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4th Floor, MMA House, 124, Jalan Pahang, 53000 Kuala Lumpur.
Tel: (03) 4042 0617, 4041 8972, 4041 1375 Fax: (03) 4041 8187
E-mail: info@mma.org.my / mjm@mma.org.my
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The Medical Journal of Malaysia
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Acknowledgements:
Acknowledgements of general support, grants, technical assistance, etc., should be indicated. Authors are responsible for obtaining the consent of those being acknowledged.

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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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Panirchellvum V. 'No outdoor activities if weather too hot'. the Sun. 2016; March 18: 9(col. 1-3).

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Central corneal thickness and topographic indices in Malaysian children with vernal keratoconjunctivitis

Wan Mohd Mohd-Alif, MMed[1,2,3], Tengku Norina Tuan Jaffar, MMed[3], Ismail Shatriah, MMed[1,2]

[1]Department of Ophthalmology and Visual Science, School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia, [2]Ophthalmology Clinic, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [3]Department of Ophthalmology, Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan, Malaysia

ABSTRACT

Introduction: Vernal keratoconjunctivitis (VKC) is a chronic allergic disease characterised by intense ocular surface symptoms and corneal involvement. There is limited data about the corneal changes in children with VKC based on severity of the disease. We aimed to compare the central corneal thickness (CCT) and corneal topographic indices in Malaysian children with VKC, as well as among the varying grades of VKC severity.

Materials and Methods: This study is a comparative, cross-sectional and hospital-based study. We recruited 83 children with VKC and 83 healthy children as controls. All children underwent complete ocular examinations, CCT measurement using an ultrasound pachymeter and corneal topography using a Placido disc corneal analyser.

Results: There was a statistically significant difference of means CCT and topographic indices in children with VKC compared to controls (p<0.05). The probability keratoconus reached 18% in children with VKC. The mean CCT was observed to be thinnest in the severe-to-very severe groups of VKC compared to the mild-to-moderate (p<0.05). The means simulated-K1 and -K2, apical keratometry, apical gradient curvature, superior-inferior index and keratoconus prediction index were significantly different in severe-to-very severe VKC compared to mild-to-moderate VKC and controls (p<0.05). However, there was no significant difference in mean cylinder value and percent probability keratoconus when comparing different groups of severity of VKC (p=0.912 and 0.070 respectively).

Conclusion: Children with VKC have thinner CCT and topographic indices changes compared to healthy children. Similar pattern was observed between groups with VKC. Degree of astigmatism and probability of keratoconus were similar in mild-to-moderate and severe-to-very severe groups.

KEYWORDS:
Central corneal thickness, corneal topographic indices, children, vernal keratoconjunctivitis, severity

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral, seasonal allergic inflammatory disease of the ocular surface. It is a chronic disease with episodes of acute exacerbation, primarily involving the tarsal and bulbar conjunctiva.[1,2] VKC has a wide geographical distribution. In the Asia-Pacific region, especially in Southeast Asian countries, no widely accessible studies have examined the prevalence of VKC. The closest available data that can be obtained is from the Allergies in Asia Pacific survey, which studied eight Asia Pacific countries and found that about 6-8% of the respondents from Malaysia had a physician diagnosis of acute rhinoconjunctivitis.[3]

VKC commonly occurs in school-age children aged six to 11 years old.[4,5] A male preponderance has been observed, especially in patients under 20 years of age,[4] who commonly present with symptoms of pruritus, hyperaemia, chemosis, photophobia and filamentous and sticky mucous discharge. VKC can be classified based on the site of predominant involvement, either tarsal, limbal or mixed type.[1] The late stage of the disease can present with severe and blinding complications involving the cornea, such as corneal scarring,[6] and amblyopia may be due to corneal opacity, irregular astigmatism and keratoconus.[7]

There are few studies highlighted corneal changes in VKC patients and control groups.[8-12] The chronic microtrauma caused by VKC can result in a chronic inflammatory process that damages the cornea, leading to a gradual loss of stromal mass. This can cause corneal thinning and steepening, resulting in acquired astigmatic refractive errors and, in severe cases, keratoconus which can be detected through pachymetry and corneal topography.[11]

Based on a PubMed search using corneal topography, VKC and severity as the keywords, we were unable to find published data comparing the severities of VKC in central corneal thickness (CCT) and corneal topography. It is essential for an early detection of subclinical keratoconus in patients with VKC. Early identification and prompt treatments should be instituted to prevent further complications leads to visual threatening conditions. This study aims to compare the mean CCT and corneal changes among these children with VKC, based on severity of the disease in two tertiary hospitals in the East Coast of Peninsular Malaysia.

MATERIALS AND METHODS

This research concerns a cross-sectional study conducted in the Ophthalmology Clinics of Hospital Universiti Sains

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Corresponding Author: Ismail Shatriah
Email: shatriah@usm.my

Malaysia and Hospital Raja Perempuan Zainab II, Kelantan, Malaysia, from December 2020 to May 2022. Children who were diagnosed with VKC and healthy children aged between seven and 16 years old were recruited. The study was conducted in accordance with the Declaration of Helsinki for Human Research and approved by the Human Research Ethics Committee of Universiti Sains Malaysia, Malaysia (USM/JEPeM/20100531). Written consent and assent were obtained from the children and their parents.

Children who were diagnosed with VKC attended consultation visit at the ophthalmology clinics of both institutions were prospectively enrolled in the study. The healthy children were selected from the staffs' children in both institutions. The inclusion criteria for children with VKC were children diagnosed with VKC, aged seven to 16 years old. Healthy children were recruited from the same age group with no concurrent ocular diseases. Children who were known to have ocular pathology or who had undergone ocular surgery or trauma were excluded from the study. Additionally, healthy children to have a corneal scar, previous corneal diseases and refractive error exceeding ±3.00 spherical Dioptre (D) and -1.75 cylindrical D were also excluded from this study.

All children were screened for inclusion and exclusion criteria during the interview sessions. Demographic data, including age, race, gender, family history and education level, were taken. Systemic history included a history of any co-morbidity, allergic history, duration of diagnosis and current treatment. The ocular history included ocular symptoms, past ocular history of ocular trauma, intraocular surgery and refractive surgery. Complete ophthalmic examinations were performed, including visual acuity, refraction, anterior segment, intraocular pressure measurement and fundus examination.

Children with VKC were then classified into mild-to-moderate and severe-to-very severe groups based on the symptoms and signs after careful examination by the paediatric ophthalmologist during the first presentation.[13] Parameters measured were CCT and topographic indices, i.e. anterior corneal surface and keratoconus screening. These measurements were performed on the same day.

Measurement of the CCT was performed using the Ultrasound Pachymeter Pocket II (Quantel Medical, France) machine, where the tip probe contacted the cornea at the visual centre. To ensure the repeatability of the positioning of the of the pachymeter in subsequent measurements, a fixation panel was placed in front of the children. An average of five consecutive readings were used for the data analysis.

Anterior corneal surface and keratoconus screening were measured using Corneal Analyzer CA 800 (Topcon, Europe). The device is a Placido disc based corneal topographer that generates a variety of quantitative measurements. The recorded measurements for anterior corneal surface were simulated keratometry (Sim-K1 and Sim-K2) and astigmatism. Parameters recorded for keratoconus screening included apical keratometry, apical gradient curvature, superior-inferior index, keratoconus prediction index and percent probability keratoconus. The average of three consecutive readings was documented for data analysis.

The Sim-K1 and Sim-2 calculates the average keratometry powers of the steepest and flattest meridians in the paracentral zone of the cornea. It is considered abnormal when the value is above 48 D. Cylinder is the difference between Sim-K1 and Sim-K2 of more than 1.5 D. Apical keratometry represents the value of instantaneous curvature in the corneal apex greater than 50 D. Apical gradient curvature is the average difference per length unit of the corneal power in relation to the apical power greater than 2D/mm. The superior-inferior index is the difference of average power between the superior area and inferior with a value of more than 2D. Keratoconus prediction index is considered more than 20%. Percent probability of keratoconus below 20% is considered normal, while value between 20-45% is rank suspicious for keratoconus and above 45% is considered keratoconus in this study.[14-16]

The IBM SPSS Statistics for Windows Version 27.0 programme was used for sample description calculation (mean, median, standard deviation and total index). The T-test was selected for comparison of the mean CCT and the mean corneal topography parameters between children with VKC and the control group as well as among different grades of VKC severity. The significance level was set at 5% ($p<0.05$).

RESULTS

As shown in Table I, this study consisted of 172 Malay participants. Among them, 101 were male and 71 were female. The ages of the participants ranged from 7 to 16 years old, with a mean age of 11.8 (2.5) for the children with VKC and 11.9 (2.8) for the controls. The mean duration of the illness was 2.5 (1.5) years.

The majority of children with VKC comprised the tarsal type, which was 41 (47.7%), followed by the mixed 25 (29.0%) and limbal type in 20 (23.3%) children. Twenty-four (27.9%) children were categorised as mild in disease severity, 19 (22.1%) as moderate, 38 (44.2%) as severe and five (5.8%) as very severe. About 74.4% of the children rubbed their eyes occasionally (<5 times per day), and 25.6% rubbed their eyes frequently (≥5 times per day). All children with VKC involved in this study were on treatment. Thirty-eight (44.2%) children were on topical anti-allergic only, 43 (50.0%) children were on steroids and five (5.8%) children required surgical procedures.

We did not find any statistically significant differences between the right and left eyes with regard to the variables studied; thus, only the results for the right eye were reported. Tables II shows comparisons between the VKC group and the control group. The mean CCT was 539.9 (13.40)µm in the VKC group and 546.59 (12.17)µm in the control group. A statistically significant difference ($p<0.05$) was found in the mean CCT among the two groups. Meanwhile, a comparison of the means of corneal topographic indices between the two groups showed a statistically significant difference ($p < 0.05$). Children with VKC reached 18% probability keratoconus based on corneal topographic measurements.

Table I: Demographic and clinical data of children with VKC and controls

Variables	VKC (n = 86)	Control (n=86)	p-value
Age (years), mean (SD)	11.8 (2.5)	11.9 (2.8)	0.932[a]
Gender, n (%)			
Male	57 (66.3)	44 (51.2)	0.044b*
Female	29 (33.7)	42 (48.8)	
Types, n (%)		-	-
Tarsal	41 (47.7)		
Limbal	20 (23.3)		
Mixed	25 (29.0)		
Severity, n (%)		-	-
Mild	24 (27.9)		
Moderate	19 (22.1)		
Severe	38 (44.2)		
Very Severe	5 (5.8)		
Frequency of rubbing, n (%)		-	-
Less 5 times/day	64 (74.4)		
5 times or more/day	22 (25.6)		
Duration of illness (years)Mean (SD)	2.5 (1.5)	-	-
Treatment, n (%)		-	-
Topical anti-allergic	38 (44.2)		
Corticosteroid	43 (50.0)		
Surgical procedure	5 (5.8)		

VKC = Vernal keratoconjunctivitis; SD = Standard deviation
[a]Independent t-test; [b]Pearson chi-square test; *Statistically significant difference ($p < 0.05$).

Table II: Comparison of mean CCT and corneal topographic indices between children with VKC and controls

Variables	VKC (n = 86) Mean (SD)	Control (n = 86) Mean (SD)	Mean difference (95% CI)	t-statistic (df)	p-value
Pachymetry					
CCT (µm)	539.40 (13.40)	546.59 (12.17)	-6.651 (-10.5 to -2.8)	-3.407 (170)	0.01[a]*
Anterior corneal surface					
Simulated K1 (D)	45.77 (2.99)	43.97 (1.65)	1.80 (1.07 to 2.53)	4.88 (170)	<0.001[a]*
Simulated K2 (D)	47.07 (3.03)	44.71 (1.87)	2.36 (1.60 to 3.12)	6.14 (170)	<0.001[a]*
Cylinder (D)	1.32 (1.18)	0.72 (0.63)	0.60 (0.32 to 0.89)	4.19 (170)	<0.001[a]*
Keratoconus screening					
Apical keratometry (D)	48.57 (4.52)	45.72 (2.35)	2.84 (1.76 to 3.92)	5.17 (170)	<0.001[a]*
Apical gradient curvature (D/mm)	2.11 (3.30)	0.91 (0.85)	1.19 (0.47 to 1.92)	3.24 (170)	0.001[a]
Superior-inferior index (D)	1.24 (1.10)	0.77 (0.44)	0.47 (0.22 to 0.73)	3.71 (170)	<0.001[a]*
Keratoconus prediction index	13.67 (26.70)	2.41 (10.61)	11.27 (5.15 to 17.38)	3.64 (170)	<0.001[a]*
Percent probability keratoconus	21.90 (32.49)	3.62 (6.38)	0.18 (0.11 to 0.25)	5.12 (170)	<0.001[†]
Normal (less than 20%)*	66.0	93.0	NA	NA	NA
Suspicious (20-45%)*	16.0	7.0			
Keratoconus (more than 45%)*	18.0	0.0			

VKC = Vernal keratoconjunctivitis; SD = Standard deviation; CI = Confidence interval; D =Dioptre, *percentage, NA = Not applicable
[a]Independent t-test; *Statistically significant difference ($p < 0.05$).

Table III shows comparisons between mild-to-moderate VKC and severe-to-very severe VKC in the mean CCT and corneal topographic indices, respectively. The mean CCT in the mild-to-moderate VKC group was 546.79 (12.52)µm compared to 533.09 (10.52)µm in the severe-to-very severe VKC group. The difference between the two mean CCT values was found to be statistically significant ($p<0.05$). There was a statistically significant difference ($p<0.05$) between the two groups in almost all of the indices when comparing the means of corneal topographic indices between the two groups. Only the mean cylinder value ($p=0.912$) and percent probability keratoconus ($p=0.070$) was insignificantly different between the two groups. Probability keratoconus reached 9% in mild-to-moderate group and 26% in severe-to-very severe group.

DISCUSSION

VKC has been associated with CCT and corneal topographic changes in multiple studies.[8-10] We present new data on the means of CCT and corneal topography in children with VKC in this hospital-based study. Our study differs from others because we included a comparison of both the means of CCT and corneal topography between different severities of VKC. This information is important for an early detection of

Table III: Comparison of mean CCT and corneal topographic indices between mild to moderate VKC and severe to very severe VKC

Variables	Mild to moderate (n = 43) Mean (SD)	Severe to very severe (n = 43) Mean (SD)	Mean difference (95% CI)	t-statistic (df)	p-value
Pachymetry					
CCT (µm)	546.79 (12.52)	533.09 (10.52)	13.70 (8.74 to 18.66)	5.49 (84)	<0.001[a]*
Anterior corneal surface					
Simulated keratometry1 (D)	44.51 (2.23)	47.04 (3.15)	-2.53 (-3.70 to -1.36)	-4.30 (84)	<0.001[a]*
Simulated keratometry2 (D)	45.80 (1.82)	48.35 (3.46)	-2.55 (-3.73 to -1.36)	-4.27 (84)	<0.001[a]*
Cylinder (D)	1.33 (1.42)	1.31 (0.90)	0.28 (-0.48 to 0.54)	0.11 (84)	0.912 [a]
Keratoconus screening					
Apical keratometry (D)	46.33 (1.94)	50.80 (5.23)	-4.47 (-6.16 to -2.78)	-5.26 (84)	<0.001[a]*
Apical gradient curvature (D/mm)	1.06 (1.00)	3.15 (4.34)	0.68 (-3.43 to -7.35)	-3.07 (84)	0.003[a]*
Superior-inferior index (D)	0.77 (0.44)	1.71 (1.34)	-0.94 (-1.37 to -0.51)	-4.35 (84)	<0.001[a]*
Keratoconus prediction index	1.26 (3.20)	26.09 (33.42)	-24.84 (-35.02 to -14.66)	-4.85 (84)	<0.001[a]*
Percent probability keratoconus	0.12 (0.27)	0.31 (0.35)	-0.19 (-0.32 to -0.05)	-2.80 (84)	0.070[a]*
Normal (less than 20%)*	80.0	51.0	NA	NA	NA
Suspicious (20 45%)*	9.0	23.0			
Keratoconus (more than 45%)*	9.0	26.0			

VKC = Vernal keratoconjunctivitis; SD = Standard deviation; CI = Confidence interval; D = Dioptre, *Percentage, NA = Not applicable
[a] Independent t-test; *Statistically significant difference (p< 0.05).

subclinical keratoconus prior to reduced visual acuity, changes in cylinder values and keratometric changes.

In our demographic result, there was a statistically significant difference in gender between children with VKC and controls (p<0.05). VKC was found to be two times more common in males than in females, with a total of 57 (63%) male subjects and 29 (33.7%) female subjects. This male-biased pattern is aligned with previous studies that have reported male-to-female ratios ranging from 4:1 to 2:1.[11,12,17]

Our study shows that the mean CCT is thinner in the children with VKC when compared to the control group (p<0.05). This result is consistent with several published studies on the same topic.[18-20] Meanwhile, Kavitha et al. reported no significant difference in the mean CCT between the VKC group and the controls.[21] We found a similar trend of finding when comparing the mild-to-moderate group with the severe-to-very severe group (p<0.05).

Several factors have been hypothesised to contribute to a thinner CCT in the VKC. In susceptible individuals, the act of rubbing the eyes can cause microtrauma, injuring the epithelium and triggering the release of cytokines, differentiation of myofibroblasts, a shift in biomechanical forces and thinning of corneal tissue.[22,23] Research has demonstrated that rubbing the eyes increases the level of matrix metalloproteinase-13 (MMP) in tears, which plays a crucial role in the apoptotic activity of keratocytes. This leads to a loss of stromal volume as the extracellular matrix is degraded, leading to thinning and ectasia of the cornea.[10,24,25] The tears of patients with VKC were found to contain higher levels of the active forms of MMP-2 and MMP-9 compared to healthy individuals, suggesting that these two MMPs may contribute to the corneal thinning frequently observed in VKC patients.[10,26]

In our study, children with severe-to-very severe VKC had significantly higher values in almost all corneal topographic indices (i.e. Sim-K1, sim-K2, apical keratometry, apical gradient curvature, superior-inferior index and keratoconus prediction index) compared to the mild-to-moderate VKC group (p<0.05). The mild-moderate group showed 9% probability of keratoconus, while severe-severe group reached 26% based on more than 45% probability keratoconus. This group needs a close monitoring as they may reach clinical detection of keratoconus if the disease progresses. The other previous studies reported that keratoconus-like topography ranged from 14-27% in patients with VKC.[18,27-31]

Among the recorded indices, the level of astigmatism extracted from the cylinder value was significantly higher in the VKC group compared to the controls (p<0.05). This finding is in agreement with reports published by Gupta et al. and Thiagarajan et al.[29,30] However, when comparing VKC groups based on severity, mild-to-moderate VKC and severe-to-very severe VKC, the difference in astigmatism was statistically insignificant (p=0.912). Thus, we hypothesise that these outcomes may reflect that even at a lower frequency, eye-rubbing in mild-to-moderate VKC patients causes mechanical and biochemical trauma to the cornea, which leads to mild astigmatic changes.

CONCLUSION

Children with VKC showed significantly thinner CCT and topographic indices changes compared to healthy children. The similar observations were displayed by the severe-very severe group compared mild-moderate group except for astigmatism and percent probability keratoconus remains insignificant between the two groups.

Thus, it is crucial to diagnose and treat even the mildest forms of corneal involvement in VKC, as delays in the management of corneal complications could lead to poor visual outcomes. Routine corneal thickness and topography assessment is recommended for children with VKC.

CONFLICT OF INTEREST

None

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ORIGINAL ARTICLE

The impact of mobile telenursing on fasting blood glucose levels in diabetes: an interventional study

Elly Lilianty Sjattar, PhD[1], Christin Satiawati Susana Mahaling, MKep[1,2,3], Andi Masyitha Irwan, PhD[1]

[1]Faculty of Nursing, Hasanuddin University, Makassar, Indonesia, [2]Departement of Nursing, Liung Paduli Hospital Kabupaten Kepulauan Sangihe, Indonesia, [3]Faculty of Nursing and Health Sciences, Universitas Sariputra Indonesia, Tomohon. Indonesia

ABSTRACT

Introduction: High blood glucose levels in individuals with diabetes mellitus (DM) can lead to various complications, highlighting the need for adequate management. Diabetes Self-Management Education has been proven effective in controlling glycaemic events and preventing DM complications. Telenursing is a promising method for educating DM patients. This study aimed to determine the effectiveness of cell phone-based telenursing on fasting blood glucose (FBG) levels of people with DM.

Materials and Methods: This study used a quasi-experimental on 84 participants with DM, which was randomised into intervention (n=42) and control (n=42) groups. The intervention group was provided with health education through booklets and cell phone-based telenursing for four sessions and four sessions of follow-up, while the control group was given health education according to standards from the health centre (Puskesmas). All respondents had their FBG levels checked before, one month, and two months follow-up. The data were analysed using paired sample t-tests, independent samples t-test, and repeated ANOVA.

Results: The mean FBG measurements in the intervention group prior to treatment were 210.88mg/dL, decreased to 173.21mg/dL in the first month, and 177.48mg/dL in the second month (follow-up), while the control group started at 206.36mg/dL, decreased to 182.55mg/dL in the first month, and 191.64mg/dL in the second month. The difference between the two groups was not significant in both the intervention and control groups, p=0.181.

Conclusion: Health education through mobile phone-based telenursing and standard health centres both affect FBG levels of people with DM.

KEYWORDS:
People with diabetes mellitus, health education, telenursing, cell phone, fasting blood glucose

INTRODUCTION

Diabetes mellitus (DM) is one of the diseases whose prevalence continues to increase in the world.[1] DM has become a global public health problem.[2] The World Health Organization (WHO) estimates that more than 420 million people worldwide have DM. The International Diabetes Federation (IDF) estimates that by 2030, around 643 million people will suffer from DM. It is estimated that by 2045, it will increase to 783 million. Indonesia is ranked fifth in 2021 for the number of people with 19.5 million people in the age groups 20-79 years with DM and by 2045 it is estimated to increase to 28.6 million.[3] North Sulawesi ranked the 4th highest in Indonesia (3.6%),[4] Sangihe Islands Regency is seventh out of 15 districts in North Sulawesi (2.54%). During the period from January to December 2021, the Enemawira Puskesmas in the rural area of Sangihe Islands Regency recorded the highest prevalence of diabetes mellitus (DM) with 387 visits. This was followed by Kendahe Puskesmas with 177 visits, and Kuma Puskesmas with 88 visits. All these cases involved patients with unstable blood glucose levels.[5] DM remains a global health issue with adverse impacts if left untreated, leading to the emergence of complications.

High blood glucose levels in people with DM are due to the inability of insulin to function effectively, which can lead to various complications.[6,7] The mortality and morbidity rates in people with DM are related to microvascular and macrovascular complications.[8] Optimal glycaemic control can overcome these problems through prevention or delay of complications and can be achieved if people with DM adhere to self-management behaviours such as healthy diet, physical activity, blood sugar monitoring, taking medication regularly, avoiding stress and adequate coping.[9-11] The success of DM self-management activities as described above, help to promote and maintain good health.[12] On the other hand, uncontrolled blood glucose levels in people with DM can lead to severe complications, requiring appropriate management.

The management of DM by implementing a healthy lifestyle (nutritional therapy and physical activity/exercise) and taking anti-hyperglycaemia drugs both orally and/or by injection can be facilitated through education and self-management support, which are crucial components of caring for individuals with DM.[13,14] Intervention methods used in urban areas may not be as effective in rural areas, so it is necessary to understand the appropriate strategies for rural needs and evaluate them to plan management strategies.[15] The management of people with DM needs to be carried out on an ongoing basis so that their knowledge, skills and abilities can increase, as well as activities that support the behaviour of people with DM.[16] Obstacles may arise, including limited access and low socioeconomic conditions in patients with chronic diseases because one or two visits are not enough to control their disease.[17] Therefore, effective and

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Corresponding Author: Elly Lilianty Sjattar
Email: ellyunhas@gmail.com

economical management of people with DM requires education using technology such as telenursing, which is very useful for the care and follow-up of people with DM.[18]

Several studies apply telenursing in reducing glucose levels in people with DM, including telenursing via WhatsApp® in the form of videos and chats,[19] and also using ZOOM® media.[20] However, these studies require internet facilities. At the same time, the islands, especially those in Indonesia, are not all accessible by the internet network. Therefore, these methods are not suitable especially for those who reside in border areas where internet access is limited. The benefits of telenursing are easier access and cost-effective health services.[21] The use of cellular phones serves to monitor the therapy of people with DM and save time and transportation costs, especially for those who live on the islands, which have difficult access to health service centres.[22] Many people on the Sangihe islands live on the coast and mountains, where they do not have access to the internet, and transportation to the Puskesmas is difficult. This study aimed to determine the effectiveness of cell phone-based telenursing on fasting blood glucose (FBG) levels of people with DM.

MATERIALS AND METHODS

The research design was quasi-experimental; the research was conducted in the working area of Puskesmas Kendahe, Puskesmas Enemawira and Puskesmas Kuma in Sangihe Islands Regency Indonesia, from June to September 2022. The inclusion criteria are people diagnosed with DM, can read and write, have a cell phone, aged ≥40 years and cooperative. The sample size estimation was performed using the Isaac and Michael formula. The required sample was 84 participants divided into intervention (n=42) and control (n=42) groups. The sampling method was probability sampling with a simple random sampling technique. Pre-intervention data were collected before the intervention, while post-intervention data were collected after providing health education through telenursing at the first month and the second follow-up. The same procedure applies to the control group also.

The intervention and control groups were given a booklet,[23] and the treatment group were given health education through cellular phone-based telenursing, namely the provision of health education consisting of eight sessions conducted once a week with a duration of 10-15 minutes via cellular phone, each session containing different material accompanied by follow-up. While the control group will be directly given health education according to the standards of the health centre (Puskesmas).

Instrument

Data collection was carried out using a questionnaire consisting of respondent demographic data and a management knowledge questionnaire (DSCKQ-30).[24,25] The DSCKQ-30 questionnaire is used to assess diabetic patients' knowledge about modifiable lifestyles through 18 questions, adherence to diabetes self-care practices through eight questions, and the consequences of uncontrolled blood glucose levels through four questions. Each correct answer receives a score of 1, while incorrect answers receive a score of 0. The English version of this questionnaire has been validated with a Cronbach's alpha of 0.89.24 The average correlation coefficient ranges from 0.59 to 0.68. Meanwhile, the Indonesian version has been validated with a Cronbach's alpha of 0.939.25 The observation sheet for FBG level measurements, conducted using the Accu-Chek Active glucometer from Roche, with the GB model, which has been standardised and certified by the International Organisation for Standardisation (ISO) - 15197 in 2013. The measurements of fasting blood glucose levels for each respondent were carried out by nurses.[26]

Data Analysis

The results of this study were analysed using paired samples t-test, independent samples t-test and repeated ANOVA.

Ethical Approval and Consent to Participate

This study has received ethical permission from the ethics commission of the Faculty of Public Health, Hasanuddin University. After receiving information about the purpose and procedures of the study, respondents could decide to voluntarily participate in this study by signing informed consent and receiving an explanation that they could withdraw from the study at any time and for any reason.

RESULTS

Table I shows no difference in the average characteristics of respondents. In other words, the intervention and control groups were equal/homogeneous in age, marital status, occupation, income, duration of DM diagnosis, family history, pre-test on FBG and knowledge of self-care management. The results of statistical tests in Table II showed that the intervention group experienced an increase in self-care management knowledge one month after being given health education through telenursing using cellular phones ($p<0.001$), as well as one month later still showed an increase in knowledge after follow-up ($p<0.001$). This was also evidenced by the results of the repeated ANOVA test which showed a significant value of the increase in knowledge. In contrast, the control group in the first month did not show a significant change in knowledge ($p=0.860$), after follow-up it was seen that there was an increase in knowledge ($p=0.057$), this was also evidenced by the repeated ANOVA test ($p=0.587$). Table III shows that FBG levels in the first month decreased in both the intervention group ($p<0.001$) and the control group ($p=0.017$), but in the following month, FBG in both groups increased on average intervention (n=177.48) and control (n=191.64). Table IV shows that there was a difference in knowledge of self-care management before ($p=0.297$), the first month ($p<0.001$), and the next one month ($p<0.001$) after telenursing in the intervention and control groups. Still, it differed from the results of the examination of FBG levels, both before ($p=0.687$) and after the first month ($p=0.462$). The following one month ($p=0.181$) did not show any difference because both groups showed a decrease in FBG levels, but when viewed from the mean value of the intervention group, FBG levels showed the greatest decrease.

Table I: Basic characteristics of respondents (n = 84)

Variables	Intervention group (42) Mean (SD)	Control group (42) Mean (SD)	P
Age	56.52 (7.46)	57.36 (8.97)	0.645*
	n %	n %	
Gender:			
Male	15 (35.71)	5 (11.90)	0.010**
Female	27 (64.29)	37 (88.09)	
Marital status:			
Not married	1 (2.38)	0 (0.00)	0.580**
Marry	36 (85.71)	36 (85.71)	
Widow/widower	5 (11.90)	6 (14.29)	
Education level:			
Did not finish elementary school	4 (9.52)	1 (2.38)	0.035**
Elementary school	17 (40.47)	23 (54.76)	
Junior high school	13 (30.95)	6 (14.29)	
Senior high school	4 (9.52)	11 (26.19)	
Bachelor	4 (9.52)	1 (2.38)	
Work:			
Housewife	25 (59.52)	31 (73.81)	0.142**
Merchant	1 (2.38)	2 (4.76)	
Civil servant	3 (7.14)	2 (4.76)	
Self-employed	1 (2.38)	4 (9.52)	
Miscellaneous	12 (28.57)	3 (7.14)	
Income:			
< Rp.1,000,000	25 (59.52)	27 (64.29)	0.653**
≥ Rp. 1,000,000	17 (40.47)	15 (35.71)	
Duration of DM diagnosis:			
1-5 Years	26 (61.90)	31 (73.81)	0.591**
6-10 Years	11 (26.19)	8 (19.05)	
11-15 Years	2 (4.76)	2 (4.76)	
16-20 Years	3 (7.14)	1 (2.38)	
Family history of DM:			
None	16 (38.10)	22 (52.38)	0.188**
There is	26 (61.90)	20 (47.62)	
FBG pre-test	210.88 (50.54)	206.36 (51.99)	0.687*
Pre-test self-care management knowledge	17.95 (4.54)	18.93 (3.97)	0.297*

*Independent samples t-test ** Chi-square test t

DISCUSSION

The results showed a significant difference between the intervention group providing health education through cellular phone-based telenursing, and the control group, with health education for people with DM from the Puskesmas. This is in line with research, which states that the treatment group experienced an increase in DM knowledge at baseline and follow-up. The intervention consisted of education with a duration of two hours every two months for one year and continued regular follow-up every two months.[27] Education in digital content, in general, is one of the effective ways to increase the knowledge in managing the health and care of people with DM.[28] Self-care management knowledge is information obtained through personal experience or professional orientation, which individuals acquire to manage their health conditions.[29] Field research indicated low levels of respondents' knowledge regarding self-management before the intervention, but a significant change occurred after receiving one month of education through mobile phone-based telenursing intervention and follow-up for the next month. This proves that providing health education through mobile phone-based telenursing is effective in improving self-management knowledge among individuals with DM in the intervention group.

The control group, there was also an increase in knowledge, although the change was not significant. This is because respondents received a module in the form of a booklet at the beginning and were educated by health workers at the Puskesmas every time they came to check their health. Booklet is a printed media that aims to disseminate information in the form of text and images and has several advantages, namely easy to learn at any time because it is in the form of a book, besides that, booklets can collect a lot of information and are very suitable for use as educational media for people with DM.[30,31] Currently, health literacy plays an important role in the management of DM. Maximum health literacy will enable a person to access, understand and use health information and services in making decisions about health care.[12,32] The control group was not given the intervention of telephone-based telenursing. Thus, understanding self-care management could be a faster change; this is because patients who visit the Puskesmas, in addition to checking their health, also get education through health workers. Education is provided in groups, one-way (lecture), and discussions are held if any of the participants want to ask about the material that has been presented, making it difficult to evaluate the patient's understanding of the material that has been given. Follow-up is also carried

Table II: Results of analysis of differences in knowledge of self-care management before and after telenursing in the intervention and control groups.

Knowledge Variable	Intervention group			p-value		Control group			p-value	
	Mean (SD)	Mean Difference (SD)	IK95%			Mean (SD)	Mean Difference (SD)	IK95%		
Before telenursing	17.95 (4.54)					18.93 (3.97)				
One month after telenursing	23.02 (2.19)	-5.07 (3.89)	-3.87 - -8.46	0.000*	0.000[a]	19.10 (4.47)	-0.17 (6.06)	-2.06-1.72	0.860*	0.587[a]
Two months after telenursing	25.00 (1.38)	-7.05 (4.55)	-8.47 - -5.63	0.000*		19.57 (3.91)	-0.64 (2.13)	-1.31-0.02	0.057*	

*paired samples t-test; a Repeated ANOVA-pairwise comparison (Bonferroni)

Table III: Results of analysis of differences in fasting blood glucose levels before and after telenursing in the intervention and control groups

Fasting blood glucose level	Intervention group			p-value		Control group			p-value	
	Mean (SD)	Mean Difference (SD)	IK95%			Mean (SD)	Mean Difference (SD)	IK95%		
Before telenursing	210.88 (50.54)					206.36 (51.99)				
One month after telenursing	173.21 (56.94)	37.67 (56.38)	20.10 - 55.24	0.000*	0.000[a]	182.55 (58.70)	23.81 (62.04)	4.48 - 43.14	0.017*	0.020[a]
Two months after telenursing	177.48 (43.38)	33.41 (43.06)	19.99 - 46.82	0.000*		191.64 (52.43)	14.71 (45.42)	0.56 - 28.87	0.042*	

*paired samples t-test; a Repeated ANOVA-pairwise comparison (Bonferroni)

Table IV: Results of analysis of differences in knowledge of self-care management and fasting blood glucose levels between the intervention group and the control group.

Variables	Mean (SD)	p-value	Mean difference (95% CI)
Knowledge			
Before telenursing			
Intervention group (n = 42)	17.95 (4.54)	0.297*	-0.98 (-2.83-0.87)
Control group (n = 42)	18.83 (3.97)		
One month after telenursing			
Intervention Group (n = 42)	23.02 (2.19)	0.000*	3.93 (2.40-5.46)
Control Group (n = 42)	19.10 (4.47)		
Two months after telenursing			
Intervention Group (n=42) Control Group (n=42)	25.00 (1.38)	0.000*	5.43 (4.16-6.70)
	19.57 (3.91)		
Fasting blood glucose levels			
Before telenursing Intervention Group (n=42)	210.88 (50.54)	0.687*	4.52 (11.19 - -17.73)
Control Group (n=42)	206.36 (51.99)		
One month after telenursing			
Intervention Group (n=42) Control Group (n=42)	173.21 (56.94)	0.462*	-9.33 (12.62 - 234.44)
	182.55 (58.70)		
Two months after telenursing			
Intervention Group (n=42) Control Group (n=42)	177.48 (43.38)	0.181*	-14.17 (10.50 - -35.06)
	191.64 (52.43)		

*independent samples t-test

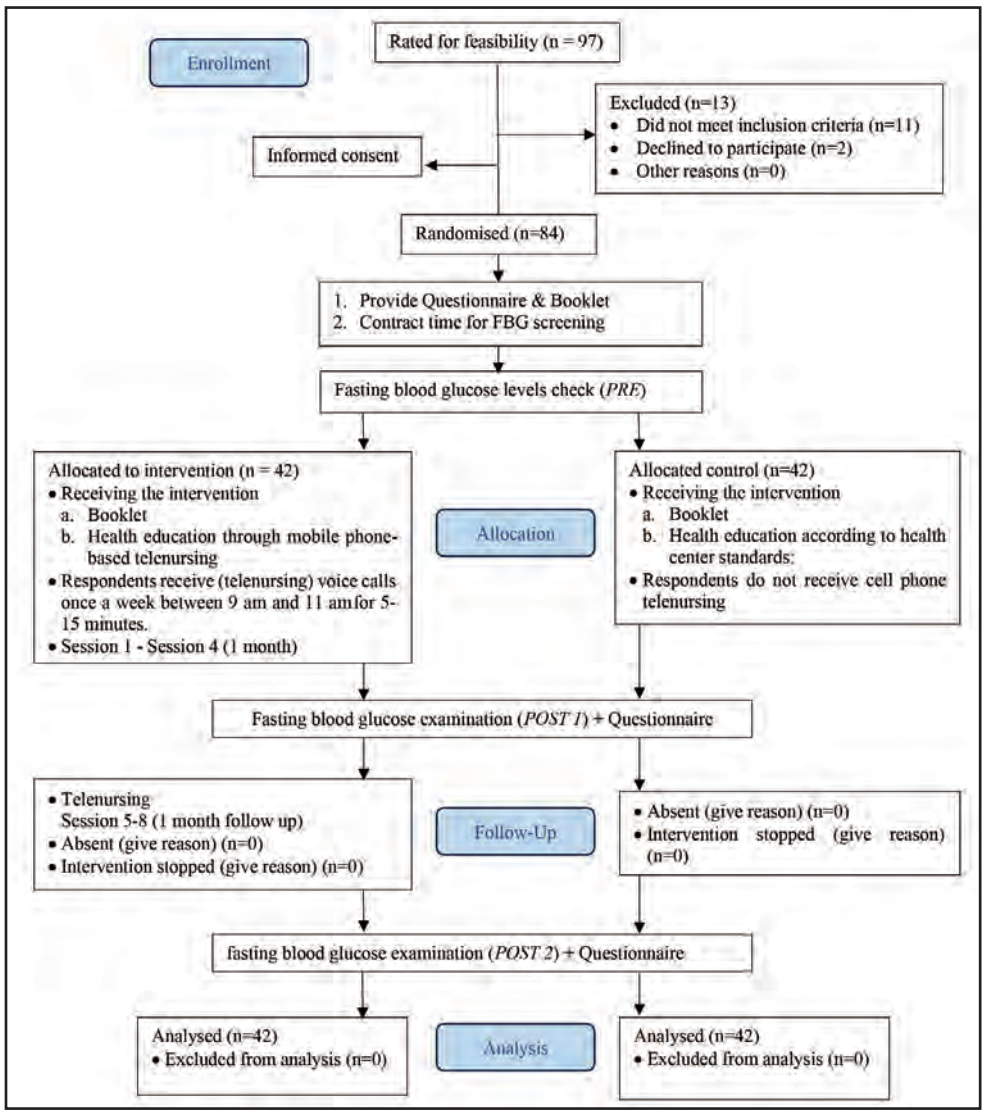

Fig. 1: Consort diagram

out during patient visits. Therefore, active and continuous health education will provide substantial control over patients to be active in increasing interest in health literacy, specifically in DM.

Providing information about DM disease management, if carried out continuously and repeatedly within a specific time accompanied by monitoring, will have an impact on strengthening and changing one's behaviour towards a particular situation.[33,34] Telephone follow- up is a beneficial and inexpensive method of assessing and assisting client care issues. It can also help with early detection of complications. It can inform the patient about the possibility of complications, so that prompt and appropriate treatment can be given to the client.[35]

The findings of this study indicate that there was a decrease in the FBG levels of the subjects in the first month following the telenursing intervention, but there was an increase in the following month. This occurred because the day before the FBG level examination, some respondents attended weddings, religious ceremonies, celebrations and other events, where food and drinks that were high in glucose were available (in the customs of the people in the Sangha islands, sweet food will bring good luck to those who organize celebrations), to honour the organisers of the celebration, guests must consume the food that has been served even though they know it will have an impact on increasing FBG levels. The decrease in FBG levels in people with DM has a positive impact on the implementation of telenursing via cellular phone for 10 to 15 minutes for four sessions and follow-up four sessions. This is supported by previous research, which states that there is a decrease in blood glucose levels for those who receive telephone calls from the nurse coordinator every Thursday (10-12 am) for 5-15 minutes.[19] Another study reported that education given to the intervention group in 1 meeting/week for 30 minutes within 4 weeks and regular follow-up by telephone (telenursing) for 12 weeks and FBG measurements taken before and after the activity can reduce the FBG levels of the intervention group.[36]

The control group in this study showed a decrease in FBG levels after receiving education in the first month and experienced a slight increase in FBG levels during the examination in the second month, although not given telenursing, but still given a booklet.[23] The same applies to the intervention group and education from health workers at the health centre. The advantage is that a person can be more precise in receiving information because it is equipped with text pictures and attractive designs tailored to the target through booklets containing DM education received by respondents.[37] Health literacy is an important asset that supports various health actions to improve well-being and prevent and manage poor health for the better.[38] This supports the idea that patients who are given booklets without telenursing education experience a decrease in blood glucose levels because with increased literacy, the community is interested in making changes from the information obtained.

The results of this study indicate that both the intervention and control groups showed changes in mean values, both in knowledge of self-care management which impacted the decrease in FBG levels. It is also observed that there was no difference in FBG levels among people with DM in the intervention and control groups. However, the average decrease in FBG levels in the intervention group was significantly higher compared to the control group. This is due to the difficulty in achieving a decrease in FBG levels to normal limits because of complicating factors and physiological damage in blood sugar regulation, which typically remain constant.[39] This study also demonstrates that providing health education through mobile phone-based telenursing accompanied by follow-up is not sufficient to change someone's habits regarding consuming high-sugar foods, which will ultimately impact the blood sugar control of respondents. This is consistent with previous researchers who stated that barriers related to habits include deliberate non-compliance, difficulty in changing old habits, culture, busy work schedules, and inadequate access due to uncertain or seasonal food supplies.[40] Therefore, it is crucial to conduct continuous and sustainable follow-up.

LIMITATION

Although this study is a quasi-experimental study comparing between the group given telenursing with conventional therapy, several unmeasured factors that may have influenced the study findings, such as: the study did not fully account for potential confounding variables that could impact self-care management knowledge and fasting blood glucose (FBG) levels. Factors such as socioeconomic status, comorbidities, dietary habits, physical activity levels and adherence to the intervention may have affected outcomes but were not adequately controlled in the analysis. Cultural practices, such as customary celebrations involving high-sugar foods, may have influenced FBG levels and confounded the study results. Cultural factors were not explicitly addressed or controlled for in the study, potentially affecting the interpretation of the findings. External factors, such as stress levels and health conditions, may have influenced FBG levels and were not adequately considered in the study design or analysis. The study primarily focused on self-care management knowledge and FBG levels as outcomes. Other relevant outcomes, such as quality of life or healthcare utilisation, were not included in the assessment, potentially limiting the understanding of the broader impact of the intervention, which should be explored in future studies.

CONCLUSIONS

This study also indicates that health education through mobile phone-based telenursing can improve the knowledge of people with diabetes mellitus regarding self-care management with a 1-month education duration followed by weekly follow-ups for a month. However, in contrast to the control group receiving education according to the standards of the health centre, there was an increase in knowledge after the follow-up. Meanwhile, there was no difference in the reduction of fasting blood glucose levels in both groups because both groups showed a significant decrease in fasting blood glucose levels.

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ORIGINAL ARTICLE

A clinical audit on the diagnosis and management of infective endocarditis in a tertiary heart centre in Malaysia

Yik Hon Ho, MRCP[1], Caryn Tsujean Lim, MRCP[1], Chelfi Zhi Fei Chua, BPharm[1], Hock Hin Chua, FRCP[2], Tiong Kiam Ong, FRCP[1]

[1]Department of Cardiology, Sarawak Heart Centre, Ministry of Health, Malaysia, [2]Infectious Disease Unit, Department of Medicine, Sarawak General Hospital, Ministry of Health, Malaysia

ABSTRACT

Introduction: Infective endocarditis (IE) has a high mortality rate in developing countries including Malaysia. This clinical audit aims to identify the shortcomings in the diagnosis and management of IE patients in a local tertiary centre to implement changes for improvement.

Materials and Methods: This retrospective audit had two cycles – the first includes all IE patients in Sarawak Heart Centre, Malaysia from January 2020 to December 2022 with different parameters (blood culture, echocardiogram, the appropriateness of antibiotics and surgery) assessed against Malaysian Clinical Practice Guideline (CPG); and re-audit from July 2023 to December 2023. Interventions before re-audit include presentation at different hospital levels and continuing medical education.

Results: Fifty patients were recruited (37 in the first cycle, 13 in the second cycle). The median age was 48.5 years with male predominance. Valve prosthesis (12.0%) and rheumatic heart disease (10.0%) were the commonest predisposing factors. Native mitral (44.0%) and aortic valves (28.0%) were most commonly involved. Twenty-eight (56.0%) patients were culture-positive. In the first cycle, most parameters (culture technique 0.0%, vegetation measured 54.1%, empirical 5.4%, culture-guided 29.7% antibiotics therapy, indicated surgery 0.0%) did not achieve the expected standard except timeliness of echocardiograms and blood culture incubation period. After initial interventions, all parameters showed statistically significant improvement (culture technique p<0.001, echocardiography p<0.001, empirical p<0.001, culture-guided p=0.021, surgery p<0.001) during the re-audit.

Conclusion: Compliance with clinical practice guidelines (CPG) on IE management was suboptimal during the first audit but improved after interventions. Hence, regular continuing medical education (CME) is essential, and a written hospital protocol may be useful. Regular audits alongside multidisciplinary teamwork are crucial efforts.

KEYWORDS:
Clinical audit, infective endocarditis, blood culture technique, echocardiogram, antibiotic therapy, surgery

INTRODUCTION

Infective endocarditis (IE) is an uncommon yet deadly disease.[1] In developing countries, the IE mortality ranges from 7-46% as shown in a systematic review involving 19 studies.[2] This is also resonated by two studies in Peninsular and East Malaysia which reported mortality rates of 35.7% and 44.4% respectively.[3-4]

IE is most commonly caused by *Staphylococcus aureus* and oral *Streptococci*.[5] These organisms can be easily identified with appropriate blood culture techniques. However, in cases of culture-negative IE, echocardiographic detection of vegetation has gained a more important position in the diagnosis of IE. This is reflected through the serial revisions of Duke's criteria since its introduction in 1992.[6-7] Many countries including Malaysia have since adopted the modified Duke's criteria in the diagnosis and management of IE.[8-10]

Although pyrexia of unknown origin and a new heart murmur are the cardinal clinical features of IE, microbiological diagnosis and clinical management of IE are often challenging, especially for clinicians unfamiliar with the condition, resonated by various studies.[5,11-13] Furthermore, timely diagnosis and management have been proven to improve mortality outcomes, especially valve surgeries.[14-17] Hence, this clinical audit was performed to identify the shortcomings in the diagnosis and management of IE patients in a local tertiary centre and to implement changes for improvement.

MATERIALS AND METHODS

Study Design and Setting

This is a retrospective audit of two cycles adopting the Plan, Do, Study, Act (PDSA) model.[18] The audit team was led by two medical officers and a clinical pharmacist, supported by a senior consultant cardiologist and a senior consultant infectious disease physician. The first cycle includes all patients who were hospitalised and treated for IE in Sarawak Heart Centre in Sarawak, Malaysia from January 2020 to December 2022. The cases were identified from the hospital patients' records with a diagnosis of infective endocarditis. The admission medical notes of all IE patients were traced and reviewed.

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Corresponding Author: Caryn Tsujean Lim
Email: carynlim1992@gmail.com

Participants
All patients with discharge diagnoses of IE were shortlisted from the medical record department and recruited by tracing their case notes (n=59). Patient without their case notes were excluded (n=9).

Data Collection
Each case was audited independently by two auditors with the data keyed into a database. Any discrepancies between the findings of the two auditors were examined and resolved by a third auditor.

The data collected were the objectives including the appropriateness of blood culture technique, the timeliness of transthoracic echocardiogram (TTE) or transoesophageal echocardiogram (TOE), the appropriateness of the empirical and culture-guided antibiotic therapy and surgery. The standards for the objectives were specific, measurable, agreed, relevant and theoretically sound (SMART).[19]

The appropriateness of the blood culture technique was assessed based on four criteria including at least three sets of cultures taken, at least 30 minutes apart, in peripheral veins and paired aerobic and anaerobic blood culture bottles. The standards of echocardiography include whether it was performed within 24 hours, vegetation size being measured based on the longest diameter and the window for which the measurement was done. The appropriateness of antibiotic therapy was assessed based on five parameters which were the choice, dose, duration, administration route and administration frequency of antibiotics.[20] Antibiotic therapy was considered appropriate if all the five parameters were fulfilled for both empirical and culture-guided antibiotic therapy. If the choice of antibiotics was wrong, the remaining four criteria would not be assessed.

Data Analysis and Presentation
The data collected were then analysed against standards to determine which standards were being met and which were not. Statistical analysis was performed with IBM SPSS version 27. Categorical data with quantitative variables were presented in frequency (percentage). Pearson's chi-square test or Fisher's exact test was used to compare independent categorical variables pre- (first audit cycle) and post-intervention (second audit cycle). Statistical significance was set at $p<0.05$. The findings of the first audit cycle were presented at the departmental and hospital levels in March 2023.

Changes Implementation and Re-audit
Regular continuing medical education (CME) was held for all healthcare professionals involved in the management of IE patients, including cardiologists, cardiothoracic surgeons, internal medicine physicians, medical officers, house officers, echocardiography technicians and nurses from April 2023 to June 2023. This was followed by a re-audit which includes all IE patients from July 2023 to December 2023.

Ethics
This study was approved by the Medical Review and Ethics Committee (MREC), Ministry of Health (MOH) in 2023 (Approval code: NMRR ID-23-01673-6JT).

RESULTS
Baseline Characteristics
A total of 50 patients were recruited from two audit cycles (37 in the first audit cycle and 13 in the second audit cycle). The median age was 48.5 (32.8 – 62.3) years. Thirty-six (72.0%) patients were male. The most common ethnic was non-Malay indigenous (40.0%). Predisposing factors of IE include chronic rheumatic heart disease (10.0%), valve prosthesis (12.0%), cardiac implantable electronic device (2.0%), history of IE (6.0%), recreational drug use (6.1%) and invasive procedure (6.0%). Sixteen (32.0%) had definite IE. Native valve IE was most common (90.0%) with the mitral valve (44.0%) and aortic valve (28.0%) being the most common valves involved. Twenty-eight (56.0%) were culture-positive with α-Streptococci (37.0%) and methicillin-sensitive *Staphylococcus aureus* (29.6%) being the most common organisms.

First Audit
In the first audit cycle, a total of 37 patients were recruited. None of the blood culture techniques fulfilled all four criteria. The compliance with each criterion is shown in Table I. All the blood cultures were incubated for at least 5 days. All the echocardiograms were performed within 24 hours of the suspected IE. TOE was performed for all patients with prosthetic valves and cardiac implantable electronic devices. TOE was also done for all patients with initially negative or inadequate TTE but with persistent suspicion of IE. Half of the echocardiogram reports had measured vegetation size and none reported the window for which the vegetations were measured. Only two had appropriate empirical antibiotic therapy whereas about one-third had appropriate culture-guided antibiotic therapy. The most common cause of inappropriate antibiotic therapy was the wrong antibiotic choice at 91.2%. Only one received the wrong dose of antibiotics. Surgical management was indicated according to recommendations for 35 (94.6%) of the patients but none of the patients underwent surgery.

Re-audit
In the re-audit, a total of 13 patients were recruited. There have been statistically significant improvements in blood culture technique, echocardiogram, appropriateness of empirical and culture-guided antibiotics therapy and surgery (Tables I and II). For those who underwent surgery, all the pathological specimens obtained were sent for histopathological examination. The in-hospital mortality rate reduced from 44.4 to 30.8%, with all the patients who underwent surgeries surviving their admissions.

DISCUSSION
Improvement seen in many areas of diagnosis and management of IE after the intervention from this clinical audit further reinstated the importance of clinical audit, especially in this condition whereby the clinical research studies on IE are scarce, with even fewer clinical audits in the region of Southeast Asia. Many countries struggle with the lack of research funding and infrastructure in this uncommon but important disease to provide stronger clinical evidence to guide clinical practice.[12] Hence, the information from this clinical audit is vital in contributing to the

Table I: Objectives assessed during the first audit and re-audit

Objectives	First audit n=37 n (%)	Re-audit n=13 n (%)
Blood culture technique	0 (0.0)	10 (76.9)
At least three sets	24 (64.9)	10 (76.9)
At least 30 minutes apart	1 (3.0)	10 (76.9)
Different peripheral veins	19 (51.4)	12 (92.3)
Paired aerobic and anaerobic blood culture bottles	16 (43.2)	12 (92.3)
Echocardiography		
Performed within 24 hours	37 (100.0)	13 (100.0)
Vegetation size was measured based on the longest diameter	20 (54.1)	11 (91.7)
Window for which the vegetation was measured	0 (0.0)	11 (91.7)
Empirical antibiotics therapy	2 (5.4)	9 (69.2)
Culture-guided antibiotics therapy	11 (29.7)	11 (91.7)
Surgery if indicated	0 (0.0)	5 (62.5)

Table II: Comparison of appropriateness pre- and post-intervention using Pearson's Chi-square test.

Appropriateness	Intervention		χ2 (df)	P-value
	Pre n (%)	Post n (%)		
Blood culture technique				
Yes	0 (0.0)	37 (100.0)	35.577	<0.001
No	10 (76.9)	3 (23.1)		
Echocardiography				
Vegetation size was measured and was based on the longest diameter				
Yes	20 (64.5)	11 (35.5)	3.814	0.051
No	17 (89.5)	2 (10.5)		
Window for which the vegetation was measured				
Yes	0 (0.0)	11 (100.0)	40.138	<0.001
No	37 (94.9)	2 (5.1)		
Empirical antibiotics therapy				
Yes	2 (18.2)	9 (81.8)	21.052	<0.001
No	32 (88.9)	4 (11.1)		
Culture-guided antibiotics therapy				
Yes	11 (50.0)	11 (50.0)	5.304	0.021
No	10 (90.9)	1 (9.1)		
Surgery if indicated				
Yes	0 (0.0)	5 (100.0)	21.937	<0.001
No	35 (89.7)	4 (10.3)		

improvement of local and global practice in the management of IE.

