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The Medical Journal of Malaysia
MJM

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Articles describing Original Research should consist of the following sections (IMRAD format): Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgment and References. Each section should begin on a fresh page.
Scientific names, foreign words and Greek symbols should be in italic.

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Clearly state the purpose of the article. Summarise the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

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Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly, identify the methods, apparatus (manufacturer's name and address in parenthesis), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well-known; describe new or substantially modified methods, give reasons for using them and evaluate their limitations.

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

When appropriate, particularly in the case of clinical trials, state clearly that the experimental design has received the approval of the relevant ethical committee.

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Present your results in logical sequence in the text, tables and illustrations. Do not repeat in the text all the data in the tables or illustrations, or both: emphasise or summarise only important observations in the text.

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Emphasise the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies.

Conclusion:
Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

Acknowledgements:
Acknowledgements of general support, grants, technical assistance, etc., should be indicated. Authors are responsible for obtaining the consent of those being acknowledged.

Referencing guide:
The Medical Journal of Malaysia, follows the Vancouver numbered referencing style. Citations to someone else's work in the text, should be indicated by the use of a number. In citing more than one article in the same sentence, you will need to include the citation number for each article. A hyphen should be used to link numbers which are inclusive, and a comma used where numbers are not consecutive. The following is an example where works 1.3,4,5.have been cited in the same place in the text.

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Example references Journals:
Standard Journal Article
Rampal L and Liew BS. Coronavirus disease (COVID-19) pandemic. Med J Malaysia 2020; 75(2): 95-7.
Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia 2020; 75(6): 613-25.
NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021; 11; 398(10304): 957-80.

Books and Other Monographs:
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.

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

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

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

Online articles
Webpage: Webpage are referenced with their URL and access date, and as much other information as is available. Cited date is important as webpage can be updated and URLs change. The "cited" should contain the month and year accessed.

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.

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

Magazine Article
Rampal L.World No Tobacco Day 2021 -Tobacco Control in Malaysia. Berita MMA. 2021; May: 21-22.

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

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The evolution of the Medical Journal of Malaysia - beyond a century

Liew Boon Seng, MS (Neurosurgery), Lekhraj Rampal, DrPH

INTRODUCTION

The Medical Journal of Malaysia (MJM) is the oldest medical journal not only in Malaysia but also in the region, serving more than 17,000 doctors, and the wider healthcare community. The vision of the MJM is to be the foremost medical journal that promotes the integration of medical research and scholarly publication across South East Asia nations in particular and the world at large. The mission of the MJM is to improve all peoples' lives by assisting and strengthening the capacities of members of the Malaysian Medical Associations (MMA) and Medical Associations of South East Asian Nations (MASEAN) by training and publishing sound scientific articles. MJM is a double-blind peer-reviewed scientific journal. It publishes multidisciplinary manuscripts that seek to advance medical and health sciences research, including all aspects of clinical and preventive medicine; political, economic, environmental social and technological (PEEST) subjects related to medical practice. The journal follows the International Committee of Medical Journal Editors (ICMJE) and Committee on Publication Ethics (COPE) guidelines with regard to concerning its editorial policies on publication ethics, scientific misconduct, consent and peer review criteria. The aim of this editorial is to record the history of MJM.

History of MJM

In this editorial, we trace the history of the MJM from its inception. The first medical journal ever published in Southeast Asia was the Journal of Straits Medical Association (JStMA). It was the official journal of the Straits Medical Association (StMA) which was established in 1890 [Figure 1(A)][1]. The StMA was then led by Dr. D. J. Galloway as the President [Figure 2 (A)][2], with Dr. W. Gilmore Ellis being the Vice President. The first edition of the journal was under the editorship of Dr. Max F, Simon who was then the principal civil medical officer of the Straits Settlements.[3]

The journal published the minutes of meetings, rules of the association, reports of the committee and the address by Dr Galloway. There were only three manuscripts in the March–September 1890 issue, on 'Puerperal Eclampsia', 'A case of Syphilitic Coma' and 'A type of Puerperal Fever' in the 48 pages issue. Dr. Max F. Simon dated 21st November 1892 mentioned that nearly all the members of the medical profession in the Straits Settlement which included the whole of the Malay Peninsular had joined as corresponding members of the StMA, which has been recognised as a branch of the British Medical Association (BMA). He stated that a journal may be established which shall contain contributions from all the practitioners in the Malay Peninsula. The headquarters of the association was in Singapore. He hoped that the journal would become a means of communication between all medical men in the whole Peninsular of Malaya, notes of cases and improved methods of treatment which may be forwarded and received for publication, besides as a record of the proceedings of the association.[3]

According to the research work by W.S. Tiew (1999) on 'Some Scholarly English Periodicals In Pre-Independent Malaysia: An Historical Overview', he found that the JStMA was one of the earliest Pre-independent Malaysian Scholarly English Periodicals, with the Journal of the Indian Archipelago and Eastern Asia was the first published in 1847, followed by the Journal of Eastern Asia (1875), the Journal of the Straits Branch of the Royal Asiatic Society (1878) and the Agricultural Bulletin of the Malay Peninsula (1891).[4]

The second issue of the JStMA (October 1890–March 1891) was edited by Dr. Max Frank Simon. There were papers on 'Parangi disease', 'Case of Myxoedema', 'Beri-beri to accompany microscopical specimens' with notes of discussion on Beri-beri, notes of cases and a memorandum on Ancylostomiasis in the 36 pages issue. The third issue (April 1891–March 1892) was with a new editor, Dr. W. Gilmore Eliis. There were eight papers including one on Leprosy. According to the editor (in his editorial), the third number of the JStMA was bulkier than the previous issues with 60 pages. The fourth issue of the JStMA (April 1892–March 1893) was edited by Dr. T.S. Kerr. A few interesting papers were papers on 'Disorders of sleep', 'Malarial diarrhea', 'Amok of the Malays', 'Treatments of sciatica' and 'Ulcerative tuberculous of the lobe of the ear' in a 75-page issue.

The fifth issue of the JStMA (April 1893–December 1894) with 17 scientific papers was the period of the transaction of the StMA until the end of 1894, which thereafter became a branch of the BMA. Interesting papers include topics on 'Acromegaly' and 'Spinal concussion' and a paper on unqualified practice in Singapore were published in the 158-page issue. It was noted in the minutes of the regular monthly meeting on 4th November 1893 that Dr. Middleton, the secretary, reported that 15 out of the 23 circulars sent to members not residing in Singapore indicated their willingness to join the BMA, with two expressing unwillingness. In the annual general meeting dated 16th December 1893, it was unanimously agreed that the secretary should draw up the necessary requisition of joining the BMA. The annual subscription of the journal was fixed at $9 with $3 as the annual subscription to the branch. All the papers in the issues were discussed in the monthly meeting prior to the publications.[5] All the first five volumes were printed by the Government Printing Office in Singapore.

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On 1st January 1894, the StMA was admitted as a branch of BMA, known as the Malaya Branch of the British Medical Association (MBBMA).[6] In their regular monthly meeting held on 6th May 1894, a committee was formed to draft new rules and by-laws for the purpose of transmission to the branch organisation committee of the BMA. The membership of the new entity was 38 members. The publication of the JStMA was discontinued following the formation of this new entity.[6]

By 1910, half of 215 registered medical practitioners in British Malaya including Singapore joined the association.[7] The revival of the journal with a new name, the Journal of the MBBMA, occurred in 1904 [Figure 1B(i)][8]. The news was published in the Straits Times on 29th June 1904. Dr. J. Kirk, as the chairman of the editorial committee, along with the assistance of Dr. McDowell, who established the local branch of the BMA, ensured the journal's reappearance with greater regularity in its issues. Articles on topics such as dengue fever by Dr. More and malarial fever by Dr. Galloway were considered relevant at that time. The second volume was published in 1905. These two volumes were printed by the Pinang Gazette Press Ltd, located in Penang, Malaya.

The third volume (Session 1905–1906 and January 1907) of the Journal of the MBBMA was published. The 118-page volume contained the minutes of the Council of the Malay Branch 1904 and 1905, minutes of meetings of the Singapore division for 1905 and 1906, the report of the Medical Registration Bill Committee and 14 other papers. [Figure 1B(ii)][9]. However, due to insufficient contributions and editorial issues, the journal could not sustain its publication in 1907.

The journal was revived in January 1911 as the Malaya Medical Journal (MMJ). It was considered as the IX volume (previously five volumes as the JStMA and three volumes as the Journal of the MBBMA). Dr. Gilbert E Brooke was the editor with his last issue in October 1912 [Figure 1C(i)[10] and 1C(ii)[11]]. The journal was the organ of the MBBMA and the Malaya Branch of the Far Eastern Association of Tropical Medicine. There were a total of two volumes, each consisting of four parts. The first volume, which was published in 1911, includes a 74-page January issue, a 66-page April issue, a 97-page July issue and a 74-page October issue. The second volume, which was published in 1912, includes a 68-page January issue, a 58-page May issue, a 34-page August issue and a 48-page October issue. The two volumes were printed by the Methodist Publishing House in Singapore [Price $4.00 per annum ($2.00 to BMA members), Single copies $1.00].

He was replaced by Dr. J.W. Scharff in 1922, and the journal was given a new name, the Transactions of the MBBMA, with 56 pages.[7] Dr. J.W. Scharff served as the editor until 1923. For the subsequent twelve volumes issued between January 1926 and March 1937, the journal was renamed as the Malayan Medical Journal, by the MBBMA. There were four editors, namely Dr. T.S. Macaulay (1926), Dr. JR. Kayo-Mouat (1927), Dr. G.H. Macalister (1928-1929) and Dr. G.V. Allen (1930-1937) for those issues [Figure 2(B)][12].

On 17th December 1926, the quarterly MMJ was officially adopted as the official organ of the MBBMA. There were six original articles in its first January–December 1926 issue, covering topics such as 'Epidemic Jaundice', 'Leptospirosis', 'A system of Intelligence as a Handmaiden of Hygiene', 'Occupational Cancer with Special Reference to the Industries of Malaya', 'Epithelioma adenoidescysticum' and 'An experiment with Paris Green as an Anopheles ludlowaelarvicide'. A special obituary notice of the late Miss Elizabeth Fletcher, Matron of the General Hospital, Singapore was published too. The subscription rate was six dollars per annum. The managing headquarters was located in Kuala Krai, Kelantan.[13]

The MMJ reverted to its previous name, the Journal of the MBBMA for its five volumes of quarterly publications between 1937 and 1941 [Figure 1D(i)[14] and 1D(ii)[15]]. The Advertising & Publicity Bureau Ltd, Singapore was the printing company of the journal. A supplementary issue of the Journal of the MBBMA was published in June 1941 which consisted of the names of Asiatic members.[16] A study done by Teng et al in 2019 showed that out of five medical journals published in pre-independence British Malaya from 1890 to 1941, the MMJ published 59.5% of the articles.[17]

There was no publication during World War II. However, following World War II with the return of the British to Malaya and Singapore, the journal reappeared as the Medical Journal of Malaya under the same association, the MBBMA, from 1946 to 1959. The journal was printed by the Young Advertising & Marketing Ltd, Singapore. The first two volumes published between 1946 and 1947 were under Dr. D.W.G. Faris as the editor, while Dr. D.E.C. Mekie was the editor for the subsequent seven volumes published between 1948 and 1954. Dr. H.M. McGladdery was the next editor for the 11th volume (September 1956) through the 15th volume (2nd issue in December 1960).

The close relationship between MBBMA and BMA can be observed in a correspondence published on 8th January 1949 in its parent journal, the British Medical Journal (BMJ). The correspondence was written by Dr. Webb Johnson, the President of the Royal Medical Benevolent Fund regarding gift parcels sent by MBBMA.[18] However in 1958, the situation changed. In November 1958, medical doctors in both the Federation of Malaya and Singapore decided to withdraw from the MBBMA and established a new entity, the Malayan Medical Association. On 5th November 1958, an article was published in the Straits Times, stating that 'the 1,500 doctors in Singapore and Federation will be holding their inaugural meeting of the Malayan Medical Association on 10th November 1958'. A draft of the constitution with 13 items was introduced.[19] However, the drafted constitution of the Malayan Medical Association was rejected by the Malaya Registrar of Societies (ROS) as reported in the Straits Times dated 7th March 1959. The rejection was on the grounds that doctors from both the Federation of Malaya and Singapore were considered separate political entities before the formation of Malaysia and a single association could not represent doctors in both territories.[20]

The Malayan Medical Association appealed against the decision, arguing that the association is a professional, non-political body and political objections should therefore not impede the formation of a pan-Malayan organisation for

Fig. 1: A:First edition of the Journal of Straits Medical Association March–September 1890; B(i): The front page of the Journal of the Malaya Branch of the BMA session 1904–1905; B(ii): The contents of the Volume 3: Session 1905–1906 of the Journal of the Malaya Branch of the BMA; C (i): The front page of the Malaya Medical Journal, January 1911, Vol IX. Part 1; C (ii): The front page of the Malaya Medical Journal, January 1912, Vol X. Part 1; D (i): The content page of the Journal of the Malaya Branch of the British Medical Association, Volume II, No. 4 (1st March 1939); D(ii): Front page of the Journal of the Malaya Branch of the British Medical Association, Volume 3, No. 3 (December 1939); E(i): Index page of the Medical Journal of Malaya, Volume 11, September 1956–June 1957; E(ii): Front page of the Medical Journal of Malaya, Volume 12, No. 2 December 1957; E(iii): Index page of the Medical Journal of Malaya, Volume 14, September 1959–June 1960; E(iv): Front page of the Medical Journal of Malaya, Volume 15, No.2 December 1960; F(i) Front page of the Medical Journal of Malaysia, Volume 47, Issue 3 September 1992; F(ii) Front page of the Medical Journal of Malaysia, Volume 59, Issue 2 June 2004; F(iii) Front page of the Medical Journal of Malaysia, Volume 64, Issue 1 March 2009

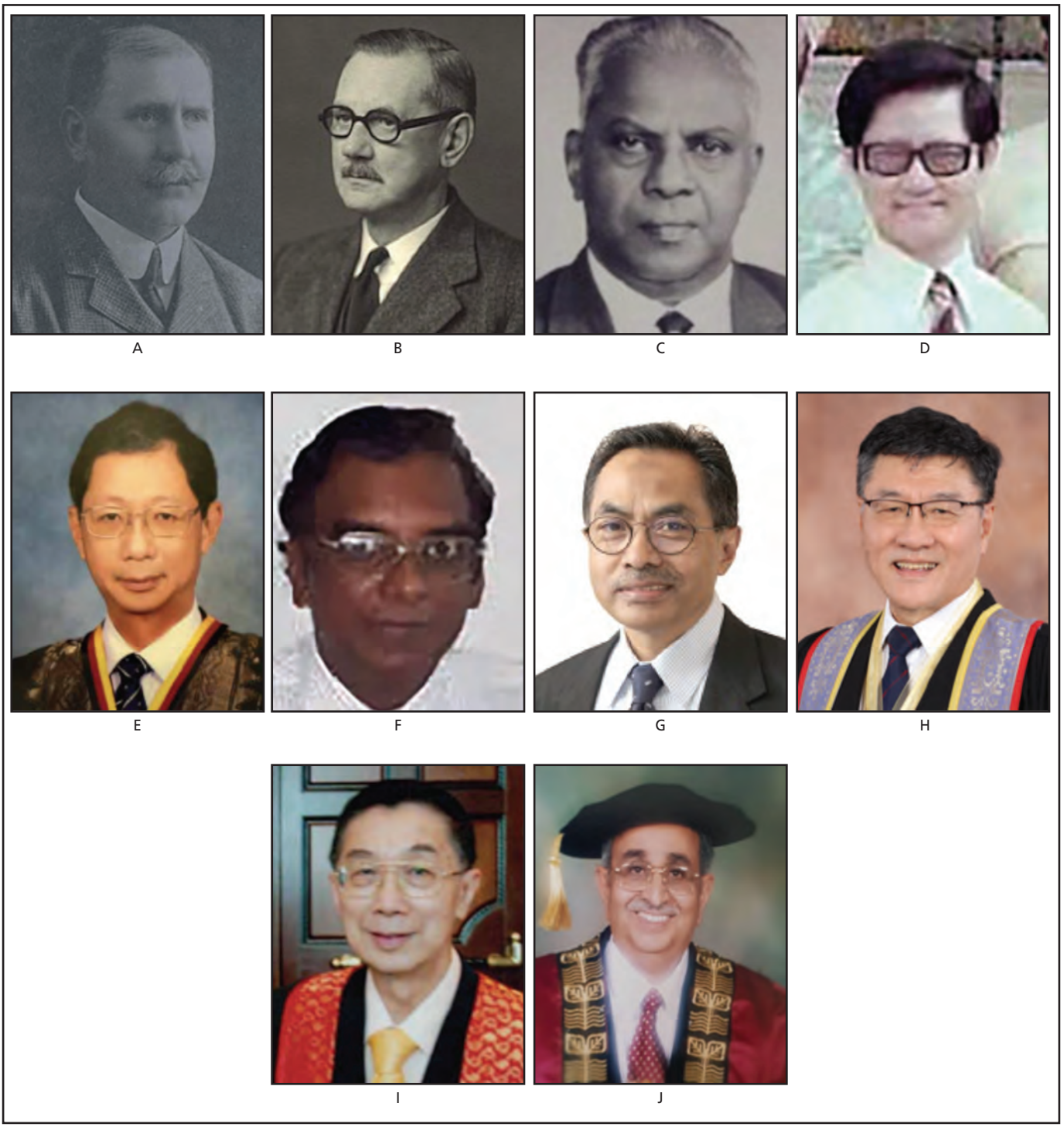
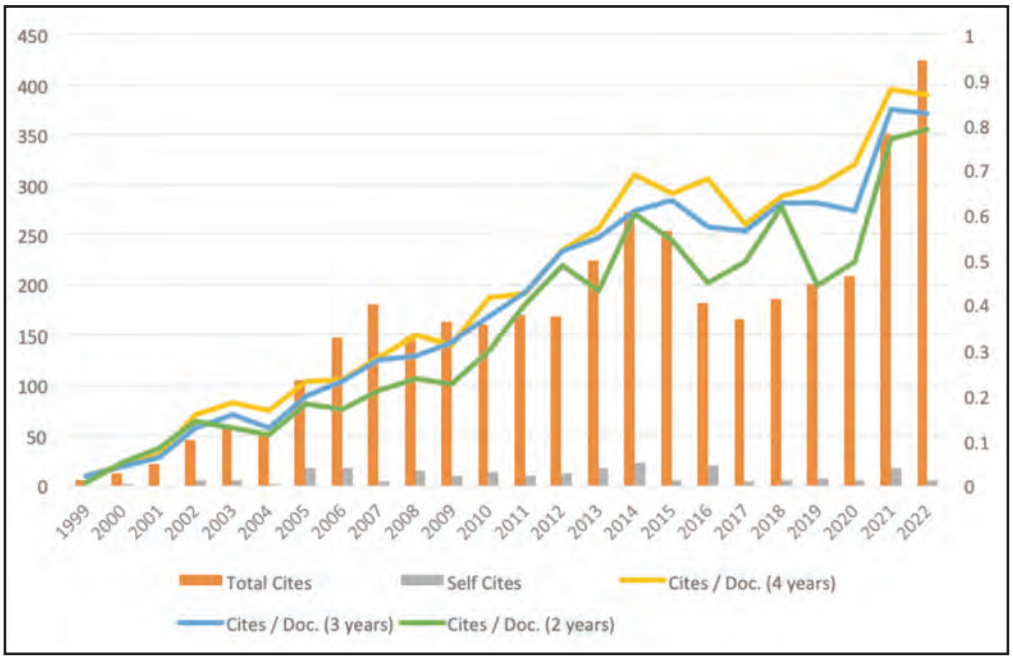


Fig. 2: (A): Dr. David James Galloway; (B): Dr. George Vance Allen; (C): Dr. A. A. Sandosham; (D): Dr. Paul C.Y. Chen; (E): Dr. Victor K.E. Lim; (F): Dr. John T. Arokiasamy; (G): Dr. Azhar M. Zain; (H): Dr. K.G. Lim; (I): Dr. Khoo Kah Lin; (J):Professor Datuk Dr. Lekhraj Rampal



*Bar graphs using left vertical axis and line graphs using right vertical axis
Source: Scimago Journal & Country Rank

Fig. 3: The Medical Journal of Malaysia Metrics 1999–2022.

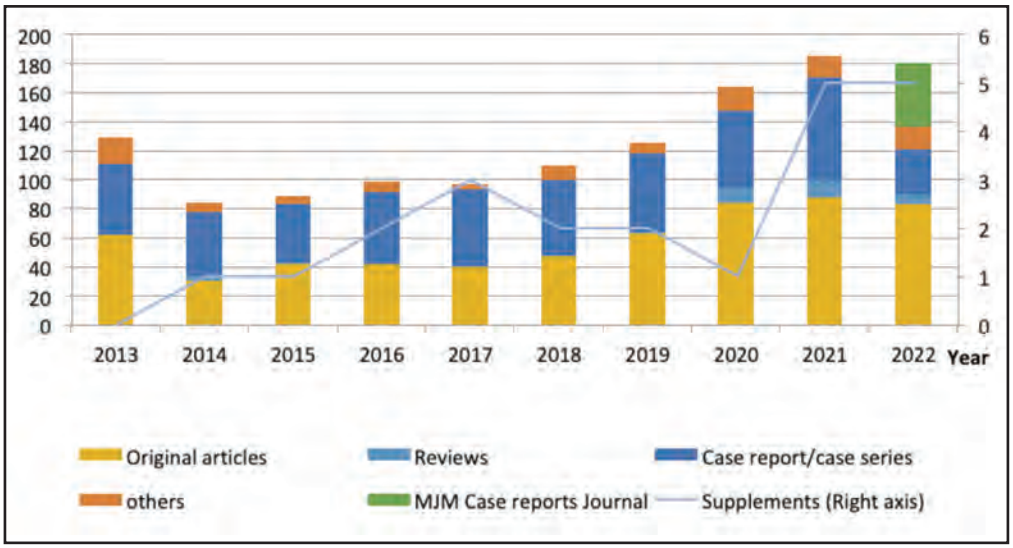


Fig. 4: The Medical Journal of Malaysia: Number of articles according to the types of articles and number of supplements in 2013–2022 (including the new 2022 MJM Case Reports journal).

doctors. On 2nd July 1959, the Federation Government again turned down the request of 1500 doctors in the Federation and Singapore to register their newly formed Malayan Medical Association. The decision was made by Mr. J. G. Adams, the Registrar of Trade Union and Societies, based on the Federation's interest in having a Federation body with Federation citizens as officials.[21]

The Straits Times, dated 4th August 1959, reported that 'The oldest medical organisation in Malaya, the MBBMA, which is more than 50 years old, will be dissolved soon'. The last president of the association was Dr. A.W.S. Thevathasan.[22] On 31st August 1959, news regarding the formation of a new medical association, the Singapore Medical Association (SMA) was reported. On 15th September 1959, the new association took over the functions of the present Alumni Association of the King Edward VII College of Medicine and the Faculty of Medicine, University of Malaya, as well as the British Medical Centre. This news was announced by Dr. V. Thambipillai, the President of the Alumni Association. He

Table I: Information on Pre- and Current volumes of the Medical Journal of Malaysia, 1890– Present

Name of the journal	Labeled volume (cumulative volume)	Published month, year	Editor/Honorary Editor/ Editor-In-Chief [Issue]
Journal of Straits Medical Association[a]	1,2 (2)	Mar,1890–Mar,1891	Dr. Max Simon
	3 (3)	Apr,1891–Mar,1892	Dr. W. Gilmore Ellis
	4,5 (5)	Apr,1892–Dec,1894	Dr. T. S. Kerr
Journal of the Malaya Branch of the British Medical Association[b]	1-3 (8)	1904–Jan,1907	Dr. J. Kirk
Malaya Medical Journal[b]	9,10 (10)	Jan,1911–Oct,1912	Dr. Gilbert E Brooke
The transaction of the Malaya Branch of the British Medical Association[b]	(11)	1922–1923	Dr. J.W. Scharff
Malayan Medical Journal[b]	(12)	Jun,1926–Mar,1927	Dr. J.W. Scharff [1,2]; Dr. T.S. Macaulay [3,4]
	(13)	Jun,1927–Mar,1928	Dr. JR. Kayo-Mouat
	(14,15)	Jun,1928–Mar,1930	Dr. G.H. Macalister
	(16-23)	Jun,1930–Mar,1937	Dr. G.V . Allen
The Journal of the Malaya Branch of the British Medical Association[b]	(23-28)	Jun,1937–Mar,1942	
The Medical Journal of Malaya[b]	1,2 (29,30)	Sep,1946–Jun,1948	Dr. D.W.G. Faris
	3–10 (31-38)	Sep,1948–Jun,1956	Dr. D.E.C. Mekie
	11-13 (39-41)	Sep,1956–Jun,1959	Dr. H.M. McGladdery
The Medical Journal of Malaya[c]	14-18 (42-46)	Sep,1959–Jun,1964	Dr. H.M. McGladdery
	19 (46)	Sep,1964–Jun,1965	Dr. H.M. McGladdery [1,2]; Dr. A.A. Sandosham [3.4]
	20-26 (47-53)	Sep,1965–Jun,1972	Dr. A.A. Sandosham
The Medical Journal of Malaysia[d]	27-30 (48-57)	Sep,1972–Jun,1976	Dr. A.A. Sandosham
	31 (58)	Sep,1976–Jun,1977	Dr. A.A. Sandosham [1-3]; Dr. Paul C.Y. Chen [4]
	32-41 (59-68)	Sep,1977–Dec,1986	Dr. Paul C.Y. Chen
	42-45 (69-72)	Mar,1987–Dec,1990	Dr. N. Chandrasekharan
	46-53 (73-80)	Mar,1991–Dec,1998	Dr. Victor K.E. Lim
	54-63 (81-90)	Mar,1999–Dec,2008	Dr. John T. Arokiasamy
	64,65 (91, 92)	Mar,2009–Dec,2010	Dr. Azhar M. Zain
	66,67 (93,94)	Feb,2011–Dec,2012	Dr. K.G. Lim
	68 (95)	Feb,2013–Dec,2013	Dr. K.G. Lim [1-3]; Dr. Khoo Kah Lin [4-6]
	69 (96)	Feb,2014–Dec,2014	Dr. Khoo Kah Lin
	70-78*(97-105)	Feb,2015–present	Dr. Lekhraj Rampal

Publishers of journal: [a]Straits Medical Association; [b]British Medical Association Malaya Branch; [c]Malayan Medical Association; [d]Malaysian Medical Association; *Until the 2023 issue

also mentioned the formation of a similar body, the Malayan Medical Association, in the Federation.[23]

Two medical associations were formed to replace the MBBMA: the SMA on 15th September 1959, and the Malayan Medical Association on 24th October 1959. Both medical associations were affiliated with the BMA, based in London. Since then, the Medical Journal of Malaya has been under the Malayan Medical Association and has been handled by the same editor, Dr. H.M. McGladdery, until 1965 [Figure 1E(i), 1E(ii) and 1E(iii)].

The SMA established its own medical journal, the Singapore Medical Journal (SMJ), in 1960.[24] The SMJ published an article entitled 'Galloway Memorial Lecture' which was written by Dr. J.W. Scharff in 1960. In that article, it was stated that 'Sir Dr. David Galloway was the first president of the Straits Medical Association in 1890. Four years later, he became the president of the newly formed MBBMA. He passed away on 5th March 1943 at the age of 85 years old'.[25]

Dr. A.A. Sandosham was the first Malaysian to serve as the editor for the Medical Journal of Malaya, appointed by the Malayan Medical Association, from 1965 until [Figure 2(C)][26]. A total of three volumes, spanning from the 3rd issue of the volume XXIV to the 4th issue of the volume XXVI, were under the editorship of Dr. A.A. Sandosham. The Straits Times Press (S) Sendirian Berhad, Thomson Road, Singapore was the printing company of the journal.

In 1972, following the formation of Malaysia in 1963, the journal was renamed as the Medical Journal of Malaysia (MJM) in September 1972, following the renaming of the Malayan Medical Association to Malaysia Medical Association (MMA) (Table I). Dr. A.A. Sandosham continued as the honorary editor of the MJM. He was replaced by Dr. Paul C.Y. Chen, the honorary editor for the 4th issue of the 31st volume, in June 1977 [Figure 2(D)].

In the 1st issue of the 37th volume of the MJM, published in March 1982, the honorary editor, Dr. Paul C.Y. Chen wrote an editorial titled 'The medical journal of Malaysia: Past and Future'. In the editorial, which marks the journal's 92nd year, he stated that 'the MJM is the leading medical journal in the region. To maintain the highest level of editorial and medical writing, the journal has acquired the part-time services of an

executive assistant, tasked with assisting in maintaining the difficult and meticulous editorial policy of the Journal'. During his tenure as the honorary editor, the journal faced financial problems as the cost of publication continued to rise.[27]

In 1987, the first BMA Congress was held in Kuala Lumpur to recognise the MMA as one of the former overseas branches of BMA. Despite the fact that MMA was an independent association in sovereign states, the BMA Congress helped to maintain the old ties and create new ones.[28] Dr. N. Chandrasekharan was the honorary editor from 1987 until 1990. He was replaced by Dr. Victor K.E. Lim in 1990 [Figure 2(E)]. The second article on the history of the MJM was published in 1995.[29] Dr. John T. Arokiasamy [Figure 2(F)] served as the next honorary editor from 1999 until 2008 and was subsequently replaced by Dr. Azhar M. Zain. [Figure 2(G)]. Dr. K.G. Lim [Figure 2(H)] took over the helm from Dr. Azhar M. Zain in 2011.

In 2011, the Honarary Editor at that time, Dr. Lim Kean Ghee wrote an editorial for the 66th volume of the MJM entitled 'The Medical Journal of Malaysia: Its History and Its Mission'.[30] The first volume is considered to date back to the publication of the Medical Journal of Malaya in 1946. However, according to him, the Medical Journal of Malaysia can claim 121 years of history based on the heritage of the forerunning medical associations such as the StMA, which was established in 1890.[30] The appearance of the MJM has been changing over years (Figure 1).

Dr. K.G. Lim's tenure as the Honorary Editor ended after the 3rd issue of the 68th volume. Dr. Khoo Kah Lin [Figure 2(I)] replaced him and served until the end of 2014 (Table I). His position as the Honorary Editor was taken over by Dr. Lekhraj Rampal in 2015. At the annual General Meeting of the Malaysian Medical Association in 2019, the post of Honorary Editor was changed to Editor in Chief. Dr. Lekhraj Rampal has been serving as the EIC of the MJM from 2015 and remains the EIC at the present tenure. A summary of all the previous and current versions of MJM and its editors, honorary editors and EICs are shown in Table I.

In 2019, the EIC, Professor Datuk Dr. Lekhraj Rampal informed the Editorial Board Members, that the time was now ripe for moving to the next level. He stated that steps need to be taken to improve the quality and quantity and its impact factor on the health sector. MJM editorial board needs to identify the bottlenecks and remove them. During the period 2019/2021, bottlenecks were identified and removed to ensure better quality and quantity. Articles that were accepted were published in the next issue. The staff was replaced. Criteria were set for applicants to join the in as editors. Younger members were admitted as Editorial Board members. They had to apply and meet certain criteria. In 2021, the Editorial Board decided to separate the MJM into two journals, namely, the Medical Journal of Malaysia and the Medical Journal of Malaysia Case Reports (MJM Case Reports). This policy change explained by Prof Rampal was that the case reports were not well cited and the journal citation index was being affected.

The first volume of the MJM without case reports was volume 77, issue no. 4, published in July 2022. However, the need for a separate journal for case reports was felt for the training of young doctors. The policy to have a separate journal for case reports was approved in the Annual General Meeting of the MMA. The first issue of MJM Case Reports was published in August 2022 with a new International Standard Serial Number (ISSN) 2948-3859. It contained 22 articles. It is being published regularly, three issues per year. Case reports represent a relevant form of advancing medical scientific knowledge, especially of rare diseases or conditions. They are important learning resources for doctors. They are usually the first encounter that trainees or residents will have in their early careers. It serves also as a platform for them to write and learn the techniques of scientific writing.

MJM: The way forward

Currently, in 2023, with the 78th volume, we are also celebrating 133rd years anniversary of the journal since the publication of its first version of the JStMA in 1890. Over one century, we have covered many milestones. The most noted is that of sustainability and an increased number of scientific manuscripts published in each volume.

The MJM continues to provide a scientific platform for medical doctors and scientists to contribute new knowledge which leads to better healthcare for the population. The reviewing and editing of our medical journal have been conducted on a voluntary basis by the medical fraternity. The MJM follows the COPE Guidelines and a double-blind peer review system. From initially being only the printed version, the MJM has since 2010 been made available online with free access. The MJM can be accessed at the uniform resource locator http://www.e-mjm.org.[31] The availability of archives of previous issues from 1980 was made available in 2013.[32] In 2020, under the leadership of the EIC, Professor Datuk Dr. Lekhraj Rampal, he and his team have performed rigorous searches for the availability of non-digitised issues of the MJM. Those issues from 1979 were first made available online in December 2020. Most of the past issues from 1960 were made available online in February 2022. The MJM is currently indexed in MEDLINE, EMBASE, PubMed and Scopus. The MJM is now moving forward to be indexed in the Directory of Open Access Journals (DOAJ) and Science Citation Index Expanded (SCIE).

MJM SCImago Journal Rank (SJR) h-index is 39 (Q3) in 2023.[33] The Medical Journal of Malaysia Metrics 1999–2022 in the SJR website shows a positive linear correlation coefficient between year and number of citations per document. The same correlation was shown between the year and the total citations with almost zero linear correlation coefficient between year and self-citation. These figures indicate that the increasing number of total citations was not due to self-citation with the number of self-citations remaining low over the past 23 years in the MJM (Figure 3). Abrizah reported that MJM was one of the Malaysian medical journals with the highest h-index score based on the Malaysian Medical Journals Indexed in MyCite in 2015 report.[34] There has been an increasing trend of original articles being submitted to the MJM. Despite the separation of case reports and case series from the MJM, there have been encouraging numbers of publications in the MJM Case

Reports. The number of proceedings from meetings held in Malaysia has been encouraging due to its high prestige (Figure 4).

CONCLUSION

The MJM has evolved from its initial publications of variously named as the Journal of Straits Medical Association in 1890, Journal of the Malaya Branch of the BMA session in 1904, the Malaya Medical Journal in 1911, the Medical Journal of Malaya in 1946 and the current MJM since 1972. MJM has been served by 22 editors since its inception in 1890. Currently, in 2023, with the 78th volume, we are also celebrating 133 years anniversary of the journal since the publication of its first version of the JStMA in 1890. Over one century, we have covered many milestones. The most noted is that of sustainability, an increased number of scientific manuscripts published, the number of issues each year and increased citations. The MJM is now the journal of choice among clinical researchers in Malaysia to publish their research findings and is one of the most cited medical journals published in Malaysia. It has marched forward to ensure the MJM remains as an open-access journal with its e-version with limited copies of the printed form. The MJM continues to improve the lives of all people by assisting and strengthening the capacities of clinicians, academicians, practitioners and scientists by publishing sound scientific articles.

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Noise-induced hearing loss among manufacturing factory workers in Kuching, Sarawak: Prevalence and associated risk factors

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ABSTRACT

Introduction: Noise-induced hearing loss (NIHL) is a common problem worldwide. Increased globalisation, as well as industrialisation, gives rise to an increase in the incidence of NIHL worldwide. Malaysia is not spared from this problem, either. The objectives were to determine the prevalence of NIHL and its associated factors among manufacturing factory workers.

Material and Methods: A cross-sectional study was done in Kuching, Sarawak, involving 173 randomly selected respondents among manufacturing factory workers. Data collected were respondents' workplace monitoring data and their audiometry records obtained from the factory record, and the otoscopy examinations performed. In addition, respondents were required to fill up an interviewer-guided questionnaire.

Results: The prevalence of NIHL was high (49.7%). The factors which were found to have a significant association with NIHL in bivariate analysis were age ($p < 0.05$, 95% CI), male gender ($p < 0.05$; OR – 7.60; CI 3.34 –18.38), duration of employment ($p < 0.05$), knowledge of noise level ($p < 0.05$; OR – 4.11; CI 1.10 – 15.28), working at polishing department ($p < 0.05$; OR – 4.23; CI 2.13 – 8.43), and smoking ($p < 0.05$; OR – 39.6; CI 16.5 – 94.8). Pack–years of smoking were also found to have a significant association with $p < 0.05$. However, only smoking was statistically significant in multivariate analysis, where the risk of developing NIHL was 27.55 ($p < 0.005$; CI 10.74 – 70.64) among smokers.

Conclusion: The high prevalence of NIHL despite the existing Hearing Conservation Program (HCP) may indicate that there may be some elements in HCP that require close monitoring by the factory management, and the importance of smoking cessation among the workers exposed to noise at the workplace should be highlighted.

KEYWORDS:
Noise-induced hearing loss, manufacturing factory, audiometry, prevalence, Sarawak

INTRODUCTION

Occupational noise-induced hearing loss (NIHL) is a prevalent occupational disorder, and hearing loss caused by workplace noise exposure is a significant health issue globally.[1] NIHL occurs due to long-term exposure to excessive noise, usually over the years. Therefore, continuous or intermittent noise in the workplace that exceeds 85dB(A) during an 8-hour shift, or impact noise that exceeds 120dB(A) , is deemed dangerous.[1,2]

Globally, NIHL is responsible for 16% of cases of debilitating hearing loss in adults, indicating that it does not directly cause early death but does result in significant disability.[2,3] In Malaysia, occupational NIHL, which includes NIHL, hearing impairment, and Permanent Standard Threshold Shift, was the most frequently reported occupational disease in 2021, accounting for 3648 cases (68.9%).[4] Although the data may not reflect the entire Malaysian population, it is clear that NIHL is a significant concern impacting many employees in Malaysia.

NIHL is related to multiple factors, and the risk factors for developing NIHL can be non-modifiable such as age and gender, or can be modifiable. In addition to occupational noise, other causes (such as organic solvents, high temperatures, lack of hearing protection devices, smoking, alcohol, heredity, comorbidities) may serve independently or synergistic effects with noise to increase the risk of NIHL.[5-6] Tobacco smoking is a risk factor for various diseases, and several scientific literatures has shown that it may be related to NIHL.[7-9] Some toxic and harmful substances like nicotine from tobacco burning may affect hearing.[10] Smokers were almost twice as likely as non-smokers to develop hearing loss. This association persisted in studies that excluded those with non-age-related hearing loss and those with no history of occupational noise exposure.[10,11] Several meta-analysis studies have found evidence of an association between cigarette smoke and hearing loss.[10-12]

The intensity, frequency, duration of exposure, and type of noise significantly impact the risk of health hazards, notably occupational hearing loss. Individuals with NIHL may endure severe morbidity due to hearing loss, concomitant tinnitus, and poor speech discrimination.[13] Non-auditory effects may impacts workplace communication and safety. The non-auditory reaction to noise may be affected by sound qualities such as the rate, loudness, consistency, complexity, duration (period of exposure) and noise meaning.[14] Noise has been linked to increased stress, cardiovascular health

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(hypertension, changes in heart rate), irritation, poor sleep and mental health issues. Because of this broad spectrum of impacts, experts believe noise can interact as a general, non-specific stressor.[14-15] Studies have proved that a sound pressure level of 95-90 dB(A) can induce hearing loss of more than 25 dB(A), whereas a sound pressure level of 85-90 dB(A) can cause hearing loss of less than 2dB(A).[16] The risk of NIHL can be minimised if noise is decreased to below 80 dB(A). Regulation six of the Occupational Safety and Health (Noise Exposure) Regulations 2019 states that the NEL as the daily noise exposure level should not exceed 85dB(A) or daily personal dose (cumulative noise exposure of an employee corrected for a typical working day of eight hours) a hundred per cent (100%). The criterion for maximum sound level pressure (SPL) exceeding 115dB(A) at any time or the peak SPL exceeding 140dB(C) necessitates the implementation of activities to reduce risk of NIHL. This dose limit uses a 3-dB time-intensity trade-off as the exchange rate.[2,18]

A thorough medical history can assist in establishing whether any of these disorders may be contributing to an individual's hearing loss.[2,17,18] Poor knowledge and awareness among employees and a lack of enforcement by governing bodies were cited as factors for the risk of NIHL. In addition, hearing protection is not often adequately fitted, and even when it is, it wears out and fails to provide the specified laboratory values of attenuation in the field.[17,18]

Research showed that occupational noise exposure is a significant concern and pervasive in the industrial industry.[19] Processing tasks are a significant aspect of the manufacturing industry, and the complexity of process noise such as forging, grinding, cutting, polishing, and welding is very noticeable.[20] Although the reported NILH cases have dramatically increased since 2010, there is a significant disparity between the number of cases diagnosed and the number of workers exposed to hazardous noise. In addition, there is no established data on NIHL among manufacturing sector workers in Sarawak. Therefore, this study aims to determine the proportion of NIHL and its associated factors among manufacturing factory workers.

MATERIALS AND METHODS

Study design

This retrospective cross-sectional study was conducted among manufacturing factory workers in Sarawak to evaluate the medical record, area monitoring, personal monitoring, and workers' audiometry assessment from the factory records.

This research has been approved by UKM ethical committee (UKM FPR.4/244/FF-2016-219) and the manufacturing company management board.

Study subject and methods

This study included all workers from the polishing and plating department of the manufacturing factory who went for an annual audiometry assessment and were exposed to noise at work above noise exposure limits (NEL) of 85 dB(A). However, workers who have underlying medical diseases that may compromise blood flow to organs and increase viscosity, like diabetes mellitus, hyperlipidaemia, and hypothyroidism, history of usage of the ototoxic drug, history of severe and frequent ear infections with or without ear surgery were excluded from the study. Additionally, workers with a history of exposure to non-occupational noise, such as involvement in the war, and loud explosion activities, such as hunting, were excluded.

Eligible workers were selected by a simple random sampling method, where each subject was chosen randomly and by chance.

Selected respondents then undergo an otoscopic examination and audiometric assessment. Those with abnormal otoscopic findings such as ear wax, ear discharge, perforated tympanic membrane, and ear infection were ruled out from the study. An audiometry assessment was conducted for selected workers after they were not exposed to noise for 14 hours before the test. Furthermore, all respondents were using hearing protective devices uniformly as they worked in an area requiring hearing protection before entry.

Factors such as age, gender, duration of working, working department in the company, smoking habits (packed year), knowledge of noise level of the workplace unit, and usage of hearing protective devices were obtained through a sociodemographic questionnaire.

Written and oral informed consent was obtained from all participants. They were assured anonymity as well as confidentiality.

Diagnosis of NIHL

1. History taking and physical examination

To ensure that the NIHL was caused by the current employment and not due to previous job exposure or other non-occupational exposure, several histories such as medical, non-occupational, previous employment, drugs, recreational and social histories of exposure risk in the history taking were included in the sociodemographic questionnaire. History of hearing loss, ear pain, ear discharge, head injury, history of tinnitus, recent surgery on ear, nose, and throat, or head surgery was considered. Hobbies that involve noise exposure, such as loud music, clubbing, hunting, and scuba diving as a hobby were documented.

Respondents underwent a thorough head, ear, neck and cranial nerve examination and an otoscopic examination.

2. Audiometric assessment

There must be a positive history of exposure to noise at the workplace. Audiometric examination results were used to determine hearing loss among the respondents. The audiometric results should have a hearing threshold of more than 25 dB(A) at 4 kHz with a characteristic dip followed by recovery at higher frequencies to determine whether hearing loss was related to noise exposure. The dip depth in NIHL alone should not be more than 75 dB(A) in higher frequencies and should not be more than 40 dB(A) in lower frequencies. If those dips were not consistent with the characteristic of noise exposure, then the hearing loss could be due to other factors such as presbycusis.

Table I: Sociodemographic characteristics of respondents (n = 173)

Variables	Frequency (n)	Percentage (%)
Age group		
20 – 24.9	51	29.5
25 – 29.9	54	31.2
30 – 34.9	42	24.3
35 – 39.9	21	12.1
40 – 44.9	2	1.2
≥ 45	3	1.7
Gender		
Male	131	75.7
Female	42	24.3
Duration of employment		
1 – 4.9	116	67.1
5 – 9.9	38	22.0
10 – 14.9	10	5.8
15 – 19.9	2	1.2
≥ 20	7	4.0
Department		
Plating	58	33.5
Polishing	115	66.5
Noise level knowledge		
Yes	14	8.1
No	159	91.9
HPD usage		
Yes	36	20.8
No	137	79.2
Smoking history		
Yes	82	47.4
No	91	52.6
Pack – years+		
< 0.9	106	61.3
1 – 4.9	37	21.4
5 – 9.9	25	14.5
10 – 14.9	3	1.7
≥ 15	2	1.2

HPD = Hearing protective device
+ smoking was quantified based on pack years which are calculated based on the number of cigarettes per day times the years of cigarette consumption.

Table II: Prevalence of NIHL

	Frequency (n)	Percent (%)
Yes	86	49.7
No	87	50.3
Total	173	100.0

Table III: Association between gender, previous employment, department, noise level knowledge, hearing protective device usage, smoking, and NIHL

Variables		NIHL (%)		c^2 value	*p* value
		Yes	No		
Gender	Male	79 (60.3%)	52 (39.7%)	24.22	< 0.001*
	Female	7 (16.7%)	35 (83.3%)		
Previous employment	Yes	5 (45.5%)	6 (54.5%)	0.085	0.77
	No	81(50.0%)	81(50.0%)		
Department	Plating	42 (72.4%)	16 (27.6%)	17.99	< 0.0005*
	Polishing	44 (38.3%)	71 (61.7%)		
Noise level knowledge	Yes	11 (78.6%)	3 (21.4%)	5.08	0.024*
	No	75 (47.2%)	84 (52.8%)		
Hearing protective device usage	Yes	20 (55.6%)	16 (44.4%)	0.62	0.43
	No	66 (48.2%)	71 (51.8%)		
Smoking	Yes	72 (87.8%)	10 (12.2%)	90.49	<0.0005*
	No	14 (15.4%)	77 (84.6%)		

* Statistically significant p < 0.05

Table IV: Association between age, duration of employment, pack-years and NIHL

Variables	NIHL	N	Mean ± Std. deviation	t-test, (t)	*p* value
Age	Yes	86	30.69 ± 7.19	3.902	<0.001*
	No	87	27.02 ± 4.97		
Duration of employment	Yes	86	5.71 ± 5.39		
	No	87	3.15 ± 2.37	4.05	<0.0005*
Pack-years	Yes	86	3.44 ± 3.36	8.62	<0.0005*
	No	87	0.22 ± 0.86		

*Statistically significant p < 0.05

Table V: Multiple logistic regression between variables and NIHL

Variables	aOR	*p* value	95% C.I. for OR	
			Lower	Upper
Age	0.98	0.70	0.91	1.07
Smoking*	27.55	0.00	10.74	70.64
Gender	2.42	0.13	0.778	7.50
Noise level knowledge	1.37	0.72	0.242	7.73
Department	2.37	0.09	0.874	6.43

*Statistically significant p < 0.05

Statistical analysis

Data analysis was done with Statistical Package for Social Sciences (SPSS) version 22. The statistical test used was Pearson's Chi-Square test, and if there were any cells with an expected value less than 5, a Chi-square test with Yates correction was performed. For qualitative data with quantitative binominal data, student t-tests were done. Two-tailed *p* values were calculated, and the *p* value of <0.05 were considered to have a significant association. Multivariate analysis using multiple logistic regression (MLR) with forward and backward stepwise analysis was used to determine the final model of this study.

RESULTS

A total of 298 respondents participated in this study. Of these 298 respondents, 125 were excluded from further analysis because they did not fulfil the inclusion criteria.

Regarding sociodemographic characteristics, as shown in Table I, most respondents were in the 25 to 30 age group (31.2%). The mean age of the respondents was 28.84 ± 6.42 years, where the youngest respondent was 21 years of age and the oldest was 54 years of age. Most were male workers (75.7%), the majority with a duration of employment between 1 to 5 years. Most respondents were from polishing department (115, 65%), while the rest were from plating department. These represent two of the significant activities in the manufacturing company.

Regarding duration of smoking, less than half of the respondents were smokers, 82 respondents (47.4%), and their mean duration of smoking was 3.94 ± 5.54 years. On the other hand, the mean pack – years calculated was 1.82 ± 2.92, and the majority of the respondents (61.3%) had pack – years of less than 0.99.

A high percentage of the workers (80.5%) have a normal otoscopy finding, and only 2% have perforated ear drums. The overall prevalence of hearing loss in this manufacturing company was 49.7%, as shown in Table II.

