extremely severe (20+); and for stress, normal (0–14), mild (15–18), moderate (19–25), severe (26–33), and extremely severe (34+).[11] The DASS-21 has been previously used in COVID-19-related research[15] and has shown high internal consistency.

The IES-R has been one of the most widely used self-report scales within the trauma literature.12 It was not developed as a diagnostic tool for PTSD; however, its discriminative validity suggests that the measure can differentiate between individuals with and without PTSD. Both scales are validated in Bahasa Malaysia (BM).

Data on PTSD were collected using the 22-items IES-R (English version) or 19-item (BM version). The IES-R is a 22-item self-administered questionnaire designed to assess subjective distress caused by traumatic events in the past 7 days. Items are rated on 5-point scale ranging from 0 (not at all or hardly ever) to 4 (extremely). Scale scores are formed for the three subscales that measure the three main symptoms of PTSD: intrusion (items 1, 2, 3, 6, 9, 14, 16, and 20), avoidance (items 5, 7, 8, 11, 12, 13, 17, and 22), and hyperarousal (items 4, 10, 15, 18, 19, and 21). The IES-R yields a total score (ranging from 0 to 88) and subscale scores can also be calculated for the Intrusion, Avoidance, and Hyperarousal subscales. It does not serve as a diagnostic tool for PTSD.[13] The Bahasa Malaysia IES-R has 19 items and shows good model fit (RMSEA=O.056, SRMR=0.058, CFI=0.933, TLI=0.923) and composite reliability (Psychological=0.89, Behavioural=0.83). The English IES-R cut off points are as follows:

24 or more: PTSD is a clinical concern. Those with scores this high who do not have full PTSD will have partial PTSD or at least some of the symptoms
33 and above: This represents the best cut-off for a probable diagnosis of PTSD
37 or more: This is high enough to suppress your immune system's functioning (even 10 years after an impact event)

Sampling

For the time period stated, Perak had witnessed 37,421 cases in total (hospitalised and unhospitalised). Using the Raosoft

Calculator (available free at: http://www.raosoft.com/samplesize.html), we calculated a sample size based on the proportion to population. Setting the margin of error at 5%, the confidence interval at 95%, the population size as 37,421 and the distribution at 50%, the sample size needed for this study was 381. The researchers could not identify from the records in total how many patients were admitted in the hospital specifically for COVID-19 as it was done based on availability. However, the researchers chose the total number (37,421) for the sample size calculation (an obvious overestimate).

Data collection

The patient information sheet was shared with participants using a google form with an informed consent form attached. Patient information sheet was shared with participants using an e-form and google form with an informed consent form appended to it. Participants who indicated "YES" on consent section were directed to the two sets of self-report questionnaires: DASS-21 to assess the psychological impact of the disease and IES-R. Participants were encouraged to answer the questionnaires within 3 months of discharge from the hospital. The responses were captured in the excel sheet and later imported into SPSS v21.0 for final analysis. The data were collected and were analysed by the principal investigator and two co-authors.

Statistical analysis

Data were initially collated into an Excel spreadsheet and were later imported into the SPSS v21.0 software for final analysis. We analysed the categorical data as frequencies and percentages whilst the continuous data as mean and standard deviation (for parametric data) or median and inter-quartile range (for nonparametric data). The Chi-square test was used to compare two categorical data and for further advanced analyses of the relationship between PTSD and relevant demographic details. A univariate analysis was first conducted and all variables with a $p \leq 0.3$ was then entered into the multivariate analysis for the final output. Other than the univariate analysis, all other p values <0.05 were considered to be statistically significant.

In this study, score of 24 and above was considered as having PTSD for the binary regression analysis (both for the English and BM questionnaire).

RESULTS

Response rate

The researchers approached 696 individuals who fulfilled the inclusion criteria, and the final number recruited into the study was 306, with a response rate of 43.97%. This response rate provided 80% of the intended sample size. Two hundred and forty-one respondents (78.8%) were Malay, 155 (50.7%) were single, 169 (55.2%) had higher education, and 207 (67.6%) were employed at the time of the survey.

Demography

From the total of 306 participants, 89.2% of them answered the questionnaire in Bahasa Melayu. The mean age for the participants was 31.69 (SD:11.19) years old. There was a near equal breakdown of both genders with the females edging out the males by being 54.2% of the sample population. From the total, 241 (78.8%) were Malay, 155 (50.7%) of them were single, 169 (55.2%) of them had higher education, and 207 (67.6%) of them were employed at the time of the survey. The only continuous variable in the demography was the variable "age" and it was distributed normally. Thus, it was reported as mean and SD (standard deviation). Details of the demographic characteristics of the participants are shown in Table I.

Measurement of the DASS-21 and IES-R scales

Table II describes the results obtained from the DASS-21 and IES-R scales. From the total, 63 (20.5%) of the participants were depressed, 119 (38.9%) had anxiety with moderate in severity and 53 (17.3%) were stressed. From the total, one-third (31.7%) of the participants were deemed to have some amount of PTSD (ranging from mild to severe).

Analytical analysis

For the analysis of the DASS-21 scale, the researchers clumped the "Normal and Mild" symptoms together as it was clinically relevant that these participants were observed without further treatment. Participants with "Moderate to Extremely Severe" were given treatment.

Depression compared to PTSD

Table III displays the relationship between depression and PTSD. From the table, we can see that 27.0% of those with depression did not suffer from PTSD. The largest proportion of those with extreme depression (89.5%) also had suffered from PTSD, and it is statistically significant (p<0.001). When a chi-square was conducted amongst the two groups, it yielded a statistically significant difference (p<0.001). From the eye-ball method, we can be assured that there is an 79.0% (sensitivity) chance of not having PTSD and if there is depression, there is a 73.0% (specificity) chance of having PTSD. An receiver operating characteristic (ROC) analysis done showed a 69.6% area under the curve (AUC) making the depression scale a moderate to good predictor of PTSD. Details of the analyses are shown in Tables III and IV.

Anxiety compared to PTSD

Table III also compares the results of the anxiety status with the PTSD status. The clumped analysis shows that 50 (42.0%) suffered from anxiety and had no PTSD. From the fragmented analysis of anxiety (Table 5), 34 (75.6%) with extremely severe anxiety also had PTSD. Chi-square analysis demonstrated a statistically significant difference between the 2 groups (p<0.001). From the eye-ball method, we can see that the sensitivity of the anxiety scale is 85.0% and the specificity is 58.0%. The ROC analysis yielded an AUC of 73.6% which was moderate to good PTSD predictor using the anxiety scale. Full details of the results can be shown in Tables V and VI.

Stress compared to PTSD

When comparing the category "Stress" to PTSD utilising the DASS-21 scale, we found that 22.6% of those with PTSD had no stress and 81.9% of those who were extremely stressed had PTSD. The sensitivity analysis showed that the stress scale was 77.9% sensitive and 77.4% specific. The AUC was 68.3% which was a moderate to good predictor of PTSD. Full details of the results are listed in the Table IV.

Table I: Demography of the participants in the study

Variable		n (%) N=306
Answered in		
BM		273 (89.2)
English		33 (10.8)
Age	mean (SD)	31.69 (11.19)
Gender		
Male		140 (45.8)
Female		166 (54.2)
Race		
Malay		241 (78.8)
Chinese		27 (8.8)
Indian		35 (11.4)
Others		3 (1.0)
Marital status		
Single		155 (50.7)
Married		138 (45.1)
Separated/ Divorced		11 (3.6)
Widowed		2 (0.7)
Highest education attained		
No formal education		6 (2.0)
Primary school		6 (2.0)
Secondary school		125 (40.8)
Higher education		169 (55.2)
Employment status		
Employed		207 (67.6)
Self-employed		26 (8.5)
Retired		6 (2.0)
Unemployed		67 (21.9)

Table II: The analysis of the DASS-21 Scale measuring Depression, Anxiety, and Stress with the IES-R scale measuring for the presence of PTSD

Variable	n (%) N=306
Depression	
Normal- Mild	243 (79.5)
Depressed	63 (20.5)
Moderate	31 (10.1)
Severe	13 (4.2)
Extremely severe	19 (6.2)
Anxiety	
Normal- Mild	187 (61.1)
Anxious	119 (38.9)
Moderate	50 (16.3)
Severe	24 (7.8)
Extremely severe	45 (14.7)
Stress	
Normal- Mild	253 (82.7)
Stressed	53 (17.3)
Moderate	25 (8.2)
Severe	17 (5.6)
Extremely severe	11 (3.6)
IESR	
Normal	209 (68.3)
PTSD	97 (31.7)

Table III: The comparison of Depression and Anxiety status (fragmented and clumped) and the PTSD status

Variable	Depression N (%)					*p* value
	Normal	*Mild*	*Moderate*	*Severe*	*Extremely severe*	
IESR						
Normal	177 (82.3)	15 (53.6)	12 (38.7)	3 (23.1)	2 (10.5)	<0.001
PTSD	38 (17.7)	13 (46.4)	19 (61.3)	10 (76.9)	17 (89.5)	
Variable	*Normal to Mild*		*Moderate to Extremely severe*			***p* value**
IESR						
Normal	192 (79.0)		17 (27.0)			<0.001
PTSD	51 (21.0)		46 (73.0)			
Variable	**Anxiety N (%)**					***p* value**
	Normal	*Mild*	*Moderate*	*Severe*	*Extremely severe*	
IESR						
Normal	139 (88.0)	20 (69.0)	32 (64.0)	7 (29.2)	11 (24.4)	<0.001
PTSD	19 (12.0)	9 (31.0)	18 (36.0)	17 (70.8)	34 (75.6)	
Variable	*Normal to Mild*		*Moderate to Extremely severe*			***p* value**
IESR						
Normal	159 (85.0)		50 (42.0)			<0.001
PTSD	28 (15.0)		69 (58.0)			

Table IV: The comparison of Stress status (fragmented) and the PTSD status

Variable	Stress N (%)					*p* value
	Normal	*Mild*	*Moderate*	*Severe*	*Extremely severe*	
IESR						
Normal	184 (81.4)	13 (48.1)	7 (28.0)	3 (17.6)	2 (18.2)	<0.001
PTSD	42 (18.6)	14 (51.9)	18 (72.0)	14 (82.4)	9 (81.9)	
Variable	*Normal to Mild*		*Moderate to Extremely severe*			***p* value**
IESR						
Normal	197 (77.9)		12 (22.6)			<0.001
PTSD	56 (22.1)		41 (77.4)			

Table V: The binary logistic regression (univariate and multivariate analysis) of those with PTSD with the relevant demographic variables

Variable	OR (95%CI)	*p* value	AOR (95%CI)	*p* value
Age	0.97 (0.95–1.00)	0.03	0.99 (0.96–1.03)	0.62
Gender				
Male	Ref	0.12	Ref	0.44
Female	1.48 (0.91–2.42)		1.27 (0.70–2.28)	
Race				
Malay	>1000	0.73		
Chinese	>1000			
Indian	>1000			
Others	Ref			
Marital status				
Single	1.76 (1.06–2.91)	0.16	1.09 (0.51–2.36)	0.90
Married	Ref		Ref	
Separated/ Divorced	1.10 (0.28–4.39)		0.58 (0.11–2.99)	
Widowed	2.94 (0.18–48.31)		1.43 (0.03–61.39)	
Employment status				
Employed	1.00 (0.56–1.80)	0.95		
Self-employed	0.75 (0.27–2.06)			
Retired	<0.001			
Unemployed	Ref			
Highest education attained				
No formal education	0.54 (0.06–4.75)	0.41		
Primary school	1.34 (0.23–7.64)			
Secondary school	Ref			
Higher education	1.47 (0.89–2.44)			
Depression				
Normal-Mild	Ref	<0.001	Ref	0.02
Moderate- Extremely severe	10.19 (5.39–19.25)		2.78 (1.21–6.36)	
Anxiety				
Normal-Mild	Ref	<0.001	Ref	<0.001
Moderate- Extremely severe	7.84 (4.56–13.48)		3.35 (1.74–6.46)	
Stress				
Normal-Mild	Ref	<0.001	Ref	0.02
Moderate- Extremely severe	12.02 (5.92–24.41)		2.86 (1.16–7.02)	

Binary logistic regression

A binary logistic regression with the outcome of comparing those with PTSD and those who did not have PTSD with demographic variables. A univariate analysis was done first including all demographic variables with a comparison to the IES-R (to detect PTSD). Variables that had a p value of ≤0.3 were included into the final multivariate analysis. Demographic variables of age (p=0.03), gender (p=0.12), marital status (p=0.16), depression (p<0.001), anxiety (p<0.001), and stress (p<0.001) were the variables included into the multivariate analysis. Based on the final analysis, the likelihood of having PTSD is 2.78 times in depression (p=0.02), 3.35 times in anxiety (p<0.001), and 2.86 times in stressed patients (p=0.02) compared to those without PTSD. The final model yielded a Nagelkerke R square 34.9% (meaning the model was 66.1% fit- moderate) and a Hosmer and Lemeshow Test p=0.61 (not significant indicating a fit model). The full details are listed in Table V.

DISCUSSION

Psychological responses towards the COVID-19 pandemic and its impact in every member in the society have been documented in many parts of the world since the outbreak.[14] In China, Wang et al[15] reported 53.8% of the respondents (N=1210) rated the psychological impact of the outbreak as moderate or severe with 16.5% depressive symptoms, 28.8% anxious symptoms and 8.1% stress categorised under moderate to severe in severity. Italy, which was the first European country to implement a national lockdown to control the spread of virus found that out of 501 subjects, 35.33% of university students classified as anxious and 72.93% as depressed.[16] In the systematic review and meta-analysis, the prevalence of depression, anxiety, and PTSD was 15.9% (95% CI, 13.24-19.13), 15.5% (95% CI, 12.29-18.54), and 21.94% (95% CI, 9.37-43.31), respectively.[14]

Previous experiences of outbreaks like those caused by SARS, Ebola, and MERS-CoV contribute to heightening the impact of the present pandemic. Perrin et al[17] found that females are more affected than males. The less educated, single people, children, and adolescents, those who have no children reported high levels of stress, anxiety, depression, and psychological impact. These subgroups, considered at greater risk for adverse psychological outcomes during a public health crisis, may be experiencing low social and emotional support, increased perceived threat to well-being and feelings of fear, isolation, and uncertainty. In our study, the ratio of males to females was almost equal, but females were more affected than males, those who were widowed, employed, and had a higher education were more affected.

In our study, we used DASS-21 scale and IES-R to understand the level of psychological distress among participants who were hospitalized for COVID-19 infection. Being diagnosed to have COVID-19 causes a number of emotional and psychological dysregulation to patients as they are not only suffering from the respiratory symptoms, but also psychosocial factors like separation from family members and relatives, fear of complications, worry about people who may be infected, loss of income, loss of loved ones, and discrimination associated with the infection may worsen their mental health. We found our participants who reported moderate to extremely severe, anxiety symptoms (moderate 16.3%, extremely severe 14.7%) are more prominent than depression (moderate 10.1%) and stress (moderate 8.2%). In one of the recent studies, Huang et al[18] found that COVID-19 survivors had anxiety or depression at 23% at 6-month visit and 26% at 12-month visit. In a cohort study by Huang et al19, 23% (367/1617) reported anxiety or depression after 6 months of COVID-19 infection.

PTSD can occur in people who have experienced a traumatic event and can be disabling. According to DSM-V,[20] clinical manifestations include recurrent and intrusive memories, flashbacks of the trauma, avoidance of trauma-related cues, and a variety of mood and dissociative as well as cognitive symptoms. In China, the majority reported worse psychological impact with overall mean IES-R scores more than 24 points, indicating the presence of PTSD symptoms.[15,20,21] In our study, the largest proportion of those with scored under the category of moderate to extremely severe depression (73.0%) is mostly experiencing prominent symptoms of PTSD (p<0.001). Janiri et al.[22] found 115 (30.2%) with PTSD after acute COVID-19 infection. The data from the final multivariate analysis showed that participants who had depression (p=0.02) had a 2.78 times likeliness of having PTSD. Similarly, participants who reported having anxiety (p<0.001) had a 3.35 times likeliness of having PTSD. Participants who reported stress (p=0.02) had a 2.86 times likeliness of having PTSD when compared to those without PTSD.

The strength of this study was the use of validated tools to analyse the impact of psychological distress. The online survey was not only feasible but also able to recruit patients during this critical moment in a safe manner. There are some limitations in the study. First, this study used online platform to collect responses from participants. Those who did not have telephone devices, understood the language, and were concerned about confidentiality could not respond to the study. Second, our study could only focus on the hospitalised participants in one centre. Third, responses from a different time frame after 1 month of diagnosis and discharge from the hospital may alter the level of intensity. Fourth, reporting bias cannot be excluded. Fifth, there is no control group for comparison in our study. Other factors like elderly people, poor internet access, migrant, or other minority groups might have missed out from the study. Therefore, the results do not represent psychological distress following COVID-19 in general.

CONCLUSIONS

With the pandemic which is still ongoing, people continue to experience psychological distress in various intensity. Our study has found patients who were hospitalized for COVID-19 infection experienced depressive symptoms, anxiety symptoms, and stressed using DASS-21. And the scoring which falls under moderate to extremely severe is highly suggestive of post-traumatic stress symptoms. Therefore, mental health service providers need to provide resources and intervention to mitigate the impact.

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DECLARATIONS OF INTEREST

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ORIGINAL ARTICLE

Methylprednisolone in severe COVID-19 with acute respiratory distress syndrome – less is more?

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ABSTRACT

Introduction: Corticosteroids, particularly methylprednisolone, are part of the treatment for severe COVID-19 with acute respiratory distress syndrome (ARDS). In this study, we aimed to compare the mortalities of patients treated with higher versus lower doses of methylprednisolone. Secondary outcomes included oxygenation, need for mechanical ventilation, length of stay in intensive care unit (ICU), secondary infection, improvement of PaO2/FiO2 (PF) ratio, and inflammatory response as expressed by C-reactive protein (CRP).

Materials and methods: A retrospective cohort study conducted at Sarawak General Hospital from 1st June to 30th September 2021. Patients who received intravenous methylprednisolone for severe COVID-19 in the ICU were identified and divided into two groups: higher dose (cumulative dose more than 10 mg per kg) and lower dose (cumulative dose less than 10 mg per kg).

Results: Out of a total of 165 patients, 40 (24.2%) patients received higher dose methylprednisolone. There was no significant difference in socio-demographic characteristics (age, gender, body mass index), COVID-19 vaccination status, laboratory parameters (lymphocyte count, CRP, lactate dehydrogenase, D-dimer), or usage of immunomodulator therapy between the groups. Overall mortality was 23.6%. Mortality in the higher dose group was twice as high compared to lower dose group (37.5% versus 19.2%) (OR 3.79, 95% CI 1.24–11.59, $p<0.05$). In addition, the higher dose cohort developed more secondary infections (87.5%) and had longer stays in ICU (median 11 days, IQR 8–15). No significant difference was found between both cohorts in terms of CRP reduction, improvement of PF ratio, or the need for mechanical ventilation post methylprednisolone.

Conclusion: In this study, the use of higher dose methylprednisolone in COVID-19 with ARDS was not associated with better clinical outcomes. A lower dose of methylprednisolone might be sufficient in treating severe COVID-19 with ARDS.

KEYWORDS:
COVID-19, methylprednisolone, acute respiratory distress syndrome (ARDS), mortality

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first recognized in Wuhan, China in December 2019. It has rapidly spread and emerged as a great challenge to the world. The common signs of illness include fever, cough, shortness of breath, myalgia, and diarrhoea. Ideally, specific adaptive immune responses eliminate virus reproduction and preclude disease progression to severe stages. However, when protective immune responses fail, the disease enters a severe inflammatory phase with cytokine release, which causes massive damage to organs with high angiotensin-converting enzyme 2 expression.[1] Acute respiratory distress syndrome (ARDS) is the most common complication leading to the need for mechanical ventilation and admission to intensive care unit (ICU).[2] Therefore, suppressing the proinflammatory response and controlling the cytokine storm is crucial in the treatment of severe COVID-19 illness.

Since 1967, the role of corticosteroids in ARDS has been widely investigated.[3] As widespread inflammatory response is found in the lungs, corticosteroids have potential benefits in reversing the pulmonary inflammation. The use of methylprednisolone in patients with COVID-19 ARDS, particularly those with elevated inflammatory markers during admission, had been reported in few studies and case series.[4-6] Following the release of the large UK-based RECOVERY trial on June 16, 2020, the approach in treating patients with COVID-19 underwent a major change. In the RECOVERY trial, the use of dexamethasone (6mg per day for 10 days) reduced mortality by one-third in patients receiving mechanical ventilation compared to usual standard care.[7] However, it was still unclear if this benefit was from dexamethasone in particular, or a class effect of corticosteroids. The efficacy of methylprednisolone compared to dexamethasone in the treatment of severe COVID-19 pneumonia is still highly debated.[8] Furthermore, there is no evidence to clarify appropriate corticosteroid doses. Many clinically important questions remain unanswered. Hence, in this report, we aimed to compare the clinical outcome of patients receiving higher dose methylprednisolone versus lower dose methylprednisolone in hospitalized ICU patients with severe COVID-19 ARDS.

MATERIALS AND METHODS

Study design

This was a single-center, retrospective, cohort study performed in Sarawak General Hospital, Sarawak, Malaysia.

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Our hospital is located in the local epicentre of the pandemic and is a major tertiary hospital responsible for the treatment of patients with severe COVID-19. All adult patients admitted to ICU with highly suspected Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2-2) infection from 1st June to 30th September 2021 were initially selected and evaluated. Eligible patients included all adults with a positive, laboratory-confirmed test for SARS-CoV-2 developing ARDS, and treated with intravenous methylprednisolone. ARDS was defined by the presence of bilateral pulmonary infiltrates not explained by an etiology other than COVID-19, with PaO2/FiO2 (PF) ratio of less than 300.

Data collection

Electronic medical records from the critical care information system were reviewed, and data were extracted for the period between admission to discharge from ICU, or death, whichever occurred first. Epidemiological, clinical, radiologic, laboratory test results on admission and during hospitalization, treatment, complications, and outcome data were collected.

Patients were divided into two different groups, depending on the dosage of intravenous methylprednisolone administered for ARDS:

- Higher dose group: cumulative dosage of intravenous methylprednisolone more than 10 mg per kg
- Lower dose group: cumulative dosage of intravenous methylprednisolone at and less than 10 mg per kg

The dosage of higher and lower dose methylprednisolone was chosen based on our national COVID-19 management guideline[9] that recommended the use of IV methylprednisolone 2 mg per kg up to 5 days which made up a total cumulative dose of 10 mg per kg. Thus, patients who received a cumulative methylprednisolone dose of more than 10 mg per kg were grouped into the higher dose. According to our local COVID-19 management guidelines[9], IV methylprednisolone 2 mg per kg for 3 to 5 days were recommended in patient requiring higher levels of oxygen support, including category 4b, 5a, and 5b. In these local guidelines, patients requiring high flow mask are sub-classified as category 4b, while those requiring noninvasive ventilation or high flow nasal cannula (HFNC) are classified as category 5a, with category 5b denoting mechanical ventilation with or without other organ failures. In our center, the methylprednisolone dosing decisions are at the discretion of the treating physicians and intensivists.

OUTCOME

The primary outcome was the mortality between the higher dose and lower dose groups. Secondary outcomes included length of stay in ICU, rate of secondary infections, improvement of PF ratio, and inflammatory response (expressed by CRP, lactate dehydrogenase and D-dimer levels).

STATISTICAL ANALYSIS

IBM SPSS statistics 22 was used for the statistical analysis. Descriptive statistics were used to compare the baseline data. Continuous variables were described as mean (standard deviation) or median (interquartile range) depending on the distribution of data, and comparison was done by using parametric or nonparametric statistical test where appropriate. Categorical variables were reported using absolute and relative frequencies and analyzed using Chi-square.

Both unadjusted and multivariable logistic regression models were performed to investigate the effect of both dosages on primary and secondary outcomes. The multivariate model was adjusted for potential confounding factors identified at baseline data. A p-value of less than 0.05 was considered statistically significant. Sample size was calculated using Power and Sample Size calculator. From the literature prior data indicate that mortality rate with lower dose methylprednisolone is 18%.[10] If mortality in the higher dose methylprednisolone group is assumed to be 39%, a sample size of 158 is needed to reject the null hypothesis with a power of 80%, p cut-off value of 5% for statistical significance. In this study, universal sampling technique was applied, with all eligible patients during the study period recruited.

RESULTS

A total of 206 patients were admitted to ICU with positive SARS-CoV-2 infection during the four-month study period. All were evaluated based on the eligibility criteria. Patients not developing ARDS (n = 10), patients with other alternative diagnosis for ARDS (n = 25), and patients not receiving intravenous methylprednisolone (n = 6) were excluded.

In total, 165 patients including 94 (57%) males and 71 (43%) females were included in the study. Ages ranged from 18 to 83 years old with a mean ± SD of 55 ± 14.5 years. The baseline characteristics of our study population was shown in Table I. Among the 165 patients, 40 (24.2%) patients received higher dose methylprednisolone. Comparing the higher dose and lower dose groups, we found no significant differences in baseline characteristics of age, gender, comorbidities except autoimmune disease, presenting symptoms, COVID-19 vaccination status, initial PF ratio and inflammatory markers such as CRP, lactate dehydrogenase (LDH), and D-Dimer.

Primary Outcome

Overall mortality recorded in this report was 23.6% (n = 165) and was two times higher in the higher dose group than in lower dose group (37.5% versus 19.2%, respectively). The unadjusted logistic regression model showed a significantly higher risk of death in patients with ARDS receiving higher dose of methylprednisolone compared to lower dose (OR 2.52, 95% CI 1.16–5.50, $p<0.05$; Table II). After adjusting for age, gender, COVID vaccination status, mechanical ventilation, and secondary infection, the results remained statistically significant (OR 3.40, 95% CI 1.09–10.63, $p<0.05$; Table II).

Secondary outcomes

After treatment with methylprednisolone, we observed an overall improvement of PF ratio from median 116 to 202 (95% CI: 77.1–99.6, p=0.001). However, there was no significant difference in PF ratio increment between the higher dose versus lower dose groups ($p=0.552$).

Table I: Baseline demographics and clinical characteristics

	All patients (n = 165)	Low-dose (n = 125)	High-dose (n = 40)	*p* value
Age (years), mean (± SD)	55 ± 14.5	55 ± 14.0	53 ± 16.0	0.335
Men, no (%)	94 (57.0)	70 (56.0)	24 (60.0)	0.657
BMI, mean (SD)	30 ± 7.5	30 ± 7.3	30 ± 8.1	0.661
Non-smoker, no (%)	124 (75.2)	92 (73.6)	32 (80.0)	0.184
Ethnic, no (%)				
- Malay	69 (41.8)	50 (40.0)	19 (47.5)	0.852
- Chinese	33 (20.0)	25 (20.0)	8 (20.0)	0.852
- Dayak	62 (37.6)	49 (39.2)	13 (32.5)	0.852
Presenting symptoms, no (%)				
- Cough	118 (71.5)	88 (70.4)	30 (75.0)	0.575
- Fever	108 (65.5)	77 (61.6)	31 (77.5)	0.066
- Dyspnoea	78 (47.3)	66 (52.8)	12 (30.0)	0.012
- Diarrhoea	29 (17.7)	24 (19.4)	5 (12.5)	0.509
- Poor appetite	35 (21.2)	28 (22.4)	7 (17.5)	0.323
Comorbidities, no (%)				
- None	44 (26.7)	30 (24.0)	14 (35.0)	0.171
- Hypertension	103 (62.4)	83 (66.4)	20 (50.0)	0.062
- Diabetes mellitus	63 (38.2)	48 (38.4)	15 (37.5)	0.919
- Cardiovascular disease	30 (18.2)	24 (19.2)	6 (15.0)	0.549
- Renal impairment	29 (17.6)	23 (18.4)	6 (15.0)	0.623
- Autoimmune disease	7 (4.2)	2 (1.6)	5 (12.5)	0.003
Laboratories on admission, median (IQR)				
- PaO2/FiO2 ratio	147 (82 - 166)	162 (82 - 170)	112 (83 - 146)	0.521
- CRP (nmol/L)	1230 (635 - 1862)	1326 (676 - 1849)	1158.5 (609 - 1931)	0.659
- Absolute Lymphocyte count (x10^9/uL)	0.8 (0.5 – 1.2)	0.9 (0.6 – 1.2)	0.8 (0.5 – 1.2)	0.677
- LDH	514 (395 – 672)	548 (395 – 678)	497 (397 – 617)	0.656
- D-dimer	2.3 (1.2 – 6.8)	2.5 (1.2 – 7.5)	1.8 (1.3 – 6.4)	0.754
Disease severity upon admission, no (%)				
- Critical / category 5	163 (98.8)	123 (98.4)	40 (100)	0.421
- Mechanical ventilation	65 (39.4)	50 (40.0)	15 (37.5)	0.778
- Acute renal replacement therapy	20 (12.1)	15 (12.0)	5 (12.5)	0.933
Concurrent immunomodulator therapy, no (%)				
- None	129 (78.1)	96 (76.8)	33 (82.5)	0.447
- Baricitinib	28 (17.0)	24 (19.2)	4 (10.0)	0.177
- Tocilizumab	9 (5.4)	5 (4.0)	4 (10.0)	0.146
COVID-19 vaccination, no (%)				
- None	76 (46.0)	53 (42.4)	23 (57.5)	0.095
- one dose	45 (27.3)	31 (24.8)	14 (35.0)	0.207
- two doses	44 (26.7)	41 (32.8)	3 (7.5)	0.002

Values are n (%) for categorical, mean (SD) for normally distributed, or medians (IQR) for non-normally distributed data.
BMI, body mass index; CRP, C-Reactive Protein; LDH, lactate dehydrogenase.

Table II: Multivariate logistic regression analysis of factors associated with mortality

Factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value
Age > 55 (years)	2.18	1.01-4.68	0.043	2.46	0.83-7.28	0.102
Male gender	2.72	1.22-6.05	0.012	3.32	1.19-9.26	0.022
Non-COVID vaccinated	1.98	0.95-4.10	0.066	2.36	0.92-6.07	0.073
Autoimmune disease	9.12	1.69-49.07	0.002	16.6	1.59-173.83	0.019
Acute renal replacement therapy	6.55	2.44-17.60	<0.001	4.45	1.25-15.52	0.019
High-dose methylprednisolone	2.52	1.16-5.50	0.018	3.40	1.09-10.63	0.035
Mechanical ventilation	11.29	3.78-33.69	<0.001	16.11	4.15-62.42	<0.001
Secondary infection	2.30	0.97-5.43	0.052	0.506	0.15-1.63	0.255

Table III: Primary and secondary outcomes among high-dose methylprednisolone group

Outcomesa	Univariate model			Multivariate model		
	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value
Primary outcome						
Mortality	2.5	1.16-5.50	0.018	3.8	1.24-11.59	0.019
Secondary outcomes						
Need for MV	1.6	0.59-4.36	0.351	1.6	0.59-4.58	0.346
Secondary infection	4.7	1.71-12.72	0.001	3.2	1.05-9.55	0.042
LOS in ICU > 7 days or death	4.3	1.85-10.2	0.001	5.3	1.98-14.93	0.001

MV, mechanical ventilation; LOS, length of stay; ICU, intensive care unit
[a]Comparison is performed with standard-dose of methylprednisolone as reference.

In terms of inflammatory response, the mean CRP level reduced significantly after methylprednisolone, from 1311 nmol/L to 507 nmol/L (95% CI: -920 to -687, p=0.001), but again, there was no significant difference in the reduction of CRP, LDH and D-dimer level between the higher dose group and lower dose group.

The overall mechanical ventilation rate in our study population was 54.5%. 65 (39.4%) patients were mechanically ventilated upon admission to ICU. Despite treatment with methylprednisolone in ICU, another 25 patients required invasive mechanical ventilation. More patients required mechanical ventilation in the higher dose group compared to lower dose group (32% vs. 22.7%, respectively) but this was not statistically significant (p=0.351; Table III).

In this study, the median (IQR) length of stay in ICU was 7 (5–12) days. Significantly longer duration of stay in ICU was observed in the higher dose cohort at 11 (8-15) days, compared to the lower dose group at 6 (4-10) days (p<0.001). Secondary infection was a common complication in ICU hospitalization. In our study population, 110 (66.7%) patients developed at least one episode of secondary infection. The commonest infections were respiratory tract infection (58.8%), followed by bacteremia (36.4%). Patients treated with higher dose methylprednisolone were at significantly higher risk of developing secondary infection compared to lower dose cohort (87.5% vs. 60.0%, p=0.001; table III). The commonest pathogens detected in our study population were *Acinetobacter baumanni*, followed by *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Multi-drug resistant *Acinetobacter baumanni* (MRO) was the most common pathogen found in both groups (35% vs. 21.2%, p=0.072). However, the high dose methylprednisolone group developed more infections from *Klebsiella pneumonia* (35%) and *Pseudomonas aeruginosa* (25%) (p<0.05).

DISCUSSION

Since the beginning of the pandemic, corticosteroids had been used extensively as part of treatment in severe COVID-19 with ARDS, in order to regulate excessive immune responses that cause systemic inflammation and tissue damage.[11,12] Administration of corticosteroids in the early pulmonary phase of illness improves oxygen saturation and inflammatory markers.[13] Treatment with methylprednisolone was found to significantly reduce recovery time, transfer to intensive care, and inflammatory markers.[8] Several studies and case series6,[13–15] had reported better outcomes and lower mortalities in COVID-19 illness, but with varying doses of methylprednisolone. There has been no evidence that a higher dose of steroids resulted in greater benefit than a lower dose.[16] Administration of methylprednisolone equivalent of 1 mg per kg per day has been recommended in moderate to severe COVID-19 with ARDS.[17]

In a retrospective study by Monreal et al, the use of higher dose methylprednisolone was associated with increased mortality in hospitalized patients with critical COVID-19 illness.[10] A similar result was seen in our study; the mortality in the higher dose cohort was twice as compared to the lower dose group. Older age has been associated with both ARDS and mortality due to declining immunocompetence.[4,18] The risk of death and need for mechanical ventilation were significantly higher in patients older than 65 years with the use of higher dose methylprednisolone.[10] Interestingly, the interaction between age and higher dose methylprednisolone was not demonstrated in our study. With our limited ICU capacity, younger patients with severe COVID-19 were more likely to be admitted to ICU during the study period. In this study, there was no significant difference found in the improvement of PF ratio, as well as the reduction of CRP, LDH, and D-dimer level between higher dose and lower dose group. In addition, the use of higher dose methylprednisolone did not reduce the need for mechanical ventilation in severe COVID-19 illness with ARDS.

On the other hand, higher doses corticosteroid was associated with more serious adverse events, especially concomitant infections.[19] Secondary infection tends to develop in severe COVID-19 patients who require ICU and advanced organ support, and it was associated with higher mortality and longer course of ICU stay.[20] In this study, we found a significantly higher occurrence of secondary infection in patients treated with higher dose methylprednisolone. A wide spectrum of secondary infection was observed and the commonest was pneumonia either ventilator or non-ventilator associated, caused by multi-drug resistant *Acinetobactor baumanni*. Therefore, prompt initiation of appropriate antimicrobials based on local surveillance and antibiogram data for secondary infections is important.[14]

LIMITATIONS

There were a few limitations in this study. First, this study was conducted in a single-centre hospital with a limited sample size. Based on calculation, we need to study 158 patients in

each arm to reject the null hypothesis with a power of 80%, p cut-off value of 5% for statistical significance. However, despite recruiting all eligible patient during the study period, the sample size was still limited. Secondly, this was a retrospective study. With the treatment decisions being at the judgment of the treating physician rather than in randomized cohorts, we were unable to exclude an indication bias completely, wherein more severe patient might receive a higher cumulative dose of methylprednisolone. On the other hand, the younger patients were prioritized for ICU admission due to limited resources in our center. This might lead to an age selection bias. Last but not least, the wide range of doses, as well as differing individual management besides the corticosteroid usage, might contribute to heterogeneity beyond our analysis.

CONCLUSION

The use of higher dose methylprednisolone in COVID-19 with ARDS was not associated with better clinical outcomes. The risks of mortality and secondary infection were higher, with longer durations of ICU stay. A lower dose of methylprednisolone might be adequate and less harmful in patients with severe COVID-19 illness with ARDS. Nevertheless, randomized, double-blind, controlled clinical trials are needed to confirm these findings.

CONFLICT OF INTEREST

There is no conflict of interest associated with the materials presented in this paper.

ETHICS

This study has been registered with the National Medical Research Register (NMRR- ID-21-02254-5QR) and obtained ethical approval from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia.

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The association between physical activity and burnout among anaesthesia postgraduate trainees in Malaysia

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ABSTRACT

Introduction: Burnout is a psychological problem which is becoming more prevalent among medical professionals resulting in various negative outcomes. Physical activity has been found to be an effective method in alleviating burnout. The aim of this study was to determine the association between physical activity and burnout among postgraduate anaesthesia trainees in Malaysia. The study also intended to determine the level of physical activity among trainees, the factors affecting this practice, and the prevalence of burnout among anaesthesia trainees.

Materials and methods: An online self-administered questionnaire was sent out to all postgraduate anaesthesia trainees between August 2020 and January 2021 via email and respondents were recruited on a voluntary basis.

Results: The prevalence of burnout among postgraduate anaesthesia trainees was high (54%). This prevalence was higher among trainees with low a level of physical activity. Half of the trainees (50.8%) engaged in moderate physical activity while only 12% reported a high level of physical activity. The postgraduate study year was found to be a significant factor affecting the practice of physical activity.

Conclusion: There is a significant association between physical activity and burnout among postgraduate anaesthesia trainees in Malaysia. Physical activity has the potential to be an essential method of reducing burnout. Hence, measures should be implemented to improve the practice of physical activity among healthcare professionals in order to reduce workplace burnout.

KEYWORDS:
Burnout, physical activity, postgraduate trainee

INTRODUCTION

Burnout is a psychological syndrome characterised by depersonalisation, emotional exhaustion, and reduced personal accomplishment as a result of a chronic exposure to stress at work.[1] It has been recognised in the early 1970s as a potential problem within a broad range of occupations and has been increasing in incidence among medical professionals. The high demands and stress levels of anaesthesia and critical care medicine account for the high incidence of burnout and suicide.[2] According to the Medscape National Physician Burnout and Suicide Report 2020, 42% of physicians were reported as burned out with anaesthesia and critical care ranking as one of the top specialties repeatedly associated with burnout over the past 5 years.[3] Burnout has negative effects on medical care by not only affecting the workforce, but it may also jeopardise patient care.[4]

In view of the numerous adverse effects of burnout on the healthcare system, it is pivotal to have in place coping mechanisms to counteract these undesirable outcomes. Regular physical activity has been found to be an effective method to reduce burnout.[5] The positive impact of exercise on general health has been well researched and there is increasing evidence to support its role in reducing stress and burnout among anaesthetists. In spite of the established benefits of physical activity, the practice of physical activity among anaesthesia trainees is low as evident by the survey on welfare conducted amongst Australian and New Zealand College of Anaesthetists (ANZCA) trainees in 2017.[6]

This aim of this study was to determine the association between the practice of physical activity and the severity of burnout among anaesthesia trainees in Malaysia. The study also researched the level of physical activity among anaesthesia trainees, the factors affecting this practice, and the perceived barriers among anaesthesia trainees.

MATERIALS AND METHODS

This was a cross-sectional questionnaire-based study conducted among all trainees in the Master of Medicine (Anaesthesiology) programme in postgraduate training hospitals in Malaysia. The study was approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) and registered with the National Medical Research Register with the ID NMRR-20-1316-55035. The email of the respondents was obtained from the Bahagian Pengurusan Latihan after approval from the MREC. An online self-administered questionnaire was sent out between August 2020 and December 2020 via email and respondents were recruited on a voluntary basis. Data collection was carried out over a period of 6 months.

Demographic details collected were age, gender, height, weight, year of postgraduate training, number of years in training, place of practice, marital status, and number of children.

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International Physical Activity Questionnaire (IPAQ) short form was used to assess practice of physical activity and the barriers. Physical activity was graded as low, moderate, or high.[7] Oldenburg Burnout Inventory (OLBI) was used to assess the level of burnout. The higher the score, the greater the level of burnout.[8] The severity of burnout was categorised into high and low by using the median of the burnout score as the cut-off point. Information about the responders remained confidential and non-attributable.

Definition of terms

Level of physical activity: Measure of the volume of activity which is computed by weighting each type of activity by its energy requirements defined in METs to yield a score in MET–minutes. METs are multiples of the resting metabolic rate and a MET-minute is computed by multiplying the MET score of an activity by the minutes performed. The level of physical activity is classified into low, moderate, and high based on the MET-min per week. (MET-min per week = MET level × minutes of activity per day × days per week).[8]

Low level of physical activity: No activity is reported or some activity is reported but not enough to meet moderate or high level of physical activity.

Moderate level of physical activity: Fulfil any of the following three criteria which are 3 or more days of vigorous activity of at least 20 minutes per day, 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day, 5 or more days of any combination of walking, moderate intensity or vigorous intensity activities achieving a minimum of at least 600 MET-minutes/week.

High level of physical activity: Fulfil any of the following 2 criteria which are vigorous-intensity activity on at least 3 days and accumulating at least 1500 MET-minutes/week, 7 or more days of any combination of walking, moderate or vigorous intensity activities accumulating at least 3000 MET-minutes/week

Physical activity: Any bodily movement produced by skeletal muscles that requires energy expenditure – including activities undertaken while working, playing, carrying out household chores, travelling, and engaging in recreational pursuits.[9]

Postgraduate anaesthesia trainee: Anaesthesia medical officers who are enrolled in the Master of Medicine (Anaesthesiology) Training Programme Malaysia

Data Analysis

Data collected were analysed using the software Statistical Package for the Social Sciences (SPSS) version 26 (Armonk, NY: IBM Corp). Categorical variables are presented as frequency and percentage (%). Normally distributed numerical variables are reported as means and standard deviation (SD) and not normally distributed variables are reported as medians and interquartile ranges (IQR). Analysis of variance or Kruskal–Wallis H test was used to analyse the association between level of physical activity and severity of burnout, as appropriate. The practice of physical activity in relation to the demographic details was analysed via ordinal regression. Multiple models were built and the model with the lowest Akaike Information Criterion (AIC) was selected as the final model. A p value of less than 0.05 was considered as statistically significant.

RESULTS

A total of 185 anaesthesia trainees out of 455 participated in this study. The mean age of the trainees was 33 years and the mean BMI was 23.9 kg/m^2. Majority of the trainees who participated in this study were females who comprised 62%. Forty percent of the trainees were in postgraduate year 4 (PGY4) followed 28% in postgraduate year 1 (PGY1), 22% in postgraduate year 3 (PGY3) and 20% in postgraduate year 2 (PGY2). Fifty-six percent of the trainees were practicing in university hospitals compared to 44% in non-university hospitals. Majority of the trainees were married (63%).

The median burnout score in this study was 40 with an IQR of 45.5–32.5. The level of practice of physical activity and burnout among anaesthesia trainees is depicted in Table I. Half of the trainees in this study were found to have engaged in moderate physical activity and only 12% reported to have a high level of physical activity. One hundred trainees reported high burnout levels accounting for 54% of the total number in the study.

Kruskal–Wallis H test showed a statistically significant difference in burnout scores between the different levels of physical activity (H=96.069, p=<0.001); with a median burnout score of 46 for low level of physical activity, 36 for moderate physical activity, and 25 for high level of physical activity (Figure 1).

There was an inverse relationship between body mass index (BMI) and physical activity (p=0.024). Postgraduate year also significantly affected the level of physical activity among trainees (p<0.05). Compared to trainees in PGY1, trainees in PGY2 and PGY3 were 65% and 64% less likely to have low physical activity, respectively. Work commitment and tiredness with laziness were perceived by 79% and 81% of the respondents, respectively, as barriers to physical activity. In particular, tiredness and laziness were found to be a statistically significant barrier (p=0.009). Anaesthesia trainees who reported this were 2.69 times more likely to unveil lower practice of physical activity (Table II).

However, on further analysis with multiple variable ordinal regression, BMI was not significantly associated with lower level of physical activity (OR=1.07; 95% CI=0.98,1.16, p=0.119). In contrary, there was a statistically significant association between postgraduate year and level of physical activity. Compared to PGY1, subjects in PGY3 (OR=0.42; 95% CI=0.19, 0.96, p=0.039) were 58% less likely to have low practice of physical activity whereas subjects in PGY2 (OR=0.41; 95% CI=0.17, 0.95, p=0.038) were 59% less likely to experience the same. Tiredness and laziness were still found to be a significant barrier associated with a lower level of physical activity (p=0.034). Trainees who stated this as a barrier were 2.27 times more likely to practice a low level of physical activity (Table III).

Table I: Level of physical activity and burnout among anaesthesia trainees

	n (%)	95% CI
Level of physical activity		
Low	68 (36.8)	30.1–43.9
Moderate	94 (50.8)	43.6–58.0
High	23 (12.4)	8.3–17.8
Burnout		
Low	85 (45.9)	38.9–53.1
High	100 (54.1)	46.9–61.1

Table II: Associated factors of low physical activity and barriers

Variable	B(SE)	OR (95% CI)	Wald (df)	*p* value
Age	-0.01 (0.04)	0.99 (0.91,1.08)	0.02 (1)	0.883
Gender (Female vs Male)	0.55 (0.29)	1.73 (0.98,3.09)	3.51 (1)	0.061
BMI	0.09(0.04)	1.10 (1.01,1.18)	5.10 (1)	0.024
Postgraduate year				
4	-0.67 (0.38)	0.51 (0.24,1.08)	3.13 (1)	0.077
3	-1.04 (0.41)	0.36 (0.16,0.79)	6.44 (1)	0.011
2	-1.06 (0.43)	0.35 (0.15,0.80)	6.25 (1)	0.012
1		Ref		
Year of training	-0.16 (0.10)	0.85 (0.70,1.04)	2.52 (1)	0.113
Place				
Non-university hospital	0.31 (0.28)	1.37 (0.78,2.39)	1.21 (1)	0.271
University hospital		Ref		
Single vs Married	-0.12 (0.30)	0.89 (0.50,1.59)	0.16 (1)	0.687
Number of children	0.21 (0.14)	1.23 (0.94,1.61)	2.18 (1)	0.140
Barriers to physical activity				
Health problem	0.62 (0.51)	1.87 (0.69,5.03)	1.52 (1)	0.217
Family commitment	0.26 (0.30)	1.30 (0.72,2.35)	0.75 (1)	0.386
Ideal body	0.71 (0.68)	2.04 (0.53,7.79)	1.08 (1)	0.299
Older age	0.16 (1.05)	1.18 (0.15,9.30)	0.02 (1)	0.878
Work commitment	0.12 (0.35)	1.13 (0.57,2.24)	0.13 (1)	0.722
Tiredness and laziness	0.99 (0.38)	2.69 (1.29,5.64)	6.89 (1)	0.009
Financial	1.06 (0.90)	2.89 (0.50,16.84)	1.39 (1)	0.239
No place to exercise	0.31 (0.35)	1.36 (0.68,2.73)	0.77 (1)	0.381

B = slope; CI = confidence interval; df = degree of freedom; OR = odds ratio; SE = standard error
Univariable ordinal logistic regression was applied using the group with higher physical activity as the reference group

Table III: Multiple variable ordinal regression for associated factors of low physical activity and barriers

Variable	B (SE)	Wald-statistic (df)	OR (95% CI)	*p* value*
BMI	0.06 (0.04)	2.43 (1)	1.07 (0.98, 1.16)	0.119
Postgraduate year				
4	-0.55 (0.39)	2.03 (1)	0.58 (0.27, 1.23)	0.155
3	-0.86 (0.42)	4.24 (1)	0.42 (0.19, 0.96)	0.039
2	-0.90 (0.43)	4.32 (1)	0.41 (0.17, 0.95)	0.038
1			Ref	
Tiredness & laziness				
Yes	0.82 (0.39)	4.51 (1)	2.27 (1.06, 4.84)	0.034
No			Ref	

B = regression coefficient; CI = confidence interval; df = degree of freedom; SE = standard error
* Ordinal regression was applied. AIC = 334.79. Proportional odds assumption was verified

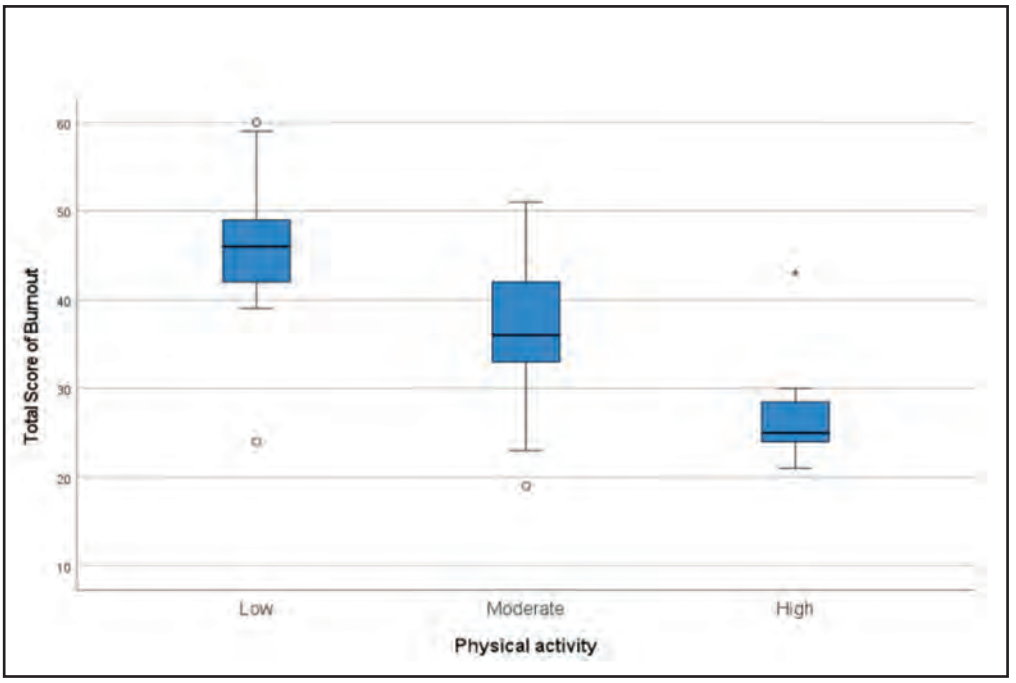

Fig. 1: Relationship between level of physical activity and severity of burnout.

DISCUSSION

This study showed an inverse relationship between the severity of burnout and level of physical activity among postgraduate trainees. The majority of trainees had a moderate level of physical activity with BMI, postgraduate year, and "tiredness with laziness" being significant contributory factors towards a low level of activity.

Burnout has been a struggle dealt with by doctors for decades and has become worse during the pandemic especially in the field of anaesthesia and intensive care.[4] It is of paramount importance to ascertain strategies to reduce the incidence of burnout. Growing evidence proposes that physical activity has a protective effect on occupational stress and has been used as an effective coping method for burnout. Jonsdottir et al suggests that the practice of physical activity is inversely related to burnout, depression, and perceived stress among health care workers.1[0] In this study, it is evident that the severity of burnout was high among Malaysian postgraduate anaesthesia trainees who had a low level of physical activity.

Majority of the anaesthesia postgraduate trainees were physically active with half of them reporting a moderate level of physical activity. However, only a small proportion were engaged in a high level of physical activity. In contrast, 79% of trainees in the ANZCA training scheme reported lack of exercise.[6] The current study was conducted during the COVID-19 outbreak when the movement control order was implemented in the country. The restrictions imposed were likely to have affected the level of practice of physical activity among trainees.

Among the various factors affecting the practice of physical activity that were investigated, only the year of postgraduate study showed a significant impact. Postgraduate anaesthesia trainees in PGY1 were more likely to be physically inactive compared to PGY2 and PGY3. This can be due to the change in workplace and environment upon starting the postgraduate training. More time is spent at work to familiarise themselves with the new training hospital demands and schedule. Besides this, PGY1 trainees lack time for physical activity due to their heightened study commitments as the primary conjoint examination is conducted in year 1. This is not the case for trainees in PGY2 or PGY3 as there are no major examinations for during those years, hence more time is available for participation in physical exercise. Being in another major examination year, trainees in PGY4 did not demonstrate any significant difference in physical activity when compared to PGY1 trainees.

BMI did not appear to be a significant factor in determining the level of practice of physical activity among trainees in this study. Similar findings were reported in a study in 2014 among physicians of residency training programmes in Saudi Arabia.[11] There have been contradicting findings among studies which revealed BMI as a significant factor. One researcher reported that respondents with higher BMI tend to have a higher practice of physical activity.[12] On the other hand, Anuar et al reported that normal or underweight respondents had better practice of physical activity.[13] Furthermore, a study among Malaysian adults based on data from the 2015 National Health and Morbidity Survey (NHMS) revealed that obese adults tend to have a poorer practice of physical activity. Nevertheless, this was only observed among men and not among women.[14] Majority of the respondents in this study were females (62%), which could explain the insignificance of BMI as a contributing factor.

Guthold et al found that females have less physical activity when compared with males (31.7% vs 23.4%).[15] Baum et al reported the prevalence of low level of physical activity was higher among females compared with males in a study conducted over 20 countries.[16] Yeliz et al and McCarthy et al also showed that the level of physical activity was lower in female students.[17,18] However, this study did not show female as a significant contributing factor towards low level of physical activity (p=0.061). This may be because the small sample size resulted in a Type II error.

As for barriers to physical activity, tiredness, and laziness was the only barrier identified to be significant. This is possibly due to the physical and mental exhaustion from the high workload and studying for examinations. Concerns pertaining to future job prospects and examinations were reported to cause severe stress in two-thirds of trainees in the Australian and New Zealand College of Anaesthetists training programme.[6]

The stressors and prolonged hours in anaesthesia and intensive care training predispose the postgraduate trainees to high levels of burnout.[2] In line with this, it is not unforeseen that more than half of the subjects in this study suffer from high levels of burnout. De Oliveira Jr. et al discovered a link between burnout and poorer quality of care delivered with increased medication errors.[19] Hence, it is essential that preventive and positive coping strategies be employed to reduce the rising prevalence of burnout among postgraduate trainees in Malaysia.

Efforts should be made to emphasize the importance of physical activity and encourage trainees to be physically active to reduce the severity of burnout. Incorporating facilities such as gymnasiums and sports halls at the workplace may be useful as it provides better opportunities for trainees to engage in physical activity. Amelioration of the anaesthesia postgraduate training programme may also prove beneficial as a method to cultivate physical exercise.

There are several limitations that need to be addressed in this study. Firstly, this study was done among postgraduate anaesthesia trainees, hence it is not possible to generalize the findings to other postgraduate trainees due to the different training demands and requirements. As this is a questionnaire-based study, there is a possible risk for under or overestimation of self-reported physical activity. Besides this, lengthy online questionnaires may pose a risk of wrong data entry by the respondents. The cross-sectional design of this study also poses limitations to causal relationships among the variables studied.

CONCLUSION

This study concludes that there is a significant association between physical activity and burnout among postgraduate anesthesia trainees in Malaysia. Physical activity reduces the risk of burnout. The implications of these findings should be directed towards strategies and methods in reducing the incidence and severity of burnout among postgraduate anaesthesia trainees. The importance of promoting a healthy lifestyle as well as facilitating trainees' participation in physical exercise should also be emphasized.

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CONFLICT OF INTEREST

We have no conflicts of interest.