Blood culture Technique

Blood culture is the primary tool for microbiological diagnosis of IE. Hence, the correct blood culture technique is vital in identifying the causative organisms. We identified several factors contributing to the poor scoring of blood culture techniques in the first audit cycle. The major weaknesses were due to poor documentation of the time and site of the blood cultures taken. Some were due to the unavailability of anaerobic blood culture bottles. Others had only one set of blood cultures taken because of low suspicion of IE in sepsis of unknown origin. This is unsurprising as many clinicians were unfamiliar with this uncommon disease. The lack of specificity in the initial presentation of IE further poses challenges in the clinical diagnosis with a high index of clinical suspicion required. Hence, the CME focused on the awareness of having high suspicion for IE and the importance of taking three sets of blood cultures and good documentation. Feedback was also given to ensure the availability of anaerobic culture bottles all times. The effectiveness of these interventions was translated into the clinical outcome of an improvement in the blood culture technique.

Echocardiography Assessment

Echocardiography assessment has been an important tool in the diagnosis and management of IE among many other radiological adjuncts.[13,21-23] In this clinical audit, all echocardiograms were performed within 24 hours of suspected IE. However, many echocardiography technicians did not measure the size of the vegetation and failed to document the window for which the measurement was taken. This has important clinical implications in the decision for surgery and the subsequent follow-up echocardiogram for comparison of vegetation size after antibiotic therapy.[22] Hence, the targeted CME for the echocardiography

technicians after the first audit stressed on these important aspects of echocardiographic assessment resulting in improvements in the subsequent re-audit results.

Antibiotic Therapy

Our first audit cycle demonstrated a low appropriateness of empirical (5.4%) and culture-guided (29.7%) antibiotic therapies which is comparable with a study in France with an overall appropriateness of 14%.[11] The reason for the wrong antibiotic choice in our first audit was due to clinicians' preference for ceftriaxone as monotherapy in the local setting. Ceftriaxone was preferred as the empirical antibiotic therapy and continued for 4-6 weeks if the cultures were negative. Due to its single daily dosing frequency with a better adverse effect profile, it is not recommended by the older guidelines.[8,9] However, it is included in the recently published ESC guideline as the alternative empirical therapy in combination with ampicillin.[10] CME on the adherence to guideline-directed antibiotics therapy and regular antibiotics review by the ward pharmacists had resulted in significant improvement in appropriateness to 69.2% for empirical therapy and 91.7% for culture-guided therapy in the re-audit.

Prior antibiotic therapy has been found to be the main contributor of culture-negative IE.[24] Hence, a meticulous history taking in recent antibiotic use can affect the management of culture-negative IE. This also highlights the importance of blood culture taking prior to administration of antibiotics to increase the accuracy of culture results in discriminating a true negative IE by fastidious organisms from false negative IE.

Surgery

There is a strong consensus on surgical treatment for patients with IE complications such as heart failure, uncontrolled infection and high risk of embolism or established embolism,[10,23,24] supported by evidence showing an improvement in clinical outcomes for indicated patients who received timely surgical intervention.[25] In the first cycle of this audit, none of the patients underwent valve surgery despite being indicated for surgery, as compared to a 30-48% surgery rate in other studies.[17,26] After the results were presented at the hospital level, a multidisciplinary team approach was adopted for all IE patients. This resulted in 62.5% of the patients undergoing surgeries in the re-audit.

Implications

The clinical audit highlighted the non-adherence to recommendations in most of the audit criteria in a tertiary cardiac centre in Malaysia. However, after interventions were carried out, all of the criteria showed significant improvement in the re-audit. This directly translated into an improvement in in-hospital mortality outcomes for the patients.

Recommendations

When IE is diagnosed, a multidisciplinary team including cardiologists, cardiothoracic surgeons, infectious disease physicians, clinical microbiologists and pharmacists should be involved as per the appropriateness of clinical indication to strive for the best management outcome. The multidisciplinary effort is supported by many other studies as well.[22,27] In addition, CME should be done regularly especially when new clinicians are joining the department. Further to that, a hospital protocol on IE should be written and uploaded onto the intranet for the reference of all healthcare professionals involved in treating IE patients. On top of the above measures, clinical audits should also be done yearly to ensure compliance with the guidelines.

LIMITATION

This is a single-centre study which did not capture all IE patients in the region as most uncomplicated patients and those who were not indicated for surgery were kept in the referring hospitals till discharge. The delay for surgery during the re-audit was also not explored in this audit. The interval between the intervention and re-audit was only 3 months which might be too short to see the complete adherence to all the audit criteria.

CONCLUSION

Compliance with the national guidelines on infective endocarditis (IE) management was suboptimal during the first audit but improved significantly during the re-audit after interventions were made. Regular continuing medical education is essential to ensure timely diagnosis and appropriate management for IE patients. A written hospital protocol may also be useful. Regular audits must be undertaken to ensure compliance with the guidelines, best achieved with multidisciplinary efforts.

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CONFLICTS OF INTEREST

All authors of this study have no conflicts of interest to declare.

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Evaluation of the retention of knowledge, skills and competency of post-neonatal resuscitation training among house officers

Teh Keng Hwang, MRCP, Lee Ii Li, PhD, Harif Fadzilah Che Hashim, MD. PGDHHSA

Kulliyyah of Medicine and Health Sciences, UniSHAMS

ABSTRACT

Introduction: The Neonatal Resuscitation Programme (NRP) was first introduced in Malaysia in 1996 to train doctors and nurses working in paediatrics and obstetrics departments who are involved with the care of newborns soon after delivery. Prompt and effective neonatal resuscitation has been documented to reduce mortality and neonatal asphyxia. The programme has been revised every five years and is now in the 8th edition. NRP training was made into a key performance indicator (KPI) by the Ministry of Health in 2016 for all house officers to be trained in this programme during their 2-year posting and this is usually conducted during the paediatric posting. This study aims to evaluate the retention of their knowledge, skills and competency at 3, 6, and 9 months after the initial NRP training.

Materials and Methods: A total of 34 house officers were enrolled in the study on joining the paediatric unit of Hospital Kulim. They were given the "Textbook of NRP" to prepare for the theory paper that consisted of 30 multiple-choice questions (MCQs). Two to four weeks later they went through a day of training on the resuscitation of the newborn using low-fidelity simulation manikins. They were taught to recognise a newborn who needed resuscitation after delivery, prepared the equipment for resuscitation and learned the skills of resuscitation. The skills included the initial steps, bag valve mask ventilation, intubation, cardiac massage, umbilical vein cannulation and use of medications. They were also taught the performance of objective structured clinical examination (OSCE) A and B. They were evaluated at 3, 6, and 9 months after the completion of their training using the MCQs and the performance checklist in the NRP textbook.

Results: The results showed that there was a significant reduction in their knowledge retention as shown by their performance in multiple choice questions. Similarly, there was a significant loss of competency in their skills and competency in resuscitation using bag mask ventilation, intubation and performance of OSCE A and OSCE B. However, their performance at initial steps showed no significant reduction.

Conclusion: In view of the observed deterioration a refresher course in NRP before transferring out to the districts is recommended to improve their overall performance.

KEYWORDS:
Neonatal resuscitation, evaluation of knowledge and skills

INTRODUCTION

The Neonatal Resuscitation Programme (NRP) was initiated with training of 37 instructors who then went on to train other doctors and nurses in the Ministry of Health (MOH). The result was a substantial number of 2806 local instructors and 14,000 candidates trained after eight years. The MOH made it into a key performance indicator (KPI) in 2016 for all house officers (HOs) to be trained in NRP. However, no study had been done to evaluate its effectiveness that is the retention of their knowledge, skills and competency after the training. This study aims to evaluate the retention of knowledge and skills over 3 months, 6 months and 9 months post-NRP training.

MATERIALS AND METHODS

This is a single-arm intervention study. HOs who have undergone the training in NRP were evaluated on their skills and competency at 3, 6 and 9 months. A total of 34 participants were enrolled. The multiple-choice questions (MCQs) were administered to the participants prior to the practical resuscitations sessions. The training in NRP included reading material, i.e., textbook on NRP, undergoing the practical resuscitations skill which included the initial steps, bag valve mask ventilation, intubation and then performed the Objective Structured Clinical Examination (OSCE) A and the mega code OSCE B. OSCE A referred to the procedure of resuscitation till bag valve mask ventilation and OSCE B referred to the full mega code starting from initial steps till intubation, cardiac massage, and medications. At each skill, they were taught how to assess the response to resuscitation before proceeding to the next step. They also needed to show leadership and teamwork as well as when to call for help. For each skill, they will be assessed using a checklist available from the NRP.

The participants were evaluated on their retention of theoretical knowledge using MCQs, and on their skills and competency at 3, 6 and 9 months post-NRP training using low fidelity manikins. Scoring was done using the checklists available in the NRP.

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Corresponding Author: Keng Hwang Teh
Email: khteh53@gmail.com

Table I: Repeated measures analysis of MCQs assessment at 3, 6 and 9 months.

		Value	F	Sig.
MCQ performance	Pillai's trace	0.385	6.568[b]	0.006
	Wilks' lambda	0.615	6.568[b]	0.006
	Hotelling's trace	0.626	6.568[b]	0.006
	Roy's largest root	0.626	6.568[b]	0.006
MCQ performance versus Gender	Pillai's trace	0.167	2.103[b]	0.147
	Wilks' lambda	0.833	2.103[b]	0.147
	Hotelling's trace	0.200	2.103[b]	0.147
	Roy's largest root	0.200	2.103[b]	0.147

Table II: Repeated measures analysis of the skills of initial steps at 3, 6 and 9 months.

		Value	F	Sig.
Skills of initial steps	Pillai's trace	0.126	1.581[b]	0.228
	Wilks' lambda	0.874	1.581[b]	0.228
	Hotelling's trace	0.144	1.581[b]	0.228
	Roy's largest root	0.144	1.581[b]	0.228

The skills of initial steps i.e., preparation of the equipment for resuscitation, providing warmth, drying, suction and positioning. Table II showed that there was no significant reduction in skills and competency of initial steps ($p>0.05$).

Table III: Repeated measures analysis of the skills at doing bag-mask ventilation and intubation at 3, 6 and 9 months.

		Value	F	Sig.
Skills at doing bag-mask ventilation	Pillai's trace	0.403	7.434[b]	0.003
	Wilks' lambda	0.597	7.434[b]	0.003
	Hotelling's trace	0.676	7.434[b]	0.003
	Roy's largest root	0.676	7.434[b]	0.003
		Value	**F**	**Sig.**
Skills of intubation	Pillai's trace	0.326	5.327[b]	0.013
	Wilks' lambda	0.674	5.327[b]	0.013
	Hotelling's trace	0.484	5.327[b]	0.013
	Roy's largest root	0.484	5.327[b]	0.013

Table IV: Repeated measures analysis of OSCE A - resuscitation skills till completion of bag valve mask ventilation at 3, 6 and 9 months.

		Value	F	Sig.
OSCE A skills	Pillai's trace	0.302	4.755[b]	0.019
	Wilks' lambda	0.698	4.755[b]	0.019
	Hotelling's trace	0.432	4.755[b]	0.019
	Roy's largest root	0.432	4.755[b]	0.019

Table V: Repeated measures analysis of OSCE B - resuscitation skills at performing a mega code at 3-, 6- and 9-months post NRP.

		Value	F	Sig.
OSCE B skills	Pillai's trace	0.473	8.964[b]	0.002
	Wilks' lambda	0.527	8.964[b]	0.002
	Hotelling's trace	0.896	8.964[b]	0.002
	Roy's largest root	0.896	8.964[b]	0.002

The results were analysed using IBM Statistical package for Social Studies (SPSS) version 26 software. Descriptive statistics were used to depict the participants' socio-demographic characteristics. Repeated measure analysis was used to determine the difference of retention of knowledge, skills and competency at 3, 6, and 9 months respectively after the initial NRP training. The significance level was set at 0.05.

A total of 34 HOs participated in the study and completed the training in NRP. They passed the MCQs and were able to perform the initial steps, bag-mask ventilation, intubation, OSCE A and the mega code OSCE B. They were evaluated at 3, 6 and 9 months after the initial training.

RESULTS

The study included a total of 34 participants. Participants were graduates from 13 different universities, with majority coming from AIMST University (16, 47.0%). This was followed by Sultan Abdul Halim Mu'adzam Shah International Islamic University (UniSHAMS) and USM KLE, each contributing three participants (8.8% each). Two participants (6.0%) each coming from SEGi University and Cyberjaya University College of Medical Sciences (CUCMS). The remaining eight participants comes from difference universities. There were 25 females (73.5%) and nine (26.5%) males with an aged ranged from 26 to 29 years.

All 34 HOs in the initial study participated in the first evaluation at three months. However, this number reduced to 30 at the second evaluation at six months and to 24 at the 3rd evaluation at nine months. The participants had left the paediatric department during the follow-up. They were posted to other disciplines in the hospital. Analysis of repeated measures revealed a statistically significant difference ($p<0.05$) in the performance of MCQs on the first, second, and third assessments. However, gender did not differ significantly in performance ($p>0.05$; Table I below).

The skills of initial steps i.e., preparation of the equipment for resuscitation, providing warmth, drying, suction and positioning. Table II showed that there was no significant reduction in skills and competency of initial steps ($p>0.05$).

Table III demonstrates a statistically significant decrease in skills at bag-mask ventilation from the first to the second to the third examination ($p<0.05$). Also, a substantial deterioration in intubation skills during the evaluations conducted at 3-, 6-, and 9-months after NRP ($p<0.05$).

Table IV demonstrated that in OSCE A resuscitation skills of a neonate requiring up to bag and mask ventilation were significantly decreased across the three examinations at 3-, 6, and 9-months ($p<0.05$).

OSCE B skills, which include the administration of advanced resuscitation techniques (mega code) such as intubation, cardiac massage, umbilical vein cannulation and intravenous medicines, decreased significantly during the three evaluations at 3-, 6-, and 9-months ($p<0.05$), as shown in Table V.

DISCUSSION

Proficiency in neonatal resuscitation is necessary to ensure the safety and well-being of the newborn infant and plays a critical role in reducing mortality and morbidity. Most deliveries usually do not require resuscitation. However, about 10% will need some form of help to transition to the extrauterine life and another 1% will need more advanced resuscitation.[1]

The World Health Organization reported that 37% of children under the age of 5 years died because of neonatal risk factors and out of these 23% died because of perinatal asphyxia.[2] Successful resuscitation within the first few minutes will reduce the neonatal mortality and morbidity. To achieve this the health care personnel involved in the care of the neonate needed to be trained and to be readily available. The NRP which was introduced in the US in 1986[3] was adopted by Malaysia under the Perinatal Society. Training started in 1996 where 37 core instructors were trained and over 2-year period a further 2806 local instructors were trained.[4] The adoption of this instructor programme nationwide was encouraging. It used the same premise as the America Academy of Paediatrics in that at least one person skilled in newborn resuscitation was presented at every birth and an additional person to be readily available if more extensive resuscitation was needed.

The success of this programme saw a reduction in neonatal and perinatal mortality and over 14,575 personnel were trained eight years later.[5] In 2016 the MOH decided to make this resuscitation course into a KPI and decided that all HOs (100%) to be trained during their 2-year posting and this would be done during the paediatric posting, which is of three months duration. They were taught the basic knowledge and technical skills in neonatal resuscitation, and this had been shown in several studies to be effective soon after the course completion.

However, due to the time lapse after the training and lack of exposure, when they were subsequently transferred out to a district hospital about two years later it was postulated that there would be a deterioration in both the knowledge, skills and competency acquired during the initial training. The skills and competency were maintained during the Paediatric posting as they had to assist the medical officers during the standby for delivery at the labour room and operation theatre. It is hypothesised that their knowledge and skills would have deteriorated after leaving the posting. Most studies find a lack of sustained improvements in those who took the NRP and then rotated through other fields where they were not involved in neonatal resuscitation.[6-9]

Evaluations of the house officers who had completed their NRP training and participated in the study showed a significant reduction at 3-, 6- and 9-months in the retention of their knowledge in the MCQs, skills and competency at doing bag valve mask ventilation, intubation and performance of OSCE A and B. OSCE A involved resuscitation until completion of bag mask ventilation and OSCE B is a mega code resuscitation which included intubation, cardiac massage and medication given via an umbilical vein cannula. The participants had left the paediatric posting

three months after the initial training and were rotating to other departments where they were not exposed to the neonates and deliveries and had no opportunities to have hands-on practice. It is postulated by the time they finished their 2-year housemanship and are ready to be posted to the districts the decay in their knowledge and skills and competency in resuscitation of the neonate might be even more apparent.[10,11]

Retention of NRP skills deteriorated rapidly after course completion.[12] Documented decreased retention of skills was also reported by Kaczorowski et al.,8 who studied 44 residents and found that they had significantly lower scores 4 months later. A similar deterioration of knowledge after 4 months was shown by Curran et al.[13]

On the contrary in a study conducted among a small group of midwives at Ridge Hospital in Ghana, there was a substantial increase in neonatal resuscitation knowledge and performance. Although their numbers were small, the hospital performed >7000 deliveries per year. Their sustained retention could be due to their work in a high-risk referral centre, and they used these skills daily.[14] A study conducted in a low-resource setting in Peru showed that helping babies to breathe knowledge and skills can be retained and even improved with simple, inexpensive interventions, including supervised on-the-job and peer-to-peer training. Short on-site training sessions and brief refresher training sessions using simulation and practice scenarios proved to be easy to integrate both at the level of health centres and a larger referral hospital.[15]

CONCLUSION

The overall decline in the knowledge, skills and competency of the house officers several months after the Neonatal Resuscitation Program (NRP) training was significant throughout the 3-, 6-, and 9-months period post training. In centres where the skills are maintained frequent practice, on-site training played an important role. A refresher course to improve the confidence in their skills and knowledge before posting to the districts might go towards ensuring their competence and this could be a subject of another study. An intervention that might help improve knowledge and skills includes introducing mock codes which can help providers become strong team members and team leaders by making them better prepared for serious situations in the delivery room. This can be done with appropriate planning and consideration for adult learning behaviours.[16,17]

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Perceptions of climate change and associated health impacts among communities in Johor River Basin, Malaysia

Kwa Yee Chu, MMedSc[1], Norlilawati Suboh, BOSM[1], Dominic Kay Shuen Wei, BSc[1], Cindy Lee Ik Sing, PhD[1], Claire L Walsh, PhD[2], Michaela L Goodson, PhD[1]

[1]Newcastle University Medicine Malaysia (NUMed), Iskandar Puteri, Johor, Malaysia, [2]School of Engineering, Newcastle University, Newcastle upon Tyne, United Kingdom

ABSTRACT

Introduction: As climate change is threatening every region of the world, extreme weather events resultant of global warming is occurring at increasing rate and scale in Malaysia. Weather-related disasters such as flood and haze pose critical challenges to the infrastructure and raise public health concerns in the country, especially when main economic sectors rely heavily on climate variability. Public perception on environmental issues is crucial for development of pro-environmental policies. Among studies conducted to understand public awareness regarding global warming, reports of perception on the health impacts were very limited. Taking this limitation into account, this study was designed to examine the perception on the health impacts of climate change among the diverse communities living in the Johor River Basin.

Materials and Methods: The cross-sectional study was conducted through cloud-data-based digital questionnaires completed by randomly selected residents in the Johor River Basin (n=647). Data was analysed with descriptive statistics using SPSS 27 (IBM®) Software. Comparisons between indigenous and non-indigenous communities were performed using Chi square analysis.

Results: Respondents in this study consisted of indigenous people (n=79) and non-indigenous people (n=568). Indigenous respondents generally perceived more frequent occurrence of extreme weather events in the next 20 years, even for the phenomena unfamiliar in Malaysian settings. All respondents showed similar concerns for health impacts of global warming, although the non-indigenous respondents perceived the risk further into the future (25 years) compared to the indigenous respondents who perceived current or imminent (<10 years) risks. Intense concerns for self, children, family members and community were shown by nearly all indigenous respondents (97-99%), while the non-indigenous people in this study expressed stronger concerns at country level and for future generations. During the last haze episode, most indigenous respondents (85%) did not notice any change in air quality nor discomfort among family members, in contrast 70% of the non-indigenous respondents claimed to have suffered from breathing problems themselves as well as others in the family. All respondents were concerned about air quality in their surroundings, indigenous people were concerned for the near future (<10 years), and non-indigenous people were concerned for the next 25 years.

Conclusion: In this study, respondents were generally concerned about the health impacts of unimpeded global warming. There was significant difference in perceptions between indigenous and non-indigenous respondents. The findings were useful, complemented with further studies, to improve understanding of public awareness and to help develop relevant education programmes accessible for wider audience.

KEYWORDS:
Public perception, climate change, global warming, indigenous community, public welfare

INTRODUCTION

Climate change is the most critical environmental challenge faced by every region across the world, and it's increasingly associated with anthropogenic causes. Global warming, as the paramount issue, is happening in an unprecedented rate due to emission of greenhouse gases. The Intergovernmental Panel on Climate Change (IPCC) reported more intense extreme weather events including heat waves, heavy precipitation, drought and rising sea levels, amid projecting global warming to exceed 1.5°C within this century.[1] In Malaysia, climate change has been observed through increase in extreme weather events such as precipitation, cyclones and heat waves,[2-5] while modelling and simulation speculating such events to occur more frequently and in bigger scale.[6,7]

The impact of unpredictable and recurrent extreme weather events could devastate the country as it threatens the basic requirements for public's wellbeing including freshwater, clean air, food security, shelter and sanitation facilities.[8] Malaysia has long coastline, therefore coastal flooding is regarded as major hydrological disaster affecting hundreds of thousands of victims and damage of high-valued infrastructure, causing prolonged disruption of livelihood, socio-economic activities and sustainability of coastal communities, especially in densely populated and economically developed states such as Selangor and Johor.[9-11] Apart from psychological stress resulting from displacement, floods and the resulting pollution to water supply system have also been associated with various infections that are bacterial, viral, parasitic and zoonotic infections.[12,13] In Malaysia, coastal erosion, greenhouse effects, deforestation, inundation following heavy precipitation and pollution are also vital environmental and public health concerns.[14-16] For

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Corresponding Author: Kwa Yee Chu
Email: yee-chu.kwa@newcastle.edu.my

instance, vegetation fires caused by controversial farming method have resulted in transboundary haze problem in Malaysia. Apart from short term disturbance to the respiratory system and worsening of asthma, exposure to repeating haze episodes had also been found to associate with lasting effect on victims' psychology, respiratory-cardiovascular systems, neurological morbidity and mortality.[17]

Agriculture industries, including fisheries, are important economic contributors in Malaysia, especially for communities living in the vicinity of freshwater sources such as river.[18] However, as agriculture relies highly on weather stability, the livelihoods of associated workers are therefore confronted by global warming and changing climate. Unpredictable weather pattern has reduced crops,[19] elevated occupational risk and increased uncertainties during harvesting operations.[18] Siwar et. al. had presented the risk of changing climate towards agricultural sustainability in Malaysia, especially for those struggling on poverty line,[20] as global warming spikes price of daily necessities. Previous study had echoed that particular subpopulations such as elderly, children, pregnant women, malnourished, chronic disease patients, physically or mentally impaired, outdoor workers and residents of flood-prone areas, were disproportionately affected by the impacts of changing climate,[21] and oftentimes underrepresented in the South-East Asia (SEA) region.[22] Implementation of mitigation policies might also face economic and social barriers that reduce efficacy and specificity towards the most vulnerable subpopulations.[23,24]

Citizen's perception and awareness towards their surroundings and environmental issues are crucial for behaviour changes and is the driving force for pro-environmental policies and decision making.[25] However, current environmental education for general public is still lacking in distribution of delivery and there is need for a more specific approach, especially for younger generations in schools.[26] Another popular source of information is media, but locally relevant climate issues might be overshadowed by Western perceptions of the problem and reporting maybe biased towards countries where westerners have political interest.[27] To close the gap between public awareness and decision making related to global warming, studies had been conducted to understand people's perception, knowledge and behavioural adaptation in Malaysia. However, representation and experiences of minority groups such as the indigenous communities were inadequately addressed in these studies, especially in Peninsular Malaysia.[28,29] With the aim of contributing to existing literature, this study examined the perception on the health impacts of climate change and global warming among the diverse communities residing in the Johor River Basin.

MATERIALS AND METHODS

In this cross-sectional study, the survey questionnaire methodology was employed to better understand the prevalence between demographics and perceptions on health impacts of climate change. The first section of the questionnaire aimed to collect information on the demographics of the respondents. The subsequent section regarding perceptions on climate change and health was adapted from Akerloft et. al., study conducted in Northern America and Malta from 2008 to 2009.[30] The last section regarding air quality was adapted from similar study in China.[31] Following ethical approval, informed consent and permission from respective village heads, this study was conducted between October 2021 and June 2022 among communities residing around Johor River Basin. The broader geographical location covered with questionnaires (Figure 1) consisted of communities living in oil palm plantations irrigated by Johor River and its tributaries. Data collectors were appointed by village heads to gather responses from the community members on the ARCGIS™ platform, where the coordinates of the location of respondents could be recorded. From each household, one representative capable of communicating in the Malay language, and agreed to participation, was recruited as respondent. Incomplete responses to the questionnaire were excluded. Data was uploaded anonymously to a secure cloud database. Data collectors visited respondents in their households and digital questionnaires via electronic tablets were used to prevent prolonged contact of non-local personnels with the vulnerable communities as the study was conducted in the latter part of the COVID-19 pandemic. Data collectors were encouraged to collect responses at different times of the day and obtain a gender-balanced pool of respondents.

A power calculation in this study was undertaken using G* Power software®. A priori data analysis was undertaken comparing two independent groups (two tailed; effect size = 0.5; α error probability = 0.05; power = 0.95) and found that the minimal sample size to detect a medium effect size would be 105 participants in each sample group.

Collected data from the questionnaires was analysed with descriptive statistics using SPSS 27 (IBM®) Software. Comparisons between indigenous and non-indigenous respondents were performed using Chi square analysis.

RESULTS

Demographics

Among the 647 respondents in this study (Table I), 79 were Orang Asli, (indigenous people) for the remaining of this article. The majority of respondents (n=568) were non-indigenous, comprising Malay (n=564), Chinese (n=2) and others (n=2). The indigenous respondents were significantly younger in this study, than the non-indigenous respondents ($p<0.001$), with 64% (n=50) aged between 17 and 35 years old, and 60% of the non-indigenous respondents were aged between 24 and 55 years old. There were more male respondents among the indigenous people (56%, n=44), but the non-indigenous respondents were more evenly distributed (51% female, 45% male, and 5% preferred not to say).

During the analysis of data from this study, the authors observed a consistent trend where respondents from the indigenous cohort perceived climate change and the relevant human health impacts in significantly different way than those from the non-indigenous cohort. Hence the authors believed comparison between the two cohorts would best

Table I: Respondent demographics and comparison between indigenous and non-indigenous communities.

	Indigenous		Non-indigenous		statistic	df	p-value
	n	%	n	%			
Respondent (n)	79	100	568	100			
Gender					$c^2 = 4.36$	2	0.113
Male	44	56	255	45			
Female	34	43	287	51			
Prefer not to say	1	1	26	5			
Age group					$c^2 = 29.59$	5	< 0.001**
18 – 24	17	22	105	18			
25 – 34	33	42	124	22			
35 – 44	19	24	104	18			
45 – 54	4	5	116	20			
55 – 64	6	8	75	13			
> 65	0	0	44	8			
Highest qualification					$c^2 = 24.88$	2	< 0.001**
School and below	77	97	406	71			
Intermediate	2	3	105	18			
University and above	0	0	57	10			
Household member					$c^2 = 3.07$	2	0.215
≤ 3	12	15	108	19			
4 – 6	54	68	330	58			
≥ 7	13	16	130	23			
Occupation					$c^2 = 18.86$	4	< 0.001**
Unemployed/home staying	41	52	196	35			
Student	1	1	66	12			
Public service	4	5	86	15			
Industry/agriculture	14	18	77	14			
Business/administrative/professional	19	24	143	25			
Household highest income					$c^2 = 17.84$	4	0.001**
Unemployed/home staying	20	25	126	22			
Student	0	0	26	5			
Public service	5	6	132	23			
Industry/agriculture	20	25	100	18			
Business/administrative/professional	34	43	184	32			
Personal monthly income (RM)					$c^2 = 38.63$	5	< 0.001**
Not fixed	46	58	169	30			
< 1,000	11	14	71	13			
1,001 – 2,000	22	28	174	31			
2,001 – 5,000	0	0	136	24			
5,001 – 10,000	0	0	14	2			
10,001 – 20,000	0	0	4	1			
Household monthly income (RM)					$c^2 = 176.82$	6	< 0.001**
Not fixed	46	58	46	8			
< 1,000	11	14	35	6			
1,001 – 2,000	22	28	141	25			
2,001 – 5,000	0	0	254	45			
5,001 – 10,000	0	0	77	14			
10,001 – 20,000	0	0	14	2			
> 20,000	0	0	1	0			

*: $p \leq 0.05$; **: $p \leq 0.005$

highlight this observation in order to accurately reflect the findings. Education level varied significantly different between indigenous and non-indigenous people in this study (p<0.001). Almost all indigenous respondents (97%, n=77) did not receive formal education beyond secondary school level, as primary level education was mandatory in the nation according to the amendment made to the Education Act 1996 in 2002, while there were 18% (n=105) of non-indigenous respondents who completed vocational training or diplomas and another 10% studied at university level. The differences in education level will likely have affected the career opportunities of respondents. This was reflected in the significant difference in occupation between the indigenous and the non-indigenous people (p<0.001). Unemployment or being homebound was common among the indigenous community (52%), followed by self-employment/small-scaled business (24%) and manual workers in agricultural and industrial factories (18%). Only 1% of the indigenous respondents were student despite averaging younger age among the cohort. Comparatively more non-indigenous people worked in administrative, business or professional roles (25%), and 15% (n=86) worked as service providers or government servants, 12% of the non-indigenous respondents in this study was students, and 35% were unemployed/homebound. The occupational profile reflected significant differences in personal and household incomes

between the indigenous and non-indigenous respondents (p<0.001) as more than half of the indigenous community did not have a fixed household income (58%) and none of the households were earning more than MYR2,000 (around USD420) per month, while 45% of the non-indigenous household had monthly income between MYR2,000-5,000. Although the indigenous respondents generally had lower income, the money was used to support family of an equivalent size to the non-indigenous respondents (p=0.215).

Frequency of Extreme Weather Events

The questionnaire asked about the perception of the participants of the frequency of extreme weather events in the next 20 years. Most of the respondents (69%) agreed that drought would crucially affect water supply (Table II). Higher percentage of indigenous respondents (76%), who were all from lower income groups, perceived increased occurrence of drought in the near future, than the non-indigenous respondents (68%).

Indigenous people in this study, whose demographic tended towards lower education level and lower income level, perceived increased occurrence of intense precipitation (76%) compared with non-indigenous people (p=0.003). Indigenous people (around 75%) perceived that there would be more starvation and poverty due to global warming, while around 20% of non-indigenous respondents, where the most educated respondents were part of, were indifferent towards the prevalence of starvation and poverty.

Respondents from the indigenous groups (76%), where many were manual workers, generally believed that heat waves would increase in the next 20 years. With continuing global warming, 74% indigenous and 63% non-indigenous people perceived more forest fires in this study, 74% of indigenous and 67% of non-indigenous respondents felt that global warming would likely cause more disease epidemics.

In relation to elevated sea levels caused by global warming, 76% of indigenous people perceived an increased need to leave coastal cities, compared to 64% non-indigenous people (p < 0.001). For refugee issues, 74% of indigenous respondents (p=0.002) perceived surging prevalence in future.

Interestingly, when asked about global warming's impact on desertification, hurricane, extinction of species and glacier melting, respondents selected similar responses. Indigenous community respondents felt that there would be deterioration and increased instances for these extreme weather in the next 20 years. Interestingly however, on the topic of species extinction, a higher percentage of non-indigenous community respondents perceived loss of wider range of species compared to other respondents.

Casualties of Global Warming

When asked to predict the annual fatality of uncontrolled global warming (Table III), most (47%) of indigenous people speculated hundreds, followed by thousands (29%), and 20% of them didn't know the response to this question. For non-indigenous respondents, there were 30% that predicted thousands, and up to 25% that predicted millions, while 24% predicted hundreds, and 16% of them hadn't a clue regarding this question. This trend is similar when the respondents were asked about mortality rate in the next 50 years (p<0.001). Compared to non-indigenous respondents, indigenous respondents perceived thousands – millions of injuries or sickness per annum (p<0.001), this perceived rate were reduced to hundreds when asked about the next five decades (p<0.001).

While most respondents were concerned about impacts of global warming towards the country and agreed that the outcome would be negative, indigenous respondents, who most were from the least educated group, were more inclined to believe the imminent damage would arrive within 10 years, but the non-indigenous respondents would believe it takes another 25 to 50 years (p<0.001). Indeed, 95% of indigenous people were concerned about global warming's impact on all people, significantly higher than the non-indigenous people (72%, p<0.001). Level of awareness became intense as 90-97% of indigenous people were very concerned about impact of global warming towards children (p<0.001), particularly the children in their household (p<0.001).

An overwhelming number of indigenous respondents (97-99%) were very concerned about impacts of global warming on themselves, especially on their health and lifestyle, compared to 50% of non-indigenous respondents (p<0.001). Apart from their own self, the indigenous respondents also showed more concerns towards their families and community than the non-indigenous people (p<0.001). None of the indigenous respondents thought global warming would have no effect on local community. Indigenous people, however, became slightly less concerned about the wider country or their region of the World. A small percentage of them thought Malaysia would only suffer little impact from the changing climate. While 20% of indigenous respondents were unable to respond, non-indigenous respondents expressed stronger concern towards Malaysia as they perceived great damage for both developed (p = 0.002) and developing countries (p<0.001). Although indigenous people were very concerned about the impacts of global warming on their children, their responses was not as concerning for future generation. Conversely, a higher percentage of the non-indigenous respondents showed great concern towards future generations (p=0.014).

Perceptions on Air Quality

This study also focused on respondents' perceptions towards air quality (Table IV). The non-indigenous community appeared to pay more attention towards air quality in their residential area as 86% expressed moderate to high concern (p<0.001). Between July and December, when haze episode was more likely to occur, respondents were affected in significantly different ways (p<0.001), as 85% of the indigenous community were not aware of any change in air quality, but up to 70% of the non-indigenous respondents claimed to suffer moderate to serious breathing problems.

When air quality dropped, indigenous respondents tended to be unaware, and 86% of them did not know if the children in their household were having breathing difficulties or not (p < 0.001). Surprisingly, 70% of non-indigenous people in this

Table II: Comparison of perception on impacts of global warming over the next 20 years if nothing is done to address it between respondents of indigenous community and non-indigenous community.

	Indigenous (n = 79)		Non-indigenous (n = 568)		p-value
	n	%	n	%	
Drought					<0.001**
Less	1	1	64	12	
No difference	2	3	30	5	
More	60	76	384	68	
Don't know	16	20	90	16	
Heavy precipitation					0.003**
Less	1	1	64	11	
No difference	2	3	65	11	
More	60	76	340	60	
Don't know	16	20	99	17	
Flood					0.005**
Less	1	1	73	13	
No difference	2	3	56	10	
More	60	76	347	61	
Don't know	16	20	92	16	
Famine					0.002**
Less	1	1	59	10	
No difference	2	3	47	8	
More	60	76	360	64	
Don't know	16	20	102	18	
Poverty					<0.001**
Less	1	1	65	11	
No difference	2	3	61	11	
More	60	76	347	61	
Don't know	16	20	17	17	
Heat wave					0.013*
Less	1	1	48	9	
No difference	2	3	40	7	
More	60	76	388	69	
Don't know	16	20	92	16	
Forest fire					0.041*
Less	1	1	52	9	
No difference	3	4	59	10	
More	59	74	361	63	
Don't know	16	20	96	17	
Epidemics					0.003**
Less	1	1	60	10	
No difference	3	4	46	8	
More	59	74	376	67	
Don't know	16	15	86	15	
Leaving coastal cities					<0.001**
Less	1	1	62	11	
No difference	2	3	50	9	
More	60	76	361	64	
Don't know	16	20	95	17	
Refugee					0.002**
Less	1	1	56	10	
No difference	4	5	80	14	
More	58	74	326	57	
Don't know	16	20	106	19	
Desertification					0.035*
Less	1	1	59	11	
No difference	4	5	57	10	
More	58	73	346	61	
Don't know	16	20	106	19	
Hurricane					<0.001**
Less	1	1	56	9	
No difference	2	3	70	12	
More	58	73	342	60	
Don't know	18	23	100	18	
Extinction of species					0.078
Less	1	1	65	11	
No difference	3	4	42	7	
More	59	74	372	64	
Don't know	16	20	89	16	
Glacier melting					0.025 *
Less	1	1	56	10	
No difference	2	3	47	8	
More	59	74	362	64	
Don't know	17	22	102	18	

*: $p \leq 0.05$; **: $p \leq 0.005$.

Table III: Comparison of perception on current and future morbidity and mortality caused by global warming between indigenous respondents and non-indigenous respondents.

	Indigenous (n = 79)		Non-indigenous (n = 568)		p-value
	n	%	n	%	
Annual global death					<0.001**
None	2	3	26	5	
Hundreds	37	47	139	24	
Thousands	23	29	168	30	
Millions	1	1	144	25	
Don't know	16	20	91	16	
Annual global injury and sick					<0.001**
None	2	3	26	5	
Hundreds	25	32	114	20	
Thousands	35	44	210	37	
Millions	1	1	127	22	
Don't know	16	20	91	16	
Death in the next 50 years					<0.001**
None	2	3	26	5	
Hundreds	43	54	103	18	
Thousands	16	20	170	30	
Millions	2	3	147	26	
Don't know	16	20	122	21	
Injury and sick in the next 50 Years					<0.001**
None	3	4	26	5	
Hundreds	37	47	99	17	
Thousands	23	29	174	31	
Millions	0	0	144	25	
Don't know	16	20	125	22	
When will global warming harm people in Malaysia					<0.001**
Now, within 10 years	61	77	282	50	
Within 25 years	2	3	160	28	
Within 50 years	0	0	63	11	
Within 100 years	0	0	27	5	
Will not happen	16	20	36	6	
Concern about effects of global warming towards everyone					<0.001**
Low	1	1	88	16	
Neutral	3	4	70	12	
High	75	95	410	72	
Concern about effects of global warming towards all children					<0.001**
Low	0	0	86	15	
Neutral	1	1	68	12	
High	78	99	414	73	
Concern about effects of global warming towards your own children					<0.001**
Low	0	0	79	14	
Neutral	1	1	62	11	
High	78	99	427	75	
Concern about effects of global warming towards people in Malaysia					<0.001**
Low	0	0	70	13	
Neutral	2	3	60	11	
High	77	97	438	77	
Concern about effects of global warming towards self					<0.001**
Low	0	0	76	13	
Neutral	1	1	57	10	
High	78	98	435	76	
Concern about effects of global warming towards own health					<0.001**
Low	0	0	75	14	
Neutral	1	1	56	10	
High	78	99	437	77	
Concern about effects of global warming towards lifestyle					<0.001**
Low	1	1	77	14	
Neutral	1	1	58	10	
High	77	97	433	76	
Harm from global warming towards self					<0.001**
None/little	0	0	59	10	
Moderate	0	0	171	30	
Many	62	78	298	52	
Don't know	17	22	40	7	

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Table III: Comparison of perception on current and future morbidity and mortality caused by global warming between indigenous respondents and non-indigenous respondents.

	Indigenous (n = 79)		Non-indigenous (n = 568)		p-value
	n	%	n	%	
Harm from global warming towards family					<0.001**
None/little	0	0	57	10	
Moderate	2	3	176	31	
Many	60	76	298	52	
Don't know	17	22	37	7	
Harm from global warming towards community					<0.001**
None/little	0	0	52	10	
Moderate	41	52	219	39	
Many	21	27	256	45	
Don't know	17	22	41	7	
Harm from global warming towards residents in Malaysia					<0.001**
None/little	3	4	51	9	
Moderate	15	19	216	38	
Many	44	56	258	45	
Don't know	17	22	43	8	
Harm from global warming towards developed countries					0.002 **
None/little	2	3	49	9	
Moderate	34	43	220	39	
Many	27	34	255	45	
Don't know	16	20	44	8	
Harm from global warming towards developing countries					<0.001**
None/little	1	1	52	9	
Moderate	20	25	223	39	
Many	41	52	256	45	
Don't know	17	22	37	7	
Harm from global warming towards future generation					0.014 *
None/little	2	3	44	7	
Moderate	30	38	211	37	
Many	30	38	258	45	
Don't know	17	22	55	10	

*: $p \leq 0.05$; **: $p \leq 0.005$.

study reported moderate to serious breathing difficulties among children, and 76% reported symptoms among adults in their households. Although most indigenous respondents seemed less affected by the decline in air quality, 76% of them still expressed concern towards current air quality and that expected in the next 10 years, while the non-indigenous respondents, comprised of higher percentage of respondents with higher education, tended to be more worry about air quality within next 25 to 50 years ($p<0.001$).

DISCUSSION

This study had a relatively large sample size and formed a typical representation of the population living in the river basin involving a range of socioeconomic groups. The sample size for the indigenous group of 105 was almost reached (n=79), but the researchers were limited in ability to access indigenous respondents as some potential participants did not live in communities and were not accessible through the Johor Orang Asli Association (JAKOA). Despite this, with permission from the JAKOA, and use of cloud-data-based electronic questionnaires, accessibility by the communities was successful in recruiting 79 indigenous and 568 non-indigenous respondents. The terminology for "climate change" in this questionnaire was uniformly replaced with "global warming" to prevent dissociated response.[32]

Freshwater accessibility was linked to the livelihood and wellbeing of the respondents in this study, hence it is a reasonable assumption that global warming and the resulting drought in the coming decades will continue to be a major concern among the communities, especially the less educated and those struggling with poverty, as obtaining a living from fishing and obtaining drinking water will likely be more problematic and difficult in the future. Similar to other developing countries that rely heavily on adequate water resource for economic growth[33,34], climate variability played a vital role in the sustainability of communities in this study. Indigenous respondents, whose occupation were generally agricultural-based, were very concerned about food security and poverty, echoing the findings of a previous study that correlated changing climate to the vicious cycle of crop depletion, income reduction and inability to afford daily necessities.[20] While low education levels made technology-based interventions more challenging in non-urban areas[24] manual workers who were most likely to spend working

Table IV: Comparison of perception on air quality in within the community between indigenous respondents and non-indigenous respondents.

	Indigenous (n = 79)		Non-indigenous (n = 568)		p-value
	n	%	n	%	
Concern towards air quality in village					<0.001**
None/little	2	3	48	8	
Moderate	30	38	266	47	
Many	29	37	224	39	
Don't know	18	23	30	5	
Breathing problem during haze					<0.001**
None/little	1	1	125	22	
Moderate	7	9	282	50	
Many	4	5	115	20	
Don't know	67	85	46	8	
Breathing problem among children during unsatisfactory air quality					<0.001**
None/little	1	1	129	23	
Moderate	4	5	246	43	
Many	6	8	153	27	
Don't know	68	86	40	7	
Breathing problem among adult during unsatisfactory air quality					<0.001**
None / Little	3	4	77	14	
Moderate	37	47	265	47	
Many	5	6	163	29	
Don't know	34	43	63	11	
Concern towards future air quality in village					<0.001**
Now	23	29	171	30	
Within 10 years	37	47	158	28	
Within 25 years	1	1	132	23	
Within 50 years	0	0	49	9	
Within 100 years	0	0	17	3	
Will not happen	18	23	41	7	

*: $p \leq 0.05$; **: $p \leq 0.005$.

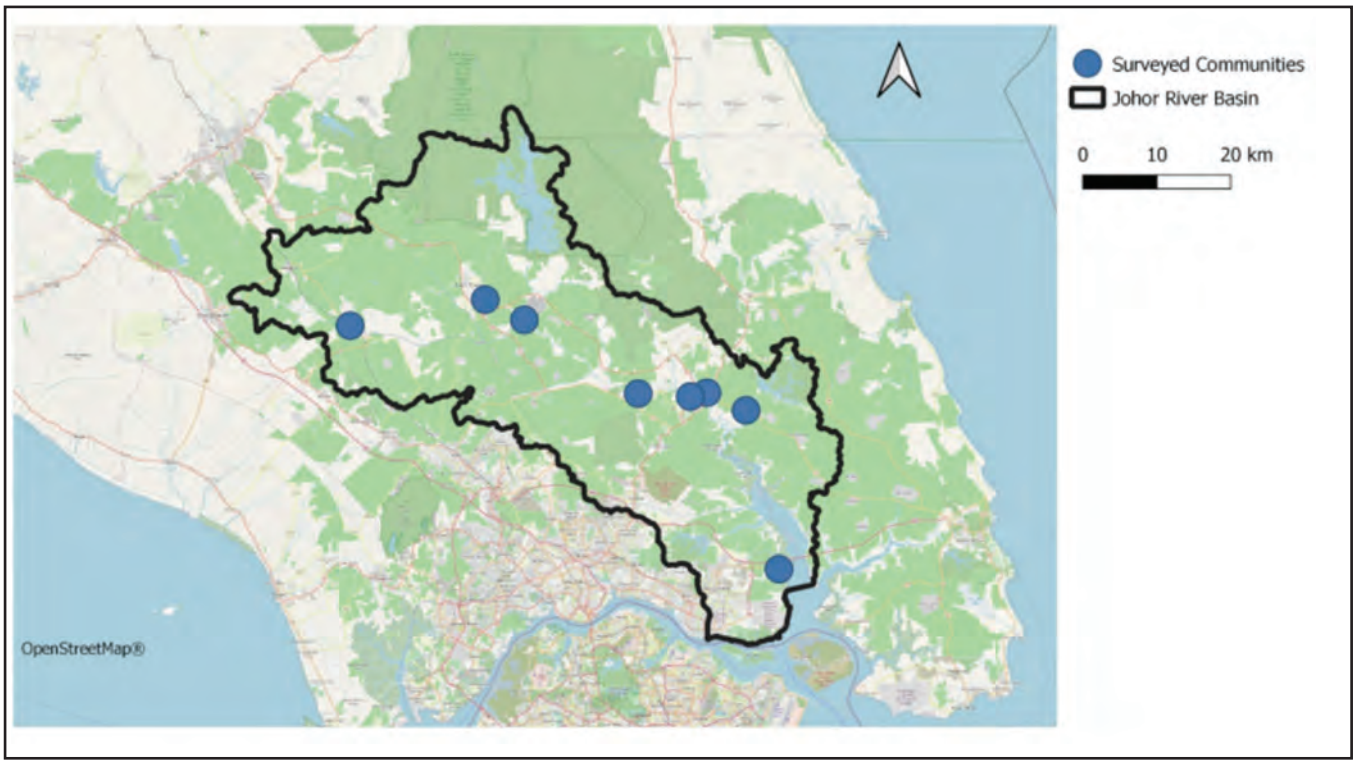

Fig. 1: Map showing area of study and distribution of recruited respondents.

hours outdoors perceived that heat waves would be an increasing problem in the future and they would increase occupational heat stroke and reduce labour productivity unless working environment practices were improved.[35]

Data collection covered most of the Johor River Basin including from flood hotspots. Some respondents in this study had experienced involuntary displacement and loss of property in the past and tended to perceive worsening conditions in future with precipitation, flood and leaving coastal areas because they were becoming more prone to flooding with elevated sea levels. Residents of rural areas such as riverside areas and plantations, many of whom were indigenous residents, were generally worried about their resilience to disaster, compared to the urban dwellers who felt they were better equipped with knowledge and financial support in times of disaster from personal income and government help. Lack of appropriate baseline knowledge regarding weather disasters and the association with global warming would be costly to the residents at flood hotspots, thus relevant public education were crucial. In Johor, most public education campaigns were deployed as post-disaster management measures and people felt they didn't have enough time to prepare for future events. It was also evident that misinformation spread easily so people were not sure what they were required to do to mitigate disaster effects most efficiently. Interestingly, respondents in this study exhibited moderate to high levels of concern towards weather events that were less relevant to the Malaysian settings such as glacier melting as well as technical phrases such as extinction. This demonstrated the willingness of communities to learn new information, as showed by previous study that communities relied on multimedia and word of mouth for knowledge gaining[36] and consequently, correct representation of global warming in the local context would be crucial to increasing knowledge in future.[27]

The World Health Organization (WHO) predicted 250,000 additional deaths annually between 2030 and 2050 due to health impacts from climate change such as malnutrition and heat stress.[37] In this study, although the indigenous respondents were worried about their health under changing climate, most of them underestimated the mortality rate by at least a factor of 10. Higher education and high-income did not prompt a closer estimation to the figure provided by WHO, and more than 20% of respondents had no idea of the mortality rate in 50 years, similar to previous study collected in multiple nations.[30] This could be due to the lack of public education, both within the formal education syllabus and public awareness campaigns.[38] As global warming continues, most respondents speculated more epidemics rather than death, which indicated their anxiety for another public health emergency after experiencing the COVID-19 pandemics. WHO estimated direct damage costs to health by global warming at USD2-4 billion per annum worldwide[37] and increasing medical costs were of great concern and seen as a unwelcome burden on top of inflation, as reflected by high income respondents that tended to disregard their concerns for climate change-borne epidemics or injuries, until 25 years' time when they might be at retirement age with a limited source of income. Although specific diseases or symptoms were not asked about, the findings from this study suggested that all respondents were aware of the health risks brought by global warming. The indigenous community were generally more concerned and sensitive towards the effect of global warming on their health and wellbeing as a current threat rather than a future threat. The response could likely be due to their existing struggle maintaining their lifestyle and livelihoods making them more vulnerable to climate change in the future. These findings are in agreement with previous studies that showed agricultural workers were generally well aware of climate change issues and were keen to learn new adaptation techniques and strategies.[23,24] Compared to non-indigenous respondents, the indigenous people in this study demonstrated intense concern for health impact of global warming towards self and family members, especially children. Besides having a sense of responsibility towards individuals close to them, such a strong response could be due to the lack of confidence in receiving help from sources outside of their communities. Healthcare inequality such as limited medical facilities and health supplementary had also affected how minority groups such as the indigenous community perceive risk under changing climate.[39] In comparison, non-indigenous respondents expressed stronger concern towards the impact of climate change on the country as a whole and future generations. This may have reflected the difference of community involvement in decision making and policy formulation at the national level.

Malaysia and the equatorial SEA countries experience southwest monsoon from June to September where the weather pattern brings pollutants resulting from forest burning, causing haze in the region.[40] As Peninsular Malaysia is one of the regions suffering worst from seasonal haze, public perception on air quality and the consequential health impacts were important for development of efficient adaptation measures. In contrast to global warming and other climate issues, non-indigenous respondents showed higher awareness on air quality issues and were more concerned towards the health impacts of declining air quality, especially during haze than non-indigenous people. The indigenous and non-indigenous respondents recalled strikingly different experience during last haze episode, as more than 80% of indigenous people did not register breathing problems and were unaware of any symptoms among their household members, but more than 70% of non-indigenous people in this study reported breathing difficulties themselves as well as among children and family members. Studies of visits to clinic and hospital admission records have shown that haze has been associated with spikes in respiratory symptoms both in Malaysia and Singapore.[17,40] However, such reports have been based mostly on densely populated urban areas, which would under-represent experiences of minorities such as indigenous communities and residents of rural areas. Previous study in various states of Malaysia have demonstrated that public understanding on association between urbanisation and air pollution were generally high, and people well educated on sources of pollutants such as industries and vehicle emissions.[14] In comparison, indigenous respondents in this study were likely to be less exposed to information regarding declining air quality and its associated health risks, so they therefore would not pay specific attention to surrounding air quality

unless otherwise notified. The nature of their occupations in agriculture and fishing might not however allow for a reduction in the amount of time spent outdoors.

CONCLUSION

This study demonstrated significant differences in the perception of the effects of global warming and associated implications on health risks between indigenous and non-indigenous respondents for the future. Further studies could improve understanding of factors underlying communities' attitude towards impacts of changing climate and the accompanying behavioural changes that may be required to mitigate risk. The findings of this study are useful for formulation of public health education programmes and refinement on current climate change mitigation policies to target and benefit the wider Malaysian society.

ETHICAL APPROVAL

Ethical approval was granted from the Newcastle University Ethics Committee (1597/2020).

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ORIGINAL ARTICLE

Distinguishing features of COVID-19 and non-COVID-19 febrile seizures in hospitalised children

Sindu a/p Mahendran, MBBS[1], Ng Boon Hong, MRCPCH[1], Lim Hui Yi, MRCPCH[1], Nur Emylia binti Zailanalhuddin, MBBS[1], Yasothai a/p Chandran, MD[1], Wong Wan Fei, MD[1], Vishnu Arvindran a/l Chandra Mohan, MBBS[1], Durairaaj Ramachandran, MRCPCH[2], Nurul Hafizah binti Mohd Yusoff, DrPath[1], David Ng Chun-Ern, MRCPCH[1]

[1]Hospital Tuanku Ja'afar, Jalan Rasah, Negeri Sembilan, Ministry of Health Malaysia, Malaysia, [2]Hospital Tuanku Ampuan Najihah, Jalan Melang, Negeri Sembilan, Ministry of Health Malaysia, Malaysia

ABSTRACT

Introduction: Febrile seizures in children can be associated with various underlying conditions, including COVID-19. Differentiating COVID-19 and non-COVID-19 related febrile seizures is crucial for tailored patient management and for implementing appropriate infection control measures to prevent nosocomial transmission. This study aimed to describe the clinical features of children hospitalised for COVID-19 and non-COVID-19 febrile seizures and to identify factors that differentiate between the two groups.