The bivariate analysis has shown that males workers (c^2=24.22, p<0.001) in the plating department c^2=17.99, p<0.05) are more likely to develop NIHL (Table III). Smokers were found to have a higher risk (unadjusted Odds Ratios, OR = 39.6; CI = 16.5 94.8) of developing NIHL than those who did not smoke. The difference was statistically significant (*p* value < 0.05). In pack -years, those with the higher pack–years of smoking were likelier to develop NIHL than those with lower pack – years (Table IV).

In the multiple logistic regression, only smoking was statistically significant with an adjusted OR of 27.55 (95%CI 10.74 – 70.64). Despite other variables having statistically non-significant results, males are two times more likely to develop NIHL than females. In addition, those who do not know the noise level are one time more likely to develop NIHL than those who know the noise level, and those in polishing department are twice more likely to develop NIHL compared to plating department after adjusting with others risk factors (Table V).

DISCUSSION

The study was done on a population of manufacturing factory workers involving 298 workers. However, only 173 respondents were eligible to be included after the exclusion. This study found that the prevalence of NIHL in this company was as high as 49.7%. It was similar to other researchers who found a high prevalence of NIHL in various industries in Asia and Malaysia.[23-25]

Age is one of the vital factors found in other research and has a statistical significance in this research, too. It proves that the older the person, the more likely she or he is to develop NIHL. This is consistent with other research showing that older people are more likely to develop NIHL. However, in

NIHL, it differs from age-related hearing loss (AHL), which appears later, as in NIHL, it appears in younger age groups. If other parameters are excluded, age can also be the most important single factor for NIHL.[26] Young age group distribution may be exposed enough to noise higher than PEL for a considerable time, thus giving an early diagnosis of NIHL.

Furthermore, the working group is primarily young and fit, likely to get employed and stay employed (Hawthorne's effect). NIHL differs as it develops earlier in adults exposed to noise than age-related hearing loss (presbycusis).[27] A young person exposed to noise shows a threshold shift compared to an older person who does not show any threshold shift, as postulated in some research. This explains the younger group population who developed NIHL in this study.[28]

Gender is important in developing NIHL, as male workers are more likely to be employed in manufacturing industries. However, few other studies also replicate that male predominance.[29,30] Hearing sensitivity also declines in men twice as fast as women of the same age and found longitudinal declines in hearing sensitivity at 30 compared to women, which is seen at a later age.[29] Furthermore, lifestyle habit, such as smoking, is more common in males than in females.

Duration of employment indicates when the person is exposed to noise and predisposed to NIHL. The longer the person is exposed to noise, the more likely they will develop NIHL. Duration of employment indicates dose—response relationship, thus corresponding with this research's findings.[28,31] The previous history of employment in a noisy environment was not statistically significant. This is probably because most workers employed at this manufacturing company are young, which is probably their first job. Plating department was statistically significant in developing NIHL compared to polishing department, although both departments are exposed to noise above NEL. That may be partly due to lacking control at the source as well. Workers aware of the NEL are more likely to develop NIHL than those not aware of the NEL. This is because those diagnosed have been told about their findings and made aware of the noise level. This contrasts with a study that indicates that those unaware of noise levels are more likely to develop NIHL.[32]

Knowledge is an essential aspect of the Hearing Conservation Program (HCP). Although some research showed that the workers' knowledge of hearing conservation was good,32 research in Malaysia shows that the knowledge, usage of Hearing Protective Devices (HPD), and attitude towards NIHL prevention were low.[25,33] Although 23.3% of the workers wore HPD at work, they may not have worn it correctly and thus did not offer complete protection compared to properly fit HPD. Properly fit HPD may attenuate 15–20 dB (A).[26] Furthermore, this was also proven during the walkthrough survey that most workers were non-compliant in wearing HPD due to a long time of usage and lack of social communication. However, using HPD on an average of 50% of the time also offers protection compared to those who did not wear HPD.[34] There could be a lack of knowledge regarding the importance of hearing conservation among the workers, and some may not adhere to it entirely—for example, proper usage of PPE and exchange of PPE once it is spoiled or damaged.

This study proves the hypothesis that there is a significant relationship between smoking and NIHL and pack–years of cigarette consumption. Smoking is a lifestyle habit that predisposes its users and those surrounding them to multiple health hazards. Cigarette smoke lacks an antioxidant effect, where reports that endogenous antioxidants significantly influences susceptibility to auditory damage.[35] Therefore, it is probable that the number of endogenous antioxidants in smokers is reduced, thus predisposing them to cochlear damage. Other researchers also found that smoking and hearing loss is statistically significant in those exposed to occupational noise with OR 1.85, 95% CI 1.33–2.57, and pack-years of smoking remained significantly associated with hearing loss.[36] The precise mechanism of smoking and NIHL is unknown. A simple additive effect of smoking and noise might be compatible with NIHL potentiation caused by long-term exposure to excessive noise and carbon monoxide exposure from smoking. Nicotine and other tobacco compounds could be ototoxic.[36,37] The fundamental pathologic processes are the established vascular changes (cochlear hair cells damaged by raising carbon monoxide haemoglobin, cochlear hypoxia, capillary vasoconstriction, or decreasing cochlear blood flow volume) associated with smoking as well as long-term exposure to loud noise.[36-41] Evidence suggests synergistic effects of smoking, noise, and age on hearing loss and a multiplicative effect of smoking and age on hearing loss. Some other studies also found that median age–corrected hearing thresholds at 3 and 4 kHz in smokers are significantly higher [7 dB (A)] than in those who do not smoke.[36,37]

This study has achieved its objectives and proved most of its hypotheses, as this manufacturing company reveals the prevalence of NIHL in almost half of the workforce. This study also manifests that the HCP, which this manufacturing company has implemented, may not be as effective as they are still weak areas of compliance. Although the seven elements of HCP have been adhered to, they may not be enough, especially on the worker's part.

The main limitation of our study was the small sample size. The targeted sample size was not achieved as turnout was not as expected, as the study was done during regular working hours, and they followed shift and team systems. In addition, the secondary data may influence the audiometric result as it can be operator dependent. Furthermore, the instructions given to the respondents may not be accurate and thus may reflect misclassification bias. Hawthorne's effect, most of the employees are young as the young and fit are most likely to be employed and remain employed. Thus, the sample population is mainly of the young age group of less than 45 years.

CONCLUSION

The study found that occupational noise exposure is a severe hazard, mainly distributed in the manufacturing industry, with the complexity of the process noise, such as forging, grinding, cutting, and welding, particularly prominent. The rising trend in Malaysia over the past few years is probably

due to the increasing nature of investments and government initiatives for small and medium-scale industries. Other than the increasing nature of industries entering Malaysia, other factors could contribute to increased cases, such as poor compliance towards HCP. Smoking cessation programmes need to be incorporated, and the benefits are of a broad range as well. Reward or merit can be given to those who successfully stopped smoking and helped reduce the incidence and prevalence of NIHL.

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ORIGINAL ARTICLE

Walking further. How surgery can help the cerebral palsy child

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ABSTRACT

Introduction: The prevalence of cerebral palsy (CP) in Malaysia is estimated at 2.6 per 1000 live births which is comparable to that of Australian and European data with ranges of 2.3- 4.2[1,2]. Surgical intervention for the improvement of gait function and mobility in CP is a common practice, however scarce literature of its outcomes is available in Southeast Asia. This paper aims to address and compare outcomes of surgical interventions in our centre with other countries.

Material and Methods: Patients with Spastic CP with Gross Motor Function Classification System (GMFCS) I-III that underwent lower limb surgical intervention in our centre from 2008-2018 were retrospectively reviewed for The Spinal Alignment and Range of Motion Measure ROM subscale (SAROMM) scores and Functional Mobility Scale (FMS) 18 months after surgery. Changes in SAROMM, FMS scores and minimal clinically important difference (MCID) were determined.

Results: 19 patients were included in the study with mean age of 12.58. All patients underwent muscle tendon procedures. Box plot analysis of SAROMM showed reduction of median scores at 6(26.3%) and 12(47.4%) months which plateaus at 18 months post-surgery. Repeated measure ANOVA analysis showed there was a statistically significant effect of time on SAROMM scores ($p < 0.001$) with MCID of 13.4. Improvement of FMS scores was the most at 50m with 13 children ($p < 0.05$), one at 5m and five at 500m. None reported worsening of FMS scores at 18 months. There were no changes of GMFCS levels by the end of 18 months.

Conclusion: Surgeries performed on GMFCS I-III patients with the aim of gait improvement translates into improved mobility with results comparable to other countries.

KEYWORDS:
Cerebral palsy, SAROMM, Functional Mobility Scale, Contracture release

INTRODUCTION

Cerebral palsy (CP) is an umbrella term to describe a group of disorders characterised my abnormalities of movement and posture, causing activity limitation due to a non-progressive brain damage during early development. Even though CP is a static encephalopathy, the musculoskeletal pathology is progressive leading to secondary deformities of bones and joints with loss of function and deterioration of their walking pattern.

There are currently no cure or treatment for the brain damage suffered by CP patients which causes the complex musculoskeletal dysfunctions. Physical therapy, medical and neurosurgical interventions serve to reduce and regulate the hypertonia while orthopaedic interventions aim to restore anatomical structures in an attempt to preserve the walking function as well as patients' activity level and therefore their quality of life.[3] Appropriate holistic care of children with CP requires myriad of disciplines to improve their long-term care considering their medical and social aspects as well as their rehabilitation, education, and assistance.[4]

Surgical intervention aims to improve gait, increase mobility and treat hip subluxation or dislocations. In a randomised control trial of surgery vs conservative treatment of CP patients by Thomason et al in 2011, the authors discovered that surgery improved the gait after one year of follow up with good quality of life and functional mobility observed at 2 years of follow up.[5] These findings were further substantiated by Firth et al., Feger et al., and Chang et al., with outcomes showing surgical intervention to be superior to conservative treatment of CP in the long run.[6–8]

MATERIALS AND METHODS

This study is a medical record review of 32 children with spastic CP that underwent orthopaedic surgical intervention between 2008-2018 at a tertiary referral university hospital for sub-specialised orthopaedic care. Nineteen patients were included in the study based on our inclusion criteria which included a diagnosis of Spastic CP of GMFCS I-III and completed 18 months of follow up. Patients that are more

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than 18 years old at time of surgery, history of dorsal rhizotomy or intrathecal baclofen surgery were excluded from the study.

Surgery was done by three surgeons throughout the 10 years who are experienced in performing these surgeries with experience of 5-20 years between them. The surgical indications included gait dysfunction, restricted knee extension and flexion, inability to achieve neutral ankle position. [5–7,9]

Patients were assessed preoperatively by a multidiscipline team of neuropaediatrician, rehabilitation physician and paediatric orthopaedic surgeon prior to decision for surgery as well as determination of surgical level and method.

Adductor release of adductor longus and gracilis were done as described by Shore et al.[10] Hamstring release involves the fractional lengthening of the semitendinosus and semimembranosus. If the increment of popliteal angle achieved is <20° then biceps femoris is also released.[11] Surgical correction of equinous deformity includes gastrocsoleus recession and triple hemisection of Achilles tendon. Both procedures involve the identification of the muscle belly and Achilles tendon with subsequent lengthening as described by Firth et al and Takahashi et al.[6,12] All patients were kept on casts for two weeks after surgery which is then continued for 6 weeks total after wound inspection. They are then changed to orthoses throughout their rehabilitation period and follow up.

Outcome data collected were changes in Gross Motor Function Classification System (GMFCS) levels[13] , Functional Mobility Scale (FMS)[14] and Spinal Alignment and Range of Motion Measure Range of Motion subscale (SAROMM).[15] Statistical analysis of data collected were analysed using SPSS version 24. Repeated measure ANOVA test was used to evaluate the statistical significance of score changes at 18 months and pre surgical intervention scores.

RESULTS

Nineteen children were included in the study with age ranging from 5-18 years old (mean=12.58). Nine male and 10 female children were enrolled. There were five GMFCS I, seven GMFCS II, and seven GMFCS III. Fifteen patients underwent single level surgery, while 4 patients underwent surgery of at least 2 levels. In total 27 lower limbs underwent surgical intervention. All patients underwent muscle tendon procedures (Table I).

There were no post-surgical intervention complications such as haemorrhage, surgical site infection. Box plot analysis of SAROMM showed reduction of median scores at 6 months and 12 months which then plateaus at 18 months (Figure 1). Repeated measure ANOVA analysis showed there was a statistically significant effect of time on SAROMM scores with mean change of 13.4 ($p < 0.001$, Standard Deviation, SD = 8.7) at 18 months after surgery.

The FMS scores at 18 months post-surgery were compared with their baseline for the distance of 5m, 50m, 500m. Improvement of FMS scores was the most at 50m with 13 children ($p < 0.05$), one at 5m and five at 500m (Table II). None reported worsening of FMS scores at 18 months. There were no changes of GMFCS levels by the end of 18 months.

DISCUSSION

The purpose of this study was to assess the impact of orthopaedic surgical intervention on children with cerebral palsy. In addition to measuring the range of motion of their joints, we also evaluated changes in their mobility, aiming to determine whether surgical intervention and concurrent physical therapy had a meaningful impact on the quality of life on these children.

The role of surgical intervention for children with cerebral palsy is to improve function and decrease discomfort with the assumption that by gait improvement, the general function of the patient will improve.[16] The SAROMM which has fair to good construct validity was used to detect change in ROM from baseline and follow up.[17] In addition, to determine if change in score is clinically relevant, the minimal clinically important difference (MCID) is also determined. The results garnered from our study shows that there is a mean change in score of 13.4 which is more than the MCID reported by Chen et al., of 4.07.[17] Thus, surgical intervention improves the ROM of contracted joints within 12 months to be of clinical significance.

Improvement in SAROMM scores peaks by 12 months and is the same at 18 months. indicating that after surgical intervention, the maximal improvement of ROM is seen by 12 months and is preserved at 18 months. Apart from this, there were no cases of recurrence detected within the 18 months period of follow up. However, recurrence of contractures, maintenance of functional levels or functional decline may not be apparent within the short period of follow up as it may require at least 5 years of follow up and up to early adulthood to detect recurrence and fully evaluate the results of contracture release.[18]

The mobility and ROM gains observed among CP children are not due to surgery alone and is in synchrony with physical therapy. Surgical intervention must be combined with an intensive post-operative rehabilitation programme individually catered and performed under the guidance of experienced physical therapists to maximise functional improvement.[5] However, in our setting, the postsurgical intervention physical therapy was not strictly controlled and the changes in physical therapy may have been confounded similar to Chang et al.[8] Couple this with inadequacy of records of therapy sessions, the impact of physical therapy on ambulatory gains are difficult to assess.

To our knowledge, this is the first study in our region to look at outcomes of surgical intervention and rehabilitation objectively among CP children. The results achieved are similar to other studies in improvements of ROM and functional mobility. The study is limited by its small sample size despite a review of 10 years. This may be due to lack of awareness and how misunderstood CP is among Malaysians. We also postulate that parents are reluctant to subject their

Table I: Summary of patients

Age	Gender	GMFCS	Limb involvement	Level involvement	Procedure
5	Female	III	Bilateral	Knee	HR
5	Male	I	Left	Ankle	GR
8	Male	II	Left	Ankle	PR + TAL
9	Female	III	Bilateral	Ankle	GR
11	Male	III	Bilateral	Knee	HR
11	Male	I	Left	Ankle	GR
12	Female	II	Left	Knee	HR
13	Female	III	Bilateral	Hip + Knee	HR + TAL
13	Female	II	Left	Knee + Ankle	HR + TAL
14	Female	III	Bilateral	Knee	HR
14	Female	II	Right	Knee	HR
14	Male	II	Right	Knee + Ankle	HR + TAL
14	Female	III	Bilateral	Ankle	TAL
15	Male	I	Left	Ankle	GR
15	Female	II	Bilateral	Ankle	TAL
15	Male	I	Right	Ankle	TAL
16	Male	I	Right	Knee + Ankle	HR + TAL
17	Male	II	Right	Ankle	GR
18	Female	III	Bilateral	Knee	HR

*HR = Hamstring release, GR = Gastrocsoleus recession, PR = Plantar release, TAL = Tendon Achilles lengthening, AR = Adductor release

Table II: FMS score improvement at 5m, 50m, 500m at 18 months compared to pre-surgery

	5M (p value)	50M	500M
N	1	13	5
	(0.351)	(0.027)	(0.351)
GMFCS I	1	3	2
GMFCS II	0	4	3
GMFCS III	0	6	0
Mean	4.74	4.32	3.89
SD	1.66	1.73	2.13

GMFCS = Gross Motor Function Classification System
SD= standard deviation

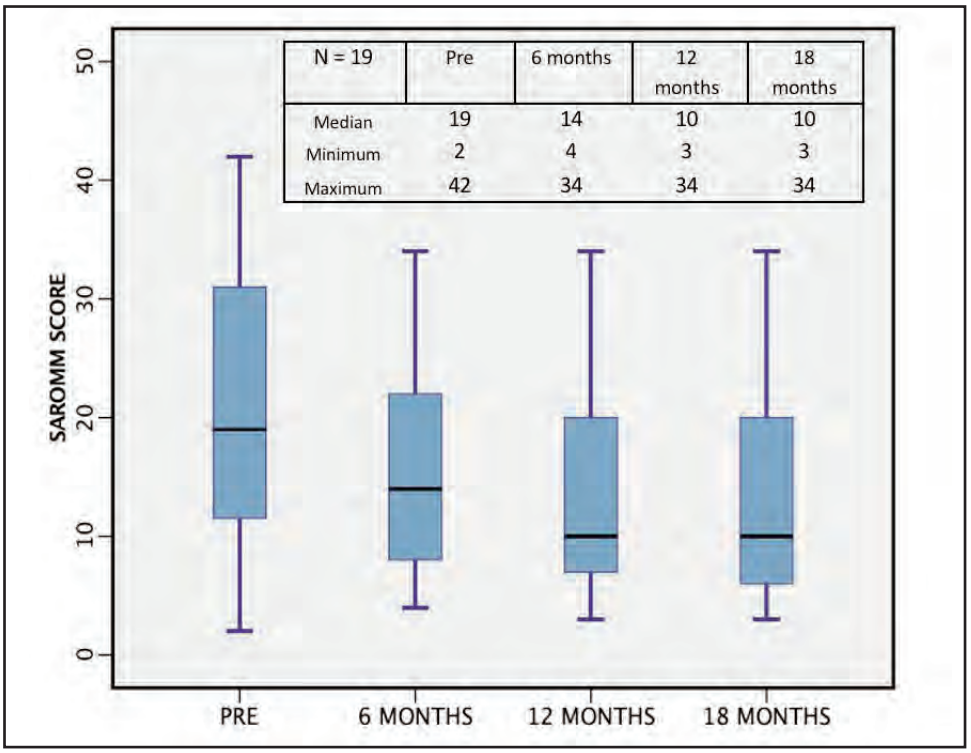

Fig. 1: Boxplot analysis of SAROMM showing reduction of median scores at 6 & 12 months which then plateaus at 18 months.

children to painful surgery for the sake of gait improvement. Apart from that, this study is limited to one centre and results are not to be generalised to the whole country to reflect the lack of access to surgical and rehabilitative facilities available for CP children.

Furthermore, the lack of a dedicated gait analysis facility at our centre hampers our ability of making accurate and concise surgical planning retarding the growth and development of Single Event Multi-Level Surgery (SEMLS) which is commonly practised in other countries. We were also concerned that the ambulatory function ratings were assigned retrospectively using the information available, which could have impacted their accuracy.

CONCLUSION

With available data from this research, surgeries performed on GMFCS I-III patients with the aim of gait improvement does translate into better mobility outcome which are comparable to present available literature[5,6,19]. This research should prove to be a steppingstone to expand the research by having longer follow up of patients thereby increasing the sample size thus the strength of the study. Longer follow up also allows us look for recurrences and how surgery has impacted the quality of life and functionality in the community. Furthermore, an addition of gait analysis facilities may enhance the decision-making process and allow more accurate surgical prescription for contracture release among CP children.

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ORIGINAL ARTICLE

Non-intubated vs. intubated video-assisted thoracoscopic bullectomy – a retrospective cohort study

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ABSTRACT

Introduction: Thoracic surgery procedures evolved enormously over time from open surgery to video assisted thoracoscopic surgery (VATS) and now non-intubated uniportal VATS. At our centre, the initial approach for bullectomy was by uniportal intubated VATS (iVATS) for most cases. Only in mid-2020, in the midst of COVID-19 pandemic, uniportal non-intubated VATS (NiVATS) took precedence. We compared the outcome of bullectomy via iVATS versus NiVATS for a period of 5 years.

Materials and Methods: We reviewed the medical records of all patients that underwent bullectomy from 1st June 2017 to 31st May 2022. Mann Whitney U-test was completed for all variables. Primary objective was to compare operating time (OT), global operating time (GOT), post-operative length of stay (LOS) and complication rate.

Results: A total of 90 bullectomies performed in which 36 were approached via iVATS and 54 NiVATS. It was found that the post-operative LOS, GOT, and OT were significantly shorter in the NiVATS as compared to iVATS. Complication rate between both groups showed no significant difference.

Conclusion: NiVATS bullectomy demonstrated a safe and reliable alternative surgical approach with superior surgical outcome than iVATS bullectomy.

KEYWORDS:
Thoracic surgery, bullectomy, NIVATS

INTRODUCTION

Traditionally thoracic cases are performed intubated with either double lumen or bronchial blocker to achieve single lung ventilation. The associated risk of intubation primarily led to transition to non-intubated approach.[1,2] The likely reason of the slow transition to non-intubated is both the familiarity of surgeon with the cases and a supportive anaesthesia team. Challenges faced during the surgery led to many cases being performed with intubated general anaesthesia. With the advancement of good regional blockade and intravenous anaesthesia, non-intubated thoracic surgery has become feasible and is an option for most thoracic procedures in recent times.[1-5]

There is no doubt that the COVID-19 pandemic brought many changes to the way institutionalised medicine has been practiced.[6] For the most part of the pandemic, it resulted in a generalised cessation of elective non-emergent procedures across specialties worldwide, leading to a backlog of cases. Being an aerosol generating procedure (AGP), non-urgent thoracic surgery procedures were put on hold. The advantage of non-intubated video assisted thoracoscopic surgery (NiVATS) not requiring intubation and hence the reduction in augmentation of the airway reduced the AGP exposure risk of healthcare personnel, in specific our anaesthesia colleagues. This is especially during the extubation period when patients cough.[7] Hence, selective thoracic surgery procedures were continued to be performed in our centre with the introduction of non-intubated technique. Bullectomy cases were regularly performed as we serve as the regional referral centre for thoracic cases.

This retrospective cohort study aimed to examine the differences in outcome for those who underwent uniportal intubated video assisted thoracoscopic surgery (iVATS) versus NiVATS bullectomy in the aspects of post-operative length of stay (LOS), global operating time (GOT), operating time (OT) and complication rate.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of all patients that underwent iVATS and NiVATS bullectomy from 1st June 2017 to 31st May 2022 in the Thoracic Unit of Hospital Kuala Lumpur. All patients with spontaneous pneumothorax within the age group of 12-80 years and with pre-operative Contrast Enhanced Computed Tomography of Thorax showing evidence of bullae or bleb were included in the study. Exclusion criteria were if patients underwent more than one procedure in the same sitting or if other pathology were identified during the surgery. All patients were given regional anaesthetic block by anaesthetists prior to induction. The surgical procedures were explained in detail to the patient and a written consent obtained.

Demographic data and pertinent information were gathered from the medical records and analysed. The primary outcome of post-operative LOS in the hospital, OT, GOT and complications were analysed. Complications were

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Table I: Demographic summary of iVATS versus NiVATS bullectomy.

Measure	Number of patients (%)		U	*p* value
	iVATS (n=36)	NiVATS (n=54)		
Gender				
Male	31 (84)	48 (89)	-	-
Female	5 (16)	6 (11)	-	-
Age (Median, year)	27.0	25.0	1148.5	0.146
Smoking/vaping	21(58)	29 (53)	927.0	0.667

Table II: Outcome summary of iVATS versus NiVATS bullectomy

Measure	Median		U	*p* value
	iVATS	NiVATS		
LOS (days)	4.5	3.0	660.0	0.008*
GOT (minutes)	149.0	90.0	256.5	< 0.001*
OT (minutes)	91.0	60.0	274.5	< 0.001*
Complications, N	3	2	1017.0	0.35
Chest drain >5 days	2	2		
Surgical site infection	1	0		

Note
*Statistical significance p < .05
N: Number of participants
LOS (days): Post-operative length of stay
GOT (minutes): Global operating time
OT (minutes): Operating time

Table III: Non-intubated thoracic surgery (NITS) cases performed

Procedures	NiTS cases, n = 94 (%)
Bullectomy	54 (57)
Decortication	7 (7)
Lymph node biopsy	7 (7)
Endoscopic thoracic sympathectomy	7 (7)
Wedge resection	6 (6)
Lobectomy	3 (3)
Tracheal resection and reconstruction	3 (3)
Pleurodesis	3 (3)
Pleural	3 (3)
Mediastinal biopsy	1 (1)

Table IV: Summary of Bullectomy Studies Performed Comparing NiVATS versus iVATS

First author (year)	Type of study	Number of patients	Outcomes (*p* value)			
			LOS	GOT	Complications	Recurrence
Ahmed et al. (2022) [12]	Retrospective	140	<0.0001*	<0.0001*	0.79	0.49
Noda et al. (2012)[13]	Retrospective	16	0.7	0.006*	0.02*	-
Pompeo et al. (2017)[14]	RCT	43	<0.0001*	<0.0001*	-	-
Irons et al. (2016)[15]	Retrospective	62	<0.001*	<0.0001*	-	N = 0
Liu, J et al. (2014)[16]	RCT	194	< 0.001*	-	0.004*	-
Palaniappa et al. (2022)	Retrospective	90	0.008*	<0.001*	0.35	N = 0

Note.
*Statistical significance p < .05
LOS (days): Post-operative length of stay
GOT (minutes): Global operating time

documented and classified as per Clavein-Dindo classification.

NiVATS in our study is defined as cases that are performed with the patient having spontaneous breathing without muscle relaxant, under deep sedation via intravenous anaesthesia and without an endotracheal tube (ETT) across the glottis.8 iVATS is when a patient is on muscle relaxant and inhalational anaesthesia under mechanical ventilation with an ETT across the glottis.[8]

LOS was defined as the post-operative hospitalisation duration. OT was defined as the time taken for the surgical procedure (skin-to-skin) whereas GOT involved operating time and anaesthesia period from induction to the time patient reaches recovery bay post-operatively.[9] All patients were followed up for a period of 1 year, after which they were discharged. Chest X-ray was performed during the first visit to the clinic at two weeks after discharge. No chest X-rays were performed in subsequent visits unless indicated. All data were statistically analysed via SPSS statistics v27. Mann Whitney U-test was performed for all variables.

RESULTS

Throughout the study duration, 90 patients underwent uniportal VATS bullectomy, out of which 36 cases via iVATS and 54 cases via NiVATS. Table I below summarises the demographic data.

All the outcome variables of the study violated the normality assumption test of Kolmogorov-Smirnov test and hence the Mann-Whitney U test was utilised. Demographically, age and incidence of smoking showed no statistical significance (Table I).

The test revealed that the post-operative LOS was significantly shorter in the NiVATS group as compared to the iVATSgroup ($p = 0.008$) with a small effect size. As for GOT and OT, it was found that patients in the NiVATS group had a significantly shorter time compared to the iVATS group with large effect size ($p < 0.001$) as shown in Table II below.

Out of the 90 cases, Five patients (5.56%) were found to have complications. Two patients (3.7%) in the NiVATS group had poor lung expansion post-operatively, requiring prolonged chest drain of more than 5 days. This was also seen in the iVATS group with an additional recorded case (8.3%) of surgical site infection. No statistical significance was seen comparing complications between patients in the NiVATS and iVATS group ($p = 0.35$). All the complications fall under the category of Clavein-Dindo Classification Grade II. There was no procedure related mortality.

DISCUSSION

Since the start of thoracic services in June 2017, thus far 1200 thoracic surgical procedures have been performed by a rather small unit (one thoracic consultant with two thoracic surgeons). Only in June 2020 did the concept of non-intubated thoracic surgery (NITS) take precedence and till date a total of 94 (8%) cases of various pathologies have been performed as shown in Table III below.

NiVATS bullectomy was the commonest NITS procedure performed (57%), hence it was chosen to be used as a comparison with iVATS bullectomy in this study.Criteria for NITS surgery are short procedure of <2 hours, simple surgery, Eastern Cooperative Oncology Group (ECOG) score of <1, American Society of Anesthesiologists (ASA) class one or two, with a good airway, a body mass index less than 30, and no significant cardiopulmonary issues.[10] However with progress among surgeons and anaesthetist and as the learning curve improves; these criteria have expanded further to include more complex surgeries as the indication arises.

Our centre has been performing bullectomy surgery by uniportal iVATS from June 2017 to May 2020 and after which till to date, NiVATS technique is used. Savitsky et al. reported the incidence of spontaneous pneumothorax to be estimated at 17 to 24/100 000 in the male population and 1 to 6/100 000 in the female population.[11] This is in line with male preponderance in our case series. Both the groups comprise of smokers or vapers without significant difference, which could be the cause of the bullae or bleb formation. There were no comorbid to report in this young cohort with the median age between 25 to 27 years.

Focusing on literature search comparing bullectomies performed via NiVATS and iVATS, a few centres have embarked and published their findings. Summary of these studies are shown in Table IV below.

Based on Table IV, it is evident that NiVATS ensures a shorter LOS and reduced GOT. Recurrence and complications rates are similar. Noda et al. showed statistical in-significant result comparing the length of stay and this could be due to the small population size of that study. Our study showed significant results for all three primary outcomes of LOS, GOT and OT. Complications showed no significant difference ($p = 0.35$). This is in accordance to previous studies done.

The shorter LOS is highly attributable to the reduced anaesthesia effect post-surgery and faster recovery. All the patients received regional anaesthesia and this helps to control immediate post-operative pain as well.[16,17] GOT and OT are lower in the NiVATS group in line with the papers published. Shorter GOT is due to the reduction of anaesthesia hours as patients are non-intubated and recovery is faster. OT on the other hand comprises only the time of procedure performed by a surgeon. The shorter time needed is likely due to the familiarity of surgeons rather than the type of anaesthesia. The steep learning curve of NiVATS requires one to adapt the skill and hence the initial cases performed may take a longer operating time.16 18 The process of transition from iVATS to NiVATS has to be in a stepwise manner. It is encouraged for thoracic surgeons to have performed at least 50 iVATS procedures including complex lobectomies and successful handling of intraoperative bleeding prior to embarking on NiVATS.[18]

It has to be highlighted that there was no conversion to intubated or open thoracotomy as far as NiVATS bullectomy is concerned and our pneumothorax recurrence rate at 1 year follow-up is zero as well. This is likely due to surgeon familiarity with bullectomy under iVATS hence the transition (NiVATS) outcome was excellent. Similarly, a meta-analysis by Tacconi et al. comprising of 1,441 participants showed a low conversion rate of 2.4%, majority being for adhesions (1.31%) followed by major bleeding (0.34%).[19] This indicates NiVATS is a safe alternative option for bullectomy in a well selected population.

In handling complications intra-operatively, the surgical and anaesthetic team should be alert and prepared for an unfavourable situation that may need conversion to iVATS or even thoracotomy. Preparation of instruments for an open surgery as well as preparedness for lateral intubation by anaesthetist has to be ensured prior to start of the case. Limitations during NiVATS must be clear with low threshold for conversion to ensure patient safety.

In our study, the complications rate was found to be insignificant, however there are reported papers with a lower complication rate in NiVATS compared to iVATS (Table IV). The likelihood of our finding is due to small sample size in both arms and short follow-up duration.

CONCLUSION

Thoracic surgery has always been deemed as a surgery with high morbidity. NiVATS bullectomy in selected group of patients is a viable safe alternative with superior outcomes compared to iVATS. Keeping the benefits in mind, the managing teams, both surgeons and anaesthetists, must also be prepared to handle crisis situation intraoperatively. The long-term efficacy of non-intubated VATS remains to be investigated via a well-designed, large-scale, multi-centred RCT.

CONFLICT OF INTEREST

None

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ORIGINAL ARTICLE

Evaluating the impact of a pre-recorded online video on Doctor's knowledge and attitude towards leprosy in Sabah and Labuan - a quasi experimental study

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ABSTRACT

Introduction: Global actions have been implemented worldwide to eliminate leprosy. However, under-recognition and stigmatisation continue to be the challenges. In Sabah, the grade two disability rate was 0.15/100,000 population in 2019, implicating a significant delay in diagnosis. This study aimed to assess the knowledge and attitude towards leprosy and the impact of lecture intervention among doctors in Sabah and Labuan, Malaysia.

Materials and methods: This study consists of two parts. First, a cross-sectional study on the knowledge of and attitude towards leprosy using an online quesitonnaire was conducted among doctors working in the primary care clinics and hospitals in Sabah and Labuan. Subsequently, the participants were asked to watched an online pre-recorded video lecture on leprosy and to answered the same questionnaire.

Results: Of the 310 participants, one fifth (20.6%) had good knowledge and 36.5% had positive attitude towards leprosy. Being a specialist (adjusted odds ratio [aOR] 4.55, 95% confidence interval [CI] 2.17–9.57, $p < 0.001$), managed ≥ 5 leprosy cases (aOR 3.37, 95% CI 1.52–7.47, $p = 0.003$), and involved in educational activities related to leprosy within last year (aOR 4.7, 95% CI 1.69–13.04, $p < 0.001$) were the significant predictors of good knowledge. Working in tertiary care was significantly associated with good attitude towards leprosy (OR 2.19, 95% CI 1.22–3.94, $p = 0.025$). There was a significant improvement in participants' knowledge post-intervention (87.0% participants post-lecture vs 20.6% participants pre-lecture with good knowledge, $p < 0.001$).

Conclusion: The proportion of doctors in Sabah and Labuan with good knowledge and attitude towards leprosy was low. Knowledge of leprosy improved significantly post-intervention. This highlights the need for educational and training programmes to improve doctors' knowledge of leprosy.

KEYWORDS:
Leprosy, Hansen's disease, knowledge, attitude, doctors

INTRODUCTION

Leprosy is an infectious disease caused by *Mycobacterium leprae* that primarily affects the skin and peripheral nerves. Untreated disease can lead to mutilating deformities and associated with social stigma. Early diagnosis and treatment play an important role in the prevention of disabilities.[1]

Globally, there were 202,256 new cases detected in 118 countries in 2019. The majority of the new cases (79%) were reported in India and Brazil. According to the WHO disability grading, grade 2 disabilities were characterised by visible deformity or visual damage.[2] Of the new cases, 10,816 cases were detected with grade 2 disabilities (G2D) with a rate at 1.4 per million population and 370 (3.4%) cases were children under the age of 15.[3]

Malaysia achieved leprosy elimination in 1994.[4] Although the number of new cases has declined over the past years, there were 198 new cases detected in 2019 in Malaysia.[5] Sabah has the highest number of cases in Malaysia with 75 (37.9%) new cases. Among which four (5.3%) cases were children and 6 (8%) cases had grade 2 disabilities with a G2D rate of 0.15/100,000.[6] Sabah did not achieve the WHO target of G2D < 0.02 per 100,000 population and new child cases of < 3%. This is an indication of late diagnosis and lack of community awareness.

In Malaysia, the public health sector comprises of three levels: primary, secondary, and tertiary care with a wide network of health clinics and hospitals. The primary care service comprises of outpatient clinics at the first point of consultation for patients at the local community. Patients may then be referred to secondary and tertiary care services.[7] Both Sabah and Labuan are located on the Northern Borneo of Malaysia. In 2019, the incidence rate of leprosy in Sabah was 1.9 per 100,000 population as compared to 0.61 in Malaysia.[5] Thus, it is important for doctors to have adequate knowledge and training in leprosy to recognise and diagnose leprosy early. This study aimed to assess the knowledge and attitude towards leprosy among medical doctors in Sabah and Labuan.

MATERIALS AND METHODS

Study design and population

This was a cross-sectional study with online questionnaire conducted among medical doctors working in the primary care clinics, district hospitals (secondary care), emergency department and medical department of specialist hospitals (tertiary care) in Sabah and Labuan from June 2021 till April

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2022. Doctors working in the Dermatology department were excluded.

The target participants were recruited by convenience sampling. A link to the questionnaire in Google Form was distributed via email to the relevant clinics and departments in hospitals. Participants answered an online self-administered questionnaire on leprosy and provided their email at the end of the questionnaire. After completion of the questionnaire, participants later received a link to the pre-recorded 5-minute video lecture and the same set of questionnaire via email. Participants were given a 3-month time frame to watch the video lecture and complete the post-video questionnaire. After completion of the questionnaire, participants received their scores and the answers on the knowledge section of the questionnaire.

This study was approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia, and was registered with the National Medical Research Registry (NMRR-21-1443-60619).

Questionnaire development and content validation

The questionnaire was developed by the investigators of this study. The content validation of the questionnaire was conducted by five senior consultant dermatologists. The questionnaire and the content validation form were sent via email to the consultant dermatologists. The dermatologists rated each question on a four-point Likert scale (1- totally irrelevant content, 2- irrelevant content, 3- relevant content, 4- extremely relevant content). The relevance rating for each item was recoded as 1 (relevance scale of 3 or 4) or 0 (relevance scale of 1 or 2). Then, the sum of the relevance rating of each item was divided by the number of the expert, e.g., (1+1+1+1+1)/5 = 1. The average content validity index (CVI) across all items was 1, which met the satisfactory level. Next, pre-testing of the questionnaire was carried out to ten potential participants. The ten responses were included in this study as there were no major changes from the pre-test.

Video lecture

The 5-minute video lecture was prepared and delivered by the principal investigator. The video lecture explained the cause of leprosy, mode of transmission, classifications, clinical features, treatment and complications. The content of the video was approved by three senior consultant dermatologists.

Questionnaire

Informed consent was obtained from all participants. Demographic data and professional characteristics of the participants were collected in the questionnaire. There was a total of 24 questions in the questionnaire: 20 questions on knowledge and 4 questions on attitude. The questions on knowledge comprised of cause of leprosy, mode of transmission, clinical features, treatment and complications. Every correct answer on the knowledge section will be awarded 1 mark; no mark will be awarded for wrong or unanswered questions. The total marks will be converted to 100% for interpretation. Categorisation of the score was as following: ≥ 70% good knowledge, 40 - 69% average knowledge and < 40% poor knowledge.

For the attitude section of the questionnaire, a five-point Likert scale was used. The score was calculated as the following: 1- strongly disagree, 2- disagree, 3- neutral, 4- agree, 5- strongly agree. Lower total score indicates better attitude. Participants who answered disagree or strongly disagree on all questions (with a score of ≤ 8) were regarded as having good attitude. A score > 8 was regarded as having poor attitude. Categorisation of the knowledge and attitude score were decided by the investigators of this study after discussion with the three senior consultant dermatologists.

Statistical analysis

The data were tabulated and analysed using IBM® Statistical Package for the Social Sciences (SPSS) Statistics, version 22.0. Descriptive analyses were conducted for demographic and professional characteristics. Continuous variables were expressed as means and standard deviations (SD) and categorical variables as frequencies and percentages. Simple logistic regression analysis was done to analyse factors associated with good knowledge and good attitude. Multivariate logistic regression analysis was conducted for variables associated with good knowledge. Forward and backward stepwise variable selection procedures were applied. McNemar's test was done to analyse participants' knowledge and attitude pre and post-intervention. A *p*-value of < 0.05 was considered statistically significant.

RESULTS

Demographic characteristics of the participants and experience with leprosy patients

A total of 310 participants were included in this study. The mean age of the participants was 31.5 ± 2.91 years. Among the participants working in tertiary hospitals, 129 (95.6%) were from medical department and 6 (4.4%) from emergency department.

The majority of the participants had limited experience with leprosy. More than 80% of them had previously came across, diagnosed, or managed less than five patients with leprosy. Higher proportion of primary care (22.5%) and tertiary care doctors (20.7%) came across ≥ 5 leprosy patients compared to the secondary care doctors (11.6%). Overall, more specialists (25%) managed ≥ 5 leprosy patients than medical officers (9.4%). The majority of the participants (84.8%) did not receive undergraduate teaching on leprosy. Two-thirds (67.7%) of the participants last accessed leprosy materials more than a year ago (Table I).

Knowledge of leprosy

As shown in Table I, participants who were specialists, working in primary care or tertiary care, being in service for ≥ 5 years, experience with leprosy patients (came across or diagnosed or managed ≥ 5 leprosy cases), previously received undergraduate teaching on leprosy and involved in educational activities related to leprosy within last year had better knowledge.

Table II shows the responses to questionnaire pre and post-video lecture. The majority of the participants were familiar with the causative microorganism (96.5%) and the investigations of suspected leprosy patients (83.5%). One-

Table I: Demographic characteristics of the participants, experience with leprosy patients, knowledge and attitude towards leprosy

Characteristics	Overall	Knowledge			Attitude	
	n (%) n=310	Good (≥70%) n = 64	Average (40-69%) n = 216	Poor (<40%) n = 30	Good (≤8) n = 113	Poor (>8) n = 197
Age - years, Mean (SD)	31.5 (2.91)	32.4 (3.45)	31.3 (2.72)	30.9 (2.58)	31.5 (2.85)	31.5 (2.94)
Gender						
Male	140 (45.2)	28 (20.0)	99 (70.7)	13 (9.3)	57 (40.7)	83 (59.3)
Female	170 (54.8)	36 (21.2)	117(68.8)	17(10.0)	56 (32.9)	114 (67.1)
Ethnicity						
Bumiputera Sabah	59 (19.0)	9 (15.3)	44(74.6)	6 (10.2)	23 (39.0)	36 (61.0)
Malay	95 (30.6)	22 (23.2)	56 (58.9)	17 (17.9)	33 (34.7)	62 (65.3)
Chinese	115 (37.1)	26 (22.6)	83 (72.2)	6 (5.2)	39 (33.9)	76 (66.1)
Indian	38 (12.3)	7 (18.4)	30 (78.9)	1 (2.6)	16 (42.1)	22 (57.9)
Others	3 (0.9)	0	3 (100)	0	1 (50.0)	1 (50.0)
Position						
Medical officer	266 (85.8)	44 (16.5)	193 (72.6)	29 (10.9)	93 (35.0)	173 (65.0)
Specialist	44 (14.2)	20 (45.5)	23 (52.3)	1 (2.3)	20 (45.5)	24 (54.5)
Workplace						
Primary care	89 (28.7)	26 (29.2)	55 (61.8)	8 (9.0)	30 (33.7)	59 (66.3)
Secondary care	86 (27.7)	8 (9.3)	61(70.9)	17 (19.8)	23 (26.7)	63 (73.3)
Tertiary care	135 (43.5)	30 (22.2)	100 (74.1)	5 (3.7)	60 (44.4)	75 (55.6)
Years of service						
< 5	174 (56.1)	29 (16.7)	124 (71.3)	21 (12.1)	59 (33.9)	115 (66.1)
≥ 5	136 (43.9)	35 (25.7)	92 (67.6)	9 (6.6)	54 (39.7)	82 (60.3)
Number of leprosy patients came across						
< 5	252 (81.3)	40 (15.9)	184 (73.0)	28 (11.1)	86 (34.1)	166 (65.9)
≥ 5	58 (18.7)	24 (41.4)	32 (55.2)	2 (3.4)	27 (46.6)	31 (53.4)
Number of leprosy patients diagnosed						
< 5	301 (97)	59 (19.6)	212 (70.4)	30 (10.0)	108 (35.9)	193 (64.1)
≥ 5	9 (3)	5 (55.6)	4 (44.4)	0	5 (55.6)	4 (44.4)
Number of leprosy patients managed						
< 5	274 (88.4)	46 (16.8)	199 (72.6)	29 (10.6)	95 (34.7)	179 (65.3)
≥ 5	36 (11.6)	18 (50.0)	17 (47.2)	1 (2.8)	18 (50.0)	18 (50.0)
Received undergraduate teaching on leprosy						
Yes	263 (84.8)	58 (22.1)	178 (67.7)	27 (10.3)	99 (37.6)	33 (70.2)
No	47 (15.2)	6 (12.8)	38 (80.9)	3 (6.4)	14 (29.8)	164 (62.4)
Last involved in educational activities related to leprosy						
Never	61 (19.7)	8 (13.1)	43 (70.5)	10 (16.4)	17 (27.9)	44 (72.1)
Within last year	39 (12.6)	18 (46.2)	21 (53.8)	0	17 (43.6)	22 (56.4)
More than 1 year	210 (67.7)	38 (18.1)	152 (72.4)	20 (9.5)	79 (37.6)	44 (72.1)
Educational source on leprosy accessed						
Website	170 (54.8)	36 (21.2)	119 (70.0)	15 (8.8)	67 (39.4)	103 (60.6)
Continuing Medical Education	104 (33.5)	27 (26.0)	69 (66.3)	8 (7.7)	48 (46.2)	56 (53.8)
Leprosy Management Manual	47 (15.2)	13 (27.7)	33 (70.2)	1 (2.1)	20 (42.6)	27 (57.4)
Textbook	118 (38.1)	25 (21.1)	82 (69.5)	11 (9.3)	40 (33.9)	78 (66.1)
Journal articles	33 (10.6)	7 (21.2)	25 (75.8)	1 (3.0)	13 (39.4)	20 (66.7)
Courses	3 (1.0)	2 (66.7)	1 (33.3)	0	1 (33.3)	2 (66.7)
Never access any leprosy related resources	30 (9.7)	5 (16.7)	21 (70.0)	4 (13.3)	8 (26.7)	22 (73.3)

third (33.5%) of the participants thought that leprosy was transmitted by direct contact. Only 64 (20.6%) participants had good knowledge (score ≥ 70%). Nearly two-thirds of the participants (69.7%) had average knowledge (score 40 - 69%) and the remaining 30 (9.7%) participants had poor knowledge (score < 40%).

Table III shows the univariate and multivariate logistic regression analysis of the potential predictors of better knowledge score. Position as a specialist (adjusted odds ratio [aOR] = 4.55, 95% confidence interval [CI] = 2.17–9.57, $p < 0.001$), previously managed ≥ 5 leprosy cases (aOR = 3.37, 95% CI = 1.52–7.47, $p = 0.003$), and last accessed educational materials related to leprosy within the last year (aOR = 4.7, 95% CI = 1.69–13.04, $p < 0.001$) were significantly associated with good knowledge.