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Sonographic evaluation of normal diaphragmatic thickness and excursion in Malaysia paediatric population: A single-institution cross-sectional study

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ABSTRACT

Introduction: Diaphragmatic dysfunction is often under-diagnosed as clinical presentation is non-specific and reference values for normal diaphragmatic excursion are inadequate. The rationale of this study is to provide a normal reference value of diaphragmatic excursion and thickness in Malaysia's paediatric population using M-mode sonography, as no previous local data are available to our knowledge.

Materials and methods: A total of 119 healthy infants and children fulfilling our inclusion and exclusion criteria were recruited. They were divided into three groups according to age – 0–2 years old in group 1; 2–6 years old in group 2; 6–12 years old in group 3. Sonography B-mode was used to assess bilateral diaphragmatic thickness and M-mode to assess diaphragmatic excursion during quiet spontaneous respiration.

Results: In our paediatric population, the normal right and left diaphragmatic thickness were 2.0 mm ± 0.5 and 2.0 mm ± 0.5 for group 1; 2.5 mm ± 0.8 and 2.4 mm ± 0.6 for group 2; 2.7 mm ± 0.7 and 2.5 mm ± 0.5 for group 3, respectively. The normal right and left diaphragmatic excursion were 7.7 mm ± 2.5 and 7.3 mm ± 2.6 for group 1; 11.5 mm ± 3.8 and 10.6 mm ± 3.8 for group 2; 13.8 mm ± 3.9 and 12.9 mm ± 3.3 for group 3, respectively (data presented in mean ± standard deviation). There were no significant differences between two genders for each group. Significant positive correlation between age, weight, height, and body surface area with bilateral diaphragmatic thickness and excursion were detected in all studied population. The percentage difference between excursions of both hemidiaphragm was below 40%.

Conclusions: M-mode sonography is the modality of choice for diaphragmatic kinetics especially in paediatric population. This study provides normal sonographic reference value of diaphragmatic excursion and thickness in the Malaysian paediatric population as well as percentile curves for right diaphragmatic excursion plotted against body weight. The availability of this data will aid in the diagnosis of diaphragmatic dysfunction and hence immediate intervention for better recovery.

KEYWORDS:
M-mode sonography; Normal diaphragmatic thickness; Normal diaphragmatic excursion; Diaphragmatic excursion against body weight; Paediatric

INTRODUCTION

Diaphragms are pair of essential organs that mankind could not live without. However, diaphragmatic dysfunction is often under-diagnosed or missed as it has non-specific clinical presentations, especially in paediatric population who may not be able to communicate their symptoms.[1] Diaphragmatic dysfunction or paralysis can lead to negative clinical repercussions if untreated, or even negative impact on survival in severe cases.[2]

Congenital and Pathology Conditions of Diaphragm

Congenital diaphragmatic abnormality includes aplasia or hypoplasia, accessory diaphragm, eventration, and hernias. Aplasia or hypoplasia of diaphragm is very rare and usually not compatible with life.[3] Accessory diaphragm or duplication of fibromuscular part of diaphragm is also rare and almost always occurs on the right.[4] On the other hand, eventration and hernia of diaphragm are relatively more common. Eventration of diaphragm is due to the congenital absence of muscle fibers and usually occurs on the anteromedial aspect of the right hemidiaphragm. Bochdalek hernia is the most common type of congenital hernia. Other type of hernia includes Morgagni and hiatal hernias.[5-7]

The pathological causes of diaphragmatic dysfunction or paralysis in paediatric population include phrenic neuropathy, catheter placement, birth injury, cardiac surgery, resection of thoracic tumours, liver transplantation, or high impact polytrauma.[5,8] In the study conducted by Epelman et al., cardiac surgery such as heart transplantation were the most common source of diaphragmatic injury.[9] Other rare causes such as Lyme disease or West Nile virus were also reported.[5,10] Primary diaphragmatic tumour is very rare in children but secondary metastasis deposition on the diaphragm contributing to dysfunction is possible.[6]

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Imaging of the Diaphragm

Imaging of the diaphragm can be divided into anatomical or functional. Chest radiograph is the most commonly performed thoracic imaging for both adult and paediatric populations; however, it only shows the anatomical position of diaphragm and is a poor predictor of normal diaphragmatic motion.[9]

The capability of computed tomography (CT) and magnetic resonance imaging (MRI) in producing multiplanar imaging and high soft tissue resolution is the choice of imaging for diaphragmatic anatomy.[11] Despite that, CT and MRI are subject to motion artefact which is difficult to control in paediatric population. The use of sedation during CT or MRI may alter the breathing pattern and result in inaccurate measurement of diaphragmatic kinetics.

Sonographic imaging is more frequently utilised for the assessment of diaphragmatic kinetics, especially in paediatric population due to its non-invasive nature. Both MRI and ultrasound have the dual benefit in assessing diaphragm's anatomy and functionality. However, ultrasound is more widely available in all centre and less sophisticated compared to MRI in operation.

Traditionally, fluoroscopy is the key imaging tool for functional assessment of diaphragm by direct visualization of the diaphragmatic kinetics during quiet respiration and sniffing manoeuvre.[5] Patient's full co-operation is vital in succeeding this examination, which is deemed unfavourable in paediatric population. This requirement in addition to the downside of ionising radiation have automatically excluded the paediatric population as a choice of diaphragmatic examination.

The actual gold standard for functionality assessment of the diaphragm is by measuring the transdiaphragmatic pressure generated by phrenic nerve stimulation. This is not practical as it is time-consuming and necessitates specialised equipment.[2] Hence, ultrasound is still nominated as the imaging of choice for both anatomical and functional assessment of diaphragm, be it in adult or paediatric population.[9,12] Nonetheless, sonographic examination is limited to operator's skill and experiences.

The rationale for this study is to provide a normal reference value of diaphragmatic thickness and excursion in Malaysia paediatric population. The current available reference values are mostly done in adult population and derived from a study in foreign countries with restricted population, which limit global generalisation. The availability of these data will be useful for the diagnosis of diaphragmatic dysfunction and hence immediate intervention for better recovery.

MATERIALS AND METHODS

This was a cross-sectional study conducted from January 2020 to December 2021 at Universiti Kebangsaan Malaysia Medical Centre. Subjects were selected by convenience sampling from patient population who came for routine ultrasound screening of the cranial or urinary system. Sample size was calculated using $n = \left[\frac{Z\sigma}{\Delta}\right]^2$, based on the formula by Lwanga SK et al.[13]

We included Malaysian infants and children aged between 0 and 12 years old with normal growth parameters in this study. They were divided into three age groups, where Group 1 was children aged 0 to 2 years old; Group 2 was children aged 2 to 6 years old; and Group 3 was children aged 6 to 12 years old. Preterm babies more than 36 weeks of pregnancy were included in this study provided their growth parameters were within normal limits with no prior history of oxygen dependency. The exclusion criteria were children with active respiratory disease; congenital heart disease; neurological disease; hepatosplenomegaly; post liver or spleen removal; previous history of thoracic or abdominal surgery; failure to thrive; obesity, and those ventilated patients.

Ethical issues

Ultrasound examination is non-invasive and non-ionizing, thus will not contribute to any radiation risk. Full written consent was taken from subject's parent or caretaker prior to examination. Ethical approval for this study has been obtained from the local institution Research and Ethics Committee with the ethical approval code of FF-2020-164.

Protocol for Sonographic Evaluation of Diaphragm

The basic information such as gender, age (calculated to the nearest month based on date of birth to date of examination), ethnicity, weight (kg), and height (cm) of each subject was recorded prior to the examination. We used Toshiba Aplio 500 or GE Logiq S8 ultrasound machine in our centre to perform this study. The 5–10 MHz linear transducer was used for infant and 3–5 MHz curvilinear transducer was used for children. Study was performed during quiet spontaneous respiration in supine position.

Both diaphragms were assessed using brightness mode (B-mode) first to locate the diaphragm, then motion mode (M-mode) for the amplitude. The transducer was fixed throughout examination between midclavicular and anterior axillary line in subxiphoid or intercostal area. Using liver and spleen as acoustic window, diaphragm was identified as an echogenic line above them. Once quiet regular breathing has been identified, we froze the sonogram. Diaphragm thickness was taken as the perpendicular distance between the pleural and peritoneal reflections or simply the perpendicular distance of the echogenic line in B-mode.[1,8,12]

To measure the diaphragmatic excursion, M-mode was utilised with the cursor place almost perpendicular to the diaphragm to obtain the maximum amplitude. During inspiration, the normal diaphragm contracts and moves caudally toward the transducer, which will create an upward motion of the M-mode tracing. On the other hand, during expiration, the diaphragm moves cephalad and away from the transducer, creating a downward motion of the M-mode tracing, as shown in Figures 1–4. Diaphragmatic excursion was taken as a perpendicular distance between the upper border of inspiration and lower border of expiration in M-mode.[1,8,12]

Two sets of data were obtained by the same trained operators (a qualified medical officer and a radiologist) for each patient and the readings were then averaged. Chest radiograph was scrutinised if available to ensure no diaphragmatic elevation

or eventration in the studied population. Data collected were tabulated and analysed using SPSS version 26.0. The difference in excursion between both hemidiaphragm was calculated using the formula $\frac{(V1-V2)}{\frac{(V1+V2)}{2}}$ x 100, where V1 was the mean of right diaphragmatic excursion and V2 was the mean of left diaphragmatic excursion.

RESULTS

We recruited a total of 119 healthy infants and children in this study, with the largest sample size number of 64 in group 1, 24 subjects in group 2, and 31 subjects in group 3. Table I shows the mean anthropometric data for all groups (age, gender, weight, height, body surface area, and body mass index). As Malaysia is a multiracial country, a variety of races were included in this study.

The normal reference value of the diaphragmatic thickness and excursion in the studied population were depicted in Table II, where the normal right and left diaphragmatic thickness were 2.0 mm ± 0.5 and 2.0 mm ± 0.5 for group 1; 2.5 mm ± 0.8 and 2.4 mm ± 0.6 for group 2; 2.7 mm ± 0.7 and 2.5 mm ± 0.5 for group 3, respectively. The normal right and left diaphragmatic excursion were 7.7 mm ± 2.5 and 7.3 mm ± 2.6 for group 1; 11.5 mm ± 3.8 and 10.6 mm ± 3.8 for group 2; 13.8 mm ± 3.9 and 12.9 mm ± 3.3 for group 3, respectively (data presented in mean ± standard deviation). From the values obtained, we concluded that the minimal diaphragmatic excursion was 4.0mm. In Table III, we compared the difference of diaphragmatic thickness and excursion between male and female. Using Independent T-test, no significant difference was detected between two genders.

Table IV shows the correlation between sonographic measurement of diaphragmatic kinetics and anthropometric data using Pearson correlation coefficient test. There were positive correlation between age, weight, height, and body surface area with diaphragmatic thickness and excursion. Thus, we plotted the percentile curve for normal right diaphragmatic excursion against body weight in the studied population, as shown in Figure 5. The 5th to 95th percentiles of right diaphragm excursion according to body weight were depicted in Table V.

In this study, the percentage difference of excursion between both hemidiaphragm across all three groups was in the range of 0–39% with mean of 13.8%. Thereby we concluded that the difference of excursion between both hemidiaphragm was always below 40%.

DISCUSSION

Diaphragm is responsible for three fourth increment of lung volume during quiet breathing. However, diaphragmatic dysfunction is often under-diagnosed as clinical presentation is non-specific and normal diaphragmatic excursion reference value are inadequate. Diaphragmatic dysfunction can be unilateral or bilateral, although the latter will require ventilation assistance. Paediatric population is more vulnerable to diaphragmatic dysfunction compared to adult in view of their poorly developed intercostal muscle with increased mobility of mediastinum. Hence, they are at higher risk of developing complication from diaphragmatic dysfunction, namely atelectasis, pneumonia, or ventilation failure.[5,9,14]

Sonographic evaluation of diaphragm is the most optimum imaging method in paediatric population. In this study, we have utilised both subxiphoid and intercostal methods to assess the diaphragm. However, in both methods, only the posterior hemidiaphragm was assessed in our study. The most challenging part in this study was patient's full co-operation during ultrasound assessment. In order to get the minimum normal diaphragmatic excursion value, patient were proposed to have quiet breathing as per resting phase. However, the infants were usually active during scan and required distraction with toys or music. Contrarily, the older children may manipulate their breathing during study but were more amenable. Thus, most of the values obtained were during "active quiet breathing" rather than "very quiet breathing". At times, we had to abandon the study if patient was inconsolable.

Based on earlier study done by Urvoas et al. (1994), diaphragm excursion for children during quiet breathing always exceeded 4 mm and the differences of excursion between both hemidiaphragm are always below 50%.[8] Another similar but more recent study with larger sample size done by El-Halaby et al. in Egypt (2015) concluded that the lowest value for diaphragmatic excursion from all groups was more than 4 mm, with significant positive correlations found between excursion of the right hemidiaphragm and body weight in all age groups from their study.[1] From the data we compiled, the minimum diaphragmatic excursion in paediatric population was 4 mm, which is identical to El-Halaby et al and Urvoas et al's studies. Comparing the normal references value provided by El-Halaby with our data, the mean diaphragmatic thickness was smaller in our population by 1 to 3 mm. We postulated that this could be due to smaller body habitus in our Malaysian paediatric population compared to Egyptian paediatric population. As stated in anthropometric data in El-Halaby et al's study, the mean weight in each group was 1–2 kg heavier and the mean height in each group was 1–4 cm taller compared to our Malaysian population of the same age groups. Thus, the difference in normal reference value of diaphragmatic thickness of two different population of similar age group can be explained and supported by the positive correlation between weight and height with bilateral diaphragmatic thickness as per Table IV.

In reverse, the mean diaphragmatic excursions were higher in our Malaysian paediatric population by 10–20% (1–3 mm) compared to Egyptian paediatric population. This could be partly attributed to the "active quiet breathing" as described above. Diaphragmatic excursion can vary depending on subject's voluntary inspiratory effort, position, abdominal contents, body mass index, underlying neuromuscular disorder, previous history of thoracic or abdominal surgery, and presence of mechanical ventilations.[15-17] Any structural abnormality of the diaphragm such as congenital diaphragmatic hernia can also contribute to a skewed data.[2]

Table I: Anthropometric data in studied population

Characteristic	Group 1 (n= 64)	Group 2 (n= 24)	Group 3 (n= 31)
Age (months)	6.4 ± 6.4	42.1 ± 12.2	104.7 ± 23.7
Gender (female–male)	21 - 43	10 - 14	11 - 20
Weight (kg)	6 ± 2.5	14.3 ± 2.7	28.2 ± 9.5
Height (cm)	60.9 ± 11.6	96.3 ± 9.9	129.0± 9 11
Body surface area (m^2)	0.3 ± 0.1	0.6 ± 0.1	1.0 ± 0.2
Body mass index (kg/m^2)	15.8 ± 2.5	15.4 ± 2.4	16.5 ± 4

Data are presented as mean ± standard deviation where applicable.

Table II: Normal reference values of the diaphragmatic thickness and excursion in the studied populations

	Group 1 (n= 64)	Group 2 (n= 24)	Group 3 (n= 31)	*p*[a]
Right diaphragmatic thickness (mm)	2.0 ± 0.5 (1.2 – 3.3)	2.5 ± 0.8 (1.4 – 4.0)	2.7 ± 0.7 (1.5 – 5.0)	<0.001
Left diaphragmatic thickness (mm)	2.0 ± 0.5 (0.9 – 3.1)	2.4 ± 0.6 (1.5 – 3.2)	2.5 ± 0.5 (1.2 – 3.4)	<0.001
Right diaphragmatic excursion (mm)	7.7 ± 2.5 (4.1 – 15.3)	11.5 ± 3.8 (6.3 – 20.7)	13.8 ± 3.9 (8.3 – 22.0)	<0.001
Left diaphragmatic excursion (mm)	7.3 ± 2.6 (4.0 – 14.4)	10.6 ± 3.8 (6.2 – 19.6)	12.9 ± 3.3 (8.2 – 21.2)	<0.001

Data are presented as mean ± standard deviation (range).
[a]p value using independent T-test.

Table III: Differences in gender on diaphragmatic thickness and excursion in studied populations

	Right Diaphragmatic Thickness (mm)			Left Diaphragmatic Thickness (mm)			Right Diaphragmatic Excursion (mm)			Left Diaphragmatic Excursion (mm)		
Group	Male	Female	*p*[a]	Male	Female	*p*[a]	Male	Female	*p*[a]	Male	Female	*p*[a]
1	2.0 ± 0.5	2.0 ± 0.5	0.946	1.9 ± 0.6	2.0 ± 0.5	0.288	7.5 ± 2.2	8.1 ± 3.1	0.468	6.7 ± 1.8	8.6 ± 3.5	0.191
2	2.5 ± 0.8	2.3 ± 0.9	0.605	2.4 ± 0.7	2.3 ± 0.4	0.622	10.9 ± 4.3	12.3 ± 3.0	0.354	9.7 ± 3.8	11.7 ± 3.6	0.205
3	2.6 ± 0.6	2.7± 0.9	0.901	2.6 ± 0.5	2.4 ± 0.6	0.369	13.5 ± 3.9	14.2 ± 4.1	0.618	13.0 ± 3.3	12.8 ± 3.5	0.861

Data are presented as mean ± standard deviation.
[a]p value using independent T-test.

Table IV: Correlation between sonographic measurement of diaphragmatic thickness and excursion with anthropometric data (all groups)

	Right diaphragmatic thickness (mm)		Left diaphragmatic thickness (mm)		Right diaphragmatic excursion (mm)		Left diaphragmatic excursion (mm)	
	r	*p*	r	*p*	r	*p*	r	*p*
Age (month)	0.48	<0.001	0.46	<0.001	0.63	<0.001	0.66	<0.001
Weight (kg)	0.52	<0.001	0.51	<0.001	0.65	<0.001	0.62	<0.001
Height (cm)	0.51	<0.001	0.49	<0.001	0.70	<0.001	0.66	<0.001
Body surface area (m^2)	0.54	<0.001	0.53	<0.001	0.68	<0.001	0.66	<0.001

r and *p* using Pearson correlation coefficient test.

Table V: Right diaphragmatic excursion by percentile and body weight

Bode weight (kg)	Right diaphragmatic excursion (mm)						
	5th	10th	25th	50th	75th	80th	95th
<5	0.3	0.7	1.7	3.5	5.2	5.6	6.6
5–10	0.7	1.4	3.6	7.2	10.7	11.4	13.6
10–15	1.0	2.0	5.0	10.0	14.9	15.9	18.9
15–20	1.2	2.4	6.0	12.1	18.1	19.3	22.9
20–25	1.4	2.7	6.8	13.6	20.3	21.7	25.8
25–30	1.5	2.9	7.3	14.6	21.9	23.4	27.8
30–35	1.5	3.1	7.7	15.4	23.1	24.6	29.2
35–40	1.6	3.2	8.0	16.0	23.9	25.5	30.3
40–45	1.7	3.3	8.3	16.5	24.8	26.4	31.4
45–50	1.7	3.4	8.6	17.2	25.8	27.5	32.7
50–55	1.8	3.6	9.1	18.1	27.2	29.0	34.4
55–60	1.9	3.9	9.7	19.4	29.1	31.1	36.9
60–65	2.1	4.2	10.6	21.2	31.9	34.0	40.4

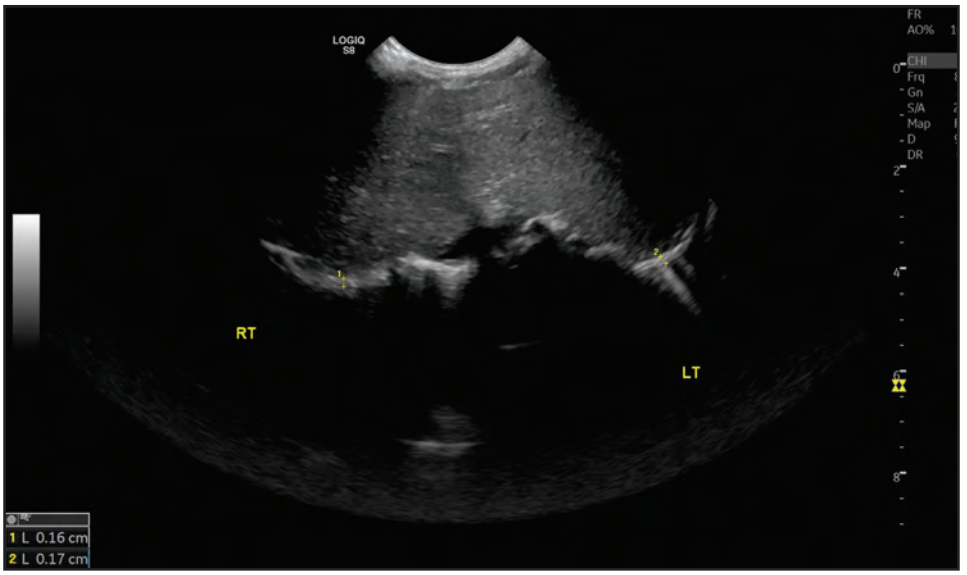

Fig. 1: Measurement of bilateral diaphragm thickness in subxiphoid view using B-mode by placing curvilinear transducer below the sternum and angle cranially. This allows visualisation of both hemidiaphragm as an echogenic line above liver and spleen at the same setting.

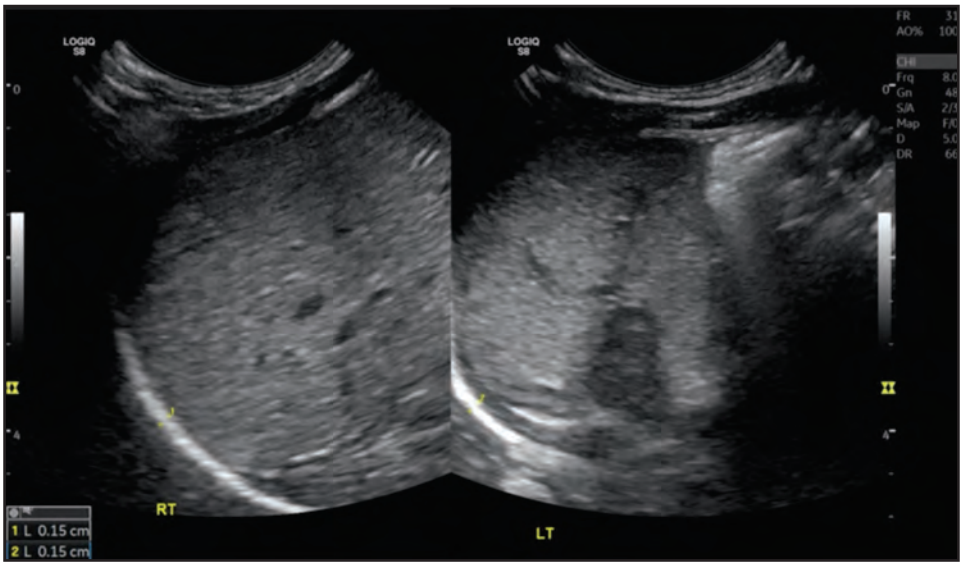

Fig. 2: Measurement of bilateral diaphragm thickness in intercostal view (between midclavicular and anterior axillary line) using B-mode and curvilinear transducer with liver and spleen as acoustic window.

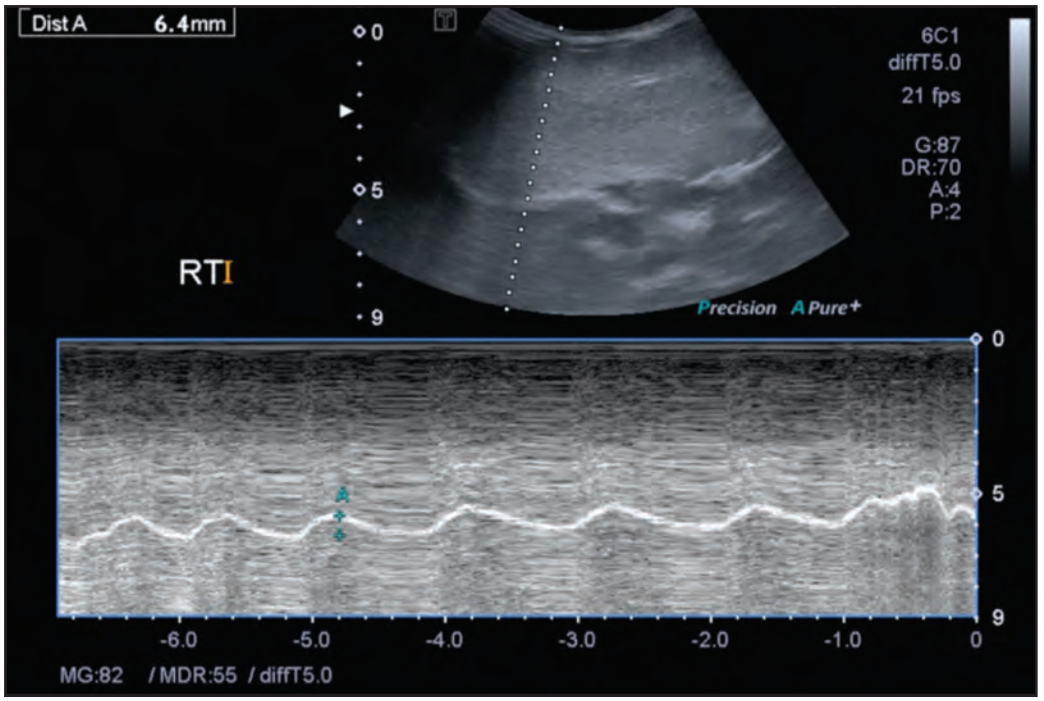

Fig. 3: Measurement of right hemidiaphragm excursion in subxiphoid view using M-mode and curvilinear transducer once regular breathing waves are established. M-mode cursor should be placed almost perpendicular to the diaphragm to obtain maximum amplitude.

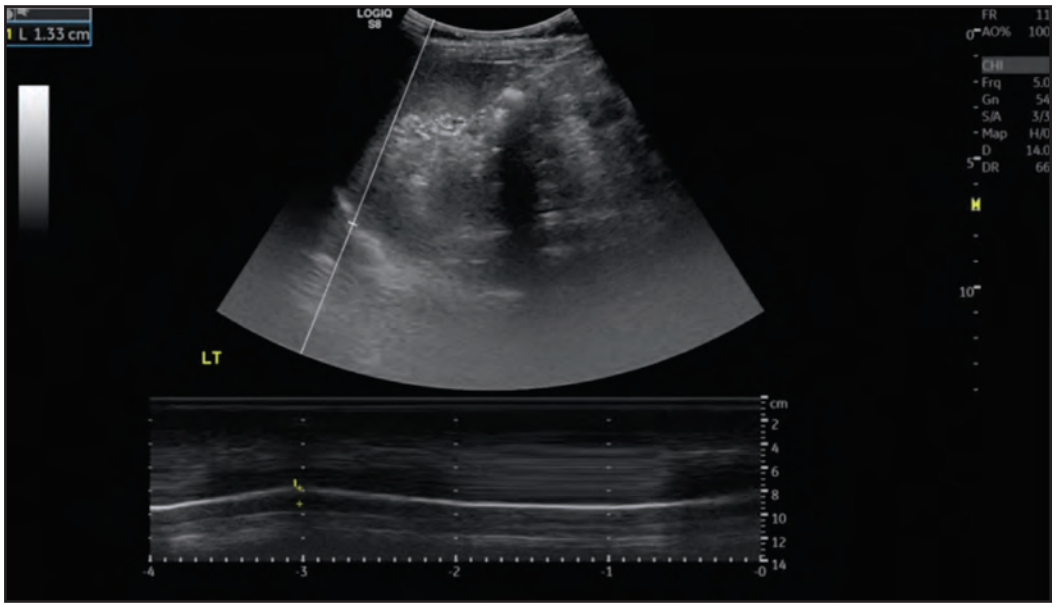

Fig. 4: Measurement of left hemidiaphragm excursion in intercostal view (between midclavicular and anterior axillary line) using M-mode and curvilinear transducer.

Hence, we have adapted these variables into our exclusion criteria to minimise misinterpretation. Nonetheless, we have to consider operator's technique and bias during sonography assessment as part of the consequences as diaphragm kinetics can alter if measures at different ultrasound beam position and direction.

As per El-Halaby et al's study, we have established that there is no gender difference for diaphragmatic excursion and thickness. Among the data we have summarised, the subject's age, weight, height, and body surface area were proportional to their diaphragmatic thickness and excursion. These findings were in accordance with the result from El-Halaby et al as well as Rehan and McCool's studies, where positive correlation between weight and height with diaphragmatic kinetics were determined.[1,18]

Both hemidiaphragm should move simultaneously and symmetrically in a normal subject. Any discrepancy should raise the suspicion of diaphragmatic dysfunction or

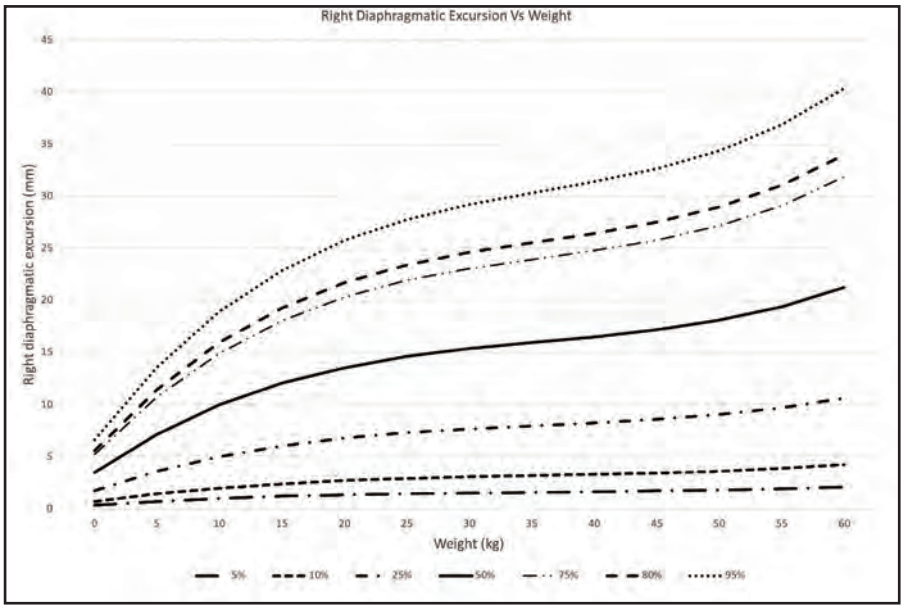

Fig. 5: Percentile curve for normal right diaphragmatic excursion plotted against body weight in the studied populations.

paradoxical movement of diaphragmatic paralysis.[5,8] As stated in Urvoas et al's study, the differences of excursion between both hemidiaphragm were always below 50% with a mean of 30% and range of 5–47%. In our study, the percentage difference of excursion between both hemidiaphragm was in the range of 0–39% with a mean of 13.8% across all studied groups, which supported Urvoas et al's statement. We have concluded that it is generally safe to exclude diaphragmatic dysfunction if the difference between two diaphragmatic excursion is less than 40%.

Having said that, the potential of misinterpretation when there is bilateral diaphragmatic paralysis must be kept in mind and counter-checked with the provided normal reference range. Alternatively, the examiner can place a hand at the patient's chest while observing the diaphragmatic excursion with M-mode sonography. During normal inspiration, the chest should rise and diaphragm would move caudally toward the transducer, creating an upward motion in M-mode tracing. The reverse applied during normal expiration. Paradoxical breathing occurs when chest rise and M-mode tracing are not synchronised.[8] This sonographic assessment should only be done during spontaneous breathing to provide accurate result, thus any ongoing mechanical ventilation need to be temporarily disconnected with continuous monitoring and expert care on standby.[5,9]

We plotted the percentile curve for normal right diaphragmatic excursion against body weight based on the data we have collected in Malaysian paediatric population. We hope that the availability of these graphs and values would provide a guide in diagnosing diaphragmatic dysfunction for our fellow paediatrician and radiologist.

CONCLUSION

Sonography M-mode assessment of diaphragmatic kinetics should be the modality of choice for the paediatric population. This study provides normal sonographic reference value of diaphragmatic excursion and thickness in the Malaysian paediatric population as well as percentile curves for diaphragmatic excursion plotted against body weight. The availability of this data will aid in the diagnosis of diaphragmatic dysfunction and hence immediate intervention for better recovery.

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Sweet's syndrome: A review from two tertiary hospitals in Malaysia

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ABSTRACT

Introduction: Sweet's syndrome (SS) also known as acute febrile neutrophilic dermatosis, is an uncommon disease characterised by acute onset of tender, violaceous or erythematous, oedematous papules, nodules or plaques, with fever. It is classified into classic, malignancy-associated, and drug-induced subtypes.The aims of this study is to evaluate the subtypes, clinical features, laboratory profiles, and treatment of patients with SS.

Materials and methods: We did a retrospective medical record review of all patients with SS from July 2014 to July 2018 at Hospital Queen Elizabeth and Hospital Pulau Pinang, both tertiary hospitals in Malaysia.

Results: Twenty-nine patients were included. Approximately half of the patients (15) were females with a mean age of onset of 50.93 (± 11.52) years. The most common subtype was classic (62.0%) followed by malignancy-associated (31.0%) and drug-induced (6.9%). Among the patients with the classic subtype, infective-related causes (50.0%) were the most common. Among the patients with malignancy, eight had haematological malignancy and one had a solid tumour. Two-third of the malignancies were diagnosed within a year after the diagnosis of SS. Eight of our patients in Sabah had mycobacterial infections with three having concomitant haematological malignancies. Patients with malignancy-associated SS had lower mean haemoglobin (p=0.018) and mean platelet count (p=0.031). Itch was associated with the presence of pustules (p=0.038). Histopathological examination of all skin lesions showed dermal neutrophilic infiltrates and 25 (86.2%) of them had papillary dermal oedema. The study was limited by its retrospective design. The sample size was small likely due to the uncommon occurrence of this condition.

Conclusion: SS is an uncommon dermatosis with distinctive clinical and histopathological features. Screening for underlying malignancy is essential especially for those who present with anaemia, thrombocytopenia, and pathergy phenomenon. Mycobacterial infection should be considered in this region due to high tuberculosis burden.

KEYWORDS:
Sweet's syndrome, acute febrile neutrophilic dermatosis, malignancy-associated, mycobacterial infection, paraneoplastic

INTRODUCTION

Sweet's syndrome (SS), also known as acute febrile neutrophilic dermatosis, is an uncommon disease that was first described by Dr Robert Douglas Sweet in 1964. SS is characterized by acute onset of tender, violaceous or erythematous, edematous papules, nodules, or plaques with predilection for the head, neck and upper extremities. These skin eruptions are often accompanied by fever. It is associated with neutrophilia and may have systemic involvement.[1] Histologically, the distinctive feature is the presence of neutrophilic infiltrate in the upper dermis and papillary dermal oedema. The first diagnostic criteria for SS was proposed by Su and Liu in 1986, which was then modified by von den Driesch in 1994 (Table I).[2] Walker and Cohen proposed the criteria for drug-induced SS in 1996.[1]

SS is classified into three subtypes – Classical, malignancy-associated, and drug-induced. Current literature reported that classical SS is the most common subtype. Classical SS may be associated with infection, connective tissue disease, pregnancy, inflammatory bowel disease, or idiopathic.[1] This is followed by malignancy-related SS which accounts for about a quarter of cases, with 85% related to haematological malignancy, with the most common being acute myelogenous leukemia.[3] The remaining 15% is related to solid tumours which include breast adenocarcinoma, gastrointestinal, or genitourinary carcinoma.[1] The association of SS with systemic diseases needs to be investigated as it may signify an undiagnosed malignancy or a relapse of a previously treated malignancy. Most patients with malignancy-associated SS were diagnosed with the malignancy prior to onset of SS.[4] For drug-induced SS, the most frequently associated drug is granulocyte-colony stimulating factor (G-CSF).[1]

Although the treatment is straightforward, the diagnosis may not be. There are broad differential diagnoses which include infections, reactive erythema, vasculitis, and neoplasms.[5,6] A study published in The Hand Surgery Journal reported that almost half of their Sweet's syndrome cases were referred as non-healing wound and that one of the patient had four previous surgeries to treat the condition.[7]

This review aimed to evaluate the subtypes, clinical features, laboratory profiles, and treatment of patients with SS presenting to Hospital Queen Elizabeth and Hospital Pulau Pinang.

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MATERIALS AND METHODS

We performed a retrospective medical record review of all patients with SS at Hospital Queen Elizabeth and Hospital Pulau Pinang from July 2014 to July 2018. The diagnosis of SS was made by the treating dermatologists, with the criteria established by Su and Lui and revised by von den Driesch[2] (Table I). Drug-induced SS was diagnosed using the diagnostic criteria proposed by Cohen et al.[1] Approval from the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia was obtained prior to commencement of the study.

Data collection

Demographic data, clinical presentations, lesion morphology and distribution, subtypes, laboratory and histopathological findings, treatment, and outcomes were extracted using a structured data collection form.

Statistical analysis

All data were analyzed using SPSS version 22.0. Parametric data were expressed as mean ± standard deviation (SD). Non-parametric data were expressed as median and interquartile range. Descriptive statistics were provided for the numerical and categorical variables using mean ± SD and percentage distribution where appropriate. For analysis of numerical variables between subgroups, Mann–Whitney test or independent t-test was used. For analysis of nominal variables between subgroups, Chi-square test or Fisher exact test was used. p value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

A total of 29 patients were included. There were 14 (48.3%) males and 15 (51.7%) females. The mean age was 50.93 (± 11.52) years (range 27-70 years). Of the 29 patients, 11 (37.9%) were indigenous group of Sabah, eight (27.6%) were Chinese, seven (24.1%) were Malays, and one (3.4%) was an Indonesian. Majority of the patients (65.5%) had documented fever associated with skin lesions. The skin lesions were described as erythematous or violaceous plaques (100.0%) (Figure 1), pseudo-vesicles (48.3%) (Figure 2), papules (37.9%), nodules (34.5%), or pustules (24.1%). More than 90% of the patients had upper limbs involvement. The lesions were reported to be infiltrated (79.3%), tender (65.5%), and had associated pruritus (24.1%). Pruritus was associated with the presence of pustules (p=0.038), which was reported in four patients. Fifteen patients were checked for pathergy phenomenon, and it was present in 6 (40%) patients with five of them in the malignancy subgroup.

Subtypes of SS

The most common subtype was the classical type (18 cases, 62.1%) which was subclassified into infection-related (9 cases), idiopathic (8 cases), and pregnancy (1 case). Of those patients with infections, two had respiratory infection and gastrointestinal infection, respectively, three had mycobacterium tuberculosis (MTB) infection and two had non-tuberculous mycobacterial (NTM) infection. This was followed by the malignancy subtype (9 patients, 31.0%) with eight patients with hematological malignancy and one patient with a solid tumour. Of those with hematological malignancy, five had acute myeloid leukemia, two had lymphoma and one had myelodysplastic syndrome. The patient with the solid tumour had nasopharyngeal cancer. Three patients were diagnosed with malignancy prior to SS while six patients were diagnosed with malignancy within a year after diagnosis of SS. Three patients with malignancy had concurrent infection with two patients having MTB infection and one with NTM infection. Two patients had drug-induced SS. The causative drug was radio-contrast and sulfamethoxazole-trimethoprim, respectively.

Of all patients, five patients had MTB infection (two with TB lymphadenitis, three with disseminated TB) and three patients had NTM infection. In the MTB group, two patients were diagnosed based on culture, another two patients based on caseating granulomatous inflammation on histopathological examination with positive Ziehl–Neelsen stains and one patient based on TB QuantiFERON. The patients in the NTM group were initially treated for MTB, however had poor response to treatment thus was empirically treated for NTM and all of them responded well to NTM treatment.

Laboratory Investigation Findings

Twenty-four (82.8%) of our patients had neutrophilia. Two patients had leukopenia, and both had malignancy-associated SS. Anaemia was present in 23 (79.3%) patients. Eighteen of 25 patients (72.0%) had elevated C-reactive protein (CRP). Erythrocyte sedimentation rate (ESR) was recorded in 20 patients and 17 (85.0%) had raised ESR.

Histopathological Findings

All skin lesions demonstrated neutrophilic dermal infiltrate. Twenty-five (86.2%) of them had papillary dermal oedema. Other cell types were also observed in the specimens namely lymphocytes (69.0%), histiocytes (69.0%), and eosinophils (31.0%). Most of the specimens had no epidermal changes (86.2%). Perivascular neutrophilic infiltration was observed in 12 specimens (41.4%) and there was leukocytoclastic vasculitis in four specimens (13.8%). Four of the patients with malignancy-associated SS in Hospital Queen Elizabeth had dermal infiltrate of histiocytoid cells of myeloid origin. These cells were positive for CD68 and myeloperoxidase and negative for CD34 and CD117, supporting the diagnosis of histiocytoid SS.

Clinicopathological Features in Patients with or without Concurrent Malignancy

A comparison between the clinicopathological features in patients with or without concurrent malignancy is shown in Table II. The mean hemoglobin level was 9.69 g/dl in those with malignancy-associated SS compared to 11.36 g/dl in the subgroups that were not associated with malignancy (p=0.018). The mean platelet count was 142.7 x 10^9/L in those with malignancy-associated SS compared to 329.7 x 10^9/L in those without malignancy (p=0.0310).

Treatment and Outcomes

The treatment and outcomes were summarized in Table III. Data on treatment response was available for 28 patients. Of these, 11 (39.2%) patients had complete response within 4 weeks, 8 (28.5%) within 8 weeks, 7 (24.1%) within 12 weeks, and the remaining 2 (6.9%) patients within 16 weeks of

Table I: Modified diagnostic criteria for Sweet's Syndrome as proposed by von den Driesch[2]

Diagnosis established with the presence of two major and two minor criteria	
Major	**Minor**
1. Abrupt onset of painful erythematous plaques and nodules 2. Histology features of a dense neutrophilic inflammatory infiltrate without leukocytoclastic vasculitis	1. Preceded by a non-specific respiratory or gastrointestinal tract infection or vaccination or associated with: • Inflammatory diseases such as chronic autoimmune disorders and infections • Hemoproliferative disorders or solid malignant tumours • Pregnancy 2. Fever > 38°C 3. Abnormal laboratory values at presentation (three of four) • Erythrocyte sedimentation rate > 20 mm/h • Elevated C-reactive protein levels • Leucocytosis > 8,000 per microlitre • Neutrophilia > 70% 4. Excellent response to treatment with systemic corticosteroids or potassium iodide

Table II: Characteristics of patients with Sweet Syndrome with or without malignancy

Characteristics	Malignancy, N (%) n = 9	No malignancy, N (%) n = 20	*p* value*
Male	4 (44)	10 (50)	1.000
Symptoms/signs			
Fever	8 (89)	11 (55)	0.107
Constitutional symptoms	7 (78)	12 (60)	0.431
Painful lesions	8 (89)	11 (55)	0.107
Pruritus	2 (22)	5 (25)	1.000
Pathergy	5 (56)†	2 (10)‡	0.035
Morphology			
Papule	4 (44)	7 (35)	0.694
Plaque	8 (89)	20 (100)	0.310
Nodule	5 (55)	5 (25)	0.205
Pseudo-vesicles	5 (55)	9 (45)	0.700
Pustule	1 (11)	6 (30)	0.382
Infiltration	9 (100)	20 (100)	0.633
Distribution			
Upper limbs	7 (78)	20 (100)	0.089
Lower limbs	3 (33)	14 (70)	0.106
Trunk	7 (78)	17 (85)	0.633
Head	6 (67)	8 (40)	0.245
Histology			
Eosinophilic infiltrate	1 (11)	8 (40)	0.201
Leukocytoclasia	5 (56)	7 (35)	0.422
Treatment			
Systemic corticosteroids	8 (89)§	18 (90)	1.000
Topical corticosteroids	8 (89)§	18 (90)	1.000
Colchicine	0 (0)§	3 (15)	0.536
Dapsone	0 (0)§	1 (5)	1.000
Duration of systemic steroids			
> 6 weeks	5 (63)§	7 (35)	0.231
Recurrence	2 (25)§	5 (25)	1.000

*Fisher-exact test; †n = 6; ‡n = 7; §n = 8

treatment. Twenty-eight (96.5%) patients achieved remission except one patient who succumbed to malignancy prior to treatment response. Median duration of follow-up was 9 months (interquartile range 15 months). There was no difference between the duration of treatment to remission between patients with or without malignancy (*p*=0.231).

Seven (24.1%) patients had recurrence of SS which were successfully treated. There was no association between leukocytoclasia (*p*=0.665) with recurrence. There was no association between the patients with malignancy or mycobacterial infection compared to patients with other subtypes in terms of recurrence of SS (p = 1.000).

DISCUSSION

The slight female preponderance[8-11] and onset at middle age[8,9,12] in our patients corroborate with previous reports. Most of the patients had fever,[9,10] erythematous or violaceous infiltrated plaques, followed by papules and pseudo-vesicles,[8,10,11,13,14] leucocytosis, neutrophilia,[8,15] anemia[16] and raised inflammatory markers,[8] in line with the previous studies. Notably, 23 (80%) patients suffered from anaemia which was much higher compared to the previous studies. This may be due to the high prevalence of anaemia among the population in Malaysia, which was reported to be 24.2% in a nationwide population survey. Factors associated with

Table III: Comparison of present study with previous studies of patients with Sweet's Syndrome

	Present Study	Nelson C,[16] USA 2017	Casarin Costa,[8] San Paulo 2017	Marcoval J,[9] Spain 2016	Amouri M,[10] Tunisia 2016
Total (n)	29	83	83	138	90
Mean age (years)	50.9	57.0	48.0	51.2	46.5
Age range	27-70		7-84	18-84	4-84
Gender (Male/Female)	14/15	42/41	15/68	66/72	15/75
Subtypes					
Classic (total)	18 (62.1%)	25 (30.1%)	43 (51.8%)	97 (70.3%)	83 (92.2%)
• Idiopathic	8	-	11	54	62
• Pregnancy	1	-	2	0	3
• Infection	9	-	24	23	14
• Autoimmune/ Inflammatory	0	-	6	20	4
Malignancy (total)	9 (31.0%)	36 (43.4%)	14 (16.9%)	35 (25.4%)	6 (6.7%)
• Haematological	8	26	5	31	5
• Solid tumour	1	10	9	4	1
Drug-induced	2 (6.9%)	22 (26.5%)	26 (31.3%)	6 (4.3%)	1 (1.1%)
Presentation					
Fever	19 (65.5%)	60 (72.3%)	27 (32.5%)	81 (58.7%)	55 (61.1%)
Painful lesions	19 (65.5%)	32 (38.6%)	26 (31.3%)	36 (26.1%)	-
Pruritus	7 (24.1%)	24 (28.9%)	-	-	-
Distribution					
Upper limbs	27 (93.1%)	60 (72.3%)	73 (88.0%)	103 (74.6%)	75 (83.3%)
Lower limbs	17 (58.6%)	58 (69.9%)	35 (42.2%)	74 (53.6%)	67 (74.4%)
Trunk	24 (82.8%)	69 (83.1%)	56 (67.5%)	73 (52.9%)	12 (13.3%)
Head	14 (48.2%)	33 (39.8%)	27 (32.5%)	41 (29.7%)	25 (27.7%)
Lab Investigations					
Neutrophilia	27 (93.1%)	-	32 (38.6%)	61 (44.2%)	74 (100.0%)*
Anaemia	23 (79.3%)	64 (77.1%)	39 (47.0%)	61 (44.2%)	7 (7.8%)
Thrombocytopenia	8 (27.6%)	43 (51.8%)	-	25 (18.1%)	-
Raised ESR	17 (85.0%)†	-	64 (77.1%)	101 (73.2%)	74 (100.0%)‡
Treatment					
Systemic steroids	26 (92.9%)‖	49 (59.0%)	75 (90.3%)	99 (71.7%)	30 (33.3%)
Topical steroids	26 (92.9%)‖	32 (38.6%)	3 (3.6%)	-	4 (4.4%)
Colchicine	3 (10.7%)‖	6 (7.2%)	1 (1.2%)	-	44 (48.9%)
Dapsone	1 (3.4%)‖	14 (16.9%)	1 (1.2%)	-	-
Others	COX-2 inhibitor 3 (10.7%) NSAIDS 2 (7.1%)	Supersaturated potassium iodide 6 (7.2%)	NSAIDS 2 (2.4%)	-	-
Recurrence	7 (24.1%)‖	-	19 (22.9%)	22 (15.9%)	26 (28.9%)
Associations with malignancy	Anaemia, thrombocytopaenia, pathergy	Anaemia, thrombocytopaenia, leukopenia, absence of arthralgia, histiocytoid and subcutaneous histopathology	Anaemia, higher ESR	Older age, anaemia, thrombocytopenia, absence of arthralgia	Vesiculobullous lesions
Association with recurrence	-	-	Leukocytoclasia	-	-

*n = 74; †n = 20; ‡n = 74; ‖n = 28
Abbreviations: COX-2, cyclooxygenase-2; NSAIDS, non-steroidal anti-inflammatory drugs; ESR, erythrocyte sedimentation rate

the risk of anaemia were females, older age, and ethnicity.[17] A comparison of the features in the present study with other studies is shown in Table III.

The pathogenesis of SS remains largely unknown. It is postulated to be due to hypersensitivity reactions to infections, neoplasms, autoimmune or inflammatory diseases, and drugs. This is further supported by rapid response to systemic corticosteroids. In addition, circulating autoantibodies, cytokines, dermal dendrocytes, human leucocyte antigen serotypes, immune complexes, and leukotactic mechanisms may be contributory factors.[1] T helper 1 (Th1) cells and inflammatory cell markers such as CD3, CD163, myeloperoxidase, metalloproteinases, and vascular endothelial growth factors were found to be in higher levels in skin lesions in SS compared to other neutrophilic dermatoses.[18] Furthermore, malignancy-associated SS is postulated to be due to overproduction or impaired regulation of inflammatory cytokines such as IL-1, IL-3, IL-6, IL-8, G-CSF, and granulocyte macrophage colony stimulating factor (GM-CSF). This is further supported by SS occurrence in patients that received G-CSF or patients with neoplasms that were capable of producing G-CSF.[1,3]

Seven patients had pruritus (24.1%) in our study. Pruritus was also reported by Rochet et al[13] in one fifth of their

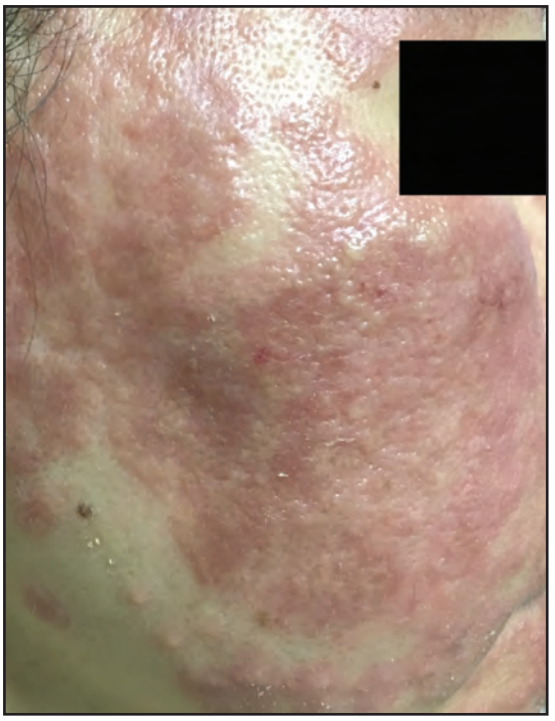

Fig. 1: Edematous, erythematous plaque on the right cheek

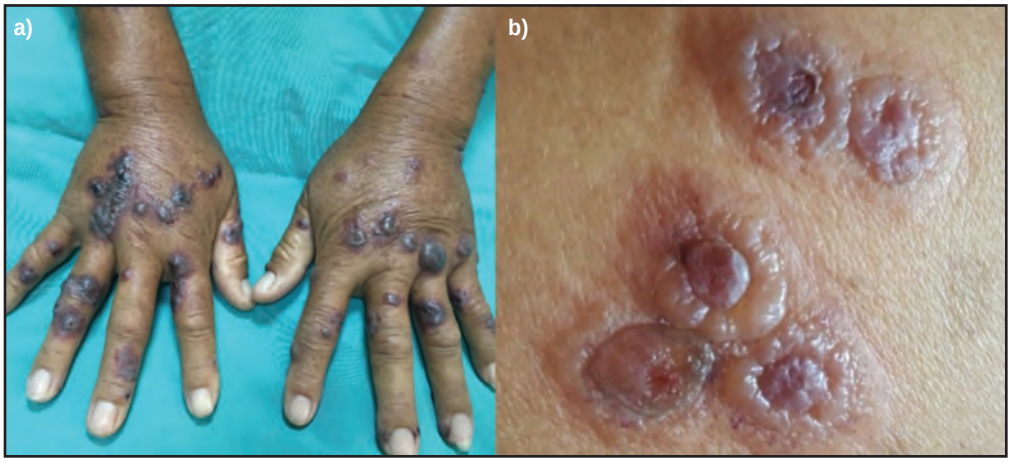

Fig. 2: a) Discrete purplish pseudo-vesicles and papules on the dorsal hands. b) Red-purplish pseudo-vesicles arranged in an annular configuration

patients (18.2%) and by Nelson et al[16] in a third of their patients. We found that pruritus was associated with pustules (p=0.038). The pruritus might be due to pruritogens secreted by the neutrophils in the pustular infiltrates. Neutrophils have been found to produce and release pruritogens such as histamine, proteases, prostaglandin E2, leukotriene B4, and S100 proteins. Hashimoto et al[19] postulated that SS is not associated with itch although it is a neutrophilic dermatosis as the neutrophilic infiltrate are deep within the dermis. However, we postulate those patients with pustules experienced itch because the pustules were more superficially located in the skin. In addition, Heath et al[20] found that apart from Th1 cells, T helper 17 (Th17) cells also play a significant role in SS. Th17 cytokines have been implicated in itch in conditions such as psoriasis and acute phase of atopic dermatitis.[21]

The main histological characteristic of SS is neutrophilic infiltrate in the dermis without evidence of leukocytoclastic vasculitis. However, several reports have described the presence of perivascular neutrophilic infiltrate with changes consistent with leukocytoclastic vasculitis with reported occurrence between 8.8 and 74.2%.[10,22,23] The presence of leukocytoclastic vasculitis was related to secondary changes as a result of massive release of toxic metabolites from activated neutrophils leading to vessel wall damage rather than primary vasculitis.[1,22,23] Furthermore, Malone et al[22] described that lesions that were present for a longer duration (median 17.5 days) were significantly associated with vasculitis compared to lesions that were present for a shorter duration (median 6 days). Additionally, direct immunofluorescence study failed to detect any immune complex or complement deposition within the vessel walls, which is commonly seen in leukocytoclastic vasculitis.[22]

In the present study, classical subtype was the most common, followed by malignancy-associated and drug-induced SS, similar to other studies.[9,10,13,24] For the classical subtype, the majority of our patients had underlying infection, which differ from the previous reports whereby idiopathic cause was more common.[9,10,24] The most common infection in our patients was mycobacterial infection. Eight (five classical SS, three malignancy-associated SS) of our patients in Hospital Queen Elizabeth were diagnosed with mycobacterial infection around the time of diagnosis of SS. Previous case series reported the association of mycobacterial infection with SS whereby majority of them had extrapulmonary or disseminated involvement. Infection with NTM was more commonly reported compared to MTB infection.[25,26] The high number of MTB infection in our patients may be explained by the fact that Sabah has the highest incidence of MTB in Malaysia.[27]

Haematological malignancy was the most common malignancy associated SS and acute myeloid leukaemia was the most frequently occurring cancer in our patients which is consistent with previous studies.[9,16] Anaemia and thrombocytopenia were associated with malignancy, in accordance with the results from the previous studies.[9,12,16]

The histiocytoid variant of SS (HSS) was first described by Requena et al[28] in 2005. The lesions in this variant demonstrate inflammatory infiltrate that resemble histiocytic mononuclear cells but are in fact immature myeloid cells. It is postulated that the immature myeloid cells are released from the bone marrow during the acute stage of the disease and are subsequently replaced by mature neutrophils as the disease evolves. These cells may be difficult to distinguish morphologically from leukemic cutis. These immature myeloid cells stain positively with myeloperoxidase (MPO) and CD68.[28] On the other hand, most of the leukemic cutis cases are immunoreactive to CD34 or CD117. However, not all cases can be distinguished reliably as some cases of hematological malignancy do not possess the markers. A summary of published cases by Bush et al.[29] reported an association of histiocytoid variant with hematological malignancy, with the most common being myelodysplastic syndrome. A review by Alegria-Lande et al.[30] did not demonstrate this association but concurred with the finding that myelodysplastic syndrome was the most common hematological malignancy encountered with the histiocytoid variant. All (4) of the patients with malignancy- associated SS in Hospital Queen Elizabeth had histiocytoid variant and were positive for MPO and CD68 and negative for CD34 and CD117. Two patients had acute myeloid leukemia, one had myelodysplastic syndrome and one had Hodgkin's lymphoma. We were not able to study the association between histiocytoid variant and malignancy as the markers were not performed on patients with other subtypes.