Materials and Methods: This retrospective cross-sectional study involved children aged 6 months to 6 years who were hospitalised for febrile seizures in Hospital Tuanku Ja'afar Seremban (HTJS) from January 2021 to June 2022. Descriptive statistics were used to summarise the differences in demographics and clinical presentations. Logistic regression analyses were performed to identify factors associated with COVID-19 and non-COVID-19 febrile seizures.

Results: Of the 345 patients (median age 22 months, IQR 15-32; 59.7% were males) included in the study, 130 (37.7%) tested positive for COVID-19, while 215 (62.3%) tested negative. There were no significant differences between both groups based on age, comorbidities, history of febrile seizures, seizure types, temperature on arrival, cough and rhinorrhoea. Multivariate analysis revealed that a family history of febrile seizures and leucocytosis were associated with increased odds of non-COVID-19 febrile seizures. In contrast, lymphopenia was associated with decreased odds.

Conclusion: The clinical presentation of COVID-19 and non-COVID-19 febrile seizures are remarkably similar, highlighting the importance of including COVID-19 screening in febrile seizures workup. Full blood count readings may be potentially useful for differentiating between these conditions.

KEYWORDS:
Febrile fit, febrile convulsions, SARS-CoV-2, paediatric

INTRODUCTION

Febrile seizures are the commonest cause of childhood seizures, affecting approximately 2-5% of children.[1] These seizures are typically brief, triggered by a febrile episode in children aged 6 months to 6 years in the absence of signs of central nervous system (CNS) infection. The aetiology of febrile seizures is multifactorial, including a combination of genetic and environmental factors.[2,3] The vulnerability of the developing CNS to fever, combined with a genetic predisposition and exposure to a diverse range of pathogens as children start interacting more with the outside world, contribute to the high incidence of febrile seizures within this age group.

During the global health crisis caused by coronavirus disease 2019 (COVID-19), severe acute respiratory coronavirus-2 (SARS-CoV-2) emerged as a novel etiological agent for febrile seizures in children.[4,5] The differentiation between COVID-19 and non-COVID-19 febrile seizures is vital not only for individual patient management, but also for effective infection control purposes. Furthermore, as SARS-CoV-2 is a novel virus, the outcomes for febrile seizures associated with it may differ from those associated with other aetiologies.

There is a paucity of studies that demonstrate the differences in clinical manifestations between these two conditions. To address this knowledge gap, our study aims to compare the clinical characteristics and outcomes between COVID-19 associated febrile seizures and non-COVID-19 associated febrile seizures.

MATERIALS AND METHODS

Design and Setting

This retrospective, cross-sectional study was conducted at Hospital Tuanku Ja'afar Seremban, Negeri Sembilan from January 2021 to June 2022. The hospital serves as the sole tertiary referral centre for the state of Negeri Sembilan, serving approximately 1,100,000 people including 215,000 children below 12 years. During the study period, the rollout of COVID-19 vaccinations for children over 5 years old in the country began in early February 2022.[6]

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Corresponding Author: David Ng Chun-Ern
Email: davidngce@gmail.com

Data Collection and Study Definitions

The study included all children aged between 6 months to 6 years who were hospitalised with a diagnosis of febrile seizures (R56.00, R56.01), as classified by the International Classification of Diseases, 10th edition (ICD-10) codes. The exclusion criteria included patients with febrile seizures who were not within the age group of 6 months to 6 years old and those who were COVID-19 negative but had recent sick contact/epidemiological link with a confirmed COVID-19 case. This study focused solely on patients with an ICD-10 diagnosis of febrile seizures. Therefore, patients with afebrile seizures, breakthrough seizures with underlying epilepsy or central nervous system infection such as meningitis, encephalitis, and meningoencephalitis were also excluded as they do not meet the inclusion criteria for febrile seizures.

The medical record of patients fulfilling the study inclusion criteria were reviewed. Information collected and analysed included sociodemographic characteristics, comorbidities, presenting symptoms (fever, nature of the seizures, accompanying symptoms such as cough, rhinorrhoea, diarrhoea, rashes) and their duration. Additional data included admission temperature, COVID-19 vaccination status and results, full blood count results, treatment received (intravenous fluids, oxygen, antibiotics, need for phenytoin loading), paediatric intensive care unit (PICU) admission, total length of stay and outcomes.

During the study period, all patients hospitalised for febrile seizures underwent routine COVID-19 testing as part of the hospital's admission protocol for infection control purposes. COVID-19 positive patients were isolated either in a dedicated COVID-19 ward or in a negative pressure isolation room within the general paediatric ward to prevent nosocomial transmission of SARS-CoV-2. Testing for COVID-19 was initially carried out by a nasopharyngeal swab for SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) until 20 May 2021. As COVID-19 prevalence increased in the community during the delta and omicron wave, SARS-CoV-2 rapid antigen detection testing was subsequently employed.

A patient was categorised as COVID-19 positive if the nasopharyngeal swab for SARS-CoV-2 RT-PCR or antigen detection test was positive. Conversely, a negative swab result indicated COVID-19 negative status. We defined those having a sick contact/epidemiological link with a COVID-19 positive case as symptomatic household or social contact (spending face-to-face contact within 1 meter for ≥15 minutes) in the preceding two weeks prior to the patient's symptom onset, as described previously.[7,8] Fever was defined as a body temperature of ≥37.5°C, consistent with our previous studies.[9,10] Simple febrile seizures were defined as primary generalised seizures lasting for < 15 minutes without recurrence within 24 hours. Complex febrile seizures were defined as focal, prolonged (≥ 15 minutes), and/or recurring within 24 hours, and/or accompanied by residual neurological deficit postictally, such as Todd's paralysis.[1] Full blood count abnormalities were defined as follows:[11,12] Leucocytosis referred to an elevated white blood cell count >14 × 10^9/L in children under 2 years, and >12 × 10^9/L in children aged 2 years and above. Lymphopenia was defined as an absolute lymphocyte count <4.5 × 10^9/L in infants < 8 months, and <1.5 × 10^9/L in children aged 8 months and above. Thrombocytopaenia was defined as a platelet count of <150 × 10^9/L, whereas thrombocytosis was defined as a platelet count of >150 × 10^9/L.

Statistical Analysis

Categorical variables were presented as frequency (number) and percentages (%), and continuous data using median and interquartile range (IQR). Data were assessed for conformance to the normal distribution using the Shapiro-Wilk test. Given that all our continuous variables were not normally distributed, we used the Mann–Whitney U test for comparisons. For categorical variables, we used the Chi-squared test or Fisher's exact test as appropriate.

We performed univariate and multivariate logistic regression analyses to identify distinguishing factors between COVID-19 and non-COVID-19 febrile seizures. Statistical filter methods (Chi-squared test, Mann-Whitney U test) were used to select significant variables for the logistic regression model. Variables that were statistically significant ($p<0.05$) in the univariate logistic regression were included in the multivariate analysis. Full blood count results were not available for all the patients in the study; no attempt was made to impute these missing data. As such, our multivariate analysis was based on the patients who had complete data. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Any results with a two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

Ethical Considerations

The Medical Research and Ethics Committee, Ministry of Health Malaysia approved this study (NMRR-22-02432-REO [2]) and waived the requirement for informed consent. All patient data were de-identified prior to analyses.

RESULTS

Baseline Characteristics of Study Population

We identified 345 patients hospitalised for febrile seizures during the 18-month study period. The median age of the patients was 22 months (IQR 15-32), with 56.3% of patients aged below 24 months. Males constituted 59.7% of the study population, corresponding to a male to female ratio of approximately 1.5:1. At least one comorbidity was reported in 39 patients (11.3%), with developmental disorders being the most common (Table I). Of the 345 patients, 130 (37.7%) tested positive for COVID-19, and the remaining 215 (62.3%) were COVID-19 negative. Most of the seizures were categorised as simple febrile seizures (n=257, 74.5%), with generalised tonic clonic seizures being the most frequently observed semiology (n=238, 69.0%). The majority of patients (n=295, 85.5%) presented with their first-ever seizure. A family history of febrile seizures was present in 70 (20.3%) patients. None of the 360 patients had received COVID-19 vaccinations.

Table I: Baseline characteristics of the study population.

Baseline Characteristics of patients	Total (n=345)
Age in months, median (IQR)	22 (15-32)
6-12 months old	53 (15.4%)
12.1-24 months old	141 (40.9%)
24.1-72 months old	151 (43.8%)
Male sex	206 (59.7%)
Comorbidities[a]	
None	306 (88.7%)
Developmental	10 (2.9%)
Prematurity (if age <2 years old)[b]	9 (2.6%)
Neuromuscular	8 (2.3%)
Cardiovascular	7 (2.0%)
Genetic	5 (1.4%)
Respiratory	3 (0.9%)
Others	3 (0.9%)
COVID-19 status	
COVID-19 positive	130 (37.7%)
COVID-19 negative	215 (62.3%)
Type of febrile seizure	
Simple febrile seizures	257 (74.5%)
Complex febrile seizures	88 (25.5%)
Episode of febrile seizures	
First episode	295 (85.5%)
Recurrent episode	50 (14.5%)
Semiology of febrile seizure	
Generalized tonic clonic	238 (69.0%)
Generalised tonic	78 (22.6%)
Atonic	22 (6.4%)
Focal	7 (2.0%)
Received COVID-19 vaccination	0 (0%)

IQR Interquartile range
[a]A patient may have more than one comorbidity
[b]Gestational age <37 weeks at birth among children aged <2 years

Comparison of Demographic, Clinical Characteristics and Outcomes of Febrile Seizures Between the COVID-19 Positive and COVID-19 Negative Group

The demographic characteristics, such as the median age, proportion of males and prevalence of comorbidities were comparable between the COVID-19 positive and negative groups (Table II). However, a higher proportion of patients in the COVID-19 negative group had a history of past COVID-19 infection (8.8% vs. 2.3%, p=0.016). Likewise, a higher proportion of patients in the COVID-19 negative group had a family history of febrile seizures (26.0% vs. 10.8%, p=0.001).

There were no significant differences between the COVID-19 and non-COVID-19 groups regarding the proportion of patients presenting with their first febrile seizure, the day of fever which the seizure occurred, the type of febrile seizures and the semiology of seizures. Similarly, the frequency of accompanying symptoms such as cough, rhinorrhoea, and rashes did not differ significantly between both groups. However, gastrointestinal symptoms such as vomiting and diarrhoea occurred more frequently in the COVID-19 negative group (21.9% vs. 13.1%, p=0.042; 15.8% vs. 5.4%, p=0.004 respectively). Physical examination findings, including temperature on arrival, signs of respiratory distress and signs of shock were similar between both groups.

Full blood count findings revealed distinct patterns. Leucocytosis was significantly more common among the COVID-19 negative group (34.9% vs. 13.6%, p=0.002), whereas a greater proportion of the COVID-19 positive group demonstrated lymphopenia (23.7% vs. 9.7%, p=0.006). The proportion of patients with thrombocytopaenia was comparable between both groups.

In terms of treatment received, antibiotics were used more often in the COVID-19 negative group (11.2% vs 3.8%, p = 0.018). However, the need for oxygen therapy, intravenous fluid therapy and intravenous phenytoin as a loading dose were similar for both groups. The need for admission to the PICU and the median length of hospital stay were comparable between the groups. No mortalities were recorded throughout the study period.

Multivariate Analysis of Factors Differentiating non-COVID-19 from COVID-19 Febrile Seizures

Table III display the results from univariate and multivariate logistic regression analyses that aimed to identify factors differentiating non-COVID-19 from COVID-19 positive febrile seizures. All variables showed a significant association from the univariate analysis. However, following adjustment in the multivariate analysis, only three variables remained statistically significant. Specifically, a family history of febrile seizures (adjusted odds ratio, aOR: 2.77; 95% Confidence Intervals, 95%CI: 1.08, 7.07) and leucocytosis (aOR: 2.85; 95%CI: 1.24, 6.57) were significantly associated with non-COVID-19 febrile seizures. Conversely, lymphopenia (aOR: 0.40; 95%CI: 0.18, 0.93) was less likely to be present in non-COVID-19 associated febrile seizures.

Table II: Comparison of demographic, clinical characteristics and outcomes of febrile seizures between the COVID-19 positive and COVID-19 negative group.

	COVID-19 positive n=130 (%)	COVID-19 negative n=215 (%)	p-value
Demography			
Age in months, median (IQR)	24 (15-35)	21 (14-30)	0.137***
Male sex	76 (58.5%)	130 (60.5%)	0.713*
Any comorbidities	10 (7.7%)	29 (13.5%)	0.099*
Type of comorbidities			
Developmental	1 (0.8%)	9 (4.2%)	0·189*
Prematurity (if age <2 years)	1 (0.8%)	8 (3.7%)	0·400**
Neuromuscular	4 (3.0%)	4 (1.9%)	0.167**
Cardiovascular	2 (1.5%)	5 (2.3%)	1.000**
Genetic	2 (1.5%)	3 (1.4%)	0.587**
Past COVID-19 infection[a]	3 (2.3%)	19 (8.8%)	0.016*
Family history of febrile seizures	14 (10.8%)	56 (26.0%)	0.001*
First episode of febrile seizures	110 (84.6%)	185 (86.0%)	0.714*
Day of fever which seizure occurred	1 (1-2)	1 (1-2)	0.529***
Type of febrile seizures			
Simple febrile seizures	96 (73.8%)	161 (74.9%)	0.830*
Complex febrile seizures	34 (26.2%)	54 (25.1%)	
Semiology of seizures			
Generalized tonic-clonic seizures	93 (71.5%)	145 (67.4%)	0.425*
Non-generalised tonic-clonic seizures	37 (28.5%)	70 (32.6%)	
Accompanying symptoms			
Cough	25 (19.2%)	33 (15.3%)	0·350*
Rhinorrhoea	23 (17.7%)	40 (18.6%)	0·832*
Vomiting	17 (13.1%)	47 (21.9%)	0·042*
Diarrhoea	7 (5.4%)	34 (15.8%)	0·004*
Rashes	3 (2.3%)	6 (2.8%)	1.000**
Physical findings			
Temperature on arrival, °C	38.5 (37.9-39.0)	38.5 (38.0-39.1)	0.316***
Signs of respiratory distress	0 (0.0%)	4 (1.9%)	0.301**
Shock	0 (0.0%)	2 (0.9%)	0.529**
Abnormal neurological examination	0 (0.0%)	0 (0.0%)	-
Laboratory investigations[b]			
Leukocytosis	8 (13.6%)	61 (34.9%)	0.002*
Lymphopaenia	14 (23.7%)	17 (9.7%)	0.006*
Thrombocytopaenia	1 (1.7%)	2 (1.1%)	1.000**
Thrombocytosis	3 (5.1%)	12 (6.9%)	0.449
Treatment			
Oxygen therapy	3 (2.3%)	6 (2.8%)	1.0000**
Intravenous fluid therapy	28 (21.5%)	55 (25.6%)	0.395*
Antibiotics	5 (3.8%)	24 (11.2%)	0.018*
Phenytoin loading	3 (2.3%)	3 (1.4%)	0.676**
Outcomes			
Paediatric ICU admission	1 (0.8%)	2 (0.9%)	1.000**
Length of stay, days	2 (1 – 2)	1 (1 – 2)	0.193***
Mortality	0 (0.0%)	0 (0.0%)	-

IQR Interquartile range
[a]defined as a documented past history of COVID-19 more than a month prior to the current hospitalization
[b]Laboratory results were available for 59 COVID-19 positive patients and 175 COVID-19 negative patients.
*Chi square test **Fisher exact test ***Mann Whitney test

DISCUSSION

In this study of hospitalised children with febrile seizures, we analysed a cohort of 345 patients over an 18-month period. To the best of our knowledge, this is the largest study of febrile seizures in children in Malaysia to date. The demographic profile of our patients, such as the median age and sex distribution, were comparable with the patterns observed in both local and international studies.[13-15] Most febrile seizures in our study were categorised as simple febrile seizures (74.5%), with generalised tonic-clonic seizures being the most common semiology (69.0%). These observations are consistent with the usual presentation of paediatric febrile seizures reported in literature.[16,17]

Viral upper respiratory tract infections are a common trigger for febrile seizures.[16-18] In our study, we added to this knowledge by demonstrating a substantial proportion of febrile seizures were associated with SARS-CoV-2 infection, thereby highlighting the neurological implications of this novel virus. Febrile seizures are one of the well-recognized neurological manifestations of COVID-19.[4,5] Previous research has shown that SARS-CoV-2 tends to be more neuropathogenic in children compared to viruses like influenza and parainfluenza.[19] The ability to distinguish between febrile seizures related to SARS-CoV-2 and those not related to the virus is crucial for both effective patient management and the implementation of appropriate infection control measures.

Table III: Multivariate analysis of factors differentiating non-COVID-19 from COVID-19 positive febrile seizures.

Variable	Univariate logistic regression			Multivariate logistic regression		
	OR*	95% CI	p-value	aOR**	95% CI	p-value
Past COVID-19 infection	4.10	1.19 – 14.15	0.025	2.31	0.48 – 11.26	0.30
Family history of febrile seizures	2.92	1.55 – 5.49	0.001	2.77	1.08 – 7.07	0.03
Vomiting	1.86	1.02 – 3.40	0.044	2.03	0.89 – 4.64	0.09
Diarrhoea	3.30	1.42 – 7.69	0.006	2.30	0.75 – 7.13	0.15
Leukocytosis	3.41	1.52 – 7.65	0.003	2.85	1.24 – 6.57	0.01
Lymphopenia	0.35	0.16 – 0.75	0.008	0.40	0.18 – 0.93	0.03

* Odds ratio calculated using COVID-19 positive group as the reference
**The multivariate analysis was based on the 234 patients with complete FBC data (59 COVID-19 positive, 175 COVID-19 negative)
OR = odds ratio, aOR = adjusted odds ratio

Our study shares certain similarities to a study done in Korea by Seo et al,[20] but there are notable differences in patient selection criteria and diagnostic workup protocols. The Korean study included a wider age range and identified a substantial portion, 21% (39 out of 186 patients) who fell into an atypical age group of under six months or over five years. However, lumbar punctures were only performed on a minority of these patients (20%, n=8/39). In contrast, we adopted stricter inclusion criteria, focusing on the typical age group for febrile seizures. We excluded patients falling outside this typical age group to avoid potential misdiagnosis of other conditions such as aseptic meningitis due to SARS-CoV-2 or other viruses, which could be mistaken for febrile seizures. This was because not all these patients underwent comprehensive diagnostic workup, including lumbar punctures. This approach ensured our patients accurately represented febrile seizures within the typical age group.

In our study, the clinical features of COVID-19 associated with febrile seizures were largely similar to those of non-COVID-19 febrile seizures. There were no significant differences across a variety of parameters such as age, gender distribution, co-morbidities, past history of seizures, seizure types, seizure semiology or onset, temperature on arrival or accompanying symptoms such as cough, rhinorrhoea and rashes. However, gastrointestinal symptoms such as vomiting and diarrhoea were more frequently observed among the COVID-19 negative group. This could be potentially due to these symptoms being an uncommon manifestation of COVID-19,[9,10,21] and may suggest the involvement of other gastrointestinal pathogens such as rotavirus, norovirus and enterovirus in triggering the seizures.[22-24] Despite the initial significance of these symptoms in our univariate analysis, it was no longer significant after adjustment for confounders through the multivariate analysis. Therefore, these symptoms may not be reliable to distinguish between COVID-19 and non-COVID-19 febrile seizures.

Our multivariate analysis revealed that a family history of febrile seizures was a significant predictor for non-COVID-19 febrile seizures. This suggests that genetic predisposition to febrile seizures play a more significant role in the non-COVID-19 group. Children with a genetic predisposition for febrile seizures could experience them in response to any febrile illness. In contrast, the neuropathogenic properties of SARS-CoV-2 might trigger febrile seizures in children,[25] irrespective of genetic predisposition. Leucocytosis also emerged as an independent predictor for non-COVID-19 febrile seizures. This could be attributed to bacterial infections such as urinary tract infections or cellulitis triggering febrile seizures in the COVID-19 negative group, which might explain the higher usage of antibiotics observed in this group. Conversely, lymphopenia was more likely to be associated with COVID-19 positive febrile seizures. The presence of lymphopenia can be one of the haematological manifestations of COVID-19, although less commonly observed in children than in adults.[26,27]

While the full blood count results could be a useful tool to distinguish between both conditions, our findings are subject to a few limitations. First, not all patients underwent blood sampling, particularly at the peak of the pandemic due to resource and manpower constraints. This may have introduced bias and potentially affect the reliability of our findings. Second, we acknowledge the possibility of false negative COVID-19 test results. The sensitivity and specificity of COVID-19 testing can vary based on the timing of testing relative to symptom onset, quality of the collected specimen, and method of testing. Nevertheless, we mitigated this potential source of error by excluding children from the COVID-19 negative group who had known epidemiological links or close contact with confirmed COVID-19 cases. A third limitation arises from the lack of routine testing for other pathogens in the COVID-19 negative group. This leaves the exact cause of their febrile seizures unidentified, potentially confounding comparisons in both groups. Lastly our study was conducted at a single centre, which may limit the generalisability of our findings to other settings or populations. Further studies should address these limitations by testing a broader range of pathogens to determine the underlying causes of febrile seizures and expanding the scope to multicentre, prospective studies to improve the understanding of COVID-19 and non-COVID 19 febrile seizures.

CONCLUSION

In conclusion, the clinical presentation of febrile seizures in both COVID-19 positive and negative patients is remarkably similar. This highlights the importance for COVID-19 testing in the diagnostic workup for febrile seizures for both individual patient management and infection control purposes. A family history of febrile seizures was more prevalent in the COVID-19 negative group, suggesting a possible genetic predisposition for febrile seizures unrelated to COVID-19 infection. We also noted haematological

differences that may be potentially useful for differentiating between these conditions. Leucocytosis was more common in COVID-19 negative group, whereas lymphopenia was more prevalent among the COVID-19 positive patients.

Despite these differences, the outcomes of both groups were similar, demonstrating the typically benign nature of febrile seizures in children. Although these findings provide insights into the differences between COVID-19 and non-COVID-19 febrile seizures, future research is needed to validate our findings, while addressing our study's limitations and incorporating the recommendations provided.

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ORIGINAL ARTICLE

Hearing instability and abnormal auditory pathways in infants with congenital cytomegalovirus infection: An audiological and radiological single-centre prospective cohort analysis

Tri Juda Airlangga, MD[1], Jenny Bashiruddin[1], Irawan Mangunatmadja[2], Jacub Pandelaki, MD[3], Saptawati Bardosono[4], Fera Ibrahim, MD[5], Semiramis Zizlavsky, MD[1], Ratna Anggraini, MD[6]

[1]Department of Otorhinolaryngology Head and Neck Surgery (ORL-HNS), Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, [2]Department of Pediatrics, Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, [3]Department of Radiology, Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, [4]Department of Nutrition, Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, [5]Department of Clinical Microbiology, Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, [6]Department of Otorhinolaryngology Head and Neck Surgery (ORL-HNS), Faculty of Medicine, Hasan Sadikin Hospital, Universitas Padjadjaran, Bandung, Indonesia

ABSTRACT

Introduction: This prospective cohort study aims to investigate the hearing dynamics and the changes in the central auditory pathways in infants with congenital cytomegalovirus (cCMV) infection.

Materials and Methods: cCMV-infected neonates aged ≤3 weeks old were recruited and underwent clinical and laboratory tests to detect viremia and symptomatic infection, hearing examinations at three and six months of age, and radiological imaging of brain auditory pathways using diffusion tensor imaging.

Results: From 26 eligible infants (52 ears), we detected symptomatic infection in nine (34.6%), viremia in 14 (14/25; 56.0%) and sensorineural hearing loss (SNHL) in 14 infants (53.8%). We observed 40 ears (76.9%) with unstable hearing thresholds, 17 (42.5%) of which fluctuated. Hearing fluctuation and progressivity were more common in symptomatic infection (66.7% vs. 14.7%, p<0.001; and 38.9% vs. 2.9%, p=0.002; respectively). A substantial proportion of ears had reduced fractional anisotropy (FA) in the medial geniculate body (59.1%), superior olivary nucleus (45.5%), trapezoid body (40.9%), auditory radiation (36.4%) and inferior colliculus (31.8%). Symptomatic infection was associated with an increased FA in the medial geniculate body (mean difference, MD: 0.12; 95% Confidence Intervals, 95%CI: 0.03, 0.22) and viremia in the inferior colliculus (MD: 0.09; 95%CI: 0.02, 0.16). An FA in the inferior colliculus of ≥0.404 had a sensitivity and specificity of 68.8% and 83.3% in predicting viremia (area under the curve 0.823; 95%CI: 0.633, 1.000, p=0.022).

Conclusion: SNHL along with its fluctuation and progression are common in cCMV-infected infants. cCMV infection may induce structural changes in the central auditory pathway.

KEYWORDS:
Auditory brainstem response, congenital cytomegalovirus, hearing instability, hearing loss, distortion product otoacoustic emission, diffusion tensor imaging

INTRODUCTION

Congenital cytomegalovirus (cCMV) infection is a pervasive concern in neonatal health due to its potential to induce a range of deleterious effects. The seroprevalence rate of cCMV infection ranges from 40-83% in developed countries to nearly 100% in developing countries.[1] In Indonesia, the seroprevalence rate is estimated to be as high as 87.8%.[2] Our centre, Dr. Cipto Mangunkusumo National General Hospital, a tertiary national referral hospital in Indonesia with an estimated 1000 hospital bed capacity,[3] reported a prevalence of 5.8% (24/411 neonates) in 2019.[4] These figures are quite detrimental especially considering the potential morbidity in the affected neonates including sensorineural hearing loss (SNHL), mental and developmental disabilities, and impaired vision.[1]

SNHL is the most common complication and may affect both symptomatic and asymptomatic neonates. The long-term sequelae of hearing loss in early life may cause debilitating effects in the growth and development of the affected neonates, especially in terms of language development.[1] This underscores the importance of early screening of hearing function in cCMV-infected infants to enable prompt treatment to prevent further complications. However, little is known about the dynamics and progressivity of hearing loss in infants infected with CMV. Foulon et al. stated that unstable hearing thresholds was observed in 29.4% cCMV-infected children, and fluctuations in 16.2%. The study also found that the hearing function of the affected children worsened in 27.3% and improved in 40.9%.[5] In addition, the current evidence focuses heavily on clinical manifestations of hearing loss in cCMV infection and there is limited evidence

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Corresponding Author: Tri Juda Airlangga
Email: airlanggamd@gmail.com

on the association between cCMV infection and structural abnormalities related to key hearing structures.[6] Hence, this study aims to evaluate the hearing dynamics in infants with cCMV infection, and to explore whether cCMV infection induces structural changes in hearing, specifically the auditory nervous system.

MATERIALS AND METHODS

The study protocol has been approved by the Health Research Ethics Committee, Faculty of Medicine Universitas Indonesia and Cipto Mangunkusumo National General Hospital (ethical clearance no. 689/UN2.F1/ETIK/2017).

Study Design and Participants

This was a prospective cohort study conducted at the paediatric outpatient clinic at the Dr. Cipto Mangunkusumo National General Hospital, a tertiary national referral hospital in Jakarta, Indonesia. Neonates up to three weeks of age were consecutively screened for congenital CMV infection between January 2018 and August 2020, and patients confirmed with either serological tests or polymerase chain reaction (PCR) were included in this study. The newborns were excluded if they had: (1) a family history of congenital deafness, (2) craniomaxillofacial abnormalities including ear canal atresia or stenosis, (3) congenital syndromes affecting the patient's hearing function, (4) a 5-minute APGAR score of ≤3, (5) a history of sepsis or mechanical ventilation for >5 days, or (6) a history of maternal consumption of ototoxic drugs during pregnancy. The parents or guardians of the neonates provided written informed consent for the children's participation in this study.

Study Procedure and Outcomes

Eligible infants were further examined clinically by a paediatric neurologist and a neurotologist during the initial visit. Clinical and anthropometrical data including age, sex, clinical manifestations, birth weight, head circumference, developmental milestones and gestational age were collected. In addition, ancillary tests such as bilirubin index and CMV viremia (with PCR or serological tests) were also conducted. Symptomatic cCMV were diagnosed when the patient manifested symptoms such as chorioretinitis and/or neurological defects (e.g., microcephaly, hypotonia, poor suckling reflex, seizures, periventricular calcification, ventriculomegaly or ventricle cysts).

The children were followed up at 3 and 6 months of age for hearing function and central auditory neuroanatomy evaluation. Otoscopic examination and tympanometry was performed before each hearing function examination. At the age of 3 months, the patients underwent audiological examinations with distortion product otoacoustic emissions (DPOAE) and auditory brainstem response (ABR) tests, and radiological imaging with diffusion tensor imaging (DTI), a magnetic resonance imaging (MRI) technique that allows the visualisation of nerve tissue integrity. The subjects were sedated by an anaesthesiologist during the MRI-DTI examination. The MRI-DTI results was analysed by two radiologists using Functool 9.4.04b software. DPOAE was performed using Bio-logic® AuDX® PRO (Natus Medical Inc.; WI, USA) and a REFER result was determined when the signal-to-noise ratio (SNR), the resultant between DPOAE amplitude with noise floor, was <6 in ≥4 frequency.[7] Meanwhile, ABR click (Natus Medical Inc.; WI, USA) was performed to evaluate the function of nerve tracts connecting the vestibulocochlear nuclei and the brainstem. An ABR result was deemed abnormal when V waves occurred at a hearing threshold of >30 dBnHL or no V waves detected, and normal if V waves were noted at <30 dBnHL.[8] Bone conduction ABR was performed if the ABR results >30 dBnHL to exclude the conductive factors.

From the MRI-DTI (GE Optima; GE Operations Indonesia, Jakarta, Indonesia), we collected fractional anisotropy (FA) values from five key auditory pathways: trapezoid body (TB, reference value 0.39±0.02), superior olivary nucleus (SON, 0.38±0.01), inferior colliculus (IC, 0.46±0.02), medial geniculate body (MGB, 0.36±0.01) and auditory radiation (AR, 0.38±0.03). Three months after the first follow-up (at the age of six months), we re-evaluated the patients' hearing function with DPOAE and ABR. According to the ABR click tests, we classified the patients' hearing to be fluctuating there were ±10 dB changes in hearing threshold compared to the first evaluation, and progressive when the hearing threshold increased by ≥10 dB during the second follow-up.[5]

Statistical Analysis

Descriptive data were tabulated and presented in frequencies and proportions for dichotomous variables, and in mean±standard deviation (SD). We analysed the association between the independent variables with hearing function at 3 months old (as tested using ABR) and the hearing thresholds changing at 3 months and 6 months of age with cCMV status (symptomatic or asymptomatic) using Pearson's chi-square or Fisher's exact tests. In addition, we also assessed the association between subject characteristics and DTI findings (FA of the five tested brain regions) using Student's t-tests. Differences between groups were expressed as mean differences (MD) and 95% confidence intervals (CI). When the FA of a brain region was found to be correlated with viremia, we calculated the sensitivity, specificity, and area under the curve (AUC), and plotted the receiving operating characteristic (ROC) curve. All analyses were performed using SPSS (Statistical Package for the Social Sciences) 24.0 (SPSS Inc., Chicago, IL).

RESULTS

Characteristics of Study Population

A total of 254 infants aged ≤3 weeks old were screened for CMV infection, of which 26 (10.2%, 52 ears) returned positive and underwent audiological examination at three months old. Of those, 15 patients (57.7%) refused to complete MRI-DTI examination, and six patients (23.1%) lost to follow-up at the six months visit. The study flow diagram is illustrated in Figure 1.

Of 26 infants, 53.8% (14 infants) were boys, 65.4% (17) had asymptomatic cCMV infection, and 44.2% (23) had developed hearing loss at the age of three months. The proportion of children with microcephaly and global developmental delay were significantly higher in those with symptomatic cCMV infection (33.0% vs. 0.0% and 88.9% vs.

Table I: Characteristics of the study participants, stratified by congenital CMV infection status and hearing function at 3 months old.

Subject characteristics	cCMV infection; n(%)				Hearing function at 3 months old; n(%)			
	Total (n=26)	Symptomatic (n=9; 34.6)	Asymptomatic (n=17; 65.4)	P-value	Total (n=52)	Abnormal (n=23; 44.2)	Normal (n=29; 55.8)	p-value
Sex			0.683[b]				0.366	
Boys	14 (53.8)	4 (44.4)	10 (58.8)		28 (53.8)	14 (60.9)	14 (48.3)	
Girls	12 (46.2)	5 (55.6)	7 (41.2)		24 (46.2)	9 (39.1)	15 (51.7)	
cCMV infection								<0.001
Symptomatic					18 (34.6)	16 (69.6)	2 (6.9)	
Asymptomatic					34 (65.4)	7 (30.4)	27 (93.1)	
CMV viremia[a]	14 (56.0)	3 (37.5)	11 (64.7)	0.389[b]	22 (44.0)	12 (42.9)	10 (45.5)	0.854
Hyperbilirubinemia (>10 mg/dL)	12 (46.2)	1 (12.5)	11 (64.7)	0.014[b]	24 (46.2)	7 (30.4)	17 (58.6)	0.043
Low birth weight (<2500 g)	13 (50.0)	3 (33.3)	10 (58.8)	0.080	26 (50.0)	12 (52.2)	14 (48.3)	0.780
Microcephaly	6 (23.1)	6 (33.3)	0 (0.0)	<0.001[b]	25 (48.1)	11 (47.8)	3 (10.3)	<0.001
Global developmental delay	16 (61.5)	8 (88.9)	8 (47.1)	<0.001	24 (46.2)	17 (73.9)	7 (24.1)	<0.001
Preterm birth	11 (42.3)	2 (22.2)	9 (52.9)	0.030	22 (42.3)	7 (30.4)	15 (51.7)	0.120
Hearing function at 3 months old				0.001[b]				
Abnormal	14 (53.8)	9 (100)	5 (29.4)					
Normal	12 (46.2)	0 (0.0)	12 (70.6)					

Unless otherwise stated, data are presented in frequencies and proportions, and p-values were derived from chi-square tests. [a]One data was missing from analysis. [b]p-value derived from Fisher's exact tests. [c]CMV, congenital cytomegalovirus infection

Table II: Changes in hearing thresholds between successive auditory brainstem response examinations at three and six months of age among the ears with fluctuating hearing.

cCMV infection	Improvement	Worsening	p-value
Symptomatic	6 ears	5 ears	0.588
Asymptomatic	4 ears	1 ear	

p-value derived from Fisher's exact tests. cCMV, congenital cytomegalovirus infection

47.1%; both p<0.001), while the proportion of infants with hyperbilirubinemia and preterm birth were higher in those with asymptomatic cCMV infection (12.5% vs. 64.7%, p=0.014; and 22.2% vs. 52.9%, p=0.030, respectively). Interestingly, all patients with symptomatic cCMV infection had hearing disorders (9/9 infants, 100%), while only 29.4% (5/17) of infants with asymptomatic cCMV infection had hearing loss (p=0.001). From the 14 patients with hearing loss, we detected 23 ears with increased hearing thresholds (44.2%). The proportion of ears with hearing loss was higher in those with microcephaly (47.8% vs. 10.3%), with global developmental delay (73.9% vs 24.1%), and with symptomatic cCMV infection (69.6% vs. 6.9%) (all p<0.001), while the proportion of ears with hearing loss was lower in those with hyperbilirubinemia (30.4% vs. 58.6%, p=0.043; Table I).

Hearing Dynamics at 3 and 6 Months Old

We observed 40 ears (76.9%) with unstable hearing thresholds based on successive ABR examinations at three and six months of age. Among the 40 ears, 23 (57.5%) had persistent SNHL and 17 (42.5%) fluctuated – ten of which (52.9%) had improved hearing and seven (47.1%) worsened. Hearing fluctuation was more common in symptomatic cCMV infection (vs asymptomatic: 66.7% vs 14.7%, p<0.001). Particularly, the rate of progressive hearing loss was higher in children with symptomatic cCMV infection compared to asymptomatic cCMV-infected children (38.9% vs. 2.9%, Fisher's p=0.002), while the rate of improvement was similar between cCMV infection type (27.8% vs. 11.8%, Fisher's p=0.247).

Changes in hearing thresholds ranged from 10-40 dBnHL on the same side of ears. Among three ears with improved hearing, one had an improvement in hearing threshold by 40 dBnHL while the other two improved by only 10 dBnHL. We observed three and four ears at three- and six-months follow-up visits with PASS result based on DPOAE tests but had a hearing threshold of ≥40 based on ABR examinations (data not shown). Details on the hearing dynamics among the ears with fluctuating hearing thresholds are summarized in Table II.

Structural Changes in Auditory System

MRI-DTI examination was done on 22 cCMV-infected neonate ears. Compared to the reference values, we found that the FA of the medial geniculate body was reduced in 13 ears (59.1%), superior olivary nucleus in 10 ears (45.5%), trapezoid body in 9 ears (40.9%), auditory radiation in eight ears (36.4%), inferior colliculus in seven ears (31.8%; data not shown). We found that CMV viremia was associated with a higher FA in the inferior colliculus (man difference, MD: 0.09; 95% Confidence Intervals, 95%CI: 0.02, 0.16), while hearing loss was associated with a lower FA in the same brain region (MD: -0.07; 95%CI: -0.14, -0.01). Additionally, in the medial geniculate body, we found that the FA was higher in children with symptomatic cCMV infection (MD: 0.12; 95%CI: 0.03, 0.22), microcephaly (MD: 0.14; 95%CI: 0.05, 0.23) and global developmental delay (MD: 0.12; 95%CI: 0.0003, 0.23), and was lower in children with hyperbilirubinemia (MD: -0.14; 95%CI: -0.04, -0.24), low birth weight (MD: -0.10; 95%CI: -0.21, -0.0001), and premature birth (MD: -0.14; 95%CI: -0.24, -0.04) (Table III). We further plotted a ROC curve to explore

Table III: Association between subject characteristics and fractional anisotropy of the selected five brain regions of auditory pathway using magnetic resonance imaging with diffusion tensor imaging (MRI-DTI) examination (n = 22 ears).

Subject characteristics	TB	SON	IC	MGB	AR
cCMV infection	p=0.327	p=0.942	p=0.286	p=0.016	p=0.960
Symptomatic (n=12, 54.6%)	0.33±0.05	0.36±0.09	0.41±0.08	0.43±0.11	0.31±0.10
Asymptomatic (n=10, 45.4%)	0.36±0.09	0.37±0.11	0.44±0.09	0.31±0.11	0.31±0.08
Δ	-0.03 (-0.09, 0.03)	-0.003 (-0.09, 0.09)	-0.04 (-0.11, 0.03)	0.12 (0.03, 0.22)	0.002 (-0.08, 0.08)
CMV viremia	p=0.614	p=0.252	p=0.017	p=0.106	p=0.771
Yes (n=16, 72.7%)	0.35±0.07	0.38±0.10	0.45±0.02	0.35±0.12	0.31±0.08
No (n=6, 27.3%)	0.33±0.07	0.32±0.10	0.36±0.02	0.45±0.11	0.32±0.10
Δ	0.02 (-0.06, 0.09)	0.05 (-0.04, 0.15)	0.09 (0.02, 0.16)	-0.10 (-0.22, 0.02)	0.01 (-0.10, 0.08)
ABR at 3 months	p=0.109	p=0.173	p=0.035	p=0.453	p=0.694
SNHL (n=13, 59.1%)	0.32±0.06	0.34±0.08	0.39±0.02	0.39±0.13	0.30±0.10
Normal (n=9, 40.9%)	0.37±0.08	0.39±0.11	0.47±0.03	0.35±0.11	0.32±0.06
Δ	-0.05 (-0.11, 0.01)	-0.06 (-0.14, 0.03)	-0.07 (-0.14, -0.01)	0.04 (-0.07, 0.16)	-0.02 (-0.09, 0.06)
Hyperbilirubinaemia (>10 mg/dL)	p=0.524	p=0.709	p =0.052	p=0.006	p =0.954
Yes (n=8, 36.4%)	0.36±0.10	0.37±0.12	0.47±0.03	0.28±0.11	0.31±0.08
No (n=14, 63.6%)	0.34±0.05	0.36±0.09	0.40±0.02	0.43±0.10	0.31±0.09
Δ	0.02 (-0.05, 0.09)	0.02 (-0.07, 0.11)	0.07 (-0.001, 0.14)	-0.14 (-0.24, -0.04)	-0.002 (-0.08, 0.08)
Low birth weight (<2500 g)	p=0.015	p=0.098	p=0.655	p=0.050	p=0.813
BBLR (n=10, 45.5%)	0.31±0.07	0.33±0.12	0.41±0.10	0.32±0.11	0.31±0.07
Normal (n=12, 54.6%)	0.38±0.06	0.40±0.07	0.43±0.07	0.42±0.10	0.31±0.10
Δ	-0.07 (-0.02, -0.13)	-0.07 (-0.15, 0.01)	-0.02 (-0.09, 0.06)	-0.10 (-0.21, -0.0001)	0.01 (-0.07, 0.09)
Microcephaly	p=0.197	p=0.932	p=0.441	p=0.005	p=0.359
Yes (n=10, 45.5%)	0.33±0.05	0.36±0.10	0.41±0.08	0.45±0.11	0.33±0.10
No (n=12, 54.6%)	0.36±0.08	0.37±0.10	0.44±0.08	0.31±0.10	0.29±0.08
Δ	-0.04 (-0.10, 0.02)	-0.004 (-0.09, 0.08)	0.03 (-0.10, 0.05)	0.14 (0.05, 0.23)	0.04 (-0.04, 0.11)
Global developmental delay	p=0.723	p=0.698	p=0.552	p=0.050	p=0.618
Yes (n=16, 72.7%)	0.34±0.07	0.36±0.10	0.42±0.08	0.41±0.12	0.31±0.08
No (n=6, 27.3%)	0.34±0.08	0.38±0.10	0.44±0.09	0.29±0.09	0.29±0.10
Δ	0.01 (-0.06, 0.09)	-0.02 (-0.12, 0.08)	0.02 (-0.11, 0.06)	0.12 (0.0003, 0.23)	0.02 (-0.07, 0.11)
Premature birth	p=0.267	p=0.804	p=0.351	p=0.010	p=0.915
Yes (n=8, 36.4%)	0.32±0.07	0.36±0.11	0.45±0.09	0.29±0.12	0.31±0.08
No (n=14, 63.6%)	0.36±0.07	0.37±0.09	0.41±0.08	0.42±0.10	0.31±0.10
Δ	-0.04 (-0.10, 0.03)	-0.01 (-0.10, 0.08)	0.04 (-0.04, 0.11)	-0.14 (-0.24, -0.04)	-0.004 (-0.09, 0.08)

Unless otherwise stated, data are expressed in mean±standard deviation or mean difference (95% confidence interval), and p-values were derived from Student's t-tests. TB: trapezoid body; SON: superior olivary nucleus; IC: inferior colliculus; MGB: medial geniculate body; AR: auditory radiation.

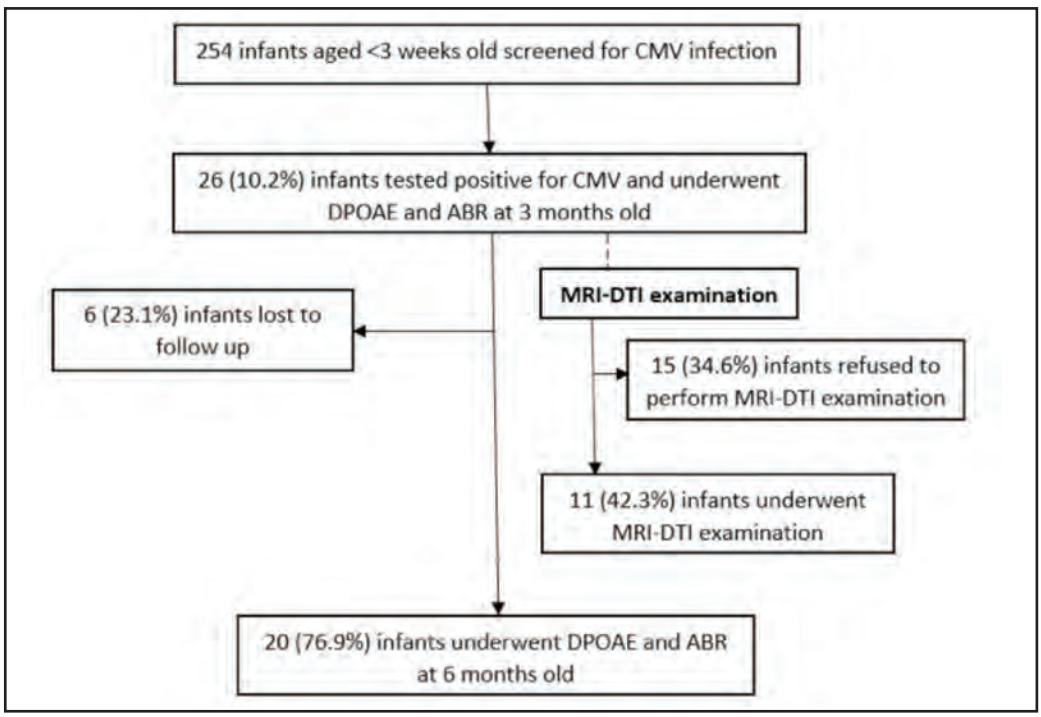

Fig. 1: Study flow diagram. ABR: auditory brainstem response; CMV: cytomegalovirus; DPOAE: distortion product otoacoustic emission; MRI-DTI: magnetic resonance imaging with diffusion tensor imaging.

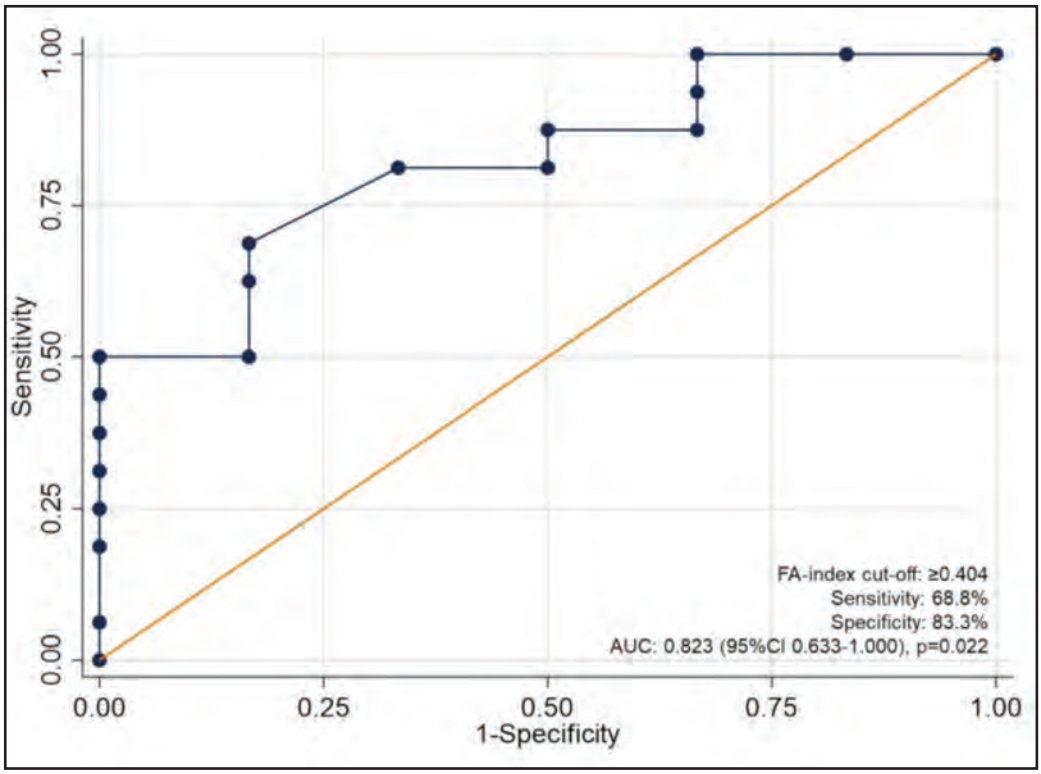

Fig. 2: Receiver operating characteristics curve for fractional anisotropy cutoff to predict viremia in inferior colliculus. AUC: area under the curve; FA: fractional anisotropy.

the discriminating performance of FA in predicting CMV viremia in the inferior colliculus region in cCMV-infected children. FA with a cut-off of ≥0.404 had a sensitivity of 68.8% and a specificity of 83.3% in predicting viremia in inferior colliculus (area under the curve, AUC: 0.823;95%CI: 0.633, 1.000, p=0.022; Figure 2).

DISCUSSION

Hearing loss in early life may induce debilitating cascading events leading to poor speech and language communication skills, cognitive and mental retardation, and low academic performance.[9] This is particularly aggravating as about 60% of cases of prelingual hearing loss in children are preventable, including CMV infection.[10] In this study, we found that the prevalence of cCMV infection in neonates was 10.2%, twice higher than a previous report in our centre which found a prevalence of 5.8% in 2016-2017.[4] This alarming prevalence surge suggests that the burden of CMV infection, particularly in neonates and infants, should not be overlooked. While it is widely known that cCMV infection may cause SNHL, there is limited evidence on the hearing dynamics in cCMV-infected children and the effects of CMV infection on structural changes in the central auditory pathways.

CMV is known to be capable of invading multiple auditory organs especially the inner and the middle ears. There are two main pathways in which cCMV infection may cause SNHL in neonates: (1) immune responses and (2) cell degeneration and injuries. In the early stage of the disease, the virus particles can invade the inner ear through blood, cochlea's aqueduct from the subarachnoid cavity or through the round window. The presence of CMV viral antigens induces immune response through the activation of inflammatory responses and release of interleukins, the interaction between the M157 on the virus surface and the LY49 cell surface receptor on NK cells, and the disruption of blood-labyrinth barrier integrity. The activated immune responses, coupled with the virus' pathogenicity, causes microcirculation disorders, hyperplasia of the organs of Corti, and apoptosis of the spiral ganglion neurons cells, thus disrupting the endolymphatic potentials and thereby causing hearing loss.[11]

In this study, we found that three out of four cCMV-infected children had unstable hearing thresholds, 57.5% of which had persistent progressive SNHL, and 42.5% of which had fluctuating hearing loss. This number is higher than those reported by Foulon et al. where only about 29.4% and 16.2% of children with cCMV infection had unstable hearing thresholds and fluctuating hearing loss, respectively. In other previous studies, the progression of hearing thresholds has been already reported varied between 43% and 62% of the congenitally infected children. The higher number of unstable hearing thresholds from ccMV infected children in our study can be caused of smaller study population and we assessed the hearing threshold disturbances based on each ear of study population.

In addition, we also found that children with cCMV infection were more likely to have progressive SNHL, while improvements were similar between children with symptomatic and asymptomatic cCMV infection. This is also in contrary to the study by Foulon et al. who found that symptomatic cCMV infection were less likely to have an

improved hearing.[5] In other study by Goderis et al found the risk developing SNHL in those symptomatic children is much higher (30-65%) than in asymptomatic children (5 to 20%).[12] Nonetheless, our study confirms previous findings suggesting that fluctuating hearing thresholds are more common in symptomatic than asymptomatic cCMV infections.[5,13] While numerous previous studies have noted the common occurrence of fluctuating hearing thresholds in cCMV-infected children,[5,11,14] its pathogenesis remains unknown. However, Fowler et al. stated that fluctuating hearing loss not explained by concurrent middle ear infections is a unique characteristic of CMV-related hearing loss.[14]

Further analysis revealed that cCMV infection resulted in a lower FA in central auditory pathways including the medial geniculate body, superior olivary nucleus, trapezoid body, auditory radiation, and inferior colliculus. In normal hearing process, sound stimuli received by the inner ear are converted to electrical stimuli and are relayed from the auditory nerve to the auditory cortex via several neuroanatomy structures including cochlear nucleus, trapezoid body, superior olivary nuclei, lateral lemniscus, inferior colliculus, medial geniculate body and auditory radiation.[15-17] All these structures especially the superior olivary nuclei and inferior colliculus are responsible of localising sound,[17] while inferior colliculus additionally generates startle responses and vestibulo-ocular reflexes.[18] The reduction of FA in these regions in cCMV-infected infants imply that cCMV infection, in addition to causing disarray in the peripheral hearing process, may also cause disintegration of central auditory tracts – as a lower FA has been thought to represent a lower neural density.[19] The presence of CMV in certain anatomical structures, including the central nervous system, may be explained by several theories. First, UL148 protein, a viral endoplasmic reticulum-resident glycoprotein influencing the viral tropism by regulating the gH/gL complexes composition on progeny virions, may enable the virus to infect certain cells, tissues and hosts, including the human central auditory pathways. Second, CMV infection may manipulate host metabolism by increasing the flow of carbons from glucose and glutamine to fatty acid metabolism, thus subsequently increasing the elongation of fatty acids to generate very long chain fatty acid tails which are essential for viral envelope formation. Third, CMV may modulate viral latency by insulating active epidermal growth factor receptor (EGFR) and regulate UL135 and UL138 proteins which antagonistically regulate viral replication thus allowing the infected cells to react to extracellular signals. Lastly, CMV-specific CD8+ T cells may accumulate over time thus extending the latency of the virus. All in all, these theories suggest that CMV infection may not only be localized in the blood and peripheral hearing organs, but also the central auditory pathways.[20]

Interestingly, we found that viremic and symptomatic cCMV infection resulted in a higher FA in the inferior colliculus and medial geniculate body, respectively. While specific reasons for these remain unknown, these may be explained by potential paradoxical atrophy or degradation of other nerve fibers,[21] or compensatory neuroplasticity following cCMV infection.[19] Previous research has found that, albeit with limited evidence, symptomatic and viremic cCMV infections may yield higher virulence and thus cause a more severe disease spectrum.[22] Hence, in these cases, the body may initiate compensatory neuroplasticity to preserve hearing function in the affected children.[23]

Altogether, our findings indicate that cCMV infection may dynamically induce structural and functional alterations in the central and peripheral hearing organs. This underscores the importance of intensive and consecutive clinical, audiological and radiological examinations in children infected with CMV to monitor their hearing function, thus ensuring their optimal growth and development. Advanced hearing examinations with DPOAE and ABR tests, as well as MRI-DTI examinations, may be performed as ancillary tests in cCMV-infected infants, especially in those with viremic and symptomatic infection. In addition, the potential morbidity risks of CMV infection, especially on their hearing and development, warrants routine screening of CMV infection in all pregnant women. While this is the case in several developed countries including the United States, Europe, Israel and Australia,[24] CMV screening is still suboptimal in most developing countries including Indonesia. In fact, CMV infection, as part of the TORCH panel, is only offered optionally to pregnant women and has yet to be included in the universal screening program.[25] Considering the scale of the potential loss of disability-adjusted life years and quality of life following CMV infection,[1] and the high rate of asymptomatic CMV infection in pregnant women,[26] we recommend CMV screening to be routinely performed in pregnant women in Indonesia.