Attitude towards leprosy

More than one-third (37.8%) of the participants thought patients with leprosy need to be isolated from the community. Only 113 (36.5%) of the participants had good attitude towards leprosy (score ≤ 8). Participants who were specialists, working in tertiary care, with working experience ≥ 5 years, experience with leprosy patients, previously received undergraduate teaching on leprosy and involved in educational activities related to leprosy within last year had

Table II: Responses to knowledge and attitude questions

Knowledge and attitude questions	Pre-video lecture, n = 310 n (%)	Post-video lecture, n = 270 n (%)
Leprosy is caused by which microorganism?		
Mycobacterium leprae*	299 (96.5)	267 (98.9)
Treponema pallidum	10 (3.2)	3 (1.1)
Madurella mycetomatis	1 (0.3)	0
Mycobacterium ulcerans	0	0
Leprosy is also known as:		
Hansen's disease*	299 (96.5)	268 (99.2)
Humphrey's disease	11 (3.5)	1 (0.4)
Hartmann's disease	0	1 (0.4)
Harry's disease	0	0
The mode of transmission for leprosy is:		
Direct contact	104 (33.5)	12 (4.4)
Droplet*	180 (58.1)	257 (95.2)
Faecal oral route	17 (5.5)	1 (0.4)
Vector	9 (2.9)	0
Leprosy primarily affects:		
I. Bone, II. Nerve, III. Skin, IV. Eyes		
I, II	2 (0.6)	1 (0.4)
II, III *	121 (39.0)	99 (36.7)
II, III, IV	128 (41.3)	146 (54.1)
All of the above	59 (19.0)	24 (8.9)
What are the typical cutaneous features of leprosy?		
I. Hypopigmented patch,		
II. Loss of sensation,		
III. Loss of hair, IV. Loss of sweating		
I, II	147 (47.4)	40 (14.8)
II, III	8 (2.6)	1 (0.4)
II, III, IV	12 (3.9)	3 (1.1)
All of the above*	143 (46.1)	226 (83.7)
What are the cardinal signs of leprosy?		
I. Skin patch with loss of sensation		
II. Enlarged/thickened peripheral nerve with corresponding loss/impairment of function		
III. Presence of acid-fast bacilli in slit skin smear		
IV. Loss of corneal reflex		
I, II	78 (25.2)	12 (4.5)
I, II, III*	125 (40.3)	235 (87.0)
II, III	14 (4.5)	6 (2.2)
All of the above	93 (30.0)	17 (6.3)
Which nerve is the most frequently affected nerve in leprosy?		
Optic	82 (26.4)	9 (3.3)
Popliteal	21 (6.8)	1 (0.4)
Sciatic	12 (3.9)	1 (0.4)
Ulnar*	195 (62.9)	259 (95.9)
Which is the most severe form of leprosy?		
Borderline tuberculoid	1 (0.3)	1 (0.4)
Lepromatous*	269 (86.8)	259 (95.9)
Mid borderline	1 (0.3)	0
Tuberculoid	39 (12.6)	10 (3.7)
Which of the following patient has leprosy? (patients' photos)		
a	6 (1.9)	3 (1.1)
b *	42 (13.6)	35 (13.0)
c	257 (82.9)	229 (84.8)
d	5 (1.6)	3 (1.1)
What are the complications of leprosy?		
I. Claw hand, II. Lagophthalmos, III. Scleritis,		
IV. Neuropathic ulcers		
I, II	45 (14.5)	15 (5.6)
II, III	8 (2.6)	6 (2.2)
II, III, IV	53 (17.1)	4 (1.5)
All of the above *	204 (65.8)	245 (90.7)

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Table II: Responses to knowledge and attitude questions

Knowledge item	Pre-video lecture, n = 310 n (%)	Post-video lecture, n = 270 n (%)
What constitutes WHO grade 2 disabilities in leprosy? I. Loss of sensation, II. Blindness, III. Resorption of digits, IV. Loss of corneal reflex		
I, II	95 (30.6)	42 (15.5)
II, III *	69 (22.3)	126 (46.7)
III, IV	39 (12.6)	20 (7.4)
All of the above	107 (34.5)	82 (30.4)
What are the clinical manifestations of type 2 reaction? I. Painful nodules, II. Fever, III. Lymphadenopathy, IV. Arthralgia		
I, II	37 (11.9)	10 (3.7)
I, II, III	56 (18.1)	36 (13.3)
II, III	40 (12.9)	4 (1.5)
All of the above*	177 (57.1)	220 (81.5)
Investigations for patients suspected of leprosy include: I. Skin biopsy, II. Slit skin smear, III. Peripheral blood smear, IV. Blood culture		
I, II*	259 (83.5)	261 (96.7)
I, II, IV	42 (13.6)	5 (1.8)
I, IV	5 (1.6)	0
II, III	4 (1.3)	4 (1.5)
Leprosy should be notified to the nearest district health office within:		
1 month	5 (1.6)	0
1 week *	139 (44.8)	247 (91.5)
2 weeks	7 (2.3)	2 (0.7)
24 hours	159 (51.3)	21 (7.8)
The following drugs are used in leprosy treatment except:		
Clofazimine	52 (16.8)	1 (0.4)
Dapsone	36 (11.6)	1 (0.4)
Isoniazid *	208 (67.1)	263 (97.4)
Rifampicin	14 (4.5)	5 (1.9)
What is the duration of treatment for paucibacillary leprosy?		
3 months	21 (6.8)	3 (1.1)
6 months*	191 (61.6)	259 (95.9)
9 months	37 (11.9)	5 (1.9)
12 months	61 (19.7)	3 (1.1)
What is the duration of treatment for multibacillary leprosy?		
6 months	23 (7.4)	3 (1.1)
9 months	31 (10.0)	4 (1.5)
12 months*	179 (57.8)	257 (95.2)
18 months	77 (24.8)	6 (2.2)
Which of the following drugs is known to cause generalized pigmentation of skin?		
Rifampicin	35 (11.3)	12 (4.5)
Dapsone	125 (40.3)	34 (12.6)
Clofazimine*	139 (44.8)	222 (82.2)
Isoniazid	11 (3.6)	2 (0.7)
Case study 1		
A 50-year-old man diagnosed with borderline leprosy, treatment was started 1 month ago. The existing plaques and patches on his trunk and arms became more erythematous and indurated in the last 4 days. How will you manage the patient before referring to a dermatologist?		
Stop his leprosy treatment immediately	37 (11.9)	20 (7.4)
Ensure the patient continues his leprosy treatment*	88 (28.4)	175 (64.8)
Arrange for an urgent slit skin smear	42 (13.6)	13 (4.8)
Perform full blood count, renal profile and liver function test	143 (46.1)	62(23.0)

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Table II: Responses to knowledge and attitude questions

Knowledge item	Pre-video lecture, n = 310 n (%)	Post-video lecture, n = 270 n (%)
Case study 2		
A 35-year-old woman with lepromatous leprosy completed her treatment 1 year ago. She complained of painful nodules over arms and legs of 2 weeks duration. Examination showed multiple, scattered, tender, erythematous subcutaneous nodules. What is your next step in management before referring to a dermatologist?		
Restart leprosy treatment	21 (6.8)	6 (2.2)
Perform a slit skin smear	139 (44.8)	51 (18.9)
Start prednisolone	81 (26.1)	104 (38.5)
Symptomatic treatment *	69 (22.3)	109 (40.4)
Leprosy patients need to be isolated from community during the treatment period.		
Strongly disagree	41 (13.2)	45 (16.7)
Disagree	88 (28.4)	76 (28.1)
Neutral	64 (20.6)	45 (16.7)
Agree	87 (28.1)	78 (28.9)
Strongly agree	30 (9.7)	26 (9.6)
If someone in your family has leprosy, you would never disclose it to anyone.		
Strongly disagree	58 (18.7)	66 (24.4)
Disagree	87 (28.1)	81 (30.0)
Neutral	109 (35.2)	78 (28.9)
Agree	46 (14.8)	32 (11.9)
Strongly agree	10 (3.2)	13 (4.8)
Leprosy patients should not take part in any social activities.		
Strongly disagree	82 (26.4)	81 (30.0)
Disagree	138 (44.5)	112 (41.5)
Neutral	61 (19.7)	37 (13.7)
Agree	25 (8.1)	29 (10.7)
Strongly agree	4 (1.3)	11 (4.1)
You will avoid working with a colleague with leprosy.		
Strongly disagree	81 (26.1)	89 (33.0)
Disagree	147 (47.4)	94 (34.8)
Neutral	57 (18.4)	58 (21.5)
Agree	19 (6.1)	20 (7.4)
Strongly agree	6 (2.0)	9 (3.3)

*Correct answer(s)

better attitude (Table I). Working in the tertiary care hospitals was an independent predictor of good attitude (OR = 2.19, 95% CI = 1.22–3.94, $p = 0.025$).

Pre and post-intervention

There was a significant increase in proportion of participants with good knowledge post-video lecture (87.0 vs 20.6, $p < 0.001$) (Table IV). However, there was no significant change of attitude post-intervention.

DISCUSSION

Only one-fifth of our study participants had good knowledge of leprosy. This finding is consistent with previous studies.[8-10] In Ethiopia, 519 (86.3%) healthcare workers had poor knowledge of the signs and symptoms of leprosy, leprosy reactions and management.[8] Similarly, a study in South Africa revealed general lack of basic knowledge of leprosy among the primary care doctors.[9] Furthermore, poor knowledge was reported among 50% of the doctors in working in the dermatology field in China.[11]

Our study participants had limited experience with leprosy patients (came across, diagnosed or managed < 5 cases of leprosy). In Italy, only 11 (10.8%) of the doctors had interaction with a leprosy case, and only 6.9% had diagnosed leprosy before and none had managed a leprosy patient.[12] In Southern Malawi, 13 (37%) healthcare workers had never seen a leprosy patient and 29 (83%) had never diagnosed leprosy before.[13] Among doctors working in dermatology field in China, 20% of them had never seen a leprosy patient and 41% had never diagnosed leprosy.[11] Lack of experience of doctors in leprosy could be due to the lack of exposure to leprosy cases in non-endemic areas.

Diagnosing leprosy is challenging as it can mimic any skin condition.[14] In Malaysia, a case series of 27 leprosy patients reported that there were missed diagnoses by primary care doctors in 12 patients (44·4%).[15] Previous experience with leprosy patients was an important predictor of better knowledge in our study and previous studies.[8,10] Abeje et al reported that good knowledge was associated with training and exposure to leprosy.[8] In Italy, higher knowledge score was reported among doctors who had diagnosed or interacted

Table III: Factors associated with good knowledge

	Good knowledge (univariate)				Good knowledge (multivariate)			
	Crude odds ratio (OR)	95% confidence interval of OR		*p*-value [a]	Adjusted odds ratio (OR)	95% confidence interval of OR		*p*-value [a]
		Lower value	Upper value			Lower value	Upper value	
Age group (years)								
< 30	1.00	1.03	4.69	**0.043**				
≥ 30	2.20							
Level of care								
Primary care	4.02	1.70	9.50	**0.006**				
Tertiary	2.79	1.21	6.41	**0.001** [b]				
Secondary	1.00			**0.016** [b]				
Position				**<0.001**				**<0.001**
Medical officer	1.00				1.00			
Specialist	4.21	2.14	8.27		4.55	2.17	9.57	
Years in service				0.052				
< 5	1.00							
≥ 5	1.73	1.00	3.12					
Number of leprosy cases came across				**<0.001**				
< 5	1.00							
≥ 5	3.74	2.01	6.97					
Number of leprosy cases diagnosed				**0.017**				
< 5	1.00							
≥ 5	5.13	1.34	19.68					
Number of leprosy patients managed				**<0.001**				**0.003**
< 5	1.00				1.00			
≥ 5	4.96	2.40	10.25		3.37	1.52	7.47	
Received teaching on leprosy during undergraduate				0.153				
No	1.00							
Yes	1.93	0.78	4.78					
Last time involved in any educational activities related to leprosy				**<0.001**				**<0.001**
Never	1.00				1.00			
More than a year	1.46	0.64	3.33	0.364 [b]	1.02	0.43	2.42	0.963 [b]
Within last year	5.68	2.14	15.04	**<0.001** [b]	4.70	1.69	13.04	0.003 [b]

[a] Likelihood Ratio (LR) test [b] Wald test
The model has no interaction terms, no multicollinearity problem and no outliers.
Hosmer-Lemeshow goodness-of-fit test for both models was not significant.
Eighty one percent cases are predicted correctly whether they have good knowledge and AUC of ROC is 72.9% (acceptable discrimination).
* No factors associated with good attitude generated from multiple logistic regression

Table IV: Pre and post-intervention knowledge and attitude

Knowledge and attitude	Pre-intervention, n = 310 n (%)	Post-intervention, n = 270 [a] n (%)	*p*-value [b]
Knowledge			**<0.001**
Good	64 (20.6)	235 (87.0)	
Average	216 (69.7)	35 (13.0)	
Poor	30 (9.7)	0	
Attitude			**0.044**
Good	113 (36.5)	114 (42.2)	
Poor	197 (63.5)	156 (57.8)	

[a] Response rate for post-intervention is 87.1%
[b] McNemar's test (knowledge regroup to two groups - good knowledge vs average to poor)

with leprosy patients.[12] Our participants who were specialists and with longer working experience had better knowledge. This is likely due to specialists having more experience managing leprosy patients (managed ≥ 5 leprosy patients). Primary care doctors with limited experience reported having less confidence in diagnosis and management of leprosy.[4] Our cohort working in primary care clinic or tertiary hospital had better knowledge compared to those working in secondary care (district hospitals). This is likely due to the primary care and tertiary care doctors having more exposure to leprosy patients (came across ≥ 5 leprosy patients). The majority of our cohort working in tertiary hospital were from the medical department. It is possible that they were well-read on leprosy as a subject in internal medicine.

The majority of our cohort did not receive undergraduate teaching on leprosy. In India, only 40% of medical students were aware of the cardinal signs of leprosy.[16] Furthermore, our study found no association between undergraduate teaching in leprosy and good knowledge and positive attitude. Among medical students in Nigeria, despite having lectures on leprosy, only 24.7% of them had good knowledge of leprosy.[10] A study in India revealed medical interns had better knowledge and attitude compared to final year medical student.[16] A 1-day training program among Indian medical students significantly improved their knowledge and attitude towards leprosy.[17] This emphasises that over and above teaching medical students about leprosy, exposure to leprosy cases and training are imperative to improve knowledge and attitude.

Recent access to educational source on leprosy was an independent predictor of good knowledge of leposy. A study in Hyderabad revealed that the government doctors had better knowledge than private practice doctors possibly due to continuing medical education programmes.[18] Private doctors in Mumbai were reported to have inadequate knowledge likely due to lack of continuing education on leprosy.[19]

Only 25.8% of healthcare workers in Ethiopia had positive attitude towards leprosy patients.[8] Negative attitude was also reported among doctors working in dermatology field in China.[11] In a Sri Lankan study, 34.3% of healthcare providers were scared of leprosy and 22.5% of healthcare providers thought that leprosy patients need to be isolated from others.[20] Similar to our findings, misconceptions were reported among the healthcare workers in Guyana, where half of them believed leprosy was transmitted through touch and half were afraid of this disease.[21] Ekeke et al reported that good knowledge of leprosy was associated with positive attitude.[10] Likewise, a study in Nigeria found that good knowledge correlate with favourable attitude towards leprosy.[22]

There was a significant improvement in participants' knowledge of leprosy post-video lecture intervention. Consistent with our findings, interns in Nigeria who attended clinical demonstration on leprosy had better knowledge.[10] A study of healthcare providers in Bangladesh demonstrated an increase in knowledge after leprosy training.[23] Similarly, there was improvement in knowledge and confidence level among family medicine physicians in Malaysia after a 3-day lecture and hands-on training course.[4] Doctors working in dermatology field in China demonstrated improvement in knowledge and attitude after a lecture and training workshop.[11] On the contrary, our study found no significant improvement in doctors' attitude post-video lecture intervention. This may be because attitude change takes time. Annually, the Sabah health department organises a one-day physical course with lectures on leprosy for the doctors and medical assistants working in government clinics and hospitals. Despite that, only a small proportion of the doctors in our study had good knowledge and attitude. This is probably because of the nature of physical course that only allows limited numbers of participants each time.

As our study was conducted during the covid pandemic, online video lecture on leprosy was done as an intervention to improve knowledge of leprosy. Post-test questionnaire was done immediately post-video lecture and we were not able to assess long term improvement in knowledge and attitude. We recommend regular video lecture training conducted by the dermatologists for the medical officers and specialists from all levels of care for exposure and revision to improve knowledge of leprosy. Teledermatology consultation is cost effective, time efficient, and will be helpful to increase knowledge among the doctors and thus optimise patients' care. Future studies to assess the impact of hands-on training workshop involving leprosy patients on knowledge and attitude towards leprosy will be valuable.

CONCLUSION

The proportion of medical doctors in Sabah and Labuan with good knowledge and good attitude towards leprosy was low. Position as a specialist, experience with leprosy patients and recent education in leprosy were associated with good knowledge and attitude. Knowledge of leprosy improved significantly post-intervention. This highlights the need for educational and training programmes to improve doctors' knowledge of leprosy.

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Contact sensitisation to fragrance allergen: A 5-year retrospective study of patients in the Department of Dermatology, Hospital Kuala Lumpur

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ABSTRACT

Introduction: Fragrance allergy remains an important cause of contact dermatitis. We aim to describe the characteristics of patients with contact sensitisation to fragrances who underwent patch testing in the Department of Dermatology Hospital Kuala Lumpur.

Materials and Methods: This is a 5-year retrospective study of patients who developed positive reactions to fragrance allergens at the Department of Dermatology, Hospital Kuala Lumpur, Malaysia between January 2017 and December 2021. Patch tests were performed with European Baseline Series and relevant extended series. Patch test readings were recorded according to the International Contact Dermatitis Research Group recommendation.

Results: A total of 854 patients underwent patch test during the study period with 133 (15.6%) patients developing at least one positive reaction to fragrance allergens. The median age of patients at presentation was 40 years (range 16-79) old with 78.2% females. The most common initial presentation was hand eczema (55.6%). Other commonly involved sites include face (38.3%), leg (35.3%) and trunk (22.6%). The most frequent sensitising fragrance allergens were Fragrance Mix I (10.5%), Balsam of Peru (7.1%) and Fragrance Mix II (4.9%). Sixty patients (45%) developed positive reaction to more than one fragrance allergens. Twelve patients (9%) developed positive patch test reactions to their own products such as skincare, hair dye and hand wash. Current relevance was recorded in 96 patients (72.2 %).

Conclusion: Contact sensitisation to fragrance allergens was detected in about 15% of our patients who underwent patch test. The most common sensitising allergens were Fragrance Mix I and II and Balsam of Peru.

KEYWORDS:
Fragrances, allergic contact dermatitis, contact sensitisation to fragrances, patch test, Balsam of Peru

INTRODUCTION

Contact dermatitis is defined as inflammation of the dermis and epidermis resulting from direct contact between a substance and the surface of the skin. It is the result of a type IV hypersensitivity reaction involving the T lymphocytes of immune system. It can arise from exposure to various allergens which include metals, preservatives, woods and plants, plastic, rubber, medicines, medical devices, cosmetics and fragrances.[1]

According to International Fragrance Association (IFRA), fragrance ingredient is "any basic substance used for its odour properties or malodour coverage."[2] Fragrances are frequently present in a variety of products for instance cosmetics (fine fragrances and aftershaves, lip balms, lipsticks, deodorants), household products (detergents), toiletries (shampoos, soaps, lotions, creams, sunscreens), wet wipes, baby products, paper products, fabric and clothes, topical pharmaceuticals, essential oils, industrial products (paints, rubber, plastic, insecticides, herbicides), and even flavouring agents in oral hygiene products, foods or drinks.[3,4] Patch testing remains pivotal in diagnosing fragrance allergy.

This study aims to describe the characteristics of patients who have contact allergy to fragrances in Hospital Kuala Lumpur, Malaysia.

MATERIALS AND METHODS

This is a 5-year retrospective study of patients who developed positive reactions to fragrance allergens upon patch testing at the Department of Dermatology, Hospital Kuala Lumpur, Malaysia between January 2017 and December 2021.

Patch tests were performed with European Standard Series and relevant extended series from Chemotechnique Diagnostics using IQ chambers™. Extended series used include cosmetic series, metal series, rubber series, dental series, medicament series, textile series, shoe series, plastic and glue series and hairdressing series. Fragrance allergens that were tested in the study included Fragrance Mix I, Fragrance Mix II, Balsam of Peru, and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) (Lyral) in the European baseline series, as well as tea tree oil (oxidised), peppermint oil, benzyl alcohol, musk mix and benzyl salicylate in the cosmetic series. Patients were also tested with their own products, including hair dye, hair shampoo, cosmetics, skin care products, soap and toothpaste. Toothpaste and leave-on cosmetics such as lipstick, facial powder, facial foundation

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Table I: Characteristics of patients who developed positive reaction to fragrance allergens in patch testing

Characteristics		n = 133 (%)
Median age in years (range)		40 (16 – 79)
Male:female ratio		1:3.6
Ethnicity, n (%)	Malay	75 (56.4)
	Chinese	41 (30.8)
	Indian	13 (9.8)
	Others	4 (3.0)
Occupations, n (%)	White collar workers	32 (24.1)
	Healthcare workers	30 (22.5)
	Blue Collar workers	15 (11.3)
	Pink collar workers	11 (8.3)
	Housewife	22 (16.5)
	Unemployed	23 (17.3)
Patch test series used, n (%)	European baseline	133 (100)
	Cosmetic	45 (33.8)
	Rubber	34 (25.6)
	Dental	18 (13.5)
	Metal	18 (13.5)
	Shoes	14 (10.5)
	Hairdressing	9 (6.8)
	Textile	8 (6)
	Medicaments	8 (6)
	Plastic and glue	4 (3)
	Own products	65 (48.9)

Table II: Sites of lesions in 133 patients who were sensitized to fragrance allergens

Sites		n (%)
Hand		74 (55.6)
Face		51 (38.3)
	Not otherwise specified	33 (24.8)
	Lips	17 (12.8)
	Ears	11 (8.3)
	Eyelids	8 (6.0)
	Nose	3 (2.3)
Leg		47 (35.3)
Trunk		30 (22.6)
Arm		17 (12.8)
Neck		12 (9.0)
Anal/genital		11 (8.3)
Scalp		8 (6.0)
Scattered generalised		8 (6.0)

Table III:The sensitisation pattern of current cohort

Allergens		Number of patient positive to allergen (Sensitisation rate %)
European baseline series	Fragrance mix I	90 (10.5)
n =854	Balsam of Peru	61 (7.1)
	Fragrance mix II	42 (4.9)
Cosmetic series	Tea tree oil oxidised	7 (2.9)
n=242	Peppermint oil	5 (2.4)
	Lyral	10 (1.2)
	Musk mix	1 (0.5)
	Benzyl alcohol	1 (0.4)
	Benzyl salicylate	0 (0)

Table IV: Combined cross-reactivity (CR) rates

Compound 1	Compound 2	CR, %
Fragrance Mix I	Colophony	12.2
	Propolis	3.3
	Sesquiterpene lactone mix	2.2
Fragrance Mix II	Colophony	9.5
	Propolis	0
	Sesquiterpene lactone mix	0
Balsam of Peru	Colophony	13.1
	Propolis	4.9
	Sesquiterpene lactone mix	1.6

Table V: Worldwide studies on contact sensitisation to fragrances

Author country	Study period	n	Common age group (years)	Positive patch test reaction (%)	Top two allergens
Frosch et al., Germany[11]	2009 to 2012	56813	>40	NA	1) Fragrance mix I 2) Balsam of Peru
Cuesta et al., Spain[13]	2004 to 2008	1253	>40	9.3	1) Balsam of Peru 2) Fragrance mix I
Vejanurug et al., Thailand[15]	2013 to 2014	312	>40	26.9%	1) Fragrance mix I 2) Fragrance mix II
Hafner et al., Brazil[16]	2000 to 2015	1870	40	13.8%	1) Fragrance mix I 2) Colophony

and deodorants were tested "as is". Cleaning products such as facial wash, shampoo and shower gel were diluted with water to 10% (w/w).

Patches were applied to the patients and removed after 48 hours. Initial reading was recorded at 48 hours and final reading was noted at 96 hours after patch application. The parameters studied include positive patch test reactions and the source of allergens. Readings were recorded according to the International Contact Dermatitis Research Group recommendation.[5,6] A positive patch test reaction is defined as a reaction that fulfils at least a 1+ reaction (i.e., +, ++ or +++). Other reactions that can be found during patch tests are irritant reaction (IR), doubtful reaction (+?) and angry back reaction, but these are not considered as a positive patch test reaction.

RESULTS

There was a total of 854 patients who underwent patch test between January 2017 and December 2021 at Department of Dermatology, Hospital Kuala Lumpur. Out of these, 133 (15.6%) patients developed at least one positive reaction to fragrance allergens. The demographic data was shown in Table I. The median age of patients was 40 years (range 17 to 79) and 78.2% of patients were female. The initial presentations include allergic contact dermatitis (18.8%), hand eczema (14.3%), contact dermatitis (12%), discoid eczema (10.5%), atopic eczema (7.5%), cheilitis (7.5%), hand and feet eczema (6.8%) and lichen planus/lichenoid reaction of oral mucosa (6.8%). Other less frequent presentations include face eczema, oral ulcer, papular eczema, stasis eczema, allergic contact gingivitis, chronic urticaria, contact urticaria, papular urticaria, feet eczema, insect bite dermatitis, irritant contact dermatitis, metal allergy, palmoplantar eczema, photoaggravated dermatitis, seborrheic dermatitis and ashy dermatoses.

The most common sites of involvement were hands (55.6%), face (38.3%), legs (35.3%) and trunk (22.6%) as shown in Table II. As shown in Table III, the most frequent sensitising allergens were Fragrance Mix I (10.5%), balsam of Peru (7.1%) and Fragrance Mix II (4.9%). Other sensitising allergens included tea tree oil oxidised (2.9%), peppermint oil (2.4%), Lyra (1.2%), musk mix (0.5%) and benzyl alcohol (0.4%). None of our patients were sensitised to benzyl salicylate. There were 60 (45%) patients who developed positive reaction to more than one fragrance allergen. For our patients who were sensitised to fragrance mix I, cross-reactivity (CR) rate to colophony was 12.2% (Table IV). In patients who were allergic to balsam of Peru, CR rate to colophony was 13.1%. Around 9% of patients who were sensitised to Fragrance Mix II also cross-sensitised with colophony. None of the patients who were sensitized to Fragrance Mix II cross-reacted with propolis and sesquiterpene lactones (SQL) mix.

There were 12 patients (9%) who developed positive patch test reactions to their own products such as skin care products (n = 4), hair dye (n = 3), hand wash (n = 3), hair shampoo (n = 1) and cosmetic (n = 1). Relevance of positive patch test reaction was assessed in all and 96 patients (72.2%) were found to have current relevance, mostly to their own toiletries (46.6%), followed by their household products (15.5%), cosmetics (9.5%), gloves (9.5%), footwear (6.9%), hair dye (3.4%) and food or flavouring (2.6%).

DISCUSSION

Fragrances represent the second most common cause of allergic contact dermatitis (ACD) after nickel.[7,8] It is known to be the most common cause of allergies to cosmetics.[9] The prevalence of contact sensitisation to fragrances differs worldwide and the most common contributing allergens were Fragrance mix I, Balsam of Peru and Fragrance mix II (Table V).[11,13,15,16] The prevalence of fragrance contact allergy in the general population is 0.7–2.6%.[10] A study across 12 European countries from 2009 to 2012 showed that 12.7% out of more than 50,000 patients patch tested revealed positive reactions to Fragrance Mix I, Fragrance Mix II, Lyral, balsam of Peru, oil of turpentine, or a combination of these.[11] In Spain, positive patch test reactions towards fragrance allergens were found in 1.7 to 15.1% of study population.[12-14] A smaller study in Thailand showed that 22.1% of 312 patients reacted to Fragrance Mix I, Fragrance Mix II, Balsam of Peru, or combinations.[15] Our study which showed a prevalence of 15.6% of fragrance allergy was similar to other studies to date.[10,16]

In a study of 3119 patients patch-tested in 2008 to 2011 across five European countries, women were found to be affected twice as often as men.[16,17] Our study presented similar characteristics. Typically, women in their mid-40s, commonly present with facial or hand eczema due to fragrance allergy,[10,16,18-20] likely due to increased use of fragranced products among women. Sensitisation is more common at an older age likely due to age-related poor skin barrier function from asteatotic eczema,[20] and increased use of, as well as cumulative exposure with age to, products with fragrance.[21] Face is commonly affected likely due to the direct

application of cosmetics, indirect transfer from contaminated hands, or airborne contact (mists, sprays, and aerosols).[10] Eyelids are the most susceptible area to fragrance allergy as it has the thinnest epidermis.[22] The other commonly involved area is the lips, especially the unkeratinised epithelium.[23] When it comes to lips involvement, food flavourings are frequently the contributor. Hands are commonly involved owing to the use of fragrance containing household products, cosmetics and topical medications.[21] It is apparent that from our study there is a significant number of our patients who had dermatitis at the groin, pruritus ani or pruritis vulva (8.3%). This could be due to the fact that topical medicaments used in these areas also contained fragrances. These areas may also develop ectopic contact dermatitis from the transfer of fragrance allergens from the hands to these sensitive areas.

Cheng et al. reported a common presentation of papular/vesicular lesions or patchy dermatitis with eczematous papules among patients presented with fragrance allergy. Chronic lichenified pruritic plaques may also be seen.[3] Our study showed similar findings where the initial presentations of fragrance allergy include eczematous lesions, papular lesions or lichen planus or lichenoid reaction of oral mucosa.

Our study revealed that Fragrance Mix I is the most common sensitising allergen (10.5%), which is similar to other studies.[3,10,18,24] Fragrance Mix I consisted of 8 fragrance chemicals including cinnamyl alcohol, cinnamal, hydroxycitronellal, amyl cinnamal, geraniol, eugenol, isoeugenol and oak moss absolute. Oak moss absolute is the most common individual allergen contributing to fragrance allergy while amyl cinnamal is the least frequent contributor of fragrance allergy.[9] Oak moss absolute is an extract derived from lichen growing on oak trees in the Mediterranean area, and it has a complex composition and has been used in many fragrance products, including perfumes, colognes and aftershaves.[8] Geraniol is a commonly used fragrance terpene (appreciated for its fresh, flowery odour), occurring naturally in many flowers and plants, and is present in high concentrations in essential oils of rose and geranium.[8] Hydroxycitronellal and geraniol are the fragrances most widely found in perfumes.[25] Cinnamal, hydroxycitronellal and isoeugenol are commonly present in deodorants. Isoeugenol can also be found in lip products, hydroalcoholics, aftershaves, women's facial and hand creams, intimate wipes, and make-up removers.

The rate of sensitisation of Balsam of Peru was comparable to previous studies.[3,10] Balsam of Peru, also known as *Myroxylon pereirae*, is a natural complex resin derived from a Central American tree (or *Myroxylon pereirae* tree).[9,26] It is frequently present in a wide variety of products ranging from drugs, perfumes, aroma compounds, cleaning products, dental cement and liquids, cosmetic products to foods. Balsam of Peru is used in topical medicaments to treat wounds as it has antibacterial properties. Its most important allergen is formed by the polymerisation of an ester of benzoic acid or cinnamic acid and coniferyl alcohol.[27] Its crude use in perfumes has been banned by International Fragrance Association (IFRA) since 1982 but its extracts and distillates can still be used in manufacturing of perfumes.[26]

The third most frequent sensitising allergen is Fragrance Mix II (4.9%), similar to previous studies.[24] Fragrance Mix II consists of hexyl cinnamic aldehyde, hydroxyisohexyl 3-cyclohexene carboxaldehyde, farnesol, coumarin, citral and citronellol. The most frequent sensitising individual allergen is hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), also known as Lyral; the least frequent one is citronellol. Since the addition of Fragrance Mix II as standard test for fragrance allergy, there has been an increase in the sensitivity for detection of fragrance sensitisation with respect to traditional markers for fragrances (Fragrance Mix I and Balsam of Peru).[9] Citronellol is most widely found in hygiene products and daily moisturizers.[25] Lyral contributes to 1.2% of positive patch test result in our cohort, similar to other study.[10] Lyral is more commonly found in deodorants.[28] It is interesting to note that not all our patients who were positive to Lyral were also positive to Fragrance Mix II. This could be due to the higher concentration of Lyral when tested as an individual allergen compared to its concentration in the Fragrance Mix II. Of note, Lyral has been banned from cosmetics products in EU since August 2021 hence it will be interesting to observe if the trend of Lyral sensitivity decreases subsequently.

A total of 45% of our patients developed positive reaction to more than one fragrance allergens in our study, likened to another study.[24] There are more than 2500 existing fragrance ingredients and at least 100 ingredients are known contact allergens.[12] Hence, it is crucial to supplement standard patch testing with patients' own products. Hair care products commonly contain a great amount of fragrances. For instance, only 2.8% of 324 styling products were free of fragrances.[10] Studies have shown significant cross sensitization between colophony, propolis and fragrance. In subjects who are allergic to colophony; fragrance and propolis may be significant cross-reactors. Similarly, in subjects who are allergic to propolis; fragrance and colophony are considered to be significant cross-reactors.[29] However, for patients allergic to fragrance, cross sensitisation to propolis or colophony is not significant in terms of cross-reactivity rate.[29] A 10% CR rate was considered to be significant enough to recommend avoidance of a potential cross-reacting allergen based on the American Contact Dermatitis Society's Contact Allergy Management Program (CAMP) recommendations.30 Nonetheless, our study showed otherwise (Table V). For our patients who were sensitive to Fragrance Mix I, colophony may be a significant cross-reactor with a CR rate of 10.5%, but not propolis and SQL mix. Patients allergic to Balsam of Peru also showed a significant cross sensitisation to colophony (13.1%) but not to propolis and SQL Mix. We therefore recommend our patients who develop contact sensitisation to Fragrance Mix I and Balsam of Peru to also avoid colophony, in view of the CR rate of more than 10%.

Clinical relevance is crucial to translating research results into clinical use. The rate of currently relevant sensitisations reflect the extent of current exposure and the consequent disease state. This may rise or decline with time, hence showing the direct effect of a fragrance contact allergy to the individual.[26] It is believed that a strong positive reaction is more likely to have clinical relevance than a weak positive reaction. The recorded relevance in our study was high

(72.2%), similar to another study.[31] This is likely due to fragrance sensitisation acting as a provoking factor for a spectrum of dermatoses. Unless fragrance-containing products are avoided, previous dermatoses will not improve despite appropriate treatment and protective measures.[13]

Contact allergy to fragrance is mostly not related to occupation[32], but more commonly originates from personal use of scented cosmetics. However, secondary occupational exposure to fragrance ingredients may happen at workplace. Previous literature showed a high prevalence of allergy to Fragrance Mix I among healthcare workers due to irritant hand contact dermatitis from repeated washing disrupting the skin barrier, allowing better allergen penetration, hence subsequent application of products containing fragrances introduces a source for allergen exposure.[3] Sensitivity to Balsam of Peru has been found to be more common among healthcare workers especially dentists.[33] Dentists also have a higher risk for allergy to eugenol (one of the components of Fragrance Mix I) due to exposure from mouthwashes, dressings, impression materials, and periodontal packings.19 About a fifth of our cohort were healthcare workers. Out of these, eight out of 30 healthcare workers (26.7%) had fragrance allergy related to work. Food handlers may be frequently exposed to components of Fragrance Mix I (cinnamal and cinnamic alcohol) and Balsam of Peru due to handling of spices and essential oils.[3] Hairdressers, beauticians and aromatherapists are also particularly at risk for fragrance allergy.[10] Overall, our study has shown a fairly equal distribution of fragrance allergy across different occupations.

As fragrances are widely used in daily products, it is extremely difficult for sensitized patients to avoid them completely without limiting their daily activities. Some products may also omit labelling fragrance in their ingredient if it was used for masking odour instead of imparting pleasant odour. Regulations have been imposed to safeguard consumer's health and safety including mandatory labelling of fragrance ingredients on products' ingredient label if products sold contained any of the 26 fragrances governed by EU regulations.[12,31] Unfortunately, neither Balsam of Peru nor the extracts and distillates are included in the mandatory labelling as yet. Hence, there should be continuous efforts in identifying common fragrance allergens and they should be regulated continuously by authority bodies. Tighter regulations should be enforced to ensure that fragrance ingredients are labelled accordingly and correctly.[10]

Essential oils are sources of fragrance allergens and expanded patch testing involving essential oils may be considered in patients suspected to have fragrance allergy. So far, our study included few individual ingredients of essential oils which are present in the cosmetic series, namely the tea tree oxidized extract and peppermint oil. From our study, there were 2.9% and 2.4% of our patients who were sensitized to tea tree oil oxidized and peppermint oil respectively, hence it is essential to monitor these fragrance allergens in our populations. Since fragrance series was not available in our setting at present, we may include cosmetic series if we are investigating patients for fragrance allergy, as it contains a few essential oils. Cosmetic series also contains sorbitan sesquioleate, which is the dispersing agent used in Fragrance mix I hence testing for this will help to differentiate between true Fragrance mix I allergy and sorbitan sequioleate allergy.

Management of patients with fragrance allergic contact dermatitis includes avoidance of products with labelled known sensitising fragrances. Clinicians may advise patients to fully avoid the use of fragrance-containing products such as perfumes and toiletries. If patients need to use such products, they should be advised to avoid applying these products at areas of skin that are potentially traumatized (beard region, hands, and shaved areas) or occluded (axilla), as well as areas of high absorption (eyelids, genitals, and axilla) and areas of chronic dermatitis (e.g., stasis dermatitis). Exposure to air and oxidation of products should be prevented by replacing lid between uses. Household products such as dishwashing liquid, clothes detergent, toilet cleaners or floor cleaners also contain fragrance and patients should avoid skin contact with these products by using gloves or boots as protection as these household products usually have no fragrance-free alternatives. We should also educate our patients to avoid using products out of its shelf life (commonly 1 year) as certain fragrance ingredients autoxidise into allergenic products.[34] Patients with sensitisation to Balsam of Peru may benefit from a balsam-restricted diet, as Balsam of Peru has been associated with systemic contact dermatitis if ingested.[35] Examples of foods and drinks rich in Balsam of Peru include citrus fruit, spices such as vanilla and cinnamon, chocolate, cola, and tomatoes.[36] In general, avoiding exposure in infants and young children is ideal as sensitisation to an allergen is lifelong once acquired.

There is limitation to this study. Individual ingredients of fragrance mix I and fragrance mix II were not tested in all subjects showing positive reaction to the mixes. We should consider to purchase the fragrance allergy series which contains more fragrance allergens in order to detect more cases of fragrance allergy. Our findings may not be representative of the whole Malaysian population as this is only a single centre study.

CONCLUSION

Contact sensitisation to fragrance allergens was detected in about 15% of our patients who underwent patch test. It is more prevalent in women and commonly involves hands and face. The most common sensitising allergens were Fragrance Mix I, Fragrance Mix II and Balsam of Peru. Current relevance of positive patch test reaction was found in almost three quarter of our patients and these were mostly towards their own toiletries, household products and cosmetics. It is crucial to test patients' own products during workup for allergen sensitisation to ensure that these relevant reactions are not missed.

CONFLICT OF INTEREST DECLARATION

The authors have no conflict of interest to declare.

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Impedance changes in cochlear implant electrodes one year after switch on: A cohort study at a tertiary referral hospital in Jakarta, Indonesia

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ABSTRACT

Introduction: Monitoring of impedance field telemetry is crucial to maintaining optimal function of cochlear implants. This study aims to investigate impedance changes in cochlear implant electrodes one year after switch on.

Materials and Methods: A retrospective repeated cross-sectional study was conducted by recruiting patients with cochlear implants presenting to the Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia between 2017 and 2021. Basal (b1, b2) and apical (a1, a2) electrodes, representing the outermost and innermost parts of the cochlear implant electrodes, were measured at switch on and at 1 year post-implantation.

Results: A total of 123 patients, with a total of 123 cochlear implant samples, were included in the analysis. We found a substantial change in electrical impedance between switch on and follow-up periods, where the impedance levels of basal electrodes decreased (b1: mean difference (MD) −1.13 [95% confidence interval (CI): −1.71, −0.54], p<0.001; b2: MD −0.60 [95%CI: −1.17, −0.03], p=0.041) and those of apical electrodes increased (a1: MD 0.48 [95%CI: −0.28, 0.99], p=0.064; a2: MD 0.67 [95%CI: 0.12, 1.22], p=0.017). We also found that the choice of surgical approaches for implant insertion may affect the electrode impedance. Cochleostomy approach resulted in a higher impedance than round window in basal (b1) and apical (a2) electrodes both at switch on and follow-up (b1 at switch on and at follow-up: p=0.019 and p=0.004; a2 at follow-up: p=0.012). Extended round window approach also resulted in a higher impedance than round window in basal (b1) and apical (a2) electrodes at follow-up (p=0.013 and p=0.003, respectively).

Conclusion: Electrical impedance of cochlear implant electrodes may change over time, highlighting the importance of regular impedance assessments for cochlear implant users to ensure optimal device function. The round window approach resulted in better initial and long-term impedance levels compared to cochleostomy, and better long-term impedance levels than extended round window. Extended round window approach also gives better impedance level than cochleostomy. Further research should investigate the potential interplay between surgical approach and other factors that may impact impedance levels to confirm our findings.

KEYWORDS:
Cochlear implant, cross-sectional, electrical impedance, follow-up studies, surgical approach

INTRODUCTION

Cochlear implants are widely used for the habilitation and rehabilitation of patients with profound sensorineural hearing loss (SNHL). Such implants use a software connecting an external component, i.e., speech processor, to an internal component consisting of an array of electrodes surgically implanted into the cochlea. The electrodes play a crucial role in aural habilitation by stimulating the auditory nerve fibers in the cochlea, enabling the brain to receive auditory input and perceive sound, thereby improving hearing and speech development especially in children with congenital SNHL.

To maintain an optimal function, it is essential to regularly examine the electrode impedance in cochlear implants. Electrical impedance, a parameter measuring the resistance or opposition of electrodes to the flow of electrical current, is evaluated both intraoperatively and during mapping sessions to describe the integrity of the electrodes and the electrical current between the electrodes and the surrounding cochlear tissues.[1,2] Any changes in impedance levels may indicate issues with the electrodes and/or cochlear implants, such as short circuits, open circuits, or damaged devices.[1,3]

Electrical impedance of a cochlear implant may be affected by several factors including electrode placement, tissue changes (e.g., inflammation or damage), electrode corrosion, and the duration of use. Long-term use of the device may lead to a reduction in its efficiency in delivering electrical current to the surrounding cochlear tissues, resulting in an increase in impedance and decreased implant effectiveness.[2-4] Therefore, it is saliently important to perform follow-up examinations post-implantation to investigate potential changes in the electrical impedance of cochlear implants over time. This study aims to investigate changes in impedance levels in patients with cochlear implants one year after implantation at a tertiary referral hospital in Jakarta, Indonesia.

MATERIALS AND METHODS

A retrospective repeated cross-sectional study was conducted by including patients using cochlear implants presenting to

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the Ear, Nose, and Throat (ENT) outpatient clinic of the Department of Otorhinolaryngology and Head and Neck Surgery, Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia between 2017 and 2021. All patients underwent complete electrode insertion using implants manufactured by MED-EL (PULSAR, SONATA, OR SYNCHRONY models; Innsbruck, Austria), Cochlear® (Slim Straight® (CI622) or Contour Advance® (CI612) models; Sydney, Australia), or Advanced Bionics™ implants (HiFocus™ 1J or HiFocus™ Mid-Scala models; Bangalore, India), and patients with device failures were excluded from this study. The parents or guardians of the children provided written informed consent for the children to participate in this study. The study protocol has been approved by the Research Ethics Committee, Faculty of Medicine Universitas Indonesia and Cipto Mangunkusumo National General Hospital (ethical no. 22-02-0181). This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[5]

Measurement of the impedance levels (kΩ) of the cochlear implants was performed at switch on and at 1 year post-implantation. The electrodes investigated in this study were basal electrodes (b1, b2) and apical electrodes (a1, a2; Figure 1). In addition, we also recorded data on cochlear implants (type of electrodes, hearing preservation technique, surgical approach for implant insertion) and comorbidities (inner ear malformation and obliteration of scala tympani). The round window insertion was used as the hearing preservation group, whereas extended round window and cochleostomy insertion were used as the non-hearing preservation group. The cochlear implantation procedures in this study were performed by two surgeons which can be consider as bias and a limitation to this study. The collected data were then tabulated, described narratively and analysed using paired sample t tests to compare values from consecutive fitting sessions, and one-way analysis of variance (ANOVA) followed by Tukey's HSD post hoc tests to compare impedance values between surgical approaches at each mapping session, whichever appropriate, to compare values from consecutive fitting sessions. Dichotomous data were presented in frequencies and proportions, while continuous data in mean ± standard deviation (SD) or mean difference (MD) and 95% confidence intervals (95% CI). All statistical analysis were performed using SPSS 24.0 (SPSS Inc., Chicago, IL), and a p value of ≤0.05 denotes statistical significance.

RESULTS

A total of 123 patients with ages ranging from 1 to 45 years old, cumulating a total of 123 samples of cochlear implantation procedures, were included in the present study. 50.4% (62/123) patients were female, and about 64.2% (79/123) received implantation on the right side. Most of the children underwent hearing preservation technique (106 patients, 86.2%) with lateral wall electrodes (114 patients, 92.7%). 71.5% (88/123) of the children underwent round window insertion, followed by an extended round window approach (18 patients, 14.6%) and cochleostomy (17 patients, 13.8%). No children presented with inner ear malformation (0/123 patients, 0.0%), and two patients (1.6%) had obliterated scala tympani (Table I).

We found a statistically significant changes in electrical impedance between switch on and 1 year post-implantation periods, where the impedance values of b1 and b2 electrodes decreased at 1 year follow-up (b1: MD −1.13 [95%CI: −1.71, −0.54], p<0.001; b2: MD −0.60 [95%CI: −1.17, −0.03], p=0.041), while those of a2 electrode slightly increased (MD 0.67 [95%CI: −0.12, 1.22], p=0.017; Table II). We also observed a slight increase in the impedance value of a1 electrode, although not statistically significant (MD 0.48 [95%CI: 0.28, 0.99], p=0.064).

We also found that the choice of surgical approaches for implant insertion contributed to the evolution of apical and basal impedance at switch on and 1-year follow-up post-implantation (Table III). In basal (b1) electrodes, cochleostomy approach resulted in a higher impedance both at switch on and follow-up compared to round window approach (p=0.019 and p=0.004, respectively), while the extended round window approach resulted in a significantly higher impedance level than round window approach only at follow-up (p=0.013). Meanwhile, in apical (a2) electrodes, both extended round window and cochleostomy approaches had a substantially higher/lower impedance levels than the round window approach at follow-up (p=0.003 and p=0.012, respectively), but not at switch on (p=0.428 and p>0.999, respectively).

DISCUSSION

Impedance field telemetry is a widely used parameter to assess the integrity of a cochlear implant device during implantation and mapping sessions. This enables clinicians to ensure the optimal function of cochlear implants in order to improve hearing and speech abilities of patients with severe-to-profound SNHL. This study, assessing the impedance levels of basal (b1 and b2) and apical (a1 and a2) electrodes, which represent the outermost and innermost part of the cochlear implant electrodes, found that significant changes in impedance levels occur over time, where the impedance values were decreased in basal electrodes and increased in apical electrodes at 1-year post-implantation.

It is known that impedance levels of a cochlear implant may change over time due to various factors affecting the tissues surrounding the device. Following implantation, fibrous tissues, protein exudates, and macrophages may surround the electrodes, caused by inflammation or other tissue changes, thereby potentially altering the electrical properties of the surrounding tissues and leading to changes in impedance levels. Additionally, the metal components of the implant may gradually corrode and thus induce further changes in impedance levels of the electrodes.6 Previous studies have shown that the impedance levels of a cochlear implant electrode will increase substantially in the first week after implantation and are expected to plateau within one to two months.[7,8] In addition to wear and tear, other factors that may also affect the impedance levels of a cochlear implant include tissue changes and electrode placement. As previously stated, the environment surrounding the device may contribute to the impedance levels of the electrodes. This indicates that any tissue changes (e.g., inflammation, infection, fibrosis) and the location of the electrodes in the

Table I: Clinical characteristics of the study population (n = 123)

Sample characteristics	n (%)
Sex	
Male	61 (49.6)
Female	62 (50.4)
Side of implantation	
Right	79 (64.2)
Left	44 (35.8)
Type of electrode	
Lateral wall	114 (92.7)
Perimodiolar	9 (7.3)
Hearing preservation technique	
Yes	106 (86.2)
No	17 (13.8)
Scala tympani approach	
Round window	88 (71.5)
Extended round window	18 (14.6)
Cochleostomy	17 (13.8)
Inner ear malformation	
Yes	0 (0.0)
No	123 (100)
Scala tympani obliteration	
Yes	2 (1.6)
No	121 (98.4)

Table II: Impedance levels (kΩ) of the measured electrodes at switch on and at 1 year follow-up

Electrode		Switch on (kΩ)	Follow-up (kΩ)	Changes		
				MD	95% CI	*p* value
Basal electrodes	b1	8.94 ± 3.75	7.81 ± 3.05	–1.13	–1.71, –0.54	<0.001
	b2	±	±	–0.60	–1.17, –0.03	0.041
Apical electrodes	a1	±	±	0.48	0.28, 0.99	0.064
	a2	6.41 ± 2.80	7.09 ± 2.35	0.67	0.12, 1.22	0.017

Unless otherwise stated, data are expressed as mean ± standard deviations. p value derived from paired t tests. CI, confidence interval; MD, mean difference.