Studies have showed that fluorescence in situ hybridisation (FISH) analysis of the cutaneous infiltrates may aid in the differentiation between SS and leukemic cutis. Carvan et al.[31] reported that six patients with haematological malignancy associated SS had chromosomal aberrations of the bone marrow biopsy specimens. FISH analysis was performed on five of the skin biopsy samples of these patients and the same cytogenetic abnormalities were identified in four of the samples and one had equivocal results. This suggests that the patients had leukemic cutis rather than SS. In a case series by Alegria-Landa et al.,[30] seven patients with FISH analysis of bone marrow specimens underwent FISH of the cutaneous biopsy specimens. Only one patient with chronic myelogenous leukaemia had similar chromosomal aberrations in the bone marrow and cutaneous specimens. In this case, there were scattered cells with the chromosomal aberrations in the dermis which suggests the coexistence of leukemic cutis and histiocytoid SS. Both papers concurred that the use of FISH to identify leukemic cutis is only possible if appropriate probes are available for the specific cytogenetic abnormality.[30,31] Unfortunately, FISH was not performed in our patients who had histiocytoid variant as the test is not readily available.

With regard to drug-induced SS, the most frequently associated drug is G-CSF.[1] Other drugs include antibiotics (minocycline, nitrofurantoin, trimethoprim-sulfamethoxazole), antiepileptic (carbamazepine), antihypertensive (hydralazine), oral contraceptives and retinoids.[32] Our patient who was given radiocontrast for a computed tomography (CT) scan developed SS a day after the procedure. Recurrence occurred a year later when he underwent another CT scan with contrast. The association of SS and radiocontrast has been reported in two case reports and both patients had vesiculobullous presentation,[33,34] which was also seen in our patient.

LIMITATIONS

The study was limited by its retrospective design. The sample size was small likely due to the uncommon occurrence of this condition. Furthermore, patients with mild SS might have received treatment at primary care and thus were not referred to us. As FISH was not performed in patients with histiocytoid SS, leukemic cutis cannot be excluded with absolute certainty.

CONCLUSION

In summary, all patients with SS should have a comprehensive history and clinical examination to evaluate for systemic disorders. Mycobacterial infection should be considered in this region due to high TB burden. Anaemia and thrombocytopenia presage an occult malignancy.

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ORIGINAL ARTICLE

Prevalence and barriers of reporting needle-stick injures amongst government pharmacists working in Perak, Malaysia

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ABSTRACT

Introduction: Needle-stick injuries (NSIs) are common amongst healthcare workers including pharmacists. Studies have reported a range of 0–5.65 per 1,000 pharmacists handling vaccinations that suffered at least one incident of NSI. The objective of this study was to determine the prevalence of NSI and the barriers encountered in reporting it amongst government pharmacists working in Perak.

Materials and methods: This was a cross-sectional study conducted amongst all government pharmacists in Perak. We excluded those who did not consent or were unreachable electronically. The researchers provided an online link that was forwarded to all heads of departments in Perak via social media. The respondents answered their demographic details, questions assessing their knowledge of NSI transmissible diseases, needle-stick handling practices, detail experiences of them suffering an NSI (all self-developed questionnaires), and their barriers in reporting an NSI (validated questionnaire). All responses were auto-tabulated in an excel sheet. A sample size of 516 pharmacists was needed for this study. A respondent was deemed to have inadequate knowledge when they answered any question wrongly about NSI knowledge-related questions and inappropriate practice in needle handling when respondents answered any questions wrongly for questions assessing practices.

Results: A total of 524 pharmacists participated. The overall prevalence of NSI was 23.1% (n=121), of which, those with contaminated NSI were 10.3% (n=54, 95%CI: 7.9-13.30). Two-thirds of the participants (66.6%) had inadequate knowledge and nearly all of them were unable to describe the appropriate needle-handling practices (94.7%). Amongst the reported barriers were "not knowing whose duty it was to report an NSI" (45.5%) and "busy schedules" (44.7%).

Conclusion: One in every five pharmacists in the state of Perak had a history of NSI, and 1 in every 10 had sustained a contaminated NSI. The barriers to reporting a NSI were mainly due to uncertainty about whose responsibility to report the incident and being too busy to report it.

KEYWORDS:
Needle-stick injuries, reporting, Pharmacists, Perak, Malaysia

INTRODUCTION

Any cut or prick to the person by a needle that is sterile/contaminated with the patient's bodily fluids and incurred within the hospital premises is referred to as a needle-stick injury (NSI).[1] The most concerning outcome of an NSI is the transmission of blood-borne infections such as HIV, Hepatitis B virus (HBV), and Hepatitis C virus (HCV). This has resulted in a significant number of HBV, HCV, and HIV infections amongst healthcare providers with an estimated transmission rate of 30%, 1.8%, and 0.3%, respectively.[2,3]

The top three procedures that induced NSI were needle recapping, intravenous line administration, and blood collection, and these NSI incidences have been prevalent amongst nurses.[4] According to a study conducted in Malaysia in 2007, medical assistants had the highest rates of NSI (50.0%), followed by nurses (37.0%), and doctors (22.7%) with pharmacists not included in the sample.[5] Limited similar research on NSI have been conducted amongst pharmacists. One study conducted amongst pharmacy students reported that the main activities related to NSI were finger-strip blood glucose monitoring and insulin delivery.[6] Most of the NSI-related research had not targeted pharmacists as respondents. The incidence of NSI amongst the pharmacy professionals could be an oversight.

In a Malaysian context, according to the Malaysian Ministry of Health's Occupational Health Unit, the most common type of injury amongst healthcare workers were NSI, which had a rate of 6 injuries per 1000 Healthcare Workers (HCW) in 2016.[7] In the same survey, it was discovered that 4.2 out of 1000 pharmacists in Malaysia (51 out of 12,048 pharmacists) suffered from NSI.[7] It is predicted that pharmacists working in government health facilities were exposed to NSI risks while providing insulin administration or functionality counselling, conducting blood sugar monitoring with a glucometer during Diabetes Mellitus Medication Adherence Therapy Clinic (DMTAC), performing Cytotoxic Drug Reconstitution (CDR), or Total Parenteral Nutrition (TPN) where these tasks involved needle handling.[8-11]

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The Malaysian Ministry of Health (MOH) requires all NSIs to be reported. However, the researchers felt that these injuries may be under-reported especially amongst pharmacists. In other nations, 36.8% of Iranian nurses with NSIs were discovered to have filed an official report.[4] Dissatisfaction with follow-ups, low risk among source patients, unfamiliarity with the reporting process, busy schedules, and low-risk perceptions were amongst the reasons for not reporting.[4] The aim of this research was to determine the prevalence of NSI amongst government pharmacists in Perak, as well as to assess their knowledge in handling an NSI, their needle handling practices, and common barriers faced in reporting an NSI.

MATERIALS AND METHODS

This was a cross-sectional study conducted from June 2017 to February 2018 amongst all government pharmacists working within the state of Perak—a central state within Peninsular Malaysia, with the second largest population in West Malaysia. There are 6 specialised hospitals, 9 district hospitals, and 11 district health offices (PKD or *Pejabat Kesihatan Daerah*) in Perak, with 88 health clinics. Government pharmacists are distributed amongst the aforementioned health facilities, along with the Pharmaceutical Services Division (BPF or *Bahagaian Perkhidmatan Farmasi*), Pharmacy Enforcement Division, and Clinical Research Centre (CRC). These pharmacists consist of two groups- the Provisionally Registered Pharmacists (PRP) and Fully Registered Pharmacists (FRP), where PRPs are usually stationed at specialist hospitals only.

We included all pharmacists hired within the government service, who were currently working in the state of Perak by sending them an online self-administered questionnaire. First, the researchers approached the Perak Pharmaceutical Services Division to request the contact list for all Chief Pharmacists in the government service within Perak. This was to enable the researchers to reach them and request permission to conduct the study in their department. Had the Chief Pharmacists agreed, they were sent an email and a *Whatsapp®* message that briefly explained about the study. They were also given a link (URL) to access the electronic participant information sheet. Upon deciding to participate, they were routed to the link with the questionnaire and no identifiers were recorded to protect respondents' identity. Those who did not consent or those that were electronically unreachable were excluded.

The self-developed questionnaire consisted of several parts (i) demography, (ii) number of NSI, (iii) knowledge on NSI transmissible diseases, (iv) needle handling practices, (v) NSI training, (vi) immediate steps to be taken after sustaining an NSI, and the last section consisted of an adapted validated questionnaire assessing (vii) barriers to reporting an NSI. For items (iii) to (vi), the Cronbach's alpha ranged from 0.60 to 0.89.

The questionnaire was pre-tested amongst 10 government pharmacists from other states (outside Perak) to assess its readability and understanding (construct validity). While the targeted respondents were pharmacists, and they were deemed to be able to comprehend the questionnaire structured in English, the researchers did not translate the questionnaire to other languages. The words-contaminated NSIs were described as "needles being contaminated with bodily fluids or contaminated with bodily wastes" before the questions were displayed.

The basic demographic details collected included age, sex, place of work, number of years in the service, and current place of work. It was followed by assessing the frequency and details of an NSI, including the condition of the needle involved in the NSI (sterile or contaminated), the frequency of NSI at work, the most common department, and institution where the NSI occurred, and whether the NSI incident was reported. Then, respondents were asked a series of questions regarding the NSI knowledge of transmissible diseases and the practices of needle-stick handling. The scoring for knowledge was done as follows: Getting all the answers right was deemed as having "*adequate knowledge*" and getting any one of the answers wrong was deemed to be having "*inadequate knowledge*". This score was decided by taking into consideration that all questions asked were basic and essential—adapted from the standard preventive guidelines by the Ministry of Health Malaysia. The appropriateness of needle handling practices was determined by—having answered all the practice questions correctly, they were considered to have "*appropriate practice*." Having any one of the practices answered incorrectly was considered to have "*inappropriate practice*." The awareness of the needle-stick reporting mechanism within the Malaysian Ministry of Health and their choice of the timing an NSI-related education (when should it be given) was assessed as well. An open-ended question was included to assess the immediate steps that would be taken by the respondent should they accidentally sustain an NSI.

The last section of the questionnaire was regarding the barriers to reporting an NSI. This questionnaire was a validated questionnaire adapted from Evans et al..[12] It consists of 19 questions that were answered as "Yes" or "No." Once the respondents were done answering, they clicked the "submit" button to affirm their responses. All responses submitted online were anonymously sent to the researchers via email. Only the researchers listed in this study had access to the content in this email box.

Sample size

After performing a check with the Pharmaceutical Services Division (BPF), it was found that there were 773 pharmacists working within the government health facilities in Perak. Thus, by using the prevalence table, the population to proportion calculation was used for the sample size (this book used the STATA sample size calculator).[13] Assuming that the population involved was deemed to be large (more than 1000), setting the precision intended for this study at 3% (3% being selected to yield a larger sample size for better generalisability), the final sample size needed for this study was 516.

Data analysis

All responses collected were tabulated in SPSS v21.0 for further analysis. A descriptive analysis was performed to analyse the respondents' demography, knowledge and practices, awareness for reporting and training, and barriers

for not reporting. The prevalence of NSI amongst the respondents was determined in the form of a percentage by dividing the accumulated NSI over the total number of pharmacists who responded to this study with 100%. The open-ended responses were recoded into themes in which respondents stated the first step they would take if they sustained an NSI.

RESULTS

Response rate

The total respondents for this study were 524 (101.5% of the intended sample size), or 67.8% of the 773 pharmacists working in Perak state at the time of the data collection.

Demography

Table I shows the basic demographic details of the respondents. The mean age of the respondents was 29.06 years (SD 3.96) of age, with a mean working experience of 4.64 years (SD 4.00). The majority of them were females (81.3%) and FRPs (86.5%). From the total, 50% of the respondents were working in tertiary hospitals.

Prevalence of NSI

A total of 54 pharmacists (10.3%, 95%CI: 7.9,13.3) from Perak self-declared that they had sustained at least one contaminated NSI. Three respondents (0.6%) mentioned that they sustained an NSI but not within Perak; these pharmacists were excluded from the final sub-group analysis (Table II).

Knowledge and practices

Approximately two-third (66.6%) of the respondents scored "*inadequate knowledge*" where knowledge of transmissible diseases was concerned. The majority (94.7%) of respondents had inappropriate needle handling practices. Overall, 98.5% of pharmacists had inadequate knowledge in NSI-related diseases or inappropriate needle handling practices.

Awareness of the NSI reporting system and education on NSI

A total of 39.5% and 42.2% of the respondents were not aware of the local NSI reporting systems and neither were they aware of the standard MOH reporting systems after an NSI. There were only 4.2% of pharmacists that had completed an NSI form—less than half of the 10.3% who had sustained an NSI. Of the total, 73.1% did not know where to locate the NSI form, and 77.1% did not know what to do with a completed NSI form. At the point of data collection, 44.7% of the respondents had been educated on the prevention and actions to be taken if an NSI happens. A majority (98.1%) of them agreed that they should be educated on NSI prevention. The majority (97.5%) also felt that they should be educated on the Standard Operating Procedure (SOP) and the NSI reporting systems. From the total, 89.5% of the respondents felt that they should be taught about NSI during their university days and 99.2% felt that it should be taught during their PRP training tenure (Table II).

Immediate steps to be taken after an NSI

Dressing with water or alcohol (52.1%), followed by getting medical attention/calling the infectious disease department (14.1%), and squeezing blood out of the injured area (5.2%) were the top three responses when they were asked for the first step they should take when sustaining an NSI. None of these answers were correct; only 3.4% of them gave the right answer of washing the wound with soap and water (Table II).[14]

Barriers to reporting an NSI

Table III shows the reasons why the respondents chose not to report an NSI incident, involving the opinions of both who have suffered and those who did not suffer an NSI. Respondents who had not sustained an NSI stated that they would not report an incident because they did not know whose responsibility it was to make the report (45.5%) and being busy (44.7%) was the other reason given. Amongst those who sustained NSI—the same two reasons were stated at 50.4% and 51.2%, respectively. Less than one-third of the pharmacists were in common agreement that (i) they did not feel that the NSI form was kept anonymous, (ii) it did not lead to any system change, (iii) was probably too complicated to fill-in, (iv) were worried about their details being accessed by others, and (v) they would never get any feedback from it.

Responses of Pharmacists that Sustained an NSI

The researchers performed a separate analysis to look at those who suffered from NSI. There was a total of 54 pharmacists who suffered an NSI. From the 54, only 19 (35.2%) of them reported the incident. From the total of 54, 98.1% of them had poor needle handling practices and

Table I: The basic demographic details of the pharmacists responded to the questionnaire

Socio-demographic data		n (%) N=524
Age	*(mean ± SD)*	29.06 ± 3.96
Years of practice	*(mean ± SD)*	4.64 ± 4.00
Gender	*Male*	98 (18.7)
	Female	426 (81.3)
Job Position	*PRP*	71 (13.5)
	FRP	453 (86.5)
Current Institution	*Tertiary hospital*	262 (50.0)
	District health office/ health clinic	166 (31.7)
	District hospital	72 (13.7)
	Perak Pharmacy Enforcement branch	13 (2.5)
	Pharmacy service division	6 (1.1)
	Clinical research centre	5 (1.0)

*PRP= Provisionally Registered Pharmacists; FRP= Fully Registered Pharmacists

Table II: Prevalence, knowledge, practices, awareness, training of NSI, and the first step initiated if a NSI is sustained

Variables	n (%) N=524
Number of respondents sustained a contaminated NSI	
Yes	54 (10.3)
Maybe (Unsure if NSI was contaminated or not)	67 (12.8)
No	400 (76.3)
Yes, but not in Perak state	3 (0.6)
Adequate NSI knowledge of transmissible diseases	
Hepatitis A	251 (47.9)
Hepatitis B	456 (87.0)
Hepatitis C	425 (81.1)
Tuberculosis	411 (78.4)
HIV	519 (99.0)
Overall adequate NSI knowledge of transmissible disease	175 (33.4)
Appropriate needle handling practices	
Recap needles after use	168 (32.1)
Disassemble used needles or sharps with hands	366 (69.8)
Wear gloves when disposing of contaminated needles	458 (87.4)
Separate the needle from the syringe prior to disposal	271 (51.7)
Throw used needles into sharp bin immediately	511 (97.5)
Wear gloves when manipulating the sharp bin	441 (84.2)
Discarding needles into sharp bin	482 (92.0)
Overall appropriate of needle handling practice	28 (5.3)
Overall knowledge and handling practices	8 (1.5)
Awareness of NSI reporting system	
Aware of a local NSI reporting system	317 (60.5)
Aware of needle stick injury system in Ministry of Health Malaysia	303 (57.8)
Ever completed a NSI report form	22 (4.2)
Know where to locate or access a NSI report form	141 (26.9)
Know what to do with a completed NSI report form	120 (22.9)
NSI-related training	
Have you ever been educated on prevention and actions to be taken if a NSI happens	234 (44.7)
Do you think pharmacists should be educated on prevention of NSI?	514 (98.1)
Do you think pharmacists should be educated on Standard Operating Procedures and reporting system of NSI?	511 (97.5)
When should pharmacist be educated on NSI — Pharmacy university	469 (89.5)
When should pharmacist be educated on NSI — Hospital PRP training	520 (99.2)
The first infection preventive step that you would take after sustaining a needle-stick injury	**n (%) N=524**
Some sort of dressing with water/alcohol	273 (52.1)
Get medical attention/call infectious disease department	74 (14.1)
Squeeze blood out of injured area	27 (5.2)
Get blood tested immediately	20 (3.8)
Run under running water, wash with soap/disinfectant, see doctor for patient's screening and blood investigations (correct answer)	18 (3.4)
Report incident	18 (3.4)
Don't know what to do	17 (3.2)
Antiviral prophylaxis	17 (3.2)
Inform Head of department/ In-charge person	9 (1.7)
Inject vaccine	9 (1.7)
Some sort of dressing and blood check	6 (1.1)
Take an antidote	5 (1.0)
Antibiotic prophylaxis	5 (1.0)
Anti-tetanus prophylaxis	4 (0.8)
Ask help from colleagues	3 (0.6)
Evaluate source of contamination	3 (0.6)
Wear gloves while handling needles/discard the needle	1 (0.2)
Others	15 (2.9)

NSI: needle stick injury; PRP: provisionally registered pharmacist

Table III: The barriers to reporting NSI

I DID NOT report OR MAY NOT report NSI because: -	Yes n (%) N=524	Those with NSI n (%) N=121
I am worried about disciplinary actions	94 (17.9)	32 (26.4)
When I am busy, I forget to make a report	234 (44.7)	61 (50.4)
I am worried about legal actions that may be taken against me	81 (15.5)	19 (15.7)
The NSI report form takes too long to fill and I just don't have time	183 (34.9)	50 (41.3)
My co-workers may be unsupportive	79.8 (20.2)	32 (26.4)
I don't know whose responsibility it is to make a report	238 (45.5)	62 (51.2)
I don't want the case discussed in meetings	143 (27.3)	35 (28.9)
I don't feel confident that the NSI report form is kept anonymous	161 (30.7)	41 (33.9)
The report is unlikely to lead to system changes that will improve the quality of care	137 (26.1)	37 (30.6)
I don't want to get into trouble	136 (26.0)	37 (30.6)
Junior staff are often blamed unfairly for NSI	149 (28.4)	35 (28.9)
I don't see any point in reporting it	65 (12.4)	18 (14.9)
If I report something, I never get any feedback on what action is taken	180 (34.4)	42 (34.7)
The NSI report form is too complicated and requires too much detail	185 (35.3)	48 (39.7)
I feel that if I discuss the case with the person involved, nothing else needs to be done	101 (19.3)	26 (21.5)
I worry about who else is privy to the information that I disclose	158 (30.2)	33 (27.2)
The incident was too trivial	104 (19.8)	30 (24.8)
It's not my responsibility to report somebody else's mistakes	75 (14.3)	21 (17.4)
Even if I don't give my details, I'm sure they'll trace me down	108 (20.6)	33 (27.3)

NSI: needle stick injury; n=121 was summation of both respondents sustained a contaminated NSI (n=54) and may be a contaminated NSI (n=67)

Table IV: Prevalence, knowledge, practices, awareness, and training of NSI amongst those who sustained an NSI, n=54

Variables		n (%) N=54
Adequate NSI knowledge of transmissible diseases		
Hepatitis A		20 (37.0)
Hepatitis B		46 (85.2)
Hepatitis C		45 (83.3)
Tuberculosis		5 (9.3)
HIV		54 (100)
Overall adequate NSI knowledge of transmissible disease		17 (31.5)
Appropriate needle handling practices		
Recap needles after use		34 (63.0)
Disassemble used needles or sharps with hands		18 (33.3)
Wear gloves when disposing of contaminated needles		39 (72.2)
Separate the needle from the syringe prior to disposal		22 (40.7)
Throw used needles into sharp bin immediately		53 (98.1)
Wear gloves when manipulating the sharp bin		42 (77.8)
Discarding needles into sharp bin		51 (94.4)
Overall appropriate of needle handling practice		1 (1.9)
Overall knowledge and handling practices		1 (1.9)
Awareness of NSI reporting system		
Aware of a local NSI reporting system		40 (74.1)
Aware of needle stick injury system in Ministry of Health Malaysia		37 (68.5)
Ever completed a NSI report form		18 (33.3)
Know where to locate or access a NSI report form		26 (48.1)
Know what to do with a completed NSI report form		20 (37.0)
NSI-related training		
Have you ever been educated on prevention and actions to be taken if a NSI happens		31 (57.4)
Do you think pharmacists should be educated on prevention of NSI?		54 (100)
Do you think pharmacists should be educated on Standard Operating Procedures and reporting system of NSI?		54 (100)
When should pharmacist be educated on NSI	Pharmacy university	48 (88.9)
	Hospital PRP training	54 (100)

Table V: Barriers among pharmacists who sustained needle-stick injury to report the incident, n=54

I DID NOT report OR MAY NOT report needle-stick injuries because:-	Yes n (%)	No n (%)
I am worried about disciplinary actions	16 (29.6)	38 (70.4)
When I am busy I forget to make a report	27 (50.0)	27 (50.0)
I am worried about legal actions that may be taken against me	12 (22.2)	42 (77.8)
The needle-stick injury report form takes too long to fill and I just don't have time	25 (46.3)	29 (53.7)
My co-workers may be unsupportive	17 (31.5)	37 (68.5)
I don't know whose responsibility it is to make a report	26 (48.1)	28 (51.9)
I don't want the case discussed in meetings	20 (37.0)	34 (63.0)
I don't feel confident that the needle-stick injury report form is kept anonymous	20 (37.0)	34 (63.0)
The report is unlikely to lead to system changes that will improve the quality of care	18 (33.3)	36 (66.7)
I don't want to get into trouble	24 (44.4)	30 (55.6)
Junior staffs are often blamed unfairly for needle-stick injuries	12 (22.2)	42 (77.8)
I don't see any point in reporting it	8 (14.8)	46 (85.2)
If I report something, I never get any feedback on what action is taken	17 (31.5)	37 (68.5)
The needle-stick injury report form is too complicated and requires too much detail	23 (42.6)	31 (57.4)
I feel that if I discuss the case with the person involved, nothing else needs to be done	12 (22.2)	42 (77.8)
I worry about who else is privy to the information that I disclose	19 (35.2)	35 (64.8)
The incident was too trivial	17 (31.5)	37 (68.5)
It's not my responsibility to report somebody else's mistakes	10 (18.5)	44 (81.5)
Even if I don't give my details I'm sure they'll trace me down	13 (24.1)	41 (75.9)

68.5% of them had poor overall knowledge of transmissible diseases from an NSI. Full details of this analysis is available in Table IV. In Table V, we described the reasons a person with an NSI would not report an incident in future. Some of the reasons those with NSI would not report: Half (50.0%) of the participants mentioned that they were too busy and forgot about it, 48.1% said they did not know whose responsibility it was to make a report, 46.3% said that reporting takes too long, 44.4% said that they did not want to get into trouble and 42.6% said that it was too complicated and required too much details.

DISCUSSION

This study found the NSI prevalence amongst pharmacists in the public service in Perak, Malaysia was 10.3%. Most NSI-related studies focused on medical officers, medical assistants, nurses, as well as the students in the medical profession, commonly leaving out pharmacists from the sample[5,7,12,14]. It is noteworthy that this study found that about 1 in 10 pharmacists sustained a contaminated NSI throughout their practice, indicating that this profession is at risk of NSI and being predisposed to the risk of blood-borne transmissible diseases. Most of them chose not to report an NSI incident as they were unsure of who was supposed to report and due to their busy schedules.

The prevalence of 10.3% of pharmacists having experienced a contaminated NSI was comparatively lower than what Wichai reported where 17.4% of the pharmacy students in Thailand experienced an NSI.[6] Nevertheless, the overall NSI prevalence, including the incidence of sterile NSI, reported by the respondents in this research was 23.1%. The rate in this study is relatively lower in comparison with other studies (reported between 36.3 and 45%) of healthcare workers in other professions and medical students had a history of NSI.[15,16] The prevalence found in this study deserves attention and stake holders should apply precautionary measures to alert pharmacists about the hazards of needle handing and NSI. Less attention has been given to the issue of NSI amongst pharmacists in the past, which could be attributed to the comparatively lower incidence of NSI occurring in this profession- perhaps due to under-reporting as found in this study. This is evident in a study conducted in 2016 by the Malaysian Ministry of Health which revealed that 6 out of every 1000 healthcare worker (HCW) had an NSI, of which medical doctors had the greatest rate of infection (21.1 per 1000 HCWs), followed by dental staff (7.5), pharmacy staff (4.2), nurses (3.7), medical assistants (3.4), and allied and auxiliary personnel (1.0).7 A comparable incidence of NSI amongst pharmacists was a study done in the United States that showed that 5.65 per 1000 immunizing pharmacists reported the incidence of NSI in a retail pharmacy setting.[17]

This study showed that about one-third of the respondents demonstrated adequate knowledge of transmissible diseases attributed to NSI. Another similar study reported that 13% of the students perceived that they had adequate knowledge regarding NSI.[17] This reflects that knowledge of NSI amongst pharmacists was deemed to be inadequate and it is high time for improvement to be made. In addition, a mere 5.3% of our study respondents had appropriate practice in needle handling. Unsafe practices such as needle recapping and inappropriate needle disposal were critical risk factors that resulted in an NSI, and unsafe practices remain a major problem.[7] The report also advised that safe and uniform practices (such as proper discarding of needles and not recapping used needles) for various healthcare practitioners should be developed, implemented, and monitored—something that has not been done for pharmacists yet.[7]

Another concern is the lack of awareness about the existence of an NSI reporting system (approximately 40%) and pharmacists being unsure on how to obtain forms as well as how/where to submit it (approximately 70%). Although it is assumed that pharmacists are given the same needle-handling training and NSI prevention as their counterpart professions across the MOH settings, this study found that not all pharmacists were exposed to the NSI reporting system. Malaysian pharmacists may be perceived as less involved in

handling needles and sharps, as evident in many NSI awareness research studies on the professions of medical doctors, dentists, and paramedics extensively, with little to no research reporting on pharmacists.[18-20] Consistently, the results reported by a Malaysian national study found that 78% of the 49 incidences of NSI events associated with insulin needle handling amongst pharmacy staff in the MOH have been categorised as other or non-specific tasks. Unlike the other professions, such as medical doctors and nurses, NSI-related tasks were specifically grouped into "giving injections," "drawing blood," and "surgical procedures".[7] To date, pharmacy staff have not received adequate attention in NSI training, and this might be due to the cliché of the profession being perceived as conventionally dispensing medications with minimal or no sharp handling.[21] Provision of the same training to pharmacists on NSI and the reporting system should be implemented- especially when there is an expansion to their current roles, including being in-charge of medication therapy adherence in diabetic clinics where handling of insulin needles is inevitable.[8] This would also include simplifying the system of reporting, making it more user-friendly and to reinforce compulsory reporting as well as making the process non-punitive.

Our study found that less than half of the pharmacists were educated on NSI, and the vast majority of them agreed that they should receive education to prevent NSI. Most of them suggested that needle handling and NSI prevention training should be included in the university undergraduate curriculum and almost all of them suggested that PRPs should be trained on NSI prevention. This indicates that pharmacists' exposure towards NSI and needle handling remained far from satisfactory. Education and training concerning NSI that have been well established for healthcare workers such as medical doctors and nurses, should be implemented in the pharmacy profession.[7,14] It is therefore suggested that the Malaysian Pharmaceuticals Service Division, Ministry of Health, should consider this suggestion by incorporating it into the PRP training modules.

The barriers perceived by the respondents in this study to reporting an NSI were not knowing whose duty it was to report and due to busy schedules. This situation was similar to those observed in other studies in the United States where the main reason for not reporting NSI amongst surgeons was attributed to the time-consuming process of reporting.[22] Meanwhile, Iranian nurses gave a different reason in this context- not reporting an NSI was mainly due to the lack of follow-up investigation(s) after a reported event.[4] Amongst some of the possible reasons for this is that the nurses felt that regardless of reporting or not, they were not going to see improvements within the process or system.[4] In general, NSI are considered as an incident that should be reported to the occupational health and safety department. As reported by medical doctors and nurses in Australia- not reporting an incident without regards to its type was due to a lack of feedback.[12] Another main reason for not reporting an NSI in this study was that they were uncertain whose responsibility it was to make an incident report for NSI. This is most likely attributed to being unaware of the NSI reporting mechanism in the Malaysian Ministry of Health, as evident in the findings of this study, where slightly more than half of the respondents were aware of the procedure for reporting NSI. Training pharmacists for NSI reporting, especially those who work in the Malaysian Ministry of Health, for the process of reporting is deemed necessary.

Strengths

This study is the first-known local study carried out amongst registered pharmacists in the government service in Perak, Malaysia between years 2017 and 2018. The sample size for this study was achieved, with 524 out of 773 Perak registered pharmacists (67.8%) participating in this study.

Study limitations

There were few limitations in this study. There may have been some "recall bias" of the timing (year) an NSI and where the injuries were sustained. The results also did not capture the job description of the pharmacists (PRP or FRP) during the NSI event. Data duplication may have also been possible—some pharmacists may have submitted the questionnaire twice by mistake. However, researchers have made efforts to screen the potential duplicate entries by checking whether there were two responses with the same demographic details submitted on the same date with very close timing. In which-such an incident could be due to clicking the "submit" button twice; nevertheless, no such incidence was encountered by the researcher during the data cleaning process.

Implications for occupational and health practice

One in every 10 pharmacists sustained an NSI. The majority of pharmacists had inadequate knowledge and needle-handling practices, whilst the main barrier to reporting an NSI was having a busy schedule and not knowing whose duty it was to report the incident. Pharmacists should be given proper training on prevention, Standard Operating Procedures for handling injectables, and the mechanism for reporting NSI. This can be done either by introducing it as a subject in the pharmacy school training syllabus or during the PRP training period. Other studies have recommended that the procedures of reporting could be made easier by simplifying the process, being anonymous and being supported by the superiors in reporting the incidents.[23] The reporting culture should be created in such a way that it is both encouraging for learning and not punitive in nature.[24]

CONCLUSION

This study affirms that NSI was prevalent among government pharmacists in Perak, with one in five having sustained NSI, of whom one in 10 pharmacists had a contaminated NSI experience. In general, they had inadequate knowledge of transmissible diseases by NSI and needle handling practices, with most of them having not received any form of NSI training and poor awareness about the reporting process. Policymakers should consider education and training for the pharmacists, especially focusing on preventing hazardous job-related injuries like sharps.

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ORIGINAL ARTICLE

Comparison of various creatinine-based estimates of glomerular filtration rate equations in the Malaysian setting

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ABSTRACT

Introduction: Kidney disease is a worldwide health concern with an increasing mortality in the past 10 years. The Kidney Disease Improving Global Outcomes (KDIGO) guideline advocates the use of estimated glomerular filtration rate equation (eGFR) to estimate renal function. We evaluated the performance of Cockroft Gault (CG), Modified Diet of Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations to measured GFR ^{99m}Tc-DTPA taking into account body mass index (BMI) and age group.

Materials and methods: This is a cross-sectional study of patients referred for ^{99m}Tc-DTPA scan at the Nuclear Medicine Centre of International Islamic University Malaysia. The record was taken from patients visiting the centre from January 2016 to December 2019.

Results: The mean measured GFR by ^{99m}Tc-DTPA scan was 42.2 ± 20.38 ml/min. These were lower than that estimated by CG, MDRD, and CKD-EPI equations. CKD-EPI had the highest correlation of 0.72, least bias (mean bias of 11.08 ± 23.08) and was more precise (r^2 = 0.4) as compared to MDRD and CG. In patients < 65 years old, CKD-EPI had the highest correlation; however, MDRD had the least bias and highest accuracy. In terms of BMI, CKD-EPI had the least bias and highest accuracy for BMI >30 and with the highest correlation for all classes of BMI.

Conclusion: CKD-EPI has the best estimation of GFR taking into account the effect of BMI and age. A further study can be done to determine the correlation of estimated GFR equations with different ethnicity in Malaysia.

KEYWORDS:
Chronic kidney disease, Chronic Kidney Disease Epidemiology equation, Modified Diet in Renal Disease equation, Cockroft Gault equation

INTRODUCTION

Kidney disease is a major concern as it contributes towards global mortality and morbidity.[1] According to The Global Burden disease 2015 study, there was a rise of death by 31.7% in 2015 as compared to 2005 which was estimated about 1.2 millions death.[2] For Malaysian population, number of patients on dialysis increased by two and a half folds from 15087 to 37183 patients in 2015.[3] According to the Kidney Disease Improving Global Outcomes (KDIGO), chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function for more than 3 months with implication for health. A reduction of glomerular filtration less than 60 ml/min/1.73m^2 alone is diagnostic of CKD.[4] KDIGO 2012 guideline advocated the use of glomerular filtration rate (GFR) estimating equation rather than serum creatinine alone to estimate GFR.[4] GFR estimating equations such as Cockroft Gault (CG), Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease-Epidemiology Collaboration (CKD–EPI) had been studied extensively and validated in different populations.[5-8]

There were conflicting data with regards to estimated glomerular filtration for different age group and BMI. Age plays an important role in predicting the equation that best estimated the glomerular filtration rate. A study by Carter et al. showed no difference between MDRD and CKD-EPI equations in determining GFR for the elderly.[9] Another study stated that CKD-EPI formula was more accurate in predicting estimated GFR for elderly.[10] With regard to BMI, study done by Michels et al. 2010 showed that CKD-EPI was most accurate for obese patient compared to other equations; however, Poggio et al 2005 and Verhave et al 2005 stated no difference in terms of BMI.[8,11] In comparison, a study done in Bangladeshi patients in both lean and obese patients showed that estimated glomerular filtration rate by MDRD formula was more accurate than CKD EPI.[12] We embark on this study to evaluate the performance of the three most commonly used estimated glomerular filtration rate equations which are Cockroft Gault, MDRD, and CKD-EPI and the effect of difference BMI and age group to the equations.

MATERIALS AND METHODS

This was a cross-sectional study using an existing record of cases conducted at the Nuclear Medicine Centre of International Islamic University Malaysia, Kuantan. The data were collected retrospectively from the patients' clinical records in which patients were referred for ^{99m}Tc-DTPA for various reasons. The records were taken from patients visiting the centre from January 2016 to December 2019.

Patients who came were advised to be well hydrated and requested to void just prior to the procedure. The patient must be in supine position and 0.8–10 mCi of ^{99m}Tc-DTPA was

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administered intravenously. The acquisition protocol was then performed immediately after the injection. The renal dynamic imaging measurements were acquired in 128 x 128 frame matrix. Region of interest for each kidney will then be drawn manually and a semi-lunar background was placed around the lower outer renal margin. By computing the patient's height and weight, the computer was able to calculate measured GFR using Gates method. The measured GFR was standardized to the body surface area of 1.73 m^2

Estimated GFR was calculated based on the CG, MDRD, and CKD-EPI equations. Demographics data of the patients that were collected include age, gender, height, weight, and ethnicity. The clinical data that was collected include: CKD aetiology, background comorbidities, vitals sign, and laboratory data which included the renal function test. The serum creatinine was measured using Jaffé method and traceable to isotope dilution mass spectrometry (IDMS). The ^{99m}Tc-DTPA-measured GFR readings were also recorded. If there were multiple measurements of scans done, the latest ^{99m}Tc-DTPA-measured GFR was taken. Renal function test must be within 3 months of when the ^{99m}Tc-DTPA scan was done. The study has been approved by IIUM research committee (IREC). Inclusion criteria include patients with age more than 18 years old and being not pregnant.

Statistical Analysis

For statistical analysis, SPSS® Statistics version 21 (IBM, New York, USA) was used. Results were presented for categorical data as frequency and percentage while for numerical data, results were presented as mean ± standard deviation (SD) if normally distributed or median (inter-quartile range) if the data was not normally distributed. For categorical data, we used Chi-squared test and for numerical data, we used Independent t-test for normally distributed data and Mann–Whitney U test for non-normally distributed data. ANOVA test was done if there were more than two categorical variables. Performance of different estimated GFR equations was assessed against measured GFR. Pearson rank correlation and linear regression were used to assess the relationship between estimated GFR and measured GFR. Bland–Altman analysis was used to assess concordance between different estimated GFR equations to measure GFR.[13,14]

RESULTS

A total of 153 data of patients who underwent ^{99m}Tc-DTPA scan was collected. After exclusions due to incomplete data, the remaining eligible data was 126 patients.

Demographic data of the patients

Table I shows the demographic of the patients. Of the 126 patients, 54% (n=68) were male and 46% (n=58) were female. The mean age was 55.04 ± 13.73 with the youngest of 18 years old and the oldest of 85 years old. About 72 % of the patients were below 65 years old while 28% of the patients were above 65 years old. All of the mean estimated GFR equations overestimated the mean of measured GFR. CG had the highest GFR of 53.81 ± 36.11 and CKD-EPI had the lowest of 53.28 ± 32.9.

Performance of CG, MDRD and CKD-EPI to measured GFR

CKD-EPI had the highest correlation to the measured GFR, with a correlation coefficient of 0.72 compared to the correlation for MDRD of 0.69 and CG of 0.64 (all $p < 0.0001$). MDRD had the highest accuracy at 30% and 50% of measured GFR which was between 45.2% and 67.4%, respectively, compared to CG and CKD-EPI (Table II). However, CKD-EPI had the highest precision with r^2 of 0.4 and the least bias of 11.08. Bland–Altman analysis was also performed to look for concordance between estimated GFR and measured GFR. (Figures 1–3) CKD-EPI had the lowest limit of agreement which was 90 compared to MDRD with a limit agreement of 98 and CG with a limit agreement of 112.

Comparison of estimated GFR for elderly and non elderly

Table III shows mean and standard deviation of all estimated GFR and measured GFR according to the subgroup of age. Patients > 65 years old had statistically significantly lower GFR estimation compared to younger patients < 65 years old for all three equations. (all $p < 0.0001$. Table III) CKD-EPI had the strongest correlation to measured GFR which was 0.75 for patient < 65 years old. For patients > 65 years old, the correlation was at moderate strength and the highest was MDRD which is 0.564. (all $p < 0.0001$)

We also looked at bias, accuracy, and precision of each equation for the different age groups. In patients <65 years old, MDRD had the least bias of 14.35 compared to CKD-EPI of 14.63 and CG of 16.69. For accuracy, MDRD had the highest accuracy of 43.96% at 30% and of 67.03% at 50% accuracy. CG had the highest precision of 0.457. For patients >65 years old, CG had the least bias of -1.61 compared to CKD-EPI and MDRD. For accuracy, CG also had the highest accuracy at 30% of 57.14% and 71.43% at accuracy of 50% of measured GFR. In addition, CG had the highest precision of 0.1 followed by CKD-EPI and MDRD.

Comparison of estimated GFR for different BMI groups

We divided the BMI according to WHO criteria of normal weight <25, pre-obesity which is 25–29 and obese BMI >30. ANOVA test was done to look for the significance of estimating GFR for different classes of BMI. The mean measured GFR was 43.54 ± 19.76 for BMI >25, 40.14 ± 20.23 for BMI 25–29, and 42.59 ± 22.99 for BMI >30. For BMI <25, all the estimated GFRs overestimated measured GFR with CG being the least that overestimated with a mean of 47.77 ± 29.32. For BMI 25–29, CKD-EPI had the best estimation to measure GFR with mean of 49.41 ± 34.82. For obese patient (BMI >30), all equations overestimated measured GFR with the least being MDRD formula where the mean was 52.03 ± 30.37. CKD-EPI had the highest correlation to mGFR compared to CG and MDRD with a correlation coefficient of 0.82 ($p < 0.0001$) for all classes of BMI. For BMI <25, CG has the highest accuracy at 30% and 50%, least bias with the highest precision. For BMI 25–29, CKD-EPI had the least bias, highest accuracy at 30% and 50% but CG had the highest precision. Similarly, for BMI >30, CKD-EPI had the least bias, highest accuracy at 30% and 50% while CG had the highest precision.

Table I: Demographic data of the patients

	N (%)/mean ± SD
Gender	
Male	68 (54%)
Female	58 (46%)
Age	55.04 ± 13.73
Below 65 years old	91 (72.2%)
Above 65 years old	35 (27.8%)
Ethnicity	
Malay	109 (86.5%)
Non-Malay	17 (13.5%)
Height (M)	1.59 ± 0.10
Weight	64.67 ± 14.66
BMI	25.67 ± 5.42
Less than 25	61 (48.4%)
25–30	41 (32.5%)
More than 30	24 (19%)
Renal/urological diseases	
Renal calculi	91 (72.2%)
Obstructive uropathy secondary to tumour infiltration	6 (4.8%)
Diabetic nephropathy	12 (9.5%)
Polycystic kidney	4 (3.2%)
Others	13 (10.3%)
Stages of chronic kidney disease	
≥90	17 (13.5%)
60–90	28 (22.2 %)
30–59	45 (35.7%)
15–29	25 (19.8%)
≤15	11 (8.8%)
Measured glomerular filtration rate by Tc DTPA (mGFR)	42.2 ± 20.38
Estimated GFR by Cockroft Gault (eGFRCG)	53.81 ± 36.11
Estimated GFR by MDRD (eGFRMDRD)	53.65 ± 34.24
Estimated GFR by CKD EPI (eGFRCKD-EPI)	53.28 ± 32.9

Data expressed as mean ± SD and n (%). BMI, body mass index; mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration; CG, Cockcroft Gault; MDRD, modification of diet in renal disease; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration

Table II: Bias, precision, and accuracy for estimated glomerular filtration rate

GFR Equations	Mean Bias	SD Bias	r^2 (Precision)	Accuracy within	
				30%	50%
eGFRCG	11.61	27.98	0.42	42.86	63.49
eGFRMDRD	11.45	25.02	0.48	45.24	67.46
eGFRCKD-EPI	11.08	23.18	0.40	42.06	64.29

eGFR, estimated glomerular filtration rate; CG, Cockcroft Gault; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration

Table III: Mean and standard deviation of subgroup of age

	Less than 65 Mean ± SD	More than 65 years old Mean ±SD	*p* value
mGFR	45.11 ± 20.43	34.62 ± 18.44	<0.0001
eGFRCG	61.80± 38.35	33.01± 16.85	<0.0001
eGFRMDRD	59.45± 36.94	38.56 ± 19.30	<0.0001
eGFRCKD EPI	59.73± 34.92	36.47± 18.63	<0.0001

eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; CG, Cockcroft Gault; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration

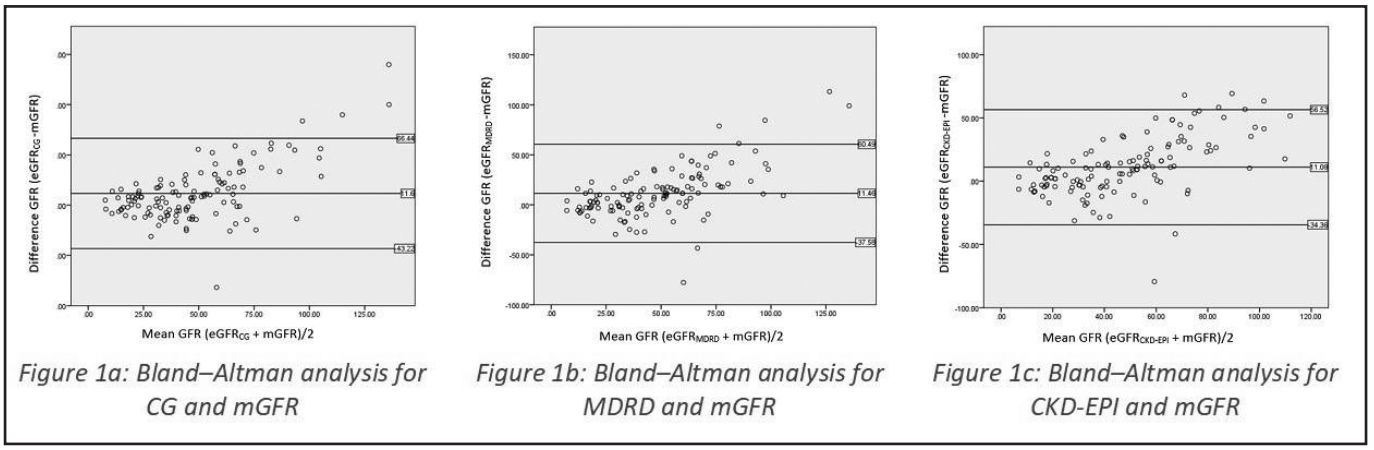

Figure 1a: Bland–Altman analysis for CG and mGFR

Figure 1b: Bland–Altman analysis for MDRD and mGFR

Figure 1c: Bland–Altman analysis for CKD-EPI and mGFR

Fig. 1: Bland-Altman analysis for estimated glomerular filtration rate and measured glomerular filtration rate

DISCUSSION

GFR is an important indicator in evaluating kidney function. However, it is difficult to measure GFR in a clinical setting. Thus, estimating GFR equations play an important role in determining the extent of a kidney injury. This study assessed the performance of the estimated GFR of CG, MDRD, and CKD-EPI equations as compared to mGFR of ^{99m}Tc-DTPA scan. ^{99m}Tc-DTPA GFR was used for measuring GFR and previous study showed that it is a good marker for GFR and comparable to inulin infusion.[15,16,17]

In general, we observed that all of the estimated GFR equations overestimated measured GFR. This finding was similar to a study by Jessani et al for the Pakistani population comparing MDRD and CKD-EPI against measured GFR.[18] According to Lamb et al., the degree of dissociation of ^{99m}Tc-DTPA can be variable which will lead to imprecision and bias. Furthermore, ^{99m}Tc bind to protein which also contributes towards GFR underestimation.[19] This study demonstrated that MDRD had the highest accuracy within 30% and 50% of measured GFR while CKD-EPI had shown the highest precision with the least bias. The findings were similar to previous study done in Malaysia by Jalalonmuhali where MDRD had the highest accuracy while CG had the least bias and highest precision. However, CKD-EPI was not tested in this particular study.[20]

We also performed Bland–Altman analysis to look at the agreement between estimated GFR and measured GFR. This study demonstrated that CKD-EPI has the lowest limit of agreement as compared to MDRD and CG. CKD-EPI had better performance in general compared to MDRD and CG as it was developed and validated using a large database with diverse clinical characteristics and it also comprises patients with and without kidney disease.[21]

Influence of Age

We divided the patients as young and elderly according to WHO classification where we took the limit of age considered as elderly as 65 years old. In this study, for patients less than 65 years old, MDRD had the least bias with the highest accuracy while for elderly more than 65 years old, CG had the least bias, highest accuracy, and least precision. Our study also demonstrated that the younger patients have higher GFR and with higher GFR, estimated GFR may be inaccurate. Variations among laboratories in the calibration of serum creatinine assay had larger effects at higher GFR level thus producing a wider variation in the results.[22,23] These inter-laboratory variations were also influenced by muscle mass, the influence of drug on creatinine clearance, dietary intake, and the differences in creatinine excretions between individuals.[22] In our study, the distribution between elderly and non-elderly is incomparable as only 27.8% of the patients had age above 65 years old. The GFR equations in elderly tends to be underrepresented as all the samples were mostly include less of the elderly populations.[24] A further research with regard to finding the best equations for the elderly is warranted.

Influence of BMI

The estimated GFR of CG, MDRD, and CKD-EPI were also compared according to the subgroup of BMI. This study showed that for both BMI 25–30 and BMI more than 30, CKD-EPI showed the highest accuracy and the least bias. However, we observed that there was no significant difference between all the three estimated GFR equations for all subgroup of BMI. The reason was the number of patients in each subgroup was too small to make a difference. Interestingly in this study, the bias of CG increased significantly with increased BMI denoting that there is a relationship between body composition and performance of estimated GFR. This finding is similar to a few previous studies done earlier.[25,26]

There were several limitations to this study. This study was done in a single centre whereby all of the patients were referred from Urology clinic. Thus, the population study did not reflect the general population in Malaysia. Furthermore, as this was a retrospective study, we could only use the available recorded data. The sample size was particularly small for certain subcategories such as the different classes of BMI and in the elderly population more than 65 years old.

CONCLUSION

Of the three estimated GFR equations studied, MDRD is the most accurate; however, CKD-EPI has a smaller bias and a

better precision when compared with measured GFR. When we included the influence of BMI, age, and looking at the performance of each estimated GFR equations for different stages of CKD, CKD-EPI gives the best estimation of GFR with almost comparable performance of MDRD.

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CONFLICTS OF INTEREST
Nil

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A retrospective study on drug survival of biologics among patients with psoriasis seen in tertiary hospital in Johor Malaysia

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ABSTRACT

Introduction: Limited information exists regarding drug survival of biologics among psoriasis patients in Malaysia. This study aimed to determine the drug survival of biologics in Malaysian psoriasis patients, the reasons for drug discontinuation and to identify the predictor of drug survival.

Materials and methods: A retrospective review of case notes on adult psoriasis patients treated with biologics in Hospital Sultanah Aminah Johor Bahru Malaysia, between January 2006 and December 2020. Drug survival was analysed using the Kaplan–Meier method.

Results: By December 2020, 100 patients with 154 treatment courses of biologics were included in the study. Male to female ratio was 1:1. The mean age at onset was 31.36 ± 11.72 years. Ustekinumab was the most frequently prescribed biologics (39%), followed by adalimumab (29.2%), secukinumab (14.9%), etanercept (13%), and infliximab (3.2%). Overall median drug survival for biologics was 25 months (interquartile range [IQR]= 12.0–.0). The median drug survival for ustekinumab was 35 months (IQR, 12–93); followed by 25 months (IQR, 12.0–), 18 months (IQR, 7–85), 17 months (IQR, 11–43), and 8 months (IQR, 1-10) for secukinumab, adalimumab, etanercept, and infliximab, respectively. The main reason for drug discontinuation was loss of efficacy (26%), inadequate funding (14.3%), loss to follow-up (10.4%), adverse events (4.5%), and patients' request (1.3%).

Conclusion: Our study shows ustekinumab has the best long-term drug survival among biologics in Malaysian patients with psoriasis in real-life setting. Further study is required to evaluate the long-term drug survival for newer biologics.

KEYWORDS:
Biologics, drug survival, psoriasis, treatment

INTRODUCTION

Psoriasis is a common chronic relapsing immune-mediated disease. Its prevalence was reported to be higher in countries with high income and older population, whereas the prevalence is relatively lower in Asian countries.[1] Malaysian clinical practice guidelines on management of psoriasis vulgaris recommended biologics if patients fulfil the following criteria: severe disease [body surface area ≥30% or Psoriasis Area and Severity Index (PASI) ≥20] and not responding, intolerant to, or having contraindications for conventional systemic treatment or phototherapy.[2]

Although clinical trials focus on efficacy and safety of the biologics, the enrolled subjects might be relatively different from those in daily practice due to the presence of stringent inclusion and exclusion criteria.[3,4] In choosing a practical tool that reflects the real-life setting, drug survival has been a useful instrument to measure the clinical success of biologics in psoriasis treatment. Drug survival is described as the time from initiation of biologic therapy to discontinuation.[5-7] In reality, drug survival is influenced by numerous factors, including efficacy, safety, patient's satisfaction, compliance, and physician preference. Specifically, median drug survival is frequently measured, indicating the length of time in which half of biologics are switched or stopped, whilst another half are still being administered.[8,9]

To date, limited information exists regarding drug survival of biologics amongst psoriasis patients in Malaysia. Our objective is to determine the drug survival of biologics, the reasons for drug discontinuation and to identify the predictor of drug survival in Malaysian psoriasis population.

MATERIALS AND METHODS

This retrospective study was done by reviewing the electronic records of all psoriasis patients who were treated with at least one biologics in the dermatology clinic of Hospital Sultanah Aminah Johor Bahru Malaysia till 31 December 2020. The following information was extracted: age at psoriasis onset and biologic initiation, gender, ethnicity, body weight, body mass index (BMI), prior systemic treatment before biological initiation (such as phototherapy, methotrexate, ciclosporin, acitretin), use of concomitant methotrexate while on biologic, presence and absence of psoriatic arthritis, type of psoriasis (namely chronic plaque psoriasis, pustular psoriasis, and erythrodermic psoriasis), comorbidities (includes high blood pressure, diabetes mellitus, and dyslipidaemia), PASI score on treatment initiation, and

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reasons for treatment discontinuation. Based on World Health Organization (WHO) Asian classification, BMI 23–27.49 and BMI ≥ 27.5 indicate overweight and obesity, respectively. During the study period, tumour necrosis factor inhibitors (TNF)-α (include infliximab, etanercept, adalimumab), interleukin-12/23p40 inhibitor (ustekinumab), and interleukin-17 inhibitor (secukinumab) were analysed. The study was approved by the Ministry of Health Institutional Review Board and Medical Research ethics committee (NMRR-19-732-47165).