The present study is limited by the small number of infants included in the analysis and the absence of healthy control. In addition, the relatively short follow-up period also suggests that we were unable to draw conclusions on the long-term trends of hearing dynamics in cCMV-infected children, and thus were unable to make recommendations on the timing of hearing examinations in the affected children. Nonetheless, to our knowledge, this is the first study reporting the association between symptomatic and viremic cCMV infection and structural brain changes in the inferior colliculus and medial geniculate body. Further larger studies with a longer follow-up period, and mechanistic studies exploring the molecular changes in the affected brain regions are required to confirm our findings.

CONCLUSION

We found a striking prevalence of sensorineural hearing loss (SNHL) among congenital cytomegalovirus (cCMV) -infected children in our cohort, in which fluctuation and progression of hearing loss are frequently encountered. Symptomatic cCMV infection is associated with an increased fractional anisotropy (FA) in the medial geniculate body, while viremic cCMV infection in the inferior colliculus. An FA of ≥0.404 has a high specificity in predicting viremia in cCMV-infected infants. Further studies with a larger sample size and a longer follow-up period, and explanatory studies investigating the molecular changes in the inferior colliculus and medial geniculate body following cCMV infection are warranted to substantiate our findings.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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A randomised controlled trial study on the effectiveness of high-fidelity simulation in enhancing skills among undergraduate medical students

Pal Bikramjit, MS[1], Chong Sook Vui, MRCP[2], Thein Aung Win, FRCS[3], Tay Ava Gwak Mui, FRCS[4], Soe Htoo Htoo Kyaw, PhD[5], Pal Sudipta, MSc[6]

[1]Newcastle University Medicine Malaysia, Johor, Malaysia, [2]Manipal University College Malaysia, Melaka, Malaysia, [3]Manipal University College Malaysia, Melaka, Malaysia, [4]Manipal University College Malaysia, Melaka, Malaysia, [5]Manipal University College Malaysia, Melaka, Malaysia, [6]Newcastle University Medicine Malaysia, Johor, Malaysia

ABSTRACT

Introduction: High-fidelity simulation (HFS) provides a high level of interactivity and realistic experience for the learner by means of using full scale computerised patient simulators. It imitates clinical experience in a controlled and safe environment that closely resembles reality. The purpose of this study was to compare the efficacy of HFS versus video-assisted lecture (VAL) based education in enhancing and consolidating retention of skills among undergraduate medical students.

Materials and Methods: A randomised controlled trial (RCT) study involving 111 undergraduate medical students was conducted where the competency of skills was assessed by objective structured clinical examination (OSCE) in the first, fourth and seventh/eighth weeks. A cohort of 12-14 students was enrolled for each session. The randomisation of the participants into control (VAL-based teaching) and intervention (HFS-based teaching) groups was achieved by implementing the computer-based random sequence generation method. VAL-based teaching module was a fully interactive face-to-face teaching session where a pre-recorded video clip was used. The video clip detailed the diagnosis of tension pneumothorax in an acute medical emergency and its management by performing needle decompression on a high-fidelity patient simulator (METIman). HFS-based teaching module was delivered as a fully interactive hands-on training session conducted on the same METIman to demonstrate the diagnosis of tension pneumothorax in an acute medical emergency and its management by performing needle decompression. OSCE scores were compared as the denominator of learning (enhancement and retention of skills) between two groups who underwent training with either VAL-based or HFS-based teachings. The OSCE assessments were used to evaluate the participants' performance as a group. These scores were used to compare the enhancement and medium-term retention of skills between the groups. The outcome was measured with the mean and standard deviation (SD) for the total OSCE scores for skills assessments. We used General Linear Model two-way mixed ANOVA to ascertain the difference of OSCE marks over assessment time points between the control and the intervention groups. ANCOVA and two-way mixed ANOVA were used to calculate the effect size and the partial Eta squared. p value less than 0.05 was taken to be statistically significant.

Results: The two-way mixed ANOVA showed no statistically significant difference in mean OSCE scores between intervention and control groups (p=0.890), although the mean score of the intervention group was better than the control group.

Conclusion: Our study demonstrated that HFS was not significantly effective over VAL-based education in enhancing skills and consolidating retention among undergraduate medical students. Further research is needed to determine its suitability for inclusion in the course curriculum considering the cost-effectiveness of implementing HFS that may supplement traditional teaching methods.

KEYWORDS:
High-fidelity simulation, simulation-based medical education, high-fidelity simulators, video-assisted lecture, undergraduate medical education, RCT, OSCE

INTRODUCTION

Healthcare simulation is a process that creates a situation where the learners are facilitated to experience a prototype of a real clinical event for the purpose of learning, practice and evaluation.[1] It nurtures a sense of critical thinking and problem-solving qualities in the learners that helps them to take an active role in the skill development processes. Simulation-based training provides an opportunity for the learners in practicing complex skills and is an important tool to facilitate effective learning by the process of scaffolding.[2] It is deemed to be more effective in achieving the learning outcomes in long-term when compared to other traditional training programmes.[3] At present, simulation-based medical education (SBME) is considered an effective tool in intensive care training.[3] It aids in providing opportunities for students to practise technical skills repeatedly in a safe environment that ultimately helps learners to attain proficiency in high-risk, less commonly encountered situations without harming

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Corresponding Author: Chong Sook Vui
Email: sookvui.chong@manipal.edu.my

the patients.[4] Simulation offers the opportunity to learn appropriate clinical skills without any harmful effect on the patients. Thus, it may diminish the occurrence of clinical errors that may impact negatively in the well-being of the patients in real settings.[5] SBME is crucial in the development of vital cognitive and behavioural skills.[6] In addition, it also helps in improving teamwork skills which is crucial in enhancing patient's safety.[7] The recently developed more advanced technologies like high-fidelity simulation (HFS) is an important tool in SBME for acquisition of skills and confidence.[2] HFS-based medical education offers an excellent interactive and complex learning system that supports the very essence of experiential learning pedagogy.[8] Experiential learning helps in enhancing the capability of the learners to develop clinical judgment. The reflective practice exercise after the simulation sessions assists learners in acquiring insights in developing clinical reasoning and judgment.[9] HFS-based education may contribute positively to the learners' understanding of self-efficacy, skills, confidence and critical thinking.[10] A study by Lee et al.,[11] showed that the acquisition of both technical and non-technical skills are the determining factors in judging the efficacy of HFS. They opined for its inclusion into training courses that involves in the learning of acute medical emergencies.[11] Although many studies showed the efficacy of HFS training modalities in acute medical set-up, there is lack of uniformity in research methodologies and selection of appropriate tools for outcome measurements. Also, little is known about the retention of the learning outcome.[12] There is paucity of standardised approaches and subsequent evidence for determining the competence and the learning outcomes among the learners in a safe environment outside the real clinical sites. HFS teaching strategies may complement the bedside teaching practices but the dearth of strong evidence that supports its effectiveness in acquisition of clinical competence results in a challenging situation for the faculty, especially, in justifying the cost of HFS acquisition and educational benefits.[13] The evidence suggesting the efficacy of HFS on learning abilities is lacking, specifically, its effectiveness in acquisition of skills for acute medical situations has not been substantially evaluated.[14] Consequently, more effective studies are needed to justify the importance of HFS and its efficacy on students' learning outcomes. In this context, our study had been designed to explore the effectiveness of HPS-based teaching when compared to a conventional classroom teaching method.

MATERIALS AND METHODS

Description of Trial Design: The study was designed as a randomised controlled trial (RCT) having parallel groups with 1:1 allocation. An important change to 'methods' was made from the pilot study involving 56 students with the same protocol by the current researchers in 2018-19.[15] There were two objective structured clinical examination (OSCE) assessments on the second week and the fourth week in the preliminary study. This study is an extension of the preliminary study with a different cohort of students where three OSCE assessments were conducted for both the control and the intervention groups, first one immediately after the randomisation on the first day, the second one after fourth week and the third one after seventh/eighth week. The modification was made following the suggestion of the institutional research committee after reviewing the results of the preliminary study.

Eligibility criteria for participants: All final year medical students at our institute who had consented for this study were enrolled after obtaining written informed consent.

Settings and locations where the data were collected: The clinical skills simulation laboratory of Manipal University College Malaysia (formerly Melaka-Manipal Medical College) was the venue for this research study. The study period was from March 2019 to February 2020.

Interventions:

Video-assisted lecture-based teaching module was used for the 'control group'. It was conducted as a small group (6-7 students) fully interactive face-to-face teaching session by a facilitator where a pre-recorded video clip was shown. The 20-minute video clip demonstrated the diagnosis and the management of tension pneumothorax on the high-fidelity simulator METIman (pre-hospital) in an acute medical emergency. The procedure of performing needle decompression on the simulator followed the guidelines as mentioned in the Advanced Trauma Life Support Manual developed by the American College of Surgeons (ATLS Subcommittee et al., 2013).[16] The video session was followed by a 20-minute interactive discussion session with the same facilitator.

HFS-based teaching module was used for the 'intervention group'. A small group of 6-7 students participated in a fully interactive hands-on training session conducted on the high-fidelity patient simulator (METIman) for the diagnosis and the management of tension pneumothorax in an acute medical emergency. Needle decompression was demonstrated on the said simulator for the management of tension pneumothorax adhering to the Advanced Trauma Life Support Manual developed by the American College of Surgeons (ATLS Subcommittee et al., 2013). The 20-minute demonstration session was followed by hands-on training on the METIman for another 20 minutes where students were provided with the opportunity to practice by themselves on METIman under proper guidance.

The total duration of teaching for both groups was 40 minutes. During these interactive teaching sessions, all the participants were made aware of the importance of pathophysiology and clinical presentation of tension pneumothorax, leading to arriving at the diagnosis and its subsequent management in the emergency set-up. OSCE assessments were conducted for both the control and the intervention groups, after the teaching session.

The participants were encouraged to reflect on their learning experiences in the form of immediate debriefing in both modes of teaching. Due emphasis was made on the teaching points related to the outcome of the study by the respective facilitator who was involved in each mode of teaching. The participants were not provided with other additional hands-on practice or video-assisted lecture sessions during the research study.

Outcome: In this study, our aim was to compare the OSCE scores as the denominator of learning (enhancement and retention of skills) between two groups who underwent training with either VAL-based or HFS-based teachings.

The sample size was calculated by using G*Power software.[17] The effect size was medium (0.323) based on our preliminary study that was conducted in 2018 and a power of 0.95 yielded a sample size of 114. Randomizer.com was used to generate the computerised random sequence numbers to randomise the participants into control (video-assisted lecture-based teaching) and intervention (HFS-based teaching) groups. A block randomisation process with a block size of two was used. The opaque envelopes containing the allocated interventions were sequentially numbered and sealed. Two independent investigators were used to enrol the participants and assign them to the interventions. The outcome assessor was kept blinded to the randomisation.

Statistical analysis

Microsoft Excel was used for data entry and SPSS software (version 25) for data analysis. The mean of each group's difference in score across the three assessments was used to compare VAL-based and HFS-based teachings. General Linear Model two-way mixed ANOVA was used to determine the difference of OSCE marks over assessment time points between the control and the intervention groups. We included one within-participant factor which is the assessment time points (1st, 2nd, and 3rd assessments) and one between-participant factor (control or intervention). The effect size and the partial Eta squared was calculated in ANCOVA and two-way mixed ANOVA; where the effect size 0.01 is small, 0.06 is medium and 0.14 is large. The effect size, Cohen's d was calculated for the comparison of the independent means and Cohen's dz was calculated for the comparison of the dependent means; where the effect size 0.20 is small, 0.50 is medium and 0.80 is large (Ellis P D 2010).[18] Unpaired t-test was used to assess intergroup difference of OSCE score at 1st, 2nd and 3rd assessment. Repeated measure ANOVA and post-hoc analysis was used to determine intragroup comparison of OSCE scores at 1st, 2nd and 3rd assessment among control and intervention groups. The level of significance was set at 0.05. The null hypothesis was rejected if $p<0.05$.

After the briefing session, each cohort of 12-14 students were randomised into control and intervention groups. Each group consisted of six to seven participants. The participants were briefed about the sessions and expected learning outcomes on the first day. The study focused on the importance of performing skills (diagnosis and managing the situation) as a group activity (forming a team). All the participants were apprised of the confidentiality of the HFS sessions, the video-assisted lecture sessions and the ethical issues involved during the briefing process. The participants were made aware of the functions and handling of the METIman. The students were assured that the evaluation scores during the research study was not part of the surgical curriculum assessment process. For the simulation sessions, METIman Pre-Hospital HI-Fidelity Simulator (MMP-0418) was used. It was an adult METIman with modelled physiology for advanced simulation functionalities and designed specifically for learners to practice, gain experience and develop skills. The simulator was suited to offer training solutions for teaching prehospital clinical skills, including airway management, chest tube management and needle decompression.

The validation of the OSCE checklist was also done during the preliminary study. It was validated after looking into the range to which the items in the checklist satisfactorily covered the specific area of interest.[19] Ten content experts in medical education reviewed the items in the OSCE checklist to determine whether they were relevant or important. The items were subjected to the calculation of the scale-level content validity index (SCVI), item-level content validity index (ICVI) and mean ICVI. As per the standard reference, the SCVI and ICVI were kept at 0.943 and 0.9 respectively.[20] The OSCE sessions were conducted with a 30-item checklist of the validated scenario where all items had equal weightage. The items in the OSCE checklist included the assessment of clinical presentation, diagnosis, management (needle decompression), documentation and professionalism. The OSCE assessment of the simulated sessions was designed to be completed within 20 minutes. The participants were debriefed by the facilitators at the end of their simulated sessions to attain the learning outcomes. The OSCE assessments were used to evaluate the participants' performance as a group (either control or intervention). These scores that were achieved were subsequently used to compare the enhancement and medium-term retention of skills between the groups (Flowchart, Figure 1).

RESULTS

The median age was 24 years for the 123 students who participated in the study. The drop-out rate was 12 (9.77%). Two students dropped out after the first OSCE assessment and 10 students dropped out after the second OSCE assessment. 111 students completed the study, out of which, 50 (45.05%) were males and 61 (54.95%) were females. We could not continue the study to achieve the minimal sample size of 111 due to the COVID-19 lockdown that was enforced on 18 March 2020 in Malaysia. The baseline demographic characteristics are shown in Table I.

Two-way mixed ANOVA was used to determine the difference of OSCE marks between intervention and control groups over assessment time points. There was one outlier in the first assessment but not in the rest, as assessed by examination of standardized residuals for values greater than ±3. OSCE marks were normally distributed in second and third assessment but not in first assessment, as assessed by normal Q-Q plot. There was homogeneity of variances, as assessed by Levene's test of homogeneity of variance ($p>0.05$). There was no homogeneity of covariances, as assessed by Box's test of equality of covariance matrices ($p=0.042$). Mauchly's test of sphericity indicated that the assumption of sphericity was met for the two-way interaction, $X2(2) = 1.578$, $p=0.454$.

Table II shows that there was no statistically significant interaction of the groups between the intervention and assessment time on OSCE scores.

Table I: Baseline demographic characteristics of the participants.

		Gender		Age (years)		Type of students		Total	
		Male	Female	Range	Median	Local	International		
Enrolled	Intervention	27	35	22 - 26	24	60	2	62	123
	Control	29	32	22 - 26	24	58	3	61	
Dropped out	Intervention	3	4	24 - 26	25	7	0	7	12
	Control	3	2	24 - 26	25	4	1	5	
Completed	Intervention	24	31	22 - 26	24	53	2	55	111
	Control	26	30	22 - 26	24	54	2	56	

Table II: The interaction between intervention groups and time points of assessment (Two-way mixed ANOVA).

Variable	Interaction	p-value	Partial $\eta^{2\#}$
OSCE score	Assessment time point*intervention	0.063	0.158

#Partial Eta squared

Table III: Intergroup comparison of intervention and control groups on OSCE score at 1st, 2nd and 3rd assessment (unpaired t-test).

Variable	n*	OSCE score		Mean difference (95% CI)	p-value	Partial $\eta^{2@}$
		Mean (SD)	Median			
1st assessment						
Intervention	9	22.67 (2.83)	24.0	2.11 (-2.29, 6.51)	0.324	0.061
Control	9	20.56 (5.55)	22.0			
2nd assessment						
Intervention	9	21.57 (4.45)	24.0	-1.78 (-5.67, 2.11)	0.347	0.055
Control	9	23.33 (3.24)	24.0			
3rd assessment						
Intervention	9	22.89 (2.47)	24.0	0.33 (-2.95, 3.62)	0.833	0.003
Control	9	22.56 (3.94)	23.0			

* Number of groups # Standard deviation
$ 95% confidence interval @ Partial Eta Squared

Table IV: Intragroup comparison of OSCE score at 1st, 2nd and 3rd assessment among intervention and control groups (repeated measure ANOVA).

Variable	n*	OSCE score Mean (SD)	p-value	Partial η2 @
Intervention				
1st assessment	9	22.67 (2.83)	0.568	0.068
2nd assessment	9	21.57 (4.45)		
3rd assessment	9	22.89 (2.47)		
Control				
1st assessment	9	20.56 (5.55)	0.017	0.399
2nd assessment	9	23.33 (3.24)		
3rd assessment	9	22.56 (3.94)		

*Number of groups
#Standard deviation
@Partial Eta squared

Table V: Post-hoc comparison of OSCE score at 1st, 2nd and 3rd assessment among intervention and control groups (repeated measure ANOVA).

Comparison		Mean difference (95% CI)	p-value
Intervention			
1st assessment	2nd assessment	1.11 (-2.25, 4.47)	0.468
1st assessment	3rd assessment	-0.22 (-2.25, 1.80)	0.807
2nd assessment	3rd assessment	-1.33 (-4.86, 2.19)	0.408
Control			
1st assessment	2nd assessment	-2.78 (-5.14, -0.42)	0.027
1st assessment	3rd assessment	-2.00 (-4.34, 0.34)	0.084
2nd assessment	3rd assessment	0.78 (-0.36, 1.92)	0.154

#95% confidence interval
The data of this study is available at https://data.mendeley.com/datasets/pxp2w28zkm/1.[21]

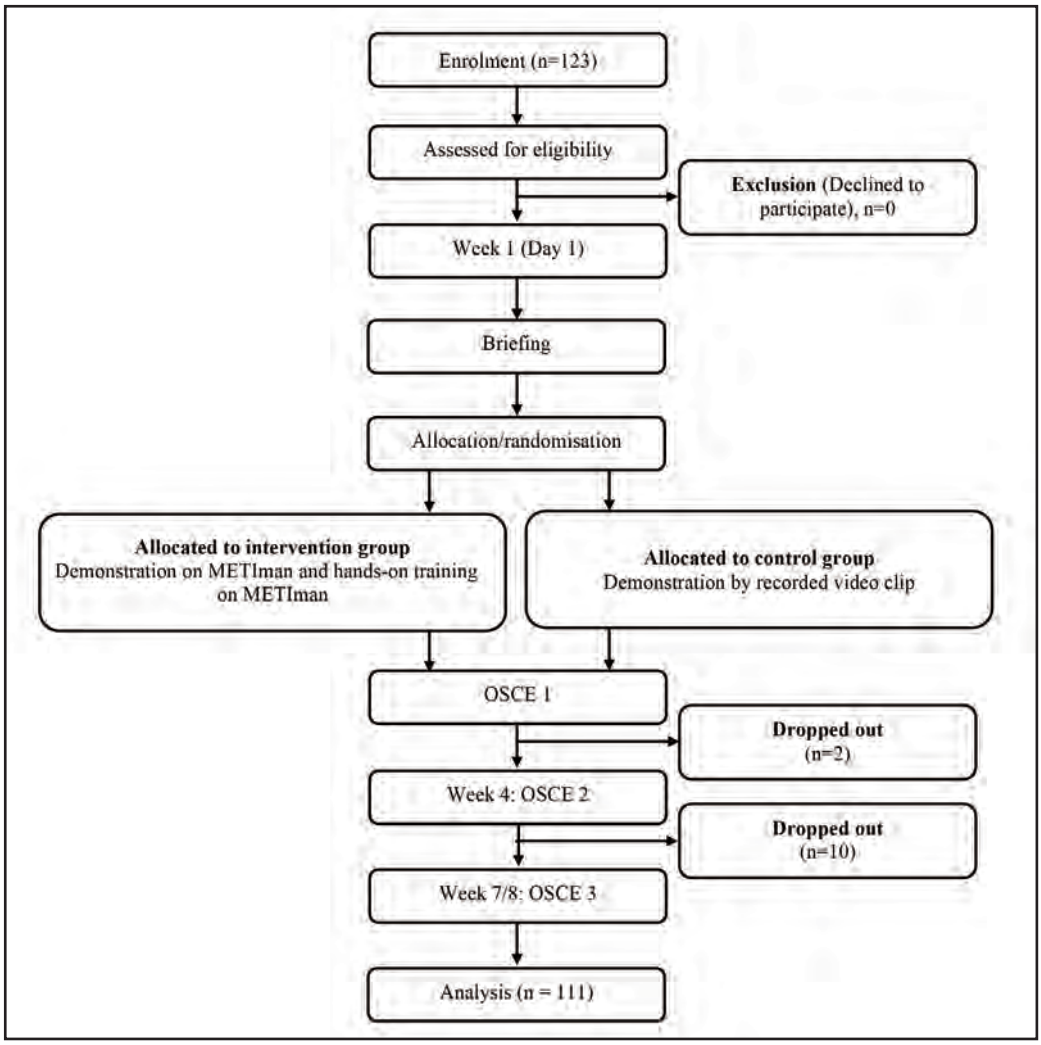

Fig. 1: Flow chart (n = number of students).

Table III shows the intergroup comparison of intervention and control groups on OSCE scores at 1st, 2nd and 3rd assessment. At first assessment, the intervention group had higher OSCE scores than the control group, but it was not statistically significant. The effect size was medium. At second assessment, the intervention groups had lower OSCE scores than the control groups, but again it was not statistically significant. The effect size was small. At third assessment, the intervention group had higher OSCE score than control group, but it was not statistically significant. The effect size was small.

Among intervention groups, OSCE scores were highest in 3rd assessment followed by 1st and 2nd assessments respectively, but it was not statistically significant. The effect size was medium. Among the control groups, there was statistically significant difference of OSCE scores between the three assessments where OSCE scores was highest in 2nd assessment followed by 3rd and 1st assessments respectively. The effect size was high (Table IV).

Table V shows post-hoc comparison of OSCE score at 1st, 2nd and 3rd assessment among intervention and control groups. There were no statistically significant differences of OSCE scores between three assessments among the intervention groups. However, among the control groups, OSCE scores were significantly higher in the 2nd assessment than the 1st assessment, but there were no statistically significant differences between 1st and 3rd assessments as well as between 2nd and 3rd assessments.

DISCUSSION

Multiple studies demonstrated that OSCE as a method of skills evaluation, is superior to other traditional assessment tools, especially, in judging student satisfaction, self-confidence and clinical knowledge acquisition.[22] OSCE is a well-recognised technique to evaluate the clinical technical and non-technical skills by judging students' performance in simulated exercises.[23] Several studies had been conducted in the domain of medical education that used simulation-based teachings for advancement of diagnostic capabilities and acquisition of psychomotor skills for future doctors, especially in acute medical emergencies.[24,25] The evidence for efficacy of simulation-based evaluation methods in the field of medical education was sparse and its advantage was mainly validated in specific specialties using specified tools for assessment when compared to other traditional evaluation methods.[24] HFS may be an appropriate teaching aid to complement traditional educational techniques if the

learners are provided with best practice methods for decision-making and learning psychomotor skills in a safe atmosphere who can meet future challenges in real life without causing any harm to the patients.[26] HFS significantly enhanced the performance and psychomotor skills of learners when compared to the control groups without HFS with a medium-to-large effect size as shown in a meta-analysis study by Shin et al. (2015).[27] Another meta-analysis and systemic review by Lei et al., demonstrated that HFS significantly increased critical thinking ability, communication skills and clinical judgement ability among the learners.[28] A study by Guerrero et al., showed that learners who had undergone HFS-based teaching along with clinical training performed better in OSCE when compared with the cohort who was exposed to clinical training only.[29] Another study also proposes the incorporation of high-fidelity simulation into advanced resuscitation training program as it was shown to help pharmacy residents achieve competency through active learning of practical skills.3[0] The combination of deliberate skill practice during HFS scenarios shows improved skill competency and retention in prelicensure nursing with reduction in errors when performing urinary catheter insertion.[31] However, in our study, there was no significant difference in enhancement of psychomotor skills when HFS was compared to video-assisted learning.

In the other hand, a RCT study conducted did not support the superiority of HFS in achieving better patient outcome and that more research is required to set the standards of HFS-based training modules.[32] Another meta-analysis study showed inconsistent evidences of HFS as an effective educational technique compared to other traditional teaching methods and therefore, more superior quality RCTs are required to validate its inclusion into the curricula.[33] In this context, our study showed no significant difference in acquisition and retention of skills in HFS when compared to VAL-based teaching in all three assessments.

The training session for HFS students involves more hands-on active participation, and thus supports psychomotor learning, as compared to video-assisted learning group. Simulation with added emotional stressors led to greater anxiety during ACLS training that correlated with enhanced performance. The anxiety generated by a simulated scenario may enhance retention through well-established learning pathways,[34] though it did not yield an edge over the conventional teaching methods in our study. However, the effects of emotion on learning and memory are not always univalent, as studies have reported that emotion either enhances or impairs learning and long-term memory.[35]

The OSCE scores for intervention group in the 1st assessment were markedly higher than the control group, though statistically not significant. This may be explained by the fact that the control group was not exposed to the hands-on training on METIman prior to the 1st assessment and there was lack of situational awareness among these students. The significant increase in OSCE scores of the VAL group from the 1st to the 2nd assessments may be due to the students getting more familiar with the simulator combined with increased situational awareness during the second assessment. There is a drop of OSCE scores from 2nd to 3rd assessment in the VAL group, though statistically insignificant. On the other hand, there is a statistically insignificant increase of OSCE scores from 2nd to 3rd assessment for the HFS group. The causes for these differences of OSCE scores in the repeat assessments were unable to be identified. Repeated exposures at 4 and 8 weeks after the initial teaching session did not consolidate the skills or enhanced its retention significantly at 8th-week, for both groups. In this context, our study does not support HFS as an effective tool to strengthen skills taught earlier. This has been corroborated by the findings of a study that showed a significant loss of cardiopulmonary resuscitation skills in HFS group as compared to traditional teaching methods in nursing students, three months after training.[36] Rather, continuous repetitive practice is possibly the key to acquisition of skills in the long run. The difference in the simulator fidelity, the complexity and the variability of the skills being taught, or the potential ceiling effect of the OSCE as an assessment tool might have affected the outcome of this study. Additional explorative studies are crucial to provide convincing evidence in determining the superiority of HFS-based education that improves technical and non-technical skills in the learners. A standardised curriculum and identical evaluation tools with established statistical validity may help in the process.[37] The most important reason for inclusion of SBME in the curricula is to minimise the risk of learners committing errors in their future clinical practice by exposing them to a variety of clinical simulated environment where they were permitted to make mistakes and consequently learn from the mistakes.[38] This needs to be considered even though our study did not provide enough evidence about its superiority over conventional educational approaches in determining the learning outcomes of clinical skills. Further studies may determine the impact of simulation learning over time and assess transference of simulation into day-to-day clinical practice. There is a need to verify its worth in promoting clinical skills retention, in addition to its potential role in enhancing knowledge, judgement, professionalism, self-motivation, reflective learning, competence, and confidence.

LIMITATIONS

Several limitations were considered in interpreting the outcomes of this study. First, the study was confined to one region of a country. Although a positive publication trend on this topic emerged in the last decade, most of the research had been conducted in North America. Consequently, generalisability of results is limited given the differences in many academic and curriculum aspects in this part of the world. Second, the comparison of learning effectiveness between traditional teaching strategy and HFS-based education for long-term retention of skills was unexplored. Apart from the sample size, there were other potential confounders in terms of students' individual learning capacities, diligence, cross-discussion before the reassessment, and respective small group dynamics. There is a need for a more comprehensive measurement of HFS activities that evaluates clinical competencies and patients' satisfaction in longitudinal studies, as well as the cost-effectiveness of implementing HFS in healthcare setting.

CONCLUSION

Integration of High-fidelity simulation (HFS) in medical education programme provides an invaluable opportunity for students to experience in real-time, a simulated, dynamic clinical scenario and to develop clinical skills in a rather controlled environment. Questions have lingered, however, regarding its effectiveness as compared to other pedagogy. Our study was designed to provide insights in this respect, as well as to contribute to the future development and improvement of HFS teaching among healthcare students. This study did not demonstrate clear advantage of HFS over video-assisted learning in clinical skills enhancement and retention.

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DECLARATION OF INTEREST

The authors have not received any funding or benefits from industry or elsewhere to conduct this study and have no conflicts of interest.

ETHICAL APPROVAL AND REGISTRATION

Ethical approval was duly obtained from the Ethical Committee/IRB of MUCM and Manipal Academy of Higher Education (MAHE). Informed consent was taken from all the participants. All information about the participants was kept confidential. The protocol of the research study was registered with the MUCM/MAHE research committee. Approval number: MMMC/FOM/Research Ethics Committee- 11/2018.

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Translation and validation study of obstructive sleep apnoea (OSA-18) questionnaire into Bahasa Malaysia (MALAY OSA-18)

Redha Asyrafi Ab Rahman, MMED, Azliana Aziz, MMED, Nik Adilah Nik Othman, MMED

Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

ABSTRACT

Introduction: According to the American Academy of Sleep Medicine, obstructive sleep apnoea (OSA) is sleep-related breathing disorder that involves a decrease or complete halt in airflow despite an ongoing effort to breathe. The OSA-18 questionnaire is a short and self-administered questionnaire to assess paediatric patients' symptoms and quality of life with obstructive sleep apnoea.

Materials and Methods: This cross-sectional study is conducted at the Otorhinolaryngology-Head and Neck Surgery (ORL-HNS) clinic of Hospital Universiti Sains Malaysia. The forward and backward translation of the OSA-18 questionnaire into the Malay language (Malay OSA-18) was performed and tested for content and face validity. The questionnaire's internal validity and reliability were tested using Pearson's correlation, Cronbach α and inter-reliability coefficient tests. The psychometric properties (validity, reliability and reproducibility) were assessed.

Results: We observed 84 patients ranging from six months up to 12 years of age. The mean age was 8 years old, and 63.1% were male patients. Among the samples, 96.4% presented with palatine tonsillar enlargement, and 84.5% presented with adenoid tonsillar enlargement. Based on the questionnaire the patient's caregiver answered, Pearson's correlation demonstrated that all the symptom scales correlate and measure the same things. The Cronbach's α coefficient value for each symptom scale was acceptable, within 0.6-0.8. The total Cronbach's α coefficient value was 0.89. The test-retest evaluation was excellent, with the value of intraclass correlation (ICC) more than 0.90.

Conclusion: The Malay version of the OSA-18 questionnaire is equivalent to the original English version. It is an effective tool to assess the paediatric OSA patient's symptoms and quality of life based on the obtained validity, reliability and reproducibility values. Therefore, it is recommended to be a screening tool in daily practice.

KEYWORDS:
Obstructive sleep apnoea, paediatrics, OSA-18 questionnaire, Malay language, validity, reliability

INTRODUCTION

Obstructive sleep apnoea (OSA) is a spectrum of sleep-related breathing disorders that involves a decrease or complete pause of airflow despite an ongoing respiratory effort. It occurs when the muscles relax during sleep, causing soft tissue in the back of the throat to collapse and block the upper airway. This leads to partial reductions (hypopneas) and complete pauses (apnoea) in breathing that last at least 10 seconds during sleep. Most pauses last between 10 and 30 seconds, but some may persist for one minute or longer.[1]

The brain responds to the lack of oxygen by alerting the body, causing a brief arousal from sleep that restores normal breathing. This can lead to abrupt reductions in blood oxygen saturation, with oxygen levels falling as much as 40% or more in severe cases. This pattern can occur hundreds of times in one night. The result is a fragmented sleep quality that often produces excessive daytime sleepiness. Most people with OSA snore loudly and frequently, with periods of silence when airflow is reduced or blocked. They then make choking, snorting or gasping sounds when their airway reopens.[1]

OSA is a common chronic illness with a consequence in neurobehavior, cardiopulmonary, metabolic systems and somatic growth. It is highly plausible that common pathogenic mechanisms are triggered by the interactions of intermittent hypoxia and hypercapnia, repeated intrathoracic pressure swings and episodic arousal. Clinical criteria usually diagnose OSA. Although polysomnography (PSG) is considered the gold standard for assessing the severity of OSA and treatment outcomes, clinical evaluations may not necessarily reflect the impact of the disease on a patient's quality of life (QOL). Based on patient reports, health-related quality of life (HRQOL) instruments usually assesses the patient's subjective perception of the impact of disease and treatment on multiple dimensions of health status. Besides functional health, the effect of OSA on QOL is of interest in literature.[2]

According to the World Health Organization (WHO), health is defined as complete physical, mental and social well-being and not merely the absence of disease or infirmity. Thus, the health domain ranges from negatively valued aspects of life to the more positively valued aspects. The boundaries of definition usually depend on why one is assessing health and

This article was accepted: 22 May 2024
Corresponding Author: Azliana Aziz
Email: az_aziz@usm.my

the concerns of patients, clinicians and researchers.2 Franco et al. developed the QOL for children with OSA-18 questionnaire, which was first reported in 2000.[3]

At this point, there are limited QOL instruments available and adapted to the Malaysian population. Therefore, using other languages requires accurate, validated translation and awareness that they are specific to social culture. The instrument's measurement properties can be affected by cultural differences even though the translation is accurate. Reliability and validity must be determined to confirm that there is no influence of cultural differences. Therefore, validation of a questionnaire is important.[2]

Almost all the well-established and recognised screening questionnaires for OSA patients, such as Berlin, STOP-BANG and Epworth sleepiness scale, cater to the adult population. Most of the items in this questionnaire are not suitable for paediatric assessment of OSA. Proper screening tools for paediatric OSA patients are needed, which can be found in the OSA-18 questionnaire.

The OSA-18 is a brief, easily administered questionnaire, ideal for use during patient encounters. It has become the reason that it is the most widely utilised QOL instrument in paediatric OSA literature. It may also be used to measure the subjective aspects of OSA-related QOL reliably. The OSA-18 consists of 18 items grouped in five domains of sleep disturbance (4 items), physical symptoms (4 items), emotional symptoms (3 items), daytime function (3 items) and caregiver concerns (4 items). Each item is scored on a seven-point Likert scale (1 = none of the time, 2 = hardly any of the time, 3 = a little of the time, 4 = some of the time, 5 = good amount of the time, 6 = most of the time and 7 = all of the time), as shown in Figure 1. The OSA-18 has been validated as an evaluative and discriminative instrument in paediatric OSA.[2]

According to Franco et al., excellent test-retest reliability of OSA-18 was obtained for the individual survey items (R>0.74). Construct validity was shown by a significant correlation of the mean survey score with the respiratory distress index (R=0.43) and adenoid size (R=0.43).[3]

There has been neither a national nor a translated instrument for assessment of QOL of paediatric OSA from literature reviews in Malaysia. The OSA-18 has waited for cross-cultural translation into the Malay language and appropriate pre-testing of the translated questionnaire. There can be advantages to translating the OSA-18 into Malay and introducing the Malay OSA-18 to determine the QOL of Malay children who suffer from OSA in clinical uses and research outcomes.[2]

PSG tests are limited to costly equipment, trained personnel and space requirements for the sleep lab. PSG is only available in selected and often specialised tertiary centres. There is insufficient such equipment available in most centres in Malaysia. This makes the screening, detection and identification of paediatric OSA patients not readily available in clinical settings, especially in primary practice.

The rationale of this study is to provide a reliable and valid tool to detect paediatric OSA patients in Bahasa Malaysia so that it can be readily applied to the majority of the patients in our setting in Malaysia. This questionnaire will facilitate early detection and hence early treatment of paediatric OSA pathology before disease progression leads to complications of diseases. It can also be applied locally regardless of the availability of a PSG machine, which is cost and time effective. Before conducting this study, written consent was obtained from the original author, Dr. Ramon A. Franco, Jr., MD, to translate his questionnaire into Bahasa Malaysia.

MATERIALS AND METHODS

Study Design

This was a cross-sectional study conducted in the Otorhinolaryngology-Head and Neck Surgery (ORL-HNS) Clinic, Hospital Universiti Sains Malaysia (HUSM) Kubang Kerian for 12 months from May 2021 until May 2022.

Study Population

For this study, 84 caregivers of paediatric patients and patients with OSA signs and symptoms were recruited from the outpatient department of ORL-HNS HUSM. Both patient and their caregiver were considered as one sample. The required sample size for this study is 65.4 Fortunately, during the period of the study, 84 samples were managed to be collected.

The age range of patients ranges from six months to 12 years. The patients with underlying cardiovascular diseases, lung diseases, neuromuscular diseases or mental retardation were excluded from the study. Children with any disease that has an impact on QOL, such as psychiatric disease and craniofacial anomalies were excluded. The patients who had already undergone adenotonsillectomy surgery and the children who were on sedative drugs were also excluded. Their caregiver must understand the Malay language well. The Malay OSA-18 questionnaire was answered by caregivers based on their observation of the child's symptoms and quality of health.

Written consent in Malay language was obtained from each participant (caregiver). All patients involved in this study answered the Malay version of OSA-18 in the ORL clinic. It was a self-administered questionnaire and took about 5 to 10 minutes for participants to complete it.

Sampling Method

The sampling method was done using the purposive sampling method whereby those patients who fulfilled the inclusion and exclusion criteria were included in the study.

Administration of the Questionnaire

The method of administration of the Malay version of the OSA-18 questionnaire was a self-administered technique.

Cross-cultural Adaptation

The translation aimed to ensure all contents of the questionnaire are equally clear, precise and equivalent in all ways to its original version. Therefore, the process of translation plays an essential aspect of a good questionnaire.

Table I: Mean age of samples and socio-demographic characteristic.

Descriptives			Statistic	Std. error
Age	Mean		8.8095	0.32775
	95% confidence interval for mean	Lower bound	8.1576	
		Upper bound	9.4614	
	5% Trimmed mean		9.0185	
	Median		9.0000	
	Variance		9.024	
	Std. deviation		3.00392	
	Minimum		1.00	
	Maximum		12.00	
	Range		11.00	
	Interquartile range		4.75	
	Skewness		-0.706	0.263
	Kurtosis		-0.329	0.520
			Frequency	(%)
Gender	female		31	36.9
	male		53	63.1
BMI	healthy		36	42.9
	underweight		2	2.4
	overweight		29	34.5
	obese		17	20.2
Palatine tonsil	grade1		3	3.6
	grade2		16	19.0
	grade3		44	52.4
	grade4		21	25.0
Adenoid	0-25 (grade 1)		13	15.5
	26-50 (grade 2)		20	23.8
	51-75 (grade 3)		30	35.7
	76-100 (grade 4)		21	25.0
OSA-18 results	Small		33	39.3
	Moderate		35	41.7
	Severe		16	19.0

Table II: The mean score for each domain.

Domain	Mean	SD
Sleep disturbance	14.70	4.36
Physical symptoms	15.43	4.54
Emotional symptoms	8.39	3.92
Daytime function	10.69	4.51
Caregiver concerns	14.48	5.66
Total score	63.62	17.79

Table III: Correlation validity between items in domains.

Item	Pearson correlation, r	p-value
Item 1	0.425**	<0.001
Item 2	0.801**	<0.001
Item 3	0.806**	<0.001
Item 4	0.637**	<0.001
Item 5	0.715**	<0.001
Item 6	0.745**	<0.001
Item 7	0.795**	<0.001
Item 8	0.547**	<0.001
Item 9	0.854**	<0.001
Item 10	0.843**	<0.001
Item 11	0.707**	<0.001
Item 12	0.786**	<0.001
Item 13	0.867**	<0.001
Item 14	0.825**	<0.001
Item 15	0.803**	<0.001
Item 16	0.907**	<0.001
Item 17	0.846**	<0.001
Item 18	0.888**	<0.001

Table IV: Correlation validity between domains.

Variables/Pearson correlation r/p-value	Sleep disturbance	Physical	Emotional	Function	Worry	Total
Sleep disturbance	1	0.582** <0.001	0.339** 0.002	0.637** <0.001	0.610** <0.001	0.829** <0.001
Physical symptoms	0.582** <0.001	1	0.328** 0.002	0.491** <0.001	0.476** <0.001	0.753** <0.001
Emotional symptoms	0.339** 0.002	0.328** 0.002	1	0.538** <0.001	0.272* 0.012	0.611** <0.001
Daytime function	0.637** <0.001	0.491** <0.001	0.538** <0.001	1	0.547** <0.001	0.831** <0.001
Caregiver concerns	0.610** <0.001	0.476** <0.001	0.272* 0.012	0.547** <0.001	1	0.792** <0.001
Total score	0.829** <0.001	0.753** <0.001	0.611** <0.001	0.831** <0.001	0.792** <0.001	1

Table V: Cronbach alpha for reliability test and test-retest reliability using the intraclass correlation (ICC) for each domain.

Domain	Cronbach alpha	ICC	95 (Lower,	CI Upper)	p-value
Sleep disturbance	0.608	0.989	0.982	0.993	<0.001
Physical symptoms	0.651	0.982	0.971	0.989	<0.001
Emotional symptoms	0.726	0.982	0.973	0.989	<0.001
Daytime function	0.766	0.992	0.987	0.995	<0.001
Caregiver concerns	0.885	0.991	0.986	0.994	<0.001
Total score	0.891	0.994	0.987	0.997	<0.001

Step one of the translations began with the original English version of the OSA-18 questionnaire translated into the Malay language. The translation was done independently by two native Malay speakers, a medical officer from the otorhinolaryngology department and a professional translator without a medical background, who were both bilingual in Malay and English language. For this study, a professional high school English tutor who has a major in teaching English as a second language (TESL) was appointed. In step two, the translations were reviewed. A panel consisting of these two translators and the principal investigator critically reviewed the translation in forming the first draft of the Malay version of OSA-18. Subsequently in step three, another two independent professional translators who had no idea of the original version of the questionnaire translated this first draft into English. The back-translation was assessed for equivalence with the original English version.

Then step four involved six otorhinolaryngologists to review the first draft for content validity.5,6 After the establishment of the content validity, the expert committee comprising of these six otorhinolaryngologists, the translator and language professionals reviewed and discussed the discrepancies between the original, forward-translated and back-translated versions. Thus, in step five, the final version of the Malay version of the OSA-18 questionnaire was produced. The feedback forms of the translated OSA-18 questionnaire from these six otorhinolaryngologists were reviewed to establish content validity. In step six, the Malay version of the OSA-18 questionnaire was distributed to ten raters independently for face validity before applying it to the study population.[5] This is to determine the clarity and comprehension of the translated version. All of the raters gave 3 to 4 scores for the face validity questionnaire, which proves excellent translation. This indicates ease of understanding the contents of the translated questionnaire and the accuracy of the translation, thus no modification was done to the finalised version. Through these multiple steps, the Malay translation of OSA-18 was polished and finalised.

Validation of the Malay OSA-18

For this study, the patients were required to answer the questionnaire two times. For the first time, the patients were required to complete the Malay OSA-18 questionnaire on the same day during a clinic visit. Subsequently, they were given two weeks' follow-up appointments to answer the questionnaire for the second time. For the retest, intervals of two weeks were used for temporal stability.[8] This means that it is short enough to prevent fluctuation in QOL status but long enough to prevent recall bias. During enrolment, all the selected patients will undergo nasoendoscopy and other clinical examinations to determine the adenoid and palatine tonsil size and grade. All of the patient's height and weight were also recorded to determine body mass index (BMI). The endoscopic findings will be scored based on the Brodsky modern assessment of tonsil and adenoid score.[7] The relation between the symptoms in the OSA-18 questionnaire, endoscopic findings and BMI were analysed.

The questionnaire's internal validity and reliability were tested using Pearson's correlation, Cronbach α and inter-reliability coefficient tests. The descriptive analysis was used to summarise the socio-demographic features of all samples. The construct validity using Pearson's correlation test was determined by correlating the responses obtained for each

item with the other items in the OSA-18 questionnaire and between each domain in the OSA-18 questionnaire. The psychometric properties (reliability, consistency and reproducibility) were carried out by the internal consistency, test-retest reliability and inter-reliability coefficient tests. The reliability or internal consistency of items in the questionnaire was tested with Cronbach's α. A second OSA-18 questionnaire was administered to the patients two weeks following the initial test to test for test-retest reliability.8 The patients who suffered from common cold, influenza, tonsillitis or respiratory tract infection between two tests were excluded from the study.

The flow of methodology can be referred in Appendix.

Statistical Analysis

Statistical analysis was performed using SPSS version 26 (SPSS Inc, Chicago, IL).[9] The descriptive analysis was used to summarise the socio-demographic features among the samples. The data obtained were expressed as mean (standard deviation, SD) for numerical and frequency (n, %) for categorical variables.

We applied Pearson's correlation, Cronhbach α and inter-reliability coefficient tests accordingly in the analysis. The p value of less than 0.05 was considered statistically significant. The construct validity by Pearson's correlation test calculated the inter-item correlation coefficient comparison between the five main domains (symptom scales) in the Malay OSA-18 questionnaire items.

The reliability or internal consistency of the items in the questionnaire was tested with Cronbach's α. Scores of 0.6-0.7 are acceptable, while a score of ≥0.7 generally indicates good internal consistency.[10]

In test-retest reliability, two-way random average measures intraclass correlation coefficients (ICC), with a positive rating for reliability given at >0.70. ICC is a method to test the agreement between total scores on two different occasions by administering the Malay OSA-18 questionnaire twice and measuring its stability.[11]

RESULTS

Demographic

This study involved 84 patients/samples, ranging from 6 months up to 12 years of age. The mean age was 8.80, with a standard deviation of 3.00 (Table I). The male gender contributes to 63.1% (n=53) of the sample, with the rest being female with 36.9% (n=31). About 42.9% of the patients were healthy, followed by overweight (34.5%), obese (17%) and underweight (2.4%). Among the samples, 96.4% presented with palatine tonsil enlargement, while 84.5% presented with adenoid enlargement. Samples presented with grade 3 palatine tonsillar enlargement were the majority with 52.4%, followed by grade 4 (25.0%), grade 2 (19.0%) and grade 1 (3.6%). For adenoid enlargement, the majority comes from grade 3 (35.7%), followed by grade 4 (25%), grade 2 (23.8%) and lastly, grade 1 (15.5%). Around 39% of the samples have a small impact on QOL, 42% have a moderate impact on QOL and 19% have a severe impact on QOL (Table I).

The OSA-18 questionnaire's lowest possible score is 18, while the highest possible score is 126. The mean total score of the OSA-18 questionnaire is 63.62±17.79, which indicates the data is normally distributed. Physical symptoms have the highest mean score at 15.43±4.54, while the lowest will be emotional symptoms (8.39±3.92) (Table II).

Construct Validity

Pearson's correlation test demonstrated a significant positive correlation between the scores of each item in the OSA-18 questionnaire. All measured items are valid ($p<0.001$). The correlations were between 0.425 and 0.907, which shows a moderate to strong correlation. This shows that all the items in the questionnaire correlate to each other and measure the same thing while not being distinct from each other (Table III).

Pearson's correlation test also demonstrated correlation validity between domains. All domains are valid ($p<0.05$). The correlations were between 0.272 to 0.637, which showed weak to strong correlations. Pearson's correlation coefficients were rated as very weak (r<0.2), weak (r=0.20-0.35, moderate (r=0.35-0.30) and strong (r>0.5).[2]

A two-tailed p-value <0.05 was considered statistically significant. Our study showed that item-to-item correlation was moderate to strong (0.425-0.907, $p<0.01$). However, if we pit each domain to one another, the correlation will be weak to strong (0.272-0.637, $p<0.01$).

The weakest correlation was between domain emotional symptoms and caregiver concerns (0.272). The strongest correlation was between sleep disturbance and daytime function (0.637). However, when compared to the total score, every domain has a strong correlation (0.611-0.831) (Table IV).

Reliability

Cronbach's α value between 0.6 and 0.8 is acceptable.[12] In this study, the total Cronbach α was 0.891, and all domains were reliable, with Cronbach α ranging between 0.608 and 0.885. Deleting any items from the scales will affect the internal consistency (Table V).

Test-retest

1. ICC estimates for sleep disturbance were 0.989, and their 95% confidence intervals were 0.982-0.993 based on a mean-rating (k=2), absolute-agreement, 2-way mixed-effects model.
2. ICC estimates for physical symptoms were 0.982, and their 95% confidence intervals were 0.971-0.989 based on a mean-rating (k=2), absolute agreement, and 2-way mixed-effects model.
3. ICC estimates for emotional symptoms were 0.982, and their 95% confidence intervals were 0.971-0.989 based on a mean-rating (k=2), absolute-agreement, 2-way mixed-effects model.
4. ICC estimates for the daytime function were 0.992, and their 95% confidence intervals were 0.987-0.995 based on a mean rating (k=2), absolute agreement, and a 2-way mixed-effects model.

5. ICC estimates for caregiver concerns were 0.991, and their 95% confidence intervals were 0.986-0.994 based on a mean-rating (k=2), absolute-agreement, 2-way mixed-effects model.

The test-retest results for each item between the first and second measurements using ICC were excellent, and all domains are valid. The correlation is between 0.982 and 0.992, with a total score of 0.994 (Table V).

DISCUSSION

Quality of life is now recognised as an essential health outcome measure in clinical medicine. Measuring QOL involves using self- or caregiver-administered instruments to quantify the impact on emotional state, physical symptoms, and family interaction.[13] Therefore, Malay OSA-18 can be very helpful as a screening tool to detect paediatric OSA patients in Malaysia.

The construct validity of the original study results was modest, particularly for the domains of emotional symptoms and daytime function. Given the multitude of factors that affect the QOL, the original author did not expect more than modest correlations to occur.[3]

The Pearson' correlation results can be affected by different demographic backgrounds too. All samples from our study came from Malay races, as Malay was predominant in Kelantan state, Malaysia. Lack of variation and sampling that did not include other races might not paint an overall picture of Malaysia's socio-demographic background, thus affecting the result. However, compared to the total score, every domain has a strong correlation (0.611-0.831, $p<0.05$). Overall, this Malay version of the OSA-18 questionnaire shows that all the items in the questionnaire significantly correlate with each other and measure the same thing while not distinct from each other. The Malay OSA-18 questionnaire can predict the severity of the impacts of OSA symptoms on the patient's QOL.

The OSA-18 questionnaire, because of its ease of administration, reliability and validity, is a practical means for the office-based determination of OSA-18 impacts on QOL. During our research, the participants were able to complete the questionnaire without difficulty in a short duration (5-10 minutes), and most of them did not need any assistance. The questionnaire was easy to understand, and the caregiver was comfortable answering all the items in the questionnaire. Furthermore, the questionnaire can be used in the outpatient setting with good acceptability and not as a burdensome tool. Analysis of the questionnaire's performance in the OSA-18 patients provides clinicians with a set of predictive parameters for various levels of OSA-18 impact on the patient's QOL.

The reliability of the Malay OSA-18 in assessing paediatric OSA patients was examined using the internal consistency Cronbach α. The overall internal consistency using Cronbach α (0.6-0.9) was acceptable and indicated its acceptable consistency. The stability of OSA-18 was demonstrated with test-retest by using ICC and showed excellent results (correlation range from 0.982-0.992 with a total score of 0.994). This showed that OSA-18 has excellent test-retest results and indicates its stability.