Table III: Comparison of impedance levels of the b1 and a2 cochlear implant electrodes between surgical approaches for implant insertion

Electrodes	Switch on				Follow-up			
	Approach to scala tympani	RW	ERW	C	Approach to scala tympani	RW	ERW	C
b1 electrode	RW		1.74 (p=0.203)	**2.68 (*p*=0.019)**	RW		**2.17 (*p*=0.013)**	2.49 (p=0.004)
	ERW	–1.74 (p=0.203)		–0.94 (p>0.999)	ERW	–2.17 (p=0.013)		0.32 (p>0.999)
	C	**–2.68 (*p*=0.019)**	0.94 (p>0.999)		C	–2.49 (p=0.004)	**–0.32 (*p*>0.999)**	
a2 electrode	RW		2.17 (p=0.428)	2.49 (p>0.999)	RW		**–1.95 (*p*=0.003)**	**–1.73 (*p*=0.012)**
	ERW	–2.17 (p=0.428)		0.32 (p=0.253)	ERW	**1.95 (*p*=0.003)**		0.22 (p>0.999)
	C	–2.49 (p>0.999)	–0.32 (p=0.253)		C	1.73 (p=0.012)	**–0.22 (*p*>0.999)**	

Data expressed as mean difference (p values). p values derived from Tukey's HSD post hoc ANOVA test. RW, round window; ERW, extended round window; C, cochleostomy

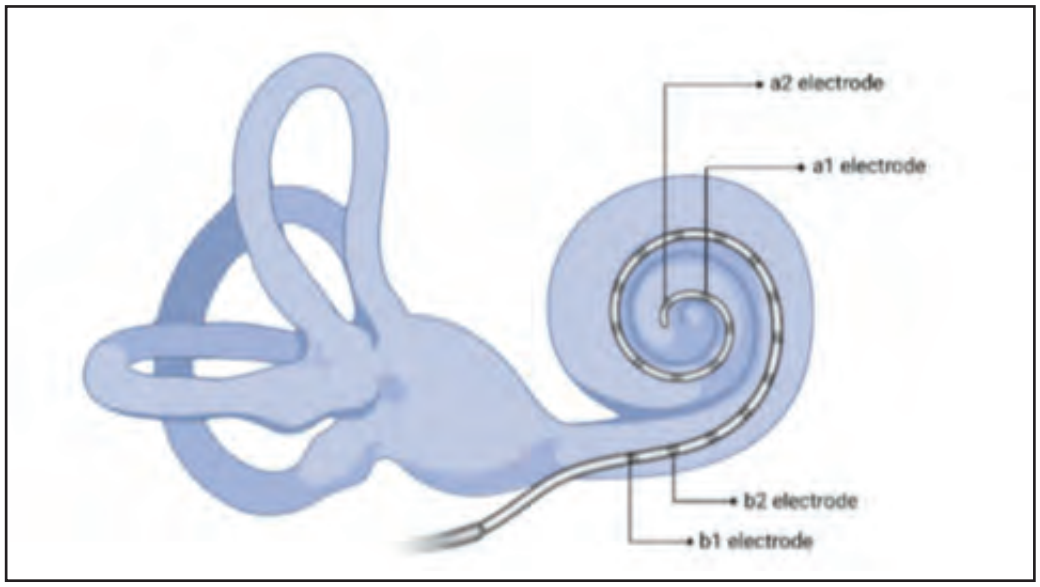

Fig. 1: Location of the basal (b1, b2) and apical (a1, a2) cochlear implant electrodes in the scala tympani.

cochlea may affect the electrical current flow and subsequently affect the impedance levels of the electrodes.[2,4] With regards to electrode placement, our findings suggest that the surgical approach to implant insertion had an effect on impedance levels of the electrodes. In this study, we recorded three surgical approaches: round window, extended round window, and cochleostomy. In brief, the round window approach is a standard method of surgery, performed by creating a small opening in the bone of the round window niche, while cochleostomy is a conventional method that involves drilling a hole in the cochlear bone to insert the electrode array.[9] On the other hand, the extended round window approach is a combination of both round window and cochleostomy approaches and is usually performed in situations where the round window is not easily visible and/or accessible.[10] To date, limited research has been conducted to compare the effect of different surgical approaches on the impedance levels of cochlear implant electrodes. A previous systematic review by Avasarala et al.[11] found that two out of three studies reported that there were no substantial differences on impedance levels between surgical approaches, while one study found that round window approach yielded a lower initial impedance value.[11] The study found that significant differences in switch on impedance were observed in the basal-middle electrodes and not in the apical region[12], which is consistent with our findings. This may be explained by the fact that traditional cochleostomy, which involves drilling a bigger hole in the cochlear bone, may induce more extensive tissue damage, resulting in higher impedance.[13,14] Previous studies foind that impedance level has a correlation to the clinical outcome of cochlear implantation. Impedance level might indirectly show the biological changes in the cochlea due to electrode insertion. Changes such as bone formation or the distance between the electrode and the modiolus will affect the impedance level at mapping. Decreased word score is correlated with an increased impedance level.[15] Nonetheless, it should be noted that the outcome of cochlear implantation surgeries is also affected by several factors such as clinical characteristics of the patients (e.g., age at implantation, comorbidities, duration of implantation, and severity of hearing loss) and surgeon's experience and available resources. This suggests that further studies are needed to confirm our findings.

The present study is limited due to its cross-sectional design, suggesting that causalities between variables were unknown. Furthermore, other potential confounding factors, such as age at intervention and characteristics of patients' hearing loss were not recorded in this study. The fact that there was no patient with inner ear anomalies and only two patients with obliterated scala tympani also limited our analysis. These suggest that future studies should also consider these potential confounding factors when assessing the impedance levels of cochlear implants over time.

CONCLUSION

This study adds to the body of evidence supporting the premise that the electrical impedance of cochlear implant electrodes may change over time, thereby highlighting the importance of regular impedance assessments for cochlear implant users to ensure the optimal function of the devices. In this cohort, the impedance level of basal electrodes decreased at one year post-implantation, while those of apical electrodes increased. The present study also suggests that the choice of surgical approach for implant insertion may play a role in the impedance levels of the electrode arrays. Further research should investigate the potential interplay between surgical approach and other factors that may impact impedance levels to confirm our findings.

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ORIGINAL ARTICLE

Intravenous thrombolysis for multi-ethnic Asians with acute ischaemia stroke in Malaysian public primary stroke centres versus acute stroke ready hospitals: Comparison of real-world clinical outcomes

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ABSTRACT

Introduction: Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator is beneficial in acute ischaemic stroke (AIS). We aim to compare the real-world clinical outcomes and service efficiency of IVT in Malaysian primary stroke centres (PSCs) versus acute stroke ready hospitals (ASRHs).

Materials and Methods: We conducted a multi-centre cohort study involving 5 PSCs and 7 ASRHs in Malaysia. Through review of medical records of AIS patients who received IVT from 01 January 2014 to 30 June 2021, real-world data was extracted for analysis. Univariate and multivariate regression models were employed to evaluate the role of PSCs versus ASRHs in post-IVT outcomes and complications. Statistical significance was set at p<0.05.

Results: A total of 313 multi-ethnic Asians, namely 231 from PSCs and 82 from ASRHs, were included. Both groups were comparable in baseline demographic, clinical, and stroke characteristics. The efficiency of IVT delivery (door-to-needle time), functional outcomes (mRS at 3 months post-IVT), and rates of adverse events (intracranial haemorrhages and mortality) following IVT were comparable between the 2 groups. Notably, 46.8% and 48.8% of patients in PSCs and ASRHs group respectively (p=0.752) achieved favourable functional outcome (mRS≤1 at 3 months post-IVT). Regression analyses demonstrated that post-IVT functional outcomes and adverse events were independent of the role of PSCs or ASRHs.

Conclusion: Our study provides real-world evidence which suggests that IVT can be equally safe, effective, and efficiently delivered in ASRHs. This may encourage the establishment of more ASRHs to extend the benefits of IVT to a greater proportion of stroke populations and enhance the regional stroke care.

KEYWORDS:
Acute ischemic stroke, thrombolysis, stroke ready hospitals, functional outcomes, efficiency, safety

INTRODUCTION

Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) has been a well-established emergency intervention in acute ischaemic stroke (AIS) since 1995.[1-9] However, such therapy may not be readily available in district/community hospitals, especially in countries with lower neurologist: population ratio. We hypothesise that as (i) the efficacy of IV rt-PA has been extensively proven,[1-7] (ii) coupled with the presence of objective, internationally standardised indications and contraindications of IV rt-PA in AIS,[1-2,9] (iii) in addition to the availability of local evidence-based protocol and (iv) the growing use of telemedicine to guide decision-making, IVT can potentially be administered in these district/community hospitals without neurologist in a timely, safe and effective manner.

Accordingly, evidence has consistently shown the beneficial effects of IVT in AIS even when administered by non-neurologists in non-stroke centres.[10-12] However, similar targeted research involving multi-ethnic Asian populations in this region is scarce. We aim to appraise and compare the real-world efficiency, effectiveness and safety of IVT among multi-ethnic Asians in Malaysian public primary stroke centres (PSCs) versus acute stroke-ready hospitals (ASRHs).

MATERIALS AND METHODS

We conducted a multi-centre cohort study (combination of historical, retrospective and prospective cohort) involving analyses of real-world data. This real-world study involved five public PSCs and seven public ASRHs in Malaysia. Qualifying criteria of PSCs and ASRHs were in accordance

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with the American Stroke Association & The Joint Commission Stroke Certification criteria. The five PSCs were Sarawak General Hospital, Queen Elizabeth Hospital, Sultanah Nur Zahirah Hospital, Seberang Jaya Hospital and Raja Permaisuri Bainun Hospital. Meanwhile, the seven ASRHs were Tawau Hospital, Taiping Hospital, Bintulu Hospital, Miri Hospital, Sarikei Hospital, Sultan Abdul Halim Hospital and Lahad Datu Hospital. Clinical data were collected through a review of medical records and extracted from the local stroke registry.

The data collection period was from December 2019 to December 2021. All patients who received IVT from 1 January 2016 to 31 December 2021 in these 12 study centres were potential subjects. These patients were being followed up for functional outcomes in Modified Rankin Scale (mRS) and mortality status. Assessments findings were documented contemporaneously in their medical records and stroke registries. This study was a combination of historical, retrospective and prospective cohort study as we included patients who (i) received IVT and had at least 3 months of follow-up post-IVT at the beginning of data collection period (historical cohort); (ii) received IVT and were still under ongoing follow-up at the beginning of data collection period (retrospective cohort); (iii) received IVT within the data collection period, followed by the standard follow-up for at least 3 months (prospective cohort).

The first author (S.J.P.), who is also the principal and coordinating investigator of the study, had full access to the data. The authors vouch for the accuracy and completeness of data, in addition to strict adherence to study protocol and statistical analysis.

Study Populations/Patients

Our inclusion criteria were patients (i) with clinical diagnosis of AIS according to WHO criteria[13], (ii) age of ≥18 years at the time of receiving IVT, (iii) received IVT within 4.5 hours from AIS onset, at a dose of 0.9 mg/kg and maximum 90 mg, (iv) ≥3 months of follow-up after IVT. Patients who died within 3 months post-IVT were included in the analyses on mortality outcome. Exclusion criteria were patients (i) aged <18 years at the time of receiving IVT, (ii) received IVT in an extended window, i.e., >4.5 hours after AIS onset, (iii) received other reperfusion therapies (e.g. intra-arterial thrombolysis, mechanical/endovascular thrombectomy) within 90 days post-IVT, (iv) no data on door-to-needle time (DNT), intracranial haemorrhages following IVT, mRS at 3 months post-IVT and mortality up to 3 months post-IVT. Anonymized real-world data were collected through a review of medical records and local stroke registry. Informed consent was obtained from all study subjects, approving the use of their anonymised data in analyses and publication of findings.

Clinical Assessments and Outcome Measures

Subtypes of AIS among study patients were grouped according to the TOAST classification.[14] These five subtypes were (i) large artery atherosclerosis, (ii) small vessel occlusion, (iii) cardioembolism, (iv) other determined aetiologies and (v) undetermined aetiologies. Stroke severity upon presentation, measured by National Institutes of Health Stroke Scale (NIHSS), was assessed by neurologists in PSCs and trained physicians in ASRHs, respectively. The Alberta Stroke Program Early CT Score (ASPECTS) were evaluated and reported by radiologists.[15,16]

The onset-to-needle time (ONT) was defined as the duration from the onset of AIS symptoms to the time of IVT administration. The DNT was defined as the duration from the time of patient's arrival at emergency department to the time of first bolus dose of thrombolytic. mRS was employed to measure the degree of disability. Intracranial haemorrhages (ICH) following IVT, namely (i) any ICH, (ii) symptomatic ICH (sICH) as per ECASS III definition[2] and (iii) fatal ICH were recorded. Mortality following IVT, namely (i) inpatient mortality, i.e., mortality within the same/index hospital admission and (ii) all-cause mortality within 3 months (90 days) post-IVT, were recorded.

AIS characteristics and severity upon presentation were evaluated by using TOAST subtypes, NIHSS and ASPECTS score. The efficiency of IVT delivery was evaluated through DNT and proportion of patients with DNT <60 minutes. The effectiveness of IVT was assessed through mRS at 3 months (90 ± 5 days), number of patients with favourable functional outcomes (mRS ≤1 at 3 months) and unfavourable functional outcomes (mRS ≥ 2 at 3 months). Meanwhile, safety of IVT was assessed by rates of any ICH, sICH, fatal ICH, inpatient mortality and 90 days all-cause mortality.

Statistical Analysis

Statistical Package of Social Sciences (SPSS) for Windows version 28.0 (IBM Corporation, Armonk, NY, USA) was employed. Baseline demographic and clinical characteristics were presented as absolute numbers and percentage for categorical variables, mean and standard deviation (SD) for normally distributed continuous variables, and median and interquartile ranges for continuous variables with skewed distribution or ordinal data. Shapiro–Wilk test was used to assess the normality of data distribution.

Upon comparing the variables between two groups (PSCs versus ASRHs), the independent sample t test and Mann–Whitney U test were used for the analyses of continuous variables, while Pearson's chi-square and Fisher's exact test were used for the analyses of categorical variables. A two-sided P value of <0.05 was considered statistically significant. Univariable and multivariable logistic regression analyses were conducted to investigate the association between various outcomes of interest and independent variables. All variables with p value of <0.1 in the univariable analyses were included in the final multivariable analyses. The results were presented in the form of crude odds ratios (OR) and adjusted OR with the respective 95% confidence interval (CI). P value of <0.05 signifies statistical significance.

Standard Protocol Approvals and Study Registrations

This study was registered with the Malaysian National Medical Research Register (study ID: NMRR-19-3731-52272). Study protocol was approved and supported by the National Institutes of Health Malaysia. Ethical approval was obtained from the Malaysian Medical Research and Ethics Committee. Approval for publication was granted by the Director-General of Health Malaysia.

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. This study was conducted in strict compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. Strictly no minor nor vulnerable subjects were enrolled in the study. Only anonymised, non-identifying data were extracted/collected.

RESULTS

A total of 313 multi-ethnic Asian patients, namely 231 (73.8%) from PSCs and 82 (26.2%) from ASRHs were included. The baseline demographic (age, gender, ethnicity) and clinical characteristics (comorbidities/vascular risk factors) of these two groups of patients were comparable, with the exception of the proportions of active smokers. Rates of prior antiplatelet and/or anticoagulant use within 7 days prior to stroke onset were similar in both PSCs and ASRHs groups (29.0% vs 29.3%) as well. Types of antiplatelets and anticoagulants used were listed in Table I.

Stroke Characteristics and Severity at Presentation

These two groups of patients demonstrated similar proportions in each TOAST subtype. Both groups recorded comparable NIHSS upon presentation, namely a median NIHSS of 11 (IQR: 8–17) in PSCs and a median NIHSS of 12 (IQR: 9–16) in ASRHs (p = 0.833). Both groups also have comparable ASPECTS, with a median ASPECTS of 9 (IQR: 8–10) in both PSCs and ASRHs (p = 0.879) groups (Table I).

Efficiency of Delivery of IVT

Both groups recorded similar ONT. Notably, the DNT was comparable between the two groups as well, namely a median of 85 (IQR: 56–118) minutes in PSCs and a median of 93 (IQR: 60–125) minutes in ASRHs, p = 0.470. In addition, the proportion of patients with DNT <60 minutes was similar, namely 30.7% in PSCs and 30.5% in ASRHs, p = 0.967 (Table II).

Clinical Outcomes Following IVT

mRS at 3 months was identical between the two groups, with a median of 2 (IQR: 1–4) in PSCs and 2 (IQR: 1–3) in ASRHs, p = 0.707. Percentage of patients with favourable functional outcomes, i.e., mRS ≤ 1 at 3 months post-IVT, was comparative as well, namely 46.8% in PSCs and 48.8% in ASRHs, p = 0.752 (Table II and Figure 1 mRS bar chart).

Haemorrhages and Mortality following IVT

Both PSCs and ASRHs groups demonstrated similar rates of (i) any ICH, 17.7% vs 18.3%, p = 0.912; (ii) symptomatic ICH, 10.4% vs 7.3%, p = 0.417; (iii) fatal ICH, 3.9% vs 4.9%, p = 0.749, (iv) inpatient mortality, 13.9% vs 11.0%, p = 0.507 and (v) all-cause mortality within 90 days post-IVT, 15.2% vs 14.6%, p = 0.910. Causes of death were listed in Table II. The most common causes of death in both groups were fatal ICH, pneumonia and acute coronary syndrome (Table II).

Subgroups Analyses

Among the 313 study patients, 148 patients (47.3%) had favourable functional outcomes (mRS ≤1) whereas 165 patients (52.7%) had unfavourable functional outcomes (mRS ≥2) at 3 months post-IVT. Patients with favourable functional outcomes demonstrated significantly (i) younger age, (ii) lower NIHSS at presentation, (iii) higher ASPECTS at presentation, (iv) shorter DNT, (v) greater proportion with DNT <60 minutes and (vi) lower rates of ICH. These two groups of patients are comparable in terms of gender, ethnicity, comorbidities/vascular risk factors, and TOAST subtype (Table III).

Univariable and Multivariable Logistic Regression Analyses

Among the overall cohort of 313 patients, factors that were significantly associated with favourable functional outcomes (Table IV) include (i) younger age, (ii) lower NIHSS at presentation, shorter DNT and (iv) absence of sICH. Notably, functional outcomes were independent of the role of PSCs or ASRHs, gender, ethnicity and comorbidities/vascular risk factors.

Factors significantly associated with any type of post-IVT ICH among the overall cohort of 313 patients (refer Supplementary Table I) included (i) older age and (ii) higher NIHSS at presentation. Meanwhile, factors significantly associated with sICH (refer Supplementary Table II) included (i) lower ASPECTS at presentation and (ii) longer DNT. The role of PSCs versus ASRHs, age, gender, ethnicity, comorbidities/vascular risk factors, NIHSS at presentation and antiplatelet or anticoagulant use were not significantly associated with ICH.

In addition, factors significantly associated with 90-day all-cause mortality among the overall cohort of 313 patients (refer Supplementary Table III) included (i) longer DNT and (ii) presence of sICH, regardless of the role of PSCs vs ASRHs, age, gender, ethnicity, comorbidities/vascular risk factors, NIHSS and ASPECTS at presentation.

In the PSC cohort, (i) factors significantly associated with favourable functional outcomes (refer Supplementary Table IV) included lower NIHSS at presentation, shorter DNT and absence of sICH; (ii) factors significantly associated with any type of post-IVT ICH (refer Supplementary Table V) included lower ASPECTS at presentation and longer DNT; (iv) factors significantly associated with post-IVT sICH (refer Supplementary Table VI) included female gender, lower ASPECTS at presentation, and longer DNT and (v) factor significantly associated with overall 90-day all-cause mortality (refer Supplementary Table VII) included older age and longer DNT.

In the ASRH cohort, (i) factors significantly associated with favourable functional outcomes (refer Supplementary Table VIII) included younger age and lower NIHSS at presentation and (ii) factors significantly correlated with overall 90-day all-cause mortality (refer Supplementary Table IX) was lower ASPECTS at presentation.

DNT ≤60 Minutes Versus DNT >60 Minutes

Almost equal proportion of patients, namely 30.7% in PSCs and 30.5% in ASRHs, recorded DNT ≤60 minutes. Among the overall cohort of 313 study patients, 96 (30.7%) recorded DNT ≤60 minutes while 217 (69.3%) recorded DNT >60 minutes. Subsequently, 59 (61.5%) of the 96 patients with DNT ≤60

Table I: Baseline Demographic, Clinical and Stroke Characteristics

Patient's characteristics	PSCs (n = 231)	ASRHs (n = 82)	P value
Age (mean ± S.D.)	57.4 ± 13.1	56.4 ± 12.6	0.540[I]
Gender (male:female)	150:81	54:28	0.881[II]
	64.9%:35.1%	65.9%:34.1%	
Ethnicity (Malay:Chinese:Indian:Others)	129:31:14:57	41:14:8:19	0.537[III]
	55.8%:13.4%:6.1%:24.7%	50.0%:17.1%:9.8%:23.2%	
Diabetes mellitus	80/231 (34.6%)	28/82 (34.1%)	0.937[II]
Hypertension	152/231 (65.8%)	58/82 (70.7%)	0.414[II]
Dyslipidemia	63/231 (27.3%)	29/82 (35.4%)	0.167[II]
Coronary artery disease	46/231 (19.9%)	15/82 (18.3%)	0.750[II]
Atrial fibrillation/flutter	39/231 (16.9%)	13/82 (15.9%)	0.830[II]
Valvular heart diseases	5/231 (2.2%)	1/82 (1.2%)	1.000[III]
History of previous CVA/TIA	33/231 (14.3%)	12/82 (14.6%)	0.938[II]
Smoking (active smokers)	87/231 (37.7%)	43/82 (52.4%)	0.020[II]
Prior antiplatelet/anticoagulant use	67/231 (29.0%)	24/82 (29.3%)	0.964[II]
I. Aspirin	52/67	18/24	
II. Clopidogrel	3/67	1/24	
III. Warfarin	7/67	4/24	
IV. NOACs	2/67	1/24	
V. Aspirin + clopidogrel	2/67	0/24	
VI. Aspirin + warfarin	1/67	0/24	
Stroke characteristics			
Subtype (TOAST classification)			
I. Large artery atherosclerosis	102/231 (44.2%)	35/82 (42.7%)	
II. Small vessel occlusion	68/231 (29.4%)	24/82 (29.3%)	N/A
III. Cardioembolism	40/231 (17.3%)	17/82 (20.7%)	
IV. Other determined aetiologies	2/231 (0.9%)	0/82 (0%)	
V. Undetermined aetiology	19/231 (8.2%)	6/82 (7.3%)	
Median NIHSS at presentation	11 (8-17)	12 (9-16)	0.833[IV]
Median ASPECTS at presentation	9 (8-10)	9 (8-10)	0.879[IV]

I. Independent sample t test
II. Pearson's chi square
III. Fisher's exact test
IV. Mann–Whitney U test

Others = natives/indigenous populations of Southeast Asia.
ASRH, acute stroke-ready hospital; CVA, TIA,

minutes recorded favourable functional outcomes while only 89 (41.0%) of the 217 patients with DNT >60 minutes recorded favourable functional outcomes at 3 months, p = 0.001. At 3 months, patients with DNT ≤60 minutes recorded median mRS of 1 (IQR: 0–2) while patients with DNT >60 minutes recorded median mRS of 2 (IQR: 1–4), $p < 0.001$.

DISCUSSION

Comparison of the efficiency, effectiveness and safety of IVT administration in public primary versus acute stroke-ready hospitals were reflected in this real-world study through performance metrics in DNT, functional outcomes by mRS, mortality and rates of intracerebral haemorrhages. Our patients in both public PSC and ASRH cohorts demonstrated similar demographics and baseline clinical characteristics, stroke subtypes as defined by TOAST classifications and stroke severity upon presentation in terms of NIHSS and ASPECTS. Comparable efficiency (DNT), effectiveness (functional outcomes) and safety (ICH and mortality rates) profiles of IVT were recorded in both groups. This may imply that IVT service can be equally safe, effective and efficiently delivered in ASRHs.

As of date, there were only 138 registered neurologists in Malaysia (both public and private sectors), which translates to 1 neurologist to almost 250,000 populations. Thus, there are critical shortage of neurologists to support the IVT service nationwide, especially in East Malaysia. Majority of the rural and remote hospitals are not equipped with in-house neurologists. Hence, there was an increasing need to establish ASRH to extend the benefits of IVT to a greater proportion of stroke patients. In Malaysia, physicians (specialists in Internal Medicine) have taken the initiative to initiate IVT service in some of these centres, guided by telemedicine consultation with neurologists. These physicians are tasked to draft acute stroke protocols and workflows while ensuring strict adherence to the protocol in daily practice.

Challenges and limitations in Malaysian ASRHs include (i) lack of certified expertise namely in-house neurologists; (ii) lack of stroke centres and regional stroke networks in close proximity; (iii) logistic constraints which limit inter-hospital transfer; (iv) lack of established telestroke network or teleradiography system; (v) limited healthcare facilities and (vi) lack of advanced neuroimaging.

The results of our study may proactively advocate the establishment of more ASRHs despite the current challenges and limitations. A few collaborative efforts and initiatives are needed, which includes (i) establishing structured training and certification programme to equip physicians in offering

Table II: Efficiency of IVT delivery,Post-IVT clinical outcomes, Incidence of haemorrhages and mortality

Efficiency of IVT delivery	PSCs (n = 231)	ASRHs (n = 82)	P value
Median onset-to-needle time (minutes)	190 (155–225)	185 (139–226)	0.276[IV]
Median door-to-needle time (minutes)	85 (56–118)	93 (60–125)	0.470[IV]
Door-to-needle time <60 minutes	71/231 (30.7%)	25/82 (30.5%)	0.967[II]
Post-IVT clinical outcomes			
Median 3 months mRS	2 (1–4)	2 (1–3)	0.707[IV]
Favourable functional outcomes (3 months mRS ≤1)	108/231 (46.8%)	40/82 (48.8%)	0.752[II]
Poor functional outcomes (3 months mRS ≥5)	40/231 (17.3%)	14/82 (17.1%)	0.960[II]
Haemorrhages and mortality			
Any intra-cranial haemorrhages (ICH) (including haemorrhagic transformation)	41/231 (17.7%)	15/82 (18.3%)	0.912[II]
Symptomatic ICH (ECASS III definition)	24/231 (10.4%)	6/82 (7.3%)	0.417[II]
Fatal ICH	9/231 (3.9%)	4/82 (4.9%)	0.749[III]
Inpatient mortality	32/231 (13.9%)	9/82 (11.0%)	0.507[II]
I. Fatal ICH	9/32	4/9	
II. Pneumonia	9/32	3/9	
III. ACS and cardiac failure	7/32	1/9	
IV. Severe stroke/massive infarct	4/32	1/9	
V. Other stroke-related complications	3/32	0/9	
90 days all-cause mortality	35/231 (15.2%)	12/82 (14.6%)	0.910[II]
I. Fatal ICH	9/35	4/12	
II. Pneumonia	10/35	4/12	
III. ACS and cardiac failure	9/35	3/12	
IV. Severe stroke/massive infarct	4/35	1/12	
V. Other stroke-related complications	3/35	0/12	

V. Independent sample t test
VI. Pearson's chi square
VII. Fisher's exact test
VIII. Mann–Whitney U test
ASRH, acute stroke-ready hospital; IVT, intravenous thrombolysis; mRS, Modified Rankin Scale; PSC, primary stroke centres.

IVT, (ii) establishing and enhancing telestroke networks and teleradiography system, hence allowing more neurologists and radiologists to remotely support IVT service, (iii) improving inter-hospital patient transfer system and (iv) increasing availability of CT machine in rural/remote areas. The national clinical practice guidelines on stroke management is an essential tool to supplement these efforts as well.

Essentially, there are multiple unmet needs in the provision of IVT in resource-limited settings, namely number of trained professionals, supporting staffs, facilities and information technology (IT) services. However, there are certain measures which can be carried out in the short run, for example, by increasing the number of training platforms/resources online, stroke simulation training or hands-on workshop organised by tertiary stroke centres to address the knowledge gap. Meanwhile, with regards to longer term planning, an increase in budget allocation to procure basic equipments, such as scan machine, beds, blood pressure/cardiac monitoring devices should be prioritised.

Findings of our regression analyses highlight the importance of shortening DNT as it is a modifiable factor significantly associated with favourable functional outcomes. Longer DNT is significantly associated with poorer functional outcomes, sICH and overall 90-day all-cause mortality. Results presented in "Subgroups Analyses" and "DNT ≤60 Minutes Versus DNT >60 Minutes" further supplement such findings. Almost 70% of study patients recorded DNT >60 minutes in both PSCs and ASRHs. Comprehensive data on door-to-CT time and CT-to-needle time was not consistently available across all centres. Hence it is not feasible to determine whether our long DNT was caused by either or both components. However, the causes of our long DNT in general may include (i) delay in decision making and offering consent by patients and/or family (ii) delay in organising neuroimaging due to limited infrastructure and (iii) stroke code workflow unfamiliarity among healthcare personnel.

We hereby propose measures which can be undertaken to shorten DNT: (i) increase public awareness regarding the availability and benefits of IVT in acute stroke through widespread campaign and education nationwide. (ii) equip high-volume public centres with more CT machines to accommodate the increasing patient's loads locally. (iii) minimise delay between steps during stroke code activation by introducing better-structured training and refresher course for stroke care personnel nationwide, (iv) conduct regular quality improvement projects and clinical audits to improve performance and consequentially quality of care and (v) establish telestroke networks involving dedicated neurologists and neuroradiologists in respective states nationwide. This may assist physicians in swift decision-making on IVT with greater confidence, especially in ASRHs.

Table III: Distribution of Modified Rankin Scale (mRS)

Modified Rankin Scale (mRS)	Overall (n = 313) mRS ≤1	mRS ≥2	*p* values
N (%)	148/313 (47.3%)	165/313 (52.7%)	-
Mean age ± SD (years)	53.6 ± 12.3	60.3 ± 12.8	<0.001
Gender (Male:Female)	90:58 61%:39%	114:51 69%:31%	0.125
Ethnicity (Malay:Chinese:Indian:Others)	73:24:8:43 49%:16%:6%:29%	97:21:14:33 59%:13%:8%:20%	0.131
DM	50/148 (34%)	58/165 (35%)	0.799
Hypertension	96/148 (65%)	114/165 (69%)	0.427
Dyslipidaemia	45/148 (30%)	47/165 (28%)	0.710
CAD	26/148 (18%)	35/165 (21%)	0.416
AF	23/148 (16%)	29/165 (18%)	0.629
Valvular CD	5/148 (3%)	1/165 (1%)	0.074
Hx of TIA/CVA	26/148 (18%)	19/165 (12%)	0.128
Active smoking	64/148 (43%)	66/165 (40%)	0.561
Prior antiplatelet/anticoagulant use	47/148 (32%)	44/165 (27%)	0.322
TOAST subtypes			
I. Large artery atherosclerosis	47/148 (31.8%)	90/165 (54.5%)	
II. Small vessel occlusion	62/148 (41.9%)	30/165 (18.2%)	
III. Cardioembolism	24/148 (16.2%)	33/165 (20.0%)	
IV. Other determined aetiology	1/148 (0.7%)	1/165 (0.6%)	
V. Undetermined aetiology	14/148 (9.4%)	11/165 (6.7%)	
Median NIHSS (at presentation)	10 (7–13)	13 (10–20)	<0.001
Median ASPECTS (at presentation)	9 (8–10)	9 (8–9.5)	<0.001
Median onset-to-needle time (minutes)	190 (160–225)	190 (150–230)	0.986
Median door-to-needle time (minutes)	75 (50–104.5)	98 (65–132)	<0.001
DNT <60 minutes	59/148 (39.9%)	37/165 (22.4%)	0.001
Any ICH	10/148 (6.8%)	46/165 (27.9%)	<0.001
sICH	3/148 (2.0%)	27/165 (16.4%)	<0.001
Fatal ICH	0/148 (0%)	13/165 (7.9%)	<0.001
Inpatient mortality	0/148 (0%)	41/165 (24.8%)	<0.001
90 days all-cause mortality	0/148 (0%)	47/165 (28.5%)	<0.001

ICH, intra-cranial haemorrhage.

The strengths of this study include (i) inclusion of 12 public centres nationwide, namely both East Malaysia and Peninsular Malaysia; (ii) inclusion of multi-ethnic Asian patients and (iii) inclusion of all consecutive patients who received IVT in all PSCs and ASRHs in Malaysia. Furthermore, prospective local stroke registries at study centres offer reliable real-world data. Despite not performing propensity score matching, there were no statistically significant differences in demographic, clinical and stroke characteristics upon comparing patients in both PSC and ASRH cohorts. In addition, univariable and multivariable logistic regression analyses with appropriate adjustments were performed to assess the role of ethnicity and types of centres (i.e. PSCs vs ASRHs) in clinical outcomes while identifying factors associated with various outcomes of interest.

Limitations of this study include (i) the observational nature of study; however, this real-world study still offers valuable insights on the benefits of IVT in both PSCs and ASRHs, (ii) lack of comprehensive data on extra-cranial haemorrhages in some study centres; however, there was no significant morbidity or mortality resulted from extra-cranial haemorrhages among all study patients and (iii) lack of detailed data on door-to-CT and CT-to-needle time, however, definite DNT was clearly documented and (iv) lack of detailed standardised blood pressure recording in some patients as the timings of blood pressure measurements were varied (any point from upon arrival to Emergency Department to immediately prior to Alteplase bolus); however, it has been a nationwide standard practice (as per national clinical practice guidelines) that blood pressure must be <185/110 mmHg prior to IVT initiation.

Given the inherent bias in an observational study, statistical adjustment techniques, i.e. logistic regression, have been employed to produce unbiased estimates of effects. Moreover, the findings from this study were replicated in other studies internationally.[10-12] Additional evidence to bolster the potential causal association with longer DNT would be an understanding of the Malaysia's healthcare landscape by the authors and inputs/reviews from the local stroke experts.

Evidence on the provision of IVT by non-neurologists is not expansive so far, especially in resource-limited regions (low-middle income countries) where the neurologist:population ratio is low and substantial proportions of acute stroke patients receive emergency care by non-neurologists. This project, with strengths and limitations as stated, is still among the largest real-world study providing real-world evidence which may suggest comparable IVT safety, effectiveness and service efficiency when administered by non-neurologists in ASRHs as compared to administration by neurologists in PSCs, in a resource-limited setting.

Table IV: Factors associated with favourable outcomes

Odd ratios	Crude OR (95% CI)	*p* value	Adj OR (95% CI)	*p* value
Centre				
ASRH	1.09 (0.66–1.80)	0.752		
PSC	Ref	–		
Age	0.96 (0.94–0.98)	<0.001	0.97 (0.95–0.99)	0.012
Gender				
Female	1.44 (0.90–2.30)	0.125		
Male	Ref	–		
Ethnicity				
Malays	0.58 (0.34–0.997)	0.049	0.52 (0.27–1.02)	0.055
Chinese	0.88 (0.42–1.84)	0.729	0.95 (0.38–2.36)	0.916
Indians	0.44 (0.17–1.17)	0.099	0.43 (0.14–1.33)	0.143
Others	Ref	–	Ref	
Diabetes mellitus				
Yes	0.94 (0.59–1.50)	0.799		
No	Ref	–		
Hypertension				
Yes	0.83 (0.52–1.32)	0.427		
No	Ref	–		
Dyslipidaemia				
Yes	1.10 (0.67–1.79)	0.710		
No	Ref	–		
CAD				
Yes	0.79 (0.45–1.39)	0.417		
No	Ref	–		
Atrial				
Yes	0.86 (0.47–1.57)	0.629		
No	Ref	–		
VHD				
Yes	5.73 (0.66–49.7)	0.113		
No	Ref	–		
CVA /TIA				
Yes	1.64 (0.87–3.10)	0.130		
No	Ref	–		
Anti-platelet/anti-coagulant				
Yes	1.28 (0.79–2.09)	0.323		
No	Ref	–		
Smoking status :				
Current/Ex Smoker	1.14 (0.73–1.79)	0.561		
Non	Ref	–		
NIHSS at presentation	0.85 (0.81–0.90)	<0.001	0.85 (0.81–0.91)	<0.001
ASPECTS	1.67 (1.33–2.11)	<0.001	1.28 (0.997–1.65)	0.053
Onset-to-needle time	1.00 (0.99–1.004)	0.998		
Door-to-needle time	0.988 (0.983–0.994)	<0.001	0.988 (0.981–0.995))	0.001
Symptomatic ICH				
Yes	0.11 (0.03–0.36)	<0.001	0.13 (0.04–0.48)	0.002
No	Ref	–	Ref	–

1. Younger age
2. Lower NIHSS at presentation
3. Shorter DNT
4. No sICH

ASRH, acute stroke-ready hospital; AF, atrial fibrillation; CAD, coronary artery disease; CVA, cerebrovascular disease; TIA, transient ischaemic attack; sICH, symptomatic intracranial haemorrhage; VHD, valvular heart disease; PSC, primary stroke centres.

CONCLUSION

This real-world study may provide translational real-world evidence which suggests that IVT in AIS can be equally safe, effective and efficiently delivered in both PSCs and ASRHs. This may further encourage the establishment of IVT service in some centres without in-house neurologists, hence extending the benefits of IVT to a greater proportion of stroke populations. Accordingly, through collaborative efforts and initiatives, the development of more ASRHs equipped with trained stroke teams should be proactively advocated to enhance regional and international acute stroke care.

DECLARATION OF INTEREST

All authors report no disclosure or conflict of interest with respect to the research, authorship and publication of this article.

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ORIGINAL ARTICLE

Effectiveness of nirmatrelvir/ritonavir (Paxlovid®) in preventing hospitalisation and death among COVID-19 patients: a prospective cohort study

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ABSTRACT

Introduction: Previous trials and real-world studies have shown that nirmatrelvir/ritonavir (Paxlovid®) reduces hospitalisation and deaths in symptomatic, high-risk, non-severe COVID-19 patients. However, there was a scarcity of data on its effectiveness in the local setting. This study aimed to determine the effectiveness of Paxlovid® in reducing hospitalisation and mortality among COVID-19 patients and to identify the types of adverse events that occur after taking Paxlovid®.

Materials and Methods: A two-arm prospective cohort study was conducted among adult patients with COVID-19 categories 2 and 3 treated with Paxlovid® and a matched control group. A standard risk-stratified scoring system was used to establish Paxlovid® eligibility. All patients who were prescribed Paxlovid® and took at least one dose of Paxlovid® were included in the study. The control patients were selected from a centralised COVID-19 patient registry and matched based on age, gender and COVID-19 stage severity.

Results: A total of 552 subjects were included in the study and evenly allocated to the treatment and control groups. There was no statistically significant difference in 28-day hospitalisation after diagnosis [Paxlovid®: 26 (9.4%), Control: 34 (12.3%), OR: 0.74; 95%CI, 0.43-1.27; p=0.274] or all-cause death [Paxlovid®: 2 (0.7%), Control: 3 (1.1%), OR 1.51; 95%CI, 0.25-9.09; *p*=0.999]. There was no significant reduction in hospitalisation duration, intensive care unit admission events or supplementary oxygen requirement in the treatment arm. Ethnicity, COVID-19 severity at diagnosis, comorbidities and vaccination status were predictors of hospitalisation events.

Conclusion: In this two-arm study, Paxlovid® did not significantly lower the incidence of hospitalisation, all-cause death and the need for supplemental oxygen. Adverse effects were frequent but not severe. Paxlovid® efficacy varied across settings and populations, warranting further real-world investigations.

KEYWORDS:
effectiveness; nirmatrelvir/ritonavir; hospitalisation; death; COVID-19; real-world; Malaysia

INTRODUCTION

As of December 2022, the coronavirus disease 2019 (COVID-19) has killed 7.5 million people globally, with more than 650 million positive cases.[1] Between January 24 and February 7, 2022, the predominant COVID-19 variant in Malaysia was Omicron, accounting for 92% of cases, followed by Delta at 8%. On February 7, 2022, the Ministry of Health declared Omicron as the dominant strain in Malaysia.[2] As of June 1, 2022, Malaysia had reported 5.10 million confirmed COVID-19 cases and 37,087 deaths related to COVID-19.[3]

In April 2022, WHO recommended the use of Nirmatrelvir/Ritonavir (Paxlovid®) for high-risk patients with non-severe COVID-19 based on the available evidence from two randomised controlled trials (EPIC-SR and EPIC-HR).[4] Nirmatrelvir is a novel SARS-CoV-2 major protease inhibitor targeting SARS-CoV-2 3CL, while ritonavir is an HIV-1 protease inhibitor that inhibits the CYP3A-mediated metabolism of nirmatrelvir.[5]

Hammond et al. found that managing symptomatic Covid-19 with nirmatrelvir/ritonavir (Paxlovid®) reduced the risk of progression to severe Covid-19 by 89% compared to placebo, with no apparent safety issues.[6] Nirmatrelvir/ritonavir (Paxlovid®) significantly reduced death and hospitalisation in the 65 and older group, with adjusted hazard ratios of 0.21 (95% CI, 0.05 to 0.82) and 0.74 (95% CI, 0.35 to 1.58), respectively.[7]

In a large-scale retrospective observational cohort study of non-hospitalised adult patients infected with COVID-19, treatment with Paxlovid® was associated with a lower rate of 28-day all-cause hospitalisation and 28-day all-cause death compared to no antiviral treatment.[8] Another retrospective cohort study conducted in Hong Kong found that the use of Paxlovid® was associated with decreased risks of death, hospitalisation and in-hospital disease progression.[9]

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Despite a few studies demonstrating the effectiveness of Paxlovid® in real-world settings,[7-10] there remains a notable gap in the existing evidence, particularly in the South East Asia setting. This study provides insights regarding the use of Paxlovid® specifically for the Omicron variant, compared to studies with larger populations and considering the diverse ethnic populations found in countries like Malaysia.

This study aims to assess the effectiveness of Paxlovid® in reducing hospitalisations and death among COVID-19 patients and determine the occurrence of adverse events associated with its use.

MATERIALS AND METHODS

This prospective cohort study included adult patients with category 2 and category 3 COVID-19 who received treatment with Paxlovid® and a matched control group. The study was conducted across 24 study sites, comprising 13 hospitals and 11 District Health District Offices in the Perak state of Malaysia.

Paxlovid® Regimen

The recommended dose for patients with normal renal function (eGFR > 60ml/min) is 300 mg of nirmatrelvir (two 150 mg tablets) and 100 mg of ritonavir (one 100 mg tablet), taken orally twice daily for 5 days. Adjusted dosage for renal impaired (eGFR 30–60 ml/min) patients is nirmatrelvir 150 mg (1 tablet) and ritonavir 100 mg twice daily.

Paxlovid® Eligibility

A standard risk-stratified scoring system was used to prioritise Paxlovid® among patients with COVID-19. One point was given to each of the following characteristics: age ≥ 60 years, immunocompromised, presence of comorbidities, incomplete vaccination (did not complete booster dose or unvaccinated), obesity and radiographic abnormalities in chest X-ray. The scores were summed up and recorded in the Paxlovid® initiation criteria checklist. Patients who scored equal or more than 2 were eligible for Paxlovid®.

Patients were not eligible for Paxlovid® if they were less than 18 years old, asymptomatic (Category 1), with symptoms onset more than 5 days, started on oxygen, diagnosed liver disease (Child-Pugh Class C) or end-stage renal failure (eGFR <30 ml/min), pregnant or breastfeeding, with the inherent risk of hypersensitivity and taking interacting medications, including carbamazepine, phenobarbital, phenytoin, voriconazole, warfarin, rivaroxaban, colchicine, atazanavir, darunavir, rifampicin, quetiapine, amlodipine, felodipine, diltiazem, nifedipine, digoxin, lovastatin, simvastatin, atorvastatin, rosuvastatin, ethinyl oestradiol, cyclosporine, tacrolimus, sirolimus, salmeterol, methadone, sildenafil, dexamethasone and methylprednisolone.

Study Inclusion and Exclusion

We included all patients prescribed Paxlovid® in May and June 2022 who consumed at least one dose of Paxlovid®. We excluded those lost to follow-up (self-reported as having COVID-19 through the Malaysian contact-tracing mobile application MySejahtera but did not seek treatment at clinics or hospitals) and did not consume any dose of Paxlovid® after receiving the medication.

Matched Control

Patients not prescribed Paxlovid® in March and April 2022 were included in the control arm in a 1:1 ratio. Control patients could not be attained in the same period as the treatment group because all eligible patients were started with Paxlovid® from May onwards. The control patients were identified and retrieved from the state-centralised COVID-19 patients registry and matched using age, gender and pre-treatment COVID-19 stage severity.

Sample Size and Sampling Method

The sample size was calculated using G-Power (proportion difference from constant, binomial test, one sample case) sample size calculator. Based on Hammond et al. 2022, 0.7% of Paxlovid® patients were hospitalised until Day 28, compared to 6.5% of placebo patients who were hospitalised or died.[6] To detect a difference of 5.8% between the two arms, an alpha error of 0.05, a power of 99% and a minimum sample size of 117 were required. Assuming 30% incomplete data, each arm's final sample size was 167. Consecutive sampling was employed, where all cases which fulfilled the inclusion and exclusion criteria were sampled.

Outcome Measures

The primary effectiveness measure was an event of 28-day hospitalisation post-COVID-19 diagnosis. Paxlovid®-related adverse events and 28-day post-diagnosis death were the secondary outcome measures.

Data Collection

The data of patients who were prescribed Paxlovid® were entered into the state centralised Paxlovid® initiation registry, and eligible patients were identified through the registry. Data retrieved included patients' age, gender, ethnicity, COVID-19 category during the first encounter, types and severity of adverse events (Days 1 to 5 post-initiation), and the total doses ingested. We solicited patients' admission or readmission outcomes, oxygen requirement and adverse events (Days 6–28) through phone follow-up on Day 28 post-initiation.

Several sources of secondary data supplemented this: (i) Paxlovid® initiation criteria checklist containing comorbidities, obesity, immunocompromised status, dose prescribed, radiographic abnormalities in chest X-ray; (ii) Centralised COVID-19 vaccine database containing vaccination status and types of vaccines administered; (iii) National Registration Department, which provided the death data; (iv) electronic hospital information system containing the admission duration, oxygen requirement and intensive care unit (ICU) admission status.

Control group data retrieved included patients' age, gender, ethnicity and COVID-19 severity category during the first encounter from the state-centralised COVID-19 patients registry and supplemented with data from the Centralised COVID-19 vaccine database, National Registration Department and hospital information system.

Data Analysis

The demographic characteristics of the patients in both the treatment and control arm were descriptively analysed. Events and duration of hospitalisation, ICU admission,

Table I: Characteristics of patients who received Paxlovid® and matched population controls (n=552)

	Paxlovid® group (n = 276)	Control group (n = 276)	*p* value
Age, median (IQR)	53 (40-66)	53 (40-63)	0.242[a]
Gender, n (%)			
Male	134 (48.6)	128 (46.4)	0.282
Female	142 (51.4)	148 (53.6)	
Ethnicity, n (%)			
Malay	157 (56.9)	171 (62.0)	0.189
Chinese	66 (22.5)	61 (22.1)	
Indian	51 (18.5)	43 (15.6)	
Others	6 (2.2)	1 (0.4)	
Covid severity at (before treatment), n (%)			
2A	258 (93.5)	258 (93.5)	0.999
2B	10 (3.6)	10 (3.6)	
3	8 (2.9)	8 (2.9)	
Comorbidities, n (%)			
Hypertension	149 (54.0)	160 (58.0)	0.346
Diabetes	90 (32.6)	101 (36.6)	0.325
Dyslipidaemia	8 (2.9)	20 (7.2)	0.020
Chronic kidney disease	6 (2.2)	11 (4.0)	0.218
Respiratory disease	24 (8.7)	26 (9.4)	0.767
Cancer	6 (2.2)	2 (0.7)	0.154
Cardiovascular disease	29 (10.5)	32 (11.6)	0.684
Others	13 (4.7)	32 (11.6)	0.003
COVID-19 vaccination status, n (%)			0.237
Completed booster dose	202 (73.5)	186 (67.4)	0.119
Completed primary doses	67 (24.4)	85 (30.8)	0.091
Unvaccinated	6 (2.2)	5 (1.8)	0.756
Adherence, n (%)			
Completed regimen (10 doses)	259 (93.8)		
Taken at least one dose	17 (6.2)		

[a] Mann-Whitney U test performed
[b] Reason of non-adherence: intolerable adverse events (n=9), patient refusal (n=5), progression to severe COVID-19 (n=1), others (n=2).

Table II: Comparison of hospitalisation, ICU admissions, oxygen requirement and all-cause death outcomes between Paxlovid® recipients and matched controls (n=552)

	Overall (n=552)	Control (n=276)	Paxlovid® (n=276)	Odds ratio (95%CI)	p-value
Hospitalisation, n (%)	60 (10.9)	34 (12.3)	26 (9.4)	0.74 (0.43–1.27)	0.274[a]
Duration of hospitalisation in days, median (IQR)	4.0 (2–6)	4.0 (2–7)	5.0 (3–6)	-	0.952[b]
ICU admission, n (%)	5 (8.3)	3 (8.8)	2 (7.7)	1.51 (0.25–9.09)	0.999[c]
Supplemental oxygen requirement, N (%)	13(21.7)	10 (29.0)	3(11.5)	3.41 (0.93–12.52)	0.05[a]
All-cause death, n (%)	5 (0.9)	3 (1.1)	2 (0.7)	1.51 (0.25–9.09)	0.999[c]

[a]Chi-square test.
[b]Mann–Whitney U test.
[c]Fisher's exact test.

supplemental oxygen requirement and all-cause death outcomes for Paxlovid® recipients were compared with matched controls using the Chi-square (χ^2) statistic and Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. Multiple logistic regression analysis was performed to determine the independent predictors of hospital admissions and death. The model was constructed consisting of variables significant at the 0.25 level. Inferential data were expressed in odd ratios and 95% confidence intervals, and a p-value of 0.05 indicates statistical significance.

Ethics Approval

This study was registered in the National Medical Research Registry (NMRR ID-22-01372-NIL) and approved by Medical Research Ethical Committee [22-01372-NIL(1)]. Consent was obtained from the treatment group patients during the first encounter regarding the 28-day phone call follow-up.