Statistical analysis

The demographic data were analysed using descriptive data. Results were expressed as number (n) and percentage (%). Descriptive statistics are presented as counts and percentages for categorical variables. Mean with standard deviation (SD) was used for normally distributed data while median with interquartile range (IQR) was used for data which were not normally distributed. Categorical variables were compared using chi-square analysis. All statistical analyses were performed using SPSS software version 22.0 (IBM Corp, Armonk, NY, USA). Drug survival was analysed using the Kaplan–Meier method. Cox proportional hazard model for multivariate analysis was applied to identify any associated predictor for drug survival such as patient age, gender, biologic therapy naïve status, and concomitant methotrexate. P-value <0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics

Overall, 100 patients were included in the study and their characteristics were summarized in Table I. The mean duration between disease onset and first administration of biologics was 10.70 ± 8.51 years. The male to female ratio was 1:1. Chronic plaque psoriasis was the most common type of psoriasis (83%), followed by erythrodermic psoriasis (26%) and pustular psoriasis (14%). Psoriatic arthritis was present in almost half of the study patients (49%). Interestingly, a significantly higher proportion of patients with psoriatic arthritis were prescribed with adalimumab compared to other biologics (p=0.00). Mean baseline PASI score before biological initiation was 18.4 ± 17.1. In total, 154 treatment series were evaluated during the study period. Ustekinumab was the most frequently prescribed biological treatments (39%), followed by adalimumab (29.2%), secukinumab (14.9%), etanercept (13%), infliximab (3.2%), and golimumab (0.6%). The mean administration period of biologics was 29.07 ± 29.83 months. Notably, one-third of the patients (33%) were taking concomitant methotrexate while on biologic treatment.

Drug survival

Regarding the drug survival analysis of the biologics, we have evaluated 153 treatment courses. The Kaplan-Meier survival curves were demonstrated in Figure 1(a-c). This analysis excluded one patient with both severe chronic plaque psoriasis and psoriatic arthritis who received golimumab treatment as the fourth biologic from rheumatologist after failure to respond to several TNF-α inhibitors including etanercept, infliximab, and adalimumab. The median drug survival in all patients was 25 months (IQR=12.0–85.0). Analysis of drug survival for individual biologics revealed statistically significant differences (log rank test p = 0.003). The estimated median drug survival for individual biologic was 35 months (IQR, 12–93) for the ustekinumab group, followed by 25 months (IQR, 12 –) for secukinumab, 18 months (IQR, 7–85) for adalimumab, 17 months (IQR, 11–43) for etanercept, and 8 months (IQR, 1–10) for the infliximab. Among the biologically naïve patients, the overall median drug survival was 24 months (IQR, 12–85). The drug survival of individual biologic in the biologic-naïve was as follows: 35 months (IQR, 12–93) for ustekinumab, 19 months (IQR, 16–50) for etanercept, 18 months (IQR, 7–85) for adalimumab, 12 months (IQR, -) for secukinumab and 1 month (IQR, 1.0–1.0) for infliximab. On the other hand, the median drug survival in biologic experienced patients was 29 months (IQR, 8.0-). The drug survival of individual biologic in the biologic-experienced was 52 months (IQR, 20 –) for ustekinumab, 13 months (IQR, 6–) for adalimumab, 9 months (IQR, 8–13) for etanercept, and 8 months (IQR, 1–10) for infliximab. It might be difficult to estimate accurately the drug survival in secukinumab cohort, as it was commercialised much later than other biologics. Multivariate analysis using Cox regression showed parameters such as age, gender, obesity, comorbidities, previous phototherapy, presence of psoriatic arthritis, biologic naïve status and concomitant methotrexate administration were not shown to significantly influence drug survival (Table II).

Reason for discontinuation

Out of 100 patients, 59 patients were still undergoing treatment at the end of the study, whereas 41 patients discontinued biologic therapy as shown in Table III. The main reason for drug discontinuation was loss of efficacy (26%), followed by inadequate funding (14.3%), loss to follow-up (10.4%), adverse events (4.5%), and patients' request (1.3%). The loss of efficacy was seen highest for adalimumab (12.8%). Inadequate funding was found specifically for ustekinumab (11.4%). Adverse events occurred mainly in 7 patients (4.5%) who were on TNF-α inhibitors. Infliximab treatment caused infusion reaction in two patients and *Escherichia coli (E Coli)* sepsis in one patient. Adalimumab was associated with adverse events in four patients including two patients with latent tuberculosis infection (LTBI), one patient with cerebrovascular accident, and another one with cutaneous squamous cell carcinoma. Prior to adalimumab administration, tuberculosis (TB) screening was negative for both patients with LTBI. They were found to have positive tuberculin skin test after 1 year of adalimumab and both subsequently completed the treatment for LTBI. One individual opted to discontinue etanercept because she was planning to conceive. Cessation of treatment was revealed in four patients after reaching sufficient improvement while on biologic.

DISCUSSION

To the best of our knowledge, this is the first study of real-world data collected over the period of more than 10 years to compare drug survival of biologics among Malaysian psoriatic patients. The overall median drug survival of all

Table I: Demographic and clinical characteristics of study population

Characteristics		n=100	Etanercept (n=15)	Infliximab (n=1)	Adalimumab (n=27)	Ustekinumab (n=46)	Secukinumab (n=11)	*p* value
Age (years, mean ± SD)	At onset	31.36 ± 11.72	33 ± 8.19	32.00 ±	31.11 ± 11.406	31.17 ± 13.578	30.45 ± 9.62	0.86
	At starting biologic	40.83 ±12.12	47.93 ± 10.33	42.00±	38.11 ± 12.79	40.72 ± 14.22	38.18 ± 10.79	0.989
Gender (n, %)	Male	52	7 (13.5%)	0	12 (23.1%)	27 (51.9%)	6 (11.5%)	0.605
	Female	48	8 (16.7%)	1 (2.1%)	15 (31.3%)	19 (39.6%)	5 (10.4%)	
Ethnicity (n, %)	Malay	43	5 (11.6%)	1 (2.3%)	15 (34.9%)	19 (44.2%)	3 (7.0%)	0.648
	Chinese	42	7 (16.7%)	0	10 (23.8%)	20 (47.6%)	5 (11.9%)	
	Indian	15	3 (20.0%)	0	2 (13.3%)	7 (46.7%)	3 (20.0%)	
Baseline weight (kg)		62.48 ± 30.06	67.13 ± 25.00	47.00 ±	61.22 ± 33.50	61.02 ± 30.62	66.73 ± 29.04	0.187
BMI (mean ± SD)		27.41 ±7.53	28.64 ± 7.06	21.00 ±	28.16 ± 7.56	26.95 ± 7.96	27.25 ± 7.07	0.616
Baseline PASI (mean ± SD)		25.57 ± 15.40	31.29 ± 11.81	7.00 ±	7.00 ± 21.22	25.30 ± 13.16	26.68 ± 13.28	0.08
Comorbidities (n, %)	Obesity	22	4 (18.2%)	0	6 (27.3%)	9 (40.9%)	3 (13.6%)	0.937
	Diabetes mellitus	20	5 (25.0%)	0	6(30.0%)	6 (30.0%)	3 (15.0%)	0.44
	Arterial hypertension	20	7 (35.0%)	0	5 (25.0%)	6 (30.0%	2 (10.0%)	0.079
	Dyslipidaemia	2	1 (50.0%)	0	0	1 (50.0%)	0	0.650
Psoriatic arthritis (n, %)		49	14 (28.6%)	0	18 (36.7%)	11 (22.4%)	6 (12.2%)	0.00
Prior treatment (n, %)	Phototherapy (NBUVB)	32	8 (25.0%)	0	4 (12.5%	16 (50.0%)	4 (12.5%)	0.110
	Methotrexate	83	11 (13.3%)	1(1.2%)	25 (30.1%)	39 (47.0%)	7 (8.4%)	0.200
	Ciclosporin	46	6 (13.0%)	0	12 (26.1%)	23 (50.0%)	5 (10.9%)	0.845
	Acitretin	45	7 (15.6%)	1(2.2%)	15 (33.3%)	20 (44.4%)	2 (4.4%)	0.223
Concomitant use of methotrexate (n, %)		33	6 (18.2%)	1 (3.0%)	12 (36.4%)	13 (39.4%)	1 (3.0%)	0.122

n, total number of biologic

Table II: Cox regression analyses. Hazard ratio for risk treatment discontinuation of etanercept, infliximab, adalimumab, ustekinumab, and secukinumab

Variable	HR	95% Confidence interval	*p* value
Age onset > 30	1.025	0.989–1.062	0.181
Female gender	1.383	0.678–2.825	0.373
Concomitant psoriatic arthritis	1.622	0.673–3.910	0.281
Obesity	0.538	0.259–1.117	0.096
Diabetes	0.717	0.208–2.470	0.598
Arterial hypertension	2.171	0.591–7.974	0.243
Dyslipidaemia	2.769	0.391–19.597	0.308
Previous phototherapy	1.665	0.748–3.706	0.212
Biologic naïve patients	0.656	0.064–6.688	0.722
Concomitant methotrexate	1.271	0.618–5.957	0.514

Table III: Reasons for treatment discontinuation of the treatment series with biologics

	Loss of efficacy n (%)	Adverse events n (%)	Loss to follow up n (%)	Inadequate funding (n, %)	Patient request (undisclosed reason) n (%)	Adequate improve-ment n (%)	Other: pregnancy n (%)	Continue n (%)	Total n (%)
Etanercept	13 (8.5 %)	0	4 (2.6 %)	0	0	0	1 (7%)	2 (1.3 %)	20 (13.1 %)
Infliximab	2 (1.3 %)	2 (1.3 %)	0	0	0	1 (0.7 %)	0	0	5 (3.3 %)
Adalimumab	18 (11.8 %)	5 (3.3 %)	6 (3.9 %)	0	1 (0.7 %)	1 (0.7 %)	0	14 (9.2 %)	45 (29.4 %)
Ustekinumab	7 (4.6 %)	0	6 (3.9 %)	16 (10.5 %)	1 (0.7 %)	1 (0.7 %)	0	29 (19 %)	60 (39.2 %)
Secukinumab	0	0	0	6 (3.9 %)	0	1 (0.7 %)	0	16 (10.5 %)	23 (15 %)
Total	40 (26.1%)	7 (4.6%)	16 (10.5)	22 (14.4)	2 (1.3)	4 (2.6)	1 (0.7)	61 (39.9)	153 (100%)

n, total number of biologic courses for each biologic.

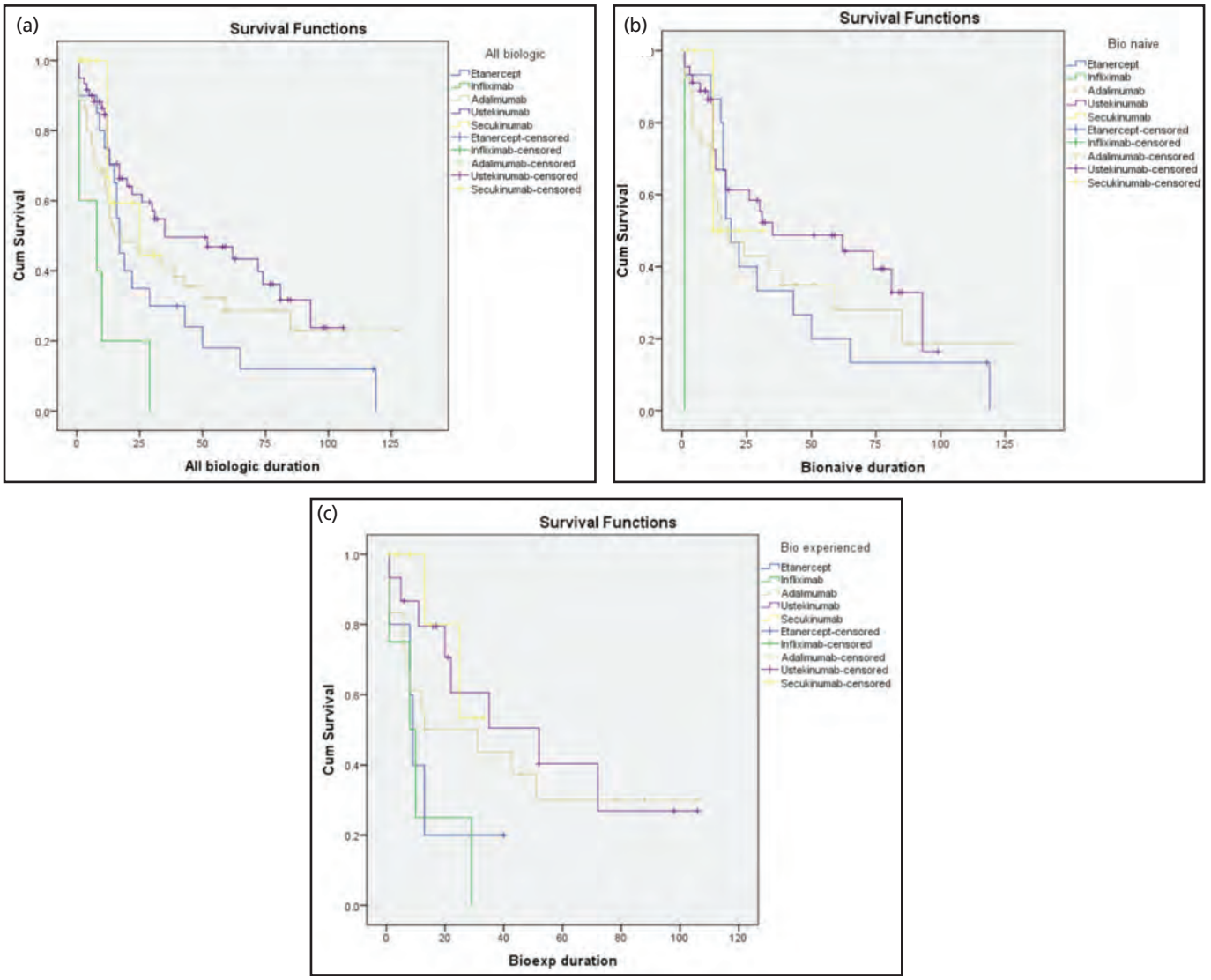

Fig. 1: (a) Kaplan–Meier plot of drug survival for all biologics. (b) Kaplan–Meier plot of drug survival for each biologic in the biologic-naïve. (c) Kaplan–Meier plot of drug survival for each biologic in the biologic-experienced.

biologics in our study was 25 months. This duration is comparable to study conducted in a single-centre Japanese series by Ohata et al[3] (25.5 months), but shorter than the duration of drug survival reported by Vilarrasa et al.[10] (31 months), Shalom et al. (27.9 months).[7] Majority of the literature published revealed ustekinumab has the longest drug survival rate among all biologics.[11,12] A systematic review by No et al.[9] reported that ustekinumab had much longer drug survival beyond 5 years when compared to TNF-α inhibitors. A meta-analysis by Liu et al suggested that ustekinumab is associated with the superior drug survival in all and biologic-naive subjects.[13] The reason for lower rate of discontinuation with ustekinumab compared to TNF-α inhibitors is likely attributed to multiple factors such as greater efficacy, favourable side effect profile, and low immunogenicity.[9] Injection site reactions were the least commonly observed in ustekinumab-treated patients. In addition, the improvement of treatment compliance is expected in patients who receive ustekinumab due to the less frequent (3 monthly) dosing regimen.[11,14,15] With regards to biologic-experienced cohort, a previous study by Cozzani et al[8] discovered that ustekinumab has less remarkable drug survival data which might be explained by the possibility of alteration in the immune system which further reduce the effectiveness of subsequent biologics. Interestingly, our analysis found that ustekinumab has greater survival in both naive and non-naive patients, and this finding is similar to the report by Menter et al.[11]

Several studies have demonstrated that female gender is considered to be negative predictors of drug survival.[10,16-18] Another study by Jacobi et al[19] revealed patients with psoriatic arthritis had longer drug survival, while those with metabolic syndrome were associated with loss of treatment retention. Previous report found that patients with concomitant methotrexate treatment have a superior drug survival rate, and this observation is thought to be associated with reduction in the formation of drug autoantibodies.[16] On

the contrary, our study did not demonstrate any significant influence of gender, obesity, comorbidities, psoriatic arthritis, biologic naive status, and concomitant methotrexate on the drug survival in the treated population.

Reason for discontinuation- Loss of efficacy

In our study, loss of efficacy was the most common reason for biologic discontinuation which is consistent with other studies.[9,11] A meta-analysis by Lin et al demonstrated ustekinumab is the biologic least frequently discontinued due to diminished efficacy, whereas etanercept is terminated most commonly following the same reason.[13] In contrast, our study revealed loss of efficacy was seen highest for both adalimumab (12.8%). The exact mechanism that causes the treatment failure is not completely understood. Immunogenicity of biologics was hypothesized to play a role in the diminished clinical response and this is illustrated by the formation of antidrug antibodies resulting in immune complexes interrupting drug interaction or bioavailability.[9,20] Interestingly, past report showed that ustekinumab stimulates fewer antidrug antibodies than TNF-α inhibitors which might explain the lower rate of discontinuation of ustekinumab.[8,21]

Reason for discontinuation- Lack of funding

Inadequate funding was the second most common reason of drug termination in our cohort, in keeping with the previous report by Choi et al.[22] In our study, four patients have paid for biologics out of their own pocket. A study on cost-effectiveness analysis of psoriasis treatment in Malaysia revealed biologic regimen has the highest effectiveness but requires the highest cost (estimated around RM54 000 or US$16 000 for 6 months duration) and that itself comprises about two-third of the overall medication cost.[23] There are different regulations on biologic funding being implemented between every country which may indirectly reflect the prescription trend of biologics.[22] Result from a study by Youn et al indicated that all patients in Korea have public health insurance, while considerably lower coverage (63%) of public health insurance were depicted in other Asia-Pacific countries including Malaysia.[24] The substantially high cost of biologics is considered one of the major contributing factor of drug discontinuation for ustekinumab in South Korea, particularly when the treatment is not reimbursed.[22] Regardless of efficacy of biologic treatment, treatment compliance may become a concern if patients have to postpone the treatments past the recommended schedule in order to reduce the cost.[24] In Malaysia, the funding for biologic is limited and in some cases, the reimbursement are not sustainable for longer than 6 months to 1 year. Regrettably, psoriasis become worsen in these group of patients once they discontinue their treatment following insufficient funding.

Reason for discontinuation- adverse events

In our cohort, ustekinumab is the least likely to be discontinued due to adverse effects, similar to previous reports.[13,25,26] Drug discontinuation due to adverse events occur in seven patients who have been on TNF-α inhibitors. We found that infliximab caused infusion reaction in two patients and *E. coli* sepsis in one patient in our cohort. Previous studies have found that among biologic-naïve subjects infliximab has the lowest overall drug survival specifically related to the adverse effects.[13,26–28] According to the study by Yiu et al, infliximab was linked to increase risk of serious infections when compared with conventional systemic therapies.[29] On the other hand, LTBI was associated with two asymptomatic patients who received adalimumab in our study. Both patients completed anti-tuberculous treatment without any major complication. A systematic review and meta-analysis by Zhang Z et al[30] suggested that the risk of developing tuberculosis is doubled whenever patients are receiving TNF-α inhibitors. A review by Fabroni et al highlighted that TNF-α inhibitors might predispose patients to the severe variants of tuberculosis predominantly extrapulmonary tuberculosis and disseminated tuberculosis.[31] Therefore, it is prudent to screen patients for latent or active tuberculosis infection before commencing TNF-α inhibitors and to consider starting anti-tuberculous prophylaxis if tested positive. Meanwhile, periodic assessment is required to identify any symptoms and/or signs of tuberculosis infection when patients receive ongoing biologics treatment. Based on the evidence available, most psoriasis patients with positive tuberculosis screening were less likely to receive TNF-α inhibitors. Instead, prescribing other type of biologics such as IL-12/23 and IL-17 inhibitor are considered to be more reasonable as the risk of tuberculosis while on these biologics is considered low.[32,33] A report by Sbidian et al[34] recommends that young individuals having chronic or latent infection such as hepatitis B infection or history of tuberculosis may consider ustekinumab as alternative treatment option. Currently, the use of relatively newer biologics such as IL-23 inhibitor might need further study to determine the drug safety especially for those with infection risk.

LIMITATION

Our study had some limitations. Firstly, this is a single-centre retrospective study and the subjects were not randomised to different treatments. Furthermore, the existing data on the biologics were heterogenous due to the differences in timing of availability and commercialization of the various biologics.

Secondly, the prescribing pattern in daily practice could be influenced by some degree of selection bias. In our study, the numbers of patients on ustekinumab and adalimumab in our analyses were considerably higher than those on etanercept and infliximab. This practice is unavoidable because certain treatments are selected according to cost, efficacy, safety profile, ease of administration as well as preferences of the clinicians and patients which reflect real-world practice.

Thirdly, we did not have adequate data on drug survival of newly available biologics in the market. Future study is needed to evaluate the long-term drug survival for the comparatively newer biologics such as interleukin-17 and interleukin-23 inhibitor.

CONCLUSION

Our study demonstrated that ustekinumab has the highest long-term drug survival among all biologics in Malaysian

patients with psoriasis in real-life setting. Further study is required to evaluate the long-term drug survival for newer biologics including interleukin 23 inhibitor. These findings are useful references for clinicians to consider in the selection of biologics for psoriasis treatment in daily clinical practice.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Factors associated with tuberculosis treatment success among tuberculosis and human immunodeficiency virus co-infected patients in Kelantan

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ABSTRACT

Introduction: Tuberculosis (TB) and human immunodeficiency virus (HIV) co-infection is a global public health issue among people living with HIV. The objective was to assess the prevalence of TB treatment outcomes (successful and unsuccessful) and associated factors with TB treatment success among TB and HIV co-infected patients in Kelantan for 5 years (2014–2018). The successful TB treatment was defined as the sum of cured patients and those who completed the treatment. The unsuccessful treatment was defined as the sum of treatment failed, died, and default.

Materials and methods: A cross-sectional study was conducted at the TB/Leprosy Unit of the State Health Department of Kelantan (JKNK) using secondary data from January 2014 to December 2018 assessed in the MyTB online system. The data were analyzed using SPSS 25.0 and STATA 14. Ethics approvals were obtained from Medical Research Ethics Committee (MREC) and UniSZA Human Research Ethics Committee (UHREC).

Results: Kelantan had 6,313 TB cases from January 2014 to December 2018. There were 703 (11.1%) cases of TB and HIV co-infection. The prevalence of successful treatment among TB and HIV co-infected patients was 57.1%. The duration of treatment and anatomy of TB location was significantly associated with TB treatment success.

Conclusion: This study's findings showed that the prevalence of TB treatment success rate was 57.1%, and the unsuccessful rate was 42.9%. The treatment duration and the TB location's anatomy were significantly associated with the treatment success rate. Improving TB treatment outcomes should be started with anti-TB treatment immediately after TB diagnosis. Therefore, the government should strengthen the TB/HIV collaborative efforts to achieve good treatment outcomes among these vulnerable patients.

KEYWORDS:
Factor associated, Tuberculosis (TB), treatment outcome, human immunodeficiency virus (HIV), co-infected patients

INTRODUCTION

Tuberculosis (TB) is an infectious disease that remains a major global health issue. It is one of the top 10 causes of mortality worldwide, and each year millions of people fall sick with TB. Due to decreased immunity, the risk of developing active TB was 20–37 times higher among people living with human immunodeficiency virus (PLHIV) than people who did not have human immunodeficiency virus (HIV).[1] The appearance of HIV has led to a resurgence of TB around the world. When the two diseases occur simultaneously in the same individuals, one will exacerbate the effects of the other.[2] Therefore, early detection of TB and HIV allows for early treatment of these two diseases and thus a better chance of survival. Without treatment, both diseases actively paralyse vital functions in the body until the infected person dies.

In 2019, 7.1 million new and relapsed TB cases were reported to the National Tuberculosis Programs (NTPs) and the World Health Organization (WHO). This figure increased from 7.0 million in 2018, 6.4 million in 2017, and 5.7 to 5.8 million per year between 2009 and 2012. Among all those affected in 2019, 8.2% of those were PLHIV. In 2018 globally, the treatment success rate for newly enrolled TB cases was 85% and 57% for people with Multidrug/rifampicin-resistant TB (MDR/RR-TB). Even though the global TB incidence rate and death rate are decreasing, most WHO regions and many high TB burden countries are still not on track to meet the End TB Strategy 2020 milestones by the end of 2019.[3]

Malaysia is located in the southeast Asia region and is categorised as an intermediate TB burden country. Several studies were conducted in Malaysia to assess the parameters associated with successful and unsuccessful treatment outcomes among TB patients. However, the results were varied and inconsistent. The treatment outcomes studies from a few states in Malaysia reported a very high heterogeneity in the results.[4–8] To date, TB and HIV co-infected patients have a lower treatment success rate than TB patients (75.0% vs 83.0%), but their death rate is much higher than TB patients (14% vs 3%).[9]

Kelantan is a Malaysian state in the east of the country that shares a border with Thailand. In Kelantan alone, the

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treatment success rate in 2017 among TB and HIV co-infection was only 27.9%.[6] Based on this, a practical method for improvement was needed, particularly in achieving a better cure rate. Many factors are recognised as barriers to treatment success, including lack of communication between patients and healthcare providers, Directly Observed Treatment Short-Course (DOTS) implementation, incentives, lost patients, difficult treatment access, supervision, and other limitations in the treatment units.[10–12]

To our knowledge, a published study looking at treatment outcomes and associated factors among TB and HIV co-infected patients in Kelantan is still lacking. We need to understand the socio-demographic characteristics and clinical characteristics that may contribute to and affect the outcome of TB treatment. Further clarity and quantification of the prevalence and associated factors are needed to better understand and evaluate management for TB and HIV co-infected patients. Thus, our study aimed to assess the prevalence of TB treatment outcomes (successful and unsuccessful) and associated factors with TB treatment success among TB and HIV co-infected patients in Kelantan for 5 years (2014–2018).

MATERIALS AND METHODS

Study design

A cross-sectional study reviewed the 5-year secondary data from January 2014 to December 2018 retrieved from the MyTB online system at the TB/Leprosy Unit of the State Health Department of Kelantan (JKNK). The population consisted of all TB and HIV co-infected patients in Kelantan based on the recommendation by WHO to evaluate patients separately.

Sample size

All TB and HIV co-infected patients who met the inclusion criteria and registered for TB treatment during the study were included. A single proportion equation was used to calculate the sample size with a treatment success rate for TB and HIV of 27.9%.[6] The minimum required sample size was 309 patients with a 95% confidence interval (CI) within a 5% precision. Assuming 15.0% dropouts, the number of the sample size should be at least 364 patients. We used 15% dropouts because the study needed to increase the sample size by the expected predicted reasons for losing subjects and were concerned about the large proportion of missing data. In this study, as the data available was 667, we decided to include all. Non-probability sampling method was applied because it was based on convenience sampling from secondary data.

Data collection procedure

The person in charge of the TB/Leprosy Unit extracted the data from MyTB online system in December 2019. They downloaded the data into excel for patients who identified themselves as TB and HIV co-infection and submitted it to the investigator. The subject ID number identified the list of all TB and HIV co-infected patients. Then, the investigator exported the data from excel to IBM SPSS statistics version 25.0 for further analysis.

The secondary data contained patients' socio-demographic characteristics, clinical characteristics, and TB treatment outcomes. The missing data (i.e., marital status and monthly income) cannot be minimised. Their records were unavailable, and their medical results were ambiguous, so these variables could not be included.

Inclusion criteria

Our target population is TB and HIV co-infected patients. The selected patients included in this study were based on secondary data from MyTB online system. Patients with TB and HIV who were ≥18 years old and proved positive for both TB and HIV were eligible.

Exclusion criteria

Patients who recorded transferred out and ongoing treatment were excluded since their treatment results could not be determined. Patients whose TB diagnoses changed were also excluded since they were later diagnosed with a different disease.

Operational definitions

According to the Malaysian Ministry of Health Clinical Practice Guidelines for Tuberculosis Management,[13] the following TB treatment outcome and operational terms were utilised in this study:

1. "Cured: Former smear-positive patient who was smear-negative in the last month of treatment and at least one previous occasion."
2. "Completed treatment: A patient who completed treatment but did not meet the criteria classified either as a cure or a failure."
3. "Treatment failed: A patient whose sputum was smear-positive at five months or later during treatment."
4. "Died: A patient died for any reason during treatment."
5. "Default: A patient who has interrupted treatment for two consecutive months or more."

In the analysis of treatment outcomes, successful TB treatment was defined as the sum of cured patients and those who completed treatment. In contrast, treatment failed, died, and default was considered as unsuccessful TB treatment.

The X-ray findings were extracted from MyTB online system reported by District TB Organizer Team based on chest X-Ray (CXR) results reported by the clinician. The severity of the lesion on the X-ray film was used to classify the CXR presentation at the time of diagnosis. It was categorised into:

1. No lesion if CXR showed no lesions,
2. Minimal if CXR showed a few lesions,
3. Moderate advance if CXR showed many lesions,
4. Far advance if CXR showed extensive lesions or miliary appearance, and
5. Not performed if CXR was not done during the diagnosis

Ethical Considerations

Privacy and confidentiality of patients were maintained. Ethics approvals were obtained from the Medical Research Ethics Committee, Ministry of Health Malaysia (NMRR-19-2628-50776 (IIR), KKM/NIHSEC/P19-2067(11)), and UniSZA Human Research Ethics Committee (UniSZA/UHREC/2019/150).

Statistical Analysis
IBM SPSS statistics version 25.0 were used to analyse the data. The socio-demographic data were presented descriptively. The numerical data were presented as a mean (standard deviation, SD), whereas the categorical data were expressed as frequency (percentage, %). Multiple logistic regression analysis determined the association between the independent variables and the outcomes. Simple logistic regression was used to determine the candidate variables to be included in multiple logistic regression. The variables with p value <0.25 were included in multiple logistic regression. Principles of best fit and biological plausibility were used to obtain the parsimonious model. Forward and backward stepwise regression analyses were applied. Multicollinearity and interaction problems were checked. The Hosmer–Lemeshow goodness of fit (GOF) test, overall properly categorised percentage, and area under the receiver operation characteristic (ROC) curve were used to assess the model fit. The outcomes were presented in the form of crude and adjusted odds ratios (OR), a 95% confidence interval (CI) and corresponding p values.

Variable Under Study
Independent Variables: The socio-demographic characteristics included age, gender, race, duration of treatment, level of education, place of residence, and occupation. The clinical characteristics retrieved were diabetes mellitus status, *Bacillus Calmette–Guérin* (BCG) scar, anatomy of TB location, CXR status, case TB category, treatment regime, DOTS status, Highly Active Antiretroviral Therapy (HAART) treatment, and detection method. Other characteristics included in the study were smoking status, source of notification, place of treatment, and district area.
Outcome variables: The study outcome was either successful (cured, completed treatment) or unsuccessful (treatment failed, died, default) TB treatment.

RESULTS

Baseline characteristics and treatment outcomes
A total of 6,313 TB cases in Kelantan were registered in the MyTB online system from January 2014 to December 2018. A total of 703 (11.1%) of these cases had TB and HIV co-infection. However, 36 cases were excluded due to transfer out (3), change of diagnosis (24) and ongoing treatment (9). Therefore, 667 cases were evaluated in this study based on inclusion criteria (Figure 1).

Table I illustrates the socio-demographic characteristics and other related factors among all study subjects (n = 667). Their ages ranged from 18 to 77, with a mean (SD) of 38.7 (7.9) years. The range of TB treatment duration was 0 to 722 days, with a mean (SD) of 202.8 (131.27) days. The treatment success rate was 57.1% (95% CI; 53.34,60.86). Successful outcomes were achieved in 381 cases, with 132 (19.8%) cases cured and 249 (37.3%) cases completed treatment. In contrast, the unsuccessful outcomes were 42.9% (95% CI; (39.14,46.66) achieved in 286 cases, with 67 (10.1%) cases defaulted and 219 (32.8%) cases of death. There were no treatment failure cases identified.

Factors associated with TB treatment successful outcomes
Table II illustrates the results of a simple logistic regression revealed that age, duration of treatment, level of education, occupation, Anatomy of TB location, CXR Status during diagnosis, smoking status, the regime of treatment, DOTS by healthcare providers, HAART treatment, source of notification, place of treatment, method of detection, and district were significantly associated with the successful treatment among TB and HIV co-infected patients.

On the other hand, gender, race, residency, diabetes mellitus status, BCG scar, and type of TB category cases were shown to have no significant association with TB treatment success.

Table III illustrates the factors associated with TB treatment success among subjects using multiple logistic regression. After adjusting confounding variables, duration of treatment and anatomy of TB location was significantly associated with TB treatment success. A person with an increased 1-day duration of treatment had 1.02 times higher odds of TB treatment success (OR: 1.02, 95% CI: 1.018, 1.025, p<0.001). A person with PTB (Pulmonary Tuberculosis) had 2.42 times higher odds of TB treatment success than those a person with EPTB (Extrapulmonary Tuberculosis) (OR: 2.42, 95% CI: 1.344, 4.361, p=0.003).

DISCUSSION

This study included 667 cases, 381 successful and 286 unsuccessful TB treatment outcomes. Among these 667 cases, 82.8% of new TB cases were reported, which is similar to that observed from 2010 to 2012 in Southwest Ethiopia (85.2%)[14] and in rural South Africa (84.9%).[15] The previous studies found that TB and HIV co-infection prevalence differed depending on study sites and population. In this study, TB and HIV co-infection was discovered in 11.1% of participants. It was comparable to the patients in Klang Valley, Malaysia (11.8%)[4] but higher than national TB surveillance between 2014 and 2017 (6.0%)[7] and in Aurangabad city, Maharashtra, in 2017 (7.28%).[16] However, the co-infection prevalence in this study was lower than Nigerian at 20.5%[17], Lagos, Nigeria at 21.6%,[18] Northern Ethiopia at 24.3%,[19] Ethiopia at 29.4%[20] and Malawi at 56.0%.[21] The co-infection prevalence was higher in third-world countries because of the diagnosis method for TB (diagnosed by chest radiography) and HIV (diagnosed based on blood analyses) than in those which used other diagnostic methods.[22]

According to the TB report, the global treatment success rate for TB/HIV patients was 78.0%.[23] In our study, data analysis revealed that TB and HIV patients had poor treatment outcomes with a success rate of only 57.1%. The high death rate (32.8%) and default rate (10.1%) contributed to this study's lower treatment success rate. Moreover, TB and HIV co-infected patients have a high risk of experiencing adverse treatment outcomes[24] due to immunosuppression, drug interactions, and lack of a rapid and sensitive TB diagnostic test. The success rate in this study is almost similar to the study in Malaysia (56.0%),[1] Klang Valley (53.4%),[4] and Western Ethiopia (58.06%).[25] This finding reveals why Malaysia is classified as an intermediate TB burden country in the world by the WHO.[26] The treatment success rate in this

Table I: Socio-demographic and other related factors among all study subjects

		Treatment Outcome		n (%)
		Unsuccessful (n = 286)	Successful (n = 381)	
Gender	Male	256 (43.4)	334 (56.6)	590 (88.5)
	Female	30 (39.0)	47 (61.0)	77 (11.5)
Race	Malays	276 (42.8)	369 (57.2)	645 (96.7)
	Non-Malays	10 (45.5)	12 (54.5)	22 (3.3)
Level of education	No education	6 (50.0)	6 (50.0)	12 (1.8)
	Primary school	29 (39.2)	45 (60.8)	74 (11.1)
	Secondary school	241 (45.0)	294 (55.0)	535 (80.2)
	Form 6/diploma/certificate	7 (21.2)	26 (78.8)	33 (4.9)
	Others	3 (23.1)	10 (76.9)	13 (1.9)
Residency	Urban	65 (42.5)	88 (57.5)	153 (22.9)
	Rural	221 (43.0)	293 (57.0)	514 (77.1)
Occupation	Government servant	7 (25.0)	21 (75.0)	28 (4.2)
	Own business	38 (47.5)	42 (52.5)	80 (12.0)
	Unemployed	132 (44.3)	166 (55.7)	298 (44.7)
	Prisoner	24 (32.0)	51 (68.0)	75 (11.2)
	Others	85 (45.7)	101 (54.3)	186 (27.9)
Diabetes mellitus	No	279 (43.2)	367 (56.8)	646 (96.9)
	Yes	7 (33.3)	14 (66.7)	21 (3.1)
BCG Scar	No	13 (38.2)	21 (61.8)	34 (5.1)
	Yes	273 (43.1)	360 (56.9)	633 (94.9)
Anatomy of TB location	EPTB	76 (46.3)	88 (53.7)	164 (24.6)
	PTB	168 (39.3)	260 (60.7)	428 (64.2)
	EPTB and PTB	42 (56.0)	33 (44.0)	75 (11.2)
CXR status during diagnose	No lesion	37 (39.4)	57 (60.6)	94 (14.1)
	Minimal	154 (39.8)	233 (60.2)	387 (58.0)
	Moderately advanced	87 (50.9)	84 (49.1)	171 (25.6)
	Far advanced	4 (80.0)	1 (20.0)	5 (0.7)
	Not done	4 (40.0)	6 (60.0)	10 (1.5)
Case TB category	New case	232 (42.0)	320 (58.0)	552 (82.8)
	Relapse case	38 (46.3)	44 (53.7)	82 (12.3)
	Case after treatment default	16 (48.5)	17 (51.5)	33(4.9)
Smoking status	No	80 (35.2)	147 (64.8)	227 (34.0)
	Yes	206 (46.8)	234 (53.2)	440 (66.0)
Regime of treatment	2SHRZ	7 (77.8)	2 (22.2)	9 (1.3)
	2EHRZ	125 (45.3)	151 (54.7)	276 (41.4)
	2HRZ	2 (66.7)	1 (33.3)	3 (0.4)
	Others	152 (40.1)	227(59.9)	379 (56.8)
DOTS by health care providers	No	77 (98.7)	1 (1.3)	78 (11.7)
	Yes	193 (33.7)	380 (66.3)	573 (85.9)
HAART treatment	No	259 (44.0)	329 (56.0)	588 (88.2)
	Yes	11 (29.7)	26 (70.3)	37 (5.5)
Source of notification	Public hospital	253(46.4)	292 (53.6)	545 (81.7)
	Public health clinic	32 (26.7)	88 (73.3)	120 (18.0)
Place of treatment	Public hospital	249 (46.0)	292 (54.0)	541 (81.1)
	Public health clinic	35 (28.5)	88 (71.5)	123 (18.4)
	Private health sector	2 (66.7)	1 (33.3)	3 (0.4)
Method of detection	Active	15 (51.7)	14 (48.3)	29 (4.3)
	Passive	251 (44.0)	319 (56.0)	570 (85.5)
	Screening	20 (29.4)	48 (70.6)	68 (10.2)
District	Kota Bharu	105 (40.90)	152 (59.1)	257 (38.5)
	Pasir Mas	22 (42.3)	30 (57.7)	52 (7.8)
	Pasir Puteh	20 (47.6)	22 (52.4)	42 (6.3)
	Tumpat	34 (43.0)	45 (57.0)	79 (11.8)
	Bachok	20 (36.4)	35 (63.6)	55 (8.2)
	Jeli	15 (55.6)	12 (44.4)	27 (4.0)
	Kuala Krai	21 (55.3)	17 (44.7)	38 (5.7)
	Machang	18 (36.0)	32 (64.0)	50 (7.5)
	Tanah Merah	25 (52.1)	23 (47.9)	48 (7.2)
	Gua Musang	6 (31.6)	13 (68.4)	19 (2.8)

Table II: Factors associated with TB treatment success among subjects using simple logistic regression

Factors		Simple logistic regression			*p* value
		b	Crude OR (95% CI)	Wald test	
Age*	-0.02	0.98 (0.97, 1.00)	2.76	0.097	
Duration of treatment*	0.02	1.02 (1.018, 1.024)	174.00	<0.001	
Gender	Male	0	1		
	Female	0.18	1.20 (0.74, 1.95)	0.54	0.461
Race	Malays	0	1		
	Non-Malays	13.32	0.90 (0.38, 2.11)	13.32	0.804
Level of education	No education	0	1		
	Primary school	0.44	1.55 (0.46, 5.28)	0.50	0.482
	Secondary school	0.20	1.22 (0.39, 3.83)	0.12	0.734
	Form 6/diploma /certificate	1.31	3.71 (0.91, 15.15)	3.35	0.067
	Others	1.20	3.33 (0.60, 18.54)	1.89	0.169
Residency	Urban	0	1		
	Rural	-0.21	0.98 (0.68, 1.41)	0.01	0.910
Occupation	Government servant	0	1		
	Own business	1.00	0.37 (0.141, 0.964)	4.14	0.042
	Unemployed	0.87	0.42 (0.173, 1.016)	3.70	0.054
	Prisoner	0.35	0.71 (0.27, 1.89)	0.47	0.492
	Others	0.93	0.40 (0.161, 0.977)	4.04	0.044
Diabetes Mellitus	No	0	1		
	Yes	0.42	1.52 (0.61, 3.82)	0.80	0.372
BCG Scar	No	0	1		
	Yes	-0.20	0.82 (0.40, 1.66)	0.31	0.575
Anatomy of TB location	EPTB	0	1		
	PTB	0.29	1.34 (0.930, 1.922)	2.45	0.117
	EPTB and PTB	-0.39	0.68 (0.392, 1.176)	1.91	0.167
CXR status during diagnose	No lesion	0	1		
	Minimal	-0.02	0.98 (0.62, 1.56)	0.01	0.939
	Moderately advanced	-0.47	0.63 (0.38, 1.05)	3.21	0.073
	Far advanced	-1.82	0.16 (0.02, 1.51)	2.55	0.110
	Not done	-0.03	0.97 (0.26, 3.69)	0.00	0.969
Case TB category	New case	0	1		
	Relapse case	-0.18	0.84 (0.53, 1.34)	0.54	0.462
	Case after treatment default	-0.26	0.77 (0.38, 1.56)	0.53	0.467
Smoking status	No	0	1		
	Yes	-0.48	0.62 (0.44, 0.86)	8.14	0.004
Regime of treatment	2SHRZ	0	1		
	2EHRZ	1.44	4.23 (0.86, 20.72)	3.16	0.075
	2HRZ	0.56	1.75 (0.10, 30.84)	0.15	0.702
	Others	1.65	5.23 (1.07, 25.50)	4.18	0.041
DOTS by Health care providers	No	0	1		
	Yes	5.02	151.61 (20.93, 1098.31)	24.70	0.000
HAART treatment	No	0	1		
	Yes	0.62	1.86 (0.90, 3.84)	2.83	0.093
Source of notification	Public hospital	0	1		
	Public health clinic	0.87	2.38 (1.54, 3.69)	15.08	<0.001
Place of treatment	Public hospital	0	1		
	Public health clinic	0.76	2.14 (1.40, 3.29)	12.28	<0.001
	Private health sector	-0.85	0.43 (0.04, 4.73)	0.48	0.487
Method of detection	Active	0	1		
	Passive	0.31	1.36 (0.65, 2.87)	0.66	0.418
	Screening	0.94	2.57 (1.05, 6.30)	4.27	0.039
District	Kota Bharu	0	1		
	Pasir Mas	-0.06	0.94 (0.52, 1.72)	0.04	0.846
	Pasir Puteh	-0.28	0.76 (0.40, 1.46)	0.68	0.411
	Tumpat	-0.09	0.91 (0.55, 1.52)	0.12	0.731
	Bachok	0.19	1.21 (0.66, 2.21)	0.38	0.538
	Jeli	-0.59	0.55 (0.25, 1.23)	2.12	0.146
	Kuala Krai	-0.58	0.56 (0.28, 1.11)	2.76	0.097
	Machang	0.21	1.23 (0.66, 2.30)	0.41	0.522
	Tanah Merah	-0.45	0.64 (0.34, 1.18)	2.06	0.151
	Gua Musang	0.40	1.50 (0.55, 4.06)	0.626	0.429

*Mean

Table III: Factors associated with TB treatment success among subjects using multiple logistic regression

Factors		Multiple logistic regression[a]			
		b	Adjusted OR (95% CI)	Wald statistic	*p* value
Duration of treatment*		0.02	1.02 (1.018, 1.025)	170.19	<0.001
Anatomy of TB location	EPTB	0			
	PTB	0.88	2.42 (1.344, 4.361)	8.67	0.003
	EPTB and PTB	-2.94	0.75 (.308, 1.806)	42	0.515

*Mean
[a] Forward stepwise likelihood ratio multiple logistic regression method was applied
Multicollinearity and interaction terms were checked and not detected.
Hosmer–Lemeshow GOF test (P<0.001), classification table (overall correctly classified percentage = 89.8%), and the area under the ROC curve (92.4%) were applied to check the model fitness.

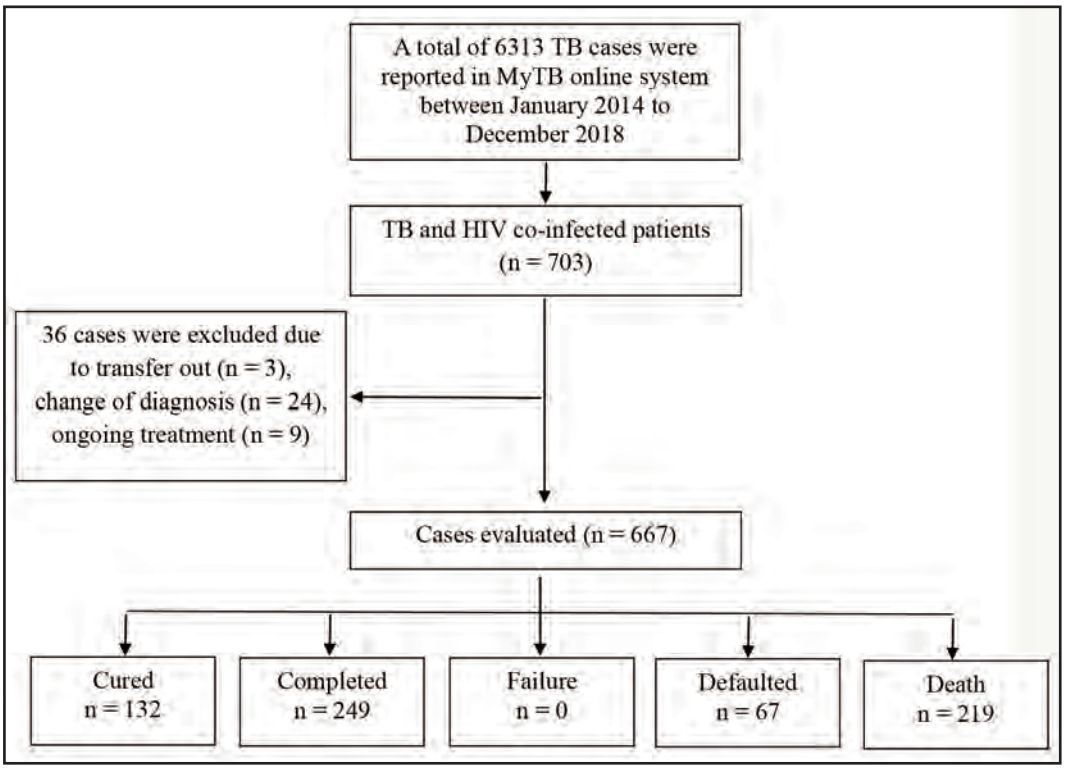

Fig. 1: Schematic diagram for selection of patients.

study was lower than the study conducted in Ghana (78.1%),[24] Ethiopia (88.2%),[20] North West Ethiopia (77.3%),[27] Western Ethiopia (60.7%),[28] and Northern Ethiopia (71.0%).[29] However, it was higher than the results obtained among TB and HIV co-infection in Kelantan between 2003 and 2012 (27.9%)[6] and in the Eastern Region of Ghana (50.0%).[30] The reasons for comparatively poor treatment outcomes in this study might be due to late detection of HIV and TB and delays in starting antiretroviral therapy (ART) or TB treatment.

This study has shown that having PTB and EPTB, moderate advanced and far advanced CXR status during diagnosis, smoking, and from the district of Jeli, Kuala Krai, and Tanah Merah may reduce the likelihood of treatment success. In Eastern Ethiopia, smear-positive PTB patients had a greater rate of ineffective treatment than EPTB and smear-negative PTB. This difference was statistically significant.[31] In Malaysia, a previous national TB surveillance study[7] found that smoking was related to unsuccessful results but not mortality. They claimed that the nature of smoking data collected in their study was self-reported by patients, influencing their findings. According to consistent evidence worldwide, smoking is linked to an increased risk of active TB, poor TB treatment results, and TB mortality.[32,33]

While having form 6/diploma/certificate and others level of education, own business, unemployed and others occupation, PTB, taken 2EHRZ and others regime of treatment, DOTS by healthcare providers, receiving HAART treatment, source of notification from the public health clinic, place of treatment at the public health clinic, and screening method detection increases the chance of having TB treatment success. A study of the DOTS program in Western Ethiopia found that HAART treatment, sputum examination, and treatment year were significantly associated with a higher treatment success rate.[28] The effect of

ART treatment on TB illness prognosis, on the other hand, is related to patients' immunological improvement after starting ART treatment in addition to the TB medicine.

After adjusting for other potential confounding variables, the duration of treatment and the anatomy of TB location was significantly associated with treatment success among TB and HIV co-infected patients in Kelantan. The mean (SD) duration of treatment in this study was 202.8 (131.27) days, equivalence to more than 6 months. The study done in Ethiopia found that the duration of treatment of 2–7 months (AOR = 14.8) contributed to the treatment success. The prior standard for first-line anti-TB treatment was eight months, which was revised to 6 months recently.[34]

In this study, PTB was more prevalent in the successful and unsuccessful groups. These findings could explain why PTB has a greater treatment success rate than EPTB and TB anatomy. A previous study in Southwest Ethiopia showed that TB/HIV co-infected patients with smear-positive PTB had a higher likelihood of treatment success.[35] According to studies conducted in various locations, TB and HIV co-infected patients with EPTB had a higher mortality risk during TB treatment than PTB patients.[4] In the study in China,[36] EPTB inpatients accounted for 48.69% of all TB patients. Patients with PTB are generally predicted to have a much better treatment outcome than PTB and EPTB.

Contrary to this, a study in Kelantan revealed the associated factors of poor treatment outcomes among PTB patients. They found that TB and HIV co-infection is a strong predictor of unsuccessful.[5] Another study found that smear-positive patients with PTB were 2.8 times more likely than patients with EPTB to have TB and HIV co-infection.[19] The study done in Ethiopia suggested that patients with advanced age and smear-positive PTB have poor treatment results.[20] In a study in Eastern Ethiopia, they found that smear-positive PTB patients had a greater rate of failed treatment (18.9%) than EPTB (14.3%) and smear-negative PTB (6.7%).[31]

The study findings of TB treatment outcomes and associated factors differed from other studies conducted in other states due to multifactorial aspects such as socio-demography, socioeconomic status, culture, level of knowledge, drugs used, and tolerance to side effects. It also may have been influenced by local service provision settings of the TB patient population. Our findings indicate a need for a strategy to improve the treatment outcomes among TB and HIV co-infected patients with TB in collaborative activities. The essential data of the patient socio-demographic, the prevalence of TB treatment outcomes, and associated factors with TB treatment success among TB and HIV co-infected patients can be used as a baseline for further study. They may also contribute to the body of knowledge regarding the treatment outcomes. Healthcare facilities, particularly in Kelantan, could be encouraged to focus on these relevant areas for a better outcome of TB treatment to achieve a better outcome of TB treatment in the future.

Nevertheless, our research has certain limitations. The study data and patient information were retrieved from the MyTB online system available in the TB/Leprosy Unit. The issue is that missing data cannot be minimised as well as getting inaccurate data. Some essential variables, such as income, are not recorded. We were unable to include these variables. Transfer of outpatients and change of diagnosis that were subsequently excluded from this study could be slightly biased in our findings. It is hoped that the efforts to begin capturing those characteristics could be made regularly.

CONCLUSION

This study's findings showed that the prevalence of TB treatment success rate was 57.1%, and the unsuccessful rate was 42.9%. The duration of treatment and the anatomy of the TB location was significantly associated with the treatment success rate among TB and HIV co-infection in Kelantan. Improving TB treatment outcomes should be started with anti-TB treatment immediately after TB diagnosis. Therefore, the government should strengthen the TB/HIV collaborative efforts to achieve good treatment outcomes among these vulnerable patients.

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ORIGINAL ARTICLE

Sexual assault cases presenting in One Stop Crisis Centre of a tertiary hospital in Malaysia: A retrospective study

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ABSTRACT

Introduction: Sexual assault is a serious social problem. Due to its stigma, it is severely underreported with the survivors delay in seeking treatment. We aim to study the patterns, clinical characteristics, and time taken to manage sexual assault cases in our One Stop Crisis Centre (OSCC), and determine the factors associated with delayed presentation.

Materials and methods: This was an observational case review study of all sexual assault cases from 2012-2017 at the OSCC of a suburban, tertiary hospital in Malaysia. A total of 304 cases were analysed.

Results: The median age of the survivors was 15 years old. Majority were females (n=291, 95.7%), single (n=290, 95.4%), students (n=235, 77.3%), and from low socio-economic class (n=230, 75.7%). Rape constitutes the majority (n=246, 80.6%) with 153 cases (62.1%) were statutory rape. The most common perpetrator was the victim's boyfriend (n=107, 35.2%) while only 60 cases (19.7%) involved strangers. Delayed presentations were more likely among victims who previously knew their perpetrators (AOR 2.53, 95% CI: 1.37 to 4.68, *p*<0.01). The median duration for management at OSCC was 6.48 hours.

Conclusion: Majority of sexual assault survivors were females, teenagers, and from low socio-economic class. Rape, mainly statutory rape, made the majority of cases. Therefore, sexual and safety education targeting primary intervention should be started early. Multidisciplinary teams must work together to optimise the management of sexual assault.

KEYWORDS:
Sexual assault, emergency department, woman, delayed presentation

INTRODUCTION

Sexual assault is a serious social problem. Although it may sound more like a public health issue, it has long become an important focus in the emergency care settings. Since its implementation in 1996, the examinations of sexual assault survivors are centred at One Stop Crisis Centre (OSCC) in the emergency department (ED) of government and university hospitals in Malaysia.[1]

Prior to the establishment of OSCC services, survivors were handled on ad-hoc basis. The development of OSCC services provides a holistic approach to ensure a continuity of care in a single unit. All involved agencies and multidisciplinary teams will be reviewing the survivors at one centre rather than sending the survivors to multiple different units. It aims to provide optimal multidisciplinary care and multilevel crisis intervention to the survivors from the crisis period to the rehabilitative phase, at the same time safeguarding their confidentiality and privacy. Another important objective of the centre is to ensure appropriate management of medico-legal evidence.

Due to its negative stigma, this topic is usually reserved, making it severely underreported with the survivors delay in seeking appropriate management. There is limited data and analysis produced on the pattern of sexual assault throughout Malaysia, let alone in the east-coast region which is more isolated and largely of rural areas.

The first objective of this study is to identify the demographic and social factors of the sexual assault survivors, their relationship with the perpetrators, and the assault characteristics. Secondly, we aim to determine the factors associated with delayed presentation. The final purpose of this study is to analyse the time taken for a complete management of the sexual assault cases at the ED level.

These data will provide information about the survivors' background and experience, creating better awareness of the characteristics which are more at risk of being sexually victimised. This greater understanding may in various ways aid not only the medical staff but also the social workers, counsellors, and police officers to approach the survivors as one whole person, rather than just a patient with mere physical injuries. The findings will also benefit the government in delivering better public health and sexual education to certain target groups, as well as the in-hospital multidisciplinary teams to improve their services.