A further second phase study needs to assess the quality of the Malay OSA-18 questionnaire quality. For example, further study needs to be done to determine response validity for patients who have undergone surgery. This is to see whether the Malay OSA-18 questionnaire can detect before-operation and after-operative changes and be used as an assessment tool to assess the quality-of-life improvement post-surgery. Other methods will be to see the external association of the Malay version of the OSA-18 questionnaire to another parameter (i.e., polysomnography, BMI, adenoid and/or tonsillar enlargement). A second phase study can be done and provide better tools, better understanding, and standardised treatment to paediatric OSA patients with the end of the pandemic.

CONCLUSION

The Malay obstructive sleep apnoea (OSA)-18 questionnaire is equivalent to the original English version. It is an effective tool to assess the paediatric OSA patients' symptoms and quality of life based on the validity, reliability and reproducibility values obtained. Therefore, its use is recommended in daily practice.

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ORIGINAL ARTICLE

Stunting and its association with feeding problem among under five children: a case-control study in Kuantan district, Malaysia

Nor Azam Kamaruzaman, MMed (Fam Med)[1], Noraini Musa, MBBS[1], Hafizah Pasi, PhD[2], Iskandar Firzada Osman, MMed(Fam Med)[3]

[1]Department of Family Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia, [2]Department of Community Medicine, IIUM, Kuantan, Pahang, Malaysia, [3]Klinik Kesihatan Jaya Gading, Kuantan, Pahang, Malaysia

ABSTRACT

Introduction: Stunting is the most prevalent form of malnutrition among infants and young children population, both globally and locally. It refers to low height-for-age children and is primarily caused by chronic under nutrition. The objective of this study is to determine the association between stunting and feeding problems and to explore the risk factors for stunting among children aged 6 to 59 months attending health clinics in the Kuantan district.

Materials and Methods: A case-control study involving 160 children that attended six health clinics in Kuantan from August to October 2021 with a ratio of 1 case: 3 controls. Data were collected from mothers using a questionnaire consisting of sociodemographic and feeding assessment adapted from a validated World Health Organization (WHO) integrated management of childhood illness (IMCI) assessment form. The data was analysed using IBM SPSS version 26.0. Binary logistic regression analysis was used to identify factors associated with stunting. The odds ratio was used to measure the strength of the association between outcome and predictor variables. The significance value was set at p<0.05.

Results: Children with identified feeding problems have more than four-time significantly higher risk of becoming stunted (Odds Ratios, OR: 4.2; 95% Confidence Intervals, 95%CI: 1.4, 12.8) as compared to children with no feeding problems. Specifically, children with inadequacy in feeding components; amount, variety and frequency of meal each have significantly six-time higher risk (OR: 6.2; 95%CI: 2.7, 14.5), four-time higher risk (OR: 4.2; 95%CI: 1.4, 12.3), and three-time higher risk (OR: 2.8; 95%CI: 1.1, 6.9), of becoming stunted as compared to children with adequate feeding. Additionally, with a decrease of one week in delivery week, one kilogram in birth weight and one centimetre in maternal height, there is a respectively significant 40.0% (OR: 0.6; 95%CI: 0.4, 0.9), 80.0% (OR: 0.2; 95%CI: 0.1, 0.7) and 11.0% (OR: 0.89; 95%CI: 0.82, 0.98) increase in the risk of become stunted among children.

Conclusion: Feeding problems specifically inadequate food amount, food variety and meal frequency not following the recommendation contribute to stunting in young children. Other factors identified are lower maternal height and children with lower birth weight and delivery week. This highlights the need for more excellent detection and intervention of nutritional concerns and risk factors to prevent stunting.

KEYWORDS:
Stunting, growth disorder, feeding problem, nutritional, under 5

INTRODUCTION

Stunting is the most prevalent form of malnutrition in the under-five population. Globally, an estimated 149.2 million children or almost a quarter of the number of children under the age of 5 are suffering from stunting[1] with as many as 79 million stunting cases are in Asia region. Likewise, in Malaysia, according to the National Health Morbidity Survey (NHMS) 2022, the prevalence of stunting in children under five was 21.8% in 2019 with the highest cases of stunting occurred in the state of Pahang at 28.2%.[2] Out of 11 districts in Pahang, the incidence in Kuantan in 2022 was 0.6% out of 6339 new attendances to the health clinics.

Stunting is a condition where a child's height is shorter than his/her height for age which mainly caused by chronic under nutrition. Stunting might leads to an increase in illnesses and deaths, as well as a decline in cognitive and psychomotor development.[5] It could later affect their academic and career opportunities and perpetuate poverty in later life.[7] It is a vicious cycle that will continuously impacts one's health. Stunting frequently starts during pregnancy until at least the first three years of a child's life thus the pregnant woman's nutritional status will impact the foetus growth. Stunting has also been identified as the target for nutritional initiatives as the majority is caused by the inadequacy of children's diets. Therefore, nutrition is one of the modifiable risk factors for stunting, which will be explored in more detail in this study.

The screening for malnutrition and assessment for feeding problem among under 5 children at the primary care level in Malaysia has been adopted from World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) program and adapted into local Approach to Unwell Children under 5 (ATUCU5 modules) in 2018. This was

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Corresponding Author: Noraini Musa
Email: norainibtmusa88@gmail.com;ainimusa_1988@yahoo.com

complemented by the guidelines for the prevention and management of under 5-year-old children with risks for malnutrition *(Panduan Pencegahan & Pengendalian Kes Berisiko Malnutrisi Dalam Kalangan Kanak-Kanak Bawah 5 Tahun)* which was developed by Family Health Development Division, Ministry of Health Malaysia in 2019. It strategizes the clinical algorithm for identification and management of malnutrition and lifestyle intervention including dietary component.[3]

MATERIALS AND METHODS

This was an unmatched case-control study, conducted for 18 months, from October 2021 to March 2023. With a ratio of 1:3, 40 cases of stunting and 120 controls with normal height for age were selected. The study design was chosen since it is the best method to examine the association between stunting and feeding problems. This study's operational definition of stunting is low height-for-age (< -2 standard deviation, SD) during the recruitment period. Operational definition for feeding problem is impaired oral intake that is not followed age-appropriate, while amount, variety, and frequency of feeding were considered inadequate if not following recommendations. It involved children aged 6 to 59 months old (paired with their mothers) who attended six government health clinics in Kuantan district in Pahang. The study tool used was from WHO IMCI programme and was adapted into local ATUCU5 modules in 2018. IMCI is a validated clinical clerking protocol developed by WHO.

The sample size was computed using OpenEpi version 3.1. The total sample size calculated was 160. Exclusion criteria for both cases and controls was children with underlying medical illnesses that could affect growth and development. Examples of chronic diseases that had been excluded were thyroid disorder (e.g., hypothyroidism), growth hormone disorder, cardiac disease and chronic lung disease. The data collection used a questionnaire which consists of child and maternal socio demographic data, child anthropometric measurements and feeding assessment adapted from IMCI. The data was analysed using IBM SPSS version 26.0. Binary logistic regression analysis was used to identify factors associated with stunting. The odds ratio was used to measure the strength of the association between outcome and predictor variables. A p-value of <0.05 was taken as statistical significance in multivariate binary logistic regression analysis.

RESULTS

Characteristics of Children

A total of 160 children (40 cases and 120 controls) participated in this study. Table I showed that the mean age of cases and controls were 27.2 (±14.1) and 22.4 (±10.5) months respectively. The majority of children in both cases and controls were girls (59.4%), Malay (91.9%), had one to two siblings (65.6%), had received complete vaccinations up to their age (99.4%), and had no history of multiple hospitalisations (96.9%). All of them were singleton birth. The mean delivery week and mean birth weight were both lower in cases than controls, being 37.5 (±1.4) and 38.3 (±1.6) weeks, and 2.6 (±0.5) and 3.0 (±0.5) kilograms, correspondingly. In terms of underlying chronic disease were five cases (5%) in this study, two of them were bronchial asthma in treatment.

Characteristics of Mother

From Table II, the mean maternal height for cases (151.0±5.1cm) was lower than controls (155.4±6.0cm). Majority of the mother in both cases and controls were housewives and had secondary level of education. The mean household income for cases (MYR2567.5±1843.3) was lower than the controls (MYR3,813.6±2604.7). Almost all caregivers have treated water as a water source (98.8%) and refrigerator for food storage (98.1%) at their homes.

Feeding Profile of Children

Exclusive breastfeeding occurred more in cases than controls. In general, children with stunting had more feeding problem (75%) than controls (25%). They had higher percentage for taking less than the recommended meal frequency for both main meal and snack. They also had higher percentage for inadequacy in the food variety (energy food, protein, vegetables, fruit and drinks) and inadequacy in the amount of food intake (energy food, protein and milk).

Factors Associated with Stunting

In the multiple binary logistic regression analysis shown in Table IV and V, delivery week, birth weight, maternal height, feeding problems (amount, variety and frequency of meal) were significant independent factors associated with stunting. Other factors were not significantly associated with stunting after adjusting for other cofounders.

It was shown that a decrease of 1 week in delivery week, 1 kg in birth weight and 1 cm in maternal height, there is a respectively significant 40.0% (Odds Ratios, OR: 0.6; 95% Confidence Intervals, 95%CI: 0.4, 0.9), 80.0% (OR: 0.2; 95%CI: 0.1, 0.7) and 11.0% (OR: 0.89; 95% CI 0.82, 0.98) increase in the risk of become stunted among children.

For feeding profile as shown in Table V, firstly, children with feeding problems have more than four times higher odds of becoming stunted (OR: 4.2; 95%CI: 1.4, 12.8) than children with no feeding problems. The findings revealed that higher risk occurred among children with inadequate intake of food amount, inadequate food variety and inadequate meal frequency. Children with inadequate feeding amounts have more than six times higher odds of becoming stunted (OR: 6.2; 95%CI: 2.7, 14.5). Secondly, children with inadequate feeding variety have more than four times higher odds of becoming stunted (OR: 4.2; 95%CI: 1.4, 12.3) and lastly, children with inadequate feeding frequency have almost three times higher odds of becoming stunted (OR: 2.8; 95%CI: 1.1, 6.9) than children with adequate feeding frequency.

DISCUSSION

Feeding Problem as a Determinant of Stunting

Adequate complementary feeding is critical to support children's optimal physical growth and to prevent stunting. Complementary foods need to be energy and nutrient-rich and be fed frequently. The most significant proportion of stunting occurs during the complementary feeding period (6-23 months), i.e., the 500-day transition from exclusive breastfeeding in the first six months of life to consuming a

Table I: Description on sociodemographic characteristic of the children.

Variables	Stunting				Total	
	Yes		No		N	%
	n	%	n	%		
Age (months), ±SD	27.2±14.1*		22.4±10.5*		23.6±11.6*	
Gender						
Boy	16	40.0	49	40.8	65	40.6
Girl	24	60.0	71	59.2	95	59.4
Race						
Malay	34	85.0	113	94.2	147	91.9
Orang Asli	5	12.5	3	2.5	8	5.0
Chinese	1	2.5	0	0.0	1	0.6
Others	0	0.0	4	3.3	4	2.5
Number of siblings						
1-2	24	60.0	81	67.5	105	65.6
3-4	16	40.0	31	25.8	47	29.4
>5	0	0.0	8	6.7	8	5.0
Immunization status						
Not complete up to age	1	2.5	0	0.0	1	0.6
Complete up to age	39	97.5	120	100.0	159	99.4
Underlying growth problem						
No	40	100.0	120	100.0	160	100.0
Yes	0	0.0	0	0.0	0	0.0
Underlying chronic disease						
No	38	95.0	117	97.5	155	96.7
Yes	2	5.0	3	2.5	5	3.1
History of multiple hospitalization						
No	37	92.5	118	98.3	155	96.9
Yes	3	7.5	2	1.7	5	3.1
Birth history						
Term	35	87.5	107	89.2	142	88.8
Premature	5	12.5	13	10.8	18	11.3
Delivery week	37.5 ± 1.4 *		38.3 ± 1.6 *		38.1 ± 1.6 *	

*Mean and standard deviation (SD)

Table II: Description on sociodemographic characteristic of the mothers.

Variables	Stunting				Total	
	Yes		No		N	%
	n	%	n	%		
Maternal height (cm), ±SD	151.0±5.1*		155.4±5.9*		154.3±6.0*	
Para						
1-2	26	65.0	81	67.5	107	66.9
3 4	14	35.0	32	26.7	46	28.7
>5	0	0.0	7	5.8	7	4.4
Maternal occupation						
Housewife	28	70.0	76	63.3	104	65.0
Working	12	30.0	44	36.7	56	35.0
Maternal education status						
Primary school	1	2.5	3	2.5	4	2.5
Secondary school	24	60.0	59	49.2	83	51.9
Higher education	15	37.5	58	48.3	73	45.6
Household income	2567.5± 1843.3 *		3813.6 ± 2604.7*		3502.2 ± 2490.8*	
Water source at home						
Non treated water	1	2.5	1	0.8	2	1.3
Treated water	39	97.5	119	99.2	158	98.8
Availability of fridge for food storage						
No	3	7.5	0	0.0	3	1.9
Yes	37	92.5	120	100.0	157	98.1

*Mean and standard deviation (SD)

Table III: The feeding profile of children.

Variables	Stunting				Total	
	Yes		No		N	%
	n	%	n	%		
Exclusively breastfeeding						
No	10	25.0	51	42.5	61	38.2
Yes	30	75.0	69	57.5	99	61.8
Frequency						
1. Frequency of main meal/ day						
0	1	2.5	0	0.0	1	0.6
1	2	5.0	1	0.8	3	1.9
2	12	30.0	21	17.5	33	20.6
3	24	60.0	89	74.2	113	70.6
4	1	2.5	9	7.5	10	6.3
2. Frequency of snack/ day						
0	3	7.5	0	0.0	3	1.9
1	15	37.5	31	25.8	46	28.8
2	15	37.5	69	57.5	84	52.5
3	7	17.5	18	15.0	25	15.6
4	0	0.0	2	1.7	2	1.3
Variety						
1. Energy type of food taken						
No	1	2.5	0	0.0	1	0.6
Yes	39	97.5	120	100.0	159	99.4
2. Protein type of food taken						
No	2	5.0	0	0.0	2	1.3
Yes	38	95.0	120	100.0	158	98.7
3. Vegetable type of food taken						
No	13	32.5	18	15.0	31	19.4
Yes	27	67.5	102	85.0	129	80.6
4. Fruit type of food taken						
No	19	47.5	44	36.7	63	39.4
Yes	21	52.5	76	63.3	97	60.6
5. Drink						
No	6	15.0	0	0.0	6	3.8
Yes	34	85.0	120	100.0	154	96.2
Amount						
1. Amount of energy food taken						
Not adequate	13	32.5	20	16.7	33	20.6
Adequate	27	67.5	100	83.3	127	79.4
2. Amount of protein intake						
Not adequate	12	30.0	3	2.5	15	9.4
Adequate	28	70.0	117	97.5	145	90.6
3. Amount of milk intake						
Not adequate	9	22.5	1	0.8	10	6.3
Adequate	31	77.5	119	99.2	150	93.7

wide range of family foods while breastfeeding continues. The adequate intake amount of food especially from the energy rich source is the most important factor that could impact child's growth followed by food variety and adequate meal frequency. A case-control study in Vietnam also showed that after adjusting for other factors in the model, children whose mothers inappropriately provided food had a 1.9 times greater risk of getting stunted than those whose mothers fed them appropriately.[20] A study has found that feeding frequency less than four times a day was 3.6 times higher among the cases than in controls.[12] Another findings indicate that 63.0% of the children had an inadequate minimum dietary diversity score (DDS).[21] The finding is similar to a study conducted in Ghana in which only 24.7% of the children had a dietary diversity score of at least four out of seven food groups.[22] Moreover, the causative factors in stunted children are micronutrient insufficiency, food scarcity and protein-energy malnutrition, which is an obvious cause of stunting.

Child Factor as a Determinant of Stunting

Several studies have shown low birth weight as a strong determinant of child stunting. Low birth weight was 4.47 times more in stunted children than those not stunted, in line with a study done in Kelantan Malaysia, which found that low birth weight had a 0.61 higher risk for stunting.[13] Moreover, researchers found that a history of low birth weight increased the risk of stunting more than 12 times compared to those with average birth weight.[14] Low birth weight can potentially have an intergenerational impact according to research that links it to mothers' nutritional quality during pregnancy and the preconception period. These findings explain the concept of stunting during the first 1000 days of life.[15] Infants have a better chance of growing to an average body height if they can catch up on their growth during the first six months of life.

Table IV: The association between factors among children and maternal with stunting.

Variables	Stunting			
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age	1.0(1.0, 1.1)	0.028	1.0 (0.9, 1.1)	0.321
Gender				
Boy	1.0			
Girl	1.0(0.5, 2.1)	0.926	-	-
Race				
Malay	1.2(0.1, 11.1)	0.870		
Orang Asli	6.7(0.5, 91.3)	0.155		
Others	1.0		-	-
Number of siblings				
1-2	1.0	0.116	-	-
3-4	1.8(0.9, 3.9)			
>5	0.0			
Underlying chronic disease				
No	1.0			
Yes	1.6(0.1, 17.8)	0.717	-	-
History of multiple hospitalization				
No	1.0	0.086	-	-
Yes	5.0(0.8, 30.8)			
Birth history				
Term	1.0			
Premature	1.2(0.4, 3.7)	0.721	-	-
Delivery week	0.7(0.6, 0.9)	0.006	0.6(0.4, 0.9)	0.035*
Birth weight	0.2(0.1, 0.5)	<0.001	0.2 (0.1, 0.7)	0.009*
Maternal height	0.9(0.8, 0.9)	<0.001	0.89 (0.82, 0.98)	0.016*
Para				
1-2	1.0	0.359	-	-
3-4	1.4(0.7, 3.1)	0.999		
>5	0.0			
Maternal occupation				
Housewife	1.0			
Working	0.7(0.3, 1.5)	0.308	-	-
Maternal education status				
Primary school	1.3(0.1, 13.3)	0.831	-	-
Secondary school	1.5(0.7, 3.1)	0.300	-	
Higher education	1.0			
Household income	1.0	0.009	1.0 (0.9, 1.0)	0.096
Water source at home				
Non treated water	0.3(0.0, 5.2)	0.420	-	-
Treated water	1.0			

*Statistically significant at p<0.05
$ Analysis for availability of fridge for food storage vs stunting status cannot be executed as all respondents who were not stunted, have fridges at home.

Table V: The association between feeding problem status among children and stunting.

Variables	Stunting			
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Feeding problem				
Yes	4.7 (2.1, 10.4)	0.0001	4.2 (1.4, 12.8)	0.011*
No	1.0			
Frequency				
Not adequate	3.7(1.7, 8.3)	0.001	2.8 (1.1, 6.9)	0.029*
Adequate	1.0			
Variety				
Not adequate	3.9(1.5, 1.0)	0.004	4.2(1.4, 12.3)	0.010*
Adequate	1.0			
Amount				
Not adequate	5.5(2.5, 12.0)	<0.0001	6.2 (2.7, 14.5)	<0.0001*
Adequate	1.0			
Breastfeeding history				
No	2.0(0.2, 17.0)	0.532	1.0 (0.44, 2.4)	0.95
Yes	1.0			

*Statistically significant at p<0.05

Maternal Factor as a Determinant of Stunting

Various studies have shown maternal stature as a strong determinant of child undernutrition. In a study done in Vietnam, maternal height and weekly weight gain during pregnancy were identified as significant predictors of a child's future risk of stunting by OR 0.86.[16] This finding is supported by a previous study that found that for each standard deviation increase in maternal height, offspring height for age at two years increased by 0.30 SD ($p<0.001$). This is in line with the cohorts study examining five prospective birth cohorts in which shorter women (<150.1 cm) were three times more likely to have a stunted child at two years.[18,19] Shorter women will likely have reduced protein and energy stores, smaller uterine volume, limited room for foetal development, reduced placental size and function and decreased quantity and quality of breast milk.

Preventive Strategies for Stunting

In primary care, prevention is the principle of healthcare service. Generally, these consist of primordial, primary, secondary and tertiary prevention. Combined, these strategies aim to prevent disease onset through risk reduction and downstream complications of a manifested disease such as stunting.[16]

Primordial prevention is done by empowering woman to practice healthier diets prior to conception and throughout the pregnancy and postnatal period. Mothers also need to be empowered to learn and adopt proper feeding recommendations for their infants and young children with particular focus should be given to adequate energy-rich food and the appropriate meal frequency and variety.[8,23] This nutritional education must be given early from the pre-pregnancy phase and delivered by the first tier (staff nurse and medical officer) with the nutritionist's guidance.

Primary prevention is also essential by identifying children at risk of stunting, such as infants with feeding problems, short maternal stature, low birth weight and pre-term delivery and children whom the growth chart crosses the centile. Delivering early intervention for identified modifiable risk factors to avoid the clinical outcome of stunting is critical.[24] As secondary prevention, a focused and intensified feeding counselling and nutritional support needs to occur in children with risk or already diagnosed with stunting to avoid complications. Lastly, further research is needed to determine which interventions could be best efficiently and economically implemented.

CONCLUSION

Feeding problems in under five years old children may lead to negative sequelae particularly stunting which is the most prevalent form of malnutrition (undernutrition) in this age group. This case control study aimed to explore feeding problems as the risk factors for stunting among infants and young children in district of Kuantan, Pahang. Identifying determinants of stunting would help to set priorities for action and design a preventive strategies and early intervention to prevent stunting. This study may offer an opportunity to review the strategies, target the significant predictors which had been identified, and empower the community and healthcare providers for early identification and intervention to break the vicious cycle of stunting.[24]

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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 (MREC) (NMRR ID: NMRR-21-1264-60135 (IIR)), Ministry of Health Malaysia (KKM/NIHSEC P21-1393(3).

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ORIGINAL ARTICLE

Oral health assessment of epilepsy patients from a tertiary hospital in Asia

Mohd Faiz Mohd Noor, MBBS[1], Muhammad Samir Haziq Abd Rahman, MD[1], Nurazfalina Azura Abdul Aziz, DDS[2], Jennifer Ting Sok Tin, DDS[2], Syed Nabil, MDS (OMFS)[3], Tan Juen Kiem, Dr. Int. Med[1,5], Rathika Rajah, Dr. Int. Med[1,5], Wan Nur Nafisah Wan Yahya, MMed[1,5], Wan Asyraf Wan Zaidi, Dr. Int. Med[1,5], Khoo Ching Soong, FRCP[1,5], Rozita Hod, PhD[4], Siti Zaleha Sahibulddin, BSc[5], Tan Hui Jan, FRCP[1,5]

[1]Department of Medicine, Faculty of Medicine, the National University of Malaysia, Kuala Lumpur, Malaysia, [2]Department of Oral and Maxillofacial Surgery, Hospital Canselor Tuanku Muhriz, Cheras, Kuala Lumpur, Malaysia, [3]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Jalan Raja Muda Abdul Aziz, Kuala Lumpur, Malaysia, [4]Department of Public Health Medicine, Faculty of Medicine, the National University of Malaysia, Kuala Lumpur, Malaysia, [5]Hospital Canselor Tuanku Muhriz, Cheras, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: Oral health problems are frequently overlooked in patients with epilepsy. We evaluate the oral health status of epilepsy patients from a tertiary teaching hospital.

Materials and Methods: We conducted a cross-sectional study of epilepsy patients from the neurology clinic, Hospital Canselor Tuanku Muhriz, Kuala Lumpur. The dental assessment included the decayed, missing and filled teeth (DMFT) criteria, as well as the plaque and periodontal status by dentists.

Results: A total of 151 patients were recruited. The median age of onset of epilepsy was 16 (IQR 7-30) years, with generalised seizures at 59.6% and focal seizures in 40.4% of patients. Fair or poor oral health was present in 59 (39.1%) and gingivitis was seen in 65 (43%). The median DMFT decayed (D), missing (M) and filled teeth (FT) was 3 (IQR 1-7). The median age of patients with fair or poor oral health was older (40 years, IQR 31-51) than the patients with excellent or good oral health (33 years, IQR 26-45), (p=0.014). Multivariate logistic regression analysis showed that carbamazepine (Odds Ratios, OR: 3.694; 95% Confidence Intervals, 95%CI: 1.314, 10.384) and hypertension (OR 6.484; 95%CI: 1.011, 41.594) are the risk factors for fair or poor oral health. Phenytoin use is 4.271 times more likely to develop gingivitis (OR 4.271; 95% CI: 1.252, 14.573).

Conclusion: Factors that contribute to fair or poor oral health include age, antiseizure medications like phenytoin and carbamazepine, and hypertension. Effective preventive strategies should be implemented to maintain oral health in epilepsy patients.

KEYWORDS:
Oral health, dental, plaque index, gingival index, epilepsy

INTRODUCTION

Epilepsy is a heterogenous neurological disorder characterised by recurrent unprovoked seizures, with about 50 million people worldwide suffering from this condition. The lifetime prevalence and incidence of epilepsy are particularly high in low to middle-income countries.[1] Malaysia is a middle-income country with a population of 34.3 million, which comprises multiethnic groups. Malaysia's lifetime epilepsy prevalence is 7.8 per 1000 persons.[2] The frequency of seizures has a significant impact on the quality of life for individuals with epilepsy in Malaysia.[3]

In Malaysia, statistics suggest that oral healthcare may not be a priority among the population. Utilisation of oral healthcare facilities is estimated at only 13.2% among healthy adults aged 18 years and above.[4] Click or tap here to enter text. Based on the National Oral Health Survey of Adults 2010, 88.9% of Malaysian adults had dental caries (treated and untreated) and 94% had periodontal conditions.[5] Patients with epilepsy tend to have significantly more deteriorating physical and psychological health than the general population including dental problems.

The World Dental Federation has defined oral health as the ability to speak, smile, smell, taste, touch, chew, swallow and convey a range of emotions through facial expressions with confidence and without pain, discomfort and disease of the craniofacial complex.[6] Oral health is one of the aspects that may affect the quality of life inadvertently. Epilepsy patients may experience oral health problems following trauma[7] from seizures or antiseizure medications. The orofacial consequences of epileptic seizures include dental trauma such as crown fractures, intrusion, avulsion,[8] dentoalveolar fractures, as well as maxilla facial injuries[9] and soft tissue lacerations. Antiseizure medications such as phenytoin, valproate, carbamazepine or phenobarbital also affect periodontal disease.

Studies have shown that epilepsy patients are more vulnerable to oral health diseases. Wang et al. state that carious and missing teeth and periodontal indexes are significantly worse in patients with epilepsy.10 There is an increased predilection to anterior dental injuries in patients with epilepsy as compared with the prevalence earlier reported for those without epilepsy in Nigeria.[8]

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Corresponding Author: Hui Jan Tan
Email: tanhuijan@gmail.com, tanhuijan@ukm.edu.my

To date, there has not been any reported data on the oral health problems in epilepsy in Malaysia. To address the significant burden of oral health problems in this specific group, additional attention is needed. Improved understanding of factors related to oral health disease facilitates the development of effective interventions. Hence, we embark on this study to delineate the prevalence and associated factors of oral health issues in epilepsy patients.

MATERIALS AND METHODS

Study Site and Participants

This cross-sectional study was conducted in Hospital Canselor Tuanku Muhriz, National University of Malaysia from 10 March 2022 to 30 November 2023. It was approved by the local Ethics and Research Board and funded by the National University of Malaysia (FF-2022-127). The study population included epilepsy patients over 18 years old who were recruited through simple random sampling. The exclusion criteria were pregnancy, non-epileptic disorders, neurodegenerative disorders and seizures secondary to alcohol or drugs. These were considered as confounding factors that could contribute to poor dentition.

Clinical Assessment and Diagnosis of Epilepsy

The selected patients were based on the specific inclusion criteria. After obtaining informed consent, data were collected on their demographics (age, gender, education), comorbid history (including psychiatric disorders such as depression, bipolar disorder, schizophrenia) and comprehensive epilepsy history (age of onset, seizure classification [focal or generalised], seizure frequency [per month, per year], cause of epilepsy [structural, genetic, infection, immunological, unknown]) and current antiseizure medications (ASM).

Oral Health Assessment

A clinical dental examination was conducted in the dental clinic for the dental assessment. The patients were interviewed using the 'Oral Health and Dental Status Questionnaire'.[10] Questions addressed tooth brushing habits, number of visits to dental clinics, oral symptoms and diagnosis, number of caries, tooth extraction, history of dental injury, tooth loss and dental restoration or repair. The level of oral hygiene, including a plaque index and periodontal status, including gingivitis and pocket depth, were measured with a periodontal probe. To score the plaque and gingival index, individual tooth was given an index score. Once all the teeth had been scored individually, the mean number of the plaque and gingival index were calculated for each participant.

Plaque index

The plaque index was used to measure the level of oral hygiene.[11] The criteria were as follows: 0 = no plaque in the gingival area; 1 = a thin plaque film adhering to the free gingival margin and adjacent area of the tooth, only recognisable by running a probe across the surface; 2 = moderate accumulation of soft deposits within the gingival pocket, on the gingival margin, and/or on the adjacent tooth surface; and 3 = abundant soft matter within the gingival pocket and/or on the gingival margin and adjacent tooth surface. Subjects with a mean index score between 0.0-0.9 were considered to have excellent and good oral hygiene while mean index between 1.0-3.0 are considered fair or poor oral hygiene.

Gingival index

Periodontal status was determined using the gingival index and the criteria were as follows[11]: 0 = normal gingiva; 1 = mild inflammation: a slight change in colour, slight oedema and no bleeding on probing; 2 = moderate inflammation: redness, oedema and glazing, and bleeding on probing; and 3 = severe inflammation: marked redness and oedema, ulceration, and a tendency to spontaneous bleeding. Subjects with scores between 1.1 and 3.0 were considered to have gingivitis. Periodontal health was measured by registering the deepest pocket on the most posterior tooth in each quadrant, and a central incisor in each jaw, or the tooth closest to it if the index tooth was missing. Subjects with a measured pocket depth of 4 mm or more on one or more of the index teeth were considered to have periodontitis.

Decayed (D), missing (M) and filled teeth (FT) (DMFT)

The numbers of carious teeth were based on the detection of untreated decayed teeth. The World Health Organisation (WHO) caries diagnostic criterion for decayed (D), missing (M) and filled teeth (FT) (DMFT) was calculated.[12] The decayed, missing, filled teeth index is well established as the key measure for caries in dental services.

Statistical Analysis

All the data was analysed using SPSS software version 21.0. Continuous variables were expressed as median (interquartile range, IQR) and categorical variables as counts and frequencies (%). The Chi-square test was used for comparing categorical variables. The dependent variable was the plaque index and gingival index. The independent variables were demographic factors (age, gender, education, comorbidity), and clinical factors (age of onset of epilepsy, seizure types, frequency of seizures, type of ASM). The types of antiseizure medications that were included in the analysis were valproate, levetiracetam, lamotrigine, phenytoin, topiramate, perampanel, carbamazepine, clonazepam, clobazam, phenobarbitone and zonisamide. The distribution of continuous variables was compared using Student's t-tests; Pearson's Chi-square tests or Fisher's exact tests were used for the allocation of categorical variables. Multivariate logistic regression was performed to determine the risk factors. A p-value <0.05 defined statistical significance.

RESULTS

Demographic and Clinical Characteristics of Study Population

Table I shows the demographic and clinical characteristics of the study population. There were 151 patients, with 83 males (55%) and 68 females (45%). The median age was 37 (IQR 28-49) years. The distribution of race was predominantly Malay (76, 50.3%), Chinese (60, 39.7%), Indian (14, 9.3%) and others (1, 0.7%). The median age of onset of epilepsy was 16 (IQR 7 to 30) years, the proportion of patients with generalised seizures was 90 (59.6%) while 40.4% of patients had focal seizures. The median frequency of seizures per year

was 1 (IQR 0-12). The proportion of patients with ASM, mean dose and number of each ASM are depicted in Table I. The patients were divided into two groups with body mass index equal to or <22.9kg/m^2 (57, 37.7%) and ≥23kg/m^2 (94, 62.3%). The distribution of patients according to the plaque index: excellent or good oral health, 0.0-0.9 (92, 60.9%) and fair or poor oral health, 1.0-3.0 (59, 39.1%). The subdivision of plaque index was as follows: 0 (8, 5.3%), 0.1-0.9 (84, 55.6%), 1.0-1.9 (49, 32.5%) and 2.0-3.0 (10, 6.6%). The distribution of patients according to gingival index: normal, 0.0-1.0 (86, 57%) and gingivitis (65, 43%). The subdivision of gingival index was as follows: 0 (11, 7.3%), 0.1-1.0 (75, 49.7%), 1.1-2.0 (63, 41.7%) and 2.1-3.0 (2, 1.3%). The median DMFT was 3 (IQR 6).

Oral Health Assessment

Table 2 shows the oral health and dental status of the study population. 140 (92.7%) of the patients reported of brushing their teeth regularly with 76 (50.3%) brushing more than 3 minutes. However, around 55 (36.4%) visited the dentist more than once per year. The following dental symptoms were reported by the patients: toothache (25,16.6%), gum bleeding (43, 28,5%), swollen gums (18, 11.9%), bad breath (38, 25.2%) and others (2, 1.3%). The proportion of patients who had dental injuries due to seizures was 17 (11.3%). Around 10% of the patients had teeth repair after dental injury. The proportion of dental disorders include pulp and periapical disease (23, 15.2%), gingivitis (19, 12.6%), periodontitis (4, 2.6%), and others (2, 1.3%).

Table III shows the plaque index and gingival index of the study population. The median age of patients with fair or poor oral health was older (40 years, IQR 31-51) than the patients with excellent or good oral health (33 years, IQR 26-45), (p=0.014). However, age was not significantly associated with the gingival index (p=0.223). Gender and race have no significant association with the plaque and gingival indexes. The type and cause of epilepsy were not significantly associated with both plaque and gingival indexes. Among the different antiseizure medications, both carbamazepine and phenytoin were significantly associated with plaque index. The proportion of patients taking carbamazepine with poor oral health in plaque index was higher (26, 44.10%) vs good oral health (23, 25.00%), p=0.015. The proportion of patients on phenytoin with fair or poor oral health in plaque index was higher (14, 23.70%) vs good oral health (10, 10.90%). The proportion of patients on phenytoin with fair or poor oral health in the gingival index was higher (15, 23.10%) vs good oral health (9, 10.50%), p=0.036.

The risk factors for a high plaque index were presented in Table IV. Carbamazepine and hypertension were risk factors for fair or poor plaque index. Carbamazepine is 3.694 times more likely to develop a higher plaque index (adjusted Odds Ratios, aOR 3.694; 95% Confidence Intervals, CI: 1.314, 10.384). Hypertension is 6.484 times more likely to develop a higher plaque index (aOR 6.484; 95%CI: 1.011, 41.594). The risk factors for higher gingival index are shown in Table V. Phenytoin use was 4.271 times more likely to develop a higher gingival index (aOR 4.271; 95%CI: 1.252, 14.573).

DISCUSSION

Oral health plays a significant part in the quality of life of epilepsy patients. However, this aspect is often neglected in the management of these patients. This cross-sectional study highlighted that 39.1% of epilepsy patients had fair or poor oral health, and 43% had gingivitis. Oral health in people with epilepsy has been studied in rural China and the findings suggest that people with epilepsy have poor oral health and are vulnerable to dental injury.[10] An epidemiologic study from Hungary showed that all aspects of oral health and dental status of patients with epilepsy have a significantly worse state than that of the general population of the same group.[13] A prevalence study of oral health disorders in patients with epilepsy in Nigeria reported 69.6% with chronic periodontitis.[8] In a refractory epilepsy patient cohort in Brazil, this group showed significantly more susceptibility to develop poor oral hygiene (84.4%), gingivitis (56.9%) and periodontitis (47.4%) compared to controls.[14] Case reports have also highlighted that patients with concurrent epilepsy and intellectual impairment suffer from the consequences of poor oral hygiene and decayed teeth.[15]

This study has found that age is significantly associated with poorer oral health outcomes in epilepsy patients. Older epilepsy patients (median age 40, IQR 31-51) had poorer oral health compared to younger epilepsy patients (median age 33.5, IQR 26-45). There is currently limited information available on the relationship between age and oral health in epilepsy patients in the existing literature. Older individuals commonly experience dental caries, periodontal disease, oral cancer, and edentulousness. It has been estimated that 30% of adults aged 65-74 years are edentulous, which is attributed to periodontal disease.[16] The World Health Organisation reported that dental caries and periodontal disease were considerable health problems in older people in the majority of countries.[17] Poor oral health can lead to various negative effects such as reduced chewing performance, weight loss, impaired communication, and overall well-being. As individuals grow older, they experience physiologic changes that can lead to poor dental health. This includes a decrease in salivary gland function, a weakening of the protective barrier of the oral mucosa, alterations in teeth due to ageing, and a reduction in the blood supply to the sub-odontogenic region.[18]

The oral health of epilepsy patients is likely to be affected by several reasons. They are prone to be edentulous earlier[13] following jaw and dental injuries from generalised tonic-clonic seizures[19] and the effects of antiseizure medications.[21] Although this study did not show any significance between the median frequency of seizures and oral health, previous studies have established that refractory epilepsy patients are at higher risk of dental trauma, and seizure frequency is linked to higher rates of dental injuries. Patients with poorly controlled epilepsy and frequent generalised tonic-clonic seizures have worse oral health compared to those with better control.[13]

Antiseizure medications have also been implicated as part of the cause for aggravation of poor oral health. Carbamazepine acts on stabilisation of the inactivated state of voltage-gated sodium channels[21] and is indicated for focal

Table I: Demographics and characteristics of the study population.

N=151		Values	Percentage (%)
Median age (IQR) (years)		37 (28-49)	
Gender			
Female		68	45
Male		83	55
Race			
Malay		76	50.3
Chinese		60	39.7
Indian		14	9.3
Others		1	0.7
Education			
No formal education		20	13.2
Primary		11	7.3
Secondary		58	38.4
Tertiary		62	41.1
Epilepsy			
Median age of onset of epilepsy (IQR) (years)		16 (7-30)	
Type of epilepsy	Focal	61	40.4
	Generalised	90	59.6
Cause of epilepsy	Structural	106	70.2
	Genetic	32	21.2
	Infection	6	4
	Immunology	3	2
	Unknown	4	2.6
Median frequency of seizure (IQR) (per year)		1 (0-12)	
Anti-seizure drugs			
Median number of anti-seizure drugs (IQR)		1 (1-2)	
Carbamazepine	No	102	67.5
	Yes	49	32.5
Clonazepam	No	142	94
	Yes	9	6
Clobazam	No	146	96.7
	Yes	5	3.3
Diamox	No	149	98.7
	Yes	2	1.3
Levetiracetam	No	76	50.3
	Yes	75	49.7
Lamotrigine	No	128	84.8
	Yes	23	15.2
Perampanel	No	148	98
	Yes	3	2
Phenytoin	No	127	84.1
	Yes	24	15.9
Phenobarbitone	No	147	97.4
	Yes	4	2.6
Topiramate	No	135	89.4
	Yes	16	10.6
Sodium Valproate	No	91	60.3
	Yes	60	39.7
Zonisamide	No	148	98
	Yes	3	2
Comorbidity			
Diabetes	No	141	93.4
	Yes	10	6.6
Hypertension	No	134	88.7
	Yes	17	11.3
Ischemic heart disease	No	149	98.7
	Yes	2	1.3
Asthma	No	148	98
	Yes	3	2
Chronic kidney disease	No	150	99.3
	Yes	1	0.7
Previous stroke	No	143	94.7
	Yes	8	5.3
Brain tumour	No	146	96.7
	Yes	5	3.3
Psychiatric disease	No	142	94
	Yes	9	6

Table I: Demographics and characteristics of the study population.

N=151		Values	Percentage (%)
Median BMI (IQR) (kg/m2)		24.17 (21.30-27.38)	
Body mass index <23.0	Normal	57	37.7
Body mass index ≥23.0	Overweight and above	94	62.3
Plaque Index	0	8	5.3
0.1-0.9	84	55.6	
1.0-1.9	49	32.5	
2.0-3.0	10	6.6	
Gingival Index	0	11	7.3
0.1-1.0	75	49.7	
1.1-2.0	63	41.7	
2.1-3.0	2	1.3	
Plaque Index	Excellent/good oral health (0-0.9)	92	60.9
	Fair/poor oral health (1.0-3.0)	59	39.1
Gingival Index	Normal (0.0-1.0)	86	57
	Gingivitis (1.1-3.0)	65	43
Median DMFTs (IQR)		3 (1-7)	

IQR Interquartile range, BMI Body mass index; DMFT decayed (D), missing (M) and filled teeth (FT)

Table II: Oral health and dental status of the study population.

Questionnaire		N=151	%
1. Do you brush your teeth regularly			
	Yes	140	92.7
Median brush per day (IQR)		2 (1-2)	
Median brush duration (IQR)		3 (1-5)	
Brushing time cutoff 3 min	<3 min	75	49.7
	≥3 min	76	50.3
2. Median dental visit per year (IQR)		0 (0-1)	
	No dental visit	96	63.6
	More than 1 dental visit/year	55	36.4
3. Do you have the following symptoms?			
Toothache	Yes	25	16.6
Gum bleeding	Yes	43	28.5
Swollen gums	Yes	18	11.9
Bad breath	Yes	38	25.2
Others	Yes	2	1.3
4. Do you have any caries	No	76	50.3
	Yes	75	49.7
Median number of caries (IQR)		2 (1-3)	
5. Do you have any tooth extracted due to caries?	No	96	63.6
	Yes	55	36.4
Median number of extraction due to caries (IQR)		2 (1-3)	
6. Do you have any dental injuries due to seizures	No	134	88.7
	Yes	17	11.3
Median number of dental injuries due to seizures (IQR)		1 (1-2)	
Median number of fracture due to seizure injuries (IQR)		1 (1-2)	
7. Do you have any dental injuries due to other reasons?	No	143	94.7
	Yes	8	5.3
Median number of dental injuries due to other reasons (IQR)		1.5 (1-2)	
Median number of fracture due to other injuries (IQR)		1 (1-2)	
8. Apart from the change of teeh as a child, have you every had natural tooth loss?	Yes	30	19.9
Median number of natural loss (IQR)		2 (1-4)	
9. Have you had your tooth repaired after dental injury or tooth loss?	Yes	16	10.6
What type of tooth repair?	Dental Crown	1	0.7
	Dental prosthesis	7	4.6
	Others	8	5.3
	Total	16	10.6
10. Have you ever been diagnosed by your dentists for:			
Dental diagnosis: Pulpal and periapical disease	Yes	23	15.2
Dental diagnosis: Gingivitis	Yes	19	12.6
Dental diagnosis: Periodontitis	Yes	4	2.6
Dental diagnosis: Others	Yes	2	1.3

Table III: Plaque index and gingival index of study population.

Variable	Plaque Index Categorical		p-value	Gingival Index		p-value
	Excellent/good oral health	Fair/poor oral health		Normal	Gingivitis	
Median age (IQR) (years)	33.5 (26-45)	40 (31-51)	0.014[U]	35.5 (26.75-45.25)	38 (29.5-51.0)	0.223[U]
Gender	n=92	n=59		n=86	n=65	
Gender						
Male	45 (48.90%)	23(39.00%)	0.231[c]	43(50.00%)	25(38.50%)	0.158 [c]
Female	47(51.10%)	36 (61.00%)		43 (50.00%)	40 (61.50%)	
Race	n=92	n=59		n=86	n=65	
Race						
Malay	47 (51.10%)	29 (49.20%)	0.824[c]	41 (47.70%)	35 (53.80%)	0.284 [c]
Chinese	35 (38.00%)	25 (42.40%)		33 (38.40%)	27 (41.50%)	
Indian	9 (9.80%)	5 (8.50%)		11 (12.80%)	3 (4.60%)	
Others	1 (1.10%)	0 (0%)		1 (1.20%)	0 (0%)	
Education	n=92	n=59		n=86	n=65	
Education level						
None	9 (9.80%)	11 (18.60%)	0.006[c]	10 (11.60%)	10 (15.40%)	0.658 [c]
Primary	6 (6.50%)	5(8.50%)		6 (7.00%)	5 (7.70%)	
Secondary School	29 (31.50%)	29 (49.20%)		31 (36.00%)	27 (41.50%)	
Tertiary Education	48 (52.20%)	14 (23.70%)		39 (45.30%)	23 (35.40%)	
Epilepsy	n=92	n=59		n=86	n=65	
Type of Epilepsy						
Focal	37 (40.20%)	24 (40.70%)	0.955[c]	31 (36.00%)	30 (46.20%)	0.210 [c]
Generalised	55 (59.80%)	35(59.30%)		55 (64.00%)	35 (53.80%)	
Cause of Epilepsy						
Structural	65 (70.70%)	41(69.50%)	0.067[c]	63 (73.30%)	43 (66.20%)	0.218 [c]
Genetic	17 (18.50%)	15(25.40%)		15 (17.40%)	17 (26.20%)	
Infection	6 (6.50%)	0 (0.00%)		4 (4.70%)	2 (3.10%)	
Immunology	3 (3.30%)	0 (0.00%)		3(3.50%)	0 (0.00%)	
Unknown	1 (1.10%)	3 (5.10%)		1 (1.20%)	3 (4.60%)	
Anti seizure medications	n=92	n=59		n=86	n=65	
Carbamazepine						
No	69 (75.00%)	33 (55.90%)	0.015[c]	62(72.10%)	40 (61.50%)	0.170 [c]
Yes	23 (25.00%)	26 (44.10%)		24 (27.90%)	25 (38.50%)	
Clonazepam						
No	86 (93.50%)	56 (94.90%)	1.000*	79 (91.90%)	63 (96.90%)	0.301*
Yes	6 (6.50%)	3 (5.10%)		7 (8.10%)	2 (3.10%)	
Clobazam						
No	88 (95.70%)	58 (98.30%)	0.649*	83 (96.50%)	63 (96.90%)	1.000*
Yes	4 (4.30%)	1 (1.70%)		3 (3.50%)	2 (3.10%)	
Diamox						
No	91 (98.90%)	58 (98.30%)	1.000*	86 (100.00%)	63 (96.90%)	0.184*
Yes	1 (1.10%)	1 (1.70%)		0 (0.00%)	2 (3.10%)	
Levetiracetam						
No	41 (44.60%)	35 (59.30%)	0.077[c]	40 (46.50%)	36 (55.40%)	0.325[c]
Yes	51 (55.40%)	24 (40.70%)		46 (53.50%)	29 (44.60%)	
Lamotrigine						
No	76 (82.60%)	52 (88.10%)	0.356[c]	71 (82.60%)	57 (87.70%)	0.385[c]
Yes	1617.40%	711.90%		1517.40%	812.30%	
Perampanel						
No	90 (97.80%)	58 (98.30%)	1.000*	85 (98.80%)	63 (96.90%)	0.578*
Yes	2 (2.20%)	1 (1.70%)		1 (1.20%)	2 (3.10%)	
Phenytoin						
No	82 (89.10%	4576.30%	0.035 [c]	7789.50%	5076.90%	0.036[c]
Yes	10 (10.90%)	14 (23.70%)		9 (10.50%)	15 (23.10%)	
Phenobarbitone						
No	90 (97.80%)	57 (96.60%)	0.644*	84 (97.70%)	63 (96.90%)	1.000*
Yes	2 (2.20%)	2(3.40%)		2(2.30%)	2 (3.10%)	
Topiramate						
No	8592.40%	5084.70%	0.136[c]	76 (88.40%)	59 (90.80%)	0.636[c]
Yes	7 (7.60%)	9 (15.30%)		10 (11.60%)	6 (9.20%)	
Sodium valproate						
No	59 (64.10%)	32 (54.20%)	0.225[c]	54 (62.80%)	37 (56.90%)	0.466 [c]
Yes	33 (35.90%)	27 (45.80%)		32 (37.20%)	28 (43.10%)	
Zonisamide						
No	91 (98.90%)	57 (96.60%)	0.561*	85 (98.80%)	63 (96.90%)	0.578*
Yes	1 (1.10%)	2 (3.40%)		1 (1.20%)	2 (3.10%)	

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Table III: Plaque index and gingival index of study population.

Variable	Plaque Index Categorical		p-value	Gingival Index		p-value
	Excellent/good oral health	Fair/poor oral health		Normal	Gingivitis	
Diabetes						
No	86 (93.50%)	55 (93.20%)	1.000*	80 (93.00%)	61 (93.80%)	1.000*
Yes	6 (6.50%)	4 (6.80%)		6 (7.00%)	4 (6.20%)	
Hypertension						
No	84 (91.30%)	50 (84.70%)	0.213c	77 (89.50%)	57 (87.70%)	0.723 [c]
Yes	8 (8.70%)	9 (15.30%)		9 (10.50%)	8 (12.30%)	
Ischemic Heart Disease						
No	92 (100.00%)	57 (96.60%)	0.151*	85 (98.80%)	64 (98.50%)	1.000*
Yes	0 (0.00%)	2 (3.40%)		1(1.20%)	1 (1.50%)	
Asthma						
No	90 (97.80%)	58 (98.30%)	1.000*	85 (98.80%)	63 (96.90%)	0.578*
Yes	2 (2.20%)	1 (1.70%)		1 (1.20%)	2 (3.10%)	
Chronic Kidney Disease						
No	92 (100.00%)	58 (98.30%)	0.391*	85 (98.80%)	65 (100.00%)	1.000*
Yes	0 (0.00%)	1 (1.70%)		1 (1.20%)	0 (0.00%)	
Previous Stroke						
No	88 (95.70%)	55 (93.20%)	0.712*	81 (94.20%)	62 (95.40%)	1.000*
Yes	4 (4.30%)	4 (6.80%)		5 (5.80%)	3 (4.60%)	
Brain tumor						
No	88 (95.70%)	58 (98.30%)	0.649*	82 (95.30%)	64 (98.50%)	0.391*
Yes	4 (4.30%)	1 (1.70%)		4 (4.70%)	1 (1.50%)	
Psychiatric disorders						
No	85 (92.40%)	57 (96.60%)	0.483*	79 (91.90%)	63 (96.90%)	0.301*
Yes	7 (7.60%)	2 (3.40%)		7 (8.10%)	2 (3.10%)	
BMI (kg/m^2)						
N ≤ 22.9 kg/m^2	36 (39.10%)	21 (35.60%)	0.662c	31 (36.00%)	26 (40.00%)	0.620 [c]
Overweight and above ≥ 23 kg/m^2	56 (60.90%)	38 (64.40%)		55 (64.00%)	39 (60.00%)	
Median age of onset of epilepsy (IQR) (years)	18 (10 to 29)	12 (2 to 34)	0.075 [u]	18 (9 to 30)	13 (6 to 26)	0.173 [u]
Median frequency of seizure (IQR)	1 (0 to 12)	4 (0 to 24)	0.312 [u]	1 (0 to 12)	3 (0 to 24)	0.336 [u]
Median number of anti seizure medications (IQR)	1 (1 to 2)	1 (1 to 3)	0.373 [u]	1 (1 to 2)	1 (1 to 3)	0.903 [u]
Median BMI (IQR) (kg/m^2)	23.76 (21.24 to 27.35)	24.46 (21.35 to 27.70)	0.41 [u]	24.22 (21.55 to 27.48)	23.66 (20.79 to 26.82)	0.415 [u]
Median DMFTs (IQR)	3 (0 to 6)	4 (2 to 9)	0.018 [u]	3 (0.75 to 7)	3 (1.5 to 7)	0.417 [u]

IQR Interquartile range; BMI Body mass index; DMFT decayed (D), missing (M) and filled teeth (FT); Fishers exact test*; Pearson Chi square testc; Mann Whitney U test [u]

Table IV: Risk factors for plaque index.

	B	S.E.	Wald	df	Sig.	Odds Ratio	95% Confidence Intervals	
							Lower	Upper
Carbamazepine	1.307	0.527	6.14	1	0.013	3.694	1.314	10.384
Hypertension	1.869	0.948	3.886	1	0.049	6.484	1.011	41.594
Psychiatric disease	-1.824	1.018	3.209	1	0.073	0.161	0.022	1.187
Age	0.031	0.021	2.206	1	0.137	1.032	0.99	1.075
Phenytoin	0.889	0.624	2.032	1	0.154	2.434	0.716	8.268
Gender	0.614	0.472	1.693	1	0.193	1.848	0.733	4.659
Frequency of seizure	0.005	0.004	1.598	1	0.206	1.005	0.997	1.014
Cause of epilepsy	1.778	1.414	1.58	1	0.209	5.915	0.37	94.599
Age of epilepsy onset	-0.024	0.02	1.49	1	0.222	0.976	0.938	1.015

B: Coefficient β, SE: Standard error, CI: Confidence interval, Exp (B): Odds ratio

seizures and primary generalised tonic-clonic seizures.[22] However, there are reports of the effects of carbamazepine on alveolar bone loss[23] and gingival hyperplasia.[24] Our study reinforces the fact that carbamazepine is a risk factor for fair or poor oral health and has 3.69 times of developing a higher plaque index. Conversely, a study in children with epilepsy on antiseizure monotherapy found that carbamazepine has no effect on gingival hyperplasia.[25] However, the number of patients was small (n=30) with a short follow-up at 6 months in this study. Another study on children and adolescents treated with carbamazepine for an average of three years, reported no intra-oral side effects from the treatment.[26]

Among the antiseizure medications, phenytoin is a first-generation anti-convulsant drug that is effective in the treatment of generalized tonic-clonic seizures, focal seizures,

Table V: Risk factors for gingival index.