RESULTS

Baseline Patient Characteristics

552 subjects were evenly divided into both arms and analysed. Of 276 patients who received Paxlovid® treatment, the median age was 53 years (IQR: 40-66 years); 142 (51.4%) were women, and 157 (56.9%) were Malay individuals. The most common comorbidities were hypertension (54.0%) and diabetes (32.6%). The baseline demographic and clinical characteristics were generally similar in both arms. Of those who received Paxlovid®, 259 (93.8%) completed the 5-day

Table III: Univariate and multivariate binary logistic regression for day 28 post-diagnosis hospitalisation event (n=552)

Variable	Crude OR (95% CI)	*p* value	Adjusted OR (95%CI)	*p* value
Age (year)	1.01 (1.00–1.03)	0.129		
Gender				
Female	1.21 (0.70–2.07)	0.50		
Male	1.00			
Ethnicity				
Non-Malay	2.08 (1.21–3.57)	0.008	2.04 (1.10–3.80)	0.024
Malay	1.00		1.00	
Severity of COVID-19 at diagnosis		<0.001		<0.001
2a	0.02 (0.01–0.07)	<0.001	0.03 (0.01–0.10)	<0.001
2b	0.12 (0.03–0.59)	0.009	0.13 (0.02–0.69)	0.016
3	1.00		1.00	
Hypertension				
Yes	1.11 (0.65–1.92)	0.697		
No	1.00			
DM				
Yes	0.94 (0.53–1.66)	0.827		
No	1.00			
Dyslipidaemia				
Yes	1.85 (0.68–5.07)	0.229		
No	1.00			
CKD				
Yes	2.63 (0.83–8.35)	0.10		
No	1.00			
Respiratory				
Yes	3.40 (1.69–6.85)	<0.001	0.40 (0.18–0.93)	0.032
No	1.00		1.00	
Cancer				
Yes	2.79 (0.55–14.2)	0.215		
No	1.00			
CVS				
Yes	2.26 (1.13–4.54)	0.022	0.43 (0.20–0.95)	0.036
No	1.00		1.00	
Others				
Yes	1.89 (0.84–4.28)	0.126		
No	1.00			
Vaccination status		0.004		0.015
Unvaccinated	6.15 (1.71–22.1)	0.005	6.33 (1.39–28.82)	0.017
Complete primary	1.92 (1.09–3.39)	0.025	1.97 (1.00–3.88)	0.049
Complete booster	1.00		1.00	
Paxlovid®				
No	1.35 (0.79–2.32)	0.275		
Yes	1.00			

Backward LR method was applied; No multicollinearity and no interaction; Hosmer Lemeshow test, p value=0.506; Classification table 90.9% correctly classified; area under receiver operating characteristics (ROC) curve was 78%. OR: Odd ratios; DM: Diabetes mellitus; CKD: Chronic kidney disease; CVS: Cardiovascular disease

course treatment. Overall, 73.5% of the patients had received a booster dose, 24.4% received the primary series, and 2.2% were unvaccinated (Table I).

Hospitalisation, ICU Admission, Oxygen Requirement and All-Cause Death

From the first day of diagnosis to day 28 post-diagnosis, 60 (10.9%) patients required hospitalisation. There were no statistically significant differences in day 28 post-diagnosis hospitalisation events between the two arms [Paxlovid®: 26 (9.4%), Control: 34 (12.3%), OR: 0.74; 95% confidence intervals, 0.43–1.27; *p*=0.274]. The median duration of hospitalisation was 4.0 days (IQR: 2–6 days). There were no significant differences in total ICU admissions and supplemental oxygen requirement in the treatment arm. Five deaths were reported at day 28 post-diagnosis, with no significant differences across both arms [Paxlovid®: 2 (0.7%), Control: 3 (1.1%), OR: 1.51; 95%CI 0.25-9.09; *p*=0.999] (Table II).

Predictive Factors of Hospitalisation

Non-Malays had 2.04 times greater odds of hospitalisation than Malays. [OR: 2.04; 95%CI 1.10–3.80; *p*=0.024]. Ironically, patients with underlying respiratory [OR: 0.40; 95%CI, 0.18–0.93; *p*=0.032] and cardiovascular disease [OR: 0.43; 95%CI, 0.20–0.95; *p*=0.036] demonstrated lower risks of hospitalisation.

The odds of hospitalisation for COVID-19 varied based on the status of vaccination. Patients vaccinated with the primary series without a booster dose were more likely to be hospitalised than boosted patients [OR 1.97; 95%CI 1.00–3.88; *p*=0.049]. The odds of hospitalisation were 6.3 times higher in unvaccinated patients compared to those who were boosted [OR: 6.33; 95%CI, 1.39–28.82; *p*=0.017].

A milder stage of COVID-19 at diagnosis was associated with decreased odds of hospitalisation. Patients who were diagnosed with Stage 2a [OR: 0.03; 95%CI, 0.01–0.10; *p*<0.001] and Stage 2b [OR: 0.13; 95%CI, 0.02–0.69; *p*=0.016]

Supplementary Table I: Demographic and clinical characteristics of the hospitalised patients (n = 60)

	Control group (n=34)	Paxlovid® group (n=26)	*p* value
Age, median (IQR)	55.5 (33.3–72.3)	58.5 (36.8–69.3)	0.715[a]
Gender, n (%)			
Male	13 (38.2)	13 (50.0)	0.362
Female	21 (61.8)	13 (50.0)	
Ethnicity, n (%)			
Malay	13 (38.2)	13 (50.0)	0.631
Chinese	14 (41.2)	8 (30.8)	
Indian	7 (20.6)	5 (19.2)	
Others			
Covid severity at (before treatment), n (%)			
2A	25 (73.5)	15 (57.7)	0.282[b]
2B	2 (5.9)	5 (19.2)	
3	7 (20.6)	6 (23.1)	
Comorbidities, n (%)			
Hypertension	19 (55.9)	16 (61.5)	0.66
Diabetes	10 (29.4)	10 (38.5)	0.582
Dyslipidaemia	4 (11.8)	1 (3.8)	0.377[b]
Chronic kidney disease	2 (5.9)	2 (7.7)	0.999[b]
Respiratory disease	8 (23.5)	5 (19.2)	0.76
Cancer	1 (2.9)	1 (3.8)	0.999[b]
Cardiovascular disease	6 (17.6)	6 (23.1)	0.747
Others	6 (17.6)	2 (7.7)	0.446[b]
COVID-19 vaccination status, n (%)			
Completed booster dose	18(52.9)	15(57.7)	0.92[b]
Completed primary doses	14(41.2)	9(34.6)	
Unvaccinated	2(5.9)	2(7.7)	
Adherence, n (%)			
Completed regimen (10 doses)		22 (84.6)	
Taken at least one dose		4(15.4)	

[a]Mann–Whitney U test was performed.
[b]Fisher's exact test was performed.

were associated with a lower risk of hospitalisation compared to stage 3 (Table III).

Adverse Events

The reported adverse events after Paxlovid® ingestion was as follows: dysgeusia (96, 61.1%), diarrhoea (49, 31.2%), nausea and vomiting (11, 7.0%), myalgia (7, 4.5%), abdominal pain (5, 3.2%), hypertension (3,1.9%) and others (41, 26.1%). There was no life-threatening adverse event reported.

DISCUSSION

This was a real-world study in a multiracial country within the ASEAN region to evaluate the effectiveness of Paxlovid® in reducing hospitalisation and all-cause death. Our study found hospitalisation and all-cause death occurred in 9% and 0.8% of Paxlovid® patients, respectively, which was higher than what was reported by previous studies.[6,11,12] Hammond et al. reported 0.77% of hospitalisation with no death,6 while Shah et al. reported 0.47% of hospitalisation and 0.01% of death in patients receiving Paxlovid®.[11] Furthermore, Malden and colleagues discovered that emergency department visits or hospitalisations were less than 1% in the 5–15 days following Paxlovid® treatment.[12] Similarly, larger real-world cohort studies[7-10] carried out during Omicron domination reported a reduction of hospitalisation and death in the Paxlovid® group, but with a lower magnitude than Hammond et al. In contrast with previous studies, we did not find a significant reduction in hospitalisation and all-cause death in patients who took Paxlovid®. Also, we did not observe any significant reduction in intensive care unit (ICU) admission and supplemental oxygen requirement among patients taking Paxlovid®. Although previous studies did not find a reduction in ICU admission among patients who took Paxlovid®, a significantly lower need for oxygen therapy was reported.[9,10] The insignificant results might be explained by several differences between the studies, including the study population and settings.

First, the population's natural immunity may have risen over time due to previous strain infections, contributing to lower severity, hospitalisation and death.[13] Second, about 7% of our study population did not adhere to the Paxlovid® regimen, which may reduce the effectiveness of Paxlovid®.[10]

Notably, the EPIC-HR trial6 included only unvaccinated patients, whereas our study included merely 2% unvaccinated subjects, and 70% had received the booster dose. Similarly, two previous studies found no significant reduction in hospitalisation or all-cause death among vaccinated inpatients who received Paxlovid®.[9,14] The action of Paxlovid® could be masked by COVID-19 vaccinations, which effectively reduce disease severity and death.[10,15] Hence, our findings may rationalise the prioritisation of Paxlovid® among unvaccinated patients, especially in resource-poor

settings. Lastly, the fact that we included fewer subjects in the over-65 age group in which Paxlovid® was found to be more efficacious[7] may have contributed to the underestimation of its efficacy.

Our analysis showed non-Malays had higher hospitalisation odds than Malays, suggesting the potential association between ethnicity and COVID-19 severity.[10,16,17] It is important to note that genetic polymorphisms may affect drug metabolism and medication response.[18] Variations in allelic frequencies of the CYP2D6*10 gene have been observed among the Chinese, Malay and Indian populations.[19] Apart from different drug metabolism profiles, ethnicity could be the surrogate for underlying factors, including socioeconomic status, exposure to virus-related- environments and access to health care.[20] Further investigation is needed in this area to reduce health inequalities across different ethnic groups.[17]

The most commonly reported Paxlovid®-related adverse events in this study were dysgeusia, diarrhoea, and vomiting, which mirrored previous findings.[6,14] While the reported adverse events were not severe, they might lead to patients' non-adherence, causing drug resistance and treatment failure.[21] Therefore, medication counselling, compliance follow-up, and pharmacovigilance are essential components of Paxlovid® dispensing.[22]

We did not observe a significant difference in the odds of death between both arms. Two deaths were reported in the Paxlovid® arm, unrelated to COVID-19 infection or Paxlovid® treatment. There were three deaths in the control group, of which two were related to COVID-19 pneumonia. In contrast, Hammond et al. reported a significant difference in all-cause death outcomes, in which no death occurred in the treatment arm and 13 deaths in the placebo arm, of which all were COVID-19 related.[4] Nonetheless, the high number needed to treat in preventing one death suggests the need to investigate the cost-effectiveness of Paxlovid®, particularly in a low-resource health setting.

This study reflected the real-world efficacy of Paxlovid® using a matched cohort, which includes both outpatients and inpatients, vaccinated and unvaccinated populations. Initiation of Paxlovid® was performed using a standard risk-stratified scoring system and closely reflected clinical practice in Malaysian health settings. Several limitations should be considered when interpreting the findings of this study. The small sample size and the exclusion of lost to follow-up cases could restrict the generalisability of the study findings. Furthermore, there was a limited representation of subjects in the over-65 age group. Matching participants based on limited characteristics may introduce bias if other unknown factors influence the outcomes studied.

CONCLUSION

The use of Paxlovid® to treat symptomatic Covid-19 did not significantly reduce the risk of hospitalisation, all-cause death and supplemental oxygen requirement compared to the control group. Adverse events were common but non-severe. The efficacy of Paxlovid® in real-world settings and different populations remains inconsistent and warrants further investigations.

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Serum interleukin-40: an innovative diagnostic biomarker for patients with systemic lupus erythematosus

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ABSTRACT

Introduction: Interleukin (IL)-40 is a recently identified cytokine with a novel role in the pathogenesis of inflammatory diseases. Since systemic lupus erythematosus (SLE) is an autoimmune disease characterised by a pro-inflammatory response, it is likely that IL-40 contributes to the underlying disease processes of this disorder. The aim of the current study was to evaluate the potential of IL-40 to act as a diagnostic biomarker for SLE.

Matrrials and methods: The study included 99 patients with SLE who attended the Rheumatology Unit at Baghdad Teaching Hospital. These subjects were divided into three subgroups according to disease status: inactive, n = 33; active moderate, n = 33; and active severe, n = 33. Additionally, 33 matched controls were studied. Full medical histories, body mass index, gender and clinical disease activity, the latter evaluated with the SLE disease activity index, were collected. Laboratory parameters measured included anti-dsDNA antibodies, C3 and C4 levels, erythrocyte sedimentation rate and C-reactive protein titres. Serum IL-40 levels were quantified using an enzyme-linked immunosorbent assay.

Results: IL-40 levels were significantly higher in patients (12.5420 ± 3.00575 ng/L) than in controls (6.1138 ± 0.59452 ng/L; p < 0.01). Mean serum IL-40 concentration was highest in the active severe group (15.2291 ± 2.26540 ng/L) and decreased, in order of disease severity, in the remaining cohorts: active moderate, 13.0643 ± 1.23927 ng/L; inactive, 9.3325 ± 1.62807 ng/L (P < 0.01); controls, 6.1138 ± 0.59452 ng/L. Serum IL-40 levels showed excellent validity for the diagnosis of SLE with a cut-off value of ≥ 9.3 ng/ml and area under the curve of 0.987. Sensitivity, specificity and accuracy were 99%, 90.9% and 96.97%, respectively (P < 0.001).

Conclusions: Serum IL-40 levels were elevated in SLE patients. It is therefore proposed that IL-40 is a novel cytokine which is associated with SLE and positively linked with disease severity.

KEYWORDS:
Systemic lupus erythematosus; SLE; IL-40; autoimmune condition; inflammation

INTRODUCTION

Systemic lupus erythematosus (SLE) is a condition that develops owing to the abnormal immune-mediated destruction of healthy tissues[1,2] caused by B and T-cell hyperactivity and coincides with reactivity to self-antigens.[3] Increased production of antibodies, defective antibody clearance and complement and cytokine stimulation are some of the typical characteristics that result in the symptoms of SLE. There is up to a 3-fold increase in mortality in patients living with SLE compared to the general population. Improved treatment options may reduce mortality rates; however, superior diagnostic methods which allow for earlier or more sensitive detection of the disease are also essential.

The earliest signs of SLE reflect constitutional symptoms, which may be accompanied by mild to moderate joint pain, suggestive of arthritis. However, the presence of an accompanying skin rash or skin lesions at various anatomical sites supports a diagnosis of SLE.[1]

Since SLE is a heterogenous condition, to date, establishing a diagnosis has proved difficult as the presentation often reflects the symptoms of alternative conditions, e.g., cancers or infectious diseases, such as human immunodeficiency virus and acquired immunodeficiency syndrome.[3] Viral serological tests and tissue histopathological testing may be performed to exclude other causes. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have proposed criteria for the diagnosis of SLE. However, as patients with mild diseases are commonly unrecognised by this classification, more rigorous testing is essential.[3]

Current diagnostic methods for the diagnosis of SLE rely on clinical symptom manifestations and are complemented by laboratory tests, such as viral or tissue investigations. The latter includes the anti-nuclear antibody (ANA) test; a positive ANA result is supported by an antigen-specific ANA for extractable nuclear antigens, which has a specificity of approximately 66% for these complexes. It is recommended that consultants collaborate with a SLE rheumatologist in order to attain a more reliable diagnosis. Only a few biomarkers have been recognised as being of value in the diagnosis of SLE, but as none of these can be utilised with confidence in disease management, novel biomarkers are urgently required in the field. Elucidation of more precise biomarkers for SLE could greatly improve detection sensitivity and reduce the time taken to diagnose patients. However, there has been little success to date.

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Previous attempts to elucidate cytokine profiling in SLE have included the analysis of tumour necrosis factor-α (TNF-α), a pro-inflammatory cytokine which evidences increased expression in a variety of autoimmune diseases.[4] In one study, no differences between serum TNF-α levels in healthy and SLE groups were determined, although another study suggested that TNF-α was a useful biomarker for SLE. Thus, at present, the role of TNF-α in the diagnosis of SLE is unclear.[5]

A potentially superior approach is to quantify the levels of cytokines secreted by B cells, since SLE is predominantly mediated by aberrant B-cell activity, with autoimmune diseases, such as SLE, characterised by the presence of autoantibodies. At least one study has demonstrated aberrant B-cell-associated cytokine profiles in which IL-4 was virtually undetectable in the serum of SLE patients and coincided with a rise in IL-6.[6] The recent discovery of the B-cell-associated cytokine, IL-40, may also be utilised to improve the diagnosis of SLE, as exemplified in other inflammatory conditions.

IL-40 is a B-cell-associated orphan cytokine encoded by the gene, C17orf99, which is secreted via activated B-cells. This gene regulates IgG production in order to maintain the physiological function of B-cells.[7] Studies have demonstrated that IL-40 accumulates in the synovial joints of patients with rheumatoid arthritis (RA); serum IL-40 concentrations in patients with RA are substantially increased compared to those detected in healthy controls.[8] In RA, IL-40 propagates pro-inflammatory cytokine release and autoantibody production; extracellular IL-40 enhances the synthesis of tissue-degrading enzymes.[9] In one study, the depletion of B-cells reduced IL-40 production by 70%, suggesting that B-cell targeted therapies may offer relief from autoimmune conditions mediated by IL-40. However, other immune cells may synthesise residual IL-40. IL-40 has also been suggested to be a useful biomarker for the detection of type II diabetes mellitus and Sjögren's syndrome, underscoring its role in the pathogenesis of inflammatory and autoimmune diseases.[10-12]

Since SLE is an autoimmune condition characterised by a pro-inflammatory response, the detection of IL-40 may be a useful strategy for the identification of individuals with SLE as aberrant B-cell activity is a hallmark of the disease. However, conflicting evidence suggests that IL-40 only regulates local inflammation and does not underlie the systemic inflammatory response observed in patients with SLE in whom IL-40 levels were comparable to those measured in controls.10 Before the utility of IL-40 in the diagnosis of SLE can be realised, further studies are required in order to investigate whether IL-40 plays a role in SLE or whether it is simply a local inflammatory mediator.

The principal objective of this present study was to thoroughly evaluate and ascertain the potential efficacy of IL-40 as a reliable diagnostic biomarker for SLE.

MATERIALS AND METHODS

This study included 99 patients, aged over 18 years, who were diagnosed with SLE according to the 2019 EULAR/ACR classification criteria.[13] They were divided into three subgroups: inactive, *n*=33; active moderate, *n*=33; and active severe, *n*=33. Thirty-three age- and sex-matched healthy controls were also included. Participants were recruited between November 2022 and January 2023 from the Rheumatology Unit at the Baghdad Teaching Hospital. Exclusion criteria were: concurrent overlapping inflammatory arthritis, connective tissue disease or seronegative spondyloarthritis; malignancy; pregnancy; evidence of infection and patient refusal. Under the direction of the rheumatologist, the full patient information page data and consent form were completed, and the Committee of Scientific Ethics from the College of Medicine, University of Baghdad approved the study. The ethics committee's approval number was 023. For each patient, gathered baseline data encompassed blood investigations, full medical histories, body mass index (BMI), gender and clinical disease activity as evaluated with the SLE disease activity index. Disease-related laboratory parameters included anti-dsDNA antibodies, C3 and C4 levels, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

The SLE disease activity scoring system consists of 24 variables which cover 9 organ systems and yield a total score of 105. A total score ≤ 3 suggests that no flare is present, a total score > 3 and ≤ 12 is considered to reflect a mild to moderate flare, and a total score > 12 represents a severe flare.[14] Serum was obtained by centrifuging blood specimens for 10 to 15 minutes at 1000–3000 rpm. Serum samples were then frozen at –20°C. The enzyme-linked immunosorbent assay technique (Sun Long Biotech Company, China) was used to measure serum IL-40 in keeping with the manufacturer's instructions. A plate reader was used to determine the absorbance at 450 nm. The immunological testing was done at the International Centre for Research and Development.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 21 (IBM). Student's t tests, analysis of variance (ANOVA) and the less significant difference (LSD) test were performed for comparisons of quantitative variables, i.e. age, BMI and serum IL–40 levels, between studied groups. Normally distributed data are expressed as mean ± standard deviation. Pearson's chi-square test (χ^2) was used for comparisons of qualitative variables between studied groups, i.e. age groups and BMI. A binomial Z-test was performed for a comparison of gender and treatment intake. Pearson's correlation test was applied in order to detect the relationships between serum IL–40 levels and age, BMI, duration of SLE disease, ESR and C3 and C4 concentrations. The validity of the ELISA test was estimated with a ROC curve, cut-off value, area under curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy. The statistical significance threshold was deemed to be a P-value < 0.05.

RESULTS

The age ranges of the 99 SLE patients and 33 control subjects were 18 to 58 years and 19 to 55 years, respectively. Table I illustrate the similarities between the two cohorts with respect to the demographic parameters of gender, age group and BMI.

Females were predominant within both studied groups, comprising 93 (93.94%) SLE patients and 30 (90.4%) controls (p=0.037).

The frequency of subjects was highest within the age range, 31–40 years, in both controls (13, 39.4%) and SLE patients (40, 40.4%), followed by the age range 18–30 years, i.e. controls (12, 36.4%) and SLE patients (36, 36.4%) (p=0.991). The mean ages of the two studied groups were similar, i.e. controls, 35.35 ± 11.783 years, and SLE patients, 34.69 ± 9.074 years (p=0.789).

The frequency of subjects assigned to the BMI classifications in the two cohorts was as follows: overweight: controls, 19 (57.6%), SLE patients, 40 (40.4%); obese: controls, 8 (24.2%), SLE patients, 34 (34.3%); normal weight: controls, 6 (18.2%), SLE patients, 25 (25.3%) (p=0.359).

Mean BMI showed a trend towards being greater in the SLE patient cohort when compared to the control group, i.e. 28.1342 ± 5.5956 kg/m^2 and 25.8926 ± 3.87481 kg/m2, respectively, but this failed to reach statistical significance (p=0.161).

When the variables were compared with respect to disease activity using ANOVA, no differences were identified (Table II). The mean BMI values of the SLE patients within all three groups of disease activity were similar: active severe, 28.7406 ± 6.27527 kg/m^2; active moderate, 28.3613 ± 6.04078 kg/m^2; inactive 27.8319 ± 4.66821 kg/m^2 (p=0.101).

LSD test values were also similar between the various levels of disease activity: inactive vs. active moderate, p=0.691; inactive vs. active severe, p=0.494; active moderate vs. active severe, p=0.775.

Mean disease durations were similar between the different disease activity groups: active moderate, 6.836 ± 5.3956 years; active severe, 5.994 ± 4.2940 years; inactive, 4.306 ± 4.7466 years (p=0.185). A within-group comparison of the LSD test data demonstrated no differences: inactive vs. active moderate, p=0.072; inactive vs. active severe, p=0.228; active moderate vs. active severe, p=0.546.

Mean serum ESR values were higher, the greater the disease activity: active severe disease, 47.18 ± 30.304; active moderate, 40.79 ± 26.415; inactive disease, 21.70 ± 11.509 (p<0.001). Similar results were obtained for the LSD test, with the exception of active moderate vs. active severe disease states (p=0.221).

Mean anti-dsDNA levels were modestly elevated in SLE patients with active severe disease (92.812 ± 143.821) when compared with those with active moderate disease (30.297 ± 24.2616); anti-dsDNA titres were decreased in patients with inactive disease (19.233 ± 3.7611, p=0.00).

Within-group comparisons were shown to be identical by the LSD test, with the exception of inactive vs. active moderate (p=0.539).

Mean C3 levels were lower in SLE patients within the active severe cohort (0.5858 ± 0.37691) compared to those with active moderate disease (0.6973 ± 0.39807) and increased in the inactive group (1.0548 ± 0.49356, p<0.001).

Significant differences (P < 0.01) were noted following the LSD test, with the exception of active moderate vs. active severe (p=0.253).

Mean C4 levels were diminished in SLE patients with active severe (0.0543 ± 0.05139) compared to those with active moderate (0.2642 ± 0.21645) and inactive disease (0.2812 ± 0.08521); these differences were significant (p<0.01) for all comparisons apart from inactive vs. active moderate (p=0.528).

Table III presents the distribution of the CRP data and treatment intake according to the severity of SLE disease. This was non-significant (p=0.164) for DMARDs intake: inactive: yes, 31 (93.9%), no, 2 (6.1%); active moderate: yes, 26 (78.8%), no, 7 (21.2%); active severe: yes, 25 (75.8%), no, 8 (24.2%).

The data showed a significant difference (p=0.033) for CRP: inactive: positive, 1 (3.03%) negative, 32 (96.97%); active moderate: positive, 2 (6.06%), negative, 31 (93.94%); active severe: positive, 6 (18.18%), negative, 27 (81.82%).

Significant differences (p<0.01) were observed for other types of treatment intakes: (i) steroid intake: inactive: yes, 12 (36.4%), no, 21 (63.6%); active moderate: yes, 25 (75.8%), no, 8 (24.2%); active severe: yes, 28 (84.85%), no, 5 (15.15%) (P < 0.001); and (ii) biologics intake: active moderate: yes, 1 (3%), no, 32 (97%); active severe, yes, 12 (36.4%), no, 21 (63.6%) (p=0.008).

Result indicates that the mean serum IL-40 ng/ml titre in SLE patients (n=99) was higher than in controls (n=33), i.e. 12.5420 ± 3.00575 ng/L vs. 6.1138 ± 0.59452 ng/L (p<0.01).

It can be clearly observed from the ANOVA and LSD tests presented in Table IV that the mean IL-40 levels in the sera of SLE patients in the active severe cohort are higher (15.2291 ± 2.26540 ng/L) than in those patients in the active moderate group (13.0643 ± 1.23927 ng/L). The latter values are elevated compared to the inactive (9.3325 ± 1.62807 ng/L) and control groups (6.1138 ± 0.59452 ng/L) (p<0.01 in all cases).

Results also show the mean distributions of IL-40 levels in the sera of SLE patients according to the type of treatment intake. For DMARDs intake, mean IL-40 values were lower in those patients taking this medication: Yes, 12.2198 ± 2.96423 ng/L; No, 14.0959 ± 2.78502 ng/L (p=0.018). Mean IL-40 levels were similar amongst patients who were or were not on steroid therapy: Yes, 12.2301 ± 2.72639 ng/L; No, 13.1383 ± 3.44324 ng/L (p=0.154), and between patients who were or were not receiving biologics: Yes, 14.2086 ± 2.74526 ng/L; No, 14.1315 ± 1.96211 ng/L (p=0.907).

A correlation study between IL-40 levels and the other SLE patient parameters revealed that there were inverse

Table I: Demographics and other parameters: distributions within the two studied groups, i.e., SLE patients and controls.

Parameters		Studied groups		*p* value
		Controls (n=33)	Patients (n=99)	
Gender	Male	3 (9.1%)	6 (6.06%)	0.337
	Female	30 (90.9%)	93 (93.94%)	NS
Age-groups (years)	18–30	12 (36.4%)	36 (36.4%)	0.991
	31–40	13 (39.4%)	40 (40.4%)	NS
	41–50	7 (21.2%)	21 (21.2%)	
	51–60	1 (3%)	2 (2%)	
BMI groups	Normal weight	6 (18.2%)	25 (25.3%)	0.359
	Overweight	19 (57.6%)	40 (40.4%)	
	Obese	8 (24.2%)	34 (34.3%)	
Age (years)	Mean	35.35	34.69	0.786 NS
	Std. deviation	11.783	9.074	
	Std. error	1.915	1.074	
BMI (kg/m^2)	Mean	25.8926	28.1342	0.161 NS
	Std. deviation	3.87481	5.5956	
	Std. error	0.63942	0.5483	

NS: non-significant (p>0.05), BMI: body mass index.

Table II: Mean distributions of parameters within SLE patient groups

SLE patient groups		Mean	Std. Deviation	Std. Error	LSD test (p value)	
BMI	Inactive	27.8319	4.66821	0.81263	A	0.691
	Active moderate	28.3613	6.04078	1.05156	B	0.494
	Active severe	28.7406	6.27527	1.09238	C	0.775
	ANOVA test (p value):		p=0.101			
Duration (years)	Inactive	4.306	4.7466	0.8263	A	0.072
	Active moderate	6.836	7.3956	1.2874	B	0.228
	Active severe	5.994	4.2940	0.7475	C	0.546
	ANOVA test (p value):		p=0.185			
ESR	Inactive	21.70	11.509	2.004	A	0.00
	Active moderate	40.79	26.415	4.598	B	0.00
	Active severe	47.18	30.304	5.275	C	0.221
	ANOVA test (p value):		p<0.001			
Anti-dsDNA	Inactive	19.233	3.7611	0.6547	A	0.539
	Active moderate	30.297	24.2616	4.2234	B	0.00
	Active severe	92.812	143.821	25.0362	C	0.001
	ANOVA test (p value):		p<0.001			
C3	Inactive	1.0548	0.49356	0.08592	A	0.00
	Active moderate	0.6973	0.39807	0.06929	B	0.00
	Active severe	0.5858	0.37691	0.06561	C	0.253
	ANOVA test (p value):		p<0.001			
C4	Inactive	0.2812	0.08521	0.01483	A	0.582
	Active moderate	0.2642	0.21645	0.03768	B	0.00
	Active severe	0.0543	0.05139	0.00895	C	0.00
	ANOVA test (p value):		p<0.001			

BMI: body mass index, ESR: erythrocyte sedimentation rate, Anti-ds DNA: Anti-double stranded DNA, C3 and C4: Complement components 3 and 4, LSD: Least Significant Difference, A = inactive vs. active moderate, B = inactive vs. active severe, C = active moderate vs. active severe.

Table III: C-reactive protein values and treatment intake distributions within SLE patient groups

Parameters		SLE patient groups			*p* value
		Inactive (n=33)	Active moderate (n=33)	Active severe (n=33)	
CRP	Positive	1 (3.03%)	2 (6.06%)	6 (18.18%)	**0.033
	Negative	32 (96.97%)	31 (93.94%)	27 (81.82%)	
DMARDs intake	Yes	31 (93.9%)	26 (78.8%)	25 (75.8%)	0.164 NS
	No	2 (6.1%)	7 (21.2%)	8 (24.2%)	
Steroid intake	Yes	12 (36.4%)	25 (75.8%)	28 (84.85%)	**<0.01
	No	21 (63.6%)	8 (24.2%)	5 (15.15%)	
Biologics intake	Yes		1 (3%)	12 (36.4%)	**0.008
	No		32 (97%)	21 (63.6%)	

**p<0.01. NS: non-significant (p>0.05), CRP: C-Reactive Protein, DMARDs: Disease- Modifying Anti-Rheumatic Drugs

Table IV: Mean distributions of IL-40 levels within SLE patient groups and controls

	IL-40 levels (ng/L)				
Severity of SLE	**Mean**	**SD**	**Std. error**	**LSD test (P value)**	
Control	6.1138	0.59452	0.07475	A	**<0.01
Inactive	9.3325	1.62807	0.28341	B	**<0.01
Active moderate	13.0643	1.23927	0.21573	C	**<0.01
Active severe	15.2291	2.26540	0.39436	D	**<0.01
ANOVA test (p value); p=0.00				E	**<0.01
				F	**<0.01

**(p< 0.01), SD: Standard Deviation, LSD: Least Significant Difference

Table V: Correlation study between IL-40 levels and other SLE patient parameters

	SLE patients (n = 99)	
Pearson Correlation		**IL40 ng/L**
BMI	r	0.069
	p value	0.495
Age	r	0.139
	p value	0.171
Duration	r	0.181
	p value	0.073
ESR	r	0.344
	p value	0.00
Anti-dsDNA	r	0.166
	p value	0.101
C3	r	-0.420
	p value	0.00
C4	r	-0.396
	p value	0.00

relationships between serum IL-40 titres and C3 (r = –0.420, p<0.01) and C4 levels (r=–0.396, p<0.01), and a positive relationship between serum IL-40 levels and ESR values (r=0.344, p<0.01).

The remaining variables demonstrated a weakly positive correlation which was insignificant (Table V).

Validity of Tests

The results given prove that serum IL-40 levels have excellent validity for use in the diagnosis or follow-up of SLE patients at a cut-off value of 9.3 ng/ml. The performance parameters were: AUC, 0.987; sensitivity, 99%; specificity, 90.9%; PPV, 97%; NPV, 96.8%; accuracy, 96.97% (p<0.001).

DISCUSSION

It is well-established that SLE arises from a complicated, multifactorial interaction between various genetic factors. Multiple genes contribute towards patient disease susceptibility, which is further refined and controlled by environmental triggers.[15-18] Research has been ongoing for several decades in order to identify relevant biomarkers for SLE,[19-22] and although some have shown promising results, no single biomarker has been able to detect SLE completely and reliably in every case. This issue arises as a result of the heterogeneous characteristics of SLE, the differing symptom presentations observed in practice,[23] and the complex patterns of hereditability and genetic variation associated with the disease.[24]

Nonetheless, previous research has indicated that IL-40 plays a central role in biological disease processes,[7-8,10,25] and the cytokine has recently been proposed as a contributing factor to the development of SLE-associated nephritis.[26] In this study, multiple blood markers were evaluated, including IL-40 titres, in order to investigate whether or not they played a role in the development and expression of SLE in the selected study population.

It was established that serum IL-40 concentrations differed significantly between patients with SLE and the controls. A positive association between IL-40 levels and lupus severity was identified, in that serum IL-40 titres increased in parallel with the severity and duration of lupus symptoms. Previous studies which have analysed serum IL-40 levels have shown a similar trend in relation to the identification of RA and concluded that IL-40 is a reliable indicator for the disease 25. IL-40 is a cytokine that plays a central role in the regulation and secretion of IgG which, in turn, supports the normal functioning of B cells and enables the body's immune system to effectively respond to antibodies.[7-8,27] IL-40 has not been widely studied, but it appears to be expressed only in mammals. It has a unique structure, which makes it incomparable to most cytokine families.[7,8] The cytokine has been shown to exert its most potent regulatory influence over B cells, acting during foetal development, and within the liver and bone marrow.[7,28-29] Studies of IL-40 knockout mice demonstrated an effect on B cell development, resulting in impaired and non-functioning cells.[8,25] Given that SLE is recognised as an autoimmune disease,[6,25] the current results support the hypothesis that IL-40 could be used to determine and diagnose autoimmune dysfunction.

The role of IL-40 and its efficacy as a biomarker for detecting disease have now been identified for a range of pathologies

including RA[8,25] type II diabetes,[10] hepatocellular carcinoma[30] and lupus.[11] The present results also imply that IL-40 is an important biomarker for the detection of SLE, and it is suggested that further work should be targeted towards the part played by IL-40 in disease development processes. Monitoring serum IL-40 levels could support future clinical diagnosis. Additionally, higher IL-40 titres were associated with SLE symptom severity and so serum IL-40 level monitoring in individuals suspected of having SLE could provide opportunities for early diagnosis and intervention.

It was determined that the complement indicators, C3 and C4, were both negatively correlated with IL-40 levels, indicating that a higher titre of IL-40, which is indicative of a positive SLE diagnosis, is associated with reduced C3 and C4 levels. This finding supports previous studies which have reported diminished blood serum complement factors in cases of lupus.[9,11]

When compared to the cohort of patients with inactive SLE, ESR values were elevated in the groups with active severe and active moderate disease, which supports existing literature showing that a high ESR indicates active lupus.[19] Elevated anti-dsDNA antibody levels were also measured in the active severe group as opposed to in SLE patients with active moderate or inactive disease, a finding which supports previous studies that suggest a high level of serum anti-dsDNA antibodies are strongly associated with lupus.

CRP has a complex role in lupus, with modest CRP elevations often seen in patients with SLE. In the current study, the inactive group exhibited more negative than positive test outcomes. Conversely, both types of active SLE patient cohorts demonstrated more positive than negative test outcomes. The reason for the variation in proportions of positive and negative tests across the different SLE types is not clear. However, these findings support previous observations, i.e. that CRP involvement in lupus appears to be part of a complex set of processes.[19]

A negative association between the use of DMARDs and IL-40 levels was observed, i.e. patients who did not take DMARDs had significantly higher serum IL-40 levels. This suggested that DMARDs may provide a protective effect against rising IL-40 levels in cases of SLE.

This study is the first to demonstrate the positive association between IL-40 levels and SLE symptom severity, adding evidence to suggest that IL-40 plays a role in SLE, and could be used as part of the diagnostic process. A robust sample size of 99 SLE and 33 controls was studied. However, it was recognised that when filtering patients by certain variables, the sample size was reduced to a less than ideal number. For instance, the sample size for SLE patients not taking DMARDs was small, i.e. 17 patients, when compared to the sample of 82 patients who were taking DMARDs. Nonetheless, it is considered that the results offer robust evidence that DMARDs may be protective against the development of SLE and support the role of IL-40 in this autoimmune condition. Sample sizes will always be a challenge in such studies, but it is recommended that, where possible, future studies should take all available steps to maximise sample sizes.

The link between IL-40 titres, and SLE symptom severity and duration, needs to be confirmed in a larger sample size, and in patient populations with greater ethnic diversity. Previous studies have highlighted that Black, Hispanic and Asian populations demonstrate higher rates of SLE,[31,32] and it is well-established that SLE is linked to genetic heritage and ancestry.[24] Furthermore, women are disproportionately affected over men.[23] A logical next step would therefore be to understand how the role and function of IL-40 may differ between different ethnic and geo-spatially distinct populations of individuals with SLE. The majority of studies have been conducted in the Western or developed world,[14-15,31,32] and a need for further studies to investigate the prevalence and presence of SLE in developing nations is recognised. This is especially relevant given that White populations appear to be at a lower risk of the condition.[31,32]

CONCLUSIONS

It was established that serum IL-40 measurements demonstrated strong validity for the identification and diagnosis of SLE, and exhibited greater accuracy than recognised in relation to other disease indications. IL-40 levels were positively correlated with SLE symptom severity and duration, indicating that this cytokine could be a promising biomarker for SLE, and play a role in early diagnosis and intervention monitoring. This study adds further evidence to support the observation that IL-40 is important with respect to the immune response and immune system regulation. It is hoped that it inspires further studies which are designed to improve the understanding of the cytokine's potential as a biomarker for SLE and other autoimmune diseases.

CONFLICTS OF INTEREST

No conflicts of interest.

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ORIGINAL ARTICLE

Clinicopathological study of gastric cancer in a Malaysian tertiary public health care centre

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ABSTRACT

Introduction: Gastric cancer (GC) is one of the leading causes of all new cancer cases globally. Although it is no longer reported in the top 10th most common cancer in Malaysia, geographical distribution and ethnic influences still obviously exist.

Materials and Methods: This is a retrospective analysis of histopathological records in a public tertiary health care centre in Malaysia. The computerised laboratory information system from the histopathology department of the hospital was retrieved for the period of 2005–2018. Descriptive analysis was done using Microsoft Excel.

Results: There was a total of 233 histologically confirmed GC cases. The burden of GC was observed to be an increasing trend from 2016 onwards. Among them, 64% were male and 36% were female. The youngest age of diagnosis was 19, while the oldest one was 93. Malaysian Chinese were found to have the highest incidences (41.63%), followed by Malays (32.19%) and Malaysian Indians (23.61%). All cases were of adenocarcinoma cell types and were found to have poorly differentiated in majority at the time of diagnosis.

Conclusion: Although this report only represents one tertiary health care centre in Malaysia, the Indian Enigma was still observed, as stated in other literatures. Over time, the incidence of GC in Malays has increased. Consideration of lifestyle modifications, health education and *Helicobacter pylori* eradication in various nations' National Health Insurance plans, are encouraged as prevention is always better than treatment or cure, including the cost load.

KEYWORDS:
Stomach neoplasms, Malaysia, Ethnic, Geographical, Enigma

INTRODUCTION

Gastric cancer (GC) is the fifth leading cause of all newly diagnosed cancer globally and the fourth leading cause of cancer-related death in 2020.[1] The incidence rate, mortality rate and the 5-year prevelance rate of GC were the highest in Asia compared to other regions.[1] In addition, around 1 in 12 cancer-related deaths were attributable to GC in 2018.[2] Although nearly a million new GC cases are diagnosed globally every year, GC is one of the most preventable cancer due to its highly behaviourally influenced nature.[2] However, the incidence, the age-standardized incidence and mortality of GC also declined globally.[3] Although GC was reported as the second-highest incidence and mortality worldwide according to the Global Cancer Observatory (GLOBOCAN) 1998, GC was reported as the fifth most common neoplasm of all new cancer cases in GLOBOCAN 2018.[3] New GC cases are still detected, especially in the Eastern Asian countries and these countries still have a high risk of GC.[3] GC was ranked as the 10th most common cancer in Malaysia in 2007–2011 (Malaysia National Cancer Registry) MNCR report but it was not reported in the top 10 list in the 2012–2016 MNCR report.[4,5]

Incidence and mortality of GC are highly variable by geography as well as are greatly influenced by diet, environmental factors, and *Helicobacter pylori (H. pylori)* infection in the community. GC was common in the United States in previous centuries, but now it is no longer prevalent.[2] This decreasing trend was most obvious in countries such as Japan and South Korea.[2] More than 50% of new incident cases were reported from developing countries. This downward trend in some regions could be due to the earlier detection of GC using screening procedures such as upper gastrointestinal endoscopy or radiography and might be due to the reduced *H. pylori* infection in some countries.[2]

The age-standardized 5-year net survival rate for GC is still between 20% and 40%, where 33.1% for the USA and 20.7% for the UK.[2] In these countries, although being the well-developed countries, GC tends to be diagnosed at an advanced stage.[2] In contrast, the age-standardized 5-year net survival rate for Eastern Asian countries such as South Korea and Japan also has higher rates. The 5-year survival rate for GC in 2010–2014 was reported as 68.9% for South Korea and 60.3% for Japan. It was strongly believed that the early detection of GC had contributed to these favourable health outcomes. However, the median survival rate of GC is less than 12 months in the advanced stage of GC.[6]

The survival rate of GC has improved globally over the decades due to improved case detection, early diagnosis, and better treatment strategies.[2] However, there is still room for improvement to achieve a favourable survival rate worldwide.[2] Early diagnosis of GC plays an important role in achieving a better survival outcome of GC and an understanding of its epidemiology, variation in ethnicity, age, gender and genetic predispositions are crucial. The

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Table I: Number of GC cases reported annually at the HTJ, Seremban, Negeri Sembilan, Malaysia from 2005–2018

Year reported	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Number of GC cases	13	11	13	5	17	23	23	12	12	17	15	22	21	29

Note: GC = gastric cancer

Table II. Age, gender, and ethnic incidences of GC cases reported annually at the HTJ, Seremban, Negeri Sembilan, Malaysia from 2005 to 2018

Gender	Ethnicity	Number of cases n (%)	Mean age of GC cases a at the time of diagnosis Age in years ± SD	Age in years (range)
Female	Chinese	31 (37.35)	68.41 ± 12.77	45–92
	Indian	26 (31.33)	59.38 ± 14.04	23–80
	Malay	24 (28.92)	57.76 ± 14.06	34–83
	others	2 (2.41)	60 ± 20	40–80
	Female (Total)	83 (100)	61.99 ± 14.64	23–92
Male	Chinese	66 (44)	66.67 ± 10.84	42–93
	Indian	29 (19.33)	54.63 ± 12.74	30–83.2
	Malay	51 (34)	63.42 ± 13.33	28–91
	others	4 (2.67)	43.25 ± 10.96	31–61
	Male (Total)	150 (100)	62.38 ± 13.7	19–93
Total	Chinese	97 (41.63)	67.23 ± 12	42–93
	Indian	55 (23.61)	55.74 ± 14.29	19–83.2
	Malay	75 (32.19)	61.61 ± 13.83	28–91
	others	6 (2.58)	48.83 ± 16.61	31–80
	Total	233 (100)	62.24 ± 14.04	19–93

Note: SD = standard deviation

objective of this study is to investigate the incidence and trend of GC in Malaysia at one of the tertiary health care centres, i.e., Hospital Tuanku Ja'afar (HTJ), Seremban, Negeri Sembilan state, Malaysia from 2005 to 2018.

MATERIALS AND METHODS

This is a retrospective cross-sectional study of the histologically confirmed GC data from 2008 to 2018. All patient records of histologically confirmed GC cases during the study period at the Hospital Tuanku Ja'afer (HTJ), Seremban, Negeri Sembilan, Malaysia were reviewed. Data collected were clinicopathological parameters which included histopathological diagnosis, age, gender, identification card number, patient registration number, ethnic group, date of biopsy and histological diagnosis. Inclusion criteria included that the patients must have attended HTJ between 2005 and 2018 and paraffin-embedded gastric biopsy must be available. The patients diagnosed with GC before 1 January 2005 or after 31 December 2018, patients who were diagnosed with oesophageal cancer alone were excluded from the study. The index date was defined as the date of the first outpatient or inpatient visit with a diagnosis of GC. Records of the patients who were first diagnosed with GC before 1st January 2005 were excluded from the study. Data were analysed using Microsoft Excel. Confidentiality of the collected information was maintained by strict measures. The names, ethnic groups and ages of the patients were kept private and confidential apart from the research team. The identities of patients were not revealed in this report.

RESULTS

There was a total of 233 cases reported as histologically confirmed GC cases in HTJ, Seremban from 2005 to 2018. The number of annual reported cases of GC from 2005 to 2018 was found to be varied. The number of reported GC cases in HTJ was observed as an increasing trend starting from 2016 onwards (Table I).

The youngest reported case was a 19-year-old Malaysian Indian man, and the oldest reported case was a 93-year-old Malaysian Chinese woman. The mean age of diagnosis is 62.24 ± 14.04 years. However, there were 38 cases whose ages were not included in the report, and the estimated age was calculated from the identification card (IC) number of the patient (which usually starts with the birth year of the person in Malaysia) and the year of the biopsy report. The number of reported and confirmed GC cases was found to be highest among the age group of 61–70, 51–60 and 71–80, respectively (Table II).

Among 233 cases, 64% (n = 150) cases were males and 36% (n = 83) were females. The youngest age of reported GC cases for females was 23, and the oldest one was 92. The youngest age of reported GC case for men was 19 and the oldest was 93. Malaysian Chinese ethnic group has the highest incidence of GC with 41.63% (n = 97), followed by Malays with 32.2% (n = 75) and Malaysian Indians with 23.61% (n = 55). There were a few cases reported from ethnic minorities 1 case each (0.43%) from Orang Asli, Singh and others (Table II).

All reported cases were adenocarcinoma 100% (n = 233). In terms of histopathological grading, 45% (n = 104) were

poorly differentiated type, 21% (n = 21) were moderately differentiated type, 3% (n = 7) were well-differentiated type, while there were 1 moderate to poorly differentiated type and 1 moderate to well-differentiated type, 30% (n = 70) were not reported. According to Lauren's classification, 13% (n = 31) were intestinal type, 15% (n = 34) were diffuse type and 1% (n = 2) were mixed type, while 74% (n = 172) did not find a report for pathological subtype. Seven reported cases with signet ring cell types which were considered as diffused type.

DISCUSSION

Comparison with Previous Findings

The shifting pattern of ethnic incidence of GC in Malaysia is the most noticeable characteristic of this study. Among the 233 laboratory-confirmed GC cases from the HTJ, Seremban from 2005 to 2018, 41.6% of diagnostically confirmed GC cases were Malaysian Chinese population, 31.8% were Malay population and 23.6% were Malaysian Indian population. An earlier study which was done at the HTJ in 2013 showed 55.0% Malaysian Chinese, 27.8% Malaysian Indian and 16.6% Malay population.[7] The second study which was carried out at the Hospital Ipoh, Perak state, Malaysia also showed 53.6% Malaysian Chinese, 36% Malaysian Indian and 26% Malay population. The study represented data from 1988 to 1998.[8] It indicates the increasing incidence of GC in Malay population.

The age-standardized rate for GC was 4–5 times lower in Malay than in the Malaysian Chinese and Malaysian Indian populations. This gap seemed to be narrower due to the increased number of GC cases in the Malay population and decreased the number of cases in the other two populations.[9] The findings from this study agrees with the fact of the increased number of GC cases in the Malay population. However, the incidence rate in the Malaysian Chinese and Malaysian Indian populations does not seem to decline significantly. This partly agrees with the MNCR report (2012–2016), which stated as the Malaysian Chinese have the highest incidence rate in both genders.[4] According to MNCR 2012–2016, the rate of GC was declined in Malaysia and was no longer listed as the 10th most common cancer. However, the incidence of GC in Seremban, Negeri Sembilan state does not seem to be declining until 2018. Globally, the highest number of cases was observed in Asia, specifically in China.[10]

The mean age of diagnosis for GC was 62.75 ± 13.95 years and only 9.8% of them (n = 23) are diagnosed under the age of 45 in this study. This agrees with the previous reports 60.8 ± 14.744 years (19–91) and 65 years (male 65.3 years and female 63.2 years, $p > 0.05$).[7,8] In our study, 9.8% of the reported cases were early-onset GC (45 years or younger) and the remaining 91.2% were conventional GC (older than 45). This finding agrees with the data from Machlowska et al (6), which stated that GC is not prevalent in younger age groups who are <45 years of age.[6] Early-onset GC was rare and not more than 10% of patients underwent disease development.[6] However, the youngest reported case in this study was a 19-year-old Malaysian Indian male patient, and such cases could have a genetic influence as a big role in the development of GC.