MATERIALS AND METHODS

Sampling method and data collection

We conducted an observational case review of all sexual assault survivors seen from 1st January 2012 to 31st January 2017 at our suburban, academic tertiary centre ED with an approximate annual attendance of 62,000 patients. The

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study duration was to obtain enough sample size to increase the power of the study to 0.8. Throughout the study duration, the census of 365 victims who were classified as alleged rape or statutory rape, incest, sodomy, child and geriatric sexual abuse, attempted rape, molestation and sexual harassment in the OSCC registry were taken as initial sample. Their medical records were reviewed after gaining ethical approval from the Human Research Ethical Committee, Universiti Sains Malaysia (study protocol code USM/JEPeM/17020074) and written permission from the Hospital Director. To ensure the confidentiality of the victims, the name list was only known to one researcher and all the patient identifications in the data collection form were coded.

The data were extracted using a standardised data collection form which included the demographic of the survivors and the incident details, as well as the duration of management in OSCC (Figure 1); that is the duration from registration at triage to their dispositions, whether being admitted, discharged home, or provided a temporary shelter. However, out of the 365 cases from the census, 61 (16.7%) were excluded due to unobtainable case notes (45 cases, 12.3%), mislabelling of sexual assault at registration (6, 1.6%), and insufficient data significant to the study (10, 2.7%), leaving a total number of 304 cases being analysed.

Data analysis

Data were entered and analysed using Statistical Packages for Social Science (SPSS) version 24.0. We used frequency and cross-tabulation analysis to describe patterns of the socio-demographic variables of the victims and the clinical characteristics of the events as well as to report mean, median, and skewness of the duration of a survivor being managed in OSCC. Simple and multiple logistic regression were used to determine the factors that were associated with delayed presentation. Variables with p values of < 0.25 from simple logistic regression (univariate analysis) were selected for multivariate analysis, in which a p value of < 0.05 is considered as statistically significant when the confounders were controlled. Forward and backward likelihood ratio (LR) were applied to run the multivariate analysis. The final classification table is 54.3% correctly classified with area under receiver operating characteristics curve of 56.9%.

Variable definitions

Sexual assault refers to the act of rape, sodomy, molestation, or sexual harassment. Rape refers to the penetration of vagina by any body part or object, without the valid consent of the victim.[2] Rape of a victim aged less than 16 years old, with or without consent is, by law defined as statutory rape.[1,2] Sodomy is a sexual intercourse between two person by introduction of penis into the anus, and is a crime, consented or not.[1] Molestation means any sexual conduct that involves physical touching against the will of the victim but does not include penetration of vagina, anus, or oral, whereas sexual harassment is that does not involve physical touching.[1]

The terms sexual assault survivor and victim are used interchangeably, referring to the ED attendees who were registered for being alleged sexually assaulted as aforementioned, bearing in mind these cases were just based on reports and complaints of the survivors but not the actual court decision whether they were true crimes. Socio-economic groups are divided into low, middle, and high class according to the Department of Statistics Malaysia definitions.[3]

There are multiple definitions of early and late presentation of sexual assault cases based on previous studies. Most similar studies clearly defined delayed presentation as presenting after 72 hours following a sexual assault.[4-6] Some other studies took different values as cut-off point to describe the time of presentation, ranging from 12 hours to 1 week, and most of these only use the time limit to group the study subjects and did not clearly define them as early or late presentation.[7-10]

In our study however, the term delayed presentation will be based on the 'One Stop Crisis Centre: Policy and Guidelines for Hospitals' published in 2015 by the Malaysia Ministry of Health. According to the guideline, the cut-off points to differentiate acute (fresh) and cold cases for rape and sodomy are 72 and 120 hours, respectively.[1] Presentation of rape cases beyond 72 hours and of sodomy cases beyond 120 hours after the sexual assault are therefore designated as late or delayed presentation. When a victim survived rape and sodomy simultaneously, she will be categorised as rape due to the lower value taken to distinguish between fresh and cold cases. The aforesaid guideline however does not define fresh and cold cases for molestation and sexual harassment; therefore 72 hours will be taken as the cut-off point for other sexual assault types (molestation and harassment) as per most similar studies.

RESULTS

There was no obvious yearly or monthly pattern in the number of our OSCC visits for sexual assault. Total attendance was 365 cases from the registry of study period although only 304 were further analysed; the highest annual attendance was 86 cases in 2015, and the lowest 52 cases in 2016. There was 71, 76, and 72 cases presenting to us in 2012, 2013, and 2014, respectively. Majority of cases were rape (n=246, 80.9%), followed by molestation (n=42, 13.8%), sodomy (n=13, 4.3%), and sexual harassment (n=3, 1.0%).

Demographic pattern of survivors

Out of 304 cases studied, there were only two victims that were not Malay, one was Chinese, and the other was a Siamese. The median age was 15 years old with positive skewness (1.3) while the mean age was 14.89 ± 5.35, ranging from 1 to 42 years old. Almost half of the victims originated from Besut district, Terengganu (n=139, 45.7%), approximately half came from Kelantan; highest from Bachok district (n=86, 28.3%), followed by Kota Bharu (n=67, 22.0%), Pasir Puteh (n=18, 5.9%), Machang (n=3, 1.0%), and other districts in Kelantan (n=11, 3.6%). The rest 10 cases or 3.3% were those who came from outside Kelantan and Besut district of Terengganu. Further details of the demographic variables of the survivors are tabulated in Table I. Data on parental marital status of the victims were not available in 30 cases (9.9%). Otherwise, we found that around one-fifth of victims had divorced parents (n=65, 21.4%) and one-tenth with either parent passed away (n=31, 10.2%), with the rest had married parents (n=178, 58.5%). More than half of total

Table I: Demographic characteristics of sexual assault victims

Variables	Early presentation (n=165) n (% within type of assault*)				Late presentation (n=139) n (% within type of assault*)				Total (%) (N=304)
	Rape	Sodomy	Molestation	Sexual harassment	Rape	Sodomy	Molestation	Sexual harassment	
Age (years)									
≤ 12	9 (6.6)	7 (77.8)	10 (55.6)	0 (0.0)	12 (11.0)	4 (100.0)	17 (60.7)	1 (50.0)	57 (18.8)
13–15	76 (55.5)	1 (11.1)	3 (16.7)	0 (0.0)	56 (51.4)	0 (0.0)	5 (17.9)	0 (0.0)	140 (46.1)
16–17	30 (21.9)	0 (0.0)	2 (11.1)	1 (100.0)	21 (19.3)	0 (0.0)	2 (7.1)	0 (0.0)	56 (18.4)
≥ 18	22 (13.3)	1 (11.1)	3 (16.7)	0 (0.0)	20 (18.3)	0 (0.0)	4 (14.3)	1 (50.0)	51 (16.8)
Gender									
Female	137 (100.0)	3 (33.3)	17 (94.4)	1 (100.0)	109 (100.0)	0 (0.0)	23 (95.8)	2 (100.0)	292 (96.1)
Male	0 (0.0)	6 (66.7)	1 (5.6)	0 (0.0)	0 (0.0)	4 (100.0)	1 (4.2)	0 (0.0)	12 (3.9)
Marital status									
Single	130 (94.9)	8 (88.9)	17 (94.4)	1 (100.0)	105 (96.3)	4 (100.0)	23 (95.8)	2 (100.0)	290 (95.4)
Married	5 (3.6)	1 (11.1)	1 (5.6)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.6)
Divorced	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.8)	0 (0.0)	1 (4.2)	0 (0.0)	6 (2.0)
Previous sexual status									
Active	66 (48.2)	1 (11.1)	2 (11.1)	1 (100.0)	46 (42.2)	0 (0.0)	1 (4.2)	0 (0.0)	117 (38.5)
Not active	71 (51.8)	8 (88.9)	16 (88.9)	0 (0.0)	63 (57.8)	4 (100.0)	23 (95.8)	2 (100.0)	187 (61.5)
Education level									
Preschool	3 (2.2)	3 (33.3)	6 (33.3)	0 (0.0)	0 (0.0)	1 (25.0)	3 (12.5)	1 (50.0)	17 (5.6)
Primary school	10 (7.3)	5 (55.6)	5 (27.8)	0 (0.0)	17 (15.6)	3 (75.0)	11 (45.8)	0 (0.0)	51 (16.8)
Secondary school	118 (86.1)	0 (0.0)	6 (33.3)	1 (100.0)	85 (78.0)	0 (0.0)	9 (37.5)	1 (50.0)	220 (72.4)
Tertiary education	2 (1.5)	1 (11.1)	1 (5.6)	0 (0.0)	3 (2.8)	0 (0.0)	1 (4.2)	0 (0.0)	8 (2.6)
Not documented	4 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.6)
Occupational status									
Student	110 (80.3)	5 (55.6)	10 (55.6)	1 (100.0)	87 (79.8)	4 (100.0)	17 (70.8)	1 (50.0)	235 (77.3)
Employed	12 (8.8)	1 (11.1)	2 (11.1)	0 (0.0)	7 (6.4)	0 (0.0)	4 (16.7)	0 (0.0)	26 (8.6)
Unemployed	15 (10.9)	3 (33.3)	3 (33.3)	0 (0.0)	15 (13.8)	0 (0.0)	3 (12.5)	1 (50.0)	43 (14.1)

* Because of rounding, some percentages do not total 100

Table II: Clinical characteristics of sexual assault

Variables	Early presentation (n=165) n (% within type of assault*)				Late presentation (n=139) n (% within type of assault*)				Total (%) (N=304)
	Rape	Sodomy	Molestation	Sexual harassment	Rape	Sodomy	Molestation	Sexual harassment	
Place of crime									
Perpetrator's house	35 (25.7)	3 (42.9)	1 (5.6)	0 (0.0)	32 (31.4)	0 (0.0)	6 (25.0)	0 (0.0)	77 (26.2)
Victim's house	15 (11.0)	1 (14.3)	8 (44.4)	0 (0.0)	19 (18.6)	0 (0.0)	4 (16.7)	0 (0.0)	47 (16.0)
Other's house†	30 (22.1)	1 (14.3)	2 (11.1)	1 (100.0)	18 (17.6)	1 (25.0)	3 (12.5)	1 (50.0)	57 (19.4)
School/Workplace	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.0)	2 (50.0)	8 (33.3)	1 (50.0)	13 (4.4)
Jungle/Bush/Plantation	16 (11.8)	1 (14.3)	1 (5.6)	0 (0.0)	6 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	24 (8.2)
Hotel/Guesthouse	6 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	11 (3.7)
Beach	5 (3.7)	1 (14.3)	0 (0.0)	0 (0.0)	3 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.1)
Car	7 (5.1)	0 (0.0)	1 (5.6)	0 (0.0)	3 (2.9)	0 (0.0)	1 (4.2)	0 (0.0)	12 (4.1)
Others	22 (16.2)	0 (0.0)	4 (22.2)	0 (0.0)	15 (14.7)	1 (25.0)	2 (8.3)	0 (0.0)	44 (15.0)
Perpetrator									
Unknown	36 (26.3)	2 (22.2)	5 (27.8)	0 (0.0)	13 (11.9)	0 (0.0)	4 (16.7)	0 (0.0)	60 (19.7)
Boyfriend	57 (41.6)	0 (0.0)	2 (11.1)	1 (100.0)	47 (43.1)	0 (0.0)	0 (0.0)	0 (0.0)	107 (35.2)
Friend	20 (14.6)	0 (0.0)	1 (5.6)	0 (0.0)	17 (15.6)	1 (25.0)	2 (8.3)	1 (50.0)	42 (13.8)
Parent/Grandparent	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.5)	0 (0.0)	1 (4.2)	0 (0.0)	8 (2.6)
Step parent/grandparent	2 (1.5)	0 (0.0)	1 (5.6)	0 (0.0)	6 (5.5)	0 (0.0)	3 (12.5)	0 (0.0)	12 (3.9)
Sibling	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)
Other relatives	7 (5.1)	0 (0.0)	4 (22.2)	0 (0.0)	5 (4.6)	1 (25.0)	4 (16.7)	0 (0.0)	21 (6.9)
Teacher	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (29.2)	0 (0.0)	8 (2.6)
Neighbour	2 (1.5)	1 (11.1)	4 (22.2)	0 (0.0)	3 (2.8)	1 (25.0)	0 (0.0)	0 (0.0)	11 (3.6)
Others known to victim	10 (7.3)	5 (55.6)	1 (5.6)	0 (0.0)	10 (9.2)	1 (25.0)	3 (12.5)	1 (50.0)	31 (10.2)
Number of perpetrator(s)									
One	96 (70.1)	9 (100.0)	15 (83.3)	1 (100.0)	85 (78.0)	3 (75.0)	23 (95.8)	2 (100.0)	234 (77.0)
Multiple	41 (29.9)	0 (0.0)	3 (16.7)	0 (0.0)	24 (22.0)	1 (25.0)	1 (4.2)	0 (0.0)	70 (23.0)
Involvement of alcohol/ drugs/weapons									
Yes	12 (8.8)	2 (22.2)	1 (5.6)	0 (0.0)	12 (11.0)	2 (50.0)	1 (4.2)	0 (0.0)	30 (9.9)
No	125 (91.2)	7 (77.8)	17 (94.4)	1 (100.0)	97 (89.0)	2 (50.0)	23 (95.8)	2 (100.0)	274 (90.1)
Was victim defensive?									
Yes	18 (13.1)	0 (0.0)	4 (22.2)	0 (0.0)	11 (10.1)	1 (25.0)	2 (8.3)	0 (0.0)	36 (11.8)
No	119 (86.9)	9 (100.0)	14 (77.8)	1 (100.0)	98 (89.9)	3 (75.0)	22 (91.7)	2 (100.0)	268 (88.2)

* Because of rounding, some percentages do not total 100

† House other than victim's or perpetrator's

Table III: Simple logistic regression for factors associated with late presentation

Variable	B	Crude OR (95% CI)	*p* value
Age (years)	- 0.02	0.99 (0.94, 1.03)	0.49
Age group			
≤ 12	0	1	
13 – 15	- 0.46	0.63 (0.34, 1.17)	0.14
16 – 17	- 0.54	0.59 (0.28, 1.23)	0.16
≥ 18	- 0.22	0.81 (0.38, 1.72)	0.58
Gender			
Female	0	1	
Male	- 0.17	0.84 (0.26, 2.72)	0.77
Previously sexually inactive	0.37	1.44 (0.90, 2.30)	0.13
Socioeconomic status*			
Low class	0	1	
Middle class; non-professional	0.23	1.26 (0.49, 3.20)	0.64
Middle class; professional	- 0.17	0.85 (0.19, 3.87)	0.83
Type of assault			
Rape	0	1	
Sodomy	- 0.58	0.56 (0.17, 1.86)	0.34
Molestation	0.52	1.68 (0.87, 3.25)	0.13
Sexual harassment	0.92	2.51 (0.23, 28.09)	0.45
Known perpetrator (acquaintance)	0.93	2.53 (1.37, 4.68)	< 0.01
Multiple perpetrator	- 0.46	0.63 (0.37, 1.10)	0.10
Involvement of drugs and alcohol	0.19	1.21 (0.57, 2.57)	0.62
Defensive victim	- 0.32	0.73 (0.36, 1.48)	0.38

Abbreviation: B = Regression Coefficient, OR = Odd Ratio, CI = Confidence Interval
*Only 256 cases being included in the analysis for socio-economic status (missing data in 48 cases)

Table IV: The mean and median of duration, in hours, taken in managing sexual assault cases in OSCC according to type of assault

Description	Type of assault	n*	Mean (SD)	Median (IQR)	Skewness
Registration to clerking	Overall	268	1.69 (2.34)	1.02 (1.32)	5.27
	Rape	216	1.63 (2.40)	1.00 (1.22)	5.76
	Sodomy	11	2.51 (2.96)	1.93 (1.82)	1.98
	Molestation	38	1.68 (1.65)	0.98 (1.65)	2.10
	Sexual harassment	3	3.05 (3.01)	1.88 (-)	1.48
Clerking to referral	Overall	147	1.47 (2.05)	1.00 (0.80)	4.41
	Rape	121	1.50 (2.12)	1.00 (0.83)	4.53
	Sodomy	7	1.67 (3.10)	0.50 (0.67)	2.59
	Molestation	18	1.26 (1.06)	1.04 (0.77)	2.03
	Sexual harassment	1	0.58 (0.00)	0.58 (-)	-
Referral to decision of disposition	Overall	116	3.67 (3.94)	2.73 (2.58)	3.71
	Rape	101	3.37 (3.22)	2.75 (2.55)	4.55
	Sodomy	7	6.60 (5.99)	4.27 (10.92)	0.63
	Molestation	7	5.32 (8.54)	2.67 (2.05)	2.54
	Sexual harassment	1	2.05 (0.00)	2.05 (0.00)	-
Decision of disposition to actual disposition	Overall	205	1.46 (1.54)	1.02 (1.07)	3.91
	Rape	170	1.41 (1.52)	1.02 (1.05)	4.59
	Sodomy	11	1.22 (0.88)	0.98 (0.77)	1.28
	Molestation	22	2.02 (1.94)	1.19 (2.77)	0.97
	Sexual harassment	2	0.56 (0.08)	0.56 (-)	-
Total duration (registration to disposition)	Overall	205	7.61 (4.77)	6.48 (3.40)	3.29
	Rape	170	1.69 (2.34)	1.02 (1.32)	5.27
	Sodomy	11	1.63 (2.40)	1.00 (1.22)	5.76
	Molestation	22	2.51 (2.96)	1.93 (1.82)	1.98
	Sexual harassment	2	1.68 (1.65)	0.98 (1.65)	2.10

SD = standard deviation, IQR = interquartile range.
* Total number of cases analysed differs due to missing data.

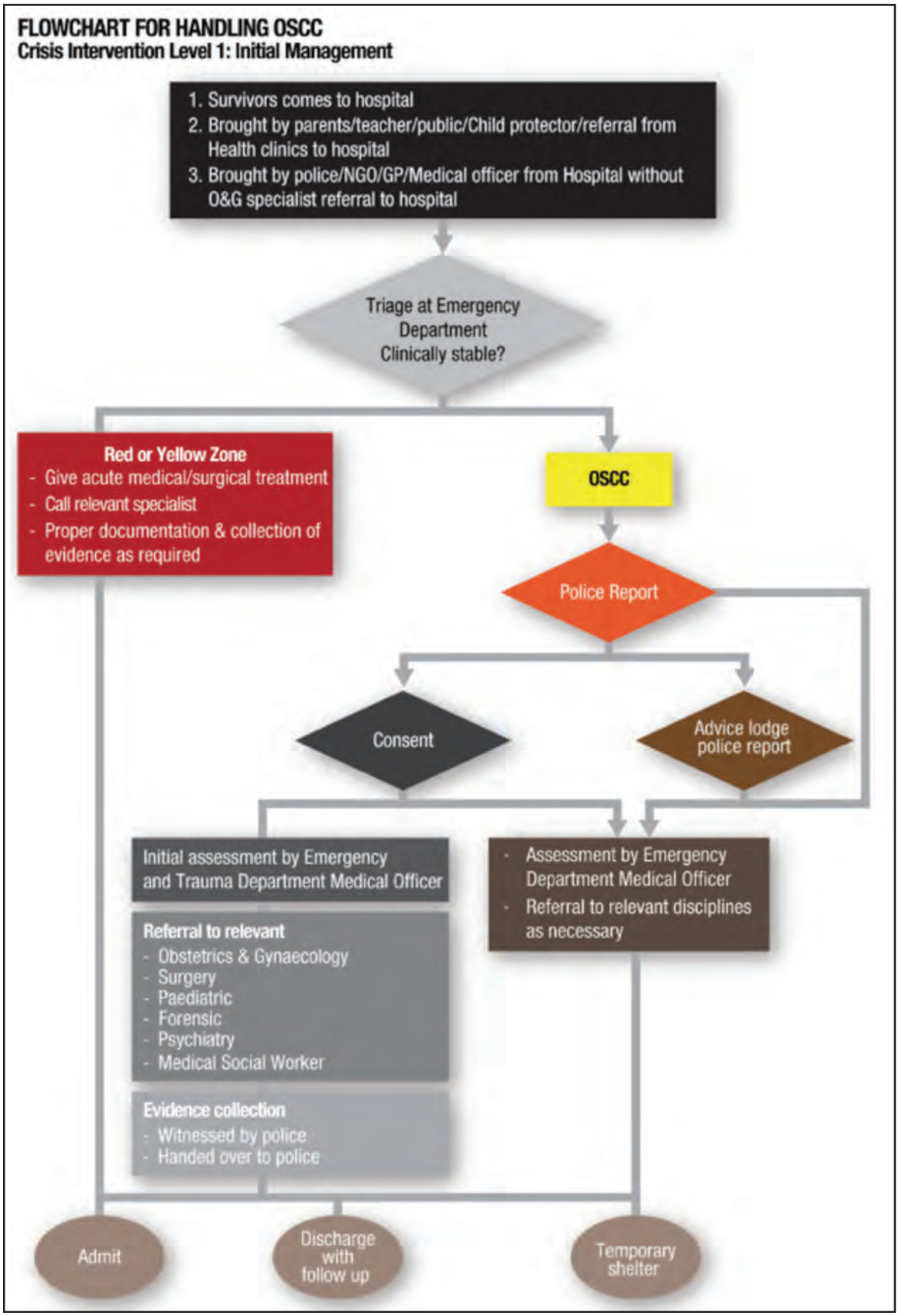

Fig. 1: Flowchart for handling One Stop Crisis Centre (OSCC).1 Duration of management in OSCC refers to duration from registration at triage to disposition of survivors. Source: One Stop Crisis Centre: Policy and Guidelines for Hospitals. Malaysia: Ministry of Health Malaysia, July 2015.

victims analysed were brought up by both parents (n=169, 55.6%), and majority stayed within nucleus family (n=245, 80.6%).

Clinical characteristics of sexual assault

The clinical characteristics of sexual assault cases including the victim–perpetrator relationship were summarised in Table II. Out of 246 rape cases, 153 (62.1%) were statutory rape. In general, majority of the assailants were known to the victims. Only 60 cases (19.7%) were committed by strangers. Majority of victims claimed they were not defensive during the assault, and even when they did so, it was only evident in 8 or 22.2% of those defensive victims.

Factors associated with delayed presentation

Among the 304 encounters, the time elapsed from assault to ED presentation ranging from 77 minutes to 1 year. Only 43 (14.1%) presented very early (less than 12 hours) post sexual assault. Another 122 cases (40.1%) presented in between 12 and 72 hours, 12 (3.9%) presented within 72 to 120 hours, and 127 (41.8%) presented more than 120 hours. When these cases are classified further into early and late disclosure by the definition for each type of assault (refer to variables definition in methodology), we found that 165 (54.3%) did present early, leaving 139 victims (45.7%) presenting late.

When the confounders were not adjusted, the crude odd ratios from simple logistic regression analysis of variables potentially associated with delayed disclosure were shown in Table III. At univariate analysis, age group, previous sexual status, type of assault, victim–perpetrator relationship, and number of perpetrators were important variables associated with late presentation (p value ≤ 0.25). All these five variables were selected for further analysis to control the confounders.

From multivariate analysis, there was a significant association between victim–perpetrator relationship towards late presentation. Victims who previously knew their perpetrators (acquaintance cases) had 2.53 times the odds to delay presentation when compared to the victims who were assaulted by strangers (95% CI: 1.37 to 4.68, $p < 0.01$). Other factors did not significantly contribute to the late disclosure of sexual assault victims.

Duration of management in OSCC

Overall, the mean duration of sexual assault survivors managed at OSCC was 7.61 ± 4.77 hours (n=205) with median of 6.48 hours (skewness 3.29) before being admitted for further evaluation (n=220, 72.4%) or discharged home (n=84, 27.6%). Details of the duration spent for each management process, overall and according to type of cases, were illustrated in Table IV. Our study showed that the longest time taken was during the review by respective teams (refer Figure 1). This was approximately 2.7 times the duration spent waiting to be seen by ED doctor, the duration of first clerking (from clerking to referral), and the duration of waiting to be admitted after being seen by all teams. With exclusion to ED team, more than half of the cases were seen by four different managing teams (n=175, 57.6%). Otherwise, cases were referred to one (n=2, 0.7%), two (n=34, 11.2%), three (n=80, 26.3%), and at most five respective departments (n = 13, 4.3%).

DISCUSSION

The incidence of sexual assault was higher in female teenagers' group, and this finding is consistent with many international literatures including the previous national studies done in Hospital Universiti Sains Malaysia and Hospital Kuala Lumpur.[11,12] We also noticed that majority of the perpetrators were known to the victims, which included victims' boyfriends and family members, similar to the previous studies mentioned.[11,12] However, there is a decreasing trend in the median age of the victims at presentation, which was 22.4 years old in the study in Hospital Kuala Lumpur in 2005, compared to 15 years old in our study. At this age, they begin to develop the secondary sexual characteristics and explore their own sexual identity. A prevalence study by Ahmad et al. in 2012 found that 8.3% of adolescents aged 12 to 17 years had sexual intercourse at least once, which suggested a four times increased prevalence compared to 2010.13 Among these, 50.6% had their first intercourse before the age of 14.[13] The intercourse might be consensual but lawfully, it is considered statutory rape as legal age of consent for sexual relationship is 16 years old for female,[1,14,15] contributing to the higher number of female victims and rape cases being reported among teenagers.

Cultural, socioeconomic, and educational disparities are usually the contributing factors to the sexual health and education of these adolescents, on top of parental involvement and peer influence. In Malaysia, sexual education is still a taboo, even though there have been efforts on making it a proper subject in schools. The importance of this could not be emphasised more by our study, which found that 84.3% rape victims were school-aged children. Sexual education programs in schools may include teaching of consent, healthy relationship, dating violence, coercion, and refusal skills. A study done in the US found that the states with sexual education program or curriculum prior to graduation have the lowest rates of rape, while the states with the highest rate of rape have policies which do not support sexual education as part of graduation. 16 Another study suggests that school-based sexual education with training in refusal skills was a protective factor and recommends that pre-college sexuality education may be effective in preventing sexual assault.[17]

Although the introduction of sexual education here in Malaysia is thought to encourage pre-marital sexual activity which is against the religious and moral values of most Malaysians, it actually did not hasten the initiation of sex but rather delayed it.[18] It is important to instil the correct concept of sexuality and sexual activities at earlier age before being misled by irresponsible media, especially in this era where sex information is readily available electronically. Young children should also be introduced to what kind of 'touch' is wrong and the importance of letting the parents or a trusted person know if there has been any breach. All of these are some of the many objectives that should be emphasised in the sexual education program.

Early presentation of sexual assault survivors to the OSCC is very crucial. It allows early assessment and management of physical injuries and nonphysical stress that might be life-threatening and provides ample time for the prevention of

other complications such as HIV post-exposure prophylaxis and emergency contraception, which are more effective when delivered sooner. There is also a greater chance of obtaining critical forensic evidence and better injury documentation with early presentation, which are generally believed to be imperative for a successful legal prosecution.[19,20]

There are few reasons to explain why the victims of sexual assault present late. Fear of perpetrator, fear of minor victim, scared of not being trusted by family or relatives, being held captive by perpetrator, intoxication, mental retardation, sick or injured, lack of faith in criminal justice system, and distance from sexual assault service centre were among the reasons identified by Adefolalu to explain why sexual assault survivors delay their presentation.[4] Younger victims might not understand what constitutes sexual assault. Other reasons can be due to fear of the stigma and its effect in the later life, as well as of the daunting medical and legal procedures. The acquired data showed that acquaintance cases were more likely to delay presentation, like what have been reported globally.[7] The victims might worry that they would jeopardise the perpetrators who are known to them, let alone if they were their own family members. This explains why in some cases, a victim can repetitively be assaulted sexually by the same person before lodging a report.

The longer the duration taken to completely manage a sexual assault case, the longer the stressful period for the traumatised victims is. Getting a proper history and addressing the survivors with good communication skills are inevitably time-consuming. This justifies why the process of clerking and review by respective teams took time, especially when there can be as many as five different disciplines reviewing the victim. Thorough clerking and proper referrals are vital in delivering the best treatment to the survivors physically and emotionally, hence it is only appropriate to allow as much time spent on these as it is for the victims' best interest.

However, duration of waiting to be seen by the doctor, as well as the administrative process of admission should be improvised to address the long duration of time elapsed from registration to disposition. This could be affected by some reasons. Firstly, if police report was not available prior to ED registration, it will be lodged from OSCC. The process of getting the police officers to arrive, get back to their department, and came back with an investigating officer and consent; these contributed to the lengthy managing time. Also, a stable victim might be attended later if ED is occupied, as priority will be given to those who are critically ill. When the survivors are decided for admission, they need to wait for hospital porters to send them to the ward, in addition to queuing for an available bed in ward. All these would also prolong the management time in OSCC.

There were a lot more that can be explored regarding our final objective. However, we were limited by incomplete documentation, in which the time of clerking, referral, being seen by referred teams, sent to ward, or discharge were not recorded in some cases.

Another limitation of our study is that we did not define who to be considered as strangers or acquaintances. In some of our samples, the assailants who were new online contacts, family friends, or employers' relatives whose names were known to victims were considered as acquaintances when the victims might just have their first contact with them when they were assaulted. A duplicate of multicentre prospective study with a pre-prepared data collection form for each sexual assault cases attending OSCC will be more effective to eliminate these limitations and provide better holistic information on the pattern of sexual assault cases in the east coast region of Malaysia.

CONCLUSION

Our study found that most sexual assault cases managed in the OSCC were rape, and mostly were statutory rape. Majority of sexual assault survivors were females, teenagers, and from low socio-economic class. The independent factor for delayed presentation was that the assailants were known to the victims. The long duration of the management of sexual assault survivors in the OSCC was mainly contributed to the time taken for review by the respective teams. To facilitate the victims in seeking help and avoid late disclosure, available services for sexual assault such as OSCC should be publicised and made easily accessible. Education on sexual assault prevention should begin earlier at the targeted groups. Multidisciplinary teams must work together to optimise and hasten the management of sexual assaults in the OSCC while providing a safe environment to the victims.

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Quality improvement project: Optimal post-void residual urine volume to guide intermittent catheterization in hospitalised older persons with acute retention of urine

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ABSTRACT

Introduction: There is no consensus on the optimal post-void residual urine volume (PVRU) as a cut-off value prior to performing intermittent catheterisation (IMC). We did a quality improvement project to determine a reasonable PVRU for use in the hospital setting.

Materials and methods: All patients admitted to the five geriatric medicine wards in a geriatric department over a 5-month period who developed acute retention of urine were included in the project. Patients who had hydronephrosis or were already on catheter for more than a week were excluded. Patients included were randomised to PVRU of 200 ml or 300ml. The male and female participants were randomised into separate groups. The primary outcome measures were success in weaning off IMC and the development of urinary tract infection (UTI). The secondary outcomes were the frequency of IMC required and the days needed to wean off IMC successfully.

Results: Both the 200 ml and 300 ml groups had equal success in weaning off IMC and were equally likely to be associated with UTI. However, the 200-ml group had more IMC done within the first 3 days (3.3, SD 2.4 vs 2.4, SD 1.6, *p* = 0.030), but was weaned off IMC earlier (3.5, SD 1.7, vs 4.8, SD 2.3 days, *p* = 0.049).

Conclusion: We conclude that PVRU of 200 ml or 300 ml are both reasonable cut-off values prior to performing IMC.

KEYWORDS:
Post-void residual urine, intermittent catheterisation, weaning off catheter, urinary tract infection.

INTRODUCTION

In our hospital, patients with acute retention of urine (ARU) are put on intermittent catheterisation (IMC) four times a day. Prior to every IMC, a post-void residual urine volume (PVRU) using a bedside bladder scan is performed.[1] PVRU is defined by the International Continence Society as the volume of urine left in the bladder at the completion of micturition.[2] This applies to both male and female patients.[3] If the PVRU is more than 200 ml, IMC will be performed, but if the PVRU is less than 200 ml, IMC will be omitted. However, there is no consensus on the optimal PVRU as cut-off value and different doctors use different PVRU values.

Both IMC and in-dwelling catheterisation (IDC) can cause adverse effects, including urinary infection, bleeding, urethral stricture, and bladder stones.[4] Though IDC is more convenient for the nursing staff as no repeated catheterisation is required, IMC is preferred to IDC.[5] To insert an IDC only for the comfort of the nursing personnel is irresponsible.[5]

The risk of developing UTI is probably higher in IDC compared to IMC.[6] The patients on IMC will not need to lug along a tube with a bag wherever they go, hindering rehabilitation. Furthermore, when the bladder recovers, the residual urine volume gradually decreases and the frequency of IMC also reduces until IMC can be discontinued. If patients have a urethral stricture or urethral injury, both IMC and IDC cannot be used. Instead, suprapubic catheterisation will be needed.[5]

Catheterisation may introduce bacteria into the urinary bladder, but a high PVRU may predispose patients to UTI due to stasis. What is the optimal PVRU before IMC should be performed? There are no evidence-based guidelines on the optimal PVRU prior to performing IMC.

Bacteriuria is expected to develop in 26% (95% confidence interval, 23%–29%) in patients who have indwelling catheters inserted for 2–10 days. Among patients with bacteriuria, symptoms of UTI will develop in 24% (95% confidence interval, 16%–32%), and bacteremia from a urinary tract source will develop in 3.6% (confidence interval, 3.4%–3.8).[7]

We did a quality improvement project to determine whether PVRU of 200 ml is comparable to 300 ml in the success in weaning off IMC and in the risk of developing UTI. We chose a higher PVRU value of 300 ml, rather than a lower value, to investigate whether fewer IMC could be done without causing more UTI or a delay in weaning off catheter.

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OBJECTIVE

To investigate whether PVRU of 200 ml is comparable to 300 ml in:

1. Success in weaning off IMC
2. Incidence of UTI
3. Number of IMC done
4. Days required to wean off IMC

MATERIALS AND METHODS

Inclusion Criteria

All patients admitted to the five geriatric medicine wards in a geriatric department who developed ARU over a 5-month period, 22 October 2018 till 21 March 2019, were included in the project.

Exclusion Criteria

The patients already on IMC or IDC (at least 1 week) preadmission or had hydronephrosis were excluded.

Ethical Consideration

The Clinical Trials and Research Unit (CTRU) of our hospital was consulted regarding consent taking from the patients. Since IMC was done as part of the management of acute retention of urine, no consent was deemed needed.

Randomisation

The patients were randomised at individual ward level to PVRU 200 ml or 300 ml using sealed envelopes. The male and female participants were assigned separately using two sealed envelopes.

Data Collection

The demographics of patients collected were age, gender, living arrangement, length of stay, life expectancy, Abbreviated Mental Test score, Barthel Index score, and the presence of faecal impaction.

The patients enrolled into the project were subjected to PVRU four times a day using a bedside bladder scan done by the ward nurses trained in bladder scanning. If the PVRU was more than 200 ml, or 300 ml, depending on randomisation, IMC was performed.

Day 1 was counted as the day the patient was randomised and started on the study.

Definition of successful weaning off catheter. If two consecutive PVRU were 100 ml or less, the patient was deemed to be successfully weaned off IMC and the study was deemed completed. The day when it occurred was noted. However, the patients were monitored for symptoms of UTI for another 48 hours.

Definition of failure of weaning off catheter. If two consecutive PVRU were not less than 100 ml yet at the end of Day 8, then it was deemed as failed weaning off IMC and the study was also deemed completed. If the patients were discharged home or transferred to another hospital or facility before they had two consecutive PVRU of less than 100 ml, they were also considered as failed in weaning off IMC. If in-dwelling catheter was inserted for whatever reason, the patient was also deemed as failed in weaning off IMC.

The patients were monitored for signs and symptoms of UTI for at least 2 days after being weaned off IMC successfully. If the patients were discharged before that a phone call was made to enquire about symptoms of UTI.

Urine microscopy and urine cultures were collected in the patients who developed dysuria, suprapubic pain, loin pain or unexplained altered mental state or fever, or raised inflammatory markers (total white cell counts, C-reactive protein, procalcitonin).

Data Analysis

For statistical calculations, t-test was used for continuous variables and Chi-square for noncontinuous variables.

RESULTS

The comparison of patient characteristics between the two groups is shown in Table I. The success in weaning off catheter, the development of UTI and bacteremia, the day patients developed UTI, and the total number of IMC done in the first 3 days are shown in Tables II–V, respectively. The time taken for IMC to be weaned off was 3.5 days (SD 1.7) in the 200 ml group and 4.8 days (SD 2.3) in the 300 ml group, p value 0.049. The study was interrupted in both groups: 4 in 200 ml group and 7 in 300 ml group. The reasons for interruption were strict in-out fluid monitoring (IDC inserted), patients being unable to cooperate with IMC, the primary team doctors' preference (IDC inserted), discharge to another facility, and death.

Both 200 ml and 300 ml groups had equal success in weaning off IMC (56.5% vs 58.1%, p = 0.910) and were equally likely to be associated with UTI (17.4% vs 29%, p = 0.322). However, the 200-ml group had more IMC done in the first 3 days (3.3, SD 2.4 vs 2.4, SD 1.6, p = 0.030), but achieved weaning off IMC earlier (3.5, SD 1.7, vs 4.8, SD 2.3 days p = 0.049).

DISCUSSION

From our project, we found that using PVRU of 200 ml or 300 ml did not significantly affect the likelihood of the success in weaning off IMC. More than 50% of the patients could be weaned off IMC by Day 4 in the 200-ml group and by Day 5 in the 300 ml group. These are very encouraging results, reaffirming the need for a trial to wean off catheters in all patients.

Using 300 ml as a cut-off may reduce the number of IMC required, thus saving nursing time. However, using 200 ml as a cut-off value may reduce the time taken to wean off IMC, thus potentially reducing the length of hospital stay.

Neither group was associated with a significantly higher incidence of UTI or bacteremia. The 300 ml group had a higher rate of UTI (9/31, 29.0%) compared to 200 ml group (4/23, 17.4%). However, 5 out of 9 UTI in the 300 ml group occurred at Day 1, suggesting that the UTI may be the consequence of ARU rather than the adverse effect of IMC.

Table I: Baseline characteristics of patients

Characteristics		200 ml group	300 ml group	*p* value
Number of patients		24	33	
Age		87 (SD 7.7)	88 (SD 7.8)	0.816*
Gender	Male	5	13	0.137**
	Female	19	20	
Living arrangement	Community	23	30	0.472**
	Institution	1	3	
Length of stay (days)		17 (SD16)	20 (SD10)	0.751*
Life expectancy < 1 year[8]	Yes	2	3	0.881**
	No	20	26	
		(2 missing)	(4 missing)	
Abbreviated Mental Test score		4.5 (SD 3.9)	3.9 (SD 3.7)	0.475*
Barthel Index score		12 (SD 6.0)	9.2 (SD 5.7)	0.768*
Faecal impaction	Yes	6	9	0.811**
	No	17	22	
		(1 missing)	(2 missing)	

#Some patients were given antibiotics for infections other than UTI.
*T-test.
**Chi-square.

Table II: Success in weaning off catheter

		200 ml group	300 ml group	*p* value
Successfully weaned off IMC	Yes	13 (56.5%)	18 (58.1%)	0.910**
	No	10	13	
		(1 missing)	(2 missing)	
Successfully weaned off IMC (after discounting those interrupted by IDC)	Yes	13 (68.4%)	18 (75.0%)	0.633**
	No	6	6	

#Some patients were given antibiotics for infections other than UTI.
*T-test.
**Chi-square.

Table III: Development of UTI and bacteremia

		200 ml group	300 ml group	*p* value
Developed UTI	Yes	4 (17.4%)	9 (29.0%)	0.322**
	No	19	22	
		(1 missing)	(2 missing)	
Developed bacteremia	Yes	2 (8.7%)	2 (6.4%)	0.756**
	No	21	29	
		(1 missing)	(2 missing)	
Antibiotic use #	Yes	13 (56.6%)	19 (61.3%)	0.724**
	No	10	12	
		(1 missing)	(2 missing)	

#Some patients were given antibiotics for infections other than UTI.
*T-test.
**Chi-square.

Table IV: Day patient developed UTI

Day of UTI	200ml group	300ml group
1	1	5
2	0	1
3	1	2
4	2	0
5	0	1
Total number of patients	4	9
Average day developing UTI	Day 3	Day 2

Table V: Total number of IMC done in first 3 days

Characteristics	200 ml group	300 ml group	*p* value
Total number of IMC done in first 3 days (not number of IMC per day)	3.3 (2.4)	2.4 (1.6)	0.030*

#Some patients were given antibiotics for infections other than UTI.
*T-test.
**Chi-square.

About half of the patients would have been weaned off IMC by Day 4. So, for better comparison, we compared the total number of IMC done in the first 3 days in both groups.

Our project was done in a real-life setting in the five geriatric medicine wards in a geriatric department. The patients were randomised at the ward level. The male and female participants were randomised separately as we thought that the success in weaning off catheter may be higher in females thus causing a bias in the results. Initially, we wanted to analyse the male and the female participants separately. However, as the numbers were fewer than expected, we combined the analysis.

The main weakness of our project is the small sample size. Also, day 1 may not be the exact day the patient first developed ARU as several days may have lapsed with IDC or IMC being started before randomisation was done. The use of two consecutive PVRU of less than 100 ml as the definition of success in weaning off catheter was arbitrary. If more stringent values were used, the success rate could have been lower. Also, we should have done randomisation at a single source rather than at the ward level. This could have avoided the chance of a marked difference in the number of men included in the study (5 men in the 200 ml group and 13 men in the 300ml group). The medications of participants were not recorded. It would be useful as medications with anticholinergic properties and alpha blockers, in males who may have prostatic hypertrophy, may affect the success in weaning off IMC.

CONCLUSION

We conclude that PVRU of 200 ml or 300 ml are both reasonable cut-off values prior to performing IMC. However, further prospective randomised-controlled trials addressing the limitations of this project may provide a higher level of evidence to inform practice in the future.

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Factors associated with diarrhoea among infants with low-birth-weight history in Indonesia

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ABSTRACT

Introduction: Diarrhoea is one of the leading causes of infant mortality and morbidity. Infants with low-birth weight (LBW) have a higher risk of diarrhoea due to their low immunity and nutritional status issues.This study aimed to analyze the factors associated with diarrhoea in infants with LBW in Indonesia.

Materials and methods: We used cross-sectional and secondary data from the 2017 Indonesia Demographic and Health Survey (IDHS). A total of 142 infants under 1 year were selected as the respondents. Chi-square test and binary logistic regression were used to examine factors associated with diarrhoea in infants with LBW in Indonesia.

Results: There are several factors more likely to increase the incidence of diarrhoea in infants with LBW, which are living in rural areas [OR = 5.65, 95% CI = 1.08–29.5] and having internet access less than the last 12 months (OR = 13.03, 95% CI = 1.48–114). Meanwhile, factors more likely to decrease the incidence of diarrhoea in infants with LBW, which are maternal age (20–24 years old) [odds ratio (OR) = 0.07, 95% CI = 0.01–0.98], cell phone ownership (OR = 0.08, 95% CI= 0.01–0.45), and the use of feeding bottles (OR = 0.22, 95% CI = 0.05–0.92).

Conclusion: This study highlights that maternal age, cell phone ownership, internet access, area of residence, and use of feeding bottles are significant factors associated with diarrhoea in infants with LBW. Health workers must enhance health education related to those factors through the Community Integrated Child Health Service (Posyandu) programs.

KEYWORDS:
Diarrhoea, infant, low birth weight, Indonesia

INTRODUCTION

More than 98% of neonatal mortality occurs in developing countries, with infections (32%) being one of the leading causes.[1] For example, in one rural area of the Belagavi district in India, the incidence of morbidity during the first year of life for neonates is still high at 14-18 episodes per year. Diarrhoea, among others, is a cause of morbidity, and it was found that the incidence of diarrhoea in the 12th month of infant age is about 0.25/infant/year.[2] In 2017, diarrhoea as an infectious disease was the leading cause of mortality in children. It kills around 480,000 children worldwide.[3] It is also the second leading cause of death in children after pneumonia, which has infected 1.7 billion children and caused the death of 525,000 children worldwide.[4] Children aged three experience about three times more diarrhoeal infections.[5] Morbidity during infancy, caused by diarrhoea, might impact an infant's growth and development.[2] Furthermore, a history of chronic diarrhoea is the most dominant risk factor for childhood stunting.[6]

Neonatal mortality is still a prevalent health issue in Indonesia. The country's infant mortality rate is 32/1000 live births, whereas the neonatal mortality rate is 19/1000.[7] The infant mortality rate in Indonesia in 2015 was 25 per 1000 live births. Although the data saw a decreasing trend compared to the previous years, the infant mortality rate in Indonesia is still relatively high compared to ASEAN member countries, which is 4.6 times, 1.3 times, and 1.8 times higher than Malaysia, the Philippines, and Thailand, respectively.[8] Infant mortality from all causes and hospitalizations were significantly higher among LBW infants compared to normal birth weight, and diarrhoea was the major cause of hospital admission and death.[9,10]

One of the factors associated with infant morbidity is low-birth weight (LBW).[2] Babies with LBW have morbidity and mortality due to infectious diseases caused by immune disorders and are at increased risk of growth failure.[11] Several studies have shown a regular pattern of increasing childhood disease in low-birth-weight children, especially in the first 2 years of life.[12] Infants with LBW experience infectious diseases more often, such as diarrhoea and acute respiratory infection (ARI), which tend to be longer and more serious (and therefore require hospitalization) compared to normal-birth weight infants.[13] Nutritional status was significantly related to the incidence of diarrhoea. The frequency of diarrhoea increased by 15% per standard deviation of the decrease in the height-for-age z-score. Episodes of diarrhoea in children <6 months last significantly longer than the episodes among older children.[14]

Many factors predispose children under five to develop diarrhoea, especially in low- and middle-income countries. A study in Kenya shows that the mother/caregiver's education level and residence area affect the incidence of diarrhoea. The prevalence of diarrhoea is higher in infants living in

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rural areas. The education of mothers/caregivers showed a considerable significance in the prevalence of diarrhoea. It was revealed that mothers/caregivers who cannot read have a higher prevalence of diarrhoea than those who have attained higher education.[15] Meanwhile, a study in Nigeria found that the age and gender of the baby did not show a significant relationship with the incidence of diarrhoea in children. The mother's educational status and occupation, and family income are significantly related to the incidence of diarrhoea in Southwest Nigeria.[16]

However, studies focusing on diarrhoea in infants with a history of LBW in Indonesia are still relatively scarce. Identifying the factors related to the incidence of diarrhoea in infants with a history of LBW is essential to formulate a better intervention strategy so that policymakers can consider them to reduce the prevalence of diarrhoea in Indonesia. With that rationale, this study was conducted to analyze the factors associated with diarrhoea in infants with LBW in Indonesia.

MATERIALS AND METHODS

Data source

This study used data from the 2017 Demographic Health Survey, conducted in Indonesia and employed a cross-sectional design. Interviews during the survey were conducted on all eligible women aged 15–49 years. In this study, the children's dataset was used. This study was conducted from July 24 to September 30, 2017, by a collaboration of the National Population Planning Board (BKKBN), Statistics Indonesia (BPS), and the Indonesia Ministry of Health (Kemenkes) with technical assistance from the Inner City Fund (ICF). Once registration was completed through the website, all datasets were downloaded from www.dhsprogram.com.

Sample size and sampling

The 2017 IDHS covered 1970 census blocks in urban and rural areas in Indonesia. 49,627 women aged 15–49 completed the survey and were interviewed across 34 provinces in Indonesia. The sample designs of this survey were two-stage probability samples drawn from an existing sample frame. The master sample of Census Blocks from the latest population census was used as the sampling frame. The two-stage stratified sampling was utilized to select the participants. The first stage was the selection of several census blocks by systematic sampling proportion size. In the second stage, 25 ordinary households were selected with systematic sampling from the listing. There were 142 children under one year old who met the inclusion criteria and were included as respondents in this study. Inclusion criteria in this study were infants under 1-year-old with a history of low-birth weight.

Instruments and data collection

The questionnaire was administered to females of child-bearing age to obtain information from those between 15 and 49 years of age. Questionnaire items consisted of respondents' background, history of pregnancy, contraception usage and knowledge, childbirth, post-childbirth examination, breastmilk, child feeding, infant mortality, childhood immunizations and diseases, marriage and sexual activities, fertility preference, spouses' background, respondents' occupation, knowledge on HIV/AIDS and other sexually transmitted infections, mother's sibling mortality, and other health issues. The selection of independent variables for the study was based on previous studies examining factors affecting children's diarrhoea. The dependent variable in this study is the incidence of diarrhoea. The data were based on the mother's perception of the baby two weeks before the survey. Meanwhile, there are several independent variables, namely: mother's age; area of residence; mother's education; father's education; television ownership; cell phone ownership; internet access; economic status; the number of children in the family; and the rest of independent variables, which are infants who have received breastfeeding; use of feeding bottles; baby gender; and vitamin A supplements.

Statistical analysis

Statistics analysis in this study is univariate analysis; chi-square tests and logistic regression were performed with a final report of odds ratio (OR) and 95% confidence intervals (CI). Stata version 14 is used in all of the analyses.

Ethics

The 2017 IDHS received ethical approval from the Inner City Fund's Institutional Review Board (ICF IRB). In addition, an ethical license was also obtained from the Indonesian Ministry of Health. Permission to use data was obtained from ICF International as part of the Demographic Health Survey program.

RESULTS

In 26 (18.31%) of the 142 infants who had LBW, diarrhoea had occurred within 2 weeks before the survey was conducted. 48 (33.80%) of the mothers who were interviewed and completed the study were in the 25 to 30 years age range. In more than half, 84 (59.15%) of the mothers interviewed had lived in rural areas, and 83 (58.45%) mothers had completed secondary education. With regards to father's education, 88 (61.97%) of the fathers had completed secondary education. 46 (32.39%) respondents were classified as very poor, and 94 (66.20%) respondents had less than three children. Out of 142 respondents, more than two-thirds, 111 (78.17%) owned a television at home, 100 (70.42%) had a cell phone, and 85 (59.86%) had internet access. Regarding the infants, 74 (52.11%) were female. In the majority of the studied infants, 114 (80.28%) received breast milk, whilst less than half, 65 (45.77%) received vitamin A supplements, and only 55 (38.73%) had used milk bottles. More details about the descriptive characteristics of respondents are presented in Table I.

Based on the bivariate analysis results, three independent variables, television ownership, breastfeeding, use of feeding bottles, and father's education, were identified as having a significant relationship with the prevalence of diarrhoea in LBW infants in Indonesia. Details about the bivariate analysis are shown in Table II. In the multivariate analysis, binary logistic regression was used to analyze the dependent and independent variables (Table III). The results of the multivariate analysis showed that the mother's age, area of residence, cell phone ownership, internet access, and use of feeding bottles were significantly associated with the

Table I: Socio-demographic characteristics of participants

Characteristics	Frequency	Percentage
Mother's age		
15–19	13	9.15
20–24	31	21.83
25–30	48	33.80
31–35	29	20.42
36–39	11	7.75
40–45	10	7.04
Area of residence		
Urban	58	40.85
Rural	84	59.15
Mother's education		
Primary	38	26.76
Secondary	83	58.45
Higher	21	14.79
Father's education		
No education	3	2.11
Primary	36	25.35
Secondary	88	61.97
Higher	15	10.56
Television ownership		
Yes	111	78.17
No	31	21.83
Cell phone ownership		
Yes	100	70.42
No	42	29.58
Internet access		
Yes, before last 12 months	4	2.82
Yes, last 12 months	53	37.32
No	85	59.86
Economic status		
Very poor	46	32.39
Poorer	41	28.87
Middle	23	16.20
Richer	32	22.54
Number of children in the family		
≥3 children	48	33.80
<3 children	94	66.20
Breastfeeding		
Yes	114	80.28
No	28	19.72
Use of feeding bottles		
Yes	55	38.73
No	87	61.27
Sex of the baby		
Male	68	47.89
Female	74	52.11
Vitamin A		
Yes	65	45.77
No	77	54.23
Diarrhoea		
Yes	26	18.31
No	116	81.69

prevalence of diarrhoea in infants in Indonesia. According to the results of this study, infants of mothers aged 20-24 are 0.07 times less likely to develop diarrhoea than other ages [Odds Ratio (OR) = 0.07, 95% CI = 0.01–0.98]. Infants living in rural areas are 5.65 times more likely to develop diarrhoea than those in urban areas [OR = 5.65, 95% CI = 1.08–29.5]. Infants whose mothers had cell phones are 0.08 times less likely to develop diarrhoea (OR = 0.08, 95% CI= 0.01–0.45). Interestingly, infants whose mothers have internet access for less than 12 months are 13.03 times more likely to develop diarrhoea (OR = 13.03, 95% CI = 1.48–114). Lastly, the use of feeding bottles in infants is 0.22 times less likely to develop diarrhoea (OR = 0.22, 95% CI = 0.05-0.92). Details of the results of the multivariate analysis are shown in Table III.

DISCUSSION

Diarrhoea is the second morbidity after ARI for LBW in the first 6 months of life.[13] The survey results in India support that the history of LBW births is associated with an increased incidence of diarrhoea by 19%.[17] This result supports our finding that by 26 of 142 (18.31%), we found LBW infants suffered from diarrhoea. Gedefaw and Berhe explained that low-birth weight is one of the determining factors of diarrhoea, partly because babies with low-birth weight have an immunocompromised immune system that makes them susceptible to various infections, including diarrhoea and pneumonia.[18] This is because premature infants with LBW have lower immunoglobulin G (IgG) levels than term infants. IgG begins to be transferred from the mother to the fetus at

Table II: Bivariate analysis of factors associated with diarrhea among infants with LBW history

Characteristics	No		Yes		X^2
	N (116)	%	N (26)	%	
Mother's age					0.126
15-19	8	6.90	5	19.23	
20-24	26	22.41	5	19.23	
25-30	43	37.07	5	19.23	
31-35	23	19.83	6	23.08	
36-39	7	6.03	4	15.38	
40-45	9	7.76	1	3.85	
Area of residence					0.110
Urban	51	43.97	7	26.92	
Rural	65	56.03	19	73.08	
Mother's education					0.584
Primary	29	25.00	9	34.62	
Secondary	69	59.48	14	53.85	
Higher	18	15.52	3	11.54	
Father's education					0.008
No education	2	1.72	1	3.85	
Primary	23	19.83	13	50.00	
Secondary	79	68.10	9	34.62	
Higher	12	10.34	3	11.54	
Television ownership					0.005
Yes	96	82.76	15	57.69	
No	20	17.24	11	42.31	
Cell phone ownership					0.116
Yes	85	73.28	15	57.69	
No	31	26.72	11	42.31	
Internet access					0.723
Yes, before last 12 months	3	2.59	1	3.85	
Yes, last 12 months	45	38.79	8	30.77	
Never	68	58.62	17	65.38	
Economic status					0.199
Very poor	33	28.45	13	50.00	
Poorer	36	31.03	5	19.23	
Middle	20	17.24	3	11.54	
Richer	27	23.28	5	19.23	
Number of Children in the Family					0.718
≥3 children	40	34.48	8	30.77	
<3 children	76	65.52	18	69.23	
Breastfeeding					0.024
Yes	89	76.72	25	96.15	
No	27	23.28	1	3.85	
Use of Feeding Bottles					0.07
Yes	49	42.24	6	23.08	
No	67	57.76	20	76.92	
Sex of the baby					0.529
Male	57	49.14	11	42.31	
Female	59	50.86	15	57.69	
Vitamin A					0.966
Yes	53	45.69	12	46.15	
No	63	54.31	14	53.85	

the 17th week of gestation, and at the 33rd week, fetal IgG levels are similar to maternal and will increase up to two times at term.[19]

The Indonesian government's program to address the health of children under five is the Community Integrated Child Health Service for Children under Five (also known as Posyandu Balita). The Community Integrated Child Health Service (Posyandu) is very integral in the promotive and preventive efforts for the community, especially in improving the nutritional status and maternal and child health issues.[20] At the Posyandu, there is already a preventive program to improve children's health. However, it is still necessary to increase health monitoring in infants with a history of LBW. This study may provide essential new information to mothers so that their babies can be healthy and, in the worst-case scenario, only suffer from mild diarrhoea.