	B	S.E.	Wald	df	Sig.	Odds Ratio	95% Confidence Intervals	
							Lower	Upper
Phenytoin	1.452	0.626	5.375	1	0.020	4.2711	1.252	14.573
Gender	0.819	0.449	3.322	1	0.068	2.269	0.94	5.475
Race	-1.5	0.825	3.302	1	0.069	0.223	0.044	1.125
Psychiatric disease	-1.565	0.982	2.536	1	0.111	0.209	0.031	1.435
Cause of epilepsy	0.658	0.519	1.605	1	0.205	1.931	0.698	5.342
Hypertension	1.136	0.915	1.539	1	0.215	3.113	0.518	18.726
Body mass index	-0.534	0.459	1.353	1	0.245	0.586	0.238	1.442
Type of epilepsy	-0.486	0.452	1.157	1	0.282	0.615	0.254	1.491

B: Coefficient β, SE: Standard error, CI: Confidence interval, Exp (B): Odds ratio

and status epilepticus. It works by blockade of voltage-dependent membrane sodium channels.[27] The effect of phenytoin on gingival hyperplasia has been well-documented in the literature.[28,29] Likewise, this study emphasised phenytoin as a risk factor with a 4.27 higher odds of developing gingivitis. In comparison, most previous reports were limited by the small number of participants. In a systematic review of anticonvulsants such as carbamazepine, ethosuximide, phenytoin, primidone, phenobarbital, and sodium valproate on gingival hyperplasia, these studies showed a correlation between different types of anticonvulsants and gingival hyperplasia. Phenytoin demonstrated the highest incidence between 15.61% and 73%.[30] A previous study examined the periodontal health of adult patients with epilepsy who had been treated with phenytoin or carbamazepine for an average of 18 years and it was observed grade 1 gingival hyperplasia developed in 35% of patients taking phenytoin compared to only 10% of patients on carbamazepine.[23]

Gingival hyperplasia is characterised by an increased amount of non-collagenous extracellular matrix associated with gingival inflammation. Mechanisms of phenytoin-induced gingival overgrowth are derived from in vitro studies documenting that cells derived from phenytoin-induced gingival overgrowth produce a cell-free extracellular matrix with special properties that regulate cell functions such as cell attachment and spreading.[31] Phenytoin also potentiates interleukin (IL-lα and IL-lβ) induced prostaglandin E2 biosynthesis in human gingival fibroblasts.[32]

This study established that hypertension is a significant risk factor for the deterioration of oral health in epilepsy patients. These results were concordant with the data from a large observational cohort of French patients where hypertension was associated with a high level of dental plaque (OR: 1.90; 95%CI: 1.55, 2.33), dental calculus (OR: 1.18; 95%CI: 1.07, 1.29) and gingival inflammation (OR: 1.56; 95%CI: 1.35, 1.80).[33] An epidemiological study has shown an inverse association between the frequency of tooth brushing and hypertension.[34] Periodontitis has been linked to higher systolic blood pressure in a more recent study.[35] Plaque accumulation around teeth leads to gingivitis, and our findings indicated a significant association between plaque index and hypertension. The mechanism of periodontitis leading to hypertension stems from oxidative stress that might contribute to functional and anatomic vascular changes in the long term, leading to arterial stiffness, increased vascular resistance and volume overload.[36]

Limitations: It's important to note that this study was performed in a single centre, so the results may not accurately represent the entire epilepsy population in Malaysia. Additionally, the study did not account for other factors, such as income, occupation, or nutritional status, which may have played a role in the negative outcomes observed. To gain a better understanding of whether the exposure being studied is truly linked to adverse outcomes, a case-control study with a control group that is age and gender-matched would be helpful.

CONCLUSION

This study highlights the fact that patients with epilepsy are prone to poor oral health and gingivitis. Factors such as age, antiseizure medications like phenytoin and carbamazepine and hypertension contribute to these conditions in epilepsy patients. It is crucial to effectively manage epilepsy and its associated oral health problems to ensure good overall health. Customised management strategies should be implemented to improve oral health.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

Two-year retrospective review of lens-induced glaucoma in Hospital Taiping, Perak, Malaysia

Zulaikha Abd Rahman, MBBS[1,2], Fhun Lai Chan, MMed[1], Ng Sok Lin, MMed[1], Shahidatul-Adha Mohamad, MMed[2]

[1]Department of Ophthalmology, Hospital Taiping, Perak, Malaysia, [2]Department of Ophthalmology and Visual Science, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

ABSTRACT

Introduction: Delayed cataract surgery has long been known to cause lens-induced glaucoma (LIG). This study examined the demographic and clinical profile, ocular characteristics and outcomes of LIG in a tertiary referral centre in Malaysia.

Materials and Methods: Data from the National Eye Database (Malaysia) for cataract surgery performed at Hospital Taiping, Perak, between January 2019 and December 2020 were reviewed. The medical records of patients with LIG were retrieved to obtain demographic data, clinical profiles and visual outcomes.

Results: Of 3233 patients who underwent cataract surgery at Hospital Taiping, Perak, between 2019 and 2020, 25 underwent emergency surgery for LIG. However, only 24 patients fulfilling the diagnostic criteria for LIG were included in the study: 14 (58.33%) patients with phacomorphic and 10 (41.6%) patients with phacolytic glaucoma. The mean age of the patients was 66±12 years. Women and men were equally affected. Most patients were Malay (75%), followed by Chinese (16.67%) and Indian (8.33%). The anterior chamber depth (ACD) was significantly shallow with a mean value of 2.72 mm. Nineteen (79.1%) patients presented with visual acuity of worse than counting fingers. The mean intraocular pressure (IOP) at presentation was 47.5±13.66mmHg, which improved to 15.08±8.09mmHg postoperatively. A best-corrected visual acuity of 6/15 and better was achieved in 20 patients (83.33%) despite glaucomatous optic neuropathy being present in 41.67% of the cases. The majority (58.3%) of surgeries were performed via extracapsular cataract extraction, while six (25%) of our patients underwent successful phacoemulsification. Seven (29.17%) patients had intraocular complications: five with zonular dialysis and two with posterior capsule rupture. Of these seven cases, four ended up with intracapsular cataract extraction, leaving two of them aphakic.

Conclusion: Prompt cataract surgery is paramount in all LIG cases to reduce IOP and achieve better visual outcomes. Despite the promising prognosis associated with early surgical intervention, patients should be counselled about the potential for a guarded visual prognosis from complicated surgery and its long-term complications.

KEYWORDS:
Lens-induced glaucoma, phacomorphic glaucoma, phacolytic glaucoma, glaucomatous optic neuropathy

INTRODUCTION

Cataract is a leading cause of blindness worldwide. Despite significant visual impairment caused by delayed cataract surgery, cataract surgeries are nonacute and elective.[1,2] Cataracts have the potential to advance into mature, intumescent or hypermature stages, resulting in lens-induced glaucoma (LIG).[1] LIG is a secondary type of glaucoma that requires immediate attention and management to prevent blindness.[3,4] A sudden significant intraocular pressure (IOP) elevation in LIG eventually mechanically damages the optic nerve, leading to blindness if treatment is delayed or left untreated.[5]

The primary mechanism responsible for elevated IOP in LIG can be distinct. In phacomorphic glaucoma, aqueous humour obstruction occurs through secondary angle closure and pupillary block.[6] This is caused by the swelling of the cataractous lens, which pushes the iris forward, resulting in the blockage of the trabecular meshwork.[7] Meanwhile, the high IOP in phacolytic glaucoma is contributed by protein leakage through the intact capsule of a hypermature cataract with resultant intense anterior chamber (AC) inflammation.[7] The diagnosis of LIG is typically established by observing classical symptoms such as eye pain, redness, headache and reduced vision, coupled with an IOP exceeding 21 mmHg.[2-5] Additionally, characteristic signs include evidence of a unilateral shallow AC depth (ACD), a fixed dilated or sluggish pupil and the presence of an intumescent cataract in cases of phacomorphic glaucoma.[2,3] In phacolytic glaucoma, diagnosis is indicated by the presence of a hypermature morgagnian cataract with an intact capsule, along with a normal or deep anterior chamber containing floating lens particles and flare.[7,8]

This retrospective study emphasised the importance of early diagnosis and treatment and examined its outcomes.

MATERIALS AND METHODS

This retrospective study included patients who underwent cataract surgery at Hospital Taiping, Perak, Malaysia, between January 2019 and December 2020. Data for cataract surgeries were retrieved from the National Eye Database (Malaysia). All patients with LIG who underwent emergency cataract surgery at our hospital were included. Patients with primary or secondary glaucoma due to other causes than LIG or traumatic cataract or those with poor general condition that made them unfit for surgery were excluded from this

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Corresponding Author: Shahidatul-Adha Mohamad
Email: shieda@usm.my

Table I: Demographic data of patients with lens-induced glaucoma.

Variable	Frequency (n)	Percentage (%)
Age (years)		
Mean±SD	66±12	
Range	43-91	
Age group		
40–49	1	4.16
50–59	6	25
60–69	7	29.17
>70	10	41.67
Gender		
Male	13	54.1
Female	11	45.83
Race		
Malay	18	75
Chinese	4	16.67
Indian	2	8.33

Table II: Clinical profile of lens-induced glaucoma.

Clinical profile	Frequency (n)	Percentage (%)
Type of LIG		
Phacolytic	10	41.7
Phacomorphic	14	58.3
Symptom duration		
<1 week	15	62.5
1–2 weeks	3	12.5
3–4 weeks	4	16.6
>4 weeks	2	8.33
Waiting time for operation		
<1 week	13	54.1
1–2 weeks	10	41.7
>2 weeks	1	4.2
Type of surgery		
Phacoemulsification	6	25.0
ECCE	14	58.3
ICCE	4	16.7
BCVA (At presentation)		
6/60	4	16.7
Counting finger	1	4.2
Hand movement	11	45.8
Perception of light	8	33.4
BCVA (postoperative)		
6/6–6/15	20	83.3
6/18–6/60	1	4.2
<6/60	3	12.5
IOP		
At presentation (mmHg)		
Mean±SD	47.5±13.66	
<40	7	29.2
>40	17	70.8
Postoperative (mmHg)		
Mean, years, ± SD	15.08±8.09	
<21	21	87.5
>21	3	12.5

Abbreviations: LIG: Lens-induced glaucoma; ECCE: Extracapsular cataract extraction; ICCE: Intracapsular cataract extraction; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure

study. We also excluded patients with subluxated and dislocated lenses due to incomplete data.

Data were recorded in terms of age, gender, race, comorbidities, visual acuity (VA), ACD, corneal condition, IOP recording using Goldmann applanation tonometry, A-scan result and postoperative refraction. The duration between symptoms and surgery was also recorded. Initial IOP was controlled using oral acetazolamide and topical antiglaucoma agents. Then, patients were scheduled for cataract extraction as soon as possible under emergency list. Postoperatively, IOP was measured on day-1, day-5 and week-6. Refraction was performed 4 to 6 weeks postoperatively to obtain the best-corrected VA (BCVA). Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 27. Descriptive statistics were used to summarise the patients' demographic and clinical profiles. The Chi-square test was used to

Table III: Ocular characteristic of lens-induced glaucoma.

Clinical profile	Frequency (n)	Percentage (%)
Axial Length (mm)		
Mean	23.31	
<22	3	12.5
22 -24	17	70.8
>24	4	16.7
Anterior chamber depth (mm)		
Mean	2.72	
<2.8	15	62.4
2.8-3.5	3	12.6
>3.5	6	25.0
Type of cataract		
Intumescent	14	58.3
Morgagnian	6	25.0
White	4	16.7
Optic disc		
Normal	14	58.3
Glaucomatous optic neuropathy	10	41.7

Table IV: Comparison between phacolytic and phacomorphic glaucoma.

Variables	Phacomorphic (n=14)	Phacolytic (n=10)	p-value*
Axial length (mm)			
<22	3	0	0.137
22-24	10	7	
>24	1	3	
ACD (mm)			
<2.8	15	2	<0.001
2.8 – 3.5	1	2	
>3.5	0	6	
Operative complication			
Nil	11	6	0.147
Zonular dialysis	3	2	
PCR	-	2	
Type of surgery			
Phacoemulsification	5	1	0.357
ECCE	7	7	
ICCE	2	2	
Type of lens			
PCIOL	12	4	0.045
ACIOL	1	5	
Aphakic	1	1	

Abbreviations: ACD: Anterior chamber depth; PCR: Posterior capsular rupture; ECCE: Extracapsular cataract extraction; ICCE: Intracapsular cataract extraction; PCIOL: Posterior chamber intraocular lens; ACIOL: Anterior chamber intraocular lens
*Chi-square test, p<0.05 is significant

determine associations between categorical variables, with p<0.05 is considered significant.

RESULTS

A total of 3233 cataract surgeries were performed in Hospital Taiping over 2 years (1981 and 1252 cases in 2019 and 2020, respectively). Twenty-five patients underwent emergency cataract surgery for LIG; however, only 24 patients who fulfilled the diagnostic criteria for LIG were included in the study. Among them, 10 were operated in 2019 and 14 in 2020. A double increase was observed from 0.5% of total cataract surgery performed in 2019 to 1.2% in 2020. The mean age was 66 ± 12 years (range 43-91 years). Women and men were equally affected, with a ratio of 1:1.18. The demographic characteristics of patients with LIG are summarised in Table I.

We observed a slightly higher number of cases of phacomorphic glaucoma (58.33%) than those of phacolytic glaucoma. During the presentation, all patients had VA worse than 6/60. Of the 24 patients, 15 (62.56%) presented with symptoms of <1 week duration. Cataract surgery was performed between 3 days to 3 weeks from presentation, as the cornea became clearer. The mean IOP at presentation was 47.5 ± 13.66 mmHg, which improved to 15.08±8.09mmHg postoperatively. Twenty (83.3%) patients achieved good visual outcome, BCVA of 6/15 or better. The clinical profile of LIG is presented in Table II.

We further analyse the ocular characteristic of our LIG patients (Table III). The mean axial length was 23.31 mm while the ACD was 2.72 mm. Majority (58.3%) of the patients had intumescent cataract. Glaucomatous optic disc changes were observed in almost half (41.67%) of the cases.

A few clinically important ocular characteristics and surgical profiles between our phacomorphic and phacolytic patients were presented in Table IV. The majority (58.3%) of surgeries were performed via extracapsular cataract extraction (ECCE), while six (25%) of our patients underwent successful phacoemulsification. Among complications observed were zonular dialysis and posterior capsule rupture, with four cases ended up with intracapsular cataract extraction (ICCE), leaving them aphakic. The categorical data were further analysed using Chi-square test. The result showed that two clinically significant findings were the ACD ($p<0.001$) and the type of intraocular lens used during the surgery ($p=0.045$).

DISCUSSION

Lens-induced glaucoma (LIG) is an important cause of secondary glaucoma in the ageing population of developing countries, with phacomorphic glaucoma being the most common etiology.[1,9] The high incidence of LIG among elderly individuals indicates that LIG is a disease of old age.[10] In our study, the highest number of LIG cases occurred in patients aged 70 years and older, in align with previous study.[9] Patients in the older age group generally have difficulty attending hospital and are unaware of potentially blinding complications in painful eyes.[10]

We observed an increase in emergency cataract surgeries due to LIG in 2020 compared with the corresponding time in 2019. This could be related to the COVID-19 pandemic in 2020, in which all elective cataract surgeries were postponed, leading to an increased incidence of LIG.[11-13] A recent study found that the number of cases of LIG increased by almost double during the pandemic (from 7.7% in 2019 to 13.2% in 2020).[11] Patients were not allowed to go out during the pandemic period because of the movement control order unless they had medical symptoms that required them to go to the hospital for treatment. Therefore, they seek treatment only when eye pain becomes significant.[11]

In our study, phacomorphic glaucoma was more common than phacolytic glaucoma, consistent with previous studies.[5,9] Intumescent cataracts were observed in patients with phacomorphic glaucoma, whereas both morgagnian and white cataracts were observed in patients with phacolytic glaucoma.[5,9] We also determined that 50% of phacolytic glaucoma cases in our study occurred in patients aged 70 years or older. Phacolytic glaucoma likely occurs because of the aggregation of high-molecular-weight lens proteins clogging the trabecular meshwork over time, often associated with advancing age.[5]

Symptoms suggestive of phacomorphic glaucoma typically occur at night because of mid-dilation of the pupil during this scotopic condition, which predisposes the patient to relative pupillary block.[4] In contrast, hypermature cataracts in patients with phacolytic glaucoma leak lens protein from the intact capsule at no specific time of day.[14] Irrespective of the type, both phacomorphic and phacolytic glaucoma eventually result in inflammation that leads to increased IOP.[14] An acute significant increase in IOP compromises optic nerve function and may lead to irreversible loss of vision if not treated on time.[15]

The presenting VA was poor in all patients in this study, 6/60 and worse due to significant lens opacity and corneal oedema. This corresponds to a previous study conducted in northeastern Malaysia.[16] A direct correlation existed between the duration of symptoms and the postoperative BCVA, indicating that prolonged symptom duration was associated with poorer visual outcomes.[9] A significant risk of poor visual outcome was established when the duration between the onset of pain and surgery exceeded 5 days.[5] Nevertheless, most of our patients had good postoperative BCVA despite late presentation of more than 3 weeks. These findings show that a good visual outcome can be achieved in LIG if glaucomatous optic neuropathy has not yet developed.

As opposed to age- and sex-matched control subjects, patients with phacomorphic glaucoma typically exhibited shallower ACD and had statistically shorter axial length (AL).[17,18] However, our in-depth analysis revealed that, among phacomorphic and phacolytic patients, only ACD was significantly different, not AL. Additionally, we found that while the type of surgery and intraoperative complications did not differ statistically between phacomorphic and phacolytic patients, there was a significant difference between the two groups in terms of the implanted intraocular lens.

The definitive and effective treatment for IOP lowering in patients with LIG is prompt cataract extraction. This is consistent with our observation that 70.8% of patients had an IOP of greater than 40 prior surgery and following operation, 87.5% patients were able to achieve a normal IOP of less than 21 mmHg without a need for antiglaucoma medication. This finding aligns with a previous study, where 89.5% of their patients recorded a postoperative IOP of less than 20 mmHg.[19] However, three cases (12.5%) in our study were found to have persistent IOP of more than 21 mmHg postoperatively, requiring at least one topical antiglaucoma. The causes for the refractory glaucoma in them were due to central retinal vein occlusion with subsequent neovascular glaucoma in one patient, another had prolonged postoperative inflammation, and the third patient had extensive peripheral anterior synechia formation. Unfortunately, we lacked data on their long-term outcomes. This limitation arose because our data collection was confined to the online database and included follow-up only up to six-weeks post-operation. Future study centred around LIG should incorporate extended follow-up periods to assess cases with postoperative refractory glaucoma.

The choice of surgery for treating LIG depends on several factors including the severity and subtype of LIG, lens density, surgeon's expertise, and the patient's overall health.[20] Majority of our patients underwent extracapsular cataract extraction (ECCE) and achieved significant VA

improvement to 6/15 or better. ECCE are often preferred at tertiary centres for managing LIG as these techniques mitigate the risk of thermal injury to the corneal endothelium, minimise zonular stress, and facilitate lens delivery.[21,22] These techniques also offer an effective solution for handling the dense nucleus of intumescent cataracts in phacomorphic cases.[22] Conversely, phacoemulsification, a modern and safe technique, has shown efficacy in IOP reduction and achieving favourable visual outcome with minimal complications in the management of LIG when performed by experienced surgeons.[23]

CONCLUSIONS

LIG poses a significant risk of vision loss. Prompt cataract extraction serves as the definitive treatment as it effectively lowers intraocular pressure (IOP) and leads to favourable visual outcomes. Despite the promising prognosis associated with early surgical intervention, patients should be counselled about the potential for a guarded visual prognosis, which may arise from complicated surgery and long-term complications following LIG and the surgery.

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Association between serum uric acid levels with essential hypertension and its metabolic variables in Hospital Universiti Sains Malaysia

Zulkarnain Mustapha, MSc[1,3], Wan Mohd Saifuhisam Wan Zain, MPath[1,3], Najib Majdi Yaacob, DrPH[2,3], Aniza Mohammed Jelani, MPath[1,3]

[1]Department of Chemical Pathology, School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kelantan, Malaysia, [2]Unit of Biostatistics and Research Methodology, School of Medical Sciences, Universiti Sains, Malaysia Malaysia Health Campus, Kelantan, Malaysia, [3]Hospital Universiti Sains Malaysia, Kelantan, Malaysia

ABSTRACT

Introduction: Hyperuricaemia is common in essential hypertension with varying results in different populations. This study sought to ascertain the association between serum uric acid levels and essential hypertension in Hospital Universiti Sains Malaysia (HUSM).

Materials and Methods: A case-control study design involving 132 subjects (88 subjects of hypertension patients for case group and 44 subjects for control group) aged 18 to 40 years old of both genders was conducted at HUSM primary care clinic and physician clinic from May 2020 to May 2021. Blood samples were collected from each of the case and control subjects and analysed for serum uric acid, urea, creatinine, total cholesterol, triglycerides, LDL and HDL on chemical analyser Architect c8000. The data were analysed by using SPSS Statistics 26.0 version.

Results: The proportion of subjects with hyperuricaemia in the case group was 48.9%. A significant difference in the uric acid levels between the case group (390.64±92.65µmol/L) and control group (352.09±86.07µmol/L), (p<0.05) was observed. There was no significant difference in the serum uric acid mean ± SD based on the duration of hypertension (<5 years and ≥5 years), (p=0.331) and stages of hypertension (p>0.05). In case group, significant correlations were established between uric acid and triglycerides (r=0.255, p<0.05), uric acid and HDL (r= -0.223, p<0.05), uric acid and urea (r=0.299, p<0.05), uric acid and creatinine (r=0.486, p<0.01). No correlation among uric acid and total cholesterol levels (p>0.05), uric acid and LDL (p>0.05). Serum uric acid was a vital variable in developing hypertension (p<0.05) but not when adapted for age and body mass index (BMI) (p>0.05).

Conclusion: Serum uric acid was significantly elevated in essential hypertension. The significant associations were established between uric acid and triglycerides, HDL, urea and creatinine in essential hypertension. Serum uric acid was a vital variable to develop hypertension, but the association was weakened by other co-founders as age and BMI. A large-scale population-based study is required to truly conclude the association between serum uric acid levels and essential hypertension in our population.

KEYWORDS:
Uric acid, hypertension, case-control, chemical pathology

INTRODUCTION

Hyperuricaemia is common in individuals diagnosed with essential hypertension.[1-3] It is defined as the concentration of serum uric acid above uric acid solubility which is approximately 420 µmol/l in men and 360 µmol/l in women.4 Approximately 25% of hypertensive individuals experience hyperuricaemia and the percentage escalates to 75% of those individuals with malignant or severe hypertension.[5-7]

A 1 mg/dl (59.48 µmol/L) elevation in serum uric acid concentration is related to a notable rise in the risk of developing new onset hypertension[8] and a 48% increase in the risk for coronary artery disease.[9] Hyperuricemia observed in individuals with hypertension signifies an initial involvement of the renal vasculature, which is linked to hypertension.[6] Serum uric acid shows a direct association with the duration and severity of hypertension.[5,10] Elevated serum urea, creatinine, total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were significantly noted in hypertensive patients with hyperuricaemia.[9]

Mechanisms involved in the occurrence of hypertension in hyperuricaemia are; 1) Uric acid influences the activation of renin-angiotensin system causing vasoconstriction;[11] 2) Uric acid causes vascular smooth muscle proliferation and endothelial cells dysfunction.[12]

Besides hypertension and gout, other diseases associated with hyperuricaemia are metabolic syndrome, kidney diseases, stroke and coronary heart disease.[13] The mechanisms involved are the combination of inflammation, endothelial cells dysfunction, oxidative stress and others.[13] Serum uric acid may affect antihypertensive treatment in the management of hypertension.[8] In hypertensive individuals with hyperuricaemia, uric acid lowering therapy may decrease blood pressure levels.[14]

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Corresponding Author: Wan Mohd Saifuhisam Bin Wan Zain
Email: wansaifu1985@usm.my

The specific objectives of this study were as followed; 1) To ascertain the proportion of hyperuricaemia among essential hypertension patients in a case-control study design in Hospital Universiti Sains Malaysia (HUSM); 2) To investigate the association between serum uric acid levels and stage as well as duration of hypertension; 3) To investigate the relationship between serum uric acid levels with routine laboratory tests specifically serum urea, creatinine, total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL); 4) To analyse the risk of essential hypertension occurrence based on serum uric acid.

To the best of our knowledge, there has been no similar study conducted in Malaysia before. Studies on other populations and countries have revealed varying results1 possible due to other confounding factors for examples dietary and lifestyle. Thus, the aim of our study is to ascertain the association between serum uric acid levels and essential hypertension in local study population.

Our hypothesis was there was an association between serum uric acid levels and essential hypertension in our study population.

MATERIALS AND METHODS

Study Design and Participants

A matched case-control design based on age was used in this study. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Setting

This study was conducted on essential hypertension patients at primary care and physician clinics at HUSM, Kubang Kerian Kelantan Malaysia from May 2020 to May 2021 for case group. Volunteers (non-hypertensive subjects) were recruited for control group during similar period of time.

Study Participants

For case group, essential hypertension patients of male and female aged between 18 and 40 years old were randomly chosen from the list of hypertension patients attending the clinics and who had fulfilled the inclusion and exclusion criteria. The age 18 to 40 years was chosen as previous study had shown the link between serum uric acid and blood pressure in this age group.[1] The inclusion criterion is individual diagnosed with essential hypertension. The exclusion criteria are secondary hypertension including renal parenchymal disease, endocrine disorders, renovascular disease, coarctation of the aorta, iatrogenic treatment with steroids and other causes of secondary hypertension. Other exclusion criteria are diabetes, pregnancy, ischaemic heart disease, congestive cardiac failure, gout, obesity, history of alcohol intake, renal insufficiency, glomerulonephritis, pyelonephritis, hereditary nephropathy, patients on drugs including levodopa, ethambutol, pyrazinamide, nicotinic acid, cytotoxic drug, low dose aspirin, thiazide diuretics, allopurinol and other drugs that can affect serum uric acid level.

The volunteers for control group were recruited randomly from the list of individuals attending clinics for regular medical check-up. The inclusion criterion is individual without medical illness aged between 18 and 40 years of male and female to match with hypertensive group. The exclusion criteria are primary and secondary hypertension in addition to other exclusion criteria similar to the hypertensive group.

The sample size was determined by G-power software version 3.1.6 with 5% of type I error, 80% of type II error, 2:1 ratio between case and control group and 10% of anticipated incomplete data (n=88 for case group, n=44 for control group).

Observational Data

The demographic data of case and control groups consisted of age, gender, gender, ethnicity, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate and smoking status.

Sample Collection and Laboratory Analysis

Fasting venous blood samples (5 ml) were taken from each subject of case and control groups. The serum was taken after centrifugation and was analysed for uric acid, urea, creatinine, total cholesterol, triglycerides, LDL and HDL on chemical analyser Architect c8000.

Data Analysis

The data were analysed by using SPSS Statistics 26.0 version. Numerical data were presented as the mean and standard deviation (SD) and categorical data were presented as frequencies (n) and percentage (%). The normality testing was performed prior to performing statistical analysis to confirm that the data exhibit Gaussian distribution. Independent t-test was used for comparing the mean of serum uric acid levels between case and control groups. An independent t-test was used to compare the mean of serum uric acid levels between case and control groups as well as the mean of serum uric acid levels between the duration of hypertension (< 5 years and ≥ 5 years). The 5 years cut-off was selected based on the previous study.16. One way analysis of variance (ANOVA) test was used for comparing mean of serum uric acid levels between stages of hypertension (Stage 1 for mild (SBP 140-159mmHg and/or DBP 90-99mmHg), Stage 2 for moderate (SBP 160-179mmHg and/or 100-109mmHg), Stage 3 for severe (SBP≥180mmHg and/or DBP≥110mmHg) based on Clinical Practice Guidelines Management of Hypertension 5th edition by Malaysia Ministry of Health. Pearson correlation was used for analysing the correlation between serum uric acid levels with serum creatinine, serum total cholesterol and serum HDL as the data were parametric. Spearman correlation was used for analysing the correlation between serum uric acid level with serum urea, serum triglycerides and serum LDL as the data were nonparametric. Baseline routine laboratory tests of both case and control groups were analysed initially. Data showed normal serum urea, creatinine, triglycerides, no major risk factor for heart disease based on HDL level and just mildly elevated for total cholesterol and LDL. Simple and multiple logistic regression analysis were used to analyse the risk of essential hypertension occurrence based on serum uric acid.

Table I: Baseline characteristics of the study subjects.

Variable	Group N = 132		p-value
	Case (n = 88)	Control (n = 44)	
Age (years)[a]	36.22 (4.13)	34.07 (3.69)	0.004
Gender[b]			
Male	52 (59.1)	26 (59.1)	1.000
Female	36 (40.9)	18 (40.9)	
Ethnic[b]			
Malay	79 (89.8)	43 (97.7)	0.271
Non-Malay	9 (10.2)	1 (2.3)	
BMI (kg/m^2)[a]	25.28 (2.10)	23.54 (2.24)	<0.001
Systolic blood pressure (mmHg)[a]	152.11 (12.05)	114.82 (11.04)	<0.001
Diastolic blood pressure (mmHg)[a]	95.72 (10.17)	73.84 (8.71)	<0.001
Heart rate (beats/min)[a]	81.25 (10.71)	73.73 (8.33)	<0.001
Stage of hypertension[b]			
Stage 1	34 (38.6)		
Stage 2	46 (52.3)	-	-
Stage 3	8 (9.1)		
Duration of hypertension[b]			
< 5 years	54 (61.4)	-	-
≥ 5 years	34 (38.6)		
Smoking[b]			
Yes	15 (17)	1 (2.3)	0.014
No	73 (83)	43 (97.7)	
Hyperuricaemia[b]	43 (48.9)	11 (25)	0.07

[a]Mean (SD) [b]no (%)

Table II: Comparison of mean serum uric acid levels between case and control groups.

Variable	Mean (SD)		Mean difference (95% CI)	t statistic	p	Reference Interval (µmol/L)
	Case group (df)	Control group value*				
Serum uric acid (µmol/L)	390.64 (92.65)	352.09 (86.07)	38.55 (5.48, 71.61)	2.306 (130)	0.023	Male: 210-420 Female:150-350

*Independent t test

Table III: Comparison of mean serum uric acid levels between stages and duration of essential hypertension.

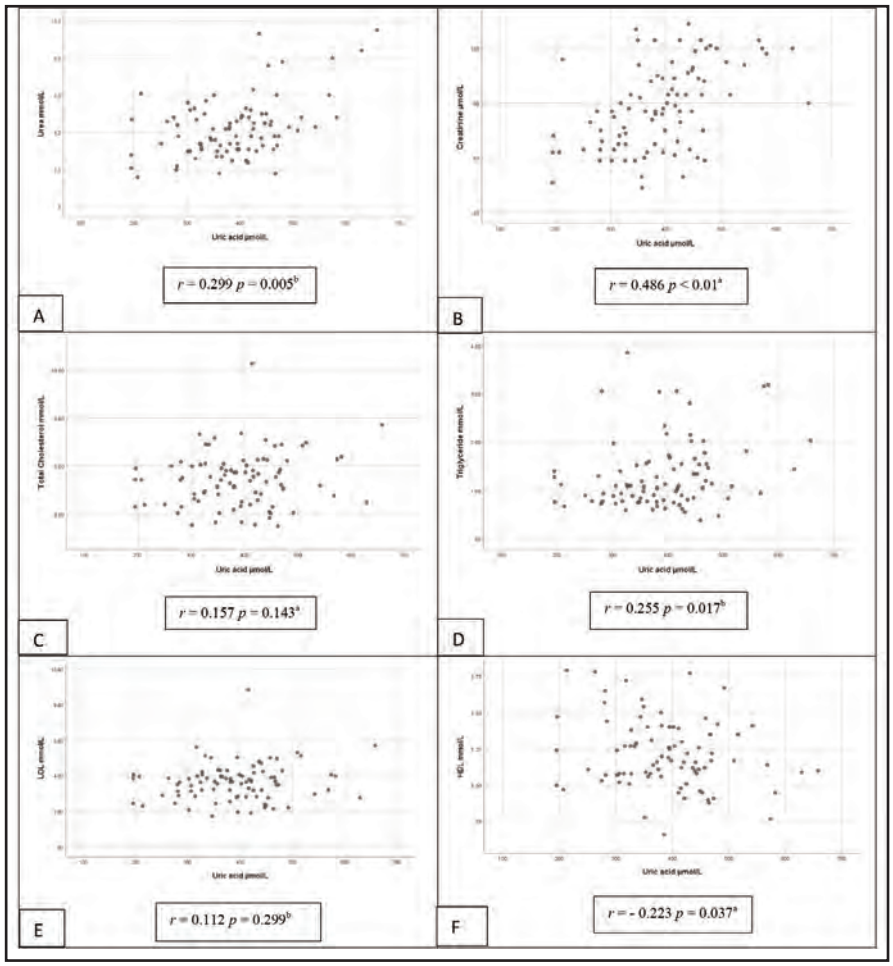
Variable (s)	Serum uric acid (µmol/L) Mean (SD)	F statistic (df)/ t statistic (df)	p-value
Stages of essential hypertension			
Stage 1 (mild)	378.20 (80.31)	2.042 (2, 85)	0.136[a]
Stage 2 (moderate)	389.37 (99.10)		
Stage 3 (severe)	450.75 (90.77)		
Duration essential hypertension			
<5 years	398.30 (86.17)	0.977 (86)	0.331[b]
≥5 years	378.47 (102.24)		

[a] One-way ANOVA
[b] Independent sample t test

Table IV: Crude and adjusted logistic regression of hypertension variables between case and control.

Variable (s)	Crude odd ratio (95% CI)	p-value	Adjusted OR (95% CI)*	p-value
Serum uric acid	1.005 (1.001, 1.009)	0.025	1.004 (0.999, 1.009)	0.082
BMI	1.408 (1.183, 1.676)	< 0.001	1.400 (1.162, 1.688)	<0.001
Age	1.137 (1.038, 1.246)	0.006	1.138 (1.031, 1.257)	0.010
Gender	1.000 (0.479, 2.088)	1.000		

*Constant= -13.717
*Backward LR method was applied
*No interaction
*Hosmer Lemeshow test, p-value= 0.236
*Classification table 72.0% correctly classified
*Area under Receiver Operating Characteristics (ROC) curve was 77.1%



[a]Pearson correlation [b]Spearman correlation

Fig. 1: Correlation between serum uric acid levels and (A) serum urea, (B) serum creatinine, (C) serum total cholesterol, (D) serum triglycerides, (E) serum LDL, (F) serum HDL in essential hypertension.

Ethical Considerations

This study was given approval by the Human Research Ethics Committee USM (HREC).
Reference code: USM/JEPeM/19120845

RESULTS

A comparison of the following variables, age, gender, ethnicity, BMI, systolic blood pressure, diastolic blood pressure, heart rate, smoking status and no of hyperuricaemic subject between the case and control groups is presented in Table I. A total 132 subjects were involved in this study in which 88 were hypertensive subjects for case group and 44 subjects for control group. There were significant differences in the mean±SD between the case and control groups in terms of age, BMI, blood pressure and heart rate. The mean (SD) for age for case and control groups were 36.22 (4.13) years old and 34.07 (3.69) years old, respectively ($p<0.05$). The mean (standard deviation) for BMI for case and control groups were 25.28 (2.10) kg/m^2 and 23.54 (2.24) kg/m^2, respectively ($p<0.001$). The mean (SD) for systolic blood pressure for case and control groups were 152.11 (12.05) mmHg and 114.82 (11.04) mmHg, respectively ($p < 0.001$). The mean (SD) for diastolic blood pressure for case and control groups were 95.72 (10.17) mmHg and 73.84 (8.71) mmHg, respectively ($p<0.001$). The mean (SD) for heart rate for case and control groups were 81.25 (10.71) beats/min and 73.73 (8.33) beats/min, respectively ($p < 0.001$). There was no significant difference between the case and control group in terms of ethnicity and gender. A significant difference between the percentage of smoker and non-smoker in case group and control group was seen. Most of the participants were non-smokers (n=116, 87.9% which [n = 73] in case group and [n = 43] in control group, $p<0.05$).

The proportion of hyperuricaemia for case and control groups were 48.9% and 25%, respectively with no significant difference ($p>0.05$).

A comparison of mean of serum uric acid levels among case group and control group are shown in Table II. There were significant differences in the mean±SD between the case and control groups for serum uric acid. Mean (SD) for serum uric acid in case and control groups were 390.64 (92.65) µmol/L and 352.09 (86.07) µmol/L, respectively ($p=0.023$). A comparison of mean of serum uric acid levels corresponding to stages and duration of essential hypertension are shown in Table III. No significant difference between the mean (SD) for serum uric acid levels and stages 1, 2 and 3 of hypertension 378.20 (80.31) µmol/L, 389.37 (99.10) µmol/L and 450.75

(90.77) µmol/L, respectively (p=0.136). No significant difference between the mean (SD) for duration of hypertension of <5 years and ≥5 years 398.30 (86.17) µmol/L and 378.47 (102.24) µmol/L, respectively (p = 0.331). A correlation between serum uric acid levels and routine laboratory tests in case group are shown in Figure 1. Among the lipid profile, significant positive correlation was found between serum uric acid levels and triglycerides levels (r=0.255, p=0.017), while an inversed correlation was observed between serum uric acid levels and HDL levels (r= -0.223, p=0.037). No significant correlation between serum uric acid levels and total cholesterol levels and LDL in essential hypertension (r=0.157, p=0.143) and (r=0.112, p=0.299) respectively. A significant correlation between serum uric acid levels and serum urea levels (r=0.299, p=0.005) and serum creatinine (r=0.486, p<0.01) was observed in essential hypertension.

To analyse the importance of serum uric acid in the development of hypertension, the association of serum uric acid with the presence of essential hypertension is shown by simple logistic regression and multiple logistic regression in Table IV. For simple logistic regression, serum uric acid was an important variable in developing hypertension at univariate analysis (p=0.025). The crude (unadjusted) odd ratio was 1.005. At univariate analysis, a person with 1 µmol/L higher serum uric acid had 1.005 times the odds to develop hypertension. The BMI was an important variable for developing hypertension at univariate analysis (p<0.001). The crude (unadjusted) odd ratio was 1.408. At univariate analysis, a person with 1 kg/m^2 higher BMI had 1.408 times the odds to develop hypertension. Age was an important variable for developing hypertension at univariate analysis (p=0.006). The crude (unadjusted) odd ratio was 1.137. At univariate analysis, a person one year older had 1.137 times the odd to develop hypertension. Gender was not an important variable for developing hypertension at univariate analysis (p=1.000).

Based on multiple logistic regression, no association was found between serum uric acid and hypertension when adapted for age and BMI (p=0.082). A significant association between BMI and hypertension when adjusted for serum uric acid and age. A person with 1kg/m^2 higher BMI had 1.400 times the odd to develop hypertension (p<0.001). A significant association was observed between age and hypertension when adjusted for serum uric acid and BMI. A person 1 year older had 1.138 times the odd to develop hypertension (p=0.010).

Results of multiple logistic regression does not support serum uric acid as a significant association with essential hypertension.

DISCUSSION

Hyperuricaemia has been linked to hypertension, which is one of the major determinants for cardiovascular, cerebral and renal diseases. The effects of serum uric acid on hypertension were observed in other epidemiological studies. However, studies conducted in different populations have shown variable results.[1]

This study had shown that the proportion of hyperuricaemia in the case group was higher (48.9%) compared to control group (25%). The previous studies which stated approximately 20-47% of hypertensive adults had developed hyperuricaemia.[15,33] The difference in percentage of hyperuricaemia in hypertensive adults in our study compared to previous study were due to our study involved few study subjects and not a general population-based study. The contributing factors for the high prevalence of hyperuricaemia are dietary style, improved life expectancy, increased obesity rate and increased medication use for example antihypertensive of diuretic type.[15] The relationship between serum uric acid and blood pressure differs at different ages in various populations.[1]

Our study showed that the serum uric acid level was significantly increased in essential hypertension as there was a notable difference between the mean (SD) of serum uric acid in hypertensive group 390.64 (92.65) µmol/L and control group 352.09 (86.07) µmol/L (p < 0.05). Our results showed an agreement with the results from studies by Divyen et al.,[5] and Meti K et al.,[16] which the mean (SD) of serum uric acid in hypertensive group were significantly higher compared to control group 367.62 (106.48) µmol/L (p<0.05) and 374.75 (65.43) µmol/L (p<0.01), respectively. However, multiple logistic regression did not support our study findings. Thus, the significant association found in univariate analysis therefore is due to co-founding factors.

The results from most of epidemiological studies of population-based had supported that hyperuricaemia was an important independent predictor for the occurrence of hypertension with a higher relative risk shown in Korean,[17] black and white from the US,[18] native Japanese[19] and Japanese immigrants in the US.[20] It was reported that high serum uric acid concentrations were linked to high blood pressure in Korean aged <40 but not ≥40 years old, whereas this association was observed in Japanese aged ≥40 but not <40 years old.[1] Our study only involved participants in age group of 18 to 40 and subjects aged more than 40 were not included in our study. Thus, the association between serum uric acid and essential hypertension with age could not be concluded in our study.

Various studies had reported that serum uric acid showed a direct relation to the duration and the severity of hypertension.[5,10] However, this study had showed that there was no notable difference between mean (SD) of serum uric acid and stages of essential hypertension (p > 0.05) and also no notable difference between mean (SD) of serum uric acid and duration of essential hypertension in <5 years 398.30 (86.17) µmol/L and ≥5 years 378.47 (102.24) µmol/L (p>0.05). These findings were in accordance with other study by Ansari[21] which stated there was no notable statistical difference found between serum uric acid level and the severity of hypertension in stage 1 and stage 2 (p>0.05). Nevertheless, the findings were contradicted with Divyen et al.,[5] study which reported a significant difference between mean (SD) of serum uric acid of stage 1 296.83 (76.62) µmol/L and stage 2 394.98 (104.16) µmol/L (p<0.001) of essential hypertension. Meti K et al.,[16] reported that there was a significant difference between mean (SD) of serum uric acid

and the duration of essential hypertension in <5 years 339.06 (77.33) µmol/L and ≥5 years 428.29 (65.43) µmol/L (p<0.001). There were several factors which contributed to the difference results of this study with the other studies. One of the factors was our study and the study by Ansari RN et al.,[21] involved smaller sample size of 132 participants (88 hypertensive, 44 control) and 100 hypertensive participants respectively compared to the two studies by Divyen et al.,[5] and Meti et al.,[16] which both studies involved 200 participants (100 hypertensive, 100 control). Another factor was the difference in the age group of participants in which this study involved participants with age group of 18 to 40 years old whereas Divyen et al.,[5] and Meti K et al.,[16] studies involved participants with age group of 41 to 80, and 40 to 70, respectively. Although our study showed statistically no significant difference between mean (SD) of serum uric acid and stages of hypertension, there was a rising trend of mean (SD) of serum uric as stages or severity of hypertension increased.

There were few studies focusing on the trend of important laboratory parameters with serum uric acid level. Alternation in serum urea, serum creatinine and lipid profiles has been recognised as the independent determinant for essential hypertension. In our study, there was significant correlations between serum uric acid levels and some parameters of renal function (serum urea and serum creatinine). These were shown by positive correlations between serum uric acid levels with serum urea and serum creatinine in essential hypertension (r=0.299, p<0.05), (r=0.486, p<0.01) respectively. Kaewput et al.,[22] stated that elevated serum uric acid level was linked to high chronic kidney disease prevalence in hypertensive patients. Aiumtrakul et al.,[23] suggested that serum uric acid levels were independently linked to the high incidence of impaired renal function and renal disease progression in a community-based population. Reddy et al.,[10] suggested that uric acid may be an early and more sensitive markers of reduce renal blood flow compared to serum creatinine. The postulated mechanism was uric acid can induce the activation of renin-angiotensin system leading to vasoconstriction, resulting in reduce renal blood flow.[11] Even so, the serum uric acid elevation could be the result of hyperinsulinaemia[10] (as the insulin could reduce renal excretion of uric acid) which may influence the mean value of serum uric acid in case group. We did not analyse the serum insulin level in our study but the obese subjects who generally associated with insulin resistance and resultant hyperinsulinaemia were excluded from the study.

There was a significant correlation between serum uric acid levels and serum triglycerides levels in essential hypertension with a fair positive correlation (r=0.255, p<0.05). A significant correlation between serum uric acid levels and serum HDL levels in essential hypertension with poor negative correlation (r= -0.223, p<0.05) was observed. These findings were in agreement with other studies.[24-27]. It is postulated that the synthesis of triglycerides requires nicotinamide adenine dinucleotide phosphate (NADPH) which will lead to an increase of uric acid production.[27] Thus, our study had shown that hyperuricaemia was associated with dyslipidaemia[28] which can predict the risk for coronary artery disease.

The association of serum uric acid with the presence of essential hypertension was shown in our study as a person with 1 µmol/L higher serum uric acid level had 1.005 times the odds to develop hypertension at univariate analysis (p<0.05). De Becker et al.,[29] stated that systemic review and meta-analysis recently disclosed that 60 µmol/L rise in uric acid level was related to an increased risk of developing hypertension by 13%. However, in our study no association was observed between serum uric acid and hypertension when adjusted for age and BMI (p>0.05) in multivariate analysis. Age and BMI are the co-founding factors which will influence the effect of serum uric acid towards the risk of developing hypertension. Loh et al.,[30] reported that age and BMI had significant associations with hypertension in which the increased in age and BMI will increase the risk to develop hypertension (p < 0.001) in a population-based study in Perak, Malaysia. The individuals aged 30 to 39 years had the adjusted odds of 1.00 and the obese individuals had the higher adjusted odds of 2.34 to develop hypertension.[30] Malaysia currently is the country with the highest prevalence of obesity among adult in Southeast Asia in which 50.1% of Malaysia's adult population were reported as being overweight (30.4%) or obese (19.7%) according to 2019 national health and morbidity survey.[31]

There were several limitations to our study. One of the limitations was we did not include the dietary history of the study participants as the possible co-founding factor for the increase serum uric acid level which may influence the mean value of serum uric acid in case group. Approximately one third of the total body uric acid is from dietary purines and the other two thirds are formed endogenously. Nevertheless, the study by Krupp et al[32] reported that uric acid was an important predictor of hypertension in Germany's general adult population independent of dietary factors. Our study showed a significant association between serum uric acid and serum triglycerides and HDL levels, but total cholesterol and LDL showed lack of significant association. This could be explained by small study sample. Further larger population-based studies may increase our understanding regarding serum uric acid, lipid profile and hypertension in our population by increasing representativeness of our population, increasing statistical power and allowing for subgroup analysis. This will generate more robust conclusions.

CONCLUSIONS

Serum uric acid concentration was significantly raised in essential hypertension. No significant difference of serum uric acid concentration related to duration and severity of essential hypertension was observed. The significant associations were established between serum uric acid and triglycerides, high-density lipoprotein (HDL), urea and creatinine in essential hypertension. Serum uric acid was an important and significant variable for developing hypertension, but this association was weakened with the presence of other significant co-founders for example age and body mass index. The association of serum uric acid and hypertension is well-established already for years in other populations. Researchers are now investigating, which one is the cause, and which is the outcome. Despite the limitations, this study was the pioneer study assessing the association of

serum uric acid with essential hypertension in Malaysia. A large-scale population-based study is required to truly conclude the association in our population.

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ORIGINAL ARTICLE

Effectiveness of sexual health training to parents with children of autism spectrum disorder

Chin Pue Siah, MRCPCH(UK), Sathyabama Ramachandram, MRCPCH(UK)

Paediatric Department, Hospital Pulau Pinang, Ministry of Health, Penang, Malaysia

ABSTRACT

Introduction: Sexual health education among individuals with autism spectrum disorder (ASD) is unique and may not be adequately addressed both at home and at school. Parents have an important role in delivering sexual health education to their children. This is a pilot study to evaluate parental awareness and effectiveness of parent sexual health training for children with ASD.

Materials and Methods: Parents of 30 children with ASD with ages ranging from 8 to 12 years attending Child Development Clinic, Hospital Pulau Pinang (CDC HPP) were recruited. Parents attended two-hour virtual parent sexual health training and educational materials were provided to be utilised at home. Follow-up via phone consultation were done at three and six months to ensure training was carried out. Both structured interview and Vineland adaptive behaviour scales (VABS-3) were done at recruitment and at eight months via phone consultation. Wilcoxon-signed rank test was used to analyse differences between pre- and post-intervention outcome measures.

Results: Statistically significant increase in number of sexual health topics taught by parents and appropriate socio-sexual behaviours of children were found. Intellectual function of children with ASD influenced the study outcomes.

Conclusion: Parent sexual health training can be done to empower parents to educate children with ASD and promote appropriate socio-sexual behaviours.

KEYWORDS:
Autism spectrum disorder, puberty, parent training, sexual health education

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by persistent deficits in social communication and interaction, restricted and repetitive patterns of behaviours, interests and activities causing significant impairment across multiple settings. The US Centres for Disease Control and Prevention reported 1 in 36 children aged 8 years was estimated to have ASD in 2020.[1]

Children of ASD will reach the pubertal stage just as neurotypical peers; however, they experience more emotional and social challenges during this complex period.[2] There has been extensive research on intervention therapy to improve social deficits but research is relatively lacking in the aspect of sexual health among individuals with ASD.[3] The reported social challenges include difficulty interpreting social cues, understanding personal boundaries and socially-appropriate behaviours.[4] Consequently, these social challenges are frequently misinterpreted as inappropriate sexual behaviours with their mature physique. Additionally, systematic review revealed that individuals with ASD have greater difficulty adhering to privacy norms and receive less formal and informal sexual health education, leaving them more disadvantaged.[5]

Barnett et al., found that those individuals with ASD in special education placement were not receiving formal sexuality education.[6] In addition, adolescents with ASD often have fewer friends and lesser informal learning from peers compared to neurotypical peers.[7]

The American Academy of Pediatrics recommends that parents help their children, both those with and without disabilities, understand sexuality in a healthy way, at early ages as they grow to adulthood.[8] Ample studies recommend parents as the primary provider of sexual education for their children or adolescents with ASD.[4,9,10] However, parents are often clueless about approach, timing, information and strategies to discuss with their children.[3,10] Healthcare providers and educators are in a better position to provide training, resources, and encouragement to these parents.[9,11] Wight D et al. showed that parents who received training on sexual education had better communication with their adolescents regarding sexual health as compared with those who did not.[12]

Recommended sexual health topics for adolescents with ASD by Beddows N et al., are puberty body changes, social rules, personal boundaries and touch, differences between public and private places and behaviours. Again, it highlighted that parents need to provide continuity of sexual education.[13] This recommendation was supported by Davies AWJ et al. with emphasis that children should be educated before puberty.[14]

Current research suggests that children should be prepared for physical changes associated with puberty before onset of menarche, erection, and nocturnal emissions. For girls with ASD, education on puberty should preferably take place between eight and ten years, before onset of menarche. This may shift to earlier years as girls are reported as having earlier puberty these days.[15-17] Teaching proper hygiene prior to menarche is essential to prepare girls with ASD to manage menstruation.[10] Parent-child communication and education

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Corresponding Author: Chin Pue Siah
Email: puesiah@gmail.com

on sexuality should ideally begin in early childhood and continue through early adulthood and be given at appropriate levels for individuals' with ASD's development and functioning.[18]

Two local studies which explored maternal perspectives on sexual education for their children with intellectual disability showed variable degrees of maternal awareness. These studies highlighted the need to increase parental awareness and appropriate delivery of sexual education, possibly with shared responsibility among all relevant stakeholders.[19,20]

There is a need to increase the parental awareness as the primary provider of sexual health education for their children with ASD. Sexual health training by health care professionals to parents of children with ASD can provide the necessary guidance and framework for parents to be empowered to educate their children in preparing for adolescence. To our knowledge, this is a first local study to evaluate awareness on sexual health education among parents of children with ASD. We also aim to ascertain the effectiveness of parental training on sexual health education for their children with ASD at Child Development Clinic, Hospital Pulau Pinang.

MATERIALS AND METHODS

This study included children with ASD and their parents who attended Child Developmental Clinic, Hospital Pulau Pinang (CDC HPP) from November 2020 to April 2022. Inclusion criteria were children aged 8-12 years old with ASD. Exclusion criteria were children with ASD with visual or hearing impairment. Diagnosis of ASD was made by a developmental paediatrician by meeting the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association (APA), 2013) criteria. 70 children were identified, of which 33 children and their parents were recruited. All parents provided written consent for their participation. Thirty parents completed the study at the final stage.

This is a quasi-experimental pre- and post-intervention study without a control group. The intervention is a two-hour virtual sexual health training given by CDC HPP team with the presence of a developmental paediatrician. Training materials from the virtual sexual health training were given to parents to supplement training of their children at home. Training progress, utilisation of training materials and other parental concerns were enquired during telephone consultations at three and six months after intervention.

As this study was designed during the COVID-19 pandemic with enforced social distancing, sexual health training, follow-ups and data collections were conducted via telehealth (mainly telephone consultation without physical contact). Parents underwent two interview sessions, before and eight months after intervention. Parental interview which was based on a self-designed questionnaire on sexual health (Appendix 2 and 3) and Vineland Adaptive Behaviour Scale-3 Comprehensive Interview Forms (VABS- 3) were conducted by the principal investigator who is proficient in Malay, English and Mandarin language. These interviews were done before intervention and at eight months after intervention.

The Vineland Adaptive Behaviour Scale-3 (VABS-3) is a standardised assessment tool that measures adaptive functions which include communication, daily living skills and socialisation in daily life. Parent satisfaction scale was completed at the end of study period at eight months (attached in Appendix 3).