There were 56.3% male patients in the study by Tata et al (7) whereas our current study indicates that 63% male, indicating male predominance in GC.[7] Both studies were done in HTJ, Seremban, Negeri Sembilan state, Malaysia. In another study done at the Hospital Ipoh, 68.4% (171 out of 250 GC patients) were male patients.[8] This clearly demonstrates the male predominance in the incidence of GC. In our study, among different populations, men had a higher incidence than women (68%, 68% and 52.7%) in all Malaysian populations: Malaysian Chinese, Malay and Malaysian Indian, respectively. The findings of our study agree with the previous reports, that there is a male preponderance in all main ethnic groups of Malaysia.[4,6] Globally, men have higher incidence than women, and double the number of cases were reported.[9]

Around the 1980s, only 3% of GC patients are diagnosed with early GC but this was increased to 27% as stages 1 and 2 in the twenty-first century, indicating an earlier diagnosis trend.[9] The mortality to an incidence rate (MIR) for GC in South East Asia (SEA) was reported as 0.88 and a similar rate was observed for Malaysia.[10] Incidence of GC in Malaysia was declined by 48% among males and 31% among females in their last reported period of 13 years.[10]

All 233 cases in our review reported as adenocarcinoma type, and this agrees with the previous study.[7] Most of the reported cases 45% were diagnosed as poorly differentiated, 21% were reported as moderately differentiated and only 3% were reported as well-differentiated. The site of the tumour was not consistently informed. In the previous study, 45.6% were diagnosed with stage 4B; 36% with stage 4A; and only 3.6% with stage 1.[8] This implied the late diagnosis nature of the disease. Survival rate of the studied cases in this report was not traced. The survival rate of GC has improved globally over the decades due to improved case detection, early diagnosis, and better treatment strategies.[2] However, there is still room for improvement to achieve a favourable survival rate worldwide.[2]

In addition, GC can be classified into intestinal type and diffuse type depending on the histopathology.[2,4] There was a decline in the sporadic intestinal-type GC, but in contrast, the incidence of diffuse-type GC has reportedly increased.[6] This study does not have any prior data to explore further.

Geographic Diversity of GC

The incidence of GC displays immense geographical diversity.[6,9] This study only represents the data from the Negeri Sembilan state, Malaysia. Geographically, Kelantan state, which is northeast of the Peninsular Malaysia, was observed as having the lowest incidence of GC and Kelantan Malays were probably having the lowest rates of GC globally.[9] Thailand Enigma was reported where the Southern part of Thailand, was also observed as a lower incidence of *H. pylori* infection compared to North, Northeast and Central Thailand.[11] Geographically, Kelantan state and the Southern part of Thailand are neighbouring states and share a significant pattern of similarity in diet and the abundance of sea foods, vegetables and deep-sea water.[12]

The Indian enigma had reported by Misra in 2014.[13] The geographical distribution of GC differs widely in the different regions of India.[13] Southern and Eastern India had shown a high incidence of GC frequency approximately four times compared to North India.[13] Non-vegetarian foods, particularly, spicy and salty meat, fish, pickled food, high rice intake, excess chilli consumption, high-temperature foods, smoked dried salted meat, use of soda and consumption of dried salted fish were observed as significant risk factors for GC compared to North India, where diet is mainly wheat-based, a greater proportion of vegetarians and a higher intake of fruits and spices such as turmeric, garlic etc. These dietary habits were proposed as one of the explanations for the Indian enigma.[13]

Globally, the age-adjusted incidence rate was observed as a downward trend in Japan which was probably due to improved early diagnosis efforts and improved treatment outcomes in Japan.[2,10] However, due to the increased number of elderly populations, the crude incidence rate of GC continued to increase, and GC was more frequently detected in Japan. After the two peaks in 2030–2034 (in men) and 2025–2029 (in women), the decreasing trend of GC could be observed as the younger generation in Japan was more aware of health, and they tend to adopt a healthy lifestyle compared to the older generation.[2] In February 2013, Japan became the first country in the world to cover *H. pylori* eradication for chronic gastritis under its National Health Insurance (NHI) system.[10] *H. pylori* eradication reduces the risk of second GC to approximately one-third that of patients who do not undergo eradication therapy (JAPANGAST study). This indicates the benefit of *H. pylori* eradication in preventing GC.[14,15]

Risk Factors of GC

As known, *H. pylori* is classified as a type I carcinogen and is reported as a major risk factor for GC, especially for non-cardia GC. The reduction of the *H. pylori* infection rate in the population has contributed to the decline in the incidence of non-cardia GC. In addition, this trend could be explained by the increased standard of hygiene, better food conservation and a high intake of fruits and vegetables.[2,4] For cardia GC, it is more related to risk factors such as body fat. It was expected that cardia GC might be more frequent in future.[2] Most of the cases are non-cardia GC in Malaysia, except in Kelantan, where the main site of involvement is cardia.[9] The site of the tumour of GC, either cardia or non-cardia did not report consistently and hence, we do not have a precise data regarding the cardia and non-cardia types in this study.

Five-Year Survival Rate of GC

The 5-year survival rate for GC in 2010–2014 was reported as 68.9% for South Korea and 60.3% for Japan. However, the 5-year survival rate of GC globally is still around 20%.[10] It was strongly believed that the early detection of GC had contributed to these favourable health outcomes. However, the median survival rate of GC is less than 12 months in the advanced stage of GC.[6] Due to its high aggressiveness and heterogeneous in nature, even with early diagnosis, GC will still constitute as a global health issue.[6]

Accessing the trend of GC from one hospital data is not sufficient despite the data obtained are more than a decade. Some data, such as the age of the patients from certain reports, were not included. Confounding factors such as family history, occupation, comorbidities (e.g., diabetes mellitus, history of gastritis), social history (alcohol drinking, smoking etc), dietary history, body mass index (BMI), status of H. pylori infection and physical activity were unable to include in this analysis.

The epidemiology of GC in different geographical locations can be sought out in future. The trend and the changes in the incidence of GC in previous low-incidence areas such as Kelantan should also be studied along with the dietary and lifestyle changes. The prevalence of H. pylori infections and the incidence of GC in different geographic locations could be studied for Malaysia as well as for Asia and globally.

CONCLUSION

In this retrospective study, we studied the clinicopathological data of GC, although the data we reported represented only one hospital. The incidence of GC cases in Malay population was observed to be increased. Late-onset GC cases were found to be more common than early-onset cases, while all reported cases were adenocarcinoma types. Globally, it was estimated that there could be 1.8 million new cases and 1.3 million deaths related to GC by 2040.[16] And a higher incidence will be found in medium and low HDI (Human Development Index) countries compared to high HDI countries, hence, the SEA countries should be observant on the burden of GC.[16] Although GC showed a downward trend in Malaysia, it could again lead to an increasing trend of GC. Because of the nature of high aggressiveness, late diagnosis, association with lifestyle and non-communicable diseases such as diabetes mellitus, the prevalence of *H. pylori* infection, variation in responsiveness and awareness of the eradication regimens, GC could still constitute a local and global health issue. Consideration of lifestyle changes, health education, detection and eradication of *H. pylori* infection and early diagnosis of GC by health check-ups should be encouraged by the authorities. Hence, the authorities should consider adapting the *H. pylori* eradication regimen as a part of the insurance scheme; detection of *H. pylori* as a part of routine health check-ups; early referral and an exploration of upper GI endoscopy of middle-aged people who are above 50 with dyspeptic symptoms should be considered. Since certain countries and regions are estimated to have more burden of GC, health authorities should plan cancer control initiatives without delay.

DISCLOSURE

The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilised in the production of this manuscript.

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Parental affordability and willingness to pay for universal masking amongst government school students in Kuching, Sarawak

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ABSTRACT

Introduction: Financial affordability to purchase commodities for disease prevention is an important public health issue. The objective of this paper is to report the financial affordability and willingness to pay amongst the parents of government students for their children's non-medical mask use, using a newly created Household Face Mask Affordability Questionnaire (MAQ).

Materials and Methods: This was a cross-sectional study involving the parents or guardians of 50.6% (44/87) government schools in the whole of Kuching Division of Sarawak. The sampling method was multistage cluster sampling, whereby stage one involved random sampling of 49.2% (30/61) primary schools and 53.8% (14/46) secondary schools in the Kuching Division, followed by stage two cluster sampling of one class per non-examination standard in each randomly sampled school. All students in the sampled classes were asked to bring a face-validated questionnaire (MAQ) back home to be answered by one of their parents or a guardian. A total of 2559 out of 3661 distributed questionnaires were collected, with a response rate of 70%. The data collection period was between April and June of 2022 so as the recall bias of the information collected, especially on the actual spending on the face masks for the school going students, was minimised. The relevant summary statistics for self-perceived face masks characteristics, face mask expenses, affordability and willingness to pay were calculated. We regress separately the monthly affordability and willingness to pay amount against age, occupation, marital status, total number of children, monthly income and monthly saving to build predictive models for affordability and willingness to pay amount per child per month.

Results: The average Scale-level Face Validity Indexes for all aspects of validity (clarity, comprehension, relevancy, representativeness) are high (0.91 to 1.00) for MAQ. Most of the respondents were mothers, married, working as private employees with a mean age of 41 and belonged to the B40 and M40 group. The average monthly saving per family was RM540, which was about 15% of the total income. The average actual monthly spending to purchase face masks for one child is RM24. On average, a family can afford to pay RM23.80 for one child per month to purchase face masks. The willingness to pay for the same was RM25.27. The median affordability, willingness to pay and actual spending for face masks per child was RM16.67 per month. Taking 75th percentile as the reasonable maximum expenses per child for face masks per month, the affordable amount by most parents is RM30, with the willingness to pay at 10% higher. Affordability to purchase a face mask is influenced by the marital status, occupation, income, saving and the number of dependent of the breadwinner of a household. The most important face mask characteristics expected by the parents are better filtration efficiency and easier breathability.

Conclusion: The affordability and willingness to pay the amount to purchase face masks amongst parents of government students in Sarawak were RM30 and RM33 per child per month, respectively.

KEYWORDS:
Affordability, willingness to pay, face mask, universal masking, COVID-19

INTRODUCTION

The COVID-19 pandemic forces the world population to adopt new norms in life, namely social distancing, wearing face masks and frequent sanitising.[1] These new norms are essential and were made compulsory in Malaysia since 1st August 2020 to the general population in an effort to prevent COVID-19 transmission in the country.[2] Amongst these new norms, the requirement to wear face mask imposes financial burden on the population, especially amongst the family with schooling children, because of the shortage in supply and single-use feature of most non-medical masks in the market.[3,4]

The World Health Organization has recommended universal masking, meaning that everyone should wear a mask for COVID-19 source control, rather than protection.[5] Source control means that if everyone is wearing a mask, then the chances of virus transmission from an unknown infected person will be reduced significantly. Hence, Malaysia government has implemented universal masking policy, either disposable or reusable, from 1st August 2020 for 2 years, to control the COVID-19 cases in the country.

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In view of the potential financial burden to the population on the use of single-use disposable mask in compliance with the universal masking policy, the authors have embarked on a study to determine the financial affordability for universal masking amongst the parents of the government school-going students in Kuching, Sarawak, as well as to develop a washable reusable fabric face mask within the determined affordability range for the use of school going students in Sarawak. Although the indoor universal masking policy has been scrapped since 7th September 2022,[6] the finding of this study is still important to serve as the basis for setting price ceiling for face masks and production of affordable reusable face masks in the future.

The objective of this paper is to report results on the affordability and willingness to pay for their children's non-medical mask use amongst the parents of government students in Kuching division of Sarawak, using a newly created Household Face Mask Affordability Questionnaire (MAQ), as there is no similar readily available questionnaire in the market.

MATERIALS AND METHODS

This was a cross-sectional study involving the parents or guardians of 50.6% (44/87) of government schools in the whole of Kuching Division of Sarawak. The sampling method was multistage cluster sampling, whereby stage one involved random sampling of 49.2% (30/61) primary schools and 53.8% (14/46) secondary schools in the Kuching Division, followed by stage two cluster sampling of one class per non-examination standard (namely, Standard 1 to 5, Form 1, 2, 3 and Lower 6) in each randomly sampled school. Following the sampling procedure, 54.5% (24/44) of schools were classified as urban schools and the rest were classified as rural schools. All students in the sampled classes were asked to bring a questionnaire back home to be answered by one of their parents or a guardian. A total of 2559 out of 3661 distributed questionnaires were collected, with a response rate of 70%. The data collection period was between April and June of 2022 so as the recall bias of the information collected, especially on the actual spending on the face masks for the school-going students, was minimised.

The questionnaire on universal masking affordability and willingness to pay, called Household Face Mask Affordability Questionnaire (MAQ), was created by the authors for this study. The MAQ is a brief simple-to-use self-administered questionnaire consisting of two parts: Part 1: Demographic Information and Part 2: Affordability and Willingness to Pay. Part 1 of the questionnaire asks about the respondent's age, occupation, marital status, relationship with the student, total number of children and total number of school-going children. Part 2 of the questionnaire asks about total monthly household income and saving, affordability and willingness to spend for face masks for all children, self-perceived important characteristics of face masks, and the actual monthly spent for face masks during the COVID-19 universal masking period where schools were reopened.

The questionnaire was designed by a Public Health Physician and a parent with school-going children originally in English and underwent forward and backward translation into each Malay and Chinese language. As the MAQ is not a psychological construct questionnaire, we performed face validation on the questionnaire on the following aspects: clarity, comprehension, relevancy and representativeness, for questions in the Part 2 of the questionnaire. The scale of the responses ranges from 1 being 'very vague', 'tough to understand', 'very irrelevant' and 'totally not representing', to 5 being 'very clear', 'very easy to understand', 'very relevant' and 'accurately representing', to the respective question. The face validation test was carried out on 18 conveniently selected parents of variable socio-demographic backgrounds in Kuching before the commencement of the actual affordability study. The Raters in Agreement frequency, Universal Agreement (UA), Item-level Face Validity Index (I-FVI), Scale-level Face Validity Index (S-FVI), average of S-FVI and S-FVI/UA were calculated to determine the face validity of the questionnaire.

The data were entered into Microsoft Excel and analysed using RStudio 2023.03.0+386 "Cherry Blossom" Release for Windows. All continuous data was examined for its distribution, with necessary transformation, if any, and its relationship with categorical variables. The relevant summary statistics for self-perceived face mask characteristics, face mask expenses, affordability and willingness to pay were calculated. We regress separately the monthly affordability and willingness to pay amount against monthly age, occupation, marital status, total number of children, monthly income and monthly saving to build predictive models for affordability and willingness to pay amount per child per month.

The study obtained ethical approval from the Universiti Malaysia Sarawak Medical Ethics Committee (Ethics Reference: FME/21/93) and study approval from the Malaysia Ministry of Education (Approval Reference: KPM.600-3/2/3-eras (11777)). All participating schools were briefed, and written consents were taken from all respondents before the data collection.

RESULTS

Validity of the Household Face Mask Affordability Questionnaire

Table I shows the validity index of the MAQ. The original questionnaire is attached in the Appendix of this paper. The I-FVI for all questions are high, ranging from 0.83 to 1.00 for all aspects of face validity (clarity, comprehension, relevancy and representativeness). Although S-FVI/UA are low for relevancy and representativeness, as some respondents claimed that questions on total income and saving are not crucial, the index is high for clarity and comprehension for all questions. The average S-FVIs for all aspects of validity are high (0.91 to 1.00) for MAQ in general, indicating the face validity of this questionnaire is good.

Socio-demographic Characteristics of the Respondents

Table II reports the socio-demographic characteristics of all respondents. The statistics are calculated based on the valid responses for each variable. Most of the respondents come from families that send their children to urban schools. Most

Table I: The validity indexes of Household Face Mask Affordability Questionnaire

Item	Clarity			Comprehension			Relevancy			Representativeness		
	Na	I-FVI	UA	Na	I-FVI	UA	Na	I-FVI	UA	Na	I-FVI	UA
Q7	18	1.00	1.00	18	1.00	1.00	15	0.83	0.00	17	0.94	0.00
Q8	18	1.00	1.00	18	1.00	1.00	16	0.89	0.00	15	0.83	0.00
Q9	18	1.00	1.00	18	1.00	1.00	18	1.00	1.00	18	1.00	1.00
Q10	16	0.89	0.00	18	1.00	1.00	16	0.89	0.00	17	0.94	0.00
Q11	18	1.00	1.00	18	1.00	1.00	16	0.89	0.00	16	0.89	0.00
Q12	18	1.00	1.00	18	1.00	1.00	17	0.94	0.00	18	1.00	1.00
S-FVI/Ave		0.98			1.00			0.91			0.94	
S-FVI/UA			0.83			1.00			0.17			0.33

Note:
1. Na represents the number of Raters in Agreement, denotes the number of rater scored "1", represents "Yes", corresponding to the scale of 3 to 5 for each aspect of validity (clarity, comprehension, relevancy, representativeness), on a particular question, and "0", represents "No", corresponding to the scale of 1 to 2 for each aspect.
2. I-FVI = Item-level Face Validity Index, is the Raters in Agreement divided by the number of raters.
3. UA = Universal Agreement, indicated by score '1' assigned to the question that achieved 100% raters in agreement in respective to each aspect of validity.
4. S-FVI/Ave = Average Scale-level Face Validity Index, is the sum of I-FVI divided by the total number of questions.

Table II: Socio-demographic characteristics of respondents

Respondent's characteristics	n	%	Mean	SD	p50	p25	p75	Min	Max
Age (years)*									
Respondent	2461	96.17	41.34	7.36	41	36	46	16	79
Spouse	2231	87.18	41.81	7.17	41	37	46	21	76
Relationship to the student (total)	2433	100.00							
Mother	1367	56.19							
Father	963	39.58							
Guardian/relative	103	4.23							
Marital status (total)	2476	100.00							
Married	2235	90.27							
Single parent	223	9.01							
Unmarried	18	0.73							
Occupation (total)	2483	100.00							
Private employee	950	38.26							
Government servant	616	24.81							
Housewife	527	21.22							
Own business	263	10.59							
Others	127	5.11							
No of children*									
Schooling	2469	96.48	3.03	1.36	3	3	2	1	10
Total	2442	95.43	2.38	1.06	2	2	2	1	7
School type (total)	2559	100.00							
Urban	2262	88.39							
Rural	297	11.61							

Note: n = frequency denotes number of respondents contributing to the statistics, with its respective valid percentage against the total of 2559 respondents.

of the respondents were mothers, married and working as private employees, with a mean age of 41. On average, each family had three school-going children to support.

Affordability and Willingness to Pay for Children's Universal Masking

The financial profile of the respondents reflects that most of the families of government students belong to the B40 and M40 income group. The average monthly saving per family was RM540, which was about 15% of the total income. The average actual monthly spending to purchase face masks for one child is RM24. On average, a family can afford to pay RM23.80 for one child per month to purchase face masks. The willingness to pay for the same was RM25.27.

It is undoubtedly that the data in Table III are skewed to the right, which is logical, reflecting the economic status of the respondents. Hence, if we consider the median as the measure of central tendency, the affordability, willingness to pay and actual spending for face masks per child was RM16.67 per month. Logically, if we consider 75th percentile as the reasonable maximum expenses per child for face masks per month, the acceptable amount by most parents is RM30.

Characteristics of Face Mask that Affects Purchasing Decision

The parents' decision to purchase the type of face mask was affected by a face mask's characteristics as shown in Figure 1. The most important face mask's characteristics are 'ability to block the particles' and 'easier to breath'. The median ranking for both 'ability to block particles' and 'easier to breath' is 5 (maximum rank is 5 = 'Extremely important characteristics'), followed by 'cheaper price' and 'comfortable

Table III: Financial profile, affordability and willingness to pay for children's universal masking during COVID-19 pandemic

Variables (RM)	n	%	Mean	SD	p50	p25	p75	Min	Max
Monthly income (I)	2310	90.27	3693.33	2930.78	2542.50	1400	5000	80	12430
Monthly saving (S)	1790	69.95	540.36	566.30	300.00	100	1000	0	2300
I - S1729	67.57	3241.67	2607.59	2400.00	1240	4800	0	12130	
Monthly face mask expenses (E)*	2363	92.34	60.40	45.23	50.00	30	100	0	200
E per child	2290	89.49	24.23	22.09	16.67	10	30	0	200
Total monthly affordability (A)	2439	95.31	58.11	45.70	50.00	24	100	0	210
Total monthly willingness to pay (W)	2439	95.31	58.11	45.70	50.00	30	100	0	210
A per child	2365	92.42	23.80	23.13	16.67	10	30	0	200
W per child	2350	91.83	25.27	24.33	16.67	10	33	0	200

Note: *This is the actual spending for face masks reported by the parents after schools reopened during COVID-19 pandemic where universal masking is still required.

Table IV.:Predictive factors for monthly (a) affordability (b) willingness to pay amount to purchase face masks for one child

Predictors	Coefficient (B)	95% CI for B		p-value
		Lower limit	Upper limit	
(a) Monthly affordability amount				
Intercept	36.8993	32.907	40.8916	<0.001
Occupation				
Others (housewife, others)	1			
Government servant	–3.1937	–6.1279	–0.2594	0.0359
Own business	2.5848	–0.7602	5.9298	0.1298
Private sector employee	–1.0984	–3.4995	1.3026	0.3697
Marital status				
Single parent/guardian	1			
Married	–5.335	–8.4874	–2.1825	0.0009
Monthly income	0.0019	0.0015	0.0024	<0.0001
Monthly saving	0.0064	0.0044	0.0084	<0.0001
Total children	–6.2717	–6.9922	–5.5512	<0.0001
(b) Monthly willingness to pay amount				
Intercept	42.0269	38.3693	45.6846	<0.0001
Marital status				
Single parent/guardian	1			
Married	–5.335	1		
Monthly income	0.0019	–7.7034	–10.9924	–4.4144
Monthly saving	0.0064	0.0012	0.0013	0.0021
Total children	–6.2717	0.0067	0.0047	0.0088

to skin' ranking at 4, and finally 'stylish/good looking' ranking at 2.

Predictive Factors for Affordability and Willingness to Pay

The final predictors retained following multiple linear regression for monthly affordability and willingness to pay amount against monthly age, occupation, marital status, total number of children, monthly income and monthly saving is shown in Table IV. We used backward stepwise analysis for both outcomes and the adjusted R-squared values for affordability and willingness to pay models are 0.2727 and 0.2712, respectively. Diagnostic plots for both models showed the models are adequate, where the residuals versus fitted plot revealed no relationship and all data points in the residuals versus leverage plot are within Cook's distance.

Hence, the final model for monthly affordability amount to pay for the face mask for one child is:

$A = 36.9 – 3.2G – 5.3M + 0.0019I + 0.0064S – 6.3C$

where:

A = Monthly affordability amount to pay for the face mask per child in RM

G = Status as a government servant valued as "1" if yes

M = Marital status valued as "1" if married

I = Total monthly income in RM

S = Total monthly saving in RM

C = Total number of children in round number

The final model for monthly willingness to pay amount for the face mask for one child is:

$W = 42.0 – 5.3M + 0.0019I + 0.0064S – 6.3C$

where:

W = Monthly willingness to pay for the face mask per child in RM

M = Marital status valued as "1" if married

I = Total monthly income in RM

S = Total monthly saving in RM

C = Total number of children in round number

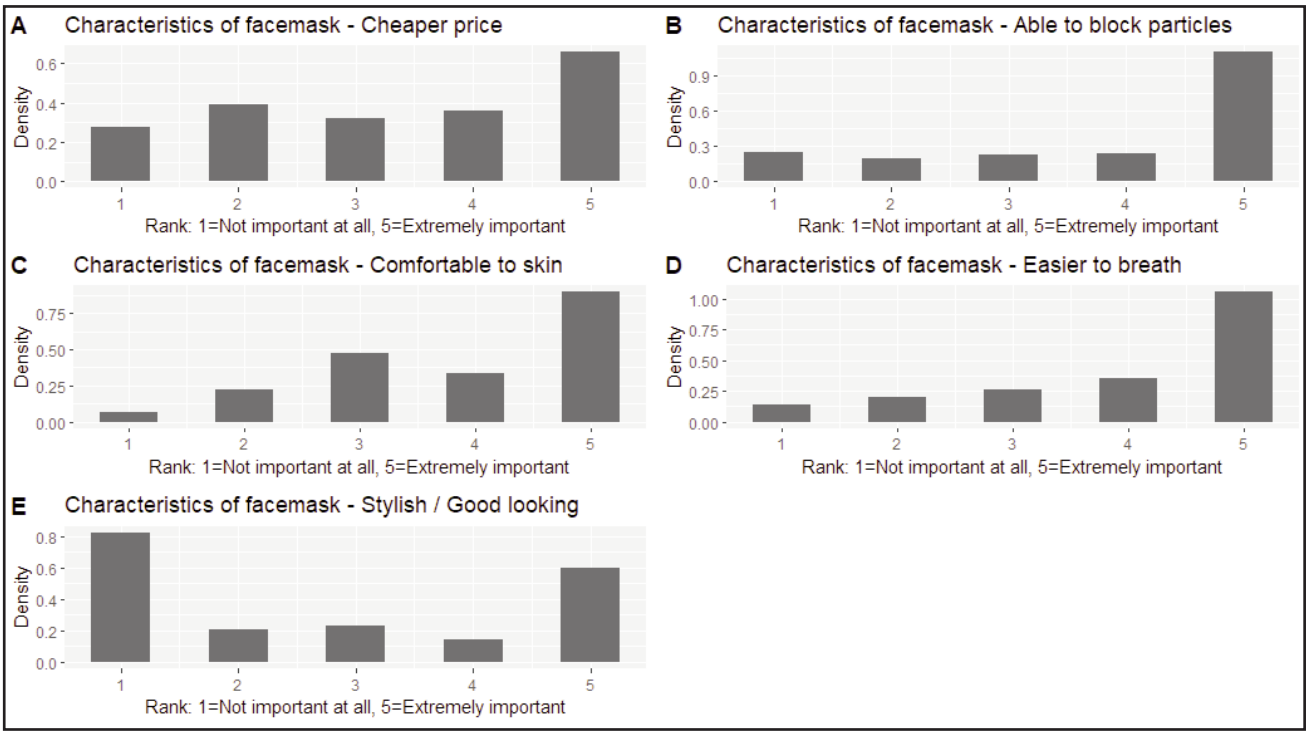

Fig. 1: Characteristics of face mask that affect purchasing decision by the parents.

DISCUSSION

Previous studies on non-medical masks use by the population focussed mainly on determinants of willingness to pay or willingness to wear face masks.[7-9] No study has been focussing on the affordability to purchase non-medical masks amongst the population when universal masking is required. Financial affordability to purchase commodities for disease prevention is an important public health issue. The current study reflects the financial affordability of the parents of government students in Kuching population to purchase face masks under universal masking policy accurately because of the large sample size and random sampling strategy. The findings of this study could be extrapolated to other states with almost similar monthly household incomes, such as Sabah, Pahang, Perak, Kedah and Perlis, where these are the states within RM500 difference of monthly household income of Sarawak (mean = RM5087 in year 2020).[10]

Currently, the retail ceiling price for face mask in Malaysia is RM0.70. It was reduced from the ceiling of RM1.50 before 1st Mac 2020, further down to RM0.70 on 1 November 2020.[11-13] The reduction was likely intuitive based on strong demand from the population. The affordability amount of RM30 per child per month found in this study is equivalent to the expenditure of RM1 per piece of disposable face mask per child per day. The finding shows that the current retail ceiling price set by the government for face masks is reasonable considering the variation in different socio-economic levels of population across the country.

The affordability and willingness to pay models derived in this study can be used to determine the ceiling price of face masks by the government in the future should the universal masking policy is required. Although the models may not be comprehensive as independent variables are limited to those taken, they can readily be used for quick estimation. The affordability model itself indicates that when policymakers want to set the ceiling price for face masks, they must take into account at least the occupation, income, saving, marital status and number of dependents of the breadwinner within a household in the targeted population.

Most studies focused on the health-related factors such as the perceived severity of disease and benefit of masking when it comes to willingness to pay for and wear face mask.[14,15] It is also important to understand the perceived expected characteristics of face mask that would affect the consumer to purchase and use the mask. Our study found that the most important characteristics of the face mask that influence the choice of the parents are filtration efficiency and breathability. This information is important in two aspects, first to the government and the supplier, to ensure that the face masks that are sold legally in the market are of certain acceptable standards of filtration efficiency and breathability. Second, the information reflects the knowledge level of the target population that serves as a benchmark for appropriate health education by public health professionals.

This study also produced the face-validated MAQ, which can be used as a simple and quick questionnaire to determine the affordability level of the target population in this country. The questionnaire was purposely made short and simple to improve the accuracy of reporting. Hence, MAQ can be used by policymakers or market survey professionals for the purpose of policymaking and setting an affordable retail price for face masks.

The findings of this study are useful to various public health stakeholders for comprehensive and timeliness public health response during pandemic. The Ministry of Health should ensure the quality of non-medical masks supplied in the country meeting the population's demand, namely filtration efficiency and breathability. The Ministry of Domestic Trade and Consumer Affairs should ensure the market price of non-medical masks within the affordable level of the population, by continuous close monitoring of its supply and demand and being sensitive to future similar pandemic given the lesson learnt from the COVID-19 pandemic. Non-medical mask manufacturers should focus on the production of efficient and cost-effective masks to meet the population's demand.

A major limitation of this study would be the restriction of study population to Kuching area due to logistic issues. Nevertheless, since there has been no similar study done before, the current findings serve as a baseline for future extrapolation to other states of Malaysia. Another strength of this research is the creation of validated MAQ, which can be used by all researchers in Malaysia for future studies.

CONCLUSION

The affordability level to purchase face masks amongst the parents of government students in Sarawak was RM30 per child per month. The willingness to pay for the same can be expected to increase by 10%. The most important face mask characteristics expected by the parents are better filtration efficiency and easier breathability. Affordability to purchase a face mask is influenced by the marital status, occupation, income, saving, and number of dependents of the breadwinner of a household.

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DISCLOSURE

The Sarawak Research Development Council was not involved in the planning, conduct and analysis of the study. The authors declare no conflict of interest with the grant sponsor in completing this study.

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A cross-sectional study on the sleep quality among type 2 diabetes mellitus patients and its associated factors

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ABSTRACT

Introduction: Poor sleep quality is common among patients with type 2 diabetes mellitus (T2DM). It has detrimental effects on physical and psychological health, as well as on quality of life. This study aimed to determine the prevalence of poor sleep quality among T2DM patients and to investigate the factors associated with this disorder.

Materials and Methods: A cross-sectional study was conducted at Klinik Kesihatan Seremban in Seremban district, Negeri Sembilan. Data were collected using the Malay version of the Pittsburgh Sleep Quality Index (PSQI-M) with a cut-off point of >5 as poor sleep quality. The Depression Anxiety Stress Scale-21 (DASS-21) was used to measure level of psychological distress. Data were collected between July 2022 until January 2023.

Results: A total of 319 patients with T2DM participated. Their mean age was 63 (11) years, 58% were women and 42.9% were of Indian ethnicity. The mean total score of PSQI was 4.04 (2.21) and 23% of the participants had poor sleep quality. Multivariate logistic regression analysis revealed that poor sleep quality was significantly associated with Indian ethnicity (Adj. OR = 2.25; 95%CI: 1.05, 4.82; *p* = 0.037), separated or widowed (Adj. OR = 2.16; 95%CI = 1.15, 4.05; *p* = 0.016), having nocturia (Adj. OR = 2.13; 95%CI = 1.18, 3.84; *p* = 0.012) and depressive symptoms (Adj. OR = 3.41; 95%CI: 1.01, 11.48; *p* = 0.048).

Conclusion: Poor sleep quality was prevalent in almost a quarter of T2DM patients studied. Indian ethnicity, separated or widowed, having nocturia, and depressive symptoms were independently associated with poor sleep quality. Despite lower prevalence of poor sleep quality compared to other studies, identification of those at higher risk warrants further exploration in lifestyle management of patients with T2DM.

KEYWORDS:
type 2 diabetes mellitus, sleep quality, psychological distress

INTRODUCTION

Sleep is a physiological need for all human beings as it is important for both physical and psychological health. Its benefits for vital functions at cellular, metabolic, neurological, cardiovascular, cognitive and emotional level are extensively studied.[1] Despite individual variability with age across lifespan, recommended optimal healthy sleep duration for adults is 7 to 9 hours a day.[1] Some indicators for good sleep quality are shorter sleep latency, fewer awakenings, less time needed to wake after sleep onset, and higher sleep efficiency.[2] Short sleep duration (< 6 hours per 24-hour) and long sleep duration (> 9 hours per 24-hour) are associated with multiple morbidities.[1,3] Poor sleep quantity and quality are implicated for the development and control of type 2 diabetes mellitus (T2DM) and obesity.[3-5] Inadequate sleep causes hormonal imbalance in the body, which induces increases in appetite, blood sugar and insulin resistance resulting in obesity and poor glycaemic control.[3] Hence, higher prevalence of sleep problem is expected among T2DM patients with obesity and poor glycaemic control.

Prevalence of sleep problems among the general adult population in Asia Pacific region ranged from 15 to 45%.[6-9] Meanwhile, approximately 33 to 81% of T2DM patients reported sleep problems[5,8,10,11] and the proportion was comparatively higher than the general population.[8] Diabetes mellitus (DM) is a growing public health concern worldwide. Globally in 2021, International Diabetes Federation reported around 537 million people live with diabetes[12], while in Malaysia it was estimated that 3.9 million (18.3%) of the adult population had deranged glycaemic index in 2019; compared to only 13.4% in 2015.[13] These numbers are forecasted to expand further in the future. Studies showed that higher age, female gender, high BMI, poor glycaemic control, longer duration of diabetes, diabetic complications and psychological factors increased the risk for poor sleep quality among T2DM patients.[5,8,10,11,14] Some of the factors are modifiable with multiple benefits such as weight management, glycaemic control and better mental health. In Malaysia, there is a dearth of information reported on sleep quality and its associated factors among T2DM patients. This study aimed to identify the prevalence of poor sleep quality and determine its associated factors among patients with T2DM.

MATERIALS AND METHODS

Study design, location, and population

This is a cross-sectional study conducted from July 2022 until January 2023 at a non-communicable diseases (NCD) clinic, Klinik Kesihatan Seremban in the Seremban district of Negeri Sembilan. Participants of this study were National Diabetes Registry (NDR) patients from the clinic. Until June 2021, this clinic had a total of 5445 registered diabetic patients

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consisting of 38.7% Indians, 38.5% Chinese, 22.1% Malay and 0.7% other ethnics (unpublished data).

Sample Size

Sample size was calculated using the population proportion formula with a population size of 5445 registered T2DM patients in the clinic, 95% confidence interval, 5% margin of error and 32% population proportion from a local sleep quality study among T2DM patients.[15] Sample size needed was 316. Considering 10% non-response rate, 347 participants should be recruited. Each answered questionnaire was immediately checked for completion to reduce non-responder.

Data Collection and Sampling Method

Systematic random sampling was carried out with a sampling interval of two, based on the T2DM patient appointment list extracted from the tele-primary care (TPC) system with up to 90 patients listed per day. Each patient is numbered, and a computer-generated random number was used to select the first patient followed by every other patient in the list to intensify recruitment.

Data collection was only done for a fixed day in a week for 24 weeks as the main researcher (NS) had clinical duties in the clinic. Recruitments were challenging as some listed patients were affected by Covid19 infection or close contact or there were other reasons hindering clinic visit.

Malaysian citizens aged 18 years and above, diagnosed with T2DM of at least six months duration, having attended diabetic follow-up at Klinik Kesihatan Seremban, having latest HbA1c result within one year and literate in Malay or English were invited to participate. Those having conditions or illness that do not permit completion of the self-administered questionnaire, working in night shifts or travelling across time zones within one month, pregnant women, breastfeeding mothers, those with type 1 diabetes mellitus (T1DM), having mental illness or use of any kind of psychotropic medication, having sleep disorder diagnosed prior to diabetes, having endocrine disorders (for example thyroid disease), chronic use of glucocorticoid and having heart failure were excluded from selection. A brief introduction about the study was given to those recruited, and written informed consent was obtained. A self-administered questionnaire was given to the participants which took about 15 minutes to be completed. A researcher was available on-site for further assistance if necessary.

Study Instruments

Data was collected using a structured questionnaire consisting of four parts: sociodemographic data, clinical profile, sleep quality questionnaire and Depression, Anxiety and Stress Scale 21-Item questionnaire (DASS-21). It was available in dual language, in Malay and English.

Part I comprised of personal data of participant such as age, gender, ethnicity, marital status, educational level, employment status, and estimated household income.

Part II documented their clinical profiles such as duration of T2DM, body mass index (BMI), HbA1c level, nocturia, comorbidities and diabetic complications. Body mass index was calculated using the weight and height measured by the standardized stadiometer with a weighing scale during the day of follow-up. The most recent HbA1c levels within the past one year were documented from the electronic medical record system. Other clinical information was collected from participants' home-based follow-up cards and confirmed with the electronic medical record system.

Part III was the Pittsburgh Sleep Quality Index (PSQI). This self-administered questionnaire developed in 1989 with the main goal of differentiating between people who slept well and poorly over the past one month.[16] It was locally translated to Malay (PSQI-M) and validated with Cronbach alpha of 0.74 for internal consistency and test-retest reliability of 0.58.[17] The PSQI is a self-reported questionnaire with 19 items from seven components that assesses subjective sleep quality. The seven components are (1) sleep quality (1 item), (2) sleep latency (2 items), (3) sleep duration (1 item), (4) sleep efficiency (3 items), (5) sleep disturbance (9 items), (6) sleep medication (1 item) and (7) daily dysfunction (2 items). Each component is given a value between 0 and 3, and the aggregate of the individual components results in a PSQI global score between 0 and 21. A score of 5 or less indicates "good sleepers," whereas a score of greater than 5 indicates "poor sleepers".[16]

For Part IV, depression, anxiety, and stress were measured using the Depression, Anxiety and Stress Scale (DASS 21).[18] Part IV contains 21 items divided into three subscales of depression, anxiety, and stress, with seven items allocated for each subscale. It inquired about recent experiences in the past week and the items were scored on a 4-point scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much, or most of the time). The range of score a participant could get for each subscale varied from 0 to 21. The total scores were summed up and multiplied by 2.[18] The recommended cut-off points were used to classify participants into normal, mild, moderate, severe, and extremely severe in terms of depression, anxiety, and stress as in Table I. Participants were classified as having depressive or anxiety or stress symptoms if they scored above the cutoff point for normal in the respective subscale. The validated Malay version of DASS21 used in this study reported Cronbach's alpha of 0.84, 0.74 and 0.79 for depression, anxiety, and stress, respectively.[19]

Data Analysis

Data were analysed using the SPSS software version 27. Descriptive analysis was performed using frequencies and percentages for categorical variables and mean ± standard deviation (SD) for continuous variables. Simple and multiple logistic regression analyses were used to determine factors independently associated with sleep quality. Variables with $p < 0.25$ in the simple logistic regression and important variables from literature were further assessed in multiple logistic regression. p-value of < 0.05 was set as level of significant.

Table I: Cutoff points for DASS-21 scale [18]

Severity	Depression	Anxiety	Stress
Normal	0-9	0-7	0-14
Mild	10-13	8-9	15-18
Moderate	14-20	10-14	19-25
Severe	21-27	15-19	26-33
Extremely severe	28+	20+	34+

Table II: Socio-demographic characteristics of all participants

Factors		Sleep quality, n (%)		n (%)
		Poor sleep (n = 74)	Good sleep (n = 245)	
Age (years)*		63 (12)	62 (10)	63 (11)
Gender	Female	50 (27.0)	135 (73.0)	185 (58.0)
	Male	24 (17.9)	110 (82.1)	134 (42.0)
Ethnicity	Malay	14 (18.9)	60 (81.1)	74 (23.2)
	Indian	41 (29.9)	96 (70.1)	137 (42.9)
	Chinese	19 (17.6)	89 (82.4)	108 (33.9)
Marital Status	Single	4 (16.0)	21 (84.0)	25 (7.8)
	Married	43 (19.4)	179 (80.6)	222 (69.6)
	Separated	5 (45.5)	6 (54.5)	11 (3.4)
	Widowed	22 (36.1)	39 (63.9)	61 (19.1)
Education level	No formal education	7 (43.8)	9 (56.3)	16 (5.0)
	Primary education	17 (19.8)	69 (80.2)	86 (27.0)
	Secondary education	44 (24.4)	136 (75.6)	180 (56.4)
	Tertiary education	6 (16.2)	31 (83.8)	37 (11.6)
Employment status	Employed	16 (18.4)	71 (81.6)	87 (27.3)
	Unemployed	42 (25.3)	124 (74.7)	166 (52.0)
	Pensioner	16 (24.2)	50 (75.8)	66 (20.7)
Household income (RM) *		2122 (3008)	1778 (2300)	1858 (2481)

*Mean (SD)

Table III: Clinical characteristics of all participants

Factors		Sleep quality, n (%)		n (%)
		Poor sleep (n = 74)	Good sleep (n = 245)	
Duration of T2DM(years)*		6.8 (6.7)	7.1 (6.2)	7 (6.0)
BMI (kg/m2)*		27.4 (5.7)	27 (4.5)	27.1 (4.8)
BMI categories	Underweight/normal (BMI ≤ 22.9)	16 (26.7)	44 (73.3)	60 (18.8)
	Overweight (BMI 23-27.4)	27 (22.5)	93 (77.5)	120 (37.6)
	Obese (BMI ≥ 27.5)	31 (22.3)	108 (77.7)	139 (43.6)
HbA1c grouping	Uncontrolled (≥7 %)	42 (23.9)	134 (76.1)	176 (55.2)
	Controlled (< 7%)	32 (22.4)	111 (77.6)	143 (44.8)
Nocturia	Yes	50 (30.1)	116 (69.9)	166 (52.0)
	No	24 (15.7)	129 (84.3)	153 (48.0)
Comorbidities	No comorbidities	3 (13.0)	20 (87.0)	23 (7.2)
	Hypertension	17 (23.3)	56 (76.7)	73 (22.9)
	Dyslipidemia	13 (28.9)	32 (71.1)	45 (14.1)
	Both	42 (21.6)	152 (78.4)	194 (60.8)
Diabetic complications	No complication	58 (22.1)	205 (77.9)	263 (82.4)
	Retinopathy	0 (0.0)	4 (100.0)	4 (1.3)
	Nephropathy	9 (33.3)	18 (66.7)	27 (8.5)
	Ischemic heart disease	5 (27.8)	13 (72.2)	18 (5.6)
	Cerebrovascular accident	2 (22.2)	7 (77.8)	9 (2.8)
Depression	Normal	63 (21.0)	237 (79.0)	300 (94.0)
	Mild	5 (50.0)	5 (50.0)	10 (3.1)
	Moderate	2 (40.0)	3 (60.0)	5 (1.6)
	Severe to extremely severe	4 (100.0)	0 (0.0)	4 (1.3)
Anxiety	Normal	64 (21.2)	238 (78.8)	302 (94.7)
	Mild	4 (44.4)	5 (55.6)	9 (2.8)
	Moderate	4 (80.0)	1 (20.0)	5 (1.6)
	Severe to extremely severe	2 (66.7)	1 (33.3)	3 (0.9)
Stress	Normal	63 (20.8)	240 (79.2)	303 (95.0)
	Mild	4 (50.0)	4 (50.0)	8 (2.5)
	Moderate	5 (100.0)	0 (0.0)	5 (1.6)
	Severe to extremely severe	2 (66.7)	1 (33.3)	3 (0.9)

*Mean (SD)

Table IV: Factors associated with sleep quality among participants using simple logistic regression

Factors		ß	Crude OR (95% CI)	Wald test	*p* value
Age (years)*		0.01	1.00 (0.98, 1.03)	0.51	0.474
Gender	Female	0.52	1.69 (0.98, 2.93)	3.58	0.058
	Male		ref		
Ethnicity	Malay		ref		
	Indian	0.60	1.83 (0.92, 3.63)	2.97	0.085
	Chinese	-0.89	0.91 (0.42, 1.96)	0.05	0.820
Marital status	Married		ref		
	Single	-0.28	0.75 (0.24, 2.29)	0.24	0.618
	Separated/widow	0.91	2.48 (1.38, 4.44)	9.39	0.002
Education level	No formal/primary education	0.46	1.59(0.59, 4.26)	0.84	0.357
	Secondary education	0.51	1.67 (0.65, 4.27)	1.15	0.283
	Tertiary education		ref		
Employment status	Employed		ref		
	Unemployed/pensioner	0.39	1.47 (0.79, 2.74)	1.53	0.215
Duration of T2DM (years)*		-0.009	0.99 (0.95, 1.03)	0.16	0.687
BMI categories	Underweight/normal (BMI ≤ 22.9)		ref		
	Overweight (BMI 23-27.4)	-0.22	0.79 (0.39, 1.63)	0.38	0.537
	Obese (BMI ≥ 27.5)	-0.23	0.78 (0.39, 1.58)	0.44	0.506
HbA1c grouping	Uncontrolled (≥7 %)	0.08	1.08 (0.64, 1.83)	0.09	0.755
	Controlled (< 7%)		ref		
Nocturia	Yes	0.84	2.31 (1.34, 4.00)	9.04	0.003
	No		ref		
Comorbidities	No comorbidities		ref		
	Hypertension	-0.01	0.99 (0.53, 1.84)	<0.001	0.983
	Dyslipidemia	0.35	1.41 (0.70, 2.87)	0.94	0.331
	Both	-0.21	0.80 (0.47, 1.36)	0.66	0.415
Diabetic complications	No complication	0.34	1.41 (0.73, 2.70)	1.09	0.296
Depression	Yes	1.64	5.17 (1.99, 13.40)	11.44	0.001
	No		ref		
Anxiety	Yes	1.67	5.31 (1.94, 14.50)	10.61	0.001
	No		ref		
Stress	Yes	2.12	8.38 (2.81, 25.00)	14.53	<0.001
	No		ref		

* Mean (SD)

Ethical Approval

This study was approved by Universiti Kebangsaan Malaysia Research Ethics Committee (JEP-2021-800) and Institute of Medical Research Ethics Committee. This project was registered with the National Medical Research Registration (NMRR ID-21-01986-E44). Permission to conduct the research was also obtained from the Negeri Sembilan State of Health Department, Seremban District Health Office, and the Family Medicine Specialist in Klinik Kesihatan Seremban.

RESULTS

Response Rate

A total of 346 T2DM patients were approached, however 15 patients refused, and 12 were excluded due to T1DM (one participant), three had underlying mental problems, four had been working night shift for the past one month and another four had thyroid disorders. All 319 participants completed the questionnaire making the response rate of 100%.

Characteristics of Participants

Mean age of the participants was 63 years and more than half of them were women (58%) (Table II). Indians made up the largest ethnic group (42.9%), more than half of the participants had at least secondary education levels (56.4%), two-third were married (69.6%) and half of them were unemployed (52%). Slightly more than half of the participants had uncontrolled T2DM with HbA1c more than 7% (55.2%) and two fifth of them were obese (43.6%) (Table III). Majority were having comorbidities (97.8%) with nearly two-third of them having both hypertension and dyslipidaemia (60.8%). Most of the participants had no diabetic complications (82.4%) and about half of them (52%) experienced nocturia for the past one month. Nephropathy was the most common complication, followed by Ischemic Heart Disease, Cerebrovascular Accident, and lastly Diabetic Retinopathy. Participants with depressive, anxiety and stress symptoms were about 6%, 5.3% and 5%, respectively.

Prevalence of poor sleep quality

The total mean PSQI score among the participants was 4.04 (2.21) with 23% participants had PSQI score of >5, indicating poor sleep quality.

Factors associated with poor sleep quality

Simple logistic regression revealed $p < 0.25$ for gender, ethnicity, marital status, employment, having nocturia and psychological distress namely depression, anxiety, and stress (Table IV). All the above variables and six other important variables identified from literature, namely age, BMI category, HbA1c group, duration of T2DM, co-morbidity and diabetic complications were also included for multivariate analysis.