According to the results of this study, infants with a history of LBW from mothers aged 20–24 years are 0.07 times less likely to develop diarrhoea. Based on the results of a study conducted in Nepal, it was found that maternal age is associated with the incidence of diarrhoea in infants.[15] In Indonesia, most women marry for the first time at 19–24. This marriage age has a strong relationship with fertility, so usually, most women give birth at this age.[21] The age of 19–20 years is considered an adult age who already has maturity in terms of physical and psychological growth, meaning they

Table III: Multivariate analysis of factors associated with diarrhoea among infants with LBW history

Characteristics	Adjusted odds ratio	95% Conf. interval	
Mother's age		Lower	Upper
15-19	1		
20-24	0.07*	0.01	0.98
25-30	0.02	0.00	0.28
31-35	0.23	0.03	2.23
36-39	0.63	0.05	7.93
40-45	0.03	0.00	1.90
Area of residence			
Urban	1		
Rural	5.65*	1.08	29.5
Mother's education			
Primary	1		
Secondary	2.88	0.62	13.3
Higher	5.36	0.30	95.6
Television ownership			
Yes	0.29	0.05	1.67
No	1		
Cell phone ownership			
Yes	0.08**	0.01	0.45
No	1		
Internet access			
Yes, before last 12 months	0.05	0.00	2.70
Yes, last 12 months	13.03*	1.48	114
No	1		
Economic status			
Very poor	1		
Poorer	1.12	0.17	7.45
Middle	0.95	0.09	9.85
Richer	1.72	0.21	14.1
Number of children in the family			
≥3 children	1		
<3 children	1.39	0.27	7.12
Breastfeeding			
Yes	3.28	0.24	44.8
No	1		
Use of feeding bottles			
Yes	0.22*	0.05	0.92
No	1		
Father's education			
No education	1		
Primary	12.84	0.16	1058
Secondary	0.52	0.01	35.6
Higher	1.08	0.01	128.9
Sex of the baby			
Male	1		
Female	2.08	0.54	7.99
Vitamin A			
Yes	1.49	0.45	4.93
No	1		

* p value < 0.05.
** p value < 0.01.

already have the maturity and mental strength, thinking ability, and ability to understand so that they can provide adequate care for their baby. This is supported by research stating that delaying the age at first birth for women in their early 20s might reduce infant mortality and improves child health. Overall, the risk of a poor health outcome dissipates by age 21.[22]

Infants with LBW who live in rural areas have a 5.65 times greater risk of suffering from diarrhoea than infants in urban areas. This result is supported by previous studies, in which the incidence of diarrhoea is also higher in infants living in rural areas than those in urban areas.[15,23,24] Many factors can cause babies living in rural areas to have a higher incidence of diarrhoea-environmental and individual factors play an essential role in it. Wambui explained that these conditions are associated with several factors: lack of safety access, inadequate water consumption, household water supplies, water storage methods, knowledge about hygienic activities and infectious disease prevention and control practices, and poor use of restrooms. For example, in rural areas, it was reported that the people do not have handwashing facilities in their baths, which contributes to diarrhoea.[15] The quality of environmental health is one of the factors that gives the most significant role to public health. Aspects of environmental health include access to clean water, access to

proper basic sanitation, waste management, and disease vectors. In Indonesia, environmental problems are still a problem. According to the research results, environmental factors significantly affect diarrhoea incidence. The majority of diarrhoea events by 77.8% occur in houses whose floors are not waterproof, by 73.9% occur in houses with family latrines that do not meet health requirements, by 47.1% occur in houses without sewerage meet the requirements, by 83.3% occur in improper household waste processing, and by 68.8% occurs in inadequate clean water availability.[25]

Infants with LBW from mothers who have cell phones are less likely to develop diarrhoea; meanwhile, infants with LBW whose mothers have had internet access for less than the last 12 months are more likely to have diarrhoea. As we all know that cell phones and internet access are essential needs for society. The Indonesian Ministry of Communication and Informatics stated that Indonesia's internet users had reached 82 million people, making Indonesia rank 8th globally.[26] Cell phones and internet access make it easier for a mother to quickly and accurately look up information through materials and articles on various subjects.[27] The study results showed that parents' benefits are getting parenting support (e.g., accessing information on parenting via the internet or social media) and connecting with their children.[28]

Infants with LBW fed using feeding bottles are 0.22 times less likely to develop diarrhoea than those without. This result might be that mothers with low birth weight babies are more exposed to health services from the beginning. This happens because the LBW baby will usually be hospitalized in the perinatology room for the stability of his condition. Mothers will receive health education about the baby's condition and care for babies with LBW. In Indonesia, this health education is packaged as discharge planning, carried out from admission until the patient leaves. The health education contains kangaroo mother care, nutrition for LBW infants (including preparation and use of feeding aids such as feeding bottles), and infection prevention. With this program, mothers have adequate knowledge and skills in providing nutrition for premature babies. This is supported by research on health education in discharge planning that can increase mothers' knowledge and skills in caring for premature babies at home.[29] It is also supported that education programs that are carried out regularly and continuously can provide information according to the needs of parents so that they can help parents to understand the information conveyed.[30] The information is about breastfeeding benefits, techniques, kangaroo mother care, infection prevention, and infant danger signs.[31]

CONCLUSION

Mother's age between 20–25, rural area of residence, cell phone ownership and internet access for less than the last 12 months, and the use of feeding bottles were found to have a significant relationship with the incidence of diarrhoea in infants with a history of LBW. The practical implications of our findings support increasing the awareness of LBW infants' families through adequate health education and promotion. Therefore, enhancing health information and services adequacy, accessibility, and affordability across all Indonesian regions is essential. Moreover, health workers also need to improve the administration of health education to the mothers of babies with LBW, who are at risk of developing diarrhoea, through Posyandu programs.

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ORIGINAL ARTICLE

Moving from long case to scenario-based clinical examination: Proposals for making it feasible

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ABSTRACT

Introduction: Our faculty used one long case (LC) and three short cases for the clinical component of the final professional examinations. During the COVID-19 pandemic, the LC had to be replaced with scenario-based clinical examination (SBCE) due to the impracticability of using recently hospitalised patients. While keeping the short case component as usual, the LC had to be replaced with SBCE in 2020 for the first time at a short notice. To evaluate the positive and negative aspects of SBCE and LC to determine the feasibility of replacing LC with SBCE in future examinations.

Materials and methods: We compared the LC scores of three previous years with those of the SBCE and studied the feedback of the three stakeholders: students, examiners, and simulated patients (SPs), regarding their experience with SBCE and the suitability of SBCE as an alternative for LC in future examinations.

Results: The SBCE scores were higher than those of the LC. Most of the examiners and students were not in favour of SBCE replacing LC, as such. The SPs were more positive about the proposition. The comments of the three stakeholders brought out the plus and minus points of LC and SBCE, which prompted our proposals to make SBCE more practical for future examinations.

Conclusion: Having analysed the feedback of the stakeholders, and the positive and negative aspects of LC and SBCE, it was evident that SBCE needed improvements. We have proposed eight modifications to SBCE to make it a viable alternative for LC.

KEYWORDS:
SBCE, scenario-based clinical examination, issues of long case, simulated patients

INTRODUCTION

Many medical schools use real-patient long case (LC) for examinations because of the longstanding tradition, its availability, and face validity. However, many western medical schools have moved away from real-patient LC, alleging it to be low in validity, reliability, and objectivity,[1] and replaced it with Objective Structured Clinical Examination and Objective Structured Long Examination Record (OSLER).[2,3] In the pandemic year of 2020, The Faculty of Medicine and Health Sciences, UNIMAS used Scenario-Based Clinical Examination (SBCE) with simulated patients (SPs) for history-taking to replace LC, as already practised by others.[4,5] The short cases tested physical examination (PE) without any changes. Our SBCE could be compared to OSLER with the exception that the former did not assess PE. The expected first response of any experienced clinical examiner would be a 'no' for the prospect of SBCE replacing LC. The traditional LC assesses the student's clinical acumen, soft skills, PE skill, depth of knowledge of multiple conditions, and drug effects. At the same time, SBCE assesses the students' history-taking skill and the knowledge domain using written scenarios and SPs. The aim of this study was to consider all the positive and negative aspects of LC and SBCE in order to determine the practicality of moving from LC to SBCE in future examinations.

MATERIALS AND METHODS

The SBCE scenarios for the final professional examination (FPE) of the year 2020 were written, and SPs were trained by the same disciplines as those regularly involved in the previous years' LC examinations. The disciplines involved were medicine, surgery, obstetrics and gynaecology (O&G), paediatrics, orthopaedics, and psychological medicine. Some examples of the topics used in the scenarios were bronchial asthma, acute rheumatic fever, anaemia, acute cholecystitis, breast cancer, antepartum haemorrhage, and gestational diabetes. The students were briefed in advance about the process of the SBCE. The lead question, based on which the history was to be taken, was provided to the student 5 minutes before entering the examiners' room, where the SP was also seated. Five teams, each with three examiners from different disciplines, assessed the students' performance. The examiners were provided with the relevant scenarios, the information to be gathered by the students, the diagnosis, and the likely clinical signs and investigation results. Each student took the history from the provided SP to reach a diagnosis and possible differential diagnoses. The examiners observed the 15-minute history-taking session uninterruptedly. During the following 30-minute discussion segment, the student presented the case summary with the diagnosis and/or differential diagnoses and answered the examiners' questions. The questions included the likely physical findings, how the diagnosis was reached, the interpretation of investigation results provided, and a management outline. The Medical Education Unit (MEU) had prepared new marking rubrics for the SBCE. It showed the

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Table I: The students' responses to the questionnaire

Students (all the 106 responded)		
Questions	**Options and responses**	**Comments**
1. Your experience with the just completed SBCE—SR	Liked it—M3 S7 P2 OG7 OR1=20 (18.87%) It was a nerve-wrecking experience—M12 S9 P6 OG6 OR1 Psy7 = 41 (38.68%) It was fair—M12 S14 P5 OG9 OR5 Psy0 = 45 (42.45%)	• SBCE does not assess clinical skills, but communication skills • Some students may take more time to organise their thoughts • SBCE is good for focussed history-taking • SBCE is very different from real patients; it is good for exam purposes. It should not replace LC entirely • SBCE is good enough to replace LC, but students need more exposure to it before the exam • The time allocation is enough only for focused history • SBCE is a textbook presentation, so it is easier than LC • Real patients are very complex with multiple issues and drug side effects. • It will be easy to create many SBCEs for practice • LC is classical, and it cannot be replaced with SBCE fully • SBCE needs quick thinking, and it will be good to have more exposure to it. • SBCE is more challenging, as it needs quick decision making. It may be the way forward • SBCE demands more thorough thinking to form the differential diagnoses • In SBCE, we need to clerk in English. It creates problem, as we tend to use medical jargon • LC focusses on history, PE, DD. In SBCE, the discussion becomes more theoretical • It will be challenging for slow-thinking students • The SPs having medical background was helpful • Real patients talk irrelevant things, but SBCE is focussed • SBCE is structured and straight to the point, unlike LC • The lead question in the scenario was too broad • The scenario should be clearer and more direct • Real patients come with multiple problems unlike SBCE • The success of SBCE depends on how well-trained the SPs are • The SP fumbled and was slow to answer • Facing lecturer as SP was nerve wrecking. But it will be OK with more practice • Clerking under observation is intimidating, but it tests the communication skills • Scenarios were straightforward in surgery, but complex cases were given medicine. • There is a risk for students training among themselves rather than going to hospital to see patients • Students need more practice on targeted history-taking • Psychiatry cases need more time
2. Should SBCE replace LC in future—SR	SBCE is better than LC—32 (30%) SBCE should not replace LC—10 (10%) Can be used only in Covid-like situations—64 (60%)	
3. History-taking while being observed by examiners—SR	It did not affect me—35 (34%) It made me nervous – —62 (58%) It affected my performance considerably—9 (8%)	
4. Your opinion about using SPs for SBCE—MR	SPs are better than real patients—46 (43.4%) SPs misled the students sometimes—8 (7.5%) I was nervous to face lecturers as SP—28 (26.5%) SP fumbled while answering my questions—8 (7.6%) SPs need more training—15 (14%)	
5. Regarding time allocation for history-taking session—SR	It was sufficient—68 (64%) It was insufficient—38 (36%) It was too long—0	
6. Rate your satisfaction with the SBCE process 1–10—SR	1 – 1 6 - 15 2 – 1 7 - 24 3 – 5 8 - 27 4 – 3 9 - 13 5 – 12 10 – 5 Mean 7.04	

DD = differential diagnoses, G = O&G, LC = long case, M = medicine, MR = multiple response, P = paediatrics, PE = physical examination, R = orthopaedics, S = surgery, SBCE = scenario-based clinical examination, SR = single response, Y = psychological medicine.

criteria for unsatisfactory, borderline, satisfactory, and excellent performance in each domain, such as history, diagnosis, investigation, and management (80%), communication skills (10%), and global assessment (10%). The MEU compiled the marks and prepared the results.

The first part of the study was to compare the scores of the previous 3 years' LC with the score of the SBCE. The second part of the study was to conduct short surveys among the three stakeholders using semi-structured questionnaires. The three questionnaires were written and vetted by the authors. Each questionnaire contained four to six questions—eliciting single or multiple 'tick responses' and free comments, which

Table II: The examiners' responses to the survey questionnaire

Examiners—16 responded – M5 S3 G5 P2 R1 Y0		
1. Regarding the just completed SBCE—SR	• It is better than LC—2 (12.5%) • It can safely replace LC – 4 (25%) • Suitable only in a covid-like situation – 8 (50%) • It is inferior to LC – 2 (12.5%)	• SPs were not quite well trained; need fine tuning; need to instruct them which history to give spontaneously and which, when asked • The SBCE scenarios were not well designed, rather artificial. • SBCE should be a temporary alternative for the much better real-patient LC. • I still prefer traditional LC. However, SBCE is adequate to replace it in special times. • SBCE is fixed and closed type of assessment. In long term, students may catch up with the questions we ask, and it will be difficult to differentiate good and weak students. • Physical examination is lacking in SBCE. • LC has more varieties. Even same disease has personal variations, management can be different. • SBCE marking scheme is rigid with no flexibility • Question stem given to the candidate is too generous providing a clue on the diagnosis • It is good enough to replace LC. • SBCE—work in progress • Very artificial. Perhaps only good for history. It is too easy for weak students to excel. Someone whom I would have given a bare pass, now able to achieve near distinction marks. It is not a good way of grading, too structured • One advantage of SBCE is the inclusion of emergency cases, not possible in LC, e.g. gastrointestinal bleeds or infectious diseases. This is useful for testing overall knowledge. • The distribution of marks seems to be arbitrarily decided; must be discussed by a panel • Taking history right under examiners' nose may put extra stress on the student. • Clinical examination in a LC cannot be compensated by short cases, as they differ widely. • SBCE can replace formal LC. • SBCE marking is more objective compared to LC • We should replace LC with SBCE. It's quite difficult to move patients from hospital to examination centre. • SBCE is not on par with LC. More pressure for students to ask SPs compared to real patients. • Definitely, SPs cannot replace actual patients. For example, in the surgical scenario of cholecystitis, student asked SP the urine colour. He answered deep yellow; deep yellow like what? SP answered, like tea. The LFT result did not show obstructive picture, which threw students off. It's just not real.
2. Regarding the scenarios used in SBCE—SR	• They were adequate – 4 (25%) • Only some of them were adequate – 7 (43.75%) • More care and thoughts should be given while writing scenarios—5 (31.25%)	
3. Regarding the SPs—MR	• Satisfied with their performance – 12 (75%) • They did not perform well—0 • They need more training – 4 (25%) • Some of them were distracting to the students—0	
4. Regarding the marking scheme—MR	• It was done nicely—11 (69%) • It was confusing and difficult to follow—1 • It needs improvement—4 • It was too wordy and confusing—0	
5. Rate your satisfaction with SBCE 1 – 10—SR	4-1 6-5 7-5 8-3 9-1 10-1 Mean 6.2	

DD = differential diagnoses, G = O&G, LC = long case, M = medicine, MR = multiple response, P = paediatrics, PE = physical examination, R = orthopaedics, S = surgery, SBCE = scenario-based clinical examination, SR = single response, Y = psychological medicine.

the respondents volunteered. Due to the time constraint, no formal questionnaire validation could be done. The respondents comprised 106 students, 16 examiners, and 18 SPs, who answered the questionnaires soon after the FPE with no incentives provided. We analysed the responses and feedback and arrived at the conclusions based on the results.

Ethics approval was obtained from Faculty Medical Ethics Committee, Universiti Malaysia Sarawak (UNIMAS), Sarawak, REF: FME/21/71. Informed consent was obtained from the participants. The methods were carried out in accordance with the country's guidelines and regulations.

RESULTS

There was no strong support from the students for SBCE replacing LC, although some considered SBCE better than LC. A quarter of them felt that it was a nerve-wrecking experience, especially to face lecturers as SPs. Majority of them opined that SBCE was suitable only in special situations. History taking under observation affected the performance of only 8% of the students. Nearly half of the respondents felt that the SPs were better than patients for giving the history. A few of the students complained about the SPs fumbling or misleading them. Thirty-six percent of them expressed that the time allocation for the history session was insufficient. The mean overall rating given by them for the SBCE was 7.04 (Table I).

Half of the examiners opined that the SBCE was unsuitable to replace LC, while a quarter of them expressed that it could safely do so. The general opinion about the scenarios was that they needed refinement and more care in their preparation. The majority of the examiners were satisfied

Table III: The simulated patients' responses to the survey questionnaire

Standardised patients: 18 (all doctors)		
1. Your discipline in SBCE—SR	M3, S6, P2 R2, G3, Y2	• SPs also need to know how the students are marked • SPs need to know how much info to reveal and when to reveal them • Professional training is needed • SBCE is better than LC, as real patients often deviate from the point • Patient is always better • SPs sometimes forced to fabricate the answers, as they do not have the entire details of the cases • SBCE is an effective method for focussed history-taking • It is easier to grade students in SBCE, because the key points are fixed. That way, it is very different from LC • Real patients, unlike SBCE, do not come with textbook presentations • Assessment of soft skills, like handling the patients, is missing in SBCE • SBCE being a role play, SPs need a lot of information about the case
2. Regarding the training and information given—SR	• It was sufficient – 14 (78%) • It was insufficient – 4 (22%)	
3. Your experience of being an SP—MR	• Enjoyed – 15 (83%) • I would not like to do it again – 0 • I had to cook-up some answers—1 • I would like to do it again—1 • It was stressful—1	
4. Rate your satisfaction with the SBCE process 1 – 10—SR	5-1 8-5 6-3 9-7 7-1 10-1 Mean 7.94	
	Mean of 3 groups = 7.06	

DD = differential diagnoses, G = O&G, LC = long case, M = medicine, MR = multiple response, P = paediatrics, PE = physical examination, R = orthopaedics, S = surgery, SBCE = scenario-based clinical examination, SR = single response, Y = psychological medicine.

Table IV: Descriptive statistics of LC and SBCE scores of the four FPEs

YEAR of FPE	*N*	Minimum	Maximum	Mean	SD	*p* value
1. 2017 LC	112	5.00	15.60	11.82	1.74	$p<0.01$**
2. 2018 LC	118	8.00	17.00	11.46	2.08	$p<0.001$***
3. 2019 LC	1 22	8.00	17.00	11.81	1.74	$p<0.01$**
4. 2020 SBCE	106	7.25	17.60	12.56	2.32	-

p value reached from independent sample t-test.
*$p<.05$, **$p<.01$, ***$p<.001$.

with the marking scheme used, while some asked for changes to make it more user-friendly. The mean overall rating given was 6.2 (Table II).

The majority of the SPs were satisfied with the training given to them, and they enjoyed the experience. Several pertinent points for improvement were mentioned in their comments. The mean overall rating given by them was 7.06 (Table III).

Comparison of the scores (out of 20) of LC and SBCE in the four FPEs

Table IV depicts the scores of LC and SBCE for 4 years. Analysis revealed that the mean score of SBCE was higher than those of the previous 3 years' LC. The independent sample t-test revealed that the mean difference was statistically significant between years 2017 and 2020 [$t(df)=2.652(216)$, $p<0.01$)]. Similar differences were found also between years 2018 and 2020 [$t(df)=3.792$ (222), $p<0.001$)] and years 2019 and 2020 [$t(df)=2.765(226)$, $p<0.01$)].

DISCUSSION

We admit upfront that SBCE could be an efficient tool only for observed and focused history-taking and viva voce to assess the student's cognitive domain and communication skills.

The survey results and feedback have brought out the plus and minus points of both SBCE and LC. It was encouraging to note that the stakeholders' overall rating for SBCE was a satisfactory 7.06.

The students who expressed that the time allocation for the SBCE history session was insufficient might be those who faced the psychological medicine and medicine scenarios, which, some students commented, were complex, while the surgical scenarios were straightforward. A good number of students opined that history-taking from SPs was better than doing it from real patients. Experiencing nervousness during examinations and the apprehension of facing lecturers as SPs all on a sudden for the first time was understandable. Such issues could be minimised in the future by more training and exposure by making SBCE part and parcel of the training and assessment. The positive feedback about SBCE could be attributed to the plus points of SBCE, such as being structured, observed by examiners, shorter than LC, assessing communication skills, and the possibility to include scenarios about emergencies. Most of the negative comments about SBCE were explainable by the hurried manner in which it was executed. More thorough vetting of the scenarios, making them focused, and giving more detailed instructions to the SPs could improve the efficacy.

The examiners' displeasure with SBCE was evident in most of their feedback. They were divided in their opinion about the suitability of SBCE to replace LC altogether. Most of the examiners were satisfied with the performance of the SPs, although they advocated more training and preparations for them. Some examiners observed that the SPs being doctors could tackle the students' unexpected questions properly without fumbling and misleading. We admit that the concerns expressed by the examiners were legitimate, and that they pointed out the areas that needed more attention. Some pertinent suggestions made by the SPs were: it would be good for SPs to be informed about the marking scheme, have more details about the case, and know when to reveal and when to withhold information. A downside of the LC mentioned was that the patients often deviated from the points, and that SBCE, being structured, was an efficient method for focused history-taking. Most of the shortcomings they mentioned were explainable by the fact that it was the first experience of SBCE for all of them.

SBCE has been criticised for being theoretical, not testing PE, not challenging enough for good students to perform, and not being well validated.[4,5] All these drawbacks were also observed in our study. Many of the students' comments highlighted these issues: "SBCE assesses communication skills, not clinical skills"; "It is textbook presentation, not challenging like real patients"; "Real patients have multiple problems, including drug side effects"; "SBCE discussion is theoretical"; "The SP's performance is vital for the success of SBCE"; "The scenarios in surgery were straightforward, while those in medicine were complex". Some of the examiners' comments in this regard were also pointing to such shortcomings of SBCE: " Some scenarios were artificial, only good for history taking"; "It is too easy for weak students to excel"; SBCE is a 'fixed and closed' type of assessment"; "PE is lacking in SBCE, and short cases cannot compensate for it"; "Some scenarios were too generous with clues to the diagnosis"; "It is more stressful for students to talk to SPs". Our FPEs assessed sufficient PE skills, as each student took three short cases from medical and surgical disciplines. Therefore, we considered our SBCE could be exempted from PE. We also realised that the construction of scenarios needed expertise, multidisciplinary vetting, and meticulous training of the SPs to avoid flaws.[6]

The student performance in LC and SBCE was comparable, with a higher mean score in SBCE. This trend was observed in other studies also.[6] Our LCs were not observed by examiners as in other studies.[1] SBCE offered the advantage of being observed. The element of luck in LC, as mentioned in other studies[1] could be halved in SBCE by doubling it to two sessions for each student in future, as pointed out in another study.[7] This change would make it more challenging and allow good students to excel, as they would take one SBCE from medical and another from surgical disciplines. Making the viva sessions shorter would make SBCE less of a theoretical discussion. LC patients becoming inconsistent and fatigued, causing problems for students, was pointed out in one study.[8] The feedback corroborated this point, which could be eliminated in SBCE. Students' opportunities to experience multiple SBCEs during their training would be useful. The practice of focused history-taking would improve the clinical acumen of students, as mentioned by several authors[9-12] and would also likely reduce their nervousness in facing lecturers as SPs.

Organising LC for a large batch of students was labour-intensive, expensive, and had inherent limitations. Getting sufficient number of patients was often impossible, leading to multiple repetitions. Patients, especially those taken from a referral hospital, as in the case of our faculty, were bound to be unstructured, inconsistent, and unreliable for an objective assessment. They were often too complicated with multiple pathologies and unsuitable for undergraduates. These issues were reflected in the feedback, too. Prior vetting of patients by examiners was practised in our FPEs, but it could not be detailed enough due to time constraints. The element of luck for students was unavoidable, as they performed only one LC. Examiners did not observe the 1-hour LC. LC has been acclaimed as a superior assessment, as it involved real-life situations [13], which could assess the real calibre of students. However, it would be impractical to use real patients for a large batch of students, as expressed by other authors.[14] LC being a significant contributor to the final scores in the FPE, it is important to eliminate the bias, as stressed in another study [14] In this regard, the SBCE would offer a practical solution, as it would enable to double the assessment by testing the students with two SBCEs in 1 hour. This would be possible by reducing the viva voce segment to 10 minutes from the current 30 minutes. Expanding the assessment to reduce case bias and examiner bias is very important for high stake examinations, as pointed out in another study.[14] A modified SBCE would meet these demands.

LIMITATIONS

This study encountered several limitations. First, it was planned at a short notice, as the faculty's decision to substitute LC with SBCE in the FPE of the year 2020 was a compromise due to the COVID-19 pandemic, which did not allow the use of real patients for the traditional LC, safely. Second, the survey questionnaires were arbitrarily prepared and not systematically validated. Third, this study involved only one cohort. The results cannot be generalised to other universities. Fourth, external examiners could not participate due to travel restrictions of the pandemic. It is recommended that any future study should validate the survey questionnaires, as required.

CONCLUSION

Some students, a few examiners, and most SPs were optimistic about the feasibility of an improved SBCE replacing the LC. Based on the survey results highlighting the limitations of LC and the advantages of SBCE, we recommend the following modifications in SBCE to make it a more reliable and valid assessment: (a) Make the 15-minute history-taking session focused, (b) shorten the viva-voce session to 10 minutes, and make it structured (c) test each student with two scenarios from different disciplines assessed by different examiners, (d) give students prior exposure to SBCE, (e) prepare focused and flawless scenarios, (f) fix the examiner questions for each scenario, beforehand (g) prepare structured, and objective marking schemes befitting each scenario, and (h) use medical professionals as SPs.

CONFLICTS OF INTEREST
None of the authors declared conflicts of interest.

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ORIGINAL ARTICLE

Perceived changes in symptoms and quality-of-life amongst patients with dizziness: A single-centre experience in Malaysia

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ABSTRACT

Introduction: Dizziness is a common complaint by patients, yet it always presents as a diagnostic challenge to the attending clinician. An accurate diagnosis is essential to correctly administer the precise treatment regime, alleviate the symptoms, and improve the quality-of-life of patients who present with dizziness. A specialised vestibular clinic with a holistic approach of meticulous history-taking, complete physical examination, a collection of audio-vestibular test battery, and facilities for vestibular rehabilitation was set up to assist in the management of these patients. This study aims to investigate the effect of vestibular clinic intervention on the symptoms and quality-of-life of patients who were managed in the vestibular clinic.

Materials and methods: A total of 64 new patients who were managed in the vestibular clinic were selected and the validated Malay – Vestibular Rehabilitation Benefit Questionnaire (My-VRBQ) was completed during the first and follow-up visits to measure the changes in symptoms and quality-of-life before and after receiving care at the vestibular clinic.

Results: Our study showed that there was a positive effect of vestibular clinic intervention on the symptoms and quality-of-life of patients who were managed by the vestibular clinic. Statistically significant improvements were seen in the total My-VRBQ scores, symptoms scores, and quality-of-life scores. The subscale scores of dizziness, anxiety, and motion-provoked dizziness also showed statistically significant improvement among the patients who received care at the vestibular clinic.

Conclusion: This indicates that the vestibular clinic was an essential part of the work-up, diagnosis, and treatment of patients with dizziness; and a specialised vestibular clinic was able to bring about positive outcomes in the symptoms and quality-of-life of patients with balance disorders.

KEYWORDS:
Dizziness, quality-of-life, vestibular diseases, vestibular function tests

INTRODUCTION

Dizziness is defined as a non-specific complaint of unsteadiness and imbalance which can originate from disorders of many systems including the peripheral vestibular system, central nervous system, and cardiovascular system.[1] Dizziness can be broadly classified based on four main presenting complaints, namely; syncope or near syncope, disequilibrium, vertigo, and light headedness.[2]

It is a symptom that affects about 15% to 20% of adults yearly in large population-based studies. Its prevalence rises with age and is about two to three times higher in women than in men.[3] For Malaysia, a retrospective review of 100 walk-in patients at a specialized neurotology clinic in dizziness at a tertiary centre showed that 66% out of 100 patients who presented with dizziness were caused by peripheral vestibular causes.[1]

However, despite its prevalence, many patients with dizziness were unable to be accurately diagnosed and the treatment for these conditions have been limited to vestibular sedatives and anti-emetics. This leads to persistent symptoms, over-dependence on the medications, and limitation to the quality-of-life of patients who suffer from dizziness. In order to facilitate the diagnosis and management of patients with dizziness in an accurate and timely manner, the specialized vestibular clinic in Sultan Ahmad Shah Medical Centre @International Islamic University Malaysia (SASMEC @IIUM) was set up in 2019.

Studies have shown that patients suffering from dizziness showed a markedly reduced physical and mental health-related quality-of-life.[4] Therefore, the purpose of this study is to assess the effectiveness of vestibular clinic intervention in improving the perception of dizziness and quality-of-life of patients with dizziness, justifying the time and resources invested in setting up specialised vestibular clinic slots and facilities for objective testing.

MATERIALS AND METHODS

The Vestibular Rehabilitation Benefits Questionnaire (VRBQ) was validated by a group of patients who had undergone vestibular rehabilitation and was found to be sufficiently

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responsive even to small measures of improvement.[5] The Malay translation of the VRBQ, the My-VRBQ; had been validated by Mohtar et al and was found to be internally reliable.[6] The My-VRBQ is a self-reporting questionnaire that consists of 22 questions, divided into part A which focuses on the experienced symptoms (11 questions) and part B which focuses on the effect to the quality-of-life of the patient (11 questions). The questions on symptoms were further subdivided into three subscales, namely; the dizziness (three questions), anxiety (three questions), and motion-provoked dizziness subscales (five questions) to examine the profile of the patient in more detail. There were seven possible responses to each question and these answers correlate with a specific score (0 to 6 for symptoms scores and –6 to 6 for quality-of-life scores).

Patients with complaints of dizziness were selected using universal sampling from the population of patients who attended the Vestibular Clinic in SASMEC @IIUM. Demographic data were gathered from their medical records. All patients were subjected to a holistic approach of meticulous history-taking and complete physical examination in the assessment of patients with dizziness, with an emphasis on otorhinolaryngological, postural blood pressure, cardiovascular, and neurological examinations; complemented by a series of clinical tests like the Dix Hallpike test, Supine roll test, screening for spontaneous nystagmus, head impulse test, head-shake test, oculomotor test, and gait test. Patients were subsequently subjected to an audio-vestibular test battery which includes pure tone audiometry, video head impulse test (vHIT), and video nystagmography test (VNG). Caloric tests, colic-vestibular evoked myogenic potentials (cVEMP), and imaging studies were applied to patients who were indicated for these investigations. After arriving at a diagnosis, the treatment was subsequently tailored to the underlying cause of dizziness. For benign paroxysmal positional vertigo (BPPV), the treatment is by the various canal repositioning manouvres depending on the semicircular canal involved. Vestibular migraine was managed mainly by lifestyle changes which includes dietary control, i.e. avoidance of coffee, chocolates, food with monosodium glutamate; and observing regular sleep, exercise and meal times. Vestibular neuritis was treated with vestibular sedatives like oral prochlorperazine 5 mg when necessary and referral for vestibular rehabilitation. The management of Meniere's disease includes oral betahistine dihydrochloride 24 mg twice daily for 2 weeks with a low-salt and caffeine-free diet. For the other diagnoses which were mostly due to central causes of dizziness, a contrast-enhanced computed tomography scan of the brain and referral to the neurology colleagues for subsequent management were done.

The My-VRBQ were given to patients to be filled after a written consent was obtained during the initial visit, and the post intervention My-VRBQ questionnaire was given at the first follow-up visit at 2 weeks from the initial visit to collect information on the perceptual changes of dizziness and quality-of-life among the patients. There were no dropouts in this study as all patients answered both pre- and post-intervention My-VRBQ questionnaires.

The My-VRBQ scores were subsequently calculated and analysed. Descriptive analysis was performed to examine the scores obtained in the My-VRBQ questionnaire done by the patients before and after vestibular clinic intervention. Statistical analysis was performed to examine the effect of vestibular clinic intervention on the My-VRBQ scores using repeated measures ANOVA. Further analysis was done to examine the relationships between the age, gender, diagnoses, co-morbidities, and the number of visits to the vestibular clinic required to achieve diagnosis among the sample population in relation to the My-VRBQ scores before and after vestibular clinic intervention.

This research was approved by the International Islamic University Malaysia Research Ethics Committee (IREC) with the approval project ID: IREC 2021-109.

RESULTS

A total of 64 samples were obtained among new patients who presented with dizziness and attended the Vestibular Clinic at Sultan Ahmad Shah Medical Centre @IIUM.

The age of the study population ranges from 22 to 80 years old, with a mode of 50 years old, median of 56 years old, and mean age of 53.59 with standard deviation of 14.76. With regards to gender distribution, most of the patients in our study population were females (45, 70.31%) while 19 were males (29.69%).

BPPV remains the most frequent diagnosis encountered with 42 patients (65.63%). This is followed by other diagnoses with eight patients (12.50%), vestibular migraine with seven patients (10.94%), vestibular neuritis with four patients (6.25%), and Meniere's disease with three patients (4.69%). Among the diagnoses encountered in the other diagnoses were other central causes like ischemic stroke (4 patients), acoustic neuroma (1 patient), labyrinthitis (1 patient), and mal de debarquement syndrome (1 patient). Upon running the repeated measure ANOVA analysis, the diagnosis of the patients does not play a significant role in the changes in the My-VRBQ scores before and after receiving care at the vestibular clinic.

A third of the patients in our study do not have any co-morbidities (21 patients, 32.81%). The most associated co-morbidity is hypertension (15 patients, 23.44%), followed by diabetes mellitus (eight patients, 12.50%) and ischaemic heart disease (three patients, 4.69%).

Forty-seven patients in our study were diagnosed within a single visit to the vestibular clinic, equivalent to 73.44%. Another 10 patients required two visits to the vestibular clinic before diagnosis was achieved (15.63%). Only 7 patients (10.94%) required more than two visits to the vestibular clinic before a diagnosis can be achieved.

As shown in Table I and Figure 2, all parts and subscales of the My-VRBQ showed improvement as evidenced by the reduction in scores after patients received care at the vestibular clinic. Among the symptom's subscales, dizziness showed the most improvement as seen by the highest

Table I: Pre- and Post-My-VRBQ scores for each part and subscale of My-VRBQ

Parts and subscales	Pre-My-VRBQ scores				Post-My-VRBQ scores			
	Min	Max	Mean	Standard Deviation	Min	Max	Mean	Standard Deviation
Symptoms	7.60	74.50	41.14	16.01	0	69.92	24.24	17.57
Quality-of-life	0	82.10	20.38	20.13	0	69.90	9.41	14.70
Dizziness	16.68	100.08	54.15	18.96	0	100.08	31.88	23.59
Anxiety	0	66.72	26.50	18.07	0	61.16	18.07	17.41
Motion-provoked dizziness	0	111.2	42.24	25.24	0	80.16	23.75	21.79
Total	12.71	103.97	42.36	19.96	0	106.28	23.35	19.57

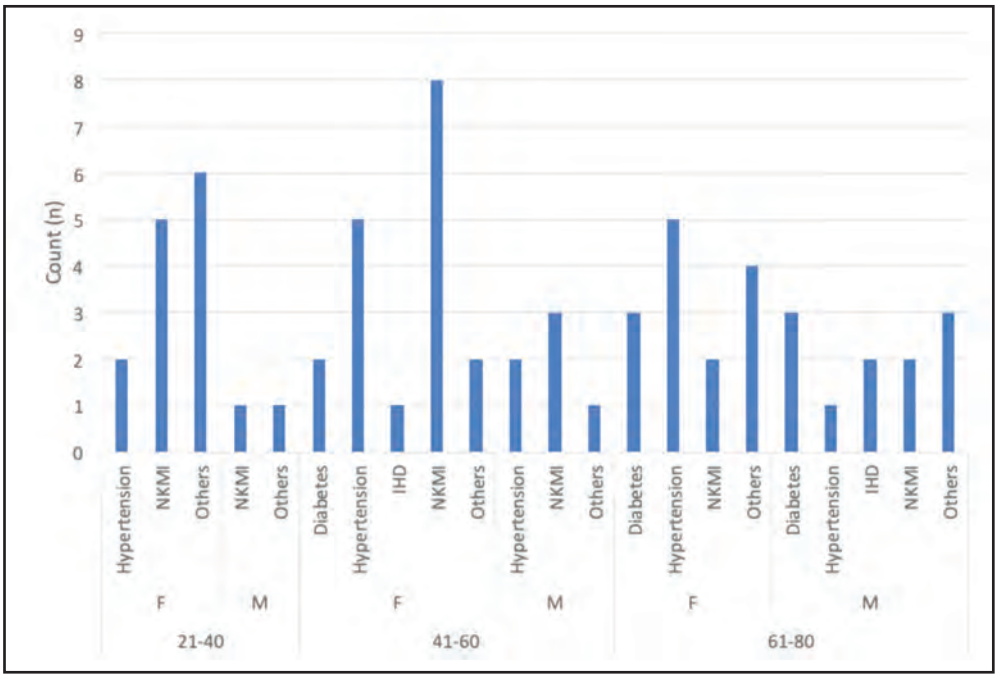

Fig. 1: Patients' age group, gender and co-morbidities. (F = Female, M = Male, NKMI = No known medical illness, IHD = Ischemic heart disease. Others include hyperlipidaemia, bronchial asthma, and stroke)

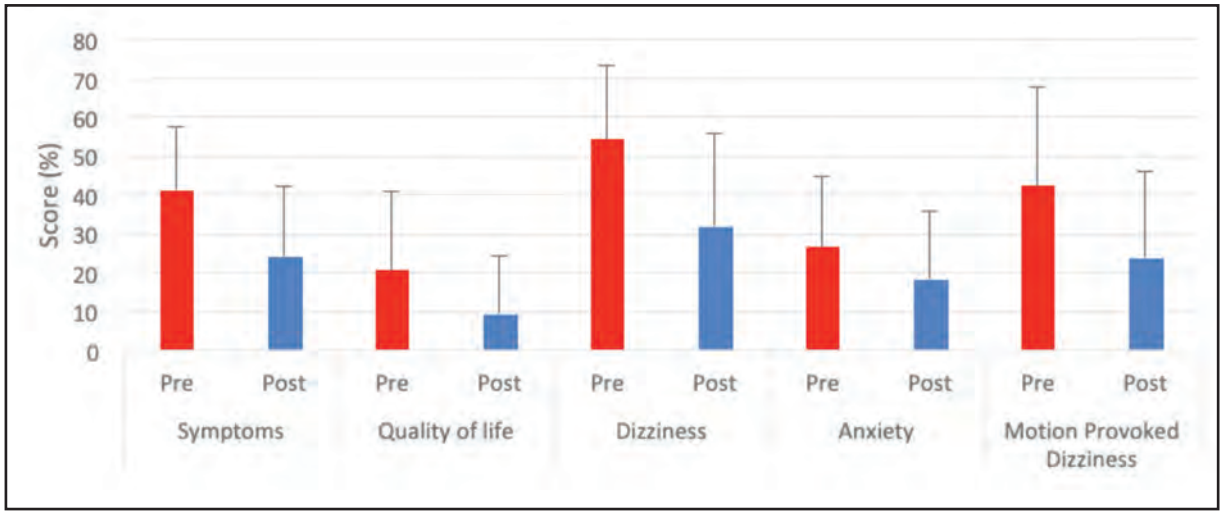

Fig. 2: Pre- and Post-My-VRBQ scores for patients who received care in the vestibular clinic

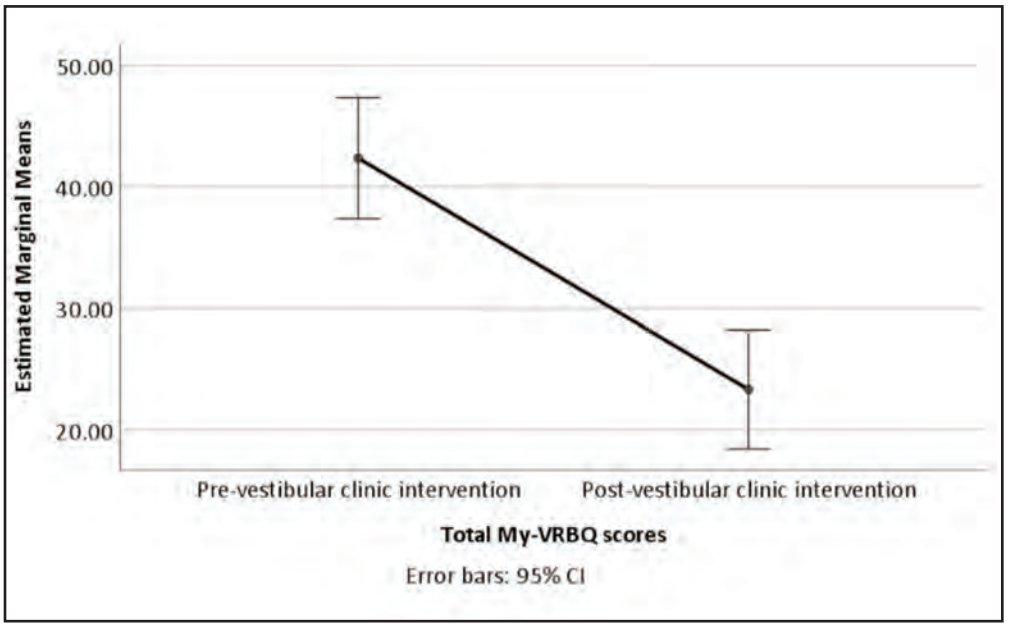

Fig. 3: Effect of vestibular clinic intervention on Total My-VRBQ scores.

reduction in the mean scores. The scores for the sample population before and after vestibular clinic intervention were analysed using repeated measures ANOVA. Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated, and therefore, a Greenhouse-Geisser correction was used. There was a significant effect of vestibular clinic intervention on symptoms scores where, $F(1,63) = 45.96$, $p<0.05$. With regards to the quality-of-life scores, there was a significant effect of vestibular clinic intervention on quality-of-life scores where, $F(1,63) = 17.01$, $p<0.05$.

Upon analysing the subscales, for the dizziness scores, there was also a significant effect of vestibular clinic intervention on dizziness scores where $F(1,63) = 48.70$, $p<0.05$. Statistical analysis on the anxiety scores also showed a significant effect of vestibular clinic intervention on anxiety scores where $F(1,63) = 15.49$, $p<0.05$. There was also a statistically significant change observed between the age groups on anxiety scores as determined by one-way ANOVA ($F(2,61) = 3.168$, $p = 0.049$). A Tukey post hoc test revealed that the mean change was statistically significant after taking the age group of 41 to 60 years old (3.94 ± 14.43) and comparing them to the 21 to 40 years old group (17.42 ± 20.46). There was no statistically significant difference between the 61 and 80 years old group when compared to 21 to 40 years old and 41 to 60 years old groups.

There was a significant effect of vestibular clinic intervention on motion-provoked dizziness scores where $F(1,63) = 28.21$, $p<0.05$, and on total My-VRBQ scores where, $F(1,63) = 38.65$, $p<0.05$. For the total overall My-VRBQ scores, male patients gained higher mean scores before vestibular clinic intervention (44.38 ± 22.83) while female patients gained higher mean scores after vestibular clinic intervention (24.27 ± 20.12). Applying the independent samples t test, on average, men showed significantly more improvement in total My-VRBQ scores compared to women ($t(62) = -2.85$; $p < 0.05$).

We found no significant effect of the different diagnoses, co-morbidities and number of visits to the vestibular clinic, with vestibular clinic intervention on the changes in My-VRBQ scores.

DISCUSSION

The mean age of our study population is 53.59, and most of our patients (39.06%) were between the age group of 61 to 80 years old. This corresponds to a Turkish validation study of the VRBQ questionnaire in which the mean age of the sample population is 47.33 ± 12.18 years.[7] Closer to our centre, a study in a tertiary hospital in Malaysia reported that about 88% of patients in their study were above the age of 40 with the mean age among males 53.1 years old and females 51.6 years old.[1] The results of our study showed that there was a significant association between the age of patients with vestibular clinic intervention on the anxiety scores changes, particularly when comparing between 21 and 40 years old age group and 41 to 60 years old age group. Before vestibular clinic intervention, the mean anxiety score was the highest among the 21 to 40 years old group (34.84 ± 12.86), followed by 41 to 60 years old group (26.87 ± 19.51) and 61 to 80 years old group (21.13 ± 17.94). A study in Germany concurs that anxiety about bodily sensations was found to be higher in younger patients than in older patients.[8]

With regards to gender, 70.3% of the study population were females while 29.7% were males, resulting in the ratio for male to female of 1:2.37. This roughly corresponds to a study in a Multidisciplinary Dizziness Clinic in Canada which reported that 66.4% of the patients were females and 33.6% were males.[9] In Malaysia, a study in a tertiary centre also reported predominantly female patients, accounting for 62.4% of the total patients.[10] However, our study showed that men had significantly more improvement in total My-VRBQ scores compared to women.

BPPV is the most prevalent diagnosis among these patients, accounting for 65.63% of the patients, followed by vestibular migraine (10.94%). This corresponds to that reported in another study, which states that the prevalence of BPPV is about 17 to 42% among patients with vertiginous symptoms.[11] A study in the UK reported that vestibular migraine was the second most common cause of vertigo with a lifetime prevalence of 3.2% in the general population.[12] In Malaysia, a study in a tertiary centre showed that BPPV was the most prevalent diagnosis, followed by Meniere's disease.[10] We concur with the study in Switzerland which showed that specialized neuro-otological assessment was able to help in the diagnosis of balance disorders; in particular, BPPV and vestibular migraine which were frequently under-diagnosed.[13] For the total overall my-VRBQ scores prior to vestibular clinic intervention, patients with vestibular neuritis experienced the worst symptoms and effect on their quality-of-life as their mean score was the highest (48.52 ± 19.94).

The United States National Health & Nutrition Examination Survey found that there were significant associations between the prevalence of vestibular dysfunction by cardiovascular risk characteristics. Heavy tobacco use (20 pack-years and more), hypertension, and diabetes were associated with higher rates of vestibular dysfunction.[14] In our study, 23.44% of patients had hypertension, 12.50% of patients had diabetes mellitus, and another 4.69% had ischemic heart disease. Patients with ischemic heart disease had the highest total overall my-VRBQ scores before (44.86 ± 31.53) and after (46.28 ± 30.51) vestibular clinic intervention. This finding was consistent with a report in the United States of America which concluded that 63% of patients with primary cardiovascular disorders experienced vertigo.[15] However, our inferential analysis revealed that the co-morbidities of the patients do not play a significant role in the changes in the My-VRBQ scores before and after vestibular clinic intervention. In fact, some patients' symptoms worsened despite receiving care from vestibular clinic. This was most likely due to the symptoms of dizziness being confounded by both the primary diagnosis and the co-morbidity of ischemic heart disease. In our study, one patient with underlying ischaemic heart disease with the diagnosis of BPPV showed an improvement in the total My-VRBQ score by 24.26 (pre-vestibular clinic intervention score of 77.40 and post-vestibular clinic intervention score of 53.14, 31.34% improvement), while another patient with underlying ischaemic heart disease with the diagnosis of vestibular migraine showed worsening of the total My-VRBQ score by 30.04 (pre-vestibular clinic intervention score of 42.74 and post-vestibular clinic intervention score of 72.78, worsening by 70.27%). While there is an association between migraine and ischaemic heart disease,[16] there is no published papers yet on the association between vestibular migraine and ischaemic heart disease which may explain the worsening of the total My-VRBQ score in this patient, compared to the patient with ischaemic heart disease and BPPV. Therefore, there is a need to evaluate the potential changes in the My-VRBQ scores among patients with co-morbidities on a case-to-case basis.

Most patients in our study required only one visit to the vestibular clinic to achieve their diagnosis (73.44%). It was not surprising that patients who required more than two visits to the vestibular clinic prior to achieving diagnosis had the highest mean of the total My-VRBQ scores before vestibular clinic intervention at 43.84 ± 21.31 while the patients who required a single visit to the vestibular clinic prior to achieving diagnosis had the lowest mean of the total My-VRBQ scores at 41.91 ± 20.36. There were no studies which analysed the number of visits required to achieve a diagnosis, but we published a paper from our clinic which revealed that 79% of patients who attended the vestibular clinic required only one visit before a diagnosis can be made, which is consistent with our current findings.[17]

CONCLUSION

Based on our observation, there was a positive effect of vestibular clinic intervention on the symptoms and quality-of-life of patients as evidenced by statistically significant improvements seen in all of the parts and subscales of the My-VRBQ questionnaire. Therefore, more dedicated vestibular clinics should be set up in Otorhinolaryngology departments to assist in the diagnosis and management of patients who present with dizziness. We recommend a vestibular clinic set-up which includes meticulous history taking and complete physical examination; complemented by a series of clinical tests like the Dix Hallpike test, Supine roll test, screening for spontaneous nystagmus, head impulse test, head-shake test, oculomotor test, gait test; and at least a basic audio-vestibular test battery which includes pure tone audiometry, vHIT, and VNG. We trust that this set-up will be able to benefit patients in terms of improvements in symptoms of dizziness and their overall quality-of-life.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest with regards to the publication of this article.

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ORIGINAL ARTICLE

Left ventricle geometry, atrial strain, ventricle strain, and hemodynamics across aortic valve before and after transcatheter aortic valve replacements

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ABSTRACT

Introduction: Transcatheter aortic valve replacements (TAVRs) has become widespread throughout the world. To date, there are no echocardiographic studies of TAVR patients from Southeast Asia (SEA). We sought to evaluate (1) changes in echocardiographic and strain values pre- and post-TAVR (2) relationship between aortic stenosis (AS) severity and strain values, (3) left ventricle geometry in severe AS, (4) relationship of flow rate to dimensionless index (DVI) and acceleration time (AT), and (5) effect of strains on the outcome.

Materials and methods: Retrospective study of 112 TAVR patients in our centre from 2009 to 2020. The echocardiographic and strain images pre (within 1 month), post (day after), and 6 months post-TAVR were analyzed by expert echocardiographer.

Results: The ejection fraction (EF) increased at 6 months (53.02 ± 12.12% to 56.35 ± 9.00%) (p=0.044). Interventricular septal thickness in diastole (IVSd) decreased (1.27 ± 0.21 cm to 1.21 ± 0.23 cm) (p=0.038) and left ventricle internal dimension in diastole (LVIDd) decreased from 4.77 ± 0.64 cm to 4.49 ± 0.65 cm (p=0.001). No changes in stroke volume index (SVI pre vs 6 months p=0.187), but the flow rate increases (217.80 ± 57.61 mls/s to 251.94 ± 69.59 mls/s, p<0.001). Global longitudinal strain (GLS) improved from −11.44 ± 4.23% to −13.94 ± 3.72% (p<0.001), left atrial reservoir strain (Lar-S) increased from 17.44 ± 9.16% to 19.60 ± 8.77% (p=0.033). Eight patients (7.5%) had IVSd < 1.0 cm, and 4 patients (3.7%) had normal left ventricle (LV) geometry. There was linear relationship between IVSd and mean PG (r=0.208, p=0.031), between GLS to aortic valve area (AVA) and aortic valve area index (AVAi) (r = – 0.305, p=0.001 and r= – 0.316, p= 0.001). There was also relationship between AT (r=-0.20, p=0.04) and DVI (r=0.35, p<0.001) with flow rate. Patients who died late (after 6 months) had lower GLS at 6 months. (Alive; -13.94 ± 3.72% vs Died; -12.43 ± 4.19%, p=0.001).

Conclusion: At 6 months, TAVR cause reverse remodelling of the LV with the reduction in IVSd, LVIDd, and improvement in GLS and LAr-S. There is a linear relationship between GLS and AVA and between IVSd and AVA.

KEYWORDS:
Echocardiography, aortic stenosis, transcatheter aortic valve replacement, global longitudinal strain, Southeast Asia

INTRODUCTION

Since it was first performed in 2002 by Alan Cribier and his team, transcatheter aortic valve replacement (TAVR) for severe aortic stenosis (AS) has become widespread worldwide.[1] Its usage has expanded rapidly from the inoperable to intermediate and most recently to low-risk patients.[2-4] Echocardiography is one of the main tools for assessment of patients with severe AS either in general or pre and post TAVR. As far as we are aware, there is no published data from Southeast Asian (SEA) patients with most studies from this region coming from South Korea and Japan.[5-7] With the advent of speckle tracking strain analysis, there were few publications from western countries looking at the changes in strain parameters pre- and post-TAVR and again there are no published data from SEA countries.[8-10] In this study of multi-racial patients in a single centre, Institut Jantung Negara (National Heart Institute), Kuala Lumpur, Malaysia, we sought to evaluate (1) immediate and 6 months changes in traditional echocardiographic and strain parameters, (2) relationship between these echocardiographic and strain parameters with AS severity, (3) pattern of left ventricle wall thickness and geometry pre-TAVR, (4) whether acceleration time (AT) and dimensionless index (DVI) is affected by flow rate, and finally (5) relationship of echocardiography and strain parameters to mortality.

MATERIALS AND METHODS

This is a single-centre retrospective study of patients with severe AS who underwent TAVR in our institution from 2009 to 2020.

Echocardiographic data

All the echocardiographic images from pre (up to 1-month pre-procedure), immediately (1-day post-procedure) and at 6 months post-procedure were analyzed. These duration for echocardiography is applied routinely for patients undergoing TAVR in our centre. We excluded those with incomplete images or those not suitable for interpretation

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(three patients excluded due to inadequate baseline images). For traditional echocardiographic parameters of left ventricle, we analyzed interventricular septal thickness at diastole (IVSd), left ventricle internal dimension at diastole (LVIDd), posterior wall thickness at diastole (PWTd), biplane Simpsons' ejection fraction (EF), and relative wall thickness (RWT). For aortic valve, we calculated aortic valve area (AVA), aortic valve area index (AVAi) from continuity equation, peak velocity (Vmax), mean gradient (meanPG), AT, AT/ejection time (AT/ET) and DVI across aortic valve. Lastly, we calculated the stroke volume index (SVi), flow rate (stroke volume/ET across left ventricular outflow tract), peak tricuspid regurgitation gradient (TRpeak PG), systolic pulmonary artery pressure (s-PAP), and left atrial volume index (LAVI).

Strain analysis

We analyzed strain by using Tom Tec software retrospectively by using apical four chamber view, apical three chamber view, apical two chamber view for global longitudinal strain (GLS), apical 4 chamber view for left atrial reservoir strain (LAr-S), left atrial conduit strain (LAc-S), and left atrial booster strain (LAbooster-S). For right ventricle free wall strain (RVFW-S), we used right ventricle focused apical four chamber views.