The content of the parent sexual health training was obtained from two resources, 'Training module "Live life, stay safe" reproductive health for children and adolescents with disabilities' by Family Division Development Division, Ministry of Health, Malaysia and 'The Healthy Bodies Toolkit for boys and girls - Parent's Guide on Puberty for Boys and girls with Disabilities' by Vanderbilt Leadership Education in Neurodevelopmental Disabilities (LEND).

The topics covered during the parent sexual health training were as follows:

I. Body parts including public and private parts.
II. Puberty changes in males and female including menstruation.
III. Personal hygiene.
IV. Differentiate public and private places and behaviours.
V. Circle of relationship.
VI. Differentiate safe and unsafe touch.
VII. Safety skills when encountering unsafe touch.

Each topic contained directions and activities supported by visual representations to enhance comprehension among individuals with ASD.

This study obtained approval from the Medical Review & Ethics Committee (MREC), Ministry of Health Malaysia, NMRR – 20 -1993 – 56284. Recruited children and parents were provided code numbers throughout study period and these codes were used in all the research documents with no mention of names or identity numbers to ensure privacy and confidentiality. All the study data including the pen drive with electronic files were stored securely at CDC HPP.

Data Analysis

In view of the small number of subjects (N=30) and non-normally distributed data, non-parametric tests of statistical analysis were selected. Wilcoxon-signed rank test was used to analyse the differences between pre- and post-intervention outcome measures. Mann-Whitney U test was used to analyse the relationship between two independent variables. Spearman rho's coefficient was used to explore potential correlation between the outcome measures. Statistical analysis was performed using SPSS Statistic-28.

RESULTS

Demographic data

The demographic data of both children and parents are presented in Table I.

For this study, the ASD severity was categorised into three levels by integrating the severity specifier of both social communication (SC) and restricted, repetitive behaviours (RRB) domains. Children with similar severity specifiers of level 1, 2 and 3 for both SC and RRB domains were categorised as mild, moderate and severe ASD respectively.

Table I: Characteristics of children and parents who participated in parent sexual health training.

Characteristic of children	N=30	%
Age (years)		
8-9	14	46.7
10-12	16	53.3
Gender		
Male	24	80
Female	6	20
ASD severity		
Mild	7	23.3
Moderate	20	66.7
Severe	3	10
Intellectual function		
Intellectual disability	22	73.3
Without intellectual disability	8	26.7
School		
Integrated Special Education Program	16	53.3
Inclusive Education Program	4	13.3
Mainstream	8	26.7
Home-school	2	6.7
Characteristic of parents (N=30 parents)		
Participation in parents training		
Mother	25	83.3
Father	5	16.7
Age of parents (years)		
<40	11	36.7
40-50	19	63.3
Education level		
Secondary education	8	26.7
Diploma equivalent	8	26.7
Bachelor's degree	13	43.3
Master's degree	1	3.3

Table II: Parental perception and satisfaction about sexual health education.

Parent interview questionnaires	Parents, N=30 (%)	
	Yes	No
Do you think that sexual health education is important for your child with ASD?	25(83.3)	5(16.7)
In your opinion, who should deliver sexual health education to children of ASD?		
Parent	27 (90)	
Teacher	3 (10)	
When is the suitable time for you to educate your child with ASD on sexual health education?		
8-12 years old	16 (53.3)	
13-17 years old	14 (46.7)	
Parental satisfaction with sexual health training	25(83.3)	5(16.7)

Table III: Median scores for outcome measures in pre- and post-intervention.

Outcome measures	Pre-intervention		Post-intervention		p-value
	Median	25th-75th percentiles	Median	25-75th percentiles	
Numbers of sexual health topics covered by parents	0	0-3.3	2.5	0-8	<0.001[b]
Parent-reported appropriate socio-sexual behaviours	4.5	4-7	8.5	4.8-10	<0.001[b]
VABS-3					
Socialisation domain	59	39.5-63.3	59	40-65	0.011[b]
Adaptive behaviour composite	62	50.8-68.3	63	53.5-68	0.568

[b] p <0.05, statistical significance from paired-sample Wilcoxon-signed rank test

Table IV: Predictor factors affecting the outcome measures.

Predictor factors	Outcome measures, p-values			
	Numbers of sexual health topics covered by parents	Parent-reported Socio-sexual behaviours	VABS-3	
			Socialisation domain	Adaptive behaviour composite
Subjects				
Intellectual function	<0.001[c]	<0.001[c]	0.04[c]	0.01[c]
Age	0.697	0.294	0.313	0.275
Gender	0.104	0.900	0.143	0.158
Parents				
Education level	0.667	0.918	0.334	0.637

[c] $p<0.05$, statistical significance from independent-samples Mann-Whitney U Test

For those with variable severity specifiers for both domains, the categorisation was based on the higher severity specifier of either domain.

Parents who felt that sexual health training is not important cited training for daily living skills and academic skills as a higher priority for their children. Among parents who voiced dissatisfaction with sexual health training, three parents of children with moderate to severe ASD and significant intellectual disability indicated no benefit while two parents were concerned that sexual health education may expose their children to sexual information and arouse curiosity toward sexuality.

Protection from sexual victimisation or exploitation (40%) and worries about inappropriate sexual behaviours in public (30%) were the two main concerns stated among parents in our cohort. Understanding social boundaries and preparation for marriage were indicated among 26.7% and 3.3% of our parents respectively.

Outcome measures

As observed from Table III, the intervention produced consistent and statistical significant improvement across most of the outcome measures, except for Adaptive Behaviour Composite in VABS-3.

Intellectual function of the subjects was the only statistically significant predictor factor of the outcome measures as indicated in Table IV.

We administered additional analysis with Spearman' correlation to determine the relationship between the study intervention and outcome measures. There were moderate positive and statistically significant correlation between the numbers of sexual health topics covered by parents in the study intervention with all the outcome measures at post-intervention ($r=0.822$, $r=0.828$, $r=0.721$, $p<0.001$).

DISCUSSION

To our knowledge, this is the first local study assessing outcomes of parent training on sexual health among children with ASD at Child Development Clinic. Our findings were consistent with previous research regarding parental awareness.[3-4,9,11,21] Majority of parents in this study are aware of the importance of sexual health education (83.3%) and that they played a major role in educating their children (90%). Parents of our study reported limited knowledge, professional support, and available resources on sexual health education.

Concerns about children with ASD having inappropriate sexual behaviours and being at risk of sexual abuse or victimisation were addressed by parents of this study group. Even though there has been a proliferation of evidence-based autism-related intervention, resources on sexual health education among children with ASD is limited. Parents across different regions faced similar concerns and challenges in supporting children with ASD.[3-4,9,10,21] Improvement in parental engagement after the training is expected and our results are no different from other similar studies.[3-4,21] Parents will be empowered to discuss sexual health topics with their children once they have appropriate training and support from professionals. 83.3% of parents of this study expressed their satisfaction and benefited from this intervention. A few parents of this study would like to have more complex sexuality topics in the future which include intimacy and pregnancy.

With better parental engagement on sexual health topics, parents in our cohort reported a significant decrease in inappropriate socio-sexual behaviours among their children at the end of the study period. This positive correlation between the intervention and socio-sexual behaviours was statistically significant. Again, it strongly supports that parent sexual health training with professional support can promote better socio-sexual behaviours among children with ASD.[22] This short-term parent sexual health training is effective in helping our parents to guide their children with ASD in understanding basic sexual health before embarking to more complicated areas of sexuality such as romantic relationships and pregnancy.

Our results showed that intellectual function was the only statistically significant predictor outcome for outcome measures where children with ASD without intellectual disability showed significant improvement in numbers of sexual health topics covered by parents, parent-reported socio-sexual behaviours, socialisation domain and adaptive behaviour composite of VABS-3. In our study, children without intellectual disability were taught by their parents about puberty changes, circle of relationship and menstruation for girls. Children with intellectual disability were taught on recognition of public and private body part, public and private places, and appropriate behaviours. These

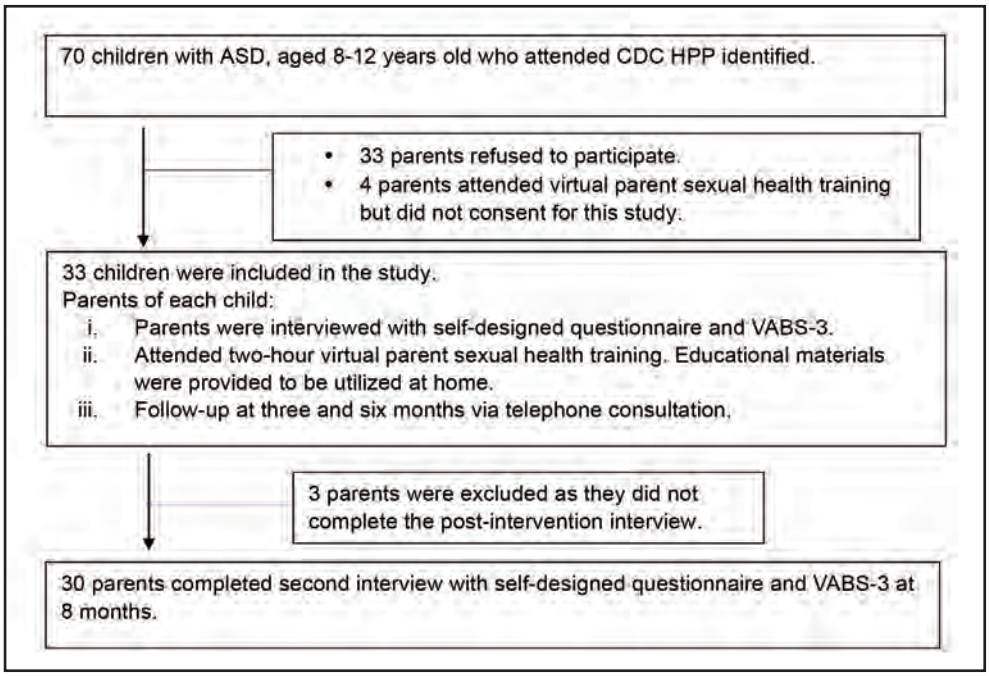

Fig. 1: Flow chart on patient recruitment

findings were consistent from previous studies indicating that the intellectual capacity of children with ASD influenced parental communication on sophisticated sexuality-related topics.[3,9] This could be due to parental perception that certain sexual health topics were irrelevant for their children with intellectual disability.[3] Perhaps the approach and materials of the sexual health education may not suitable for children with lower intellectual capacity. There is a need to address these concerns in future studies.

We also found positive changes and correlations in the socialisation domain of VABS-3. VABS-3 has not been utilised as a measurement tool for socio-sexual behaviours in previous research on sexual education. The socialisation domain of VABS-3 include interpersonal relationship, play and leisure and coping skills. We postulated that the basic concepts of appropriate socio-sexual behaviours at private and public places and behaviours and 'safe and unsafe touch' from the intervention had positively influenced interpersonal relationship skills.

LIMITATIONS

This study has several limitations. The small sample size may affect generalisation of results to general population. There is a likelihood of recall bias as the occurrence of appropriate socio-sexual behaviours was based on parental report. Apart from that, during the COVID-19 pandemic there was limited social situations in general. In fact, a large majority of children were highly vigilant about 'social distancing', as healthcare providers repeatedly emphasised this during the pandemic. The rather short study duration is another limitation.

CONCLUSION

Our findings suggest that parent sexual health training is effective in empowering parents to teach their children with ASD. This basic sexual health training can be provided to parents by trained healthcare provider at various healthcare sites either virtually or physically, providing an early start to communication and education on sexual health between parents and their children with ASD. It is important to tailor the training and resource materials according to the intellectual capacity of children with ASD.

Future studies with a larger sample and stratification based on intellectual function may provide more data on effectiveness of parent training that can be carried out not only in CDCs but also at general paediatric and primary health clinics for children with special needs.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

A scoping review on socioeconomic factors affecting tuberculosis loss to follow-up in Southeast Asia

Ahmad Yusri Abd Rani, MPH[1], Nurhuda Ismail, DrPH[1], Yuslina Zakaria, PhD[2], Mohamad Rodi Isa, DrPH[1]

[1]Department of Public Health Medicine, Faculty of Medicine, Universiti Teknologi MARA (UiTM) Sungai Buloh Campus, Selangor, Malaysia, [2]Department of Pharmacy Practice and Clinical Pharmacy, Faculty of Pharmacy, Universiti Teknologi MARA (UiTM) Puncak Alam Campus, Selangor, Malaysia

ABSTRACT

Introduction: Tuberculosis (TB) is a global public health issue. The Southeast Asian region grapples with numerous challenges in TB management, with loss to follow-up (LTFU) emerging as a critical barrier to effective control of the disease. This review synthesised published articles to identify socioeconomic factors contributing to the burden of TB losses for follow-up in Southeast Asia.

Materials and Methods: This scoping review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework developed by the Joanna Briggs Institute (JBI). A total of 10 studies were identified as eligible from the title and abstract review. The mixed method quality appraisal tool (MMAT) version 2018 was used to assess the quality of the included quantitative studies.

Results: The results showed that poverty, unemployment, low education levels, migrant status, community support, male gender, substance abuse, and regional disparities significantly impact the occurrence of TB LTFU in Southeast Asia.

Conclusion: The findings have significant implications for public health in Southeast Asia. Addressing these socioeconomic barriers through community-based strategies, educational initiatives, and policy reforms is vital for improving treatment outcomes and overall public health.

KEYWORDS:
Tuberculosis, Southeast Asia, loss to follow-up, socioeconomic factors, treatment adherence

INTRODUCTION

Tuberculosis (TB) is one of the most common chronic infectious diseases in the world, with an estimated 10 million people suffering from it. Therefore, TB remains a formidable public health challenge worldwide, with Southeast Asia being a region of particular concern because of its high TB prevalence.[1] In 2019, a large proportion of TB cases were concentrated in Southeast Asia (44%).[2] The region grapples with numerous challenges in TB management, with loss to follow-up (LTFU) emerging as a critical barrier to effective control of the disease.

TB loss to follow-up (LTFU) is a term used to describe patients who have started TB treatment but do not complete it or do not return for their scheduled follow-up appointments. According to the World Health Organization (WHO) definition, TB LTFU refers to the patients who underwent treatment for a minimum of four weeks and subsequently discontinued treatment for a continuous period exceeding eight weeks.[3] This interruption not only hampers individual health outcomes but also poses a significant public health risk by increasing the likelihood of drug-resistant TB strains.[4] LTFU is also a significant barrier to effective TB control as it can lead to continued transmission of the disease and increased morbidity and mortality among patients.[5]

Socioeconomic factors refer to the social and economic experiences and realities that shape individuals' and communities' lives, influencing their behaviour, attitudes, and opportunities. These factors encompass a wide range of elements, including income, education, employment status, social class and access to healthcare.[6] They play a crucial role in determining an individual's quality of life and can significantly impact health outcomes, including the treatment, management and outcome of diseases such as TB.[6] A retrospective cohort study in Brazil found that males, non-white ethnicity/colour, lower education level, homelessness, deprivation of liberty, drug, alcohol, and/or tobacco use, and recurrence or re-entry after abandonment were associated with higher odds of LTFU. Conversely, older age, extrapulmonary tuberculosis, deprivation of liberty, and supervised treatment were associated with lower odds of LTFU.[7] Other studies have consistently demonstrated that factors such as poverty, lack of access to healthcare, educational disparities and other socioeconomic stressors significantly contribute to patients failing to complete TB treatment.[8,9] These factors often create barriers that prevent consistent and effective treatment adherence.

In Southeast Asia, these socioeconomic factors are compounded by the high prevalence of TB, limited resources, and high population density.[2] In addition, focussing on Southeast Asia is essential because of the region's unique socio-economic and cultural landscape, such as the high number of immigrants[10] and various education levels,[11] which profoundly influence TB treatment outcomes. In one study conducted, which considered demographic characteristics, socioeconomic status, and distance to primary health centres, resulted in a higher rate of successful

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Corresponding Author: Nurhuda Ismail
Email: yuda@uitm.edu.my

treatment and a lower "lost to follow-up" rate compared with conventional programmes.[12]

Thus, the objective of this review was to synthesise published articles to identify socioeconomic factors contributing to the burden of TB loss for follow-up in Southeast Asia. The findings are important because of the diversity and complexity of socioeconomic conditions in Southeast Asia, which necessitate a targeted understanding of how these factors interact with TB LTFU, enabling more effective, region-specific interventions and strategies.

Scoping Review of the Research Questions

TB LTFU is a huge public health problem, as discussed; hence, this review aimed to answer the following questions:

1. What are the social factors that contribute to the burden of TB LTFU in Southeast Asia?
2. What economic factors influence the burden of TB LTFU in Southeast Asia?

MATERIALS AND METHODS

This scoping review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for scoping review[13] and the framework by the Joanna Briggs Institute (JBI)[14] which is the improved version of the scoping review framework developed from the earlier methodology described by Arksey & O'Malley.[15] This review was not registered in the Prospective Register of Systematic Reviews (PROSPERO) because it is a scoping review and not a systematic review.

Search Strategy

PubMed and Scopus databases were searched to retrieve articles published between 2011 and 2020. Accordingly, only studies meeting the eligibility criteria discussed below were included in the review. The search was conducted on January 7, 2023. The following search terms and keywords were used: socio-economic factors, TB LTFU, TB treatment default, TB defaulters, Southeast Asia, Malaysia, Singapore, Indonesia, Cambodia, Brunei, Laos, Myanmar, Philippines, Thailand, Vietnam, East Timor, social factors, economic factors, contributing factors and risk factors. During the data sources search process, sorting by year of publication was first applied. Next, we only considered the first 10 pages of the search results because of multiple similarities (duplicates) and unrelated articles (not about TB/not socioeconomic status).

Eligibility Criteria

Inclusion criteria

Because this is a scoping review, we used the population/concept/context (PCC) framework recommended by JBI[14] to identify eligible studies, as discussed below:

1. **Population (P):** TB LTFU patients, including both pulmonary and extra pulmonary TB.
2. **Concept (C):** Quantitative studies investigating the influence of socioeconomic factor, drivers and status on the occurrence of loss to follow among TB patients.
3. **Context (C):** We conducted our search process between January 2012 to December 2022. Only cohort, case-control, cross-sectional studies and systematic reviews evaluating socioeconomic factors influencing loss to follow among TB patients from Southeast Asian countries were included for further screening and synthesis.

Exclusion criteria

1. Publication does not peer reviewed.
2. Other reviews (editorial, commentaries), book chapters, editorials, letters and conference abstracts.
3. Publication in any language other than English.
4. Qualitative studies.
5. Publication for which we cannot access the full text.

Selection Process

Our selection method followed the guidelines outlined in Joanna Briggs Institute's online manual. Two reviewers conducted an article search based on the defined eligibility criteria. The articles obtained were then organised in MS Excel spreadsheet for checking duplication and assessing eligibility. There was a consensus on the articles chosen and screened for this review, with no disagreements noted.

Data Extraction and Analysis

The screening of titles and abstracts was independently conducted by one review author, adhering to the previously mentioned criteria. Subsequently, full-text evaluation of the studies identified as eligible from the title and abstract review was undertaken. The studies for inclusion were chosen by the reviewer after a thorough full-text assessment. Subsequently, data relevant to the study objectives were extracted and thematically analysed. This includes details such as author(s), publication year, country of origin (of the publication or study conduct), methodology and primary socioeconomic factors. The themes that emerged will be explored in the findings and discussion section.

RESULTS

Search Outcomes

On January 7, 2023, an initial search resulted in the identification of 28 articles from PubMed and 22 from Scopus. Following a preliminary screening of titles and abstracts, 19 articles were selected for further evaluation. This subset comprised 11 articles from Scopus and eight from PubMed. However, three articles were subsequently identified as duplicates and thus excluded. The remaining 16 articles, consisting of 16 quantitative studies, underwent a full-text review and were further assessed for suitability. Of the 16 articles reviewed in full, only 10 met the eligibility criteria for inclusion in this study. Figure 1 depicts a schematic representation of the search methodology and the outcomes of the article selection procedure.

Study Setting and Summary of the Reviewed Articles

Among 10 eligible articles selected for review, three studies were conducted in Malaysia, two in Vietnam, two in Indonesia, two in the Philippines and one in Myanmar. There is only one prospective cohort study. The remaining studies consisted of three cross-sectional studies, five retrospective cohort studies and one case–control study. Table I presents the characteristics of the study population. Table II shows a summary of all 10 eligible articles, with a specific focus on the socioeconomic factors that influence the TB LTFU

Table I: Characteristics of the study population.

Characteristic	n	%	Citation
Mean age	41.8	-	(11, 16-24)
Sex			
Male	55843	65.5	(11, 16-24)
Female	29711	34.5	
Average duration of the study	49 months	-	(11, 16-24)
Treatment outcome			
Completed treatment/treatment success.	21803	24.0	(11, 16-24)
Loss to follow-up	2162	2.4	
Others (died, treatment failure)	1715	1.9	
Not evaluated	65078	71.7	

group. These studies broadly focussed on socioeconomic risk factors, social issues, and financial issues. There were 11 articles that focussed solely on social aspects, four focussed only on financial/economic issues, and five covered both social and economic aspects. Of the selected articles, with the updated search, one was a cross-sectional study focussing on social aspects and a systematic review covering both social and economic aspects.

Emerged Themes from the Studies Reviewed:

1. **Social issues influencing TB lost to follow-up in Southeast Asia**
   From the studies identified in the search, eight examined the social issues influencing TB LTFU in Southeast Asia. This included the level of education, immigrant status, support from the community, substance abuse and gender.

1.1. Education level: From the eligible studies, two found that education level can have some impact on the occurrence of TB LTFU.[11,17] Those with a low level of education have a higher risk of becoming TB LTFU than those with a higher education level.[11] Furthermore, those with an education level below secondary level are even more vulnerable.[17]

1.2. Migrant status: Compared with permanent residents, short-term, inter-province migrants are most likely to have a higher TB LTFU rate.[18] In addition, economic migrants, particularly those crossing provincial borders, have a higher risk of poor TB treatment outcomes.[18]

1.3. Community support: Two studies have described how community support may influence the rate of TB LTFU.[19,23] In Indonesia, there is a community social organisation that aids TB patients to complete treatment within a specified period, known as Aisyiyah, actively involved in TB management, particularly in North Sumatra, Indonesia. The organisation has established a communication network to prevent TB through the formation of the TB-HIV Care Aisyiyah team. This team consists of cadres who work at the community level, including villages, to provide services in collaboration with local health centres (Puskesmas). These cadres are tasked with humanitarian duties that prioritise human values without discrimination based on race, religion, or ethnicity.[25] Receiving this support contributes to a lower LTFU rate.[19] In the Myanmar, patients who reported having received any type of assistance (including travel support) from the TB programme showed a significantly lower risk of LTFU.[21]

1.4. Substance use: Tobacco and alcohol are the most common substances used, with two studies showing that they can affect the TB LTFU rate. There are increased odds of TB LTFU among alcoholics,[22] whereas there are noticeable higher TB LTFU rates among smokers.[20]

1.5. Gender: Being a male will most likely increase the risk of LTFU as compared to female, according to two studies in Malaysia and Myanmar.[17,21]

2. **Economic Factors influencing TB LTFU in Southeast Asia**
   From the studies identified in the search, several economic factors were found to contribute to the TB LTFU in Southeast Asia. This included the household income, employment status, health insurance and accessibility to healthcare.

2.1 Household income: Lower household income can contribute to TB LTFU. In Malaysia, risk of TB LTFU significantly increases by those in lower income group below RM2160 as compared to those that earn more.[11]

2.2 Employment status: Those that was unemployed was found to be more likely to become TB LTFU as compared to those with employment status[11] according to study in Malaysia. Similar findings were found in Indonesia where those with their household's head was self-employed were more likely to default TB treatment as compared to those with their household's head work as government employees.[23]

2.3 Health insurance: In Indonesia, those covered by health insurance are more likely to comply with treatment and follow-up as compared to those that not covered.[23] Furthermore, those that have to pay out of pocket are more likely to stop seeking treatment and follow-up altogether.[16]

2.4 Accessibility to healthcare: Poor accessibility to health centres is also an issue. People who received travel support to access the health facility were significantly lower risk of becoming TB LTFU.[21] People who had no access to transport and were forced to walk to health centres were most likely to default to TB treatment.[23] As comparison, the decentralisation of treatment to facilities near a patient's residence reduced default during treatment.[24]

Quality of Evidence

The Mixed Method Quality Appraisal Tool (MMAT) version 201826 was used to assess the quality of the included quantitative studies. Two people reviewed the articles to judge their quality. They looked at different aspects such as

Table II: Summary of eligible articles with specific focus on the socioeconomic factors that influence the group with TB LTFU

No.	Author/ references	Year	Study location/ countries of Origin	Method/ study design	Main socioeconomic findings
1	Sharani et al.[11]	2022	Malaysia	Cross-sectional study using secondary data	Risk of TB LTFU significantly increases by 1. Working age population aged 32–41 and 42–53 years 2. Malaysian nationality 3. Patients staying in an urban area 4. Income level less than RM2160 5. Unemployed 6. Have a low education level (below high school),
2	Wrohan et al.[16]	2022	Vietnam	Retrospective cohort study	Loss to follow-up was less common among patients covered by social health insurance compared with those who paid for treatment out-of-pocket
3	Shaifuddin et al.[17]	2022	Malaysia	Cross-sectional study using secondary data	Those significantly associated with default treatment were as follows: 1. Gender, 2. Age 3. Education levels
4	Vo et al.[18]	2020	Vietnam	Cross-sectional study	Short term, interprovince migrants have higher default rates
5	Kusmiati et al.[19]	2020	Indonesia	Retrospective cohort study	Significant correlations between cure and default outcome in DR-TB patients accompanied by Aisyiyah compared with those unaccompanied. (2.8% vs 28.3%; p = 0,002)
6	Khan et al. [20]	2020	Malaysia	Retrospective cohort study	Proportion of defaulters higher in the smoking group
7	Aung, et al.[21]	2019	Myanmar	Retrospective cohort study	1. Patients with older age, male sex, patients residing in hilly regions, and HIV coinfection were risk factors for loss to follow-up 2. Patients who received travel support were less likely to be lost to follow-up
8	Tupasi et al.[22]	2016	Philippines	Case–control study	1. Increased odds of default in alcoholics 2. Reduce odds of default in those with better TB knowledge, and higher levels of trust in from physicians and nurses.
9	Rutherford et al.[23]	2013	Indonesia	Prospective cohort study	The default was associated with 1. Characteristics of the head of the household being self-employed 2. Walking to the clinic
10	Gler et al.[24]	2012	Philippines	Retrospective cohort analysis	Protective factor: 1. Have health insurance 2. Paying for diagnosis (as opposed to non-paying) Decentralization reduces the risk of default

the purpose of the study, how well it was conducted, the design, how participants were chosen, how data was collected and analysed, and the conclusions drawn from the findings. The quality score indicates how good the studies are, with scores below 50% being considered low quality, scores between 51% and 75% being average quality, and scores between 76% and 100% being high quality. All 10 quantitative studies included in this assessment were of high quality, scoring between 76% and 100%. None of the studies were considered to be of low quality. Evaluation of the quality of evidence is done in a separate MS Excel file. The risk of bias was considered very low in these studies.

DISCUSSION

Socioeconomic stressors such as poverty, unemployment and low household income critically impact TB treatment adherence and completion, leading to LTFU.[11,17] These factors create a dilemma in which individuals prioritise immediate economic survival over health care. Poverty can limit access to TB services and necessary nutrition, whereas unemployment and low income may lead to inadequate living conditions, reducing the ability to adhere to treatment schedules.[27] These circumstances often force individuals to choose between earning a livelihood and attending healthcare appointments, thereby increasing the risk of LTFU.

Educational levels significantly influence TB treatment outcomes. Lower education levels are often correlated with higher LTFU rates.[11] This can be attributed to limited health literacy, which affects understanding and adherence to treatment regimens. In addition, community support plays a crucial role in improving adherence to TB treatment. Strong community networks provide education, awareness, and support systems, encouraging patients to continue their treatment and reducing the incidence of LTFU.[19,22] These factors highlight the importance of integrating educational and community-based approaches into TB management strategies.

The findings highlight the pivotal role of community support in enhancing TB treatment adherence and reducing LTFU rates. In Indonesia, the Aisyiyah organisation's approach to TB management underscores the effectiveness of community-based interventions. The establishment of the TB-HIV care Aisyiyah team, which integrates cadres working closely with local health centres, is a prime example of leveraging local community networks to support TB patients. These cadres perform crucial roles, including patient education, medication adherence support, and facilitating access to healthcare services.[25] Their humanitarian approach, emphasising equality and non-discrimination, is likely to foster trust and cooperation among TB patients, thereby enhancing engagement and continuity of care.[28] The scenario in Myanmar provides further evidence of the importance of support mechanisms in TB treatment regimes. The provision of assistance, such as travel support from the TB program, addresses one of the significant barriers to sustained treatment adherence—accessibility to healthcare facilities. For many patients, especially those from rural or impoverished backgrounds, the cost and logistics of travel can be prohibitive factors that discourage regular clinic visits, thereby increasing the risk of LTFU.[28] By alleviating these logistical challenges, the TB program not only ensures that patients can attend their appointments but also communicates a level of care and support that may encourage patients to complete their treatment regimen. This type of support is particularly crucial in settings where economic hardships are prevalent and can be a determinant factor in the success of public health interventions.

This scoping review has identified two critical risk factors that exacerbate the odds of TB LTFU: alcoholism and smoking. Alcoholics demonstrate increased odds of TB LTFU, which could be attributed to the potential for alcohol to impair judgment, reduce adherence to treatment schedules, and diminish the effectiveness of TB medications due to interactions between alcohol and the drugs used in TB treatment.[29-31] Similarly, the review highlights a noticeable elevation in TB LTFU rates among smokers.[11,32] Smoking may contribute to this trend through several mechanisms, including the exacerbation of pulmonary symptoms, which could complicate the TB treatment process, and a potential decrease in the efficacy of TB treatment due to the harmful effects of tobacco on the respiratory system. Both alcoholism and smoking are indicative of broader socio-behavioural patterns that may include reduced access to healthcare, lower socioeconomic status, and a higher likelihood of engaging in behaviours that compromise health. These findings underscore the importance of integrating comprehensive support services, including smoking cessation and alcohol abuse treatment programs, into TB treatment plans to address these risk factors and improve treatment adherence and outcomes.

The finding that being male increases the risk of LTFU compared to females finds some support in the literature, particularly in studies focusing on health behaviours and treatment delays in specific populations. For instance, a study conducted in Selangor, Malaysia, found that male pulmonary TB patients experienced a longer total delay from symptom onset to treatment initiation than their female counterparts, which could potentially increase their risk of LTFU.[33] Factors contributing to this delay included symptoms like weight loss and employment status, which might complicate timely access to healthcare. Similarly, gender-specific differences in health-seeking behaviours were noted in a study on high-risk sexual behaviours among methamphetamine users in Myanmar, where gender played a significant role in the engagement with health services.[34] These findings suggest that gender differences in health behaviours and access to treatment could influence the likelihood of LTFU, with males potentially at higher risk due to factors such as longer delays in seeking treatment and specific lifestyle or employment conditions that hinder regular follow-up.

Migrants face unique challenges in TB treatment, leading to a higher risk of LTFU.[18] These challenges include a lack of stable housing and employment, which contributes to inconsistent treatment adherence.[35] The transient nature of migrants often results in interrupted treatment due to relocation and the inability to access consistent health care.[35]

Additionally, migrants may face language barriers and limited knowledge of health care systems, further hindering their ability to seek and continue treatment. These factors necessitate tailored approaches in TB management for migrant populations to reduce LTFU rates.

The relationship between health insurance coverage and TB treatment compliance, as well as the impact of out-of-pocket payments on treatment-seeking behaviour, underscores a critical aspect of public health management. Studies have shown that individuals covered by health insurance are more likely to adhere to TB treatment and follow-up protocols, suggesting that financial barriers significantly influence patient compliance.[36-38] For instance, the introduction of multichannel financing in China, which includes medical insurance and local funds to cover the medical expenses of TB patients, has been associated with improved medical security and reduced economic burden for these patients.[36] Conversely, the financial strain of out-of-pocket payments can deter individuals from continuing or seeking TB treatment, as evidenced by the higher loss to follow-up rates among those facing higher out-of-pocket costs.[39,40] This financial fragility, particularly among the married middle working class in urban area, highlights the socioeconomic burdens that can exacerbate the public health challenge posed by TB, especially with the emergence of multi-drug resistant strains.[37] Therefore, enhancing health insurance coverage and reducing out-of-pocket expenses could be pivotal in improving TB treatment compliance and reducing the overall burden of the disease, aligning with global health objectives to combat TB effectively.

In Southeast Asia, regional variations significantly impact TB LTFU, which is reflected in the results. These variations are often due to the differing economic performance, healthcare infrastructures and cultural differences across the region. Some areas with well-developed health care systems have lower LTFU rates, whereas regions with limited resources face higher challenges in maintaining TB treatment adherence.[41] Social and cultural differences, including beliefs about health and medicine, also play a role in how communities perceive and engage with TB treatment, influencing LTFU rates.[22] These regional disparities highlight the need for context-specific strategies in TB management across Southeast Asia.

Limitations of the Review

This scoping review faces limitations, including potential biases in selected studies and the quality of these studies, which may affect the interpretation of findings. In addition, the generalisability of the results to Southeast Asia might be limited due to regional differences in socioeconomic conditions and health care systems.

Implications for public health policy and practice: The findings have significant implications for public health in Southeast Asia. Addressing socioeconomic barriers through community-based interventions, educational campaigns, and policy changes could improve TB treatment adherence. Tailored approaches to accommodate different regional healthcare capacities and cultural backgrounds are essential.

Recommendations for Future Research

Future research should focus on longitudinal studies to understand the long-term impact of socioeconomic factors on TB LTFU. Investigating specific subpopulations and testing interventions aimed at reducing socioeconomic barriers can provide more targeted solutions. This research is crucial for developing effective strategies to decrease TB LTFU rates in Southeast Asia.

CONCLUSION

In conclusion, socioeconomic factors play a critical role in tuberculosis loss to follow-up (TB LTFU) in Southeast Asia. Poverty, unemployment, low education levels, and regional disparities significantly impact treatment adherence. This review highlights the necessity for targeted interventions, including community-based strategies, educational initiatives and policy reforms, to address these socioeconomic barriers. Addressing these factors is vital for improving TB treatment outcomes and overall public health in Southeast Asia.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Hirschsprung disease associated enterocolitis: a systematic review and meta-analysis

Hery Poerwosusanta, PhD[1], Yusuf Almalik Saputra, MD[2], Angga Setya Budi, MD[3], Donny Aditia, MD[4], Gunadi, PhD[4]

[1]Paediatric Surgery Division, Department of Surgery, Faculty of Medicine, Lambung Mangkurat University/Ulin Hospital, Banjarmasin, Indonesia, [2]Emergency Department, Labuha General Hospital, South Halmahera, North Maluku, Indonesia, [3]Emergency Department, Sultan Agung Banjarbaru Islamic Hospital, Komplek Kota Citra Graha, Kalimantan Selatan, Indonesia, [4]Paediatric Surgery Division, Department of Surgery, Faculty of Medicine, Gadjah Mada University/Dr. Sardjito Hospital, Yogyakarta, Indonesia

ABSTRACT

Introduction: Hirschsprung's disease-associated enterocolitis (HAEC) remains a substantial morbidity and mortality risk in Hirschsprung's disease. HAEC is a challenge. Its p athophysiology is still a mystery, and no adequate treatment strategy exists. The aim of the study is to analyse the pre-and post-operative, mortality and complications: strictures, anastomotic leak, constipation and incontinence associated with HAEC.

Materials and Methods: Adjust to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020; this study met all the requirements and was up-to-date. The search approach was online publications between 2013 and 2023 in Pubmed and SagePub. It was decided not to consider review pieces that had already been published and half done. The STATA 18th version was used for meta-analysis.

Results: Our search results included 370 PubMed and 149 SagePub articles. Since 2013, 134 PubMed and nine SagePub articles have been obtained, and seven studies have met the criteria.

Conclusion: Disorders of intestinal motility in the aganglionic segment and accumulation of faeces disrupt the balanced microbiota population, which are factors of pre-operative HAEC. Major congenital anomalies and low birth weight worsen pre-operative HAEC. Pre-operative HAEC can continue and affect the post-operative. Constipation and fecal incontinence are still the main challenges after HSCR surgery.

KEYWORDS:
Hirschsprung disease associated enterocolitis, incidence; etiology, complication

INTRODUCTION

Since the description of Hirschsprung's disease (HSCR) in Berlin in 1886, remarkable discoveries have been made regarding its aetiology, pathophysiology, optimal medical-surgical management and follow-up care. Hirschsprung's disease (HSCR) is characterised by an absence of enteric nervous system (ENS) ganglion cells in the myenteric and submucosal plexuses, failing proximal to distal migration of neural crest cell1 and leading to functional obstruction.[2]

Hirschsprung disease-associated enterocolitis (HAEC) is an inflammatory complication that can present either in the pre- or post-operative period and is associated with increased morbidity and mortality. HAEC is a medical challenge, and the pathogenesis remains poorly understood,[2] and there is no adequate treatment strategy yet.[3] The study aims to analyse pre- and post-operative, mortality, anastomosis stricture, and the leakage, constipation, and incontinence associated with HAEC.

MATERIALS AND METHODS

Protocol

The review adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines, to ensure comprehensive and transparent reporting.

Criteria for Eligibility

This meta-analysis analyses pre- and post-operative, mortality, anastomosis stricture, and the leakage, constipation and incontinence associated with HAEC. The included studies must fulfil the following requirements: 1) The paper must be written in English to determine the best management of HCSR and HAEC. 2) Studies published between 2013 and the initiation of this systematic review are considered relevant.. 3) Only original research articles with a DOI are included. Editorials, submissions without a DOI, previously published review articles, and entries that are essentially identical to journal papers already published are excluded.[4]

Search Strategy

We used "Hirschsprung disease associated enterocolitis" and "Hirschsprung disease" as keywords. The search for studies to the PubMed and SagePub databases by inputting the words: (("Hirschsprung"[MeSH Subheading] OR "enterocolitis"[All Fields] OR "Hirschsprung enterocolitis"[All Fields]) AND ("Hirschsprung"[All Fields] OR " Hirschsprung disease"[All Fields]) AND ("enterocolitis"[MeSH Terms] OR ("enterocolitis"[All Fields]) OR ("Hirschsprung associated enterocolitis"[All Fields]) AND "incidence of Hirschsprung"[All

This article was accepted: 24 June 2024
Corresponding Author: Hery Poerwosusanta
Email: herpoerwo@ulm.ac.id

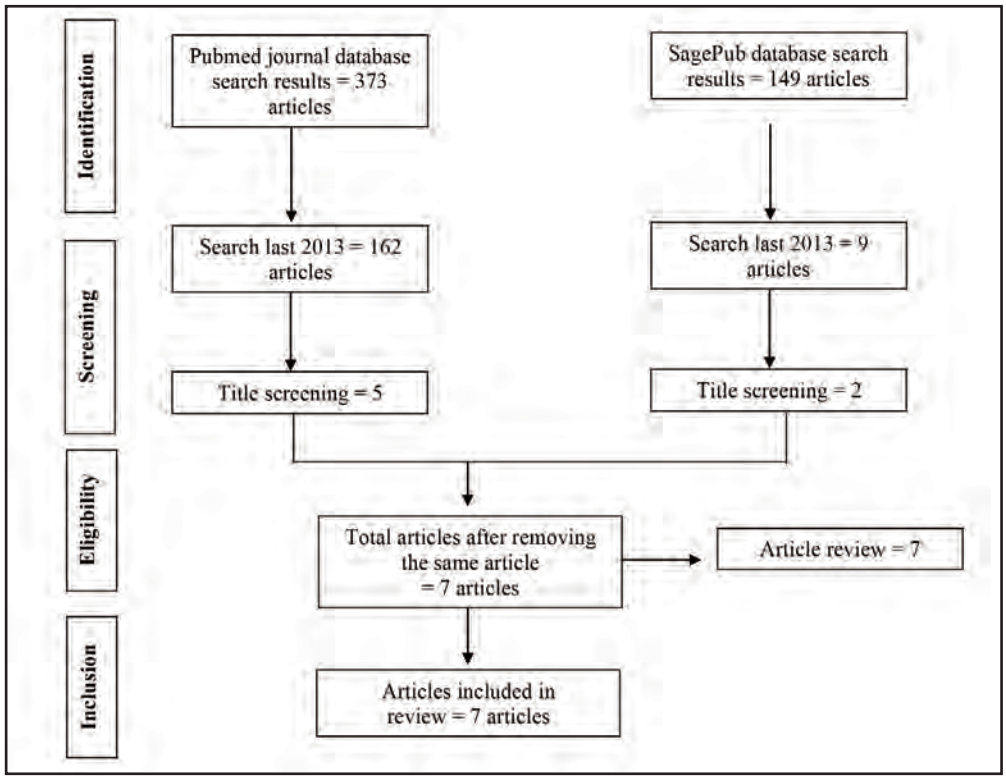


Fig. 1: Article search flowchart.

Fields]) OR ("prevalence of Hirschsprung"[All Fields]) OR ("Hirschsprung mechanism"[All Fields]) OR ("mechanism of Hirschsprung"[All Fields]) AND "treatment of Hirschsprung "[All Fields])) AND ("treatment"[All Fields]) AND (clinicaltrial[Filter])) used in searching the literature. [4]

Data Retrieval

After reading the abstract and the title, the authors examined the studies to determine the inclusion criteria, decided on previous research to use as sources and selected those for the article. The conclusions of this selected previous study followed the same trend, were written in English, and could not be seen in publication.[4]

For the systematic review, inclusion criteria were meticulously defined to narrow the results to only those studies pertinent to the search. Studies that did not meet these predefined criteria were excluded. The findings from the included studies will be subjected to thorough analysis. The following data were extracted: study titles, authors, publication dates, locations, study activities, and parameters.[4]

Quality Assessment and Data Synthesis

Each author reviews the titles and abstracts of the studies to determine their eligibility for further exploration. This review process aligns with the purpose of the systematic review, encompassing assessment and evaluation criteria. Previous studies that meet these criteria are included in the review.[4]

Statistical Analysis

Statistical analysis was conducted using the STATA 18th version. The "metathesis" command pooled the prevalence of single-proportion outcomes (i.e., pre-operative, post-operative, mortality, anastomosis stricture, anastomosis leakage, incontinence, and constipation in HAEC). The "proportion" command was used to compute the effect size of each study. Cochrane's Q and I2 tests added the pooled estimations variation and heterogeneity, respectively, with the p-value < 0.05 considered statistically significant. A fixed effect model was employed to calculate the pooled prevalence. The random effects model estimated the pooled prevalence if the heterogeneity was higher than 50%; otherwise, the fixed effect model was used. The sequentially omitting individual studies with the "metaninf" command were conducted using sensitivity analyses. The pooled mean estimate without it was not within the 95% CI bounds of the overall mean and was considered influential in the study. The result was visualised and evaluated publication bias by forest-plot using the "forest-plot" command.

This study was approved by the Faculty of Medicine and Health, Lambung Mangkurat University Research Ethics Commission N0: 032/KEPK-FKIK ULM/EC/III/2024.

RESULTS

Study Characteristics

In the database, there were 373 PubMed and 149 SagePub articles. In 2013, we found 162 PubMed and nine SagePub articles. We collected seven papers, five from PubMed and two from SagePub, that met the criteria.

Le-Nguyen et al.,[5] showed that other congenital malformations significantly risk developing pre-operative

HAEC (Odds Ratio, OR: 2.63; 95% Confidence Intervale, 95%CI: 1.11, 6.24)). Low-birth-weight patients with pre-operative HAEC (OR: 0.48; 95%CI: 0.25, 0.93). Post-operative intestinal obstruction is significantly associated with pre-operative HAEC (OR: 8.2, 95%CI: 3.18, 21.13). Patients with earlier pull-throughs did not have a lower risk of developing post-operative HAEC.

Parahita et al.,[6] showed that 100 patients (71 Soave vs. 29 Duhamel, p=0.62) had higher significant HAEC in the Duhamel than in the Soave group (28% vs. 10%, respectively, p=0.03). HAEC following pull-through had a substantial association with pre-operative enterocolitis (p=2.0×10-4), and the long-segment aganglionosis had a higher risk of HAEC to short-segment HSCR after Soave pull-through (p=0.015).

Chung et al.,[7] showed that the overall incidence of HAEC was 20.8% (n=20), and 65.0% (n=13) of HAEC occurred within the first year of operation. Three risk factors for HAEC were identified: 1) Presence of other major anomalies (OR: 1.43; 95%CI 1.12, 2.32); (2) Defunctioning stoma (OR: 2.28; 95%CI: 1.47, 3.23); (3) Extension of aganglionosis (OR: 1.89; 95%CI 1.05, 3.19). A significant association of HAEC with pre-operative defunctioning stoma (OR: 1.81, 95%CI 1.08, 3.22) and extension of aganglionosis to the sigmoid colon (OR: 1.91; 95%CI: 1.37, 2.98).

Adiguzel et al.[8] showed that vomiting and abdominal distension were the most common symptoms in 43 boys vs. seven girls at a mean age of 3 months (range 0 to 96 months). Barium enema, anorectal manometry and rectal biopsy were the most widely used; one patient underwent laparotomy with biopsy. The enteral feeding started at 2.2±1.1 days, and the follow-up period was 26.7±20.8 months. Perianal excoriation, enterocolitis, anastomotic stricture, soiling, recurrent constipation, prolapse of the pull-through colon, anastomosis leak and rectovestibular fistula were the post-operative complications.

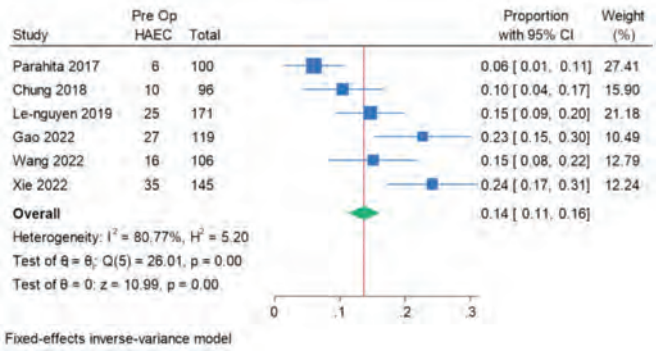
Gao et al.,[9] showed that 119/154 patients were followed up successfully. Post-operative, 53 patients had complications, and 66 patients had no complications. HAEC (33), faecal incontinence (22) and constipation (8) patients were complications. There were no significant differences in operative age, gender, pre-operative HAEC or haemoglobin levels between the Soave, modified Soave, laparoscopic and modified Duhamel operations. However, there were significant differences in the risk of post-operative HAEC in surgical procedures, serum albumin level, clinical classification and one- or two-stage operation (p<0.05).

Wang et al.,[10] showed that 106 patients were discharged 5-7 days after the operation, 150 (100-190) minutes of surgery median time and 6 (3-10) ml was the median bleeding volume. The post-operative daily defecation frequency was 4-11 times (short-term), 3-7 times (within 6 months), and 2-3 times (after 6-12 months). Anastomotic leakage in two, perianal dermatitis in 13, anastomotic stenosis in four, adhesive bowel obstruction in two, enterocolitis in 16, soiling in 11, and constipation recurrence in three cases were post-operative complications.

Xie et al.,[11] showed that pre- and post-operative HAEC incidence was 24.1% and 20.7%, respectively, in 145 patients. The post-operative HAEC in the first year after Soave occurred in more than 90% of patients. Long-segment aganglionosis was the risk factor of pre-operative HAEC (OR: 5.8; 95%CI: 2.4, 14.2) and was significantly associated with post-operative HAEC (OR: 4.2; 95%CI: 1.6, 10.8).

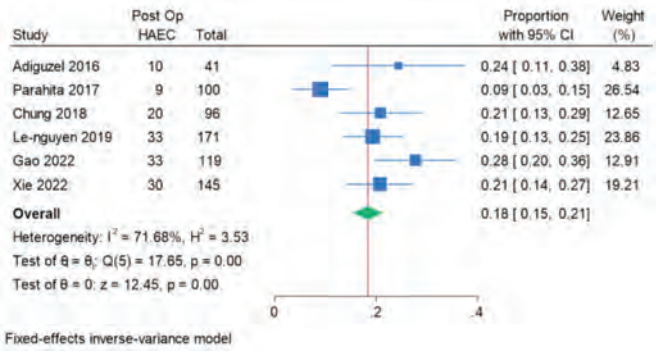
This meta-analysis of this pooled study examines the prevalence of a single proportion of outcomes in pre-operative, post-operative, mortality, anastomosis stricture, anastomosis leakage, incontinence and constipation in HAEC. The patients evaluated 737 for pre-operative HAEC, 672 for post-operative HAEC and 408 for HAEC mortality. Three hundred fifty-seven for anastomosis stricture and 212 for anastomosis leak.

Pre-operative Hirschsprung Associated Enterocolitis



A total of 119 among 737 patients experienced pre-operative HAEC. The overall pooled prevalence of pre-operative HAEC is 0.14 (95%CI: 0.11, 0.16), Cochran Q test, p=0, I^2=80.77%. One hundred twenty-two patients (14%) developed pre-operative HAEC. The 95% confidence interval (CI) of 0.11-0.16 indicates that the actual prevalence in the population is 11% and 16%. A p-value of 0 indicates significant heterogeneity and prevalence among different studies, which is more critical than expected. An I2 value of 80.77% suggests a very high level of heterogeneity.

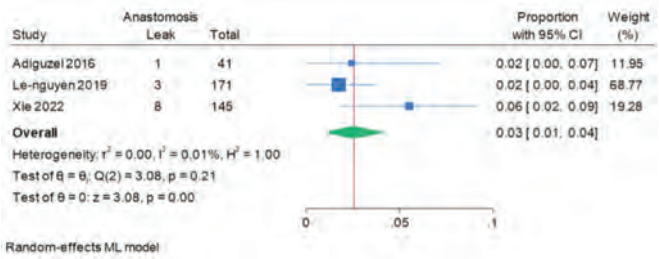
Post-operative Hirschsprung Associated Enterocolitis



A total of 135 among 672 patients experienced post-operative HAEC. The post-operative HAEC overall prevalence was 0.18 (95%CI: 0.15, 0.21), Cochran Q test, p=0, I^2=71.68%. One hundred thirty-six patients developed post-operation HAEC. The prevalence was 18% (95%CI: 0.15, 0.21), with a 95% probability that the actual prevalence in the population lies

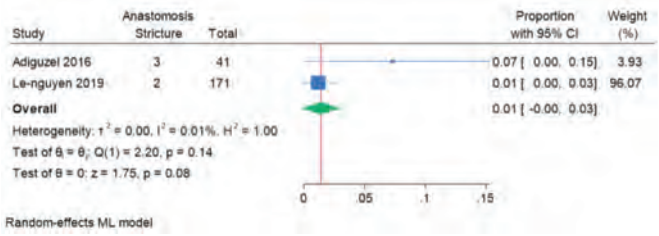
between 15% and 21%. A p-value of 0 indicates significant heterogeneity and prevalence among different studies, which is more critical than expected. I^2=71.68% suggests a high level of heterogeneity.

Anastomosis Leakage in HAEC



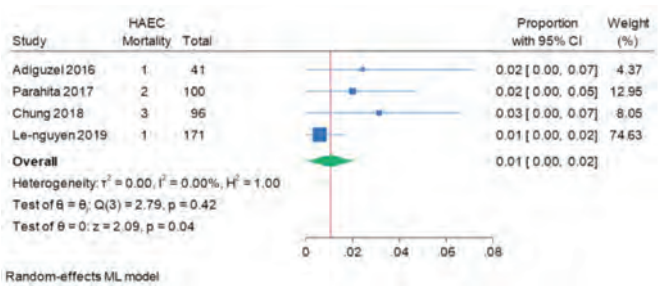
A total of 12 among 357 patients were assessed for anastomosis leak. The overall pooled prevalence is 0.03 (95%CI: 0.01, 0.04), using the Cochran Q test, p=0.21, and I^2=0.01%. Twelve patients were assessed for anastomosis leak. The prevalence is 3%, and a 95% probability that the prevalence of anastomosis leaks in the population between 1% and 4%. A p-value of 0.21 indicates no significant heterogeneity, and the variability in anastomosis leak prevalence among different studies is not more significant than expected. An I^2 value of 0.01% suggests virtually no observed heterogeneity, indicating that the prevalence rates of anastomosis leaks are highly consistent across different studies.

Anastomosis Stricture HAEC



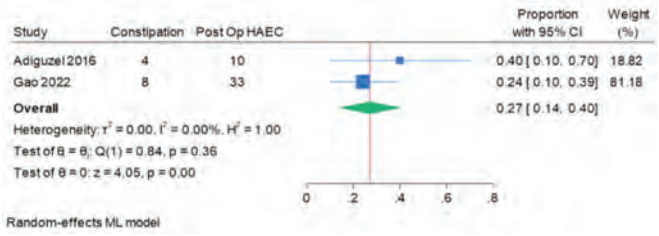
Anastomosis stricture was assessed in five out of 212 patients. The overall pooled prevalence is 0.01 (95%CI: 0.00, 0.01), Cochran Q test, p=0.14, I^2=0.01%. Five patients who experienced an anastomosis stricture were evaluated, and the prevalence is 1%. There is a 95% probability that the anastomosis stricture in the population lies between 0% and 1%. The negative lower bound of the CI was statistically effective at 0%. A p-value of 0.14 indicates no significant heterogeneity, and the variability in anastomosis stricture prevalence among different studies is insignificant. An I^2 value of 0.01% suggests no heterogeneity and is highly consistent across different studies.