Table V: Factors associated with poor sleep quality using multiple logistic regression

Factors		Multiple logistic regression[a]			*p* value
		ß	Adjusted OR (95% CI)	Wald test	
Ethnic	Malay	ref		6.17	0.046
	Chinese	0.16	1.18 (0.51, 2.71)	0.15	0.701
	Indian	0.81	2.25 (1.05, 4.82)	4.37	0.037
Marital	Married	ref		7.21	0.027
	Single	-0.46	0.64 (0.19, 2.05)	0.58	0.446
	Separated/widow	0.77	2.16 (1.15, 4.05)	5.81	0.016
Nocturia	Yes	0.76	2.13 (1.18, 3.84)	6.36	0.012
	No	ref			
Depressive symptoms	Yes	1.23	3.41 (1.01, 11.48)	3.92	0.048
	No	ref			

[a]Backward stepwise likelihood ratio multiple logistic regression method was applied.
Multicollinearity and interaction terms were checked and not detected.
Hosmer–Lemeshow GOF test (p < 0.001), classification table (overall correctly classified percentage = 76.8%) were applied to check the model fitness.

In the multiple logistic regression analysis shown in Table V, Indian ethnicity, having nocturia, separated or widowed, and having depressive symptoms were significant independent factors associated with poor sleep quality. Indian participants had 2.25 times the odds (Adj. OR = 2.25; 95% CI = 1.05, 4.82) of having poor sleep quality compared to Malays. Those who were separated or widowed had two times the odds (Adj. OR = 2.16; 95% CI = 1.15, 4.05) of having poor sleep quality than those who were married. T2DM patients with nocturia had 2.13 times the odds (Adj. OR = 2.13; 95% CI = 1.18, 3.84) of having poor sleep quality than T2DM patients without nocturia. Those with depressive symptoms have more than 3 times higher risk (Adj. OR = 3.41; 95% CI = 1.01, 11.48) of having poor sleep quality compared to those without depressive symptoms.

DISCUSSION

Prevalence of Poor Sleep Quality

The results of the present study demonstrated that 23% of T2DM patients participated had poor sleep quality. This finding is the lowest prevalence compared to other studies among T2DM patients.

Internationally, studies showed prevalence of poor sleep quality among T2DM patients ranging from 33.6% in China,[10] 38.1% in Iran,[20] 47.2% in Ethiopia,[21] 47.6% in Kanagawa, Japan[5] to 81% in Jordan.[11] Another study in Japan reported 43.9% poor sleep quality among T2DM patients compared to 38.4% among control group.[8] Meanwhile in east coast Malaysia, a recent study among 350 T2DM patients in Kelantan found 32% of them having poor sleep quality.[15] Lower prevalence in our study could be attributed to different socio-demographic and clinical characteristics of the participants as seen in a study among multiethnic population in Singapore.[22] Other local studies among various population groups reported higher proportion of poor sleep quality such as in working adults (45%),[17] nurses (57.8%),[23] secondary school teachers (61%)[24] and pre-clinical medical students (63.9%).[25]

Nevertheless, more importantly the impact of both diabetes mellitus and poor sleep was associated with higher risk of all-cause mortality compared to either condition alone, as reported in UK Biobank cohort data.[26]

Associated Factors for Poor Sleep Quality

Indian ethnicity, separated or widowed, having nocturia and having depressive symptoms showed four independent factors of poor sleep quality in this study. Another local study among T2DM patients in Kelantan reported nocturia, restless leg syndrome and emotional distress were significantly associated with poor sleep.[15]

The ethnic distribution of our study participants were 42.9% Indians, 33.9% Chinese and 23.2% Malays, almost similar to the NDR proportion in the clinic. Comparison for ethnicity was limited by unavailability of local study among T2DM patients of multiethnic groups. Local studies among secondary school students and elderly population showed higher proportion of poor sleep quality among Indian participants compared to all participants, though the difference was not statistically significant.[27,28] A population study of sleep quality among Singapore residents with multiethnic representation showed Indian and Malay ethnicities were at higher odds of poor sleep quality compared to Chinese.[22] A review of sleep studies in the United States of America showed that ethnic minorities were at a disadvantage for sleep health disparities compared to White populations.[29] Psychosocial stressors, neighbourhood context, socioeconomic status and access to and utilization of health care were some factors attributed to the sleep health disparities which could possibly explained the higher prevalence of poor sleep among Indians in our study.[29]

In terms of marital status, a study in Singapore reported that those divorced/separated were at higher risks of poor sleep quality compared to married participants, which is consistent with our findings.[22] Those divorced and widowed could possibly be at socioeconomic disadvantage and under higher psychosocial stressor.[29,30]

Participants having nocturia had more than two times the odds of experiencing poor sleep compared to those without nocturia. Nocturia among T2DM patients was another independent predictor of poor sleep quality in our study consistent with a local study done among T2DM patients in Kelantan.[15] Among Asian population, another study in Singapore similarly reported nocturia as the only significantly associated factor with poor sleep quality among 199 elderly with T2DM, hyperlipidaemia and hypertension.[31] A recent large meta-analysis explored the relationship

between diabetes and nocturia, and found that diabetes itself increased the risk of nocturia by approximately 49%.[32] Poor glycaemic control has been implicated as a cause for nocturia. Nonetheless, in our study, post-hoc analysis showed less than a third of the participants (29.7%) with nocturia had poor glycaemic control, which could explain why nocturia was significantly associated with poor sleep quality but poor glycaemic control was not. Hence, the presence of nocturia should be assessed in people with poor sleep quality as it was not necessarily related to poor glycaemic control.

Psychological distress was another factor that showed significant association with poor sleep quality. National Health Morbidity Survey 2019 reported depression in 2.3% of adults in Malaysia with Negeri Sembilan had among the highest prevalence at 5%.[13] Similarly the proportion of participants with possible depression in our study was 6%. In this study, we found that those with depressive symptoms had more than three times the odds of having poor sleep quality compared to those without depressive symptoms. The association between psychological distress and poor sleep quality had been consistently reported in many other studies. Local studies on sleep quality among secondary school students and the elderly attending a primary care clinic reported psychological distress was significantly associated with sleep quality.[27,28] Studies among T2DM patients locally and abroad reported similar association.[14,15,21] A study conducted among 289 T2DM patients in outpatient diabetic clinic of a private hospital setting in Myanmar showed 27.7% of participants had depression and it was significantly associated with poor sleep quality (AOR = 7.52, 95%CI = 3.38–14.76).[33] Another study in China among 281 T2DM patients with comorbid metabolic syndromes also found depressive symptoms as an independent predictor of poor sleep quality and reported further association between depressive symptoms with long sleep latency and short sleep duration.[34] This association is understandable as insomnia or hypersomnia are established symptoms of depression in The Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[35] Emotion regulation, described as various efforts to modify the experience and expression of emotions, has been implicated to sleep quality and depression.[36] Impaired emotion regulation was reported as a mediator to current and prospective relationship between poor sleep quality and depressive symptoms.[36]

Higher BMI and poor glycaemic control were two important factors that were not significantly associated with poor sleep quality in our study. We postulated, higher BMI, as one of the critical risk factors for the development of Obstructive Sleep Apnea (OSA) could be associated with poor sleep quality, in our study. NHMS 2019 reported overweight (BMI >25 kg/m²) and obesity (BMI>30 kg/m²) in about 50% of Malaysian adults.[13] In our study, using lower cut-off point we found higher proportion of overweight (BMI 23-27.4 kg/m²) and obesity with (BMI ≥27.5 kg/m²) at 37.6% and 43.6%, respectively. Interestingly both groups with overweight and obesity reported lower proportion of poor sleep quality at 22.5% and 22.3%, respectively. Consistent with our finding, a local study done among T2DM attending a primary care clinic also did not find significant association between higher BMI with poor sleep quality even though 91.7% of their participants were overweight or obese with BMI >23 kg/m².[15] Further exploration is needed to investigate sleep quality among our overweight and obese populations.

Studies reported inconsistent association between poor glycaemic control and poor sleep quality. A Japanese study found diabetes patients with higher quartile HbA1c >7.9% had significantly higher global PSQI score than the other group with better glycaemic index.[5] Studies in Jordan and Ethiopia also found poor glycaemic control was associated with poor sleep quality.[11,21] However, another local study and other studies in Japan, Iran, Myanmar, and Saudi Arabia reported no significant association.[8,14,15,33,37] A systematic review and meta-analysis highlighted that short sleep less than 5 hours and long sleep durations more than 8 hours were associated with an increased HbA1c compared to normal sleep.[38] Even though in our study more than half of participants (55.2%) had uncontrolled HbA1c >7%, it was not significantly associated with poor sleep quality. Hence, further investigation assessing amount of sleep as well as broader stratification of HbA1c could be useful to see its association with glycaemic control. Keeping continuous variables such as BMI and HbA1c for continuous analyses instead of categorical analyses could be more meaningful.[39]

One of the limitations in this study was that the sleep quality was subjectively assessed using the PSQI. Apart from its acceptance as a standardized tool, it is not an objective measure like polysomnography. Secondly, a cross-sectional design of this study can only suggest an association, not the cause and effect, for poor sleep quality. In interpreting our results, caution is needed due to the single-centered setting. Our findings would be at most, inferred from the local population attending our primary care clinic. Other than that, mode of treatment especially insulin use, nocturnal hypoglycaemia, painful neuropathy and restless leg syndrome which could be related to poor sleep quality among T2DM were not assessed in this study.

CONCLUSION

This study found that 23% of our studied population have poor sleep quality. Indian ethnicity, separated or widowed, having nocturia and depressive symptoms were independent factors significantly associated with poor sleep quality. Assessment of sleep quality should be considered in the management of T2DM patients. Improving sleep quality might involve a simple measure that does not cost much and the ultimate outcome is to maximize the care towards our diabetic patients indirectly improving their quality of life.

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FUNDING AND CONFLICT OF INTEREST

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

ETHICAL APPROVAL

The ethical approval was obtained from Medical Research & Ethics Committee's (MREC), Ministry of Health Malaysia (NMRR ID-21-01986-E44), and Research Ethics Committee of Universiti Kebangsaan Malaysia (JEP-2021-800).

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Efficacy and safety of adjunctive treatment with perampanel in epilepsy patients

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ABSTRACT

Introduction: Epilepsy is a neurological disease with high global prevalence. Almost one-third of epilepsy patients continue having seizures despite adequate treatment. Perampanel has been widely used in the Western countries as an adjunctive therapy for both generalized and focal seizures. Owing to its high cost, the use of perampanel is limited in our country.

Materials and Methods: We conducted a descriptive, retrospective study among epilepsy patients treated with perampanel. We aimed to assess the efficacy and safety of perampanel as an adjunctive in our hospital.

Results and Conclusions: From our cohort of 25 patients, most of the patients were either on one or three anti-seizure medications (ASMs) prior to initiation of perampanel. Perampanel was added in 88% of them due to persistent seizures. Twenty-two (88%) patients experienced reduction in seizure frequency. 12% experienced mild side effects, which were leg cramps, hyponatremia and drowsiness. Only 1 patient stopped perampanel due to its side effects.

Conclusion: Perampanel is a well-tolerated ASM that should be widely used as an adjunctive. More studies with regards to its efficacy and safety involving more centres are encouraged in Malaysia.

KEYWORDS:
Epilepsy, refractory, anti-seizure medication, perampanel, dizziness

INTRODUCTION

Epilepsy is a chronic brain disorder, characterised by two or more unprovoked seizures occurring more than 24 hours apart, due to the abnormal excessive or synchronous neuronal activity in the brain. The prevalence of epilepsy differs in different countries, ethnics, and socioeconomic statuses, with an overall lifetime population prevalence, worldwide, of 7.60 per 1,000.[1] The overall lifetime prevalence of epilepsy in Asian countries correlates with the worldwide data, varying from 1.5 to 14.0 per 1000 population, and it is reported as 7.8 per 1000 population in Malaysia.[2]

Treatment for epilepsy includes anti-seizure medications (ASMs), which are expected to achieve seizure freedom in 70% of patients. The remaining 30% of patients might need a substitution or an addition of a second ASM.[3] All ASMs can be categorised into broad- and narrow-spectra. Broad-spectrum ASMs such as valproic acid are commonly initiated in generalized or uncertain type of epilepsy; whereas narrow-spectrum ASMs such as carbamazepine and phenytoin are used in the treatment of focal seizures.[4] Recent years, many new ASMs with a wide variety of mechanisms of action were introduced with high hopes for a better seizure control. However, prospective audits on new ASMs such topiramate, levetiracetam, zonisamide, pregabalin, and lacosamide as an adjunctive therapy were disappointing with a low seizure freedom rate of less than 25%.[5]

Perampanel is one of the new ASMs introduced as an adjunctive therapy for epilepsy. It is a selective, non-competitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors on post-synaptic neurons.[6] Many promising data were reported in the Western countries for the use of perampanel as an adjunctive therapy in refractory focal-onset seizures as well as generalized tonic-clonic seizures.[7-9] The commonly reported side effects of perampanel are dizziness, convulsion, and somnolence, which are statistically insignificant at low doses.[10] The utilisation of perampanel in the Asian population, especially in South East Asia is relatively low as compared to the Western countries, with limited information on its clinical performance and safety profile. More clinical studies are warranted for better cognizance of perampanel as an adjunctive treatment in the Asian population.

The aim of this study was to determine the change in seizure frequency and responder rate upon initiation of perampanel as an adjuntive ASM. We also studied the adverse events related to perampanel and the reasons for its discontinuation.

MATERIALS AND METHODS

This was a single-centre, descriptive, retrospective study done at the Hospital Canselor Tuanku Muhriz after obtaining approval of the Research Ethics Committee (Project Code: FF-2021-422). All patients with epilepsy treated with perampanel were included in this study. Those with missing data were excluded.

Twenty-five epilepsy patients treated with perampanel as an adjunctive therapy from January 2015 till December 2020

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Table I: Patients' demographic characteristics (n = 25)

Characteristics	n (%)
Ethnicity	
Malay	11 (44.0)
Chinese	12 (48.0)
Indian	1 (4.0)
Others	1 (4.0)
Age (year)	
0-20	3 (12.0)
21-40	11 (44.0)
41-60	9 (36.0)
61-80	2 (8.0)
Gender	
Male	17 (68.0)
Female	8 (32.0)
Medical diseases	
Metabolic	3 (12.0)
Brain related	3 (12.0)
Malignancy	1 (4.0)
Genetic	3 (12.0)
Autoimmune	1 (4.0)
None	14 (56.0)

Table II: Epilepsy characteristics (n = 25)

Characteristics	n (%)
Type of epilepsy	
Generalised onset	13 (52.0)
Focal onset	12 (48.0)
Unknown onset	0 (0.0)
Duration of disease (year)	
Less than one	2 (8.0)
1-10	10 (40.0)
11-20	8 (32.0)
21 and above	5 (20.0)
Aetiology	
Structural	5 (20.0)
Genetic	2 (8.0)
Infectious	5 (20.0)
Metabolic	1 (4.0)
Unknown	12 (48.0)
EEG	
Normal	3 (12.0)
Abnormal spikes	22 (88.0)
MRI	
Normal	14 (56.0)
Abnormal	11 (44.0)

were recruited from the Neurology Clinic of our hospital. The patients' demographics and characteristics of their seizures were collated in a data collection sheet.

The statistical analysis was performed using IBM Statistical Product and Service Solutions (SPSS) version 26.0. Descriptive statistics were used to present the variables recorded. We tabulated the descriptive statistics to summarize our data. Normally distributed data were expressed using mean ± standard deviation; whereas data that was not normally distributed were reported using median (inter-quartile range).

In this study, the efficacy of perampanel (seizure reduction) was taken as at least 50% reduction in seizure frequency compared to the baseline; whereas the safety of perampanel was measured as presence of any side effects among patients who were on perampanel.

RESULTS

A total of 25 patients had perampanel as an adjunctive ASM. Twelve (48.0%) were Chinese, 11 (44.0%) Malay and 1 (4.0%) each, were Indian and other races. The mean age (± standard deviation [SD]) of our patients was 37.5 years (± 13.4 years), with predominantly males (17, 68.0%). Eleven (44.0%) patients had other medical illnesses, which included metabolic diseases (3, 12.0%), brain related diseases (3, 12.0%), genetic diseases (3, 12.0%), malignancy (1, 4.0%) and autoimmune diseases (1, 4.0%) (Table I).

The mean duration of epilepsy in our cohort was 1.6 years (± 0.9 years). Regarding the types of epilepsy, they were almost equally distributed between generalised (13, 52.1%) and focal (12, 47.9%) epilepsy. The aetiology of epilepsy in most of our patients was unknown (12, 48.0%), while a small number were contributed by structural (5, 20.0%) and infectious (5, 20.0%) causes (Table II).

Table III: Perampanel and epilepsy (n = 25)

Characteristics	n (%)
Number of ASMs prior to perampanel	
1	7 (28.0)
2	6 (24.0)
3	7 (28.0)
4 and more	5 (20.0)
Indications for adding perampanel	
Persistent seizures with previous ASM	22 (88.0)
Side effects from previous ASM	0 (0.0)
Both	3 (12.0)
Changes in seizure frequency	
No change in seizure frequency	3 (12.0)
Seizure reduction[$]	22 (88.0)
Increase in seizure frequency	0 (0.0)
Duration on perampanel (year)*	
Less than 1	5 (23.8)
1-2	5 (23.8)
2-3	6 (28.6)
More than 3	5 (23.8)
Side effects from perampanel	
Yes[†]	3 (12.0)
No	22 (88.0)
Continuation of perampanel	
Yes	13 (52.0)
No	12 (48.0)
Reasons discontinuing perampanel (n = 12)	
Due to side effects	1 (8.3)
Others[#]	11 (91.7)

*4 missing data as patients died/defaulted follow up / transferred care to another hospital
[†]Side effects reported include leg cramps, hyponatremia, drowsiness.
[#]Other causes such as patients died or defaulted follow up.
[$]Seizure reduction refers to at least 50% reduction in seizure frequency from baseline (efficacy of perampanel).
ASM = Anti-seizure medication

Most of our patients were on at least one (7, 28.0%) or three (7, 28.0%) ASMs (mean ± SD = 2.4 ± 1.1) prior to the addition of perampanel. More than three-quarter (22, 88.0%) had perampanel added due to persistent seizures with previous ASMs. Three (12.0%) patients had both persistent seizures and side effects from the previous ASM, which led to the addition of perampanel. After adding perampanel, 22 (88.0%) experienced at least 50% reduction in seizure frequency from their baseline, and only three (12.0%) had no change in seizure frequency.

The mean (± SD) duration of perampanel use among our patients was 1.5 years (± 1.1 years). Only 3 (12.0%) complained of side effects, which were leg cramps, hyponatremia and drowsiness. Thirteen (52.0%) patients are still on perampanel; 1 (4.0%) on the other hand stopped treatment due to drowsiness. The remaining 11 (44.0%) patients were not on perampanel as they defaulted follow up or died (Table III).

DISCUSSION

Most of our patients with epilepsy are of Malay (11, 44.0%) and Chinese (12, 48.0%) ethnicity. This is representative of the national population whereby Malay and Chinese form the two largest ethnic groups in Malaysia. In the West, whites are more prone to having primary generalized epilepsy, whereas no racial differences were seen in temporal or frontal lobe epilepsy.[11] However in Malaysia, there are no recent studies to suggest ethnic preponderance towards types of epilepsy. Our epilepsy patients are predominantly male (17, 68.0%). This can be explained by the fact that they are more vulnerable to head injuries, stroke and CNS infections leading to seizures.[12]

Keezer et al., mentioned in their paper that almost half of the adults with epilepsy have at least one medical comorbidity. Diseases such as depression, dementia, anxiety, heart related diseases and peptic ulcer diseases are strongly related to epilepsy due it its bidirectional relations.[13] In our current cohort, they did not have any psychiatric or heart related issues.

When treating epilepsy, the gold standard is to use monotherapy at its most tolerated dose. Most of the time, a second or third agent is needed, thus achieving seizure freedom in more than half patients.[14] The average ASMs used by our patients were two ASMs, prior to addition of perampanel. Almost all of them had perampanel added due to persistent seizures and/or adverse effects from other ASMs. The recent PERaMpanel pooled analysIs of effecTiveness and tolerability (PERMIT) study showed that perampanel can be used as mono, or an adjunctive therapy to treat epilepsy, owing to its broad-spectrum properties.[15,16] The use of perampanel contributes to a significant reduction in seizure frequency, similar to our study in which up to 88.0% of the patients had seizure reduction.

Patients on perampanel commonly reported experiencing side effects, namely dizziness, fatigue, somnolence and irritability.[10] This was seen among those on perampanel 12 mg per day and the discontinuation rate among this group was as high as 5% due to its side effects. The incidence of dizziness among this group was as high as 20%.[17] One of our patients had to discontinue perampanel owing to dizziness affecting the daily activities.

Although the incidence is low, one of the most concerning side effects of perampanel is worsening of depression and aggression when not used in caution in patients with pre-existing psychiatric illness.[10] None of our patients suffered from any neuropsychiatric illnesses. We noted that one patient had hyponatremia secondary to perampanel. Hyponatremia caused by perampanel was rarely reported and the incidence is only less than 1% of general population.[18]

Our study has several limitations. The sample size was too small due to the high cost of perampanel, which most patients could not afford. This is a single-centre and retrospective study, the findings of which might not be generalizable. Many patients also lost to follow up while on perampanel.

CONCLUSIONS

Perampanel is a well-tolerated ASM that could be considered as an adjunctive treatment among epilepsy patients in Malaysia. More studies on the efficacy, retention rate and side effects of perampanel involving a larger population are encouraged.

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CONFLICT OF INTEREST

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Outcomes of cardiopulmonary resuscitation in the emergency department of a tertiary hospital in Malaysia

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ABSTRACT

Introduction: There are insufficient data available regarding the outcome of cardiac arrest (CA) resuscitated in the emergency department in Malaysia. This study aims to determine the incidence of CA, the return of spontaneous circulation (ROSC), survival to admission (STA), survival to discharge (STD) and factors influencing the overall outcome of CA.

Material and Methods: This is a retrospective observational study done in Hospital Sg Buloh (HSB), a tertiary referral centre in an urban area located north of Kuala Lumpur, Malaysia's capital city, from January until December 2018, involving 289 patients. All cases with CPR and a sustained return of spontaneous circulation (ROSC) were included in the study and followed up until discharged or died in the hospital.

Results: Out of 236 patients recruited, 25.8% achieved ROSC, 15.7% survived on admission, and 4.2% of patients were discharged alive. Of 74.1% of witnessed OHCA, only 17.5% received bystander CPR. Factors with favourable outcomes include CA in ED (p<0.001), the initial rhythm of ventricular fibrillation (p=0.003), defibrillation (p=0.024), OHCA witnessed by emergency medical services (EMS) (p=0.024) and intravenous adrenaline administration (p=0.001). When using multivariate regression analysis, positive outcomes were associated with the cardiac and respiratory cause of CA (Adjusted Odd Ratio (AOR) 3.66; 95% Confidence Intervals, 95%CI: 2.52 - 12.61 and AOR 8.76; 95%CI: 5.76- 15.46, respectively) as well as OHCA witnessed by EMS (AOR 10.81; 95%CI: 1.84- 19.52).

Conclusions: Despite being an upper-middle-income country and having advancements in the healthcare system, a relatively lower STD rate among survivors of CA in the ED was observed in this study. There was underutilization of the EMS among patients with CA. The bystander CPR rate among patients with CA in Malaysia is also worryingly low. Aggressive community participation in cardiac arrest awareness programmes is much required. Additionally, in achieving better outcomes, implementing standardized post-resuscitation care protocols with existing resources will be a challenge for physicians managing cardiac arrest cases.

KEYWORDS:
Cardiac arrest, Cardiopulmonary resuscitation, Emergency Department, Survival to discharge, In hospital cardiac arrest, Out of hospital cardiac arrest, middle-income country

INTRODUCTION

Since the introduction of modern cardiopulmonary resuscitation by Peter Safar in the 1950s, the resuscitation technique has improved with advanced development and protocols.[1] Over the years, with a better understanding of the best practice in resuscitation, many countries have advocated a standardised approach governed by respective societies and associations.

Malaysia has produced its version of cardiac arrest (CA) resuscitation protocol through the National Committee on Resuscitation Training (NCORT) based on the evidence from the International Liason Committee on Resuscitation (ILCOR) since 2006.[2] Since then, the hospitals in Malaysia have adopted the NCORT recommendation apart from the guidelines from American Heart Association.

The emergency department in Malaysia has developed rapidly, from an admission unit for the in-patient ward 20 years ago to advanced acute medical care provided by specialised doctors and equipped with the latest technologies. As a frontline, advanced critical care provider, cardiopulmonary resuscitation (CPR) and subsequent management are core elements in emergency department (ED). However, despite rigorous training among the healthcare staff on standard CPR and resuscitation techniques, there was no official nationwide registry to assess the outcome of post-cardiac arrest management in the emergency department. The PAROS database and many other studies concentrate on out-of-hospital cardiac arrest (OHCA) and their performances without much emphasis on the ED.[3,4]

In a small sample size study on the East Coast of Malaysia, the rate of return of spontaneous circulation (ROSC) post-CPR in the ED is 30.2%.[5] This is comparable to a study in China by Xue et al. (25.8%) and in Pakistan by Moosajee et al. (27.4%).[6,7] The survival to discharge (STD) ranges between 5.6 to 11% in studies outside Malaysia.[5-9] Unfortunately, there is no data on STD for post-cardiac arrest in the ED or in-hospital available in Malaysia.

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Amongst the factors affecting the outcome is the initial rhythm (shockable vs non-shockable), the aetiology (trauma vs non-trauma), witnessed arrest and bystander resuscitation, the age, and the interval between collapse and initiation of CPR. [5,7]

As the nation develops as a model of an upper-middle-income country in Asia, there is an urgent need to assess the overall outcome of CA and the factors affecting it in the local emergency department. This study aimed to examine this, consisting of out-of-hospital and in-department cardiac arrests.

MATERIALS AND METHODS

This is a retrospective study done in Hospital Sg Buloh (HSB), a 620 bedded tertiary referral centre in an urban area located north of Kuala Lumpur, Malaysia's capital city. The ED receives nearly 13,000 patients in a month. Consultants and specialists were available 24 hours in the emergency department, with 36 beds in yellow, red and observation zones. The resuscitation equipment is complete and considered state-of-the-art. It also encompasses a pre-hospital and trauma fellowship training centre for emergency physicians and paramedics.

Data were retrieved from the hospital information system (HIS) electronic record from January until December 2018. A total of 289 patients that underwent CPR in ED during the study period were included. The inclusion criteria consisted of all cases of CA in the ED, aged 18 and above. This consists of those whose CA developed in the ED while undergoing treatment and those brought into the ED with active CPR ongoing. Cases with incomplete data, not-for-active-resuscitation (NAR) or existing do-not-resuscitate (DNR) advance directives and aged less than 18-years-old were excluded from this study. Thus, 236 patients fulfilled the inclusion criteria and were included in the study.

The data collected adhered to the Utstein template, which consisted of core elements of patients variables (demographic, comorbidities, initial CA rhythm, location of cardiac arrest), pre-event variables (presence of witnessed collapse, presence of bystander CPR), CA variables (initial CA rhythm, defibrillation, use of resuscitation medications) and outcome variables (return of spontaneous circulation [ROSC], survival to in-patient admission, and survival to discharge).[10] The supplemental elements consisted of the aetiology of cardiac arrest. All cases with CPR and a sustained ROSC for more than 30 minutes were considered positive outcomes. Those with a sustained ROSC of less than 30 minutes were considered negative results. The positive outcome was further divided into eventual death in the ED while awaiting transfer to the critical care unit or ward, death in the critical care unit or ward after admission and those who survived and were discharged alive from the hospital.

Emergency department cardiac arrest (EDCA) was defined as a CA in the ED. In contrast, OHCA were those with CA outside the hospital and brought into the ED with ongoing CPR or resuscitation by emergency medical system (EMS) transportation provided by the government (Ministry of Health, Ministry of Education, Ministry of Defense) and trained personnel from Red Cross Malaysia and St John Ambulance Malaysia or private ambulances from other modes.

The CA incidence rate was calculated by dividing that year's total number of cardiac arrests by the estimated total number of ED visits, multiplying by 1000. The estimated total number of ED visits is 154,00

Statistical Package for Social Sciences, version 25.0 (SPSS Inc, Chicago, IL) was used for data analysis. The descriptive statistics were presented using mean and standard deviation for the numerical variable, whereas the categorical variable was presented using frequency and percentage. The normality of the data was tested statistically using Kolmogorov-Smirnov Test. The Mann-Whitney U and chi-square tests were used to assess the p-values for continuous and categorical data, respectively.

The dependent variable was the status of ROSC, divided into yes and no ROSC. Patients with ROSC were further divided into discharged alive and died in the ward or the ED. The factors affecting the dependent variable of ROSC were analysed with univariable logistic regression analysis. Crude odds ratios (c OR) were reported with 95% confidence intervals (95% CI). A manual selection of covariates with a cut-off p-value of less than 0.25 were included in the multivariable models. Multivariable stepwise backward logistic regression models were created to control for confounding factors. p-value 0.05 (two-tailed) was set for statistical significance.

RESULTS

This study included 236 patients who had CA with CPR in the ED of HSB in 2018. There were 61 ROSC (25.8%) after CPR. 83.6% of those with ROSC, or 21.6% of patients who received CPR, died in ED or the ward. Only 16.4% of those with ROSC, or 4.2% of total CPR, survived and were discharged alive from the hospital. These findings are described in detail in Figure 1. The incidence of CA, calculated based on yearly ED visits, is 1.9 for every 1000 visits.

The demographics, clinical and other CPR characteristics of the patient population with stratification by ROSC and no ROSC were described in Table I. There were more males than females with CA, with the mean age group equally distributed. The most frequent cause of CA was non-trauma, with the majority being cardiac or presumed cardiac causes. Most were OHCA cases compared to EDCA (70.3% vs 29.7%). During resuscitation, 13.6% had an initial shockable rhythm, and 19.5% had defibrillation at least once throughout CPR. Interestingly, only 87.3% received intravenous adrenaline.

When assessing CPR outcomes, those with CA in ED were associated with ROSC ($p < 0.001$). A similar significant association was seen in those with a history of defibrillation ($p = 0.019$) and those who received intravenous adrenaline ($p = 0.007$). There was no association between males and females and ROSC ($p = 0.9$). There was also no association between the mean age for those who attained ROSC and those who did not ($p = 0.900$).

Table I: Characteristics of patients with cardiac arrest (CA) with or without return of spontaneous circulation (ROSC)

	No ROSC (n=175)	Outcome			*p* value
		Discharged alive (n=10)	ROSC Died in ward (n=37)	Died in ED (n=14)	
Race:					
Malay	101 (57.7%)	6 (60.0%)	25 (67.6%)	9 (64.3%)	0.812**
Chinese	20 (11.4%)	2 (20.0%)	5 (13.5%)	2 (14.3%)	
Indian	37 (21.1%)	2 (20.0%)	5 (13.5%)	1 (7.1%)	
Others	17 (9.7%)	0 (0.0%)	2 (5.4%)	2 (14.3%)	
Gender:					
Male	122 (69.7%)	6 (60.0%)	25 (67.6%)	9 (64.3%)	0.900**
Female	53 (30.3%)	4 (40.0%)	12 (32.4%)	5 (35.7%)	
Age:					
Mean (SD)	51.39 ± 15.86	50.40 ± 13.45	53.68 ± 15.37	52.21 ± 12.64	0.858#
Range	18 - 85	29 - 79	22 - 80	21 - 69	
Comorbidities:					
Less than 3	59 (61.5%)	4 (57.1%)	12 (46.2%)	8 (72.7%)	0.410**
3 and more	37 (38.5%)	3 (42.9%)	14 (53.8%)	3 (27.3%)	
Initial rhythm during cardiac arrest:					
Arrest location					
ED	36 (20.6%)	7 (70.0%)	17 (45.9%)	10 (71.4%)	<0.001*
OHCA	139 (79.4%)	3 (30.0%)	20 (54.1%)	4 (28.6%)	
Any witness (OHCA)? (n = 166)					
Yes	103 (74.1%)	2 (66.7%)	18 (90.0%)	4 (100.0%)	0.277**
No	36 (25.9%)	1 (33.3%)	2 (10.0%)	0 (0.0%)	
Who witnesses the arrest? (OHCA)(n = 127)					
Family	74 (71.8%)	2 (100.0%)	10 955.6%)	2 (50.0%)	0.138**
EMS	15 (14.6%)	0 (0.0%)	7 (38.9%)	2 (50.0%)	
Layperson	14 (13.6%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	
Bystander CPR performed for OHCA? (n = 72)					
EMS	44 (61.1%)	0 (0.0%)	9 (100.0%)	2 (100.0%)	0.083
Non EMS	28 (38.8 %)	1 (100.0%)	0 (0.0%)	0 (0.0%)	

*Chi-Square, **Fisher Exact test, #NOVA
ROSC, Return of spontaneous circulation; ED ,Emergency Department ; SD ,Standard Deviation;PEA, Pulseless Electrical Activities ;VF , Ventricular Fibrillation ; VT,
Ventricular Tachycardia ; OHCA ,Out of hospital cardiac arrest ;CPR ,cardiopulmonary resuscitation;EMS ,Emergency medical services; CA – Cardiac arrest

Assessing for predictors of ROSC using a multivariate logistic regression model, the non-trauma cause, specifically cardiac (aOR 3.66; 95%CI: 2.52 12.61), respiratory cause of CA (aOR 8.76; 95%CI: 5.76 15.46) and OHCA initial arrest witnessed by EMS (aOR 10.81; 95%CI: 1.84 19.52) has a better chance of survival compared to other factors (Table II).

DISCUSSION

In this study, the incidence of CA is comparable with the UK National Cardiac Arrest Audit data of 1.6 for every 1000 in-hospital patients.[11] The percentage of CA patients receiving CPR attaining ROSC in the ED is lower than the study by Chew et al. (30.2%) but almost similar to other studies by Xue et al. (25.8%) and Moosajee et al. (27.4%). However, only 4.2% of cases attained STD, lower than other studies in this region, where the STD ranges from 5.6 to 11%, but is similar to the cardiac arrest survivor rate in an ED in Brazil.[5–9,12]

A crucial data that needs further research is the mean age of patients with CA in this study, which is 51.3 years, contrasted with other studies of 66 years in the US and Brazil and 73.9 years in the UK.[12–14] A similar pattern of the high rate of natural deaths at 41-50 years was also reported in an autopsy study in Kuala Lumpur in 2007, but not much has been explored further ever since.[15] This might be linked to the younger age group in Malaysia diagnosed with coronary artery disease as reported in the National Cardiovascular Disease Database Registry and a study on East Coast.[16,17] Nevertheless there is need for further research on this, as it seems in paradox with the national aim of achieving high income nation.[18,19]

The ROSC rate was significantly better in EDCA compared to OHCA, with 1 ROSC for every 2 EDCA vs 1 ROSC for every 6 OHCA. The ratio for survival to discharge is also markedly better in EDCA (1:10 vs 1:55). The 10% rate of STD within EDCA is similar to studies conducted on in-hospital CA in Japan but lower than rates reported in the US and UK.[14-16] However, there is no available local data for comparison. Factors such as pre-hospital response time, early defibrillation, witnessed CPR and bystander CPR could have contributed to the better overall EDCA CPR outcome.[20]

As for OHCA, it is essential to examine the factors affecting this cohort since they comprise of the largest group. Only

Table II: Univariate and multivariate analysis related to the return of spontaneous circulation (ROSC) among cardiac arrest patients in ED

Variables	ROSC achieved			
	p value	OR (95%CI)	*p* value	Adj. OR (95%CI)
Race:				
Malay	0.374	1.68 (0.53, 5.31)		
Chinese	0.344	1.91 (0.50, 7.33)		
Indian	0.901	0.92 (0.24, 3.47)		
Others	Ref	Ref		
Gender:				
Male	0.549	1.21 (0.65, 2.24)		
Female	Ref	Ref		
Age				
52 and above	0.943	0.98 (0.55, 1.75)		
Less than 52	Ref	Ref		
Comorbidities (n = 192):				
0	Ref	1		
1–3	0.008*	2.90 (1.32, 6.36)		
More then 3	0.216	1.96 (0.68, 5.69)		
Initial rhythm during cardiac arrest:				
Asystole	Ref	Ref		
PEA	0.067	2.10 (0.95, 4.66)		
VF	0.003*	3.86 (1.60, 9.32)		
VT	0.764	1.29 (0.25, 6.65)		
Defibrillation performed:				
Yes	0.024*	2.20 (1.11, 4.35)		
No	Ref	Ref		
Non-trauma cause of CA (n = 191):				
Cardiac or presume cardiac	<0.001*	4.24 (2.02, 8.92)	0.003	3.66(2.52,12.61)
Respiratory	0.001*	5.59 (1.98, 15.79)	0.001	8.76 (5.76,15.46)
Others	Ref	Ref	Ref	Ref
Arrest location:				
ED	< 0.001*	4.86 (2.61, 9.08)		
OHCA	Ref	Ref		
Any witness? (n = 169) (OHCA)				
Yes	0.109	2.80 (0.79, 9.84)		
No	Ref	Ref		
Who witnessed the arrest? (n = 127) (OHCA				
Family	Ref	Ref	Ref	Ref
EMS	0.024*	3.17 (1.16, 8.66)	0.008	10.81(1.84,19.52)
Layperson	0.365	0.38 (0.05, 3.11)	0.227	8.02(0.27,23.24)

Multivariate analysis was done with the backward method, model fits well (Hosmer & Lemeshow test), Cox & Snell R2 = 0.314
ROSC, Return of spontaneous circulation; ED, Emergency Department ; SD ,Standard Deviation;PEA, Pulseless Electrical Activities ;VF , Ventricular Fibrillation ; VT, Ventricular Tachycardia ; OHCA ,Out of hospital cardiac arrest ;CPR ,cardiopulmonary resuscitation;EMS ,Emergency medical services; CA – Cardiac arrest; OR , Odds ratio, Adj OR , Adjusted odds ratio.

17.5% of OHCA received bystander CPR by non-EMS, which is at the lower end of the range 10.6 - 41.6% in other Pan Asian countries and much lower than 47.4% in Europe.[3,21] This might be attributed to the low willingness to perform CPR, as portrayed by a study on college students in Malaysia by Karuthan et al., which stated that respondents were not willing to perform hands-only CPR due to limited knowledge of CPR.[22] Additionally, there might be concerns about legal liability and lack of confidence while performing CPR.[23] As bystander CPR is the most amenable factor in improving the outcome of OHCA, there is an urgent need for public education on the importance and technique of CPR.[24]

Most cases were non-shockable as the initial documented rhythm was asystole and PEA compared to VF and VT. This is not much different from the studies on non-shockable rhythms in the East Coast of Malaysia (84%), the US (76 – 81%%) and Taiwan (87.4%).[5,13,25,26]

The low adrenaline administration rate is surprising as it is one of the core drugs and the standard management for all cardiac arrests. However, it is comparable to a study done in Sweden.[27] Perhaps a local study needs to be done to analyse compliance with all the standard cardiac arrest management and the factors affecting it.

Regarding the low rate of STD after ROSC, there might be a need for improvisation of care after cardiac arrest. The lack of standard protocolised post-cardiac-arrest management, as recommended by the American Heart Association in the chain of survival, mainly due to limited resources, might be one of the reasons for the low STD. The paramount issue in Malaysia's ED, i.e., the lack of acute beds and ED longboarding, might also hamper the ideal post-resuscitation care protocols.[28]

As this is a small study, we included and analysed the trauma and non-trauma cohorts together, as were the studies done in Sweden, the UK and Japan.[11,29,30] Future studies shall

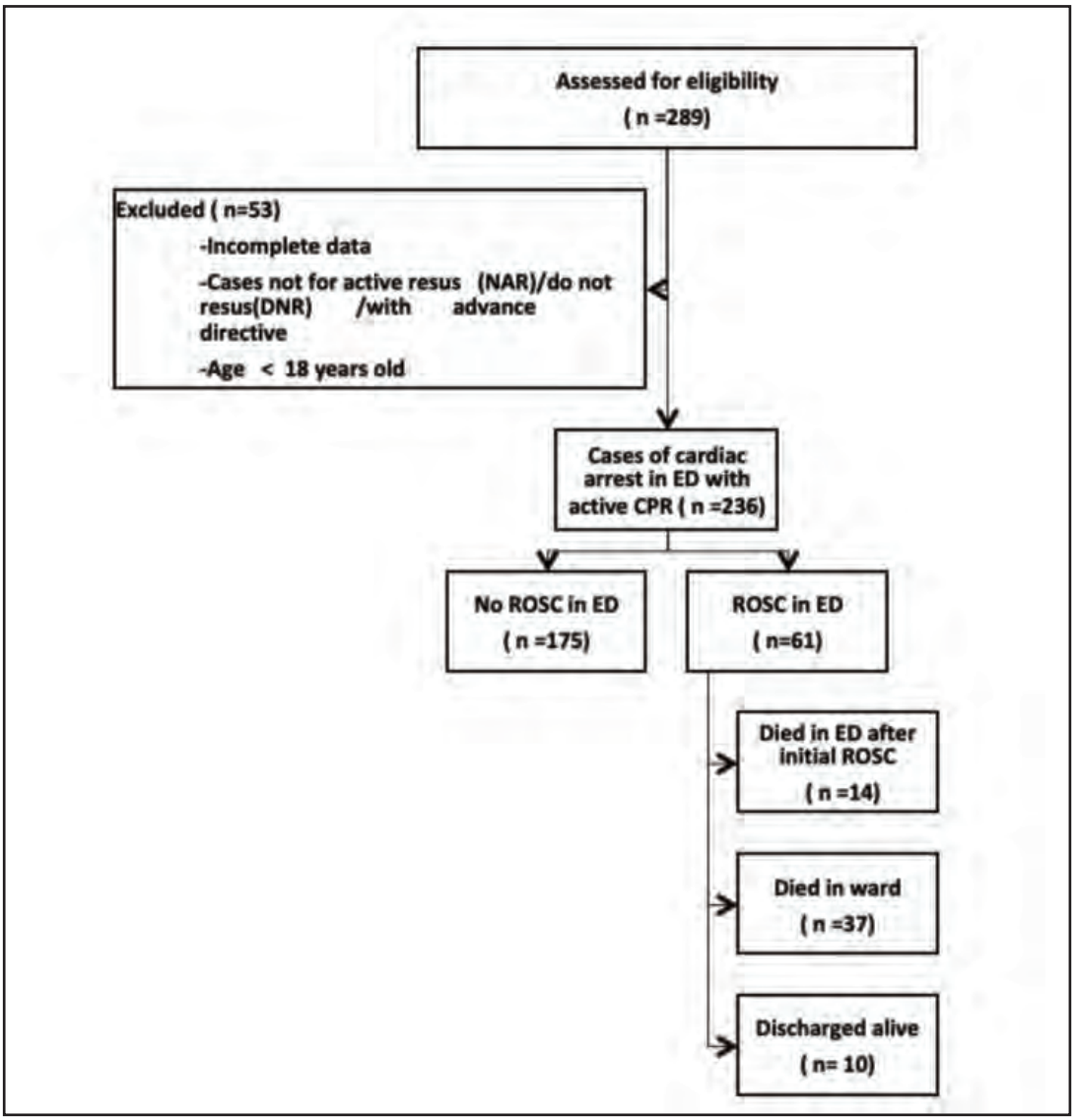

Fig. 1: Outcome of cardiopulmonary resuscitation of patients with cardiac arrest in the emergency department.

focus on examining each cohort separately with longer study periods and larger sample sizes to gain a better understanding. The majority of CA is caused by non-traumatic events, with 26.9% ROSC and 4.8% STD, whereas for trauma cases, 17% ROSC and none with STD. In contrast, the STD for post-traumatic CA in the PROPHET and Epistry Trauma registries is 6.8%.[31] This result is despite the study hospital being a trauma centre with the necessary subspecialist care available.

With univariable logistic regression analysis, CA in ED, VF as first rhythm, history of defibrillation, EMS attended CA and IV adrenaline administration were associated with a better chance of attaining ROSC. These findings are consistent with previous studies in the literature.[6,7,32–34]

Through multivariate analysis, independent predictors for ROSC were cardiac and respiratory causes of CA, and EMS attended CA. Due to the small number of STDs, we chose not to perform the multivariate analysis as the result might not be accurate.

Looking at it from a different perspective, during our research, we discovered that the main challenge we faced in gathering the data was the insufficient information recorded. Whilst the Utstein template was introduced in 1990 and revised in 2004, it was never widely adopted in Malaysia.[10] The variables, consisting of the patient variables, the hospital variables, the CA variables, and the outcome variables would be comprehensive for documentation and data retrieval purposes. Unfortunately, from our observation, until this article was written, there was no standard way of documenting a CA event, even within a single centre. This is the major reason for the variance in term definitions and the missing important data, including the details during the CA and the long-term neurological outcomes. Since this study is retrospective, we made every effort to maintain the accuracy of the data by adhering to the template. Future registry implementation based on this template will produce robust research comparisons between nations. For that, official policy and continuous administrative support is needed.

Although the research has reached its primary aims, there were unavoidable limitations. Our study was performed retrospectively in a single tertiary centre for a year. The data collected were limited based on the above reasoning. As more hospitals in Malaysia are not tertiary, the result should not be generalised. Hence, our results should be interpreted cautiously. We were also unable to ascertain the factors influencing the survival to discharge after the patients left the ED resuscitation area; thus, the patient's actual survival and neurological status were not captured.

There is a need to create a cardiac arrest registry in Malaysia. The ROSC and STD rate will directly imply the quality of the healthcare system and the gap to be addressed. The American Heart Association's Get With The Guidelines-Resuscitation (GWTG-R) registry and the Danish In-Hospital Cardiac Arrest Registry (DANARREST) can be emulated to be implemented in Malaysia.[35]

CONCLUSION

Despite being an upper-middle-income country and having advancements in the healthcare system, a relatively lower STD rate among survivors of CA in the ED was observed in this study. There was underutilization of the EMS among patients with CA. The bystander CPR rate among patients with CA in Malaysia is also worryingly low. Aggressive community participation in cardiac arrest awareness programmes is much required. Additionally, in achieving better outcomes, implementing standardized post-resuscitation care protocols with existing resources will be a challenge for physicians managing cardiac arrest cases.

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DECLARATION

This study was approved by the Malaysian Research Ethics Committee (MREC) (NMRR-19-1766-47833) and Universiti Teknologi MARA (UiTM) Research Ethics Committee (REC/334/19). All methods were performed according to the ICH Good Clinical Practice Guidelines, Malaysia Good Clinical Practice Guidelines and the Declaration of Helsinki.

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ORIGINAL ARTICLE

Development of an online animated sexting prevention module based on the prototype willingness model to reduce intention and willingness to sexting among diploma students

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ABSTRACT

Introduction: Sexting refers to the act of sending and receiving sexually explicit content in the form of in the form of texts, photos, or videos via the Internet and mobile phones. This behaviour is associated with many negative health consequences among young people. However, there is a lack of intervention studies to curb this behaviour. We have developed a new sexting prevention module and tested it using a randomised controlled field trial. This paper reported the phase one of the study i.e., the development of an animated sexting prevention module using the prototype willingness model (PWM) to reduce the intention and willingness to sext amongst diploma students in Malaysia.

Materials and Method: The initial phase involved a review of previous interventions, validation from field experts, and the process of developing video. Then the module pilot was tested among 30 diploma students from a public university. They were given access to the newly developed videos posted on a private YouTube channel and asked to evaluate the videos quantitatively and qualitatively by using the acceptability of the intervention module (AIM), intervention appropriateness measure (IAM) and feasibility of the intervention measure (FIM). The minimum and maximum scores of each measure were 12 and 24 respectively whereby a higher score indicated greater acceptability, appropriateness and feasibility.

Results: The intervention consisted of five sections addressing the constructs of PWM, namely attitude, perceived norm, prototype perception, as well as intention and willingness of sexting. The contents were then converted into five videos with a total duration of 23 minutes. Based on the pilot test, the scores of AIM, IAM and FIM were not normally distributed and their median and the interquartile range values were 20 (4), 21 (4) and 22 (4) respectively. Most of the respondents gave favourable opinions on the intervention besides providing some input for improvement.

Conclusion: This animated sexting intervention module based on PWM to reduce the intention and willingness was novel. The module was acceptable, appropriate and feasible to be implemented among undergraduate students. Further evaluation of this intervention module can be performed to provide more comprehensive evidence of its effectiveness.