Statistical analysis

The categorical variables were presented as percentage and the continuous variables were presented in terms of mean and standard deviations. Repeated measures ANOVA were used to compare differences between groups at different time points with a Greehouse-Geisser correction and post hoc analysis of Bonferroni correction where applicable. The linear association between variables was determined using Pearson correlation coefficients. p values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS ver. 27.0 (SPSS, Chicago, IL, USA).

RESULTS

There was n=112 patients included in the study (female;57 and male; 55). The average age was 77.97 ± 5.01 years old. 45.5% (n=51) were Malay, 22.3% (n=25) were Chinese, 22% (n=19.6) were Indian, 5.4% (n=6) were of other races from Malaysia and 7.1% (n=8) were patients from other countries. The procedures were done with both self-expandable and balloon expandable TAVR valves. There are two procedure failures, and both are caused by left ventricle (LV) perforations. Overall, 6 (5.4%) patients died in the hospital and 7 (6.3%) patients died within 6 months of procedure (Total 6 months mortality was 13 patients,11.6%). 34 (30.4%) patients died after 6 months, and 64 (57.1%) patients are still alive. One patient was lost to follow-up after the procedure. Therefore, they were 98 patients that have complete echocardiographic and strain data until 6 months post-procedure (34 who died after 6 months plus 64 that is still alive). 12 (10.7%) patients need pacemaker implantations. Pre-procedure, most patients are in NYHA II (48.2%) and III (28.6%), and at 1 month, majority of patients are in NYHA I (83.9%). Immediately post procedures majority of patients have mild paravalvular (83.9%) and mild transvalvular (86.6%) regurgitation (Table I).

At 6 months post-TAVR, AVA increased from 0.68 ± 0.19cm^2 to 2.02 ± 0.73cm^2 (p<0.001), peak aortic velocity went down from 4.45 ± 0.64 m/s to 2.06 ± 0.59 m/s (p<0.001), and mean PG came down from 49.94 ± 13.53 mmHg to 9.49 ± 6.09 mmHg (p<0.001). Interestingly, there were no significant changes in SVi (46.42 ± 13.71 mls/m2 to 49.00 ± 13.95 mls/m^2; p=0.187) although the flow rate increased significantly to upper limit of normal (217.80 ± 57.61 mls/s to 251.94 ± 69.59 mls/s; p<0.001) (Table II)

For other echocardiographic parameters at 6 months, EF increased from 53.02 ± 12.12% to 56.35 ± 9.00% (p=0.004). Both IVSd and LVIDd reduced significantly (IVSd; 1.27 ± 0.21 cm to 1.21 ± 0.23 cm, p=0.022 and LVIDd; 4.77 ± 0.64 cm to 4.49 ± 0.65 cm, p<0.001). As expected, AT decreased from 120.00 ± 26.33 ms to 75.98 ± 16.82 ms (p<0.001) and DVI increased from 0.21 ± 0.06 to 0.60 ± 0.17 (p<0.001). There were no significant changes in PWTd (p=0.136), RWT (p=0.831), LAVI (p=0.183), and s-PAP (p=0.772) immediately and at 6 months (Table II).

From analysis of speckle tracking strain, both GLS and LAr-S had significant overall improvement at 6 months (GLS; from -11.44 ± 4.23% to -13.94 ± 3.72%, p<0.001 and LAr-S from 17.44 ± 9.16% to 19.60 ± 8.77%, p=0.033). This was interesting as LAVI did not change significantly post-TAVR. There were no significant changes in left atrial conduit strain (LAc-S, p=0.326), left atrial booster strain (LA booster, p=0.562), and RVFW-S (p=0.543). There was a greater relative increase in GLS compared to EF (21.85% vs 6.28%) and relative increases in LAr-S were more than relative to decreases in LAVI (12.39% vs 5.38%). Patients who died after 6 months had lower GLS at 6 months (-12.43 ± 4.19% vs -13.94 ± 3.72%, p=0.001) (Table II). We also analyzed the bull's eyes appearance of the GLS for apical sparing define by: (Average apical GLS/ (Average basal GLS + average mid GLS)> 1. However, none of our patients fulfilled those criteria.

We performed linear regression analysis to evaluate the relationship between pre-TAVR IVSd and strain with AS severity. IVSd had moderate but significant direct relationship with MeanPG (r=0.208, p=0.031) and AVA (r=0.239, p=0.013). GLS had stronger and significant inverse relationship with AVA (r=-0.305, p=0.001) and AVAi (r=-0.316, p=0.001) while RVFW-S had weak but significant inverse relationship with AVAi (r=-0.179, p=0.041) (Table III, Figure 1a to 1d). AT had significant inverse relationship with flow rate (r=-0.199, p=0.040) and DVI had significant direct relationship with flow rate (r=0.347, p<0.001) (Table III, Figure 1e). We also found 4 patients (3.74%) to have had normal LV geometry followed by eccentric hypertrophy, n=13 (12.15%) and concentric remodelling, n= 23 (21.5%). Majority had concentric hypertrophy=67 (62.62%) (Figure 2a). 8 patients (7.5%) had IVSd < 1.0cm while 13 patients (12.1%) had PWTd < 1.0cm (Figures 2b and 2c).

DISCUSSION

This study involved 112 severe AS patients from different ethnicities in Malaysia, a country in SEA where there is no existing published data about echocardiographic and strain parameters pre- and post-TAVR procedures. As expected, the

Table: I Demographics, TAVR patient characteristics, and outcomes

Variables		TAVR (N = 112)
	Demographics	
Age, mean ± SD	77.97 ± 5.01	
Female; N (%)	57 (50.9)	
Race group	Malay; N (%)	51 (45.5)
	Chinese; N (%)	25 (22.3)
	Indian; N (%)	22 (19.6)
	Other Malaysian; N (%)	6 (5.4)
	Foreigner; N (%)	8 (7.1)
	TAVR Patient Characteristics	
Valve type	Corevalve; N (%)	37 (33.0)
	Corevalve Evolut-R; N (%)	26 (23.2)
	Edwards Sapien; N (%)	13 (11.6)
	Edwards Sapien 3; N (%)	23 (20.5)
	Edwards Sapien XT; N (%)	10 (8.9)
	Myval; N (%)	3 (2.7)
	Outcomes	
In-hospital death; N (%)		6 (5.4)
Follow up	Death ≤ 6 months; N (%)	7 (6.3)
	Death > 6 months; N (%)	34 (30.4)
	Lost to follow-up; N (%)	1 (0.9)
	Alive; N (%)	64 (57.1)
Pacemaker implantation; N (%)		12 (10.7)
NYHA pre-procedure	I; N (%)	17 (15.2)
	II; N (%)	54 (48.2)
	III; N (%)	32 (28.6)
	IV; N (%)	9 (8.0)
NYHA post-procedure at 1 months	I; N (%)	94 (83.9)
	II; N (%)	7 (6.3)
	III; N (%)	1 (0.9)
	IV; N (%)	0 (0)
Post-procedure paravalvular regurgitation	None; N (%)	14 (12.5)
	Mild; N (%)	94 (83.9)
	Moderate; N (%)	3 (2.7)
	Severe; N (%)	1 (0.9)
Post-procedure transvalvular regurgitation	None; N (%)	14 (12.5)
	Mild; N (%)	97 (86.6)
	Moderate; N (%)	1 (0.9)
	Severe; N (%)	0 (0)

AVA increased while peak aortic velocity and meanPG decreased significantly, immediate and at 6 months post-TAVR. In term of EF, our patients showed significant improvements post-TAVR, like previous publications involving patients of different races[11-15]. Next, we analyzed the changes in IVSd, LVIDd, and PWTd pre- and post-TAVR. Like TAVR, there are echocardiographic studies in surgical aortic valve replacement patients showing significant regression of these parameters.[16,17] For TAVR patients, however, most of the studies utilize cardiac magnetic resonance imaging rather than echocardiography to demonstrate reverse remodeling[18-20]. In this study, there were significant reductions in IVSd and LVIDd at 6 months post-TAVR but there were no differences in PWTd and RWT. Flow (volume of blood ejected in a single heartbeat per body surface) and flow rate (volume of blood ejected per second) are different parameters. There is one prior study that illustrates how TAVR improves SVi[21], but we could not find any publication looking at flow rate post-TAVR. In our study, we found that the SVi did not increase significantly but flow rate increased almost 16% from baseline.

Prior studies tend to look at a single aspect of strain, but in this study, we analyzed almost all aspects of strain. There were many prior publications showing improvement in GLS after TAVR procedures, thus suggesting that baseline GLS can be predictive of outcome.[8-10,22] Our study showed no improvement in GLS immediately post-TAVR, but significant improvement (21.9%) at 6 months post-AVR. The relative improvements in GLS were much higher than in EF (21.85% vs 6.28%). There was no difference in baseline GLS between those who died after 6 months versus those who did not, but patients who were still alive exhibited higher GLS at 6 months post-TAVR. Studies on LAr-S, LAc-S and LAbooster-S in TAVR are rare but published data did show improvement in LAr-S post-TAVR.[23,24] In our study, LAr-S did not increase immediately but only improved at 6 months post-TAVR (relative increase of 12.4%). There was no significant difference in LAc-S and LAbooster-S post-TAVR. Lastly, there are many different parameters of RV function, but RVFS-S has been suggested as single best parameter for right ventricle assessment and is predictive of mortality.[25,26] However, there was no significant improvement and no difference in

Table II: Bias, precision, and accuracy for estimated glomerular filtration rate

Characteristics	Pre	Post Immediate	Post 6 months	Overall *p* value	*p* value posts hoc analysis			% Mean Difference (pre- to 6 months)
					Pre-to-post	Post-to-6 month	Pre-to-6-month	
Echocardiographic Parameters								
IVSd	1.27 ± 0.21	1.26 ± 0.19	1.21 ± 0.23	0.022	1.000	0.174	0.038	–4.72
PWTd	1.19 ± 0.24	1.17 ± 0.22	1.12 ± 0.20	0.136		–5.88		
LVIDd	4.77 ± 0.64	4.60 ± 0.58	4.49 ± 0.65	<0.001	0.044	0.288	0.001	–5.87
RWT	0.51 ± 0.14	0.52 ± 0.12	0.51 ± 0.11	0.831		0.00		
EF	53.02 ± 12.12	56.64 ± 11.31	56.35 ± 9.00	0.004	0.004	1.000	0.044	6.28
AVA	0.68 ± 0.19	2.07 ± 0.73	2.02 ± 0.73	<0.001	<0.001	1.000	<0.001	197.06
AVAi	0.42 ± 0.12	1.28 ± 0.44	1.25 ± 0.47	<0.001	<0.001	1.000	<0.001	197.62
Peak velocity	4.45 ± 0.64	1.98 ± 0.50	2.06 ± 0.59	<0.001	<0.001	0.463	<0.001	–53.71
Mean PG	49.94 ± 13.53	8.57 ± 4.51	9.49 ± 6.09	<0.001	<0.001	0.226	<0.001	–81.00
SVi	46.42 ± 13.71	46.34 ± 13.54	49.00 ± 13.95	0.187		5.56		
AT	120.00 ± 26.33	73.74 ± 16.86	75.98 ± 16.82	<0.001	<0.001	1.000	<0.001	–36.68
AT/ET	0.35 ± 0.07	0.25 ± 0.05	0.24 ± 0.05	<0.001	<0.001	1.000	<0.001	–31.43
Flow rate	217.80 ± 57.61	249.32 ± 69.75	251.94 ± 69.59	<0.001	<0.001	1.000	<0.001	15.67
DVI	0.21 ± 0.06	0.62 ± 0.18	0.60 ± 0.17	<0.001	<0.001	0.851	<0.001	185.71
TR Peak PG	30.44 ± 14.34	29.59 ± 12.41	29.10 ± 10.62	0.806		–4.40		
s-PAP	34.96 ± 16.37	34.46 ± 14.42	33.29 ± 12.12	0.772		–4.78		
LAVI	52.96 ± 15.29	51.93 ± 16.74	50.11 ± 17.42	0.183		–5.38		
Strain Parameters								
GLS	-11.44 ± 4.23	-11.65 ± 5.13	-13.94 ± 3.72	<0.001	1.000	0.003	<0.001	21.85%
LAr-S	17.44 ± 9.16	16.69 ± 7.98	19.60 ± 8.77	0.033	1.000	0.041	0.203	12.39%
LAc-S	10.17 ± 6.56	8.96 ± 5.26	10.07 ± 6.28	0.326		-0.98%		
LA booster	10.85 ± 5.90	11.24 ± 5.57	12.01 ± 6.02	0.562		10.69%		
RVFW-S	-19.01 ± 6.88	-18.26 ± 6.75	-19.27 ± 6.44	0.543		1.47%		

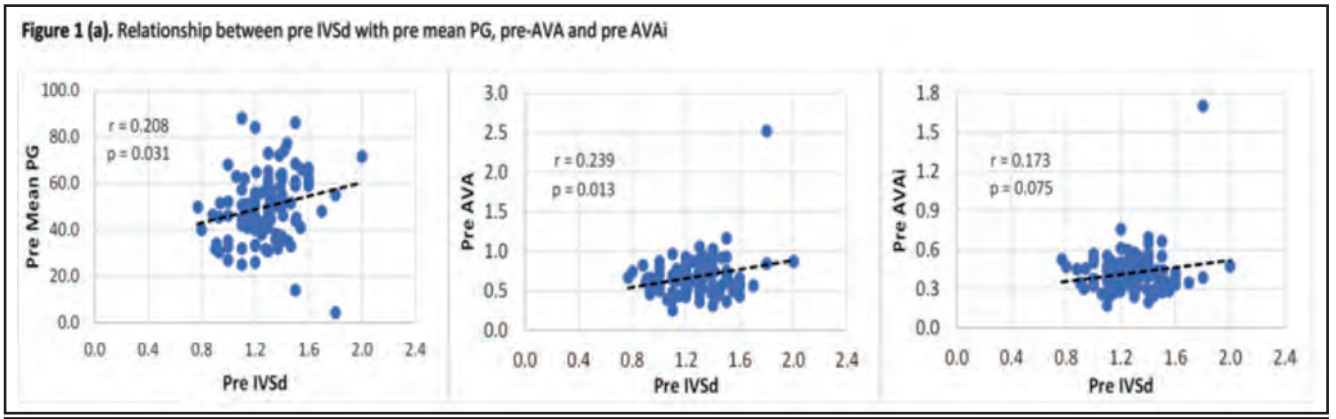
Echocardiographic and Strain Parameters with mortality

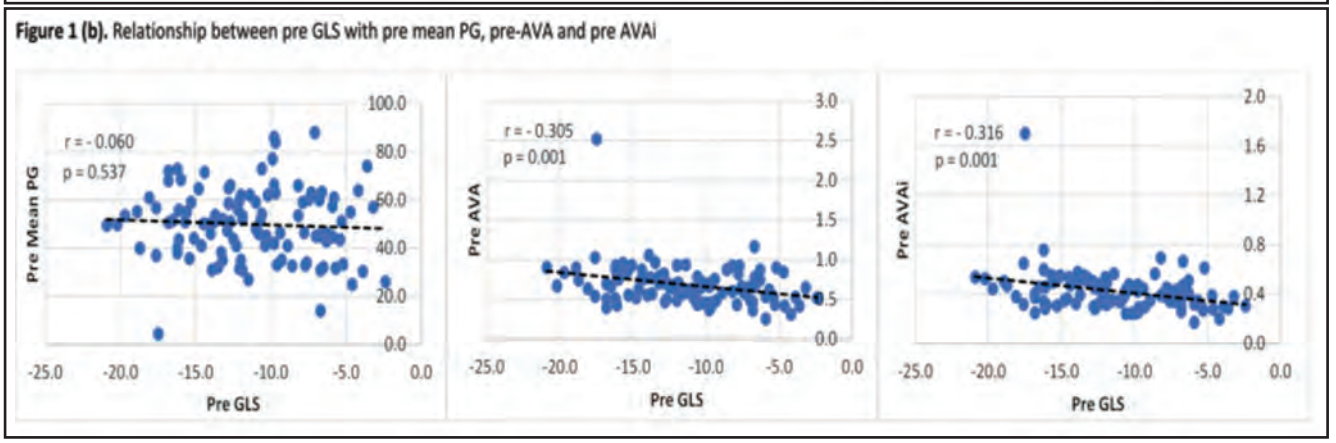
Characteristics		Pre	Post immediate	Post 6 months	% Mean Difference (Pre- to-6-month)	p value[1]	p value[2]	*p* value[3]
LAr-S	Overall	17.44 ± 9.16	16.69 ± 7.98	19.60 ± 8.77	12.39%	0.563		
	Alive	16.90 ± 8.12	16.93 ± 7.17	20.12 ± 7.51	19.00%		0.898	0.405
	Death	18.52 ± 11.07	16.21 ± 9.56	18.58 ± 10.98	0.31%			
GLS	Overall	-11.44 ± 4.23	-11.65 ± 5.13	-13.94 ± 3.72	21.80%	0.001		
	Alive	-11.53 ± 4.29	-11.84 ± 5.31	-14.69 ± 3.25	27.48%		0.206	0.246
	Death	-11.28 ± 4.19	-11.25 ± 4.84	-12.43 ± 4.19	10.19%			
RVFW-S	Overall	-19.01 ± 6.88	-18.26 ± 6.75	-19.29 ± 6.44	1.48%	1.000		
	Alive	-18.98 ± 7.45	-18.85 ± 6.66	-20.89 ± 6.34	10.09%		0.067	0.051
	Death	-19.06 ± 5.73	-17.06 ± 6.90	-16.07 ± 5.45	-15.68%			

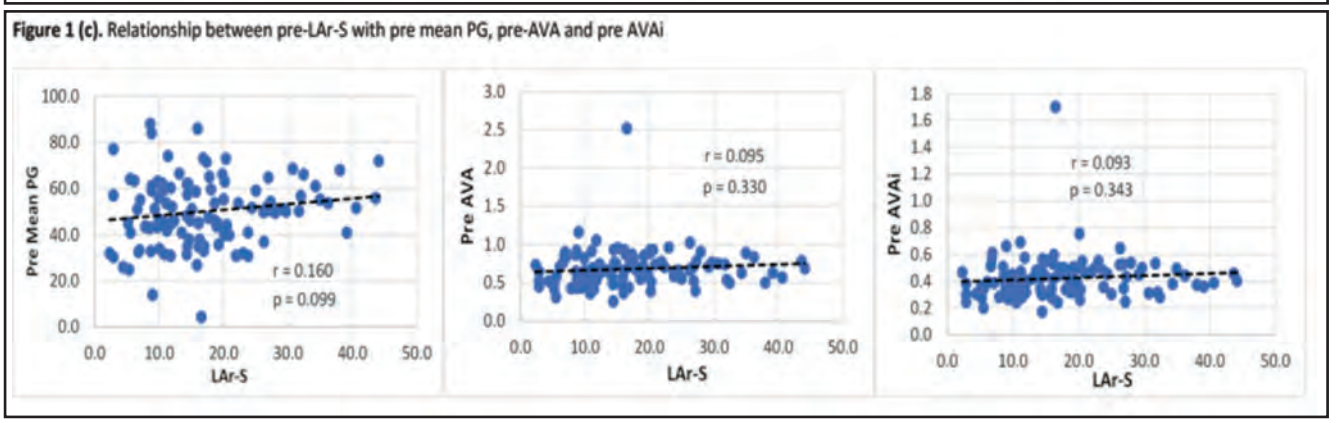
p value[1] suggested any statistically significance of value differences at % difference pre to post 6 months. *p* value[2] suggested any statistically significance of value differences between groups regardless different time points and *p* value[3] suggested any statistically significance of possible interaction of value differences between groups and different time points

Table III: Relationship between IVSd, strains with meanPG, AVA and AVAi and relationship between DVI/AT and flow rate. N = 112

	Relationship between IVSd, Strains with MeanPG, AVA and AVAi			
		MeanPG	**AVA**	**AVAi**
IVSd	Correlation coefficient, r	0.208	0.239	0.173
	p value	0.031	0.013	0.075
GLS	Correlation coefficient, r	- 0.060	- 0.305	- 0.316
	p value	0.537	0.001	0.001
Lar-S	Correlation coefficient, r	0.160	0.095	0.093
	p value	0.099	0.330	0.343
RVFW-S	Correlation coefficient, r	- 0.172	- 0.151	- 0.197
	p value	0.076	0.122	0.041
	Relationship between DVI/AT and Flow Rate			
		AT	**DVI**	
Flow rate	Correlation coefficient, r	- 0.199	0.347	
	p value	0.040	<0.001	







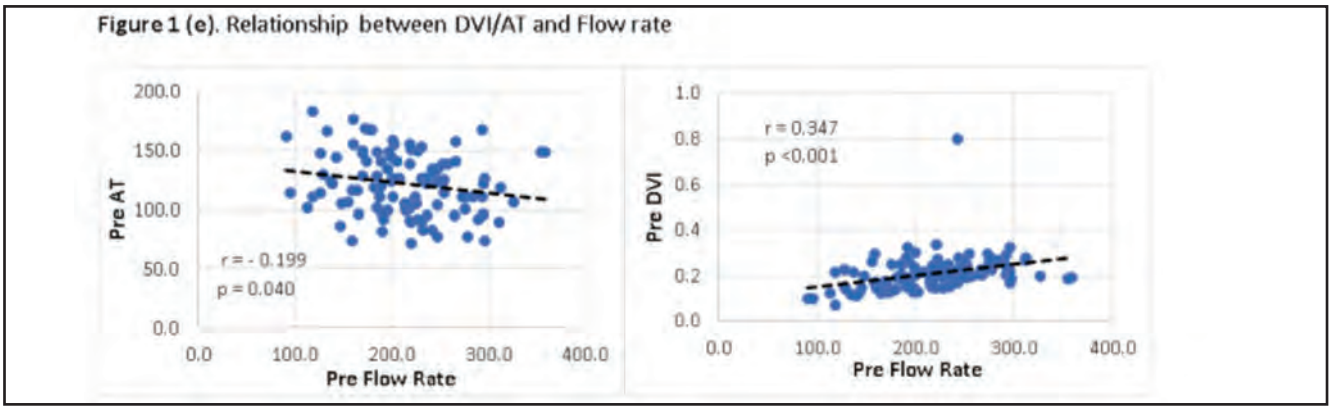
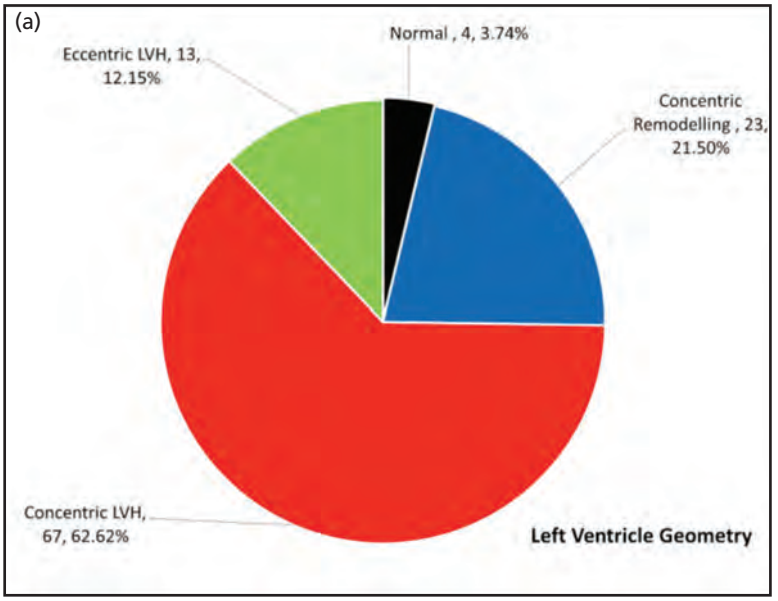
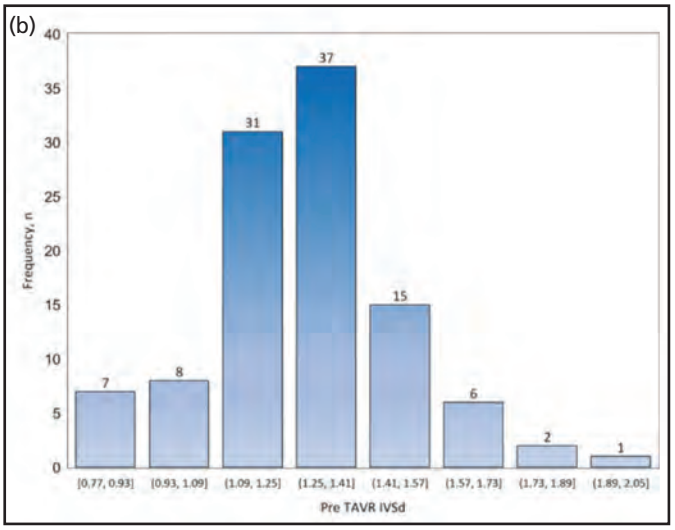


Fig. 1: (a) Relationship between pre IVSd with pre-mean PG, pre-AVA, and pre-AVAi. In pre-TAVR patients, IVSd have a moderate but significant direct relationship with meanPG and AVA but not AVAi. (b) Relationship between pre-GLS with pre-mean PG, pre-AVA, and pre-AVAi. In pre-TAVR patients, GLS have a strong and significant inverse relationship with AVA and AVAi but not meanPG. (c) Relationship between pre-LAr-S with pre-mean PG, pre-AVA, and pre-AVAi. In pre-TAVR patients, LAr-S have no significant relationship with AS severity. (d) Relationship between pre RVFW-S with pre-mean PG, pre-AVA, and pre AVAi. In pre-TAVR patients, RVFW-S have a weak but significant inverse relationship with AVAi only. (e) Relationship between DVI/AT and flow rate. Both AT and DVI have a significant linear relationship with flow rate. The relationship is stronger between DVI and flow rate.





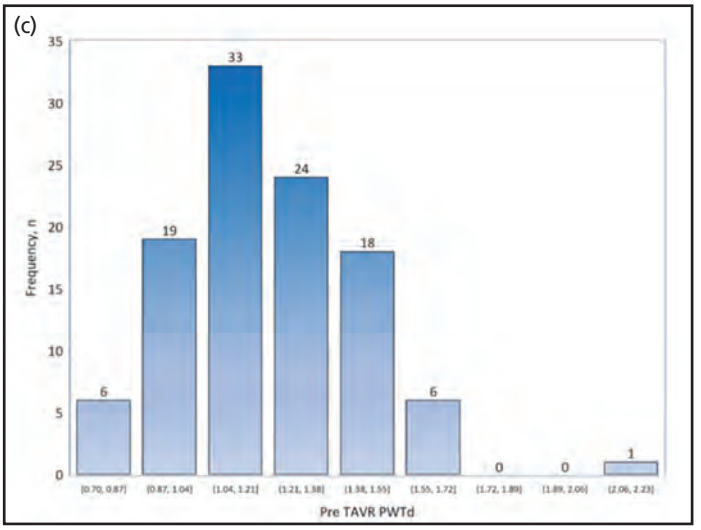


Fig. 2: (a) Left Ventricle Geometry. (b) Pre-TAVR IVSd. (c) Pre-TAVR PWTd.

baseline RVFW-S between those who were alive and those who died in our study at 6 months post-TAVR.

AS causes increase in afterload and therefore increase in LV wall thickness. There were studies previously showing that it was possible to have normal LV wall thickness and normal LV geometry in severe AS.[6,18] This was seen in small group of our patients who have normal LV geometry (n=4; 3.74%) and wall thickness < 1.0 cm (IVSd n=8;7.5% and PWTd n=13;12.1%). There are not many studies looking at relationship between IVSd, PWTd, strain parameters, and AS severity.[5,27] There is moderate direct relationship between IVSd and AS severity (meanPG and AVA), moderate inverse relationship between GLS and AS severity (AVA and AVAi) and finally weak inverse relationship between RVFW-S and AS severity (AVAi).

AT and DVI are echocardiographic parameters that was initially utilized for prosthetic aortic valve dysfunction assessment but recently has also been studied in native aortic valve patients.[6,9,10,21] In this study, we wanted to see whether these parameters were related to flow rate, and indeed, we found that AT had moderate but inverse relationship with flow rate whereas DVI had stronger and direct relationship with flow rate. Therefore, flow rate should be considered when using these parameters.

CONCLUSION

Our study of multiracial patients in a single centre showed that TAVR improved EF, IVSd, LVIDd, GLS, and LAr-S at 6 months. Both IVSd and GLS have a linear relationship with AS severity and the AT and DVI were significantly affected by flow rate.

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ORIGINAL ARTICLE

Workplace violence among nurses in a Penang hospital: Prevalence and risk factors

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ABSTRACT

Introduction: Workplace violence (WPV) has become a universal concern and is perceived as a serious safety and health threat, especially in healthcare settings. Very few studies have been done previously to determine the prevalence of WPV and associated risk factors among nurses in Malaysia. Among the health professionals, nurses spend most of their time with patients compared to other healthcare professionals. Several studies suggested that nurses had a higher risk of experiencing WPV. This study determined the prevalence and associated risk factors of WPV among nurses in a government hospital.

Materials and methods: This cross-sectional study involved 410 randomly selected respondents among nurses in a government hospital in Penang, Malaysia. Data were gathered through a self-administered questionnaire consisting of a standardised questionnaire regarding WPV.

Results: The prevalence of reported WPV was 43.9%. The most common forms of WPV were verbal abuse (82.2%), followed by psychological violence (8.9%), physical violence (8.3%), and sexual violence (0.6%). The perpetrators were primarily among relatives of patients (51.7%), followed by patients (30%). Multiple logistic regression demonstrated that nurses working in the emergency department (ED) were six times more likely to experience WPV than in other departments (adjusted odds ratio (AOR) 6.139, 95% CI: 1.28 – 4.03). In addition, nurses in the age group of ≤30 years old were twice more likely to experience WPV (AOR 2.275, 95% CI: 3.4–11.08).

Conclusion: This study indicates that the prevalence of WPV among nurses is high and most common among young nurses and those working in ED. Hence, hospital management should develop guidelines and comprehensive policies to prevent WPV. In addition, education and training, especially among young nurses and those working in the ED, are needed to increase their knowledge in the management and prevention of WPV and counselling sessions for nurses who have experienced WPV.

KEYWORDS:
Workplace violence, prevalence, hospitals, risk factors, government

INTRODUCTION

Workplace violence (WPV) has become a universal concern and is perceived as a serious safety and health threat, especially in healthcare settings.[1,3] Health professionals have a higher risk of experiencing WPV than other professionals.[2] From 2002 to 2013, severe WPV incidents (those requiring days off for the injured worker to recuperate) were four times more common in healthcare than in private industry. Among the health professionals, nurses spend most of their time with patients compared to other healthcare professionals. As a result, nurses have a higher risk of experiencing WPV. A meta-analysis of 136 studies on 151,347 nurses worldwide demonstrated that the prevalence of WPV varied by region, with the Middle Eastern region having the highest at 61.3%, followed by the Asian region at 51.3%, and the European region having the lowest (38.3%).[4] A study by Zainal et al. reported that 71.3% of healthcare workers in Hospital Kuala Lumpur, Malaysia, were subjected to at least one of the four types of violence: verbal abuse (70.6 %), bullying/mobbing (29.4%), physical violence (11.0%), and sexual misconduct (6.6%). However, this study does not explicitly focus on WPV among nurses.[1]

Stressors such as reduced co-worker and supervisory support, lack of workgroup harmony, and layoff worry are associated with violent outcomes.[5] Similarly, job characteristics such as workplace and experience are important determinants of experiencing WPV. The level of WPV among nurses working in the Emergency Department (ED) was higher than that of those other units.[6] Younger doctors and nurses were more vulnerable to WPV exposure than their older counterparts.[1] The most frequent aggressions against nurses and physicians were committed by patients, followed by patients' relatives and professional colleagues.[7] An individual personality can result in them being victimised and an easy target of aggression and can make them vulnerable when faced with interpersonal aggression and conflicts. Some studies have indicated that personality traits may function as predictors and outcomes of WPV.[8-10]

This study was designed to determine the prevalence of WPV among nurses and the association between socio-demographics and job characteristics with WPV within 12 months. This study is about nurses who have experienced WPV from patients, relatives, visitors, colleagues, or other professional groups in a government hospital during their work. Moreover, it also identifies the problems these nurses encountered and hopes that appropriate support and treatment can be given to prevent further anxiety and stress.

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MATERIALS AND METHODS

Study design

This cross-sectional study was conducted from March to October 2020 among all clinical nurses in Penang General Hospital, Malaysia. Ethical approval for the study was obtained from Medical Ethical Board University Kebangsaan Malaysia and the Medical Research and Ethics Committee of the Ministry of Health Malaysia through the National Medical Research Registry.

Study subject

This study included all clinical nurses aged 18 to 60 years old, Malaysian, and have worked in a clinical setting for at least 1 year. Those in the administrative work setting were excluded. Written and oral informed consent was obtained from all participants.

Sample size

The sample size for this study was calculated using the formula $z^2 1\text{-}\alpha/2PQ/d^2$, taking a confidence interval (CI) of 95% (1.96), and absolute precision was 5% (α = 0.05). Based on Zainal et al. (2018), the prevalence of WPV among healthcare workers at 71.3% was used as the reference. Therefore, a minimum of 393 respondents was randomly selected to cover the non-response rate of 20%.

Procedure and Instruments

Name list of clinical nurses obtained from the Human Resource Department, Penang General Hospital -was stratified into five major departments (Surgical, Emergency, Medical, Paediatric, Obstetrics, and Gynaecology). Then, the nurses were selected from each department (strata), and the proportion was based on the total number of nurses in a particular department. Finally, a simple random technique was used to select each selected department.

A validated Workplace Violence Questionnaire was utilised in this study. The reliability and validity test with Cronbach's α was 0.872 by Ruth (2009).[14] There were six parts with 15 questions in this questionnaire: Part A—socio-demographic background; Part B—job characteristic (includes place of work and years of experience since completion of training); Part C—violent incident (violence incident at the workplace in the last 12 months, location and the form of the violence); Part D—Characteristics of the Perpetrator (who was the perpetrator and the perpetrator's gender); Part E— Situational Factors of WPV (WPV happened during weekdays or weekend and whether it happened during the morning or night shift); and Part F— Feelings Post Violence.

The definition of WPV adopted in this study was according to the Department of Occupational Safety and Health, Malaysia (2001), which was *incidents where employees are abused, threatened, assaulted, or subject to other offensive behaviour in the circumstances related to their work*.[21]

Statistical analysis

Data collected were analysed using Statistical Package for the Social Sciences (SPSS) for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive analysis for continuous variables presented as mean with standard deviation (SD). In contrast, categorical variables were presented as frequency and percentage, including social-demographic data, job characteristics, types of violence, characteristics of the perpetrator, and feelings of the participant post-violence. The association of the risk factors with WPV was tested using the chi-square test for categorical variables at the bivariate level. In addition, all significant factors were analysed using simple logistic regression and multiple logistic regression to determine the contribution toward WPV. The adjusted odds ratio (AOR) is an expected analysis for each significant independent variable. The test's significance was set at a p value < 0.01 and 95% CI.

RESULTS

Socio-demographic and job characteristics of the respondent

Most were female respondents, with 98.8%, and 1.2% were male (Table I). The age ranged from 22 to 54 years old, with a mean age of 31.72 (SD=5.932). Malay respondents consisted of 83.9%, followed by Indian (9.5%), Chinese (2.2%), and other races (4.4%). In addition, 80.5% of respondents were married, and the remaining were single. A total of 40.2% of respondents had 1–5 years of working experience. Furthermore, respondents with working experience of 6–10 years (33.9%), 11–15 years (16.8%), 16–20 years (5.1%), and 3.9% with working experience of more than 20 years (Table I).

Prevalence and type of WPV

A total of 180 respondents (43.9%) had experienced WPV in the past 12 months, most of whom were exposed to verbal violence (82.2%). In addition, psychological violence and physical violence accounted for 8.9% and 8.3%, respectively. One respondent (0.6%) was subjected to sexual abuse and violence (Table II).

Characteristics of the perpetrator and situational factors of WPV

The majority of the perpetrators were male (68.3%). On the other hand, the female perpetrator only contributed 31.7% of the total number. Patient's relatives contributed to the most significant percentage of WPV, 51.7%, followed by 30% of WPV from patients, 10.6% from working colleagues, and management/superior with 7.8% of WPV. A number of 67.2% of cases were reported during day shifts, whereas 32.8% of cases happened during night shifts. Further stratification based on weekday and weekend shifts demonstrated that most violent cases occurred during weekdays (66.7%), and the remaining 33.3% happened during weekends (Table II). Feeling post-violence incidence of embarrassment, anger, and depression accounted for 22.8%, 22.2%, and 19.4%, respectively. In addition, a faction of victims was shocked (17.2%), fearful (10.0%), and 8.3% felt confused post-violence.

Association independent variables and WPV

Age and marital status positively affect the socio-demographics of nurses with WPV. Nurses aged 30 years old and younger (50.0%) have a higher risk of experiencing WPV compared to those who are older (36.8%) (p<0.05). On the other hand, single (53.8%) has a higher risk of WPV compared with the married (41.5%) (p<0.05) (Table III). In addition, respondents working in ED (76.6%) have a higher risk of experiencing WPV compared with respondents working in other departments (36.3%) (p<0.05) (Table IV).

Table I: Socio-demographic and job characteristics of the respondent

Variables	Frequency (n)	Percent (%)
Age		
20–29	180	43.9
30–39	183	44.6
40–49	40	9.8
50–59	7	1.7
Gender		
Female	405	98.8
Male	5	1.2
Ethnic background		
Malay	344	83.9
Chinese	9	2.2
Indian	39	9.5
Others	18	4.4
Marital status		
Single	80	19.5
Married	330	80.5
Working experience		
1–5 years	165	40.2
6–10 years	139	33.9
11–15 years	69	16.8
16–20 years	21	5.1
>20 years	16	3.9
Place of work		
Medical department	94	22.9
Surgical department	76	18.5
Paediatric department	80	19.5
Emergency department	77	18.8
O&G department	83	20.2

Table II: Descriptive data of types of violence and characteristics of the perpetrator

Variables	Frequency (n)	Percent (%)
Type of violence		
Verbal violence	148	82.2
Psychological violence	16	8.9
Sexual violence	1	0.6
Physical violence	15	8.3
Characteristics of the perpetrator		
Gender of the perpetrator		
Female	57	31.7
Male	123	68.3
Category of perpetrator		
Patient	54	30.0
Patient's relative	93	51.7
Colleague	19	10.6
Management/superior	14	7.8

Table III: The association between sociodemographic of nurses with workplace violence

Risk factors	x^2	Workplace violence		*p* value
		Yes n (%)	No n (%)	
Age++				0.007*
≤30 years old	0.58	110 (50.0)	110 (50.0)	
>30 years old	3	70 (36.8)	120 (63.2)	
Gender	0.192			0.102
Male		4 (80.0)	1 (20.0)	
Female		176 (43.5)	229 (56.5)	
Marital status	1.637			0.048
Single		43 (53.8)	37 (46.3)	
Married		137 (41.5)	193 (58.5)	
Ethnicity++	1.159			0.584
Malay		149 (43.3)	195 (56.7)	
Non-Malay		31 (47.0)	35 (53.0)	

++ Adjustment to the age group and ethnic group was made. For the age group, the respondent was regrouped into two groups: respondents with less or equal to 30 years old and respondents over 30 years old. For ethnic background, respondents were regrouping into two groups: Malay and Non-Malay.
* Chi-Square test significant $p < 0.05$.

Table IV: The association between job characteristics of nurses with workplace violence

Risk factors	x^2	Workplace violence		*p* value
		Yes n (%)	No n (%)	
Place of work++	0.174			<0.001*
Emergency department		59 (76.6)	18 (23.4)	
Other department		121 (36.3)	212 (63.7)	
Experience++	0.749			0.208
≤10 years		139 (45.7)	165 (54.3)	
>10 years		41 (38.7)	65 (61.3)	

++Adjustment to the place of work and experience group was made. For the place of the workgroup, the respondent was regrouped into two groups: the respondent working in the emergency department and the respondent working in other departments. For working experience, the respondent was regrouped into two groups: respondent with working experience less or equal to 10 years and respondent with working experience of more than ten years.
*Chi-Square test significant $p < 0.05$.

Table V: Multivariate analysis of associated risk factors of workplace violence

Risk factors	AOR	95% CI	*p* value
Age	2.275	1.284–4.030	0.005*
Gender	2.308	0.222–23.978	0.484
Marital status	0.741	0.433–1.268	0.274
Ethnic	0.785	0.444–1.388	0.405
Experience	0.723	0.379–1.380	0.326
Place of work	6.139	3.401–11.082	<0.001*

*Chi-square test significant $p< 0.01$. AOR: adjusted odd ratio, CI: confidence interval.

Multiple logistic regression analysis demonstrated that age ($p = 0.005$) and working place ($p < 0.001$) were significant factors related to WPV (Table V). Respondents in the ED were six times more likely to report WPV than those in other departments (AOR 6.139, 95% CI: 1.28–4.03). In addition, nurses younger than 30 years old were twice more likely to experience WPV than older respondents (AOR 2.275, 95% CI: 3.4–11.08).

DISCUSSION

This study demonstrated a 43.9% prevalence of WPV among nurses exposed to at least one of four types of violence in their workplace. This finding was comparable with other studies, where the prevalence of WPV in Ethiopia, South Korea, Jordan, Germany, and Iran was 18.22% to 56.0%, and 49.6% in Taiwan.[2,3,11] However, a study done in Hospital Kuala Lumpur, Malaysia, exhibited that 71.3% of the doctors and nurses reported being victimised by at least one of the four types of violence. The nature of work performed by healthcare workers in each study and the definition of respondents taken into the study could vary the prevalence rate.[1] Furthermore, hospital capacity and the number of departments in the hospital may influence WPV incidence, which Hospital Kuala Lumpur has a higher prevalence comparatively. Most violent cases occurred during the day shifts, 121 cases (67.3%) during the day shift, and the remaining 59 cases (32.8%) during the night shift. These findings seem reasonable because much of the activities of daily living and highly technical and complex care take place during the day, while most patients rest or sleep, and patients' relatives are not allowed in the hospital at night. Nurses are inevitably more involved in violent situations during the day. The same explanation can be applied where most highly technical and complex procedures are carried out during weekdays compared to weekends. Therefore, during the weekdays, the staff becomes more involved with the patients, thus putting them more vulnerable to violent situations.[12,13] This study demonstrated that verbal violence is the most frequent type of violence among nurses in the workplace, followed by psychological violence, physical violence, and sexual violence.[11,14,15] Previous studies have shown that the prevalence of verbal violence among nurses is the highest of all four types, approximately 70.6%, 63.8% to 89.58%, and 46.3%.[1,2,11] Verbal abuse is frequently reported as the initial stage of subsequent physical violence.[14,15] It can lead to many consequences, particularly on psychological and organisational levels.[17] Patients' relatives and patients made up most of the perpetrators in our study. Again, these results are consistent with previous studies showing that patients and their relatives committed between 72% and 98% violent acts toward nurses.[18] The familiar feelings experienced post-violence by the nurses were an embarrassment, anger, depression, shock, fear, and confusion.8 This exhibited how WPV affects healthcare professionals differently, depending on the situation, perpetrator, and personal emotional state. Therefore, it is of utmost importance for the management to proactively deal with WPV, curb its effects and create a healthy and safe working environment, as those who have experienced WPV are more likely to suffer from depression and anxiety than those who have not.[19,20]

In this study, two sociodemographic variables, age, and one job characteristics variable of the nurses are significantly associated with WPV. This is similar to a study in South Korea; WPV is experienced mainly by junior nurses.[6] Respondents younger than 30 years old were twice more likely to experience WPV than the older respondent. Younger age may mirror a lack of work experience and lower education, resulting in less skill in dealing with violence. In

government hospitals in Malaysia, with an overwhelming number of patients and overtime demand, working as nurses is exacting, and a lack of coping skills in WPV will worsen the effects. Given job characteristics, place of work was found to be a significant risk factor for WPV. This factor has continued to be significant in predicting WPV even after controlling other variables; nurses working in the ED were six times more likely to experience WPV than nurses working in other departments. This finding was indistinguishable from other studies, whereby nurses working in EDs were at the most significant risk of violence in many countries.[1-3,15] This is probably due to the frustration of long waiting times in the ED, not satisfied with the treatment, being under the influence of alcohol or drugs, and poor waiting areas.[1,2,6,7,11] On the other hand, the language barrier is a common problem as Malaysia has a diverse population with different languages and dialects.

Hopefully, the information obtained from this study will be beneficial in improving findings related to risk factors and prevalence of WPV and developing related general guidelines and fact sheets to improve understanding of risk factors and prevalence of WPV.

The current study had a few limitations. Firstly, the findings were only confined to Penang General Hospital, and a generalisation is not conceivable. Besides, the questionnaire used was a self-reported questionnaire. Furthermore, respondents needed to recall the incident of WPV in the past twelve months, which might have been affected by other events or experiences in the past 12 months.

There is a widespread lack of organisational controls against violence. Nurses must develop their ability to protect themselves from violence through educational programs. Violence toward nurses is a subject that should be studied more adequately, and nurses who are victims of violence should receive appropriate occupational and institutional assistance. Moreover, nurses who have been victims of violence should be offered professional assistance and support.

It is recommended that this study can be done as a cohort study to establish a causal relationship between risk factors and the prevalence of WPV among nurses. In addition, the study population should be more generalised to other populations of nurses in Government Health Clinics and the Private Sector so that it can create more variation in terms of data collected and prevent selection bias.

CONCLUSION

This study confirms that nurses are considered a professional group at high risk for violence in healthcare, likely due to organisational and individual factors, which calls for more effective measures to overcome this problem. It is also time for nurses to demand a healthy working environment to provide effective and productive nursing care. Education and training are needed to increase their knowledge in the management and prevention of WPV and counseling sessions for nurses who have experienced WPV.

The main limitation of our study was that respondents needed to recall the incident of WPV in the past 12 months. Therefore, the accuracy of respondent recall of WPV incidents may be affected by other events or experiences for the past 12 months.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Overview of situational awareness in healthcare and the need for early exposure

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ABSTRACT

Medicine and healthcare can rightly be considered as High Reliability Organization (HRO) when it strives to promote and maintain reproducible and safe outcomes for all patients. Situational awareness (SA) as a concept meant to augment patient safety has often been discussed in the literature, but our own local contribution to this important discussion is decidedly deficient. Being initially implemented in the aviation industry, this concept has been extended to be a crucial element in high-demand activities, including healthcare. As such, extensive exposure is given early on during the training of medical personnel in many countries. We believe that our own medical students and other healthcare candidates in training should be similarly exposed to this concept as it can have a tremendous impact on patient well-being and safety. This paper attempts to provide a short overview of the SA in healthcare and how we can similarly promote its inclusion in our training programmes.

KEYWORDS:
Situational awareness, patient safety, medical education, training

INTRODUCTION

Situational awareness (SA) is a concept initially brought forward within the aviation industry after the Korean War when US pilots were out looking for the enemy. It has since been inculcated extensively into the aviation and other high-reliability industries. Only recently has SA been gaining more foothold in healthcare in order to deliver a more enhanced patient safety with improved clinical outcomes.[1,2]

SA can be defined as 'the perception of elements of the environment within a volume of time and space, the comprehension of their meaning and the projection of their status in the near future'.[3] Essentially, SA requires an individual maintains an adequate internal representation of the environment in interacting domains where time constants are short, and conditions may change on extremely short notice. It allows a person, in this case a healthcare personnel, to always remain cognisant of his immediate surroundings (patient, patient data, monitor readings, verbal communications, etc.) while he attempts to focus his attention on his role and responsibility, being prepared to immediately shift gears in response to any change in the environment. SA is not only a fundamental and critical aspect of clinical decision-making, performance, and teamwork. It is also an important precursor due to the restraints of time and space.[4,5] By maximising SA, apart from striving for better clinical outcomes, it is even possible to improve the understanding of diagnostic errors, thereby potentially reducing them and their consequence.[2] Loss of SA inexplicably leads to a downward spiraling situation that can lead to serious morbidity and even mortality.[1]

The main purpose of this review is to introduce the vast concept of SA to those unfamiliar with it, in a broad manner. A secondary purpose is to impart the importance of establishing SA amongst clinicians in their daily practice and to inculcate early exposure of the concept amongst novices.

COMPONENTS OF SA

SA can be viewed in several individually distinct, but inter-related, dimensions.

Individual SA

As expounded by the definition, 'Individual SA' can be divided into three hierarchal levels: perception (SA level I), comprehension (SA level II), and projection (SA level III). SA level I involves the exposure to stimuli and information from the environment. The individual identifies key elements that define the current environment: patient's history, relevant clinical findings, investigations results, ebb and flow of the patient's vital signs, team interactions, and so forth.

At SA level II, the individual attempts to compile and integrate, interprets, and retains all the disjointed information he has accumulated at level I. In a way, all the different data he has acquired are individual paint strokes that will come together to form a 'big picture' that will serve him in his designated role and responsibility. From there, clinical judgment forms in relation to the scenario at hand.

SA level III allows the individual to then use that judgment to plan for the immediate future of the patient and the dynamics that can happen if that judgement if followed through or not. As can be imagined, the accuracy of this level of SA is highly dependent on the precision of the perception and comprehension phases (Levels I and II).

Some authors have suggested a level IV of SA (resolution). This involves a situation whereby more than one possible judgment is formed, and the individual then seeks identify the best path to follow out of all the possible options available (Table I).

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In the development of SA from level I through III (or IV according to some authors), the necessary knowledge base and clinical skills and acumen are gained through experience. It is not surprising therefore that trainee and novice doctors are able to receive environmental input but may have difficulty in interpretation, whereas clinical judgment and their possible outcomes are more in the realm of senior clinicians.

Team SA

Clinicians generally work within a team to provide the best possible inter-disciplinary healthcare for patients. Each team member brings their own individual SA for their designated role and responsibilities; collective decisions are then made based on input from all members. As with any team lineup, there will be an overall leader (usually the one with SA level III) overseeing the other members. Each member in their designated role pursues an agreed upon mental model(s) for the planned and unplanned (contingency) events.

In determining the effects of teamwork on healthcare with particular emphasis on labour and delivery, Harris et al. found significant challenges in creating a teamwork culture without obstacles such as hierarchical gradient preventing effective communication between members. While total avoidance of all adverse events could not be avoided with teamwork alone, ongoing vigilance and the establishment of an effective teamwork culture eventually promotes an environment of safety.[6]

In line with the team approach towards improving patient safety especially the avoidance of surgical mistakes, the World Health Organization (WHO)-led initiative of Safe Surgery Saves Lives (SSSL) was implemented. Malaysia joined the initiative in 2009 under the banner of "Safer surgery through better communication", with some of the main strategies being 'improving communication and team building to ensure safer surgery' and the 'creation of checklist(s) to improve the standards of surgical safety'.[7] A multi-centre study involving eight hospitals in eight cities managed to show that such checklist implementation is associated with concomitant reduction in the number of surgical morbidity and mortality. Between October 2007 and September 2008, in-patient complication rates dropped from 11.0% to 7.0% while the percentage of deaths was reduced to 0.8% from 1.5%.[8] The success of the SSSL initiative is a clear endorsement of effective teamwork and team SA.

Distributed SA (DSA)

Patient care has become increasingly complicated with advances of medical science and technology. As these advances play some role in the delivery of input (especially at SA level I), their contribution is recognized as Distributed SA (DSA). This recognition allows for better overall understanding of the interaction between individuals (e.g., surgeons, aneaesthetists, nurses) and external objects (charts, medical equipment, etc.) to form a coherent picture. DSA emphasizes the continuous, mutually altering interaction between the individual (or team) and the environment the individual (or team) is engaged in reference.[9] It is interesting to note that sometimes it takes someone 'from the outside' to provide the necessary input to stimulate a different mental model and thus and unexpected outcome.

Mental model

A platform of common ground is important for effective communication between team members to occur, so that a mutual goal can be achieved.[11] Mental models between team members can be defined as "individually held knowledge structures that help team members function collaboratively in their environments".[12] They comprises inter-related memories, concepts, and beliefs that create an understanding of how a system works and can be held at a higher or lower level of acuity based on the individual's own knowledge and experiences.[13] Different team members being their own perspective of the situation at hand to the table – without this common ground of shared mental models, effective communication, and thus improved patient safety, is difficult at best.

A mental model can then be thought of as a common action plan that is carried out when an expected outcome is reached in the workflow, "What happens next?". Additionally, it can help envisage a contingency plan should the unexpected be encountered, "What should I do if…?". With a shared mental model, planned and unplanned possible scenarios can be tackled with greater efficiency and is less disruptive. Furthermore, other team members with lesser roles to play may anticipate and render assistance to those requiring it.[4]

How can SA be lost?

It is conceivable that certain scenarios may happen as to cause disruption of individual SA, which inevitably may similarly disrupt the overall team dynamics.

SA level I: One of the main culprits is information overload upon a novice personnel. It must be accepted that not all the information received are relevant to the patient/situation at hand. If the novice is unable to discern which input are vital, important, and useful from the useless ones, it is unlikely that a clearer 'big picture' can be created. Another reason for loss of SA is distraction and interruption from the work at hand – again, from the multiple simultaneous input sources. Fatigue has also been shown to be a major disruptor of SA at all levels.

SA level II: Here, the individual involved has compiled all data, but failed to attach significance to them. As a result, the 'big picture' he created does not truly reflect the actual condition of the patient, or the severity of the situation. There are a few hypotheses that attempt to explain this, which in effect, is akin to tunnel vision:

Primacy effect – when the individual refuses to consider other possible causes for the situation when faced with two or more 'confirmatory evidence'

Confirmation bias – the willingness to accept evidence that 'confirm' the individual's belief/diagnosis rather than those that support the contrary i.e., contradicts (1).

SA level III: This situation is more likely the culmination of the loss at levels I and II. The resulting understanding of the situation thus far has led to the individual choosing the wrong subsequent course of action. However, the situation may still be redeemable if the senior clinician/team leader is able to revisit and re-evaluate from the beginning and revise the mental model.

Table I: Individual Situational Awareness (SA) levels

SA level	Main function	Competency level	Example of SA failure
Level I (Perception)	Receive environmental input	Trainee/Novice doctor	Informational overload
Level II (Comprehension)	Integrates input into useful 'bigger picture'	Mid-level registrar/medical officer	'Big picture' not reflective of patient status/tunnel vision
Level III (Projection)	Decides on plan for immediate future	Senior clinician/consultant	Future not correctly anticipated
Level IV (Resolution)	Chooses best of possible paths		

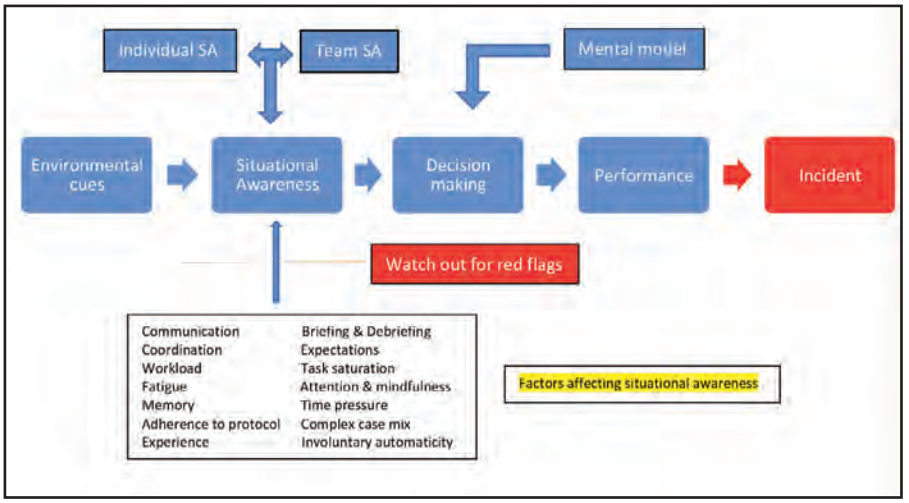

Fig. 1: Factors that shape situational awareness (Adapted from Edozien LC. Situational awareness and its application in the delivery suite.[10]

Team SA loss: A lot of work has been done on teamwork in high-reliability industries such as aviation, petrochemical, electrical, and the military. In healthcare, SA compromise could be due to a multitude of issues such as distraction, complacency, task saturation, e.g. high patient-to-staff ratio, inability to comprehend display monitor and data display etc.[4,5,14] Fatigue, for example, is known to cause lapses in attention and memory, with reduced speed and accuracy of brain processing capacity.[5] This could happen to any member irrespective of their SA level.