HAEC Mortality



The mortality rate of HAEC was seven among 408 patients. The prevalence of HAEC mortality is 0.01 (95%CI: 0.00, 0.02), Cochran Q test, p=0.42, I^2=0%. The mortality prevalence is 1%, and there is a 95% probability that the population lies between 0% and 2%. The negative lower bound of the CI was statistically effective at 0%. A p-value of 0.42 indicates no significant heterogeneity. An I^2 value of 0% suggests no observed heterogeneity, indicating that the mortality rates are consistent across different studies.

Constipation of Post-operative HAEC



Constipation was assessed in 12 patients from 43 post-operative HAEC. The overall pooled prevalence is 0.27 (95%CI: 0.14, 0.40), Cochran Q test, p=0.36, I^2=0%. 12 out of 43 patients were assessed for constipation. The overall pooled prevalence is 27%. There is a 95% probability prevalence of constipation between 14% and 40% in this population. A -- value of 0.36 indicates no significant heterogeneity, and the variability in constipation prevalence among different studies is not more significant. An I^2 value of 0% suggests no observed heterogeneity, indicating that the prevalence rates are consistent across different studies.

Faecal Incontinence of Post-operative HAEC

Only one study assessed faecal defecation; 22 among 33 post-operative HAEC underwent faecal incontinence.[9]

Based on a meta-analysis of these five variables. The pre-and post-operative HAEC variables had Cochran Q test value, p=0, and heterogeneity test I^2 value >50%. The pooled prevalence was significant for the entire study and had heterogeneous data. Meanwhile, HAEC mortality, HAEC anastomosis leakage, and HAEC stricture anastomosis have a p>0.05 and an I^2 value <50%. The pooled prevalence is insignificant in the study and has low data heterogeneity.

DISCUSSION

The pathogenesis of HAEC remains poorly understood, but intestinal dysmotility, dysbiosis, impaired mucosal defence and intestinal barrier function play a significant role. Severe HAEC is a potentially lethal complication of HSCR. HAEC's classical variable clinical presentation is fever, lethargy, abdominal distention, foul-smelling, and explosive diarrhoea, which can occur pre- and post-operatively.[12]

Pre-operative Hirschsprung Associated Enterocolitis

Peristalsis disruption in the aganglionic segment, accumulation of faeces, decreased secretion of immunoglobulin-A and immature mucosa, abnormal mucin secretion, leukocyte dysfunction, and abnormal gut microbiota, which will result in pre-operative HAEC. Local and systemic inflammatory responses and long-segment

aganglionic facilitate the development of HAEC via bowel obstruction and increase intraluminal pressure, lead bacterial stasis, overgrowth, and translocation.[5] Microbiota dysbiosis is essential pathogenesis of HAEC.[13] Age at diagnosis correlates to HAEC incidence, and severe HAEC induces thymic involution, B lymphocyte suppression, and splenic lymphopenia. An immunity deficiency in Trisomy 21, significant cardiac anomaly induced pre-operative HAEC.[5] The age at surgery did not correlate with post-operative HAEC.[14]

Impaired mucosal defence in HSCR correlated with the role of secretory immunoglobulin A (sIgA). The transfer of sIgA across the gastrointestinal wall is impaired in HSCR despite increased sIgA levels in the lamina propria plasma cells and decreased in those with HAEC. The production and transport of intestinal mucins may be abnormal in HSCR and may have a potential role in the pathogenesis of HAEC. MUC-2 is the predominant mucin expressed in humans, and it can prevent bacterial translocation across the intestinal wall.[15]

Pre-operative incidence is 6-60%, while post-operative incidence is 25-42%. HAEC mortality is 5-50%, with higher prevalence in the neonatal period before definitive surgical correction. Mortality rates have declined to less than 1% after surgical and medical care. HAEC is reported as the HSCR symptom in up to 25% of infants. HAEC with bowel perforation in the neonatal period was the most common complication due to increased luminal pressure, transmural inflammation and vascular accidents leading to ischemia and perforation.[12]

Post-operative Hirschsprung Associated Enterocolitis

HAEC is a severe complication after an operation, including a pull-through. Laparotomy pull-through showed a lower HAEC incidence than trans-anal or laparoscopy.[5] The age at surgery did not correlate with post-operative HAEC.[8,14]

Diverting ostomy before corrective pull-through can be considered in the decompensating neonate with long-segment HCSR to lower failure rates of rectal wash-outs. Diversion ostomy may not entirely resolve HAEC, but it does improve the patient's clinical status and quality of life.[16] HAECs still develop after surgical correction or ostomy diversion, indicating the presence of an intrinsic defect at the level of the enteric nervous system that causes dysmotility,[15] prolonged dysbiosis, impaired mucosal defenses and bacterial overgrowth inside the mucosa.[13] Genetic factors, allergies can trigger post-operative HAEC.[10]

HAEC Anastomosis Leakage and Stricture

HAEC is a non-optimal condition and the main factor in anastomotic leakage. Immediate rectal wash-out, optimisation and diversion of the colostomy benefit recovery, and stage surgery are recommended.[9]

Anastomotic stenosis is commonly found in the distal cuff after mucosectomy8 and is treated with a dilation program. Post-operative stenosis increases the incidence of HAEC.[10]

HAEC Mortality

HAEC mortality is between 5-50% depending on the type of infection and age. Pre-operative HAEC in premature babies and major congenital abnormalities is a significant factor in mortality. Prophylactic enterostomy, adequate pull-through, rectal irrigation and close post-operative follow-up are recommendations in severe HAEC.[14]

Constipation and Fecal Incontinence of Post-operative HAEC

Faecal incontinence and constipation are necessary and common complications after a definitive pull-through. The incidence of constipation is relatively high after SOAVE. Mucosectomy to the peritoneal reflection and short cuff increases the risk of pelvic floor injury to nerves and internal sphincter. The sub-epithelium anal canal, colonic motility, anal sphincter and anorectal sensation are the main factors in faecal continence. TEPT reduces the risk of soiling compared to SOAVE.[9]

Limitation of the study was that it did not discuss the molecular biology of HAEC as an essential factor. The following HAEC further studies promising research areas, including intestinal microbiota analysis, personalisation therapy, stem cell study to restore the motor function of the aganglionic bowel, and treatments for colonic mucus barrier properties to prevent the onset of enterocolitis in HSCR.

CONCLUSION

Impairment of bowel motility in the aganglionic part and faecal accumulation causes dysbiosis microbiota, which are factors of pre-operative Hirschsprung's disease-associated enterocolitis (HAEC). Major congenital anomalies and low birth weight worsen pre-operative HAEC. Pre-operative HAEC can continue and affect post-operative. Constipation and Fecal Incontinence are still the main challenges after HSCR surgery.

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Identifying postoperative cognitive dysfunction after elective coronary artery bypass graft surgery in a tertiary centre in Malaysia

Siti Hajar Abdull Rahman, MRehabMed[1], Mazlina Mazlan, MRehabMed[1], Anwar Suhaimi, MRehabMed[1], Noorjahan Haneem Md Hashim, MAnaes[2]

[1]Department of Rehabilitation Medicine, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia, [2]Department of Anaesthesiology, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia

SUMMARY

Postoperative cognitive dysfunction (POCD) is a significant concern, with incidences reported up to 70% following cardiac surgery. Therefore, we aim to evaluate the incidence of POCD after elective coronary artery bypass graft (CABG) surgery at our single centre over a one-year period from August 2021 to July 2022. We included 34 patients in the study and conducted serial cognitive assessments up to three months post-surgery. Interestingly, our findings indicated an absence of POCD among patients who underwent elective CABG. Reasons contributing to this outcome are multifactorial, which may include the patients' younger age, higher educational levels, lack of pre-existing neurological disorders, meticulous intraoperative cerebral saturation monitoring, and the duration of aortic cross-clamp and cardiopulmonary bypass time.

INTRODUCTION

Postoperative cognitive dysfunction (POCD) is a decline in cognitive abilities following surgical procedures. It is particularly prevalent after cardiac surgery, with reported incidences ranging between 50-70%.[1] Identified risk factors for POCD encompass a variety of patient-related elements, intraoperative factors including hypotension, reduced haematocrit levels, and extended surgical duration, as well as anaesthesia-related factors like the depth and duration of anaesthesia, ventilation duration in the intensive care unit, and types of anaesthetic medications, have also been recognized.[2]

Malaysia has a significant prevalence of cardiac disease contributing to 17% of deaths in 2020,[3] and thus, coronary artery bypass graft (CABG) surgery is frequently performed in various centres, including public and private hospitals. Among these, the University Malaya Medical Centre (UMMC) stands out as a public tertiary centre equipped with cardiologists, cardiothoracic surgeons, a dedicated anaesthesia team and a cardiac rehabilitation team.

Despite the known global incidence of POCD, there has been a lack of specific data from Malaysia. Therefore, this study was conducted to investigate the incidence and outcomes of POCD following elective CABG at UMMC. This is also the first report from Malaysia and this paper highlights the utilisation of multiple neurocognitive tools and stringent criteria to ascertain the incidence of POCD.

MATERIALS AND METHODS

We conducted a prospective study of all adults undergoing elective CABG surgery at UMMC from August 2021 to July 2022, with approval from the Medical Research Ethics Committee. Ten age-matched patients with ischemic heart disease were selected as controls from the Cardiac Rehabilitation Clinic. Exclusion criteria for both groups included pre-existing cognitive impairment, visual, hearing, or language disabilities, alcohol or recreational drug dependence and unwillingness to return for postoperative cognitive assessment.

Consenting patients underwent a baseline examination one day before surgery, followed by evaluations at 6 weeks and 3 months post-surgery, utilising a combination of standardised neurocognitive tools. The tools were Montreal Cognitive Assessment test, Trail Making Test (Parts A and B), Digit Symbol Substitution Test and Digit Span Test. The incidence of POCD was determined using the Z-score method, adapted from previous ISPOCD studies as described in the systemic review.[4] POCD was defined if an individual's Z-score in two or more cognitive tests, or a combined Z-score, was >-2. The control group also underwent the assessments at similar timeline.

Data collected for potential POCD risk factors included the patient's demographic data, intraoperative data, postoperative data, and medications used during intraoperative and postoperative periods. This numbers of patients who underwent bispectral index (BIS)guided anaesthesia and patient state index (PSI)-guided anaesthesia were recorded, along with the frequency of intraoperative complications. Numerical data was reported as mean, while categorical data was presented as frequency and percentage.

RESULTS

In this study, 34 patients (94.1% male) with an average age of 57.7±9.6 years completed all cognitive assessments. Demographic details are summarised in Table I, revealing that majority of patients presented with multiple

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Corresponding Author: Prof Dr Mazlina Mazlan
Email: drmazlina@gmail.com; mazlinamazlan@ummc.edu.my

Table I: The demographic characteristics of the patients.

Patient characteristic	Number of patients, n (%)
Age, mean ± SD	57.7±9.6
Gender	
Males	32 (94.1)
Females	2 (5.9)
Race	
Malay	17 (50.0)
Chinese	12 (35.3)
Indian	5 (14.7)
Education Level	
Primary	8 (2.9)
Secondary	26 (61.8)
Tertiary	17 (35.3)
Current comorbidities	
Dyslipidaemia	32 (94.1)
Hypertension	26 (76.5)
Diabetes mellitus	20 (58.8)
Kidney disease	4 (11.8)
Peripheral vascular disease	0 (0)
Liver disease	0 (0)
Smoking status	13 (38.2)
Alcohol consumption	0 (0)

Table II: Intraoperative and postoperative data of the patients.

Parameters	Number of patients, n (%) *mean±SD
Surgical data	
Surgery duration (hours)*	5.5±1.2
Aortic cross clamp time (min)*	96.9±37.1
Cardiopulmonary bypass time (min)*	139.2±50
BIS-guided anaesthesia	14 (42.4)
PSI-guided anaesthesia	19 (57.6)
Intraoperative complications	
Cerebral desaturation	10 (29.4)
Hypotension	13 (38.2)
Homologous blood transfusion	6 (17.6)
Postoperative data	
Mechanical ventilation (days)*	1 ± 0.2
Length of ICU stay (days)*	4.5 ± 2.1
Length of hospital stay (days)*	9.9 ± 4.5

*Values are presented as mean±SD
BIS = Bispectral Index; PSI = Patient State Index

Table III: Mean scores of the individual cognitive tests at baseline (1 day before surgery), 6 weeks and 3 months after surgery for the case (patients underwent CABG surgery) and comparison with the control group.

	Baseline		6 weeks after surgery		3 months after surgery	
	Case n=34	Control n=10	Case n=34	Control n=10	Case n=34	Control n=10
MoCA	25.6	24.9	26.5	26.1	26.9	26.4
TMT-A (seconds)	45	60.8	41.8	48.2	37.1	41.3
TMT-B (seconds)	82.1	104.4	74.5	99.4	71	79.4
DST-forward	6.8	6.2	6.5	6.5	7.1	7.1
DST-reverse	3.4	3.4	3.3	2.8	3.6	3.4
DSST	28.3	31.9	31.5	32.7	34.0	35.1

MoCA = Montreal cognitive test, TMT-A = Trail making test-A, TMT-B = Trail making Test-B, DST = Digit span test, DSST = Digit symbol substitution test

Table IV: Cumulative Z-score of the 25 patients who completed the assessment at 6 weeks and 3 months after surgery.

Patient	Cumulative Z-score		Patient	Cumulative Z-score	
	6 weeks	3 months		6 weeks	3 months
1	0.045	-0.092	13	0.055	0.125
2	-0.070	-0.066	14	0.011	0.035
3	-0.061	0.035	15	-0.029	-0.045
4	-0.053	-0.048	16	0.081	0.089
5	0.095	0.029	17	0.011	-0.009
6	-0.099	-0.028	18	-0.045	0.021
7	0.049	-0.021	19	-0.113	-0.066
8	0.089	-0.031	20	0.069	0.009
9	0.006	-0.034	21	0.024	0.015
10	0.054	0.029	22	0.004	0.029
11	-0.076	-0.035	23	-0.037	-0.026
12	-0.062	-0.049	24	-0.058	-0.065
			25	0.050	-0.063

comorbidities. There was no statistically significant difference when compared with the control group.

Table II detailed the intraoperative and postoperative data, including the mean surgery duration, aortic cross-clamp (ACC) time, and cardiopulmonary bypass (CPB) time. All complications were resolved immediately during the surgery.

Cognitive test scores post-surgery showed no significant decline from baseline levels, as detailed in Table III. Among the participants, none met the POCD criteria, therefore, no incidence of POCD was observed at 6 weeks and 3 months post-surgery, including in the patients who experienced cerebral desaturation during surgery.

In this study, remifentanil, sevoflurane, midazolam and morphine were the most frequently used medications during CABG surgery, while dexmedetomidine, fentanyl and tramadol were commonly administered postoperatively in the ICU.

DISCUSSION

In the current study, we found no incidence of POCD among patients undergoing elective CABG surgery at UMMC. This result could be attributed to multiple factors. The patients in our centre were comparatively younger, and free from neurological diseases or alcohol abuse, contrasting with previous literature which identified old age (above 60 years), pre-existing neurological disease and alcohol abuse as risk factors for POCD.

Notwithstanding, there are limitations in our sample size representing the local population. The small sample size was inevitable due to the reduction in CABG procedures performed during the COVID-19 pandemic, coupled with a high dropout rate for follow-up appointments. While the mean age in our study aligns with the younger demographic reported in the acute coronary syndrome registry,[5] a larger sample size would provide more generalisability and confirm the broader applicability of our findings.

The other mechanism attributed for POCD development is cerebral hypoperfusion and micro emboli caused by cardiopulmonary bypass. Although it remains under debate, studies suggest that CPB exceeding 180 minutes and ACC exceeding 150 minutes are associated with adverse outcomes.[6,7] Click or tap here to enter text.In our study, both CPB and ACC times remained below these thresholds. In our practice, NIRS is also utilised to monitor intraoperative cerebral regional saturation of all the patients, with a standardised protocol in place for addressing desaturation, as suggested in the literature.[8]

The selection of medications could also influence POCD outcomes. Remifentanil, an ultrashort-acting drug, has minimal impact on cognition. Postoperatively, dexmedetomidine was used for sedation and analgesia in the ICU, which, according to recent studies, may reduce POCD incidence and offers neuroprotective effects.[9] Despite the use of long-acting medications (morphine and midazolam) and sevoflurane, the use of processed EEG (BIS and PSI) to monitor depth of anaesthesia to guide drug titration may contribute to the reduction of POCD.

The challenge in POCD studies lies in the lack of universally accepted definitions and criteria. Our study adhered to the recommendations by the Perioperative Cognition Nomenclature Working Group[10] to avoid cognitive assessments within the initial 30 days post-surgery, allowing sufficient time for the dissipation of acute effects from drugs, anaesthesia, pain, and emotional stress. The neurocognitive tests employed and the diagnostic criteria for POCD were adapted from large scale ISPOCD studies.[4] All the tests are effective in detecting domains affected by POCD, such as executive function, processing speed, memory, and attention. Additionally, the use of a standard anaesthesia technique in a single centre helped reduce variability in the approaches examined.

CONCLUSION

Elective coronary artery bypass graft (CABG) surgery is not significantly associated with cognitive dysfunction, given the detailed preoperative preparation and the controlled setting of the planned procedure. Further studies with larger sample sizes and multi-centre recruitment are recommended. Assessing patients at longer follow-up intervals may provide additional insights into the potential delayed onset of cognitive decline.

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Assessing informal caregiver burden as well as knowledge on positioning and feeding of stroke patients in a tertiary hospital in Kelantan, Malaysia

Al Mizan Mustapa, MMed[1], Sharif Ahmad, MMed[1], Muhammad Hafiz Hanafi, MMed[2,4], Nazri Mustaffa, PhD[3,4]

[1]Faculty of Medicine, Universiti Sultan Zainal Abidin, Medical Campus, Kuala Terengganu, Terengganu, Malaysia, [2]Rehabilitation Medicine Unit, Universiti Sains Malaysia, Jalan Raja Perempuan Zainab 2, Kubang Kerian, Kelantan, Malaysia, [3]Department of Medicine, School of Medical Sciences, Universiti Sains Malaysia, Jalan Raja Perempuan Zainab 2, Kubang Kerian, Kelantan, Malaysia, [4]Hospital Universiti Sains Malaysia, Jalan Raja Perempuan Zainab 2, Kubang Kerian, Kelantan, Malaysia

SUMMARY

A significant proportion of stroke patients in Malaysia are supported by informal caregivers who often lack sufficient training. This lack of preparation contributes to an escalation in caregiver burden. A cross-sectional study was conducted using Caregiving Knowledge Questionnaire (CKQ-my) and Zarit Burden Interview (ZBI) with convenient sampling. The findings revealed that caregivers had limited knowledge regarding proper positioning, and most of them reported experiencing mild burden. Multiple logistic regression analysis showed that informal caregivers who were also the primary caregivers for severe stroke patients experienced a higher burden. Recognising and understanding the factors that contribute to caregiver burden in stroke cases is essential for developing effective programs to improve the quality of life for both stroke survivors and their informal caregivers.

KEYWORDS:
Stroke, caregiver, positioning, feeding, burden

INTRODUCTION

Approximately 54% of stroke patients in Malaysia suffer from physical and cognitive disabilities upon discharge from hospital.[1] Therefore, they require long-term care and varying degrees of assistance to perform daily activities after discharge. In Malaysia, most stroke care is provided by informal caregivers such as family members of patients.[2] Without proper knowledge, the application of poor or wrong techniques when caring for stroke patients may lead to secondary complications such as pressure ulcers, aspiration pneumonia and shoulder pains.[3]

There is a need for more extensive information regarding the background knowledge regarding such issues among stroke caregivers in Malaysia. Additionally, there is no Malaysian data on the correlation between stroke care knowledge and caregiver burden. Measuring the level of this knowledge among caregivers at our centre, focusing on stroke patients' positioning and feeding, will allow us to explore the level of their understanding regarding stroke patients' care. Knowing the correlation between knowledge and caregiver burden will alert us to the importance of educating caregivers. Consequently, we plan to use the findings of this study to design caregivers' education programs to benefit our local population.

MATERIALS AND METHODS

A cross-sectional study was conducted using convenient sampling involving informal caregivers of stroke patients who attended the Rehabilitation Unit of Hospital Universiti Sains Malaysia from December 2021 to February 2022. This study was a questionnaire-based research that consisted of three questionnaires: a proforma capturing caregiver demographic data; a validated questionnaire, CKQ – My that assessed knowledge on positioning (28 items) and feeding (6 items),[4] and the Zarit Burden Interview (ZBI)[5] which measured caregiver burden (22 items). The 'patient positioning' subscale has a cut-off score of 20 to differentiate between good and poor knowledge, while the 'feeding' subscale has a cut-off score of 10. Respondents experiencing caregiver burden may be classified as having mild, moderate or severe burden.

Inclusion criteria were adult informal caregivers aged more than 18 years old and taking care of stroke patients for more than three months. Exclusion criteria were caregivers who could not complete the questionnaire due to illiteracy and language barriers. Sample size was calculated using a web-based sample size calculator (Ariffin, W.N. 2020).

Statistical analyses were performed using SPSS version 26. Descriptive analysis was used to characterise subjects' sociodemographic characteristics and knowledge scores. Based on their normality distribution, numerical data were presented as mean (SD) or median (IQR). Categorical data were presented as frequency (percentage). Associated factors of caregiver burden were analysed using single and multiple logistic regression. A two-tailed $p<0.05$ was considered statistically significant for all analyses.

Ethical approval was obtained from the Human Research and Ethics Committee, Universiti Sains Malaysia (USM/JEPeM/21120839).

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Corresponding Author: Dr Nazri Mustaffa
Email: nazri.mustaffa@usm.my

Table I: Score of knowledge in positioning and feeding among informal caregivers of stroke patients in Hospital Universiti Sains Malaysia.

Variables	Total (%)
Knowledge positioning (Range of score 0 – 29)	
Good (≥20)	10 (13.2)
Poor (<20)	66 (86.8)
Score of knowledge positioning	15.88 (3.74)*
Knowledge feeding (range of score 0 – 19)	
Good (≥10)	45 (100)
Poor (<10)	0 (0)
Score of knowledge feeding	15.69 (2.29)*

*Mean (SD)

Table II: Burden score among informal caregivers of stroke patients in Hospital Universiti Sains Malaysia (n=76).

Variables	Total (%)
Burden score	
No burden	39 (51.3)
Mild to moderate	32 (42.1)
Moderate to severe	5 (6.6)
Very severe	0 (0)

Table III: Sociodemographic factors for caregivers' burden among informal caregivers of stroke patients in Hospital Universiti Sains Malaysia using simple and multiple logistic regression model (n=76).

Variables	Simple logistic regression			Multiple logistic regressiona		
	(b)	Crude OR (95% CI)a	p-value	(b)	Adjusted OR (95% CI)a	p-value
Stroke Severity (MRS)						
1-3	0	1	0.065	0	1	0.032
4-5	0.87	2.39		1.59	4.9 (1.5, 15.96)	
Type of caregiver						
Primary	0	1	<0.001	0	0.06 (0.02,0.247)	0.001
Non-primary	-2.26	0.1		-2.72		

RESULTS

Seventy-six participants were enrolled in this study. The mean age of caregivers was 44.0 years, while the mean age of patients was 63.3 years. The majority of caregivers were female (57.9%). In terms of ethnicity, most were Malay (93.4%), followed by Chinese (2.6%) and Indian (3.9%). Nearly half had tertiary education (48.7%) and high household income (40.8%). Around half were children's caregivers (53.9%), and around a third were spousal caregivers (32.9%). Only a small percentage (1.3%) had received extra training. The most common duration of diagnosis was less than one year (51.3%).

The CKQ-My questionnaire component on knowledge regarding proper positioning consists of 28 items where respondents are required to indicate the correct pictures of patient positioning. Results show that most caregivers for this study have a poor (86.8%) rather than a good knowledge of proper positioning (13.25%). The mean score for positioning was 15.88, with a standard deviation of 3.74. Meanwhile CKQ-My regarding feeding consists of six questions pertaining to knowledge on proper Ryle's tube patient feeding. Respondents need to select the correct answer for each question. In our study, all participants had good knowledge of feeding techniques, with a mean score of 15.69 and a standard deviation of 2.29. Approximately half (48.7%) of participants had a burden, while the rest (51.3%) had no burden. Most caregivers had a mild to moderate burden (42.1%), followed by (6.6%) with a moderate to severe burden, and there were no caregivers with a very severe burden in this study.

Multiple linear regression showed that informal caregivers of severely dependent stroke patients (MRS 4-5) increased the risk of experiencing burden by 4.9-fold as compared to those taking care of independent to moderately dependent stroke patients (Adjusted Odds Ratio, aOR: 4.9; 95% Confidence Intervals, 95%CI: 1.5, 15.96), Primary informal caregivers of stroke patients had an increased risk of experiencing burden by 16-fold as compared to non-primary caregivers (aOR: 0.06; 95%CI: 0.02, 0.247).

DISCUSSION

This study found that the majority (86.8%) of informal caregivers of stroke patients had poor knowledge of positioning, which is consistent with a previous Malaysian study.[6] A similar result was also observed in an Indian study.[7] These findings indicated that most informal caregivers of stroke patients need to obtain prior knowledge on how to take care of stroke patients. Thus, they should be educated and appropriately trained. This result differs from a study

conducted among formal caregivers who showed higher levels of good knowledge. Knowledge may be improved by giving the caregiver more specific and frequent training, as several studies from Thailand[8,9] and the US[7,8] have shown regular and proper training from rehabilitation experts will increase caregivers' knowledge and improve patient outcomes.[3]

The ZBI is used as a survey to assess burden, as it considers various aspects of life such as health, finances, social life, emotional well-being, personal life, and interpersonal relationships. Our study discovered that the severity of stroke, as measured by the Modified Rankin Scale (MRS), and the category of caregivers (primary vs. non-primary caregivers) were the only significant risk factors for caregiver burden in this study. Otherwise, no other significant factors were found for caregiver burden, including caregiving knowledge. The more dependent the patients, the more tasks for the caregivers and the more hours of care required, eventually increasing their burden. Therefore, we proposed that the functional disability of stroke patients is the primary determinant factor of the caregivers' burden in the present study.[10,11]

Primary caregivers had more tasks than non-primary caregivers, leading to longer time spent caring for the patients, resulting in a higher burden on caregivers. Various literature have linked the duration of caring (hours) with caregivers' burden.[11-13]

However, our study failed to find other associated factors for caregiver burden. Our result shows that the knowledge of burden and non-burden caregivers could be improved. Additional studies should be conducted with a larger number of participants to assess the correlation between all burden categories and caregiver knowledge.

The results for knowledge and caregiver burden in this study are consistent with other recent papers despite a small sample size. However, it is important to note that this study used a self-reporting method, which is vulnerable to social desirability bias and may be influenced by respondents' honesty, understanding, and reflective ability. A recommendation is to include a larger number of subjects to better understand association between knowledge and caregiver burden. Additionally, conducting a multicentre study would be ideal, as it would provide a more representative assessment of the burden faced by caregivers who manage patients with stroke.

CONCLUSION

This brief study on informal caregivers of patients with stroke revealed a need for education on knowledge regarding proper positioning techniques. These results underscore the significance of caregiver training and support programs as essential resources for caregivers to enhance their comprehension of caring for patients with stroke. Additionally, our findings highlight the fact that primary informal caregivers and those coping with patients that have a more severe stroke are particularly susceptible to experiencing high levels of burden.

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SHORT COMMUNICATION

Technical tips, diagnostic yield and safety of endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy

Chun Ian Soo, FCCP[1], Nai-Chien Huan, FCCP[2], Sze Shyang Kho, MRCP[3]

[1]Division of Respiratory Medicine, Department of Medicine, University Malaya Medical Center, University Malaya, Lembah Pantai, Kuala Lumpur, Malaysia, [2]Respiratory Department, Queen Elizabeth Hospital, Jalan Penampang, Kota Kinabalu, Sabah, Malaysia, [3]Division of Respiratory Medicine, Department of Medicine, Sarawak General Hospital, Jalan Hospital, Kuching, Sarawak, Malaysia

SUMMARY

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is commonly used to diagnose and stage lung cancer. In clinical practice, cytology specimens from EBUS-TBNA may be low in cellularity, especially with necrotic lesions. Endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy (EBUS-TBMC) has recently become the preferred method for obtaining histology biopsy. This retrospective cohort study analysed the first 30 patients who have undergone EBUS-TBMC in a tertiary centre in Malaysia. EBUS-TBMC demonstrated a high diagnostic yield and good safety profile. All the samples obtained were adequate for the detection of driver alteration by next-generation sequencing.

INTRODUCTION

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is an established technique for diagnosing and staging of lung cancer.[1,2] In clinical practice, cytology specimens from EBUS-TBNA may be low in cellularity,[3] especially with necrotic lesions. This hinders further ancillary diagnostic techniques such as immunohistochemistry, flow cytometry, molecular analysis and detection of driver alteration by next-generation sequencing (NGS) in non-small-cell lung carcinoma (NSCLC). Endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy (EBUS-TBMC) is a new technique that has recently gained popularity for obtaining histology specimens. The EBUS-TBMC procedure involves a flexible cryoprobe that is precisely inserted into the same needle track (NT) created from EBUS-TBNA. A cryobiopsy can be extracted from the lesion through rapid freezing of the cryoprobe. After withdrawing the probe en-bloc with the EBUS-bronchoscope, the cryoprobe tip is submerged in saline to thaw and release the specimen.[4]

MATERIALS AND METHODS

We conducted a retrospective cohort analysis on patients who have undergone EBUS-TBMC following EBUS-TBNA at a single tertiary centre between July to December 2022. The data required for this study was traced using the hospital's electronic medical records. The EBUS-TBNA and EBUS-TBMC were performed by a European Respiratory Society-accredited EBUS-bronchoscopist. The procedure was conducted under conscious sedation or general anaesthesia, following established guidelines.[5] During EBUS-TBNA, four passes were performed for each lesion. Samples were processed in cytology smears and cell blocks. For EBUS-TBMC, a 1.1-mm flexible cryoprobe (Erbecryo 20402-401, Tubingen, Germany) was used. The frozen biopsy tissues were fixed in formalin. The choice of needle size (19, 21 or 22-gauge) and the number of cryo-activations per biopsy was determined by the operator's discretion. A positive diagnostic yield is considered when a definitive histology diagnosis is obtained from the cryobiopsy specimen.

RESULTS

Data from 30 patients were analysed. Twenty-eight patients underwent EBUS-TBNA followed by EBUS-TBMC, while two patients had EBUS-TBMC only. EBUS-TBMC was performed on 36 lesions. Insertion of the cryoprobe was unsuccessful for two lesions. EBUS-TBMC was performed on a single lesion in 83.4% (25 patients) of cases. 80% of the procedures were conducted under conscious sedation. On average, three EBUS-TBMC were conducted per patient (interquartile range [IQR]: 3-4), with a cryo-activation time of 6 seconds (IQR: 6-8). 83.3% (30 biopsies) targeted lymph nodes, while the remaining 16.7% (six biopsies) targeted masses.

The median cumulative tissue size retrieved from EBUS-TBMC was 6 mm (IQR: 5-8). 86.1% (31 lesions) had a positive histology yield, contributing to an overall diagnostic yield of 83.3% (25 cases). The patients' baseline characteristics and a comparison between the diagnostic yields of EBUS-TBNA and EBUS-TBMC are shown in Table I, respectively. In terms of safety, mild bleeding after EBUS-TBMC occurred in six cases (16.7%). No incidences of pneumothorax, pneumomediastinum, mediastinitis or other complications were observed.

DISCUSSION

To perform EBUS-TBMC, the main challenge is the insertion of the cryoprobe into the target lesion. As the tip of the probe is blunt, creating a good NT during EBUS-TBNA is important. It is crucial to avoid the bronchial cartilages, and the needle agitations should follow a consistent trajectory with every needle pass. The hyperechoic sonographic feature from each needle pass serves as a guide for the bronchoscopist to locate

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Corresponding Author: Chun Ian Soo
Email: scianray@gmail.com

Table I: Baseline Characteristics and Diagnostic yield of EBUS-TBNA versus EBUS-TBMC

Baseline characteristics			
Variable	Number (%)		
Total number of patients	30		
Number of patients undergone EBUS-TBNA	28		
Number of patients undergone EBUS-TBMC	30		
Sex			
Male	19 (63.3)		
Female	11 (36.7)		
Type of sedation			
Conscious sedation	24 (80.0)		
General anaesthesia	6 (20.0)		
Number of lesions attempted EBUS-TBMC/patient			
1	25(83.4)		
2	4(13.3)		
3	1(3.3)		
Number of EBUS-TBMC/lesion			
2	7 (19.4)		
3	12 (33.3)		
4	11 (30.6)		
5	4 (11.1)		
6	2 (5.6)		
EBUS-TBMC activation time			
<7 (3-6sec)	21 (58.3)		
≥7 (7-10 sec)	15 (41.7)		
Type of lesions			
Lymph nodes	30 (83.3)		
Mass	6 (16.7)		
Lymph nodes (station)			
4R	9 (30.0)		
11/10R	2 (6.7)		
7	16 (53.4)		
11/10L	1 (3.3)		
4L	1 (3.3)		
Others	1 (3.3)		
Mass			
Paratracheal mass	2 (33.3)		
Posterior tracheal lesion	2 (33.3)		
Hilar mass	2 (33.3)		
Overall diagnostic yield	25 (83.3)		
Diagnostic yield of EBUS-TBNA vs. EBUS-TBMC			
	TBNA (n = 28)	TBMC (n = 30)	p value
Overall diagnostic yield	20 (71.4)	25 (83.3)	0.28
NSCLC	15 (75.0)	15 (60.0)	0.29
Others	5 (25.0)	10 (40.0)	

EBUS-TBNA: Endobronchial ultrasound guided transbronchial needle aspiration; EBUS-TBMC: Endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy

the NT. If the hyperechoic sonographic feature is not well seen, the bronchoscopist must rely on precise recognition of the surrounding anatomical landmarks to trace and identify the NT. A pictorial narrative of the EBUS-TBMC procedure is shown in Figure 1. The use of a high-frequency needle knife to create a NT is not necessary, although it may potentially reduce the overall procedural time.[6] In terms of location, performing EBUS-TBMC on lesions situated at the hilar and posterior trachea can be challenging. This is due to the limitations of the EBUS scope in reaching lesions at an acute angle and the absence of a rotator function at the insertion tube of the EBUS scope.

Incoperating EBUS-TBMC to EBUS-TBNA but may have added value in the diagnosis of benign mediastinal lesions, lymphomas, and other rare malignancies.[6-9] In our study, EBUS-TBMC recorded an overall non-significant higher diagnostic yield when compared to EBUS-TBNA. A more important clinical implication lies in the ability of EBUS-TBMC to provide sufficient tissue for complete molecular profiling in the treatment of NSCLC.[9] EBUS-TBMC demonstrated similar diagnostic yield to EBUS-TBNA in 15 cases of NSCLC and the histology specimens from EBUS-TBMC were preferred over cytology cell blocks for NGS testing in all patients. Other conditions diagnosed by EBUS-TBMC (missed by EBUS-TBNA) included two cases of sarcoidosis, one case of mediastinal lymphoma, a sarcoid-like reaction, and a tuberculous mediastinal lymphadenopathy. However, intra-lesion necrosis, heterogeneity or fibrotic lymph nodes may still limit tissue availability, resulting in a potential reduction in diagnostic yield.[10] This is evident in our study where EBUS-TBMC was not able to establish a diagnosis in three cases

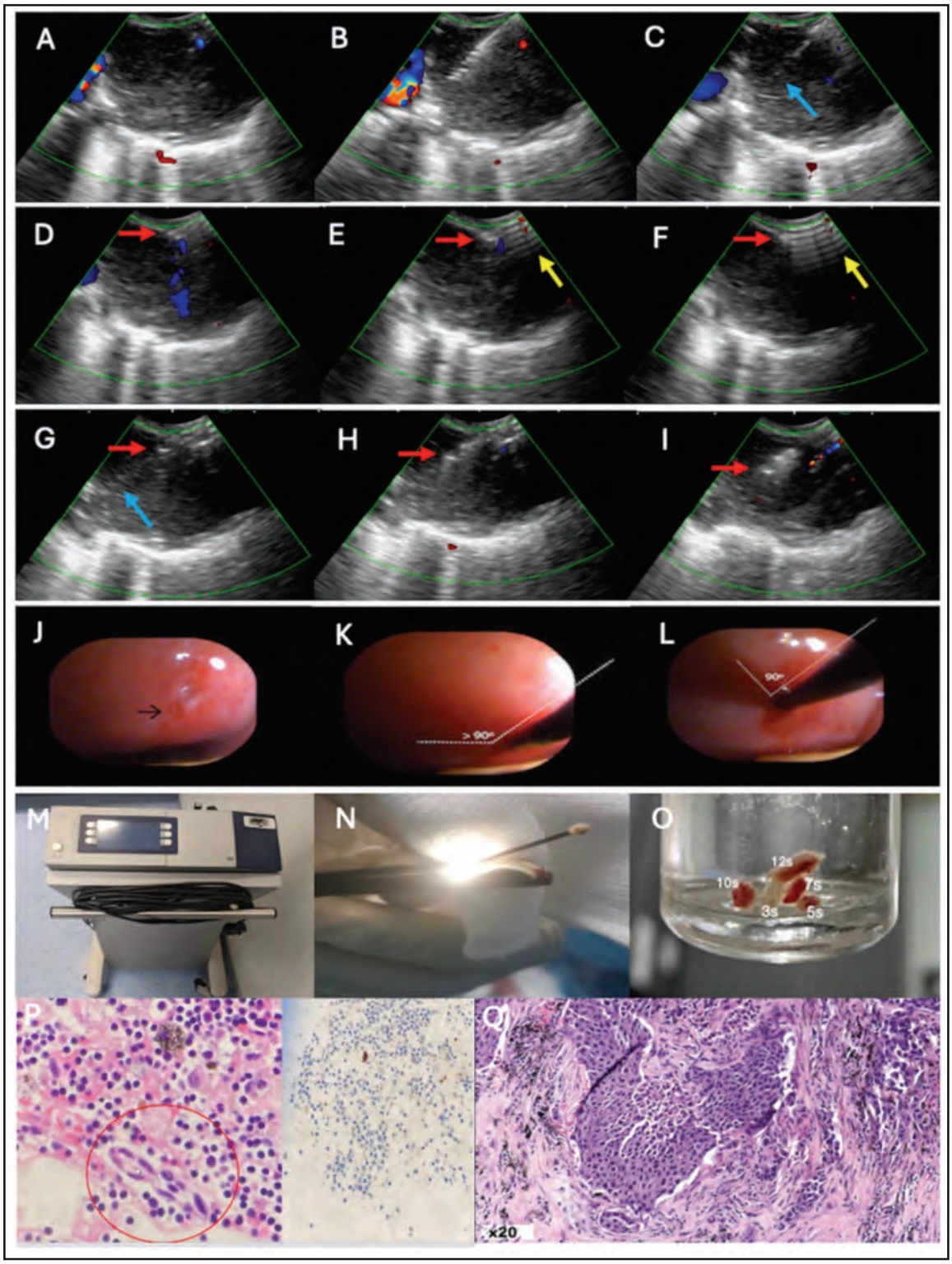

Fig. 1: Pictorial narrative of the EBUS-TBMC procedure.
(A) A lymph node seen on EBUS with colour doppler, (B) An EBUS-TBNA needle is inserted into the lymph node, (C) A faint hyperechoic needle track (blue arrow) after EBUS-TBNA passes, (D,E,F) Failed insertion of the cryoprobe (red arrow) into the needle track. Ultrasound artifact from the cryoprobe is seen (yellow arrow), (G,H,I) Successful insertion of the cryoprobe (red arrow) into the needle track (blue arrow), (J) Entry point after a 22 gauge TBNA needle puncture (black arrow) on endoscopic view, (K) Avoiding entry of cryoprobe at obtuse angle, (L) Maintain perpendicular entry of cryoprobe, (M) A cryosurgery unit, (N) Frozen biopsy at the tip of the cryoprobe, (O) Histology specimen obtained at different cryo-activation time, (P) A small cluster of atypical cells seen on cytology cell block obtained from EBUS-TBNA (red circle) (x 40 magnification), (Q) Histology sample from EBUS-TBMC shows stroma infiltrated by malignant cells which form solid nests. Both squamoid and glandular differentiation are seen. Findings are consistent with poorly differentiated adenosquamous carcinoma (x20 magnification)

involving lesions with extensive necrosis. Poor tolerance to procedure and imprecise biopsy location resulted in negative diagnostic yield in the remaining two cases.

EBUS-TBMC has manageable and self-limiting complications.[6-9] Rare incidents of minor bleeding, pneumothorax and pneumomediastinum have been reported.[6] We did not encounter any complications apart from six cases of minor bleeding from the NT which was self-limiting.

While EBUS-TBMC appears promising, one significant drawback is the cost of the single-used flexible cryoprobe. Maturu et al.,[8] proposed a diagnostic algorithm, utilizing EBUS-TBNC selectively when rapid on-site evaluation (ROSE) yielded inconclusive results. This approach led to an additional diagnostic yield of 43.7%[8] Hence, the bronchoscopist needs to necessitate careful consideration and justification of its use.

CONCLUSION

EBUS-TBMC potentially offers a higher diagnostic yield than EBUS-TBNA. It has the advantage of minimising the need for repeat biopsies and delay in diagnosis, which could translate into overall cost savings. Further prospective studies are needed to validate these findings before permanently adopting this new procedure into our clinical practice.

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Conception and design: Chun Ian Soo and Nai-Chien Huan; Provision of study materials: All authors; Collection and acquisition of data: Chun Ian Soo; Data analysis and interpretation: Chun Ian Soo; Manuscript writing: All authors; Final approval of manuscript: All authors.

CONFLICT OF INTEREST

The authors declare no conflict of interest relevant to this article. This study has been approved by the Medical Research Ethics Committee, Universiti Malaya Medical Centre (MECID. No: 2024418-13645)

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COMMENTARY

Obtaining assent for research involving children in Malaysia: a position statement from the Academy of Medicine of Malaysia College of Paediatrics

Erwin Jiayuan Khoo, FRCPCH[1,2], Bin Alwi Zilfalil, PhD[3], Meow Keong Thong, MD[4], Sin Chuen Yong, FRCPCH[5], Seok Chiong Chee, MMed(Paeds)[6], Jimmy Kok Foo Lee, FRCPCH[7], Siao Hean Teh, MRCPCH[8], Fahisham Taib, FRCPCH[9], Fook Choe Cheah, PhD[10,11]

[1]Department of Paediatrics, International Medical University, Kuala Lumpur, Malaysia, [2]Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, United States, [3]Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia, [4]Department of Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, [5]Pantai Hospital Kuala Lumpur, Jalan Bukit Pantai, Kuala Lumpur, Malaysia, [6]Taylor University, Taylor's Clinical School, Jalan Hospital, Selangor, Malaysia, [7]Monash University Malaysia, Clinical School Johor Bahru, Jeffrey Cheah School of Medicine and Health Sciences, Johor, Malaysia, [8]Department of Paediatrics, Hospital Umum Sarawak, Jalan Hospital, Sarawak, Malaysia, [9]Department of Paediatrics, School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia, [10]Department of Paediatrics, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Kuala Lumpur, Malaysia, [11]Placenta and Perinatal Research Group, Universiti Kebangsaan Malaysia, Bangi, Selangor, Malaysia

SUMMARY

The Academy of Medicine of Malaysia College of Paediatrics acknowledges the role of children in research and this position statement explores the ethical considerations in obtaining assent from minors in the Malaysian context. It highlights the importance in respecting children's agency and navigating cultural complexities. The College proposes flexibility in the minimum age for assent of at least nine years old, while emphasising the need for a tailored assent procedure. Addressing language and cultural diversities and expanding local empirical research on a formal assent process are some building blocks in developing a standardised nationwide process in obtaining assent from children.

INTRODUCTION

The Academy of Medicine of Malaysia College of Paediatrics (the College) recognises the importance of involving children in research conducted within Malaysia. This acknowledgment serves to not only ensure inclusive representation but also to bolster the applicability of study findings across all age groups. Traditionally perceived as a vulnerable population, the exclusive reliance on research outcomes from adult studies, for example, is now deemed insufficient for establishing the essential evidence required to support the safe prescription of therapies or justify off-label drug use in children. Despite this imperative shift, responsibly engaging minors in research presents distinctive challenges, with one notable aspect being the process of obtaining assent.

In delineating this relationship between researchers and child participants, it is crucial to clarify the distinction between consent and assent. While informed consent is a well-established process requiring capacitated participants to voluntarily agree to take part in research after being fully informed about the study's objectives, procedures and potential risks; assent, by convention, pertains specifically to minors. Assent is the affirmative agreement from a child who may not have the legal capacity to provide full consent. Furthermore, children's cognitive capacity is not fixed but rather develops with age. As such, assent cannot be similarly applied to adults with impaired capacity.[1,2] Unlike informed consent, which is legally binding, assent is a more nuanced concept, recognising the evolving cognitive and decision-making abilities of children. It serves as a process through which researchers engage with minors, respecting their agency (the right to express themselves and influence decisions that concern them) and ensuring they understand the research to the extent of their developmental capabilities. The incorporation of assent requirements in research involving children marks a significant shift in research ethics, emphasising researchers' responsibility to acknowledge and respect children's preferences, choices and agency. This departure from the sole focus on children's cognitive capacity represents a broader consideration of moral concerns in our interactions with others. Although the concept of assent is theoretically clear, its ethical underpinnings and practical application remain less defined.

The College acknowledges that researchers may obtain assent merely as a procedural formality, prompting a call for a deeper and committed standard of practice. This concern has been amplified by the focused discussions on the challenges inherent in seeking assent, a key theme during a workshop led by Steven Joffe in the Third National Paediatric Bioethics Symposium, an event organised by the College.[3] The authors of this position statement, who are experts actively involved in paediatric research, clinical management and contributions to relevant guidelines, participated in the workshop and are integral to the Academy of Medicine of Malaysia's Ethical Professional Practice or Executive Council Members of the College.

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Corresponding Author: Fook Choe Cheah
Email: cheahfc@ppukm.ukm.edu.my

By appreciating the evolving capacity of minors in decision-making and the need to facilitate their comprehension of the research they are partaking in, this position statement aims to describe the challenges and articulate the essential elements needed to ensure the development of best practices in obtaining assent from children involved in research in Malaysia.

CHALLENGES

One of the primary challenges is determining the appropriate age for seeking assent, as specified by the Malaysian Research and Ethics Committee guidelines, which range from seven to 18 years old.[4] While the age of majority is 18 in Malaysia, the rationale behind the age of seven probably stems from the significant cognitive shifts that occur around this point.[5] At this age, children exhibit less egocentrism, display an ability to consider perspectives of others, and comprehend the consequences of their actions on others. However, differing perspectives exist. Grisso and Vierling[6] argued that minors only start to demonstrate competency comparable to that of adults at the age of 15. They even suggested caution for those between 11 and 14 years, proposing a need for careful consideration of their capacity to understand treatment complexities; and clearly states that those below 11 years old lack the intellectual capacity or tend to defer authority and self-determination, potentially falling short of legal standards for competent consent. Empirical data also lends substantial support to these considerations. For instance, while a study reveals that 14-year-olds exhibit no significant disparity from adults in their capacity to comprehend and reason about treatment information, 9-year-old demonstrate comparatively lower proficiency when compared to adults in their ability to grasp and rationalise the provided treatment information.[7] In a separate analysis focusing on children's assent in clinical anaesthesia or surgery studies, it was observed that those under the age of 11 displayed limited comprehension of disclosure elements and their role as research participants.[8] Additionally, Ondrusek et al concluded that the majority of children below nine years old lack the cognitive capacity to provide meaningful informed consent or assent to participate in clinical research.[9] With such diverse reported findings and recognising the lack of concrete studies to establish the most appropriate age threshold for assent, it appears reasonable to select the option that minimises the potential resulting harms. Until instruments are developed to assess the assent capacity reliably, it has been proposed that the threshold be fixed at the age of 14.[10,11] Collectively, the requirement for assent documentation in children also varies among research ethics committees. Kimberly et al.,[12] observed that while certain committees required assent from children as young as 6, others did not mandate assent documentation for children under 15 years, even when utilising the same research protocol. Correspondingly, a scoping review[13] of 116 articles conducted until November 2020 revealed that the reported minimum age for obtaining assent ranged between 5 and 13 years, with a median of 7.5 years. Only a handful of studies provided a rationale for their decision; some proposed a "school-age threshold", highlighting the "considerable capacities of five- to seven years old children", while others contended that children under 11 years possess a limited comprehension of research information.[10]

Recognising the language diversity in our country, the College acknowledges a second challenge related to literacy and potential communication barriers. Malaysia has a multi-ethnic population with speakers of 137 distinct living languages,[14] although only a fraction of them are inhabitants in Peninsular Malaysia. Even among the three major ethnic groups—Malay, Chinese and Indian—there are notable dialect variations that hold considerable influence as children communicate in their mother tongues. This linguistic complexity further highlights the importance of considering factors such as intellectual development, life experiences and proficiency in each language. These elements significantly impact a child's comprehension during the process of obtaining their assent in research. It is imperative to address these linguistic subtleties to ensure effective communication and a thorough understanding of the research context across diverse language communities.

Cultural differences in Malaysia extend beyond language and literacy, delving into complex cultural dynamics deeply rooted in tradition. The third challenge arises from the diverse socio-cultural and religious practices within each ethnic group, exerting a profound influence on decision-making and lifestyle choices. These factors amalgamate into established social hierarchies, defining specific roles for children within society. An even greater challenge is the involvement of underprivileged children as research subjects in a conservative society that requires cultural humility and proper assent practices.[15] In understanding and differentiating the roles of mothers and fathers, particularly in a predominantly patriarchal society, navigating these dynamics becomes even more critical. The process involves balancing the values of dignity, autonomy and family integrity, considering the aspects of respect, family connections and social relationships. Some decisions are influenced by the collective actions of people, rather than by individual choices. Collective agency, which refers to the ability of people to act together for a common purpose, provides a nuanced explanation for these decisions, challenging the traditional understanding and operationalisation of 'autonomy' in bioethics, which focuses on the rights and preferences of each person.[16]

Adding to these challenges is the discordant decision-making process in consenting and assenting to research participation. The issue of whether a researcher should proceed with enrolment when a parent or guardian consents but the child dissents, raises an ethical dilemma in the local setting. Conversely, situations may also arise where a child assents, but the parent or guardian does not consent. These are unsettled issues and warrant continued conversation. In any case, effective communication becomes crucial to address concerns and misconceptions, fostering a shared understanding and trust among all parties involved. Obtaining assent within the context of a complex network of family, community and culture structures will help researchers support the process of value-concordant and culturally appropriate decision-making for parents, guardian, and child.

RECOMMENDATIONS

Considering the challenges associated with obtaining ethical and effective assent for research involving children in Malaysia, the College proposes several recommendations to address these issues towards best practice.

1. Recognising the importance of respecting children as individuals with their own rights, the College suggests a flexible approach to the minimum age for assent. Specifically, the College recommends raising the minimum age to at least nine years old, guided by current available evidence. Additionally, this flexibility should be applied with consideration for the complexity of the research, ensuring that the assent process is age appropriate. Such an approach not only acknowledges the child's agency but also aids in the development of decision-making skills crucial for adulthood, contributing to the cultivation of trust in an era of evolving healthcare systems.
2. The College emphasises the need for tailored assent procedures that account for varying educational levels among children. To enhance comprehension, the College suggests customising assent procedures by integrating visual aids, multimedia resources, verbal explanations and open question sessions. Innovative methods, such as combining images with text or utilising multimedia, can further ensure the development of its best practice.
3. The College calls attention to the dynamic nature of the assent process, emphasising that obtaining assent is a dialogue. While the College advocate for researchers documenting a child's assent for accountability, the process is not a one-time signature on a form, that could all the more so place a burden on the child to engage in a significant act they might not fully comprehend. Recognising assent as an ongoing and dynamic process, continuous evaluation is desirable.
4. The College addresses the diverse linguistic landscape of Malaysia by recommending proactive language accessibility. This includes addressing translation needs to ensure inclusivity. Furthermore, the College advises granting sufficient time and privacy for consultations with parents, guardians and children. Additionally, extending this process to include discussions with extended family members or community members, as applicable, is deemed crucial. Cultural nuances that may influence the assent process should be acknowledged and navigated accordingly.
5. Given the absence of data on the appropriate age for obtaining assent in Malaysia, the College recommends and supports the conduct of local empirical research in this area. This research aims to better understand the cultural contexts within Malaysia and subsequently formulates the basis for developing assent practices nationwide. Such an approach stresses the importance of tailoring assent procedures to the unique cultural diversity present in Malaysia.

CONCLUSION

Addressing the challenges of obtaining assent from minors in Malaysia requires a multifaceted approach. This position statement by the College not only delineates its challenges but also outlines a path forward, emphasising the importance of respecting children's developing capacity and ensuring effective communication, while navigating Malaysia's socio-cultural landscape. Establishing local policies and guidelines must be dynamic and responsive to evolving research and societal norms. Advocating for best practices at a local level will deepen understanding and inform the formulation of standardised nationwide assent practices.

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DISCLAIMER

The recommendations in this position paper are based on the expert opinion of the authors, after seeking the best available and current evidence on assent from children. These may change when more studies are conducted in the future and new evidence emerges.

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