Disruptions in the dynamics of team SA could be from a lack of communication between members, primarily due to the presence of a 'hierarchical gradient'.[1] A steep gradient occurs when a senior clinician who is considered beyond reproach and could do no wrong, received no cues from other knowing staff even as he is about to embark on a ghastly mistake. Or, the gradient could be flat in that the team leader lacks the self-confidence and assertiveness, especially in a crisis, to effectively manage his team. An effective team is more possible when members can respectfully voice concerns and suggestions both ways without fear of blame or retribution.[15,16] It is essential that these non-technical skills be reiterated across the board to be as equally important as leadership and decision-making skills, in an environment inculcated with mutual respect.[17,18]

In response, Crew Resource Management (CRW) training programmes were borrowed from the aviation industry. They attempt to increase patient safety by considering the role that human factors play in the performance and delivery of patient care.[17] Across the world, various training protocols and programmes have been set up to address this dire need to promote effective communication and teamwork.[19]

Need for early exposure to SA

Many authors have expounded the implementation of SA into their workflow, from obstetrics,[10] and orthopaedics,[20] to emergency medicine[21] and surgery and the operating theatre.[22] Due to the increasing need to improve patient safety and outcome in line with increasing medical and technological advancement, it is prudent that SA be exposed early in the medical career. Multiple papers have shown the results of earlier exposure to SA, and how this could be instilled in medical undergraduates.[23–29] Most are based on simulation assessment of SA with end-of-course debriefing and discussions on results, member involvement, and self-enhancement. Fischer and colleagues further explored how SA amongst medical students could be assessed using the widely accepted Objective Structured Clinical Examination (OSCE) stations: their findings of the literature indicated that such an approach could enhance information gathering and processing with improvement in the ability to read and understand clinical scenarios (clinical reasoning).[30] Another innovative approach towards instilling SA amongst students involve early exposure to visual and verbal clinical clues and cues[25]: presence of a walking cane indicates mobility issues, inhalers by the bed might represent a patient with asthma, etc. Repeated enforcement will ultimately promote SA, and eventually effective clinical reasoning.

Clinical reasoning (CR) is an attribute all clinicians strive for. Definition of this skill is varied[30-32] but can be simplified as complex interconnecting thinking process of interpreting a patient's problem and presentation, culminating in the sound formulation of treatment and rehabilitation regimen. SA is a major component of CR acquisition, and just like SA, CR develops exponentially as the clinician blossoms from novice to expert with increasing experience and exposure to myriad of cases. Both can be exposed early in the training of potential healthcare providers and enhanced further in their careers.[30]

State of affairs in Malaysia

It can thus be seen how a strong SA at all levels of patient care can only improve patient outcome and safety. As far as medical students in Malaysia are concerned, no clear advocacy is made to inculcate this trait as they transition from students to novice/trainee doctors just as the more senior clinicians have developed their own SA over years of service and experience. Students still undergo traditional training of a pre-clinical organ-based approach, before venturing into a more 'clinical' medical interview and physical examination. While standard interviews and physical examination inculcate certain levels of SA, SA in and of itself is not formally addressed.[33] In Malaysia, there is scarce literature specifically addressing SA. While the MOH (WHO-initiated) SSSL programme is a sound example of team SA being promoted,[7] it does not exactly extend beyond the operating theatre and into the other specialties of medicine in this country. Singh and Nasruddin recently addressed issues affecting patient safety in a private hospital using the Donabedian model of High Reliability Organizations: issues that ultimately reflect team SA in healthcare provision.[34] It was in noticing this lack of local literature that prompted this short review, and hopefully a more robust discussion on the topic.

CONCLUSION

It is well established that SA is an essential element for improvement in patient safety and clinical outcomes. And we have outlined the different aspects of SA as well as how it can fail. Because the development of high-quality clinical acumen and judgment takes time and is primarily dependent on training and experience, we propose the early exposure of medical students and trainees. Real-time simulations appear to be the best platform for training and assessment.

CONFLICT OF INTEREST

There is no conflict of interest related to this review article.

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Application of socio-ecological model in developing preventive strategies against suicidal ideation and suicidal attempt among youth in low and middle-income countries: A scoping review

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ABSTRACT

Introduction: Suicide is recognized as an important public health concern, as it is the second leading cause of death among young people. About 80% of all suicide cases occur in low- and middle-income countries (LMICs). Understanding the risk factors for suicidal behaviours among young people in LMIC is important in developing preventive strategies; however, evidence on this is still lacking. Socio-ecological model (SEM) is a suitable framework in explaining the factors of suicidal behaviour. The aim of this review is to identify the factors associated with suicidal ideation and suicidal attempt among young people in LMIC, guided by the SEM model, and eventually develop its preventive strategies.

Materials and methods: This review has two parts. The first part is a scoping review of the factors associated with suicidal ideation and attempt among young people. The search was conducted in Pubmed, Scopus, and PsycInfo. The second part is the development of preventive strategies according to the identified factors. Both parts will be guided by the SEM model.

Results: A total of ten studies with 45,278 participants that matched the criteria are included in this review. The review found that the risk factors for suicidal ideation among young people in LMIC are being female, psychiatric illness, psychology problem, smoking, alcohol intake, victim of abuse, bullied, and food insecurity. The preventive strategies include policy, mental healthcare services, awareness programme, and coping strategies.

Conclusion: More epidemiological studies are needed to evaluate the risk factors of suicide that are unique in LMIC, such as help-seeking behaviour and available mental healthcare services. Suicide prevention requires concerted effort of policymakers, healthcare services, community and individual; thus, SEM framework is suitable as a guidance for suicide prevention.

KEYWORDS:
Suicidal attempt, suicidal ideation, suicide, young people, socio-ecological model

INTRODUCTION

Suicide is recognized as an important public health concern by the World Health Organization (WHO) in its Comprehensive Mental Health Action Plan. Approximately, 800,000 people die from suicide every year and account for 1.4% of all deaths worldwide.[1] About 80% of all suicides occur in low- and middle-income countries (LMICs). Economic variables have been associated with suicidal behaviour.[2] Poverty was reported to have a positive association with suicide.[3] Furthermore, a psychiatric illness which is a common risk factor for suicidal behaviour in high-income countries was reported to have a lower prevalence in LMIC.[4] Understanding the risk factors for suicidal behaviours in LMIC is important to develop preventive strategies; however, evidence on this is scarce.[5] While the prevalence of the suicide rate is higher among older people, it is important to note that suicide is the second leading cause of death in youth (aged 24 years and younger). It is also the most frequent cause of death among young females.[6,7] A population-based study among adolescents in LMIC reported that approximately one in five have suicidal ideation (16.9%) and suicidal attempt (17%).[8] The same trend was reported in another study among adolescents in 40 LMIC. In addition, the prevalence of suicidal attempt range from 6.7% to 61.2%.[9] Apart from life loss, these preventable deaths among young people also cause substantial economic losses.[10]

Suicidal behaviour is a constellation of symptoms comprising of suicidal ideation, suicidal attempt, and suicide. Suicidal ideation is defined as the "thought of engaging behaviour intended to end one's life". A suicide attempt is defined as "engagement in potentially self-injurious behaviour with at least some intent to die", while suicide is defined as a "fatal self-injurious act with some evidence of intent to die".[11] Generally, psychiatric, psychological,[12] physical, personal, familial, and social were domains associated with suicidal behaviour.[13] Similarly, among the key risk factors for suicide among youth were mental disorders, specific personality characteristics, genetic, and family processes.[12–14] Another systematic review found that the socio-family environment and unhealthy behaviour are the factors associated with suicidal behaviours among youth in China.[15] The social–ecological model (SEM) provides a comprehensive framework in explaining the risk factors.16 SEM describes individuals as a part of a larger social system and the interactive

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characteristic of individuals that underlie health outcomes. The model was then modified and incorporates five levels of influence on health behaviour: intrapersonal factors, interpersonal process and primary groups, institutional factors, community factors, and public policy.[17] In addition, possible intervention strategies according to the levels were also described.[18] The Centre of Disease Prevention and Control has also adopted the SEM Model as a framework for suicide prevention.[19] As SEM is a comprehensive framework in describing suicide preventive strategies, this scoping review will therefore follow SEM framework.

It was estimated that for every suicide, there were 10–20 times suicide attempts. About 74.9% transitioned from ideation to plan and 71.2% transitioned from ideation to attempt.[7] This shows that there is room for preventive measures. Suicide is an indicator of the Sustainable Development Goal 3.4.2, which is to reduce by one-third premature mortality from non-communicable diseases through enhanced prevention, treatment, and promotion of mental health and well-being. The WHO recommends understanding the pattern of suicide as an important public health action to prevent suicidal behaviour.[20] The National Suicide Prevention Strategies also outlines risk factors identification and prevention as approaches that can be taken to change environments, protect people against suicidality and eventually change the behaviour that puts people at risks.[21] A review by Robinson et al. on youth suicide prevention mentioned that only limited studies were conducted in LMIC.[5] Two previous reviews that conducted on suicide in LMIC, however did not focused on young people and only focused on economic relationship with suicide.[3,22] On that account, this review aims to evaluate the factors associated with suicidal ideation and suicidal attempt and its preventive strategies among young people in LMIC according to the SEM model.

MATERIALS AND METHODS

This review has two parts. The first part is a scoping review of the factors associated with suicidal ideation and attempt among young people. The second part is the development of preventive strategies according to the identified factors. Both parts will be guided by the SEM model.

Search strategy

Electronic database searches were done in PubMed, Scopus, and PsycInfo. The search was conducted up to April 2021. Keywords combination of suicide OR suicidal ideation OR suicide attempt AND factors OR determinants OR predictors AND young people OR youth OR student were used for the search. The search was limited to 10 years as to reflect an update on the economic situation.

Studies selection

Articles were selected if they were conducted in LMIC and if they were in the English language. The countries were determined to be as LMIC if they were listed as such by World Bank Data. Studies that assessed risk factors of suicidal ideation and suicidal attempt were included. Studies were included if the population was among young people (aged 10–24 years old). Observational studies including cross-sectional or cohort study design were included. Qualitative studies, reviews, proceedings, and protocols were excluded.

Identified factors were classified according to the SEM model based on the description below:

1. Individual: Characteristics of the individual, including, knowledge, attitude, behaviour, developmental history.
2. Interpersonal: Formal and informal social factors, social support system including family, and friends.
3. Community: Relationship among organizations, institutions, and informal network
4. Societal: Local, state, and national laws and policies.

Data Extraction

The titles and abstracts of the articles retrieved from the databases were searched by one person. Two persons assessed and documented the articles as either include, exclude, or unclear. Full text of the articles that were classified as include or unsure were further assessed according to the eligibility criteria by two persons. Data were extracted from all potential studies and documented in a table. The table includes information on study characteristics (study design, total participants, and study duration), participant characteristics (mean age, gender, and level of education. Factors that reported a significant ($p < 0.05$) adjusted estimates (odds ratio (OR)) were also recorded.

RESULTS

Search results

Based on three electronic databases searches, 1760 articles were identified. A total of 312 duplicate articles were removed, and a further 1395 articles were excluded following titles and abstracts screening. Fifty-three full-text articles were assessed for eligibility, of which 43 articles were removed.

Characteristics of studies

A total of 10 studies with 45,278 participants that matched the criteria are included in this review.[23-32] Two studies were conducted in Brazil.[23,25] While other studies were conducted in Mozambique,[26] Ethiopia,[31] Ghana,[29] Nepal,[28] sub-Saharan Africa,[24] Iran,[27] Bangladesh[32], and Malaysia,[30] respectively. All studies were cross-sectional study design. The percentage of female in the study ranged from 45% to 60%. Table I shows the details of the characteristics of the studies.

Factors of suicidal ideation and suicidal attempt

The risk factors for suicidal ideation and suicidal attempt are categorized according to SEM. For personal level, the factors are demography, psychiatric, psychology, and substance abuse. For interpersonal level, the factors are abuse in home or school, and social support or close friends. The only factor identified for societal level is food insecurity. The factors associated with suicidal ideation and suicidal attempt is described in Figure 1.

Individual Demographic

The only contradictory finding is the gender risk on suicidal behaviour. Some of the studies reported male possess higher risk, while others reported female,[23-25,28-30] with the highest odds reported of aOR 5.12 (95% CI 3.32, 7.89). In terms of ethnicity, only one study showed significant odds of suicidal ideation in between ethnicity in Malaysia.[30]

Table I: Characteristics of Studies and Factors of Suicidal Ideation and Suicidal Attempt

Study	Country	Study design	Total sample size	Female (%)	Suicidal Ideation	Suicidal Ideation
Seidu et al., 2020	Mozambique	Cross-sectional	1918	N/A	Anxiety, having close friends, peer support, current smoker, experienced hunger, bullied, fight, attack, injury, truancy	Anxiety, having close friends, current smoker, experienced hunger, bullied, fight, attack, injury, parental understanding
Amare et al., 2018	Ethiopia	Cross-sectional	573	51.7	Absenteeism, felt lonely or sad and hopeless, poor social support, disappointed with school results, physically hurt	Living alone, absenteeism, loneliness, and feelings of hopeless and sadness, sleep disturbance, being physically hurt, poor social support
Asante et al., 2017	Ghana	Cross-sectional	1984	45.7	Male, anxiety, loneliness, truancy, bullied, attacked, in a fight, food insecurity	Anxiety, truancy, bullied, attacked, in a fight, food insecurity, parental understanding
Pandey et al., 2019	Nepal	Cross-sectional	6,531	N/A	Female, anxiety, loneliness, initiation of drug use, food insecurity	Female, anxiety, loneliness, having close friends, truancy, current smoker, and bullied
Ahmad et al., 2014	Malaysia	Cross-sectional	25,174	50.4	Female, Chinese, and Indian ethnicity, parental divorce/widow, stress, depression, anxiety, current smoker or drinkers, bullied, physically or verbally abuse at home, close friends	Not measured
Sharma et al., 2015	Brazil	Cross-sectional	916	53.6	Female, perceived unhappiness, smoking, in fight, insulted, attacked, sexual intercourse initiation	Female, perceived unhappiness, alcohol consumption, illicit drug use, in fight, insulted, attacked
Silva et al., 2014	Brazil	Cross-sectional	2207	62.1	Female, violent behaviour, cigarette smoking, alcohol consumption	Female, violent behaviour, cigarette smoking, alcohol consumption
Ziaei et al., 2017	Iran	Cross-sectional	1517	52.1	Smoking, ideation to use alcohol or other drugs, sexually abuse, being worried that you could not eat or did not feel hungry	Not measured
Mamun et al., 2020	Bangladesh	Cross-sectional	665	32.5	Separated/divorced, social media addiction, depression, anxiety, stress	Not measured
Shayo et al., 2019	Sub-Saharan Africa	Cross-sectional	3,793	52.1	Loneliness, anxiety, food insecurity, parental care	Loneliness, anxiety, food insecurity

Table II: Preventive Strategies according to Socio-ecological Framework

Level	Preventive Strategies
Individual	Awareness of mental disorders and substance abuse, self-help strategies on managing stress
Interpersonal	Home: Awareness programs among parents School: Awareness program among teachers and students, gatekeeper, peer leadership, skills training, screening, or assessment
Community	Training of healthcare providers and usage of artificial intelligence for prompt identification of suicidal behaviour and management of mental disorders
Societal	Policy making for food security Awareness programme among public

Psychiatric and psychology

Psychiatric disorders that were reported to have associated with suicidal ideation and suicidal attempt among young people are depression and anxiety. Higher odds of getting suicidal ideation among those who have anxiety were reported in four studies,[26,28-30] with the highest odds of 2.54 (95% CI 1.49, 4.30). While, the risk of having suicidal attempts among young people having depression was only reported in one study (aOR 2.25, 95% CI 1.97, 2.58).[30]

In terms of psychology, hopelessness was found to have been associated with suicidal ideation and attempt in one study.[31] In another study, adolescents who perceived unhappiness have a higher risk of having suicidal ideation or attempt.[25]

Substance use

Substance use such as smoking, alcohol intake, and drug were associated with an increased risk of having suicidal ideation and attempt.[23,25,26,28,30] Young people who are smokers have three times higher risk of getting suicidal ideation (aOR 3.00, 95% CI 1,69, 5.30)[27] and attempt (aOR 3.13, 95% CI 1.36, 7.23).[28]

Interpersonal abuse

Seven studies found that young people who gets abuse either physically, verbally, or sexually abuse at school or home has been associated with an increased risk of suicidal behaviour. Among those, sexual abuse had the highest odd (aOR 2.63, 95% CI 1.32, 5.24) of having suicidal intention.[27] In another study, young people who are physically hurt are four times more likely to have suicide attempt (95% CI 1.77, 10.20).[31]

Social support/close friends/loneliness

Young people with a good support system or having close friends are protective factors for both suicidal ideation and attempt.[33,34] Young people with close friends have lower risk of suicidal ideation (aOR 0.694, 95% CI 0.496, 0.971) and suicidal attempt (aOR 0.529, 95% CI 0.384, 0.729).[26]

Truancy

Another risk factors for suicidal behaviour among young people is truancy or absenteeism.26,28,29,31

Societal food security

At the society level, food security has been associated with an increased risk of having suicidal ideation or attempt in four studies.[24,26,28,29] The risk of having suicidal ideation was reported to be aOR 1.56 (95% CI 1.09, 2.23), while a suicidal attempt was aOR 1.48 (95% CI 1.05, 2.09).[29]

DISCUSSION

The aim of this review is to identify the factors associated with suicidal ideation and attempt among young people in LMIC according to the SEM model and recommend the preventive strategies. The review founds that the risk factors for suicidal ideation among young people in LMIC are being female, having psychiatric illness, or psychology problem, smoking or alcohol intake, being an abuse victim or bullied and experienced food insecurity. Whereas the protective factors are having good social support and close friend. Similar findings were reported in other reviews of factors of suicidal behaviour among young people.[13,15,35-37]

Risk factors

The factors for suicidal behaviour among young people in LMIC reported in this review are not distinctive from the common factors of suicidal behaviours. This could be contributed by lack of evaluation of socio-economic factors. Poor socio-economic status was identified as one of the important factors associated with suicidal behaviour.[38,39] Finding reveals suicide rates increase with unemployment, low income, and low housing quality. Another review also reported that although socio-economic position such as asset, education, and financial difficulty is associated with suicidal behaviours, however, findings are severely limited.[22] In addition, the socio-economic factors could moderate the existing factors which can cause a higher weightage on the suicide risk. Variables such as education, food insecurity, housing, socio-economic possess a strong association with mental disorders, thus, increase suicide behaviour.[40,41] In another example, the environmental factor associated with low income, may precipitate violence or abuse, thus increase the risk of suicidal behaviour.[42] Furthermore, another important factor which is mental health resources was also not studied. Mental health services problems in LMICs include a lack of budget and overburdened systems.[43]

Individual

Individual risk factors for suicidal ideation and attempt are psychiatric illnesses (anxiety, depression), psychology (stress, sleep disturbances), and substance abuse (smoking, drug, alcohol). Similar findings were reported in a meta-analysis, whereby 45% (95% CI 30% - 61%) of those who engaged in non-fatal suicidal behaviour in LMIC have a psychiatric disorder. The most prevalent disorder reported was mood disorder.[4] In another study, a significant direct relationship was found between baseline anxiety with suicidal ideation.[44] As for psychological factors, communication difficulties, decision-making impulsivity, and aggression were found to be significant risk factors for suicide attempts.[12]

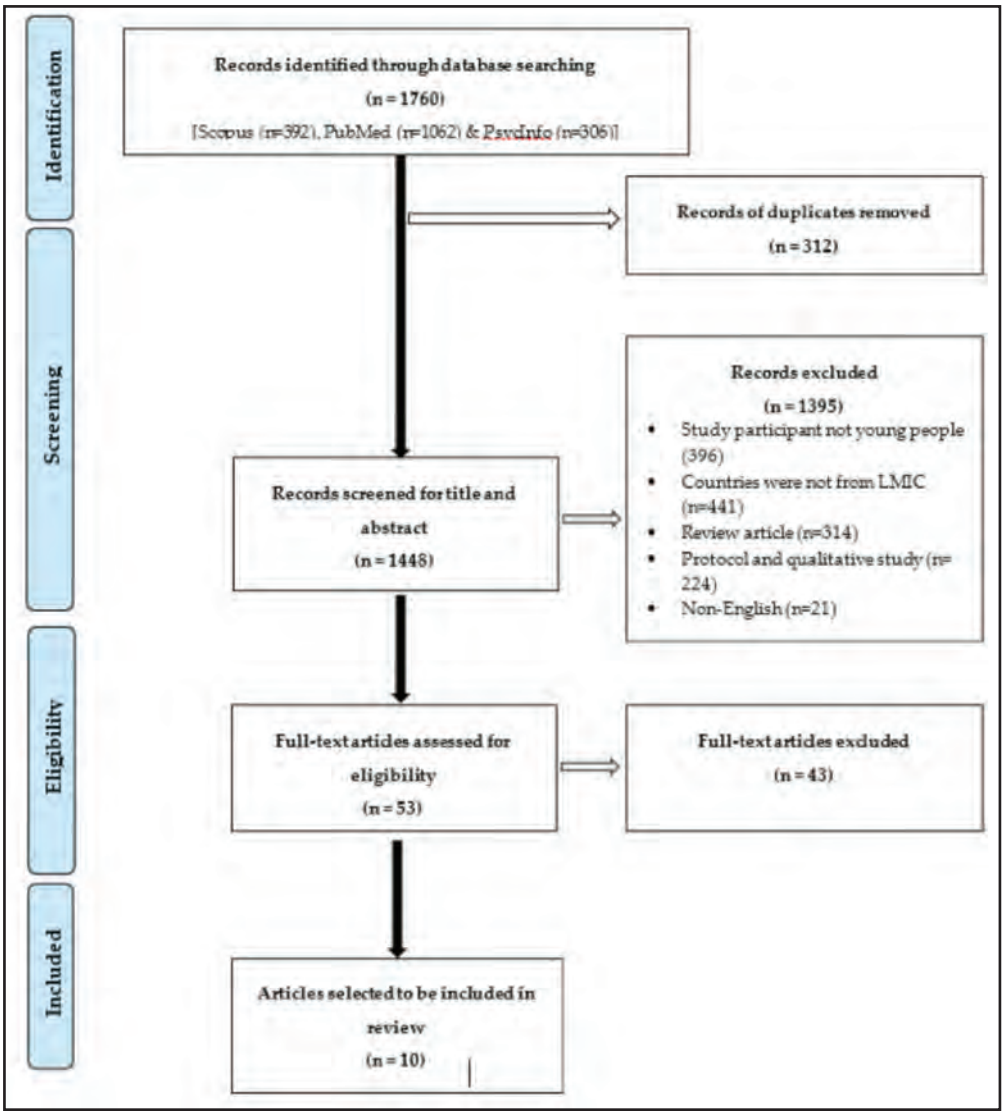

Fig. 1: PRISMA Flowchart

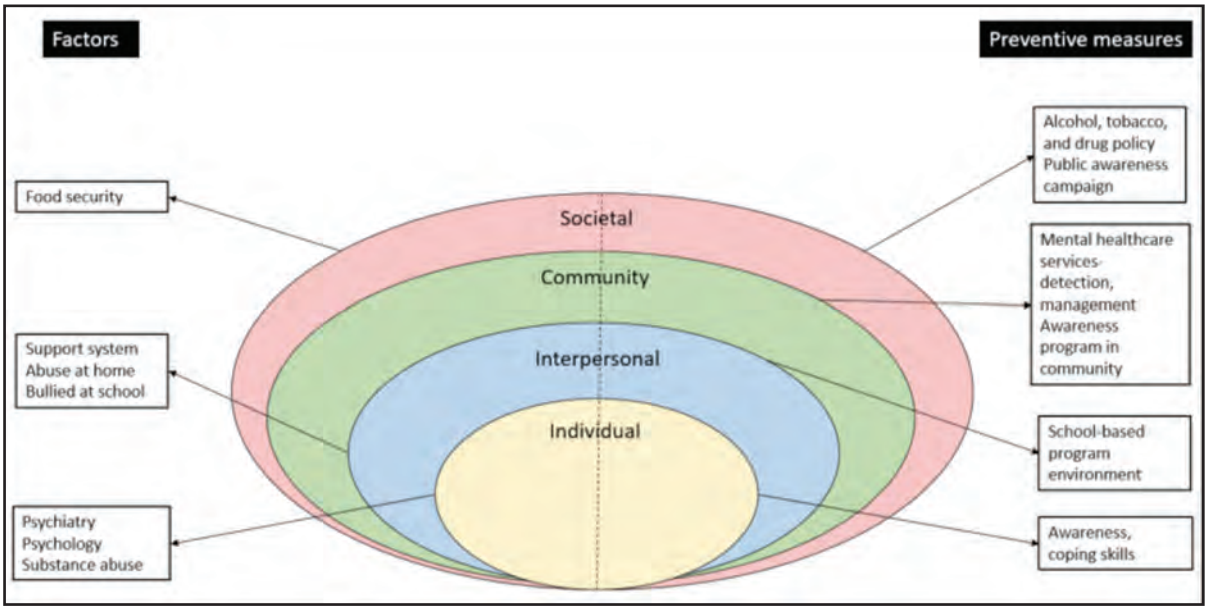

Fig. 2: Factors associated with suicidal behaviour and the preventive measures according to SEM framework

The only contradictory finding is the gender risk. Difference factors lead to suicidal behaviour between the gender. Internalizing emotional and behavioural problems leads to female suicidal behaviour such as eating disorder, post-traumatic stress disorder, bipolar disorder, being victim of dating violence, depressive symptoms, and history of abortion. While externalizing emotional and behavioural problem leads to male suicidal behaviour such as disruptive behaviour, hopelessness, parental separation, friend's suicidal behaviour, and access to lethal means.

Interpersonal

Main risk factor for interpersonal level is abuse and bully, consistent with previous findings.[45] Both violent and non-violent forms contributed to the increased risk of suicidal ideation.[46] A significant relationship was reported between adverse childhood experience with suicidality.[47] In terms of the type of abuse, sexual, physical, emotional, and neglect were all associated with suicidal attempts.[48] In contrast, those who have good social support includes having a close friend are protective factors of suicidal ideation and attempt. Similar findings were reported, whereby lower support, accounting for parent and friend independently predicted suicidal attempt.[34,49] In another study, negative relationship quality with parents predicted suicidal ideation even with parents who had no history of suicidal ideation.[50] Other than school and house settings, a meta-analysis reported that cyberbullying was more strongly related to suicidal ideation compared to traditional bullying.[51] None of the included studies assessed different types of bullying, thus it is unknown if cyberbullying is one of the risk factors. However, one of the studies reported that social media addiction is one of the risk factors for suicidal ideation.

Community

The SEM framework for community level examines the settings such as schools, and neighbourhoods, where social relationship occurs and seeks to identify the characteristics of these settings. The factors leading to suicide at community level may be exposure to community violence, or high crime levels, local drug trade, or barriers to healthcare access. Unfortunately, none of the studies included have assessed these variables. Although most of the studies had large study participants, however, as most of them used data from Global School-based Student Health Survey (GSHS), thus, the variables are the same.

Societal

At societal level, only food insecurity was found to be the risk factor for suicidal behaviour. This could be explained by food insecurity be associated with poorer psychological well-being or mental health and sleep health.52–54 A cross-sectional study of food security with suicide attempts among adolescents reported similar findings. However, the association was similar despite the difference in the income level of the countries.[55]

Preventive strategies

Preventive programmes are designed to identify vulnerable groups and improve the assessment and care of people with suicidal behaviour. Among the preventive measures taken were restricting access to lethal means, school-based awareness programs, lithium and clozapine use, and psychotherapeutic effort for depression.[56] National Suicide Preventive Programs that have been conducted in some countries have been proven effective.[57] However, the strongest effects of preventive strategies were seen in groups aged 25 to 44 years old and 45 to 64 years old.[57] The scope of suicide prevention among young people for this review covers the spans of primary and secondary prevention based on the SEM framework.

In view of similar factors, the recommended preventive strategies for LMIC are also general. However, LMIC must focus on strengthening of the strategies. This is because, evidence of the intermediate effectiveness of suicide preventive programme such as mental health literacy is still poor compared to high-income countries.[58,59] Poor mental health literacy will then lead to low help-seeking rate.[60] In addition, lack of access to or services for mental healthcare in these countries may increase suicidal behaviour.[61] Among the challenges that mental healthcare services in LMIC face are legislation and policy, resources, and availability of evidenced-based intervention.[62] Figure 2 summarizes the risk factors and the preventive measures according to the SEM framework.

Individual

The primary prevention for individual level may include awareness of mental disorders and substance abuse, and self-help strategies on managing stress. However, the effectiveness of this awareness programme is not available.[63] This is mainly due to the unavailability of the outcome measured. Most studies measured the intermediate outcome, which is an increase in knowledge and attitude. In view of an increase in knowledge and attitude may not represent changes in behaviour, the true reduction in the suicide rate is not available.[64]

Interpersonal

Primary prevention for the interpersonal level may include awareness programmes among parents and teachers. School is an ideal setting for a suicide prevention program, in view of truancy of absenteeism is associated with suicidal ideation. Previous school programme for suicide includes education and awareness, gatekeeper, peer leadership, skills training, and screening or assessment.[64,71] In a study of cyberbullying victimization and suicidal ideation, school connectedness was found to be moderating bullied victim with suicidal ideation.[72] Thus, it is worthwhile to strengthen interventions in school.

Community

Prompt identification and management of mental disorders are warranted for secondary prevention at the individual level. Accordingly, the training of healthcare providers in detecting suicidal behaviour has been proven effective.65 Recently, the use of artificial intelligence (AI) has been getting attention in the detection of suicide, either medically or socially.[66,67] In terms of management of mental disorders for suicide prevention, the review has shown a reduction in suicidal rate with the usage of Lithium, a mood stabilizer. Psychotherapy, particularly cognitive behavioural therapy (CBT) and dialectical behavioural therapy has also been

shown promising for the management of depression and anxiety.[68-70] Computerized CBT (cCBT) could be an alternative suicide preventive method among youth. In view of youth are generation ubiquitous with digital usage, online psychotherapy and AI through the social platform may be helpful.

Societal

The prevention strategies at societal level for food insecurities requires policy making especially at school level. This may include food programme at school for low-income students.[73] Awareness programme among public may also be beneficial. A study on the effect of public awareness campaigns on suicide showed reduction in the number of suicide following the intervention.[74] Table II summarizes the preventive strategies according to SEM framework.

LIMITATION

Although this review aims to focus on the factors associated with suicidal ideation and attempt exclusive in LMIC. However, the factors from the studies did not evaluate economic factors such as low family income, low educational level, or access to healthcare which may be the contributing factors for these countries. Thus, the review recommends that more studies focus on the factors associated with poverty and suicidal behaviour specific for LMIC. This is crucial in developing a well-informed suicide prevention strategy tailored to socio-economic context.

All studies were conducted in school setting. In addition, most of the studies used data from GSHS, thus the data were abundance and comparable. However, this causes studies to have similar results, although located in different sites. All studies were cross-sectional study design, thus causal inferences are not possible. In view of this is a scoping review, the search is not exhaustive. Furthermore, meta-analysis is not conducted which might limit the strength of evidence of the factors.

CONCLUSION

The factors associated with suicidal ideation and suicidal attempt are multifactorial, including psychological and psychiatric. These factors are also interconnected and can be explained by the SEM. Thus, the suicidal prevention strategies must take into consideration social, economic, and cultural factors. It needs a concerted effort from political such as smoking and alcohol policy for underage, ascertainment of food security, organization such as school and healthcare providers, and community.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SHORT COMMUNICATION

Initial experience of laparoscopic retroperitoneal partial nephrectomy in an academic hospital in Malaysia

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SUMMARY

Laparoscopic retroperitoneal partial nephrectomy (LRPN) is a technically demanding kidney surgery due to the limited space and unfamiliar approach in the retroperitoneal space. The aim of this study is to review the outcome of our initial experience in performing this procedure. All patients who underwent LRPN between 2019 to 2022 were included in this retrospective review. A total of 23 patients underwent LRPN. The mean operating time was 178±43 minutes and mean warm ischemia time was 20±5 minutes. The average estimated blood lost was 89±68ml and the mean postoperative hospital stay was 3.6±0.8 days. Two patients (11.1%) had positive margin and no local recurrence was seen after mean follow up of 15.8±12.0 months. Our initial experience on LRPN showed promising results to perform partial nephrectomy safely and effectively

KEYWORDS:
Nephrectomy, Kidney, Laparoscopy, Surgery

INTRODUCTION

Radical nephrectomy had been the standard treatment of localized renal tumour. It was performed to achieve an optimum oncological outcome, but this is associated with loss of renal function and a potential increase in cardiovascular events.[1,2] Hence, nephron sparing surgery or partial nephrectomy was recommended for the treatment of small renal tumour with comparable oncological outcome and less adverse events.[3]

Laparoscopic partial nephrectomy subsequently gained traction with comparable oncological outcomes to open surgery and better peri-operative outcome such as less blood loss, less transfusion, and shorter hospital stay.[4] Laparoscopic retroperitoneal partial nephrectomy (LRPN) is one of the more technically demanding kidney surgeries due to the limited space and unfamiliar approach. There are advantages with this approach including avoiding hostile intraperitoneal environment, containment of spillage in the retroperitoneal space, and faster postoperative recovery.[5-7]

Our centre started performing LRPN in February 2019 and since then, it has been our preferred technique for partial nephrectomy. This paper highlights our surgical technique and the outcome of our initial experience in performing LRPN.

MATERIALS AND METHODS

A retrospective data collection was done for all consecutive patients who underwent LRPN in Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia between February 2019 and April 2022. Patients' demographic data, characteristic of lesions, peri-operative data, histopathology findings, pre-, and post-operative serum creatinine were collected and analysed. Post-operative serum creatinine is defined as serum creatinine level taken at least one month after surgery.

Statistical analyses were performed using SPSS ver. 26.0 for Windows (IBM Corp., Armonk, NY, USA). Data with parametric distribution were expressed as mean ± SD while data with non-parametric distribution were expressed as median (interquartile range (IQR)). The correlation between various factors, i.e., characteristic of lesions, peri-operative parameters, and serum creatinine, were analysed using Pearson correlation (continuous variables) and Chi-square test (categorical variables).

Patients who were suitable for LRPN were selected and consented for surgery. Following general anaesthesia, patient was placed in flank position with ipsilateral side up on a flexed table. A 3-cm skin incision was made at the posterior axillary line below the 12th rib and thoracolumbar fascia was breached with forceps. Retroperitoneal space was created with finger dissection and expanded using an inflated sterile glove with 700–800 ml of air. A 12-mm camera port was inserted above the iliac crest and another two working ports were inserted at the anterior axillary line and the initial incision site.

After identification of the peritoneal reflection and lateroconal fascia, the fascia was incised to expose perirenal fat which was then mobilised to expose the tumour. Renal artery was identified, skeletonized, and prepared for clamping. Tumour margin was then identified and marked. Intraoperative ultrasound was used for endophytic tumour and tumour margin identification if required.

Bulldog clamp was applied to the renal artery. Tumour with a rim of normal tissue was excised using cold scissor. Stratafix™ spiral knotless tissue control device (Ethicon, NJ, USA) size 2/0 was used to close the medula and renal cortex in running fashion and Hem-o-lok clips (Weck Closure Systems, Research Triangle Park, NC, USA) were applied to

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Table I: Characteristics of the renal lesions

	n	%
Radius		
<4cm	14	60.9
4-7cm	9	39.1
>7cm	0	0
Laterality		
Right	17	73.9
Left	6	26.1
Anterior or Posterior		
Anterior	13	56.6
Posterior	10	43.5
Tumour location		
Upper pole	8	34.8
Mid pole	11	47.8
Lower pole	4	17.4
Exophytic or Endophytic		
Exophytic	16	69.6
Endophytic	7	30.4
Complexity (RENAL nephrometry score)		
Low (4-6)	12	52.2
Intermediate (7-9)	11	47.8

RENAL nephrometry score – scoring system to predict the complexity of the renal mass and the potential complications associated with partial nephrectomy. A higher score indicates a more complex renal mass and higher likelihood of complication from surgery.

Table II: Perioperative outcomes

	Mean	SD
Operating time (min)	178	±43
Warm ischaemia time (minutes)	20	±5
Estimated blood loss (milliliter)	89	±68
Mean post-operative hospital stay (days)	3.6	±0.8

keep suture in place. Bulldog clamp was removed and haemostasis was checked (Figure 1).

RESULTS

A total of 15 males (65.2%) and 8 females (34.8%) with a mean age of 60.7 ± 10.3 years underwent LRPN during this period. The characteristics of the lesions were listed in Table I and the peri-operative outcomes were summarised in Table II. The mean nephrometry score was 6 ± 1. There is a significant positive correlation between nephrometry score and warm ischemia time (WIT) (r=0.632, $p<0.05$), and nephrometry score and estimated blood loss (r=0.624, $p<0.05$).

One patient (4.3%) had radical nephrectomy due to segmental artery injury. There were 2 cases (8.7%) of Clavien Dindo Grade ≥2 complications. One patient had severe pain which required patient-controlled analgesia while the other patient had metabolic acidosis required monitoring at intensive care unit.

Twenty patients have post-operative serum creatinine results. Compared with pre-operative creatinine, there was an increase of serum creatinine by 8.5 ± 20.0 umol/L, or 13% (2.2-23.0%) increase. There is a significant positive correlation between warm ischemia time and percentage of change in serum creatinine (r=0.492, $p<0.05$).

The histopathology examinations revealed 18 renal cell carcinoma (RCC) (78.3%), 4 angiomyolipoma (17.4%), and one complex renal cyst (4.3%). Among the patients with RCC, there were two patients who had positive surgical margin (11.1%). No local recurrence or port site metastases was noted in patients with RCC after a mean follow-up of 15.8 ± 12.0 months.

DISCUSSION

LRPN has not been widely adopted due to the technical challenge faced during surgery. However, it provides a direct access to the renal hilum and posterior tumours. Meta-analysis had shown the additional benefits of less blood loss, shorter operating time, and shorter hospital stay in patients

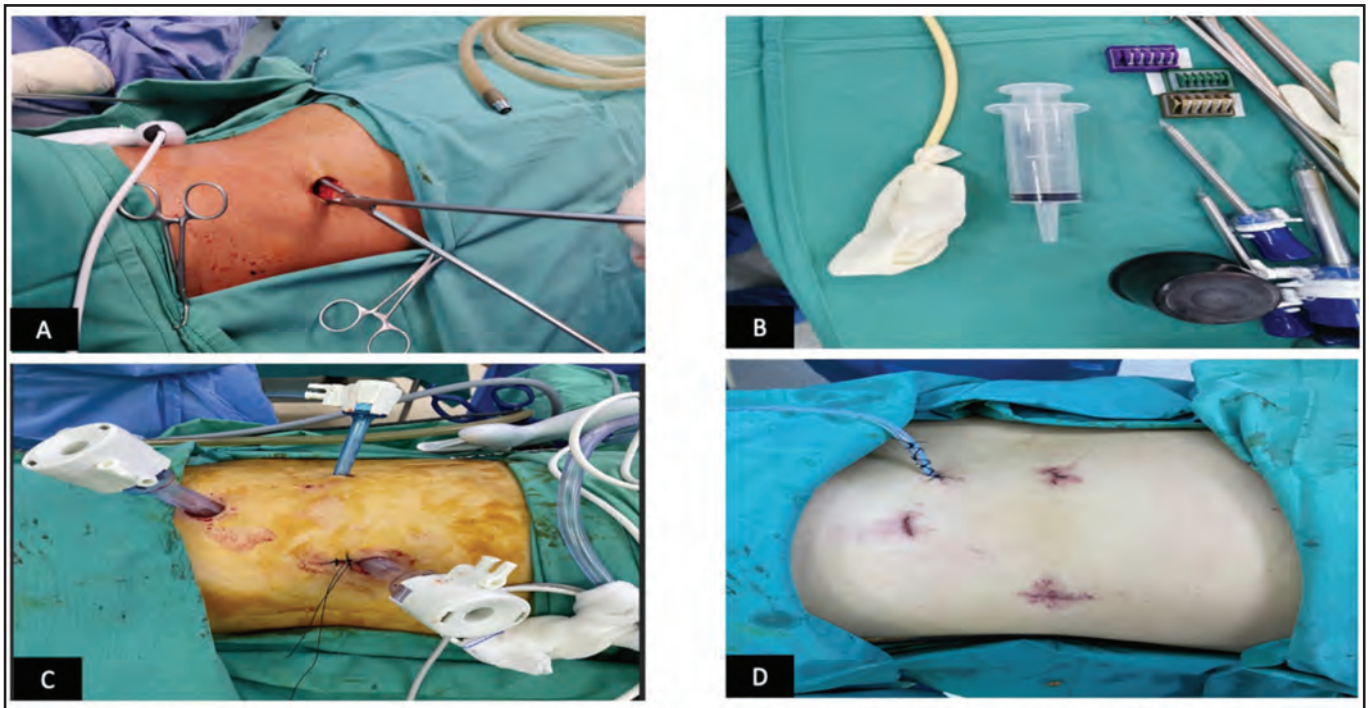

Figure 1: (A) Thoracodorsal fascia breach with forceps. (B) Sterile glove expander. (C) Port position. (D) Wound closure with drain insertion (*photographs with permission from patient)*

with LRPN.[6] Even a recent prospective multi-centre trial showed that minimally invasive retroperitoneal approach had lower complication rate and faster recovery.[7]

In our initial experience, our mean operating time was 178 minutes. The time was slightly longer compared to other series by Porpiglia et al. (median 150 min), Kumar et al. (mean 132.5 min), and Ouzaid et al. (mean 154 min).[7-9] Despite a longer operating time, our WIT was an average of 20 minutes which was comparable to the other series in the range of 20–35 minutes.[5,7-9] The longer operating time was likely due to our initial learning curve but by keeping the WIT short, the impact on the renal function was minimised.

The patients had an average increased serum creatinine of 8.5 umol/L (13%) postoperatively. The differences were less compared to the series reported by Pyo with an increase of 0.2mg/dL (17.7 umol/L).[5] The rise in serum creatinine was expected due to the loss of renal parenchyma from the surgery itself and the effect of ischaemia.

Two patients (8.7%) had Clavien Dindo Grade ≥2 complications in our series. This result was higher compared to results seen in the large multi-institutional cohort reported by Porpiglia et al. (3.4%), but lower than those reported in smaller series by Kumar et al. (16.7%) and Ouzaid et al. (29.9%).[7-9] Complications reported included deep vein thrombosis, bleeding requiring transfusion and embolization, fistula requiring stenting or nephrostomy, acute pulmonary embolism and acute renal failure requiring dialysis.[7-9] With increasing volume and experience, the number of complications is expected to decrease.

Patients with higher nephrometry score had longer WIT and estimated blood loss. This was expected due to the complexity of the tumour requiring more careful dissection and suturing. Similar result was seen in a retrospective review which showed higher complexity tumour and tumour size predicted higher WIT.[10]

Two patients had positive surgical margin with 8.7% positivity rate which was slightly higher than reported by Porpiglia et al. (5.6%), Kumar et al. (4.1%), and Ouzaid et al. (3%).[7-9] Both lesions were endophytic and thus highlighted the difficulty to identify the margins of endophytic tumour even with intraoperative ultrasound.

Despite the positive outcomes, there were limitations associated with this study. This was a retrospective analysis from a single centre with a small sample size. There was also a lack of comparative arm. Despite these limitations, we believe that the encouraging results will provide a framework for further study on the long-term oncological and functional outcome in our centre.

CONCLUSION

Our initial experience showed that LRPN can be a safe and good alternative to perform partial nephrectomy. Further study is required to assess the peri-operative, long-term oncological, and functional outcome of this procedure.

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SHORT COMMUNICATION

Changes in blood pressure after Messenger RNA COVID-19 vaccination

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SUMMARY

The SARS-Cov-2 (COVID-19) vaccination began in Malaysia in March 2021 among frontliners and healthcare workers. Everyone at our hospital received the tozinameran (BNT162b2) Messenger RNA COVID-19 vaccine. Although hypertension has not been mentioned explicitly as an adverse event, concerns were raised after some healthcare staff observed an increase in their blood pressures. In response to that, the hospital began collecting vital signs during second-dose appointments. Vital signs were measured before, immediately after and 15–30 minutes post-vaccination. We report our findings from the institution-wide effort to monitor changes in blood pressure among its staff and respond to any possible unwanted events.

KEYWORDS:
Hypertension, blood pressure, SARS-Cov-2, COVID-19, mRNA vaccine

INTRODUCTION

The SARS-Cov-2 (COVID-19) vaccination in Malaysia began in March 2021 among frontliners and healthcare workers. In preparation for the program, our hospital collected information on demographics, comorbidities, and willingness to be vaccinated among all its healthcare and essential workers using an online survey.

Vaccination at our hospital began on March 1. Everyone received the tozinameran (BNT162b2) mRNA COVID-19 vaccine. By the end of the month, 4904 staff members had received at least one dose (1225 completed two doses distanced 21 days apart, while another 3679 had yet to receive their second dose). Although hypertension has not been mentioned explicitly as an adverse event,[1] concerns were raised after some healthcare staff observed an increase in their blood pressure post-vaccination.

In response to that, the hospital began collecting vital signs during second-dose appointments. Vital signs were measured three times for each staff member using automated blood pressure monitors that have been calibrated by the vendor of the machines. With the exception of emergencies where the subjects were in a supine pose, all blood pressures were measured in a seated position with the cuff on the arm that was not vaccinated.

Pre-vaccination vital signs were recorded when the staff members arrived at the vaccination site, while post-vaccination vital signs were measured immediately after vaccination and again 15–30 minutes later in a waiting room. They were allowed to leave if their vitals were stable or if they had no complaints. As there was a high load of subjects at the site, vital signs measured immediately post-vaccination were actually delayed by a few minutes. For the same reason, we could not afford to monitor for delayed or extended effects on blood pressure.

RESULTS

Characteristics of the subjects are shown in Table I. Most of the subjects did not report any adverse effects from both first and second doses. Among those who experienced adverse effects, 84.5% claimed the severity was worse for the second dose. The most common adverse effects were redness, pain or swelling at the injection site, tiredness, fever, chills, headache, and myalgia.

Mean pre-vaccination systolic and diastolic blood pressures were 130.1 (SD 17.38) mmHg and 80.2 (SD 11.62) mmHg, respectively. Both systolic and diastolic blood pressures were significantly higher among those with underlying hypertension compared with those without (SBP difference: 19.9 (95% CI 17.77, 22.0) mmHg, $p<0.001$; DBP difference: 8.9 (95% CI 7.58, 10.29) mmHg, $p<0.001$).

Compared with baseline, blood pressure was increased in more than half of the subjects immediately and 30 minutes post-vaccination. The mean changes across all measures were highly significant, but the difference may not be clinically important. When we looked at those with hypertension (n = 244), paired t-tests revealed that only increases in diastolic blood pressure were significant (Table II).

The mean increase in systolic blood pressure immediately postvaccination was significantly lower for females compared to males (1.96 (SD 12.20) vs 3.19 (SD 13.26), $p = 0.001$). There were no significant changes in mean blood pressure among those with history of SARS-Cov-2 infection compared with those without previous exposure to the virus.

Overall, 58 (1.02%) were admitted into the observation room either due to hypertensive urgency or complaints of

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Table I: Characteristics of subjects, N = 4906

Characteristics	
Age in years, mean (SD)	33.6 (8.3)
Females, n (%)	3074 (62.7)
Current smokers, n (%)	370 (7.5)
History of serious allergic reaction, n (%)	309 (6.3)
History of confirmed SARS-CoV-2 infection, n (%)	51 (1.0)
History of comorbidities, n (%)	
Hypertension	244 (5.0)
Diabetes mellitus	141 (2.9)
Hyperlipidaemia	18 (0.4)
Asthma	207 (4.2)
Cardiovascular disease	43 (0.9)
Baseline (pre-vaccination) blood pressure in mmHg, mean (SD)	
Systolic	130.1 (17.38)
Diastolic	80.2 (11.62)

SD, standard deviation.

Table II: Changes in blood pressure immediately and 15–30 minutes after vaccination compared with baseline (pre-vaccination)

Blood pressure	Immediately after vaccination compared with baseline	15–30 minutes after vaccination compared with baseline
Mean systolic change (95% CI), mmHg		
All subjects, n = 4906	2.3 (1.95, 2.66) **	1.1 (0.76, 1.48) **
Subjects with hypertension, n =244	1.4 (-0.41, 3.26)	-1.0 (-2.87, 0.91)
Subjects with cardiovascular disease, n =43	3.8 (0.28, 7.39) *	2.0 (-1.78, 5.74)
Mean diastolic change (95% CI), mmHg		
All subjects, n = 4906	2.4 (2.13, 2.68) **	2.2 (1.87, 2.43) **
Subjects with hypertension, n =244	3.1 (1.58, 4.51) **	2.2 (0.76, 3.58) **
Subjects with cardiovascular disease, n =43	1.8 (-1.21, 4.89)	2.2 (-0.80, 5.13)

SD standard deviation
Paired t-test significance: * p <0.05, ** p <0.001

giddiness. Their mean baseline systolic and diastolic blood pressures were 159.5 (SD 20.19) and 96.4 (SD 12.92), respectively. Ten (17.2%) had underlying hypertension. Eighteen (31.0%) whose complications did not improve were transferred to the Emergency Department for further monitoring and treatment as necessary.

DISCUSSION

Our findings extend similar occurrences that have been reported previously in several European countries to the Asian population.[2-5] A recent paper by Bouhanick et al.[6] has suggested a possible increased risk of hypertension with the Pfizer/BioNTech vaccine. Several mechanisms for hypertension have been suggested involving interactions between components of the vaccine and the renin-angiotensin system; however, they remain hypothetical and causality is yet to be established.[3,6]

Our findings indicated a general increase in blood pressure in more than half of the subjects; however, only a small fraction reacted symptomatically. Pain, stress, or other emotional triggers on changes in blood pressure could not be ruled out. We were also unable to monitor if these changes persisted or if there were any delayed effects on the blood pressure. Thus, it may be in the interest of future studies to observe for extended effects of the vaccine on blood pressure. In our subjects, history of hypertension or other comorbidities was voluntarily reported and there may be cases where hypertension had been undiagnosed.

Overall, the increases were relatively small and may not prevail over the benefits offered by vaccination. Nevertheless, on the safety side, monitoring of blood pressure and other related symptoms may be warranted to prevent any unexpected serious events.

DECLARATION

Ethics approval and consent to participate

Approval and waiver of informed consent were obtained from the Medical Research and Ethics Committee (MREC) Malaysia (Ref: 21-02036-YOX (2)).

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Oral health is crucial among people with dementia

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Dear Editor,

It is expected that the number of people with dementia will continue to rise as the number of older adults increases globally and in Malaysia. Dementia affected approximately 57 million people worldwide in 2019, and it is estimated that this will increase to 150 million people in 2050.[1] Malaysia has the same trend of population ageing, with a 0.5% increase of those aged 60 years and above from the year 2020 (3.5 million;10.7%) to 2021 (3.6 million; 11.2%). The Department of Statistics Malaysia reported that 7.2% population were aged 65 years and over in 2020 and will increase to approximately 15% by 2040. The dental annual report 2019, reported a 1.3% increase in the number of people retaining natural teeth more than 20 among the older adults over 2 years period (2018–2019). Thus, it is likely that there is a potential for those who live with dementia will retain their natural teeth.

Many studies have reported poor oral hygiene among individuals with dementia compared to individuals without dementia. Good oral health is crucial to prevent pain and infections, as well as to ensure balanced diet among this vulnerable people. The oral health conditions deteriorate as the individual's clinical condition is associated with the progression of their dementia. As the dementia conditions progresses in severity, the dependency level increases, requiring more intensive oral hygiene care and support. Basic oral hygiene care such as toothbrushing twice daily may no longer be appropriate. The prevalence of tooth decay, missing and filled teeth, soft tissue lesions, and periodontal disease are higher in individuals with dementia than in individuals who do not have a diagnosis of dementia. Despite the poor oral health conditions reported among people diagnosed with dementia in many studies, there is still limited research on the importance of good oral health and oral health intervention studies aiming to improve their oral health conditions and quality of life. However, a few intervention studies, such as caregivers' education and oral health care, have shown improvement in the quality of life and oral health conditions among those diagnosed with dementia. Hence, more studies on insight of oral health awareness and knowledge for people diagnosed with dementia and their caregivers are warranted.

Poor oral health conditions, mainly periodontal disease, have been shown to be associated with the risk of developing or progressing of a systemic disease such as cardiovascular disease, cerebrovascular disease, and pulmonary disease. Despite this existing relationship, recent evidence-based studies have shown that periodontal disease may significantly impact cognitive function and increase the risk of developing dementia.[2,3] It has been suggested that the bacterial load and the inflammatory markers that link to periodontal disease can intensify inflammation in the central nervous system, resulting in increasing the risk of dementia. However, there is still lacking evidence in this area. Nevertheless, few studies have shown a reduction in periodontal prevalence may lower the number of people with dementia. A longitudinal study of ten years in Taiwan concluded that those who had periodontal treatment and dental prophylaxis were at a lower risk of developing dementia than those who had not received any periodontal treatment. The same finding was also reported in another 10 years follow-up study in Korea; there was an increased risk of developing dementia (aHR=1.06; 95% CI=1.01–1.11) and Alzheimer's disease (aHR=1.05; 95% CI=1.00–1.11) among those diagnosed with chronic periodontitis compared with subjects who did not have chronic periodontitis. Although high heterogenicity and different study types, periodontal diseases have been suggested as a potentially modifiable risk factor for dementia. Thus, reducing or preventing periodontal diseases related to dementia through timely intervention, enhanced screening services, and efficient dental treatment and care would help to reduce the impact and risk of developing dementia.

Despite the growing number of ageing population with dementia, there is still a lack of awareness and studies on dementia and oral health-related dementia in Malaysia, particularly identifying prevention and prognostic factors. A scoping review of published studies on the older adult population with dementia in Malaysia from 2010 to 2019 claimed that most studies focus on the identification and management of dementia, mainly on screening tools, methods, and prevalence of dementia in Malaysia. In contrast, as there is no cure for dementia, many studies in developed and other developing countries have embarked on prevention strategies, interventions, and identifying factors in reducing the impact of dementia, including those related to oral health and dementia.

In short, awareness of the importance of good oral health mainly to prevent periodontal disease and tooth loss among people diagnosed with dementia and their caregivers is still lacking. More evidence-based studies are required to determine the best approach for a different type of dementia to ensure they have a better quality of life.

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