KEYWORDS:
Social media, intention, Malaysia, students, sexting, pilot projects

INTRODUCTION

The term sexting is a combination of sex and texting. It refers to the act of sending and receiving sexually explicit content in the form of texts, photos, or videos via the Internet and mobile phones.[1,2]

Sexting is a new form of sexual communication among the young population in discovering sexual needs and desires as well as for them to maintain sexual intimacy.[3] However, recent studies reported that sexting might cast some adverse psychosocial consequences on young people, for example, cyberbullying, depression and attempted suicide.[4–8] Furthermore, it is also associated with sexually risky behaviours such as sexual intercourse with multiple partners. Due to the profound impact of sexting and its association with other risky behaviours that can burden young people's health, sexting must be curtailed. In relation to that, sending obscene content via media is a punishable act under Malaysian law, and the penalty is more severe if minors were involved.[9,10]

Currently, interventional studies are scarce on sexting-related issues. The majority of previous studies followed a within-subject experimental study design that focused on the effects of social images on the prototype perception and willingness to sext among adolescents.[11] To date, observational studies have asserted that engagement in sexting can be forecasted by intention and willingness to sext.[12–14] By definition, intention refers to a deliberately planned behaviour[15] while willingness refers to an individual's spontaneous response to risky circumstances.[16] Both intention and willingness are involved in the behaviour that precedes any cognitive process.[17] By focusing on the intention and willingness to sext, the intervention aimed at preventing sexting amongst those who have never sexted, reducing the act of sexting among those who have sexted and minimising multiple risky behaviours associated with sexting.

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The application of a theory-based intervention is more likely to yield a better outcome.[18,19] Therefore, we used the prototype willingness model (PWM) theory as the backbone of our intervention to reduce the intention and willingness to sext. The PWM has been applied to predict risky behaviours amongst the adolescents and young adult population.[14,20–22] However, this theory has not been applied to sexting interventions to date. To our knowledge, this is the first intervention module developed based on PWM for sexting. The evaluation of the effectiveness of this module involved two phases, i.e., phase one involved the development and validation of the newly developed module and the second phase involved evaluating the effectiveness of this module using randomised controlled trial (RCT). In this paper, we reported phase one of the study. The second phase is reported elsewhere.

MATERIALS AND METHODS

Phase one involved the identification of the suitable contents for the intervention based on the respective constructs of the PWM before matching them with the suitable behavioural change techniques (BCT).[18] These processes involved reviewing previous literature and consultation with experts in the field. Three public health experts and a clinical psychologist were invited to examine the content validity. Once the contents were agreed upon by all the experts, the storyboard and scripts for the animated video was created. A private multimedia company was then appointed to develop the animated video. The animated video used to deliver the intervention was assessed for its objective, structure, presentation and relevance as a part of the validation process. A series of reviews of the scripts and the flow of the storyboard was also conducted by the same experts before it was finalised. The flow of the development of the video as in Appendix 1.

Later, a pilot study was conducted at a public university, which is the same university where phase two of the study was conducted. The university has 13 diploma programmes. One programme was randomly selected for the pilot study. The remaining 12 programmes were involved in phase two of this study, where a randomised controlled field trial (RCT) was conducted to test the effectiveness of this module. Thirty voluntary students who fulfilled the inclusion criteria of the RCT but were not included in the main study were invited to participate in the pilot study. The sample size of 30 was derived from 10% of the sample size calculated for the RCT.[23]

YouTube channel was utilised as the online medium to distribute the newly developed video as it was convenient and easily accessible. The videos were set to be private and only those with access could view them. The pilot study aimed to determine the acceptability, appropriateness, and feasibility of the intervention module by using quantitative measures.[24] Acceptability is a form of personal judgment made by individuals about the intervention and it can vary according to individual needs, preferences or expectations. In comparison, appropriateness refers to the perceived fit, relevance or compatibility of the intervention to be practiced in a given setting. In other words, it assesses the technical or social perspective towards the intervention. Feasibility, on the other hand, is the practicality with which the new intervention can be successfully carried out in a given setting.

Three quantitative scales were used, namely acceptability of intervention measure (AIM), intervention appropriateness measure (IAM) and feasibility of intervention measure (FIM).24 Each of these scales consisted of four-item statements. The response scale for all item statements ranged from 1 (completely disagree) to 5 (completely agree). The minimum and maximum scores of each of the measures are 12 and 24 respectively. A higher score indicates greater acceptability, appropriateness and feasibility. The respondents were also requested to provide opinions and feedback on the videos.

The studies involving human participants were reviewed and approved by the Ethics Committee for Research Involving Human Subjects at Universiti Putra Malaysia (JKEUPM-2020-321). The patients/participants provided their written informed consent to participate in this study. The RCT of this intervention module was prospectively registered in the Thai Clinical Trials Registry (TCTR20201002001). The approval from the administration department of the higher education institution and the head of the program, as well as respondents' written consent, were obtained before the commencement of the study.

RESULTS

The PWM consists of five constructs, i.e. intention, willingness, attitude, perceived norm and prototype perception. Figure 1 illustrates the theoretical construct of the PWM.[21,25]

The intervention was developed in the Malay language to suit the target population. It comprises five sections, namely Section 1 (Sexting and Z generation), Section 2 (What are the implications of sexting?), Section 3 (Who is behind sexting?), Section 4 (What others' opinion?) and Section 5 (What can you do?). The summary of constructs and contents in each section of the intervention is summarised in Table I.

Section 1: Sexting and Z generation
This was an introductory session that was delivered via an animated video. Participants were informed of the definition of sexting and the population was deemed to be at risk of being involved in it.

Section 2: What are the implications of sexting?
Participants were educated on the consequences of sexting from four aspects, including sexual and reproductive health, cyberbullying, mental health and the legal aspect. The content of this section was based on the literature review on the implications of sexting.[2,6–8,26–28] In this section, the participants were also exposed to the real scenario of negative consequences of sexting as reported in the local media.

Section 3: Who is behind sexting?
Participants were exposed to the different personalities of people who are more prone to engage in sexting (for example, individuals with a high sensation-seeking

Table I: Summary of the sexting intervention module (SIM)

Section	PWM constructs	Aim	Behaviour change techniques	Duration
Section 1 Sexting and Z generation	-	To increase the knowledge of sexting amongst the participants.	2. Provide information about the sexting trend amongst the Z generation and the reasons why it is common among them.	2.4 minutes.
Section 2 What are the implications of sexting?	Attitude	To improve the attitude towards sexting. To reduce the intention and willingness to sext amongst participants.	i. Provide information on the negative consequences of sexting from four aspects which are sexual and reproductive health, cyberbullying, mental health and legality. ii. Provide real world negative and legislation consequences of sexting to the individuals based on the reports by local media.	9.3 minutes.
Section 3 Who is behind sexting?	Prototype perception	To improve the prototype perception. To reduce the intention and willingness to sext amongst participants.	i. Provide information about the characteristics or personality of individuals who are associated with sexting behaviour.	3 minutes.
Section 4 What others' opinion?	Perceived norm	To reduce the perceived norm, intention and willingness to sext amongst participants.	i. Provide opinions of parents and other young adults on individuals who are involved in sexting.	3.2 minutes.
Section 5: What you can do?	Perceived norm Prototype perception	To reduce the perceived norm, prototype perception, intention, and willingness to sext amongst participants	i. Provide information on potential scenarios that might lead to sexting. ii. Provide information on potential barriers of resisting sexting. iii. Provide skills to resist sext requests by others and information on where to get help.	5.4 minutes.

Table II: Acceptability intervention measure (AIM)

Items	Item statement	Responses (n=30)				
		Completely disagree (%)	Disagree (%)	Neither agree nor disagree (%)	Agree (%)	Completely agree (%)
AIM 1	This SIM meets my approval	0	0	17%	53%	30%
AIM 2	This SIM is appealing to me	0	0	20%	50%	30%
AIM 3	I like SIM	0	0	23%	50%	27%
AIM 4	I welcome SIM to be given to other students	0	0	10%	47%	43%

Table III: Appropriateness measure

Items	Item statement	Responses (n=30)				
		Completely disagree (%)	Disagree (%)	Neither agree nor disagree (%)	Agree (%)	Completely agree (%)
IAM 1	This SIM seems fitting in the sexting prevention effort	0	0	10%	50%	40%
IAM 2	This SIM seems suitable for university students	0	0	13%	50%	37%
IAM 3	This SIM seems applicable	0	0	13%	40%	47%
IAM 4	This SIM seems like a good match with the current technology era.	0	0	13%	37%	50%

Table IV: Feasibility of intervention measure

Items	Item statement	Responses (n=30)				
		Completely disagree (%)	Disagree (%)	Neither agree nor disagree (%)	Agree (%)	Completely agree (%)
FIM 1	Things that we learn from SIM seem implementable	0	0	13%	37%	50%
FIM 2	Things that we learn from SIM seem possible	0	0	13%	37%	50%
FIM 3	Things that we learn from SIM seem doable	0	0	13%	37%	50%
FIM 4	Things that we learn from SIM seem easy to apply in real life	0	0	13%	37%	50%

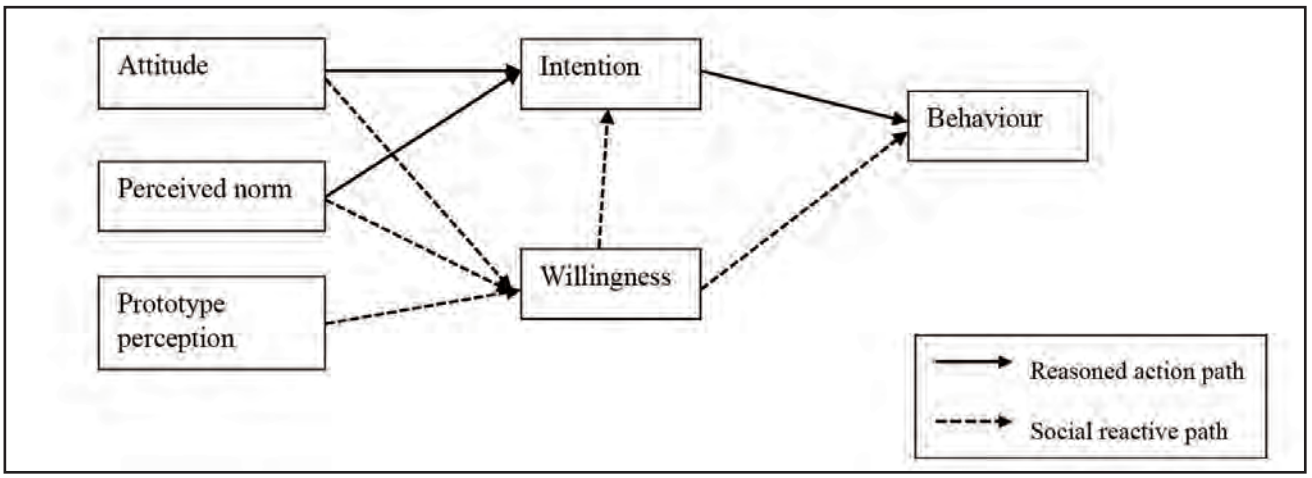

Fig. 1: The theoretical construct of the prototype willingness model.

personality trait, low agreeableness, neuroticism and attachment anxiety). The content of this section was based on the findings from the literature review on studies of the relationship between personality type and sexting behaviour.[28-30]

Section 4: What others' opinion?
Participants were provided with relevant information on the perceived and actual prevalence of sexting in Western and Asian countries as a comparison. Besides, they were also provided with information about the perception and approval of others about sexting behaviour, particularly parents, friends, religion and culture. The content was adapted from the findings of quantitative and qualitative studies obtained during the literature review.[31–33]

Section 5: What can you do?
Participants were provided with the instructions on how to resist social pressure to sext, such as a demonstration on how to resist sext requests by others. The participants were also reminded to use prompts, whereby they are taught to identify environmental prompts that can be applied as a reminder for them to avoid potential situations that can lead to sexting. The participants were also prompted to think about the potential barriers that can prevent them from engaging in sexting and to identify ways to overcome the behaviour.

Based on the response of the pilot study, the majority of the respondents found this intervention module to be acceptable (Table II). The scores were not normally distributed, giving a median (interquartile range, IQR) of 20 (4). Qualitatively, respondents suggested improvement in the video's graphics and animation, as well as increasing examples using real-world sexting scenarios. Furthermore, some respondents recommended for the intervention be expanded to school children.

Based on the response, the majority of the respondents found this intervention to be appropriate (Table III). The scores were not normally distributed, giving a median (IQR) of 21 (4). No additional comment was made qualitatively in this section.

Based on the response, the majority of the respondents found that this intervention was feasible (Table IV). The scores were not normally distributed, giving a median (IQR) of 22 (4). Qualitatively, the respondents suggested uploading the video on social media platforms such as TikTok to gain more attention.

DISCUSSION

In this paper, we reported the development of an online animated sexting intervention module based on the PWM aimed at reducing the intention and willingness to sext among diploma students in Malaysia. The PWM was chosen as the model to address the intention and willingness of sexting, both of which represented important precursors to sexting behaviour. This model has also been used in previous interventions for the reduction of risky behaviours.[14,20–22] Therefore, this intervention module was established based on the previous interventions using PWM, and consultation with experts, before being validated via a pilot study involving a subgroup of the study population who were not participants of the main RCT.

Sexting is a complex behaviour that has been explained by several behavioural theories, including PWM. The application of PWM in the design of the intervention video in this study represented a systematic approach to determine its efficacy in reducing the sexting intention and willingness among young adults. Since most of the published literature focused on the use of PWM for smoking, skin tanning prevention and prevention of alcohol consumption, it is necessary to acknowledge how PWM could contribute to the reduction of the intention and willingness to sext among undergraduate students.

Next, the design of this intervention was adapted from the several experimental studies that were conducted based on PWM.[34–37] Based on an experimental study, sharing the negative social consequences of having unsafe sex with university students has been effective in decreasing their willingness to perform unsafe sex.[34] One of the possible reasons could be how the information might change their attitude with regard to their willingness to have unsafe sex. Therefore, we postulated that the provision of relevant information on possible negative outcomes resulting from engagement in sexting behaviour might contribute to the change in attitude and subsequently the willingness to sext among young adults.

With regard to the best approach to improve the perceived norm of sexting, we included information on the pattern of sexting behaviour globally and locally, previous opinions on sexting prevalence, and others' opinions on sexting behaviour in the intervention module. These were based on an experimental study that provided information on the typical drinking behaviour, average drinking behaviour on campus, and previous thoughts on the average drinking behaviour on campus for undergraduate students in the USA.[35] The study outcome showed a successful reduction in the perceived norm regarding drinking among the respondents. Therefore, in our study intervention, we provided the opinions of parents and other young adults on individuals involved in sexting in order to reduce the perceived norm among the respondents.

Lastly, the review findings of the behavioural change techniques used in PWM were applied to improve the prototype perception towards the sexters.[38] Several studies provided positive and negative identities for the actors or abstainers.[34,39] For example, a study has described the personality of people who practiced unsafe or safe sex in a bogus survey created for the intervention which in turn, the technique was found to successfully increase participants' willingness to wear condoms.[34] This technique was considered adequate to modify the prototype perception.[36] Therefore, in our intervention, we provided information on the type of personality associated with sexting behaviour and a brief explanation of why this type of person would be more prone to engage in sexting.

Based on the results from the pilot study, the online video was considered to be a form of acceptable, appropriate and

feasible intervention. Furthermore, these videos were uploaded to a private YouTube channel, making it convenient for the participants to access during their free time. Besides, the videos were considered to be more attractive for the participants because they were in the form of animation, easy to understand, with contents that might relate to them and short (only took a few minutes of their time to complete viewing). However, they provided some comments on improving the graphics and animation of the video, apart from incorporating more examples based on real-world sexting scenarios. In addition, they also suggested that the videos be uploaded to other social media platforms once the effectiveness of this intervention has been established. Last but not least, they also recommended that the intervention module be expanded to school children.

Despite the positive feedback from this pilot study on our module, we acknowledge that this module will be one of the strategies to prevent sexting and cannot be a standalone strategy. There are several other factors that could influence sexting that are beyond the scope of this module. For example, family dynamics, interrelationships between family members and peers, and financial constraints. Therefore, other strategies could be implemented in parallel with the implementation of this module in order to have a greater impact on sexting prevention. Such strategies include parental involvement, peer-to-peer education, digital literacy programmes, sexting-related legislation awareness, reporting mechanisms for sexting victims, religious workshops, moral guidance and public campaigns on sexting that emphasise the importance of responsible online behaviour.

CONCLUSION

This animated sexting intervention module aimed at reducing the intention and willingness to sext represented an important contribution to the body of literature on the use of prototype willingness model (PWM). The intervention was deemed acceptable to the majority of diploma students that were involved in this study. However, a randomised controlled field trial (RCT) can be undertaken to establish its effectiveness.

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CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare that they have no competing interest.

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Stress perceived by drivers in public healthcare facilities in Negeri Sembilan during the first year of the COVID-19 pandemic

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ABSTRACT

Introduction: Healthcare drivers, including ambulance drivers, were less concerned about health and safety during the COVID-19 pandemic, with not only the risk of COVID-19 infection but also a higher risk of prolonged states of alertness, stress, burnout, fatigue and road traffic accident. This study aimed to determine the prevalence of stress and its associated factors among healthcare drivers, especially during the COVID-19 pandemic.

Materials and Methods: This study employs a cross-sectional study design and utilises self-reported data obtained from locally validated personal stress inventory questionnaires. The data collection period spanned from August 1 to 31, 2020. The study sample consisted of 163 healthcare drivers affiliated with the Negeri Sembilan State Health Department. The Chi-square test and Fisher's exact test were the first used to determine the association between variables prior to conducting multiple logistic regression to predict the relationship between dependent and independent variables.

Results: In COVID-19's first year, 7.4% (n = 12) of healthcare drivers reported perceived stress with ambulance drivers reporting more stress (10.6%; n = 5) than non-ambulance drivers (6.0%; n = 7). Simple statistical analysis identified perceived stress significantly associated with household income, smoking status and performing on-call. Further analysis by multiple logistic regression found that perceived stress was significantly related to smoking (aOR 19.9, 95% CI: 1.86-213.90), and performing on-call (aOR 8.69, 95% CI 1.21-62.28). Nevertheless, no association was found between perceived stress and age, ethnicity, marital status, education, household income, co-morbidities, driving assignment, employment duration, needing a part-time job or motor vehicle accident history.

Conclusion: The study found that the perceived stress amongst Malaysian healthcare drivers during the COVID-19 pandemic was relatively low. This could be due to fewer life-threatening tasks, emergencies, assigned tasks and increase income due to overtime during the COVD-19 pandemic. The OSH team's efforts to provide consistent safety and health training, including stress management, may have contributed to the healthcare driver's ability to effectively manage the stressful circumstances encountered during the pandemic. In order to enhance salary competitiveness, employers should provide financial management education alongside subsidised housing and childcare provisions. Healthcare drivers who smoke should be taught different stress reduction techniques so that they can handle their stress in a healthy way.

KEYWORDS:
Healthcare; health drivers; ambulance drivers; EMS drivers; stress; perceived stress; COVID-19; pandemic; prevalence

INTRODUCTION

The Global populations have been devastated by the COVID-19 epidemic. The impact has existed for almost 2 years since the World Health Organization (WHO) announced the Public Health Emergency of International Concern (PHEIC).[1] Every part of human life was affected by the COVID-19 epidemic, but economic and social devastation stood out.[2,3] Nevertheless, there are over 8 million confirmed COVID-19 infections worldwide, with two million deaths in 2020, and it is increasing day by day.[4] Low-income and poor countries were badly affected and had difficulty surviving during the COVID-19 pandemic, as warned by the WHO and the World Bank Organisation.[5,6]

This pandemic has given a strike to the healthcare system capacity. The occupancy of COVID-19 patients is more than the capacity of healthcare facilities and hospitals worldwide. Certain countries (South Africa, the United Kingdom, Germany, China and Malaysia) built field hospitals to cope with the pandemic situation.[7–9] The impacts of the COVID-19 pandemic are completely different in countries such as Italy, Spain and Malaysia, which experienced a surge of cases but relied on the inadequacy of hospital beds and healthcare professionals.[7,10] But, more importantly, during the COVID-19 pandemic, overwhelmed, short-staffed healthcare facilities lead to stress and burnout among healthcare workers,

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especially on the front lines. The WHO has alerted worldwide healthcare organisations and governments to identify and tackle the unprecedented issues related to healthcare workers during the COVID-19 pandemic.[11]

Tiredness, mental stress and burnout are some of the major issues among healthcare workers during the COVID-19 pandemic.[12] The well-being of healthcare workers, on the other hand, is much more important in maintaining a high standard of quality care for patients because it is directly related to healthcare worker productivity.[13–15] Healthcare workers are expected to work intensely because of the high burden of COVID-19 patients and a lack of staff (because of being infected or affected more by the pandemic). The 11th Revision of the International Classification of Diseases (ICD-11) defined burnout as a syndrome conceptualised as resulting from chronic workplace stress that has not been successfully managed.[16] But tackling stress issues among healthcare workers is crucial and more beneficial to reducing burnout among frontline healthcare workers and maintaining the productivity of healthcare services.

Frontline healthcare workers comprise medical physicians, nurses, medical doctor assistants, healthcare assistants, receptionists, cleaners and ambulance drivers.[17] Ambulance drivers are less concerned with health and safety compared to doctors and nurses during the COVID-19 pandemic. Some reports suggest that ambulance workers may be particularly vulnerable to first-responder mental health issues.[18] Ambulance drivers are not only at a higher risk of COVID-19 infection, but they are also at a higher risk of road accidents due to high driving speeds under emergency conditions and encountering unpleasant aspects of life.[19] They often work under time pressure and at irregular hours, which leads to prolonged states of alertness and fatigue.[20,21] Afshari et al. identified six main stressors for emergency medical service (EMS) drivers: complexity of patients' clinical conditions, interruption of EMS provision, health hazards, interpersonal issues, inter-professional interactions and legal conflicts.[22]

Healthcare and ambulance drivers are comparable to full-time professional drivers, who are exposed to a variety of stressors, such as the behaviour of other drivers, congested roads, ergonomic considerations, noise, climate conditions and job scheduling, resulting in deteriorating well-being and performance.[23,24] John and Linda's 2006 study also revealed that older driver, women and those with a history of reported accidents in conditions of limited visibility, adverse weather and while performing common driving tasks are more prone to experience stress.[25] Despite that, according to Magaña et al.[26], the level of stress experienced while driving can be influenced by four factors: the well-being (physical and mental condition) of the driver, the road and traffic conditions, the condition of the vehicle and external disturbances.

The Institute for Health System Research (IHSR) reported that 129 ambulance accidents occur in Malaysia on average each year.[27] This situation is problematic for the organisation as a result of increased turnover, absenteeism and exposure to substantial claims for compensation. The majority of ambulance accidents (70.4%) occurred during the day, and 55.7% occurred on weekdays. Accidents occurred on straight roads in 49.7% of cases and on 35.4% of federal roads. According to Syazmin et al., health drivers or ambulance drivers were ranked second among Malaysian healthcare workers involved in road traffic accidents, with a 53.7 per 10,000 worker accident rates.[28] The mental health of a driver is critical because it directly influences their driving behaviour. Assessment of the stress status of frontline healthcare drivers is critical before it progresses to burnout with increasing mental distance from one's job and feelings of isolation especially during the COVID-19 pandemic. Thus, this study aimed to determine the prevalence of stress and its associated factors among healthcare drivers, especially during the COVID-19 pandemic.

MATERIALS AND METHODS

The Study Design

The stress among drivers in public healthcare facilities survey was a cross-sectional study conducted from 1st August until 31st August 2020. It covers seven district health offices, seven district dental offices and seven hospitals under the Negeri Sembilan State Health Department (SHD). The responsibilities of healthcare drivers within the department (ambulance driver or non-ambulance driver) are interchangeable depending on where the driver is posted (hospital, district health or dental office or primary care clinics). However, all drivers were deployed as front-liners in managing COVID-19 in the hospital and community. Simple random sampling was used to select drivers based on the 397 drivers in the list provided by the Negeri Sembilan SHD.

The total sample size required was 149 based on the 95% confidence interval (CI), marginal error of 5% and the nearest expected stress prevalence among drivers based on the emergency care personnel met posttraumatic stress disorder; 18.6%.[29] The sample was increased by 10% to account for the non-response rate, which resulted in 164 but rounded into 170 respondents.

The inclusion criteria comprise working at the present workplace for at least 6 months, having Malaysian nationality, working during the COVID-19 pandemic for at least the last 2 weeks, and being a registered driver under the Negeri Sembilan SHD. The selection of a 6-month service duration was based on the understanding that individuals typically require a period of 3–6 months to adapt to a new workplace environment. Drivers diagnosed with mental health illnesses and those on long-term sick leave were excluded from this study.

Survey Instrument

A validated Malay version of the Personal Stress Inventory (PSI) survey was distributed to healthcare drivers. The inventory comprised 51 items with 11 subscales using a four-point Likert scale from ‘never’ (0), ‘once or twice’ (1), ‘every week’ (2) and ‘nearly every day’ (3). The healthcare drivers' replies to each of the 51 items, with scores ranging from 0 to 153, were added together to create a final score. Rokiah validated this inventory in Malaysia with a sensitivity of 95.1%, specificity of 77% and a total score of over 36, signifying respondents were experiencing stress.[30] The Cronbach alpha of this instrument is 0.968. One answered the questionnaires anonymously to maintain the driver's privacy.

Table I: Prevalence of perceived stress among healthcare drivers (n=163)

Variables	n	%	Frequency (n)	
			Stress (%)	None stress (%)
Healthcare drivers	163	100	12 (7.4)	141 (92.6)
Ambulance drivers	47	28.8	5 (10.6)	42 (89.4)
Non-ambulance drivers	116	71.2	7 (6.0)	109 (94)

Table II: Demographic characteristics of health drivers and association with perceived stress (n=163)

Variables	n	Percentage (%)	p-value
Demographic characteristics			
Age groups			0.710
<30	5	3.1	
30–39	81	49.7	
40–49	52	31.9	
>50	25	15.3	
Household income			0.044[a]
MYR <2000	76	46.6	
MYR 2000–3000	43	26.4	
MYR >3000	44	27.0	
Ethnic			0.649
Malay	154	95.7	
Chinese	1	0.6	
Indian	6	3.7	
Marital status			0.519
Single	12	7.4	
Married	145	90.1	
Divorced/Widow	4	2.5	
Level of education			0.385
High School Certificate	145	90.1	
Certificate	12	7.5	
Diploma	4	2.5	
Health status			
Body mass index (BMI)			0.241
Underweight	3	1.9	
Normal	45	28.0	
Overweight	63	39.1	
Obese	50	31.1	
Non-communicable diseases			
Diabetes mellitus	22	13.7	0.498
Hypertension	14	8.7	0.725
Hypercholesterolaemia	1	0.6	0.926
Heart diseases	1	0.6	0.926
Comorbidities			0.811
Single	28	17.2	
Double	5	3.1	
No comorbid	130	79.8	
Smoking status			0.009[a]
Smoker	89	55.3	
None smoker	72	44.7	
Alcoholic status			0.579
Drinker	2	1.2	
None drinker	159	98.8	

[a]Chi-square test.

Data Variables

The questionnaires encompass various categories of data, including demographic data (age, gender, ethnicity, marital status, level of education, healthcare facilities), co-morbidities (height, weight, tobacco use, drug use, hypertension status, diabetes status) and occupational demography (employment duration in MOH, employment years at unit, number of drivers at working unit, working hours, main driving assignment driver, work schedule, on-call status, satisfaction on work schedule, part-time job and had a part-time job).

During a minimum duration of 1 month amid the COVID-19 pandemic, the management allocated the principal responsibility, which entailed determining the primary driving assignment. This involved either performing duties as an ambulance operator or operating the management vehicle to facilitate the transportation of healthcare personnel or the delivery of parcels. The work schedule was established by considering the driver's availability during regular office hours (8 a.m. to 5 p.m.) as well as the three available shift hours (7 a.m. to 3 p.m., 3 p.m. to 11 p.m. and 11 p.m. to 7 a.m.).

Table III: Occupational characteristic of healthcare drivers (n=163)

Variables	n	Mean (SD)	p-value
Employment years at Ministry of Health	163	10.6 (7.4)	0.120
Employment years at Unit	163	8.0 (6.8)	0.168
Num. of driver at working unit	163	7.9 (7.8)	0.073
Working hours (hours/week)	163	54.7 (20.0)	0.313
Variables	**n**	**Percentage (%)**	
Main driving assignment			0.330
Ambulance driver	47	28.8	
Non-ambulance driver	116	71.2	
Work schedule			0.435
Office hour	135	82.8	
Shift hour	28	17.2	
On-call status			0.032[a]
Yes	83	50.9	
No	80	49.1	
Satisfaction on work schedule			0.373
Yes	157	96.3	
No	6	3.7	
Part-time job			0.464
Require	128	78.5	
Not require	35	21.5	
Had a part-time job			0.866
Yes	58	35.6	
No	105	64.4	
Motor vehicle accident (MVA)			
MVA with department vehicle			0.446
Yes	7	4.3	
No	156	95.7	
Num. of accidents last 6 months			0.446
None	156	95.7	
At least once	7	4.3	

[a]Fisher's exact test.

Table IV: Logistic Regressions of perceived stress risk factors among healthcare drivers during the COVID-19 pandemic

Variables	Simple logistic regression			Multiple logistic regression		
	cOR	95% CI	p	aOR	95% CI	p
Age	1.049	0.97–1.12	0.194	1.06	0.94–1.19	0.316
Marital status						
Single/widow/divorce	1425419.79	0.00–0.00	1.00	11177.57	0.00–0.00	0.998
Married			Reference			Reference
BMI	0.96	0.85–1.08	0.490	0.91	0.78–1.05	0.198
Smoking status						
Yes	9.76	1.23–77.51	0.030	19.99	1.86–213.90	0.013*
No			Reference			Reference
Comorbidities	0.77	0.16–3.71	0.749	0.71	0.10–4.52	0.712
Education level			0.447			0.665
High school cert	1.24	0.14–10.64	0.841	1.11	0.07–17.21	0.940
Diploma	4.56	0.43–48.00	0.206	8.40	0.08–851.18	0.366
Degree			Reference			Reference
Household income						
<MYR 2000	0.61	0.06–6.14	0.677	0.60	0.03–11.22	0.737
MYR 2000–3000	2.41	061–9.53	0.209	3.60	0.48–26.73	0.210
>MYR 3000			Reference			Reference
Driving assignment						
Ambulance driver	1.85	0.55–6.16	0.314	0.40	0.06–2.41	0.317
Non-ambulance driver			Reference			Reference
Employment at unit	1.07	1.00–1.16	0.044	1.09	0.98–1.21	0.110
Working hours	0.595	0.15–2.35	0.460	1.10	0.16–7.14	0.921
On-call status	5.342	1.13–25.20	0.034	8.69	1.21–62.28	0.031*
Schedule satisfaction						
Yes	0.377	0.04–3.51	0.391	1.63	0.01–148.54	0.831
No			Reference			Reference
Had a part-time job						
Yes	0.952	0.27–3.31	0.938	1.27	0.30–5.33	0.741
No			Reference			Reference

*Significant result.
COR = crude odds ratio.
[a]OR = adjusted odds ratio

Meanwhile, the designation of on-call status was established in response to the need for individuals in a shift-based work system to be available for post-office hours or double shifts. A motor vehicle accident was operationally defined as an incident involving a driver operating a healthcare vehicle who was involved in a collision while carrying out their professional responsibilities. The health status of the healthcare drivers was determined based on the yearly health assessment, either by the Occupational and Environmental Health Unit in district health offices or the Occupational Safety and Health Unit in hospitals.

Data Collection

The questionnaires were distributed and collected by the Occupational and Environmental Health Officer in each district and hospital. The chosen drivers were approached at work and given a study explanation as well as a participant information sheet. They were given a week to decide whether or not to participate in this study, and informed consent forms were given to them after they agreed to participate and were then provided with a series of questionnaires. They had 3 days to finish the questionnaires. The completed questionnaires were submitted to the Occupational and Environmental Health Officer in each district and hospital upon completion.

Data Analysis

The Statistical Package for the Social Sciences (SPSS) version 22 was used to analyse the data. The distribution of the data was not normal. Thus, the association between demographic characteristics, health status, occupational characteristics and stress status was determined using the Chi-square test, Fisher Exact test, Mann–Whitney test and Kruskal–Wallis test depending on the data variables. Moreover, the collected data underwent multiple logistic regression analysis in order to validate the significant risk factors associated with perceived stress among healthcare drivers in Negeri Sembilan during the first year of the COVID-19 pandemic.

Ethical Consideration

This study was registered in the National Medical Research Registry (NMRR-20-2187-56430 (IIR)). The study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (KKM/NIHSEC/ P20-2576 (4)), on 25 January 2021.

RESULTS

The total number of participants in this study was 163, resulting in a response rate of 95.8%. In general, non-ambulance drivers make up 71.2% (n = 116) of the healthcare drivers working for the Negeri Sembilan SHD, while ambulance drivers make up 28.8% (n = 47) of the workforce. At the end of the first year of the COVID-19 pandemic, 7.4% of healthcare drivers reported experiencing some degree of perceived stress. Moreover, from the findings presented in Table I, ambulance drivers at the Negeri Sembilan SHD had perceived higher levels of stress (10.6%) compared to non-ambulance drivers (6.0%).

As shown in Table II, the majority of respondents were aged 30–39 (49.7%), had a monthly household income of less than MYR 2,000 (46.6%), were Malay (95.7%), were married (90.1%) and had their highest education of a high school certificate (90.1%). In addition, 70% of healthcare drivers are overweight or obese; 55.2% are smokers and 98.8% do not consume alcohol. The majority of drivers in the SHD are in good health (79.8%), whereas 20.8% have at least one comorbid disease; 13.7% have diabetes, 8.7% have hypertension, 0.6% have hypercholesterolaemia and 0.6% have heart disease. A majority of them are smokers (55.3%), whilst only 1.2% consume alcohol. In addition, a correlation exists between household income (p = 0.044), smoking status (p = 0.009) and perceived stress. However, there is no significant relationship between other demo-graphic parameters (such as age, race, marital status and education level) and experienced stress, or between perceived stress and other health concerns (like BMI, diabetes mellitus, hypertension, hypercholesterolaemia, heart diseases, comorbidities and alcoholism).

More than 7 out of 10 healthcare drivers working with the Negeri Sembilan SHD are assigned as non-ambulance drivers or department transport service drivers. They have been working with the ministry of health on average for 10.6 ± 7.4 years, and the majority of them work during office hours (82.2%). On average, the healthcare drivers in the department have been with the ministry of health in the current hospital or district health office unit for 8 ± 6.8 years. On average, they worked around 52.6 ± 20 hours per week during the COVID-19 pandemic. More than half of them did work on an on-call basis (50.9%) after office hours and were satisfied with their working schedule (96.3%). Nevertheless, perceived stress among healthcare drivers was associated with on-call status (p = 0.032). Having said that, most of them still feel that they need a part-time job (78.5%) on top of their full-time job, but only 35.6% of them have a part-time job. On the category of motor vehicle accidents involving department vehicles, seven healthcare drivers had a history of motor vehicle accidents involving department vehicles during their employment, with 4.3% reported accidents during the COVID-19 pandemic. However, there is no association found between perceived stress and duration of employment, working hour duration, work schedule, having part-time job and motor vehicle accident.

A logistic regression analysis was conducted to examine the association between perceived stress and several variables among healthcare drivers during the COVID-19 pandemic. The result indicated that three variables were found to be statistically significant (p<0.05) predictors of perceived stress. These variables included smoking (OR 9.76, 95% CI 1.23–77.51), duration of employment at the current unit (OR 1.07, 95% CI 1.00–1.16) and on-call status (OR 5.34, 95% CI 1.13–25.20). Meanwhile, the multiple logistic regression revealed that healthcare drivers who are smokers had a significantly higher odds ratio of 19.99 (95% CI 1.86–213.90) compared to non-smokers. In addition, these individuals were found to have 8.69 times the odds (95% CI 1.21–62.28) of engaging in on-call duties compared to healthcare drivers not doing an on-call.

DISCUSSION

Drivers in the healthcare industry play an important role because their jobs include moving people's lives. Stress level of healthcare drivers or ambulance drivers is very dynamic depending on the stressors at the workplace. The level of stress among healthcare drivers at the SHD of Negeri Sembilan remained under control at the end of the first year of the COVID-19 pandemic, in contrast to the pool prevalence of stress among first responders including ambulance drivers for medical emergencies, which reported 17% stress prevalence during the first year of the COVID-19 pandemic.[31] Despite that, the level of perceived stress in almost similar prevalence with the study conducted by Nordin et al. on healthcare workers in northwest Malaysia, who reported a 6.4%[32] with almost a similar study timeframe. However, with regards to an Asia-Pacific study among healthcare workers in 2020, which involved India, Singapore, Malaysia, Vietnam and Indonesia, Malaysia was found to be the second highest (5.7%) after Indonesia, which was 6.8%.[33] However, the prevalence of stress would vary depending on the healthcare facilities and respondents, even though the studies were conducted in a nearly identical timeframe, such as a study in the Sarawak Hospital, Malaysia that recorded 57.1%[34] and a study in the primary health clinics of Selangor, Malaysia which reported it to be at 2.8%.[35] Based on this study, ambulance drivers experienced higher prevalence compared to non-ambulance drivers, which differ in job assignments.

Furthermore, this study also noted that low household income (less than MYR 2,000), performing on-call and smoking were associated with perceived stress among healthcare drivers. Household income of less than 2,000 Malaysian Ringgit (MYR) is the lowest of the four categories of household income below the B40 threshold in Malaysia.[36] However, further analysis using multiple logistic regression revealed no significant association between stress and household income. Nonetheless, employers should prioritise healthcare drivers when allocating resources like government-subsidized housing and child care in order to manage their salary competitiveness. Financial management education may be useful for this occupation category as well. The stress of being on call has been established by other studies,[37] but prospective healthcare drivers should still be reminded of their responsibilities. However, this may also be the result of working excessive hours without taking adequate breaks or poorly managing a roaster.[38] According to a study conducted in the USA, medium to high levels of inter-shift recovery were highest for shifts over 12 h in length (61.6%), lowest for shifts under 12 h in length (47.7%) and highest for shifts of 12 h (40.2%).[39] Nevertheless, the Occupational Safety and Health (OSH) team must conduct locality assessments of workers to determine safe maximum workweeks and break times, as varying working conditions may have a cumulative effect on employee productivity.[40]

Drivers in the healthcare industry play a crucial role, so it is imperative that they are in good physical and mental health. Based on this study, more than half of the healthcare workers in the Negeri Sembilan SHD are smokers. This puts them at risk for cardiovascular diseases and cancers such as hypertension, heart disease, peripheral arterial disease and lung cancer, despite the fact that the vast majority of them (8 out of 10) are healthy and have no other health issues. Contrarily, a study of Swedish ambulance workers revealed that they had a higher prevalence of heart problems (paroxysmal tachycardia, atrial fibrillation, flutter, and other cardiac arrhythmias), high blood pressure and dorsopathies than individuals in other occupations.[41] As cardiovascular diseases can result in motor vehicle accidents,[42] a yearly physical examination and fitness certificate must include a heart evaluation, such as an electrocardiogram (ECG). Furthermore, continuous awareness and participation in interventional activities at the workplace need to be emphasised by the Occupational Safety and Health team.

Additionally, this study did not find significant associations between stress among ambulance drivers and other factors such as gender, age, household income, type of shift work, risk of getting COVID-19 infection, adequacy of personal protective equipment, history of accidents within 1 year and pressure from family members and patients compared to the other studies.[43,44] According to the study conducted by Amro et al. found that younger female drivers displayed higher levels of stress compared to both male and older ambulance drivers.[43] In contract to gender, the observation that driving is predominantly associated with males in Malaysia is expected, as there is a notable lack of female applicants for such positions. In contrast to the present study, Pinnalin et al. conducted a study that revealed supplementary variables linked to stress levels among ambulance drivers amidst the COVID-19 pandemic. These variables encompassed monthly household income, the nature of shift work, the ambulance driver's accident record within the previous year, as well as the influence exerted by family members and patients.[44]

Despite the fact that the perceived stress levels of healthcare drivers appear to be under control, the OSH team must continue to exert effort to maintain the situation. Because stress management training continuously increases drivers' awareness, train them to control, reduce and tolerate the internal and external demands of a certain situation in which their individual resources are exceeded. Even though, according to a study conducted in Switzerland, paramedics require less psychological support than other professions due to their high level of experience and long-standing training in stress management over the course of their careers, they are often used to address stressful situations as they are part of a coordinated and ordered emergency response and have to constantly handle very high levels of stress. According to research by Lawn et al., the needs of ambulance workers in terms of mental health can be classified into four main categories: organisational support, informal support, the use of humour and individual ways of coping, such as detachment and external support.[18] In a general way, stopping unpleasant emotions and thoughts is the most effective coping strategy for the reduction of stress levels and an increase in positive mental states.

A limitation of this study is that it was unable to identify the factors associated with each driver, as the sample size may not have been adequate given that the study was conducted in a single stratum and addressed the study objective, as the stress associated with ambulance drivers may differ from that

of other drivers. In addition, this is a cross-sectional study that only reflects the assessment conducted during the study. Following up from this study, the OSH team could initiate another research on the adaptability of healthcare drivers in Malaysia to varying working hours in terms of environmental adaptation, which would help policymakers, set the working hours limit for healthcare drivers, especially in relation to adequate breaks for on-call drivers. In addition, an interventional study based on the healthcare driver's behaviour therapy could enhance the overall performance of drivers in terms of occupational safety and health as it increases the driver's insight.

CONCLUSION

The study found that perceived stress among Malaysian healthcare drivers during the OVID-19 pandemic was relatively low. The implementation of movement control orders during the COVID-19 pandemic in Malaysia resulted in a reduction in the frequency of life-threatening tasks, emergencies and assigned tasks. The consistent provision of safety and health training by the OSH team, which includes stress management and a smoking cessation programme, potentially contributed to the healthcare driver's ability to manage the stressful situation. In order to enhance salary competitiveness, employers ought to offer financial management education alongside subsidised housing and childcare provisions.

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DECLARATION OF INTEREST

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Three-year epidemiology of hospitalised paediatric burn patients in a Malaysian Tertiary Hospital 2016 – 2018

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ABSTRACT

Introduction: Burn injuries incur not just significant morbidity but also long-term psychosocial impact. This study aims to identify the clinico-demographics of children hospitalised for burns and factors associated with prolonged hospitalisation.

Materials and Methods: Written medical records of burn patients admitted to the Sultanah Aminah Hospital paediatric surgical ward, from January 2016 to December 2018, were retrospectively reviewed. Details on the patients' socio-demographic background, burn injuries, management and outcomes were recorded and analysed with logistic regression.

Results and Conclusion: Of the 255 children included in the study, the majority were males (62.7%), children aged between 1 to 3 years (43.1%), and of the Malay ethnic group (83.1%). The commonest injury mechanism was scalds burns (81.2%). Staphylococcus aureus remained the commonest organism cultured from paediatric burn wounds. Most patients (66.4%) were hospitalised for less than 1 week. A significant number of patients experienced complications from their injuries. Multivariate analysis showed burns affecting total body surface area > 10% (adjusted OR, 13.45 [95% CI 6.25 - 28.96]; p = < 0.001) and non-scald burns (adjusted OR, 2.70 [95% CI 1.12 - 6.50]; p = 0.027) were the two main factors associated with prolonged hospitalisation of more than 1 week. These findings describing the epidemiology and outcomes of paediatric burn cases in a tertiary centre in Malaysia may inform future practice. More importantly, the information may contribute to the identification of at-risk populations and advise the development of effective prevention strategies to reduce the incidence and morbidity associated with paediatric burns in this region.

KEYWORDS:
Epidemiology, paediatric, burns, Malaysia, prevention

INTRODUCTION

Burns are a significant cause of mortality and morbidity for patients and incur high economic burden on healthcare systems.[1] Burn injuries in the paediatric population are potentially more severe compared to adults as children have several physiological disadvantages, such as thinner layers of skin, less subcutaneous tissue and a larger surface area to volume ratio, which gives rise to increased risk of rapid percentage of fluid loss.[2] It is clear that paediatric burns are largely preventable injuries, as various primary prevention campaigns have been effective in reducing the incidence of burn-related hospitalisation.[3,4] However, the ability to formulate an effective campaign requires the availability of epidemiological data on the various socio-demographic and clinical factors surrounding paediatric burns.

Through our literature search, only three small studies produced epidemiological data on paediatric burn patients in the Malaysian setting. Two out of the three papers included both adults and children, with the most recent study on paediatric burns being published almost 20 years ago in 2002.[5-7] In addition, the total combined number of patients (adults and children) from the three studies only amounted to 379 patients. More recent data is available in the form of a poster presentation, which provided some descriptive statistics on 94 paediatric patients who were admitted into the Malacca Hospital from January 2016 to December 2018.[8] It is clear that epidemiological data with larger sample sizes are needed to inform burns prevention strategies.

This study aims to collect the epidemiological data on the clinic-demographic factors of hospitalised paediatric burn patients from the main tertiary burns referral centre in the Southern part of Peninsula Malaysia in order to identify the parameters associated with the patients. In addition, we aim to determine factors associated with poorer outcomes by using prolonged hospitalisation, defined as hospital stay greater than 7 days, as the measurement tool.

MATERIALS AND METHODS

This is a retrospective observational study. Ethical approval has been obtained from the Medical Research Ethics Committee (MREC) of the Malaysian Ministry of Health (Approval no: NMRR-19-1111-48223) as well as the Monash University Human Research Ethics Committee (MUHREC). All children less than 12 years of age who were admitted to Hospital Sultanah Aminah Johor Bahru for burn injuries from January 2016 to December 2018 were included in this study. This study excluded burn patients treated in the emergency department, outpatient setting and patients with missing medical records. Details on the patients' socio-demographic background, management measures and

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outcomes of each individual burn case, such as demographic factors (age, sex, ethnicity), circumstances surrounding the injury (mechanism of burns, location of burns, provision of first aid), clinical presentation (extent of burns) and outcomes (length of hospitalisation, need for surgical debridement, need for blood product transfusion, need for ICU admission, wound culture results and mortality) were recorded in the case report forms (CRF).

Sultanah Aminah Hospital is the largest referral hospital in the State of Johor and the main paediatric burn referral centre for patients in the Southern region of Peninsula Malaysia. All the patients under 12 years of were managed by paediatric surgeons in the general paediatric surgical unit. Although patients were not routinely screened for methicillin resistant staphylococcus aureus (MRSA) or extended – spectrum beta lactamase (ESBL) organisms, those with known MRSA or ESBL organisms were placed under contact precautions. Burn patients generally receive management in terms of analgesia, dressings and/or fluid resuscitation. The total burn surface area (TBSA) was estimated using the Lund and Browder chart. Patients with TBSA > 10% are automatically given fluid resuscitation using Parkland formula with Hartmann's solution with a goal to maintain end organ perfusion. Adequacy of perfusion and fluid resuscitation was monitored via urine output, mean arterial pressure and occasionally blood gas measurements. Common dressings regimes used at the study centre included the following: silver sulfadiazine, carboxymethylcellulose (CMC), Bactigras™, Jelonet™ or Intrasite™.

Wound swabs, blood cultures, blood products administration and antibiotics administration were not routinely performed unless deemed clinically indicated by the treating consultant paediatric surgeon. Wound swabs were performed in circumstances where the burn wounds demonstrated signs of infection, such as pus or persistent slough. Blood cultures were generally done in patients who developed signs of sepsis. The local practice was for antibiotics to be prescribed in suspected burn wound infections, evidenced by occurrence of fever 3 days after the date of injury. The first-line antibiotic is intravenous cloxacillin, with intravenous ceftazidime and/or amikacin as second-line therapies. In addition, blood transfusions were considered in patients with haemoglobin levels less than 8 g/dL, undergoing debridement procedures or were septic. Patients with burns affecting joint areas, hands or face, severe extensive burns with TBSA > 10% and second- or third-degree burns were referred to the plastic surgery unit for review and consideration of split skin grafting. Patients with extensive burns with TBSA > 10% were also referred for dietetics input for high protein formula and inpatient dietary modifications.

Data was analysed using SPSS® Statistics 26 (IBM Corporation, Armonk, NY). Descriptive statistics were used to present the clinico-demographics of patients. Univariate analyses were carried out to identify possible associations between factors and eventual outcome of burn patients. Binary logistic regression was performed on the factors which produced a significant result to assess the impact of those individual factors on the dependent variable (prolonged hospitalisation defined as stay greater than seven days). Statistical significance was attained when $p < 0.05$.

RESULTS

Patients' Description

All of the patients in this study were aged 12 and below. Records from the Burns Registry on the paediatrics surgical ward showed that a total of 327 patients were admitted between 2016 to 2018. Despite limitations of a paper-based record, 80% of the patient records (255 out of 327 patients) were included while others were excluded due to missing data. Descriptive statistics were derived from the 255 patient records that we have identified, after removing the second and third admissions for those with numerous admissions. From the 255 patients, a further five patients were discharged against medical advice and 14 patients who were transferred in/out to/from other hospitals. After excluding these patients, a total of 236 patients were included in the association analysis to identify factors associated with prolonged hospitalisation to enhance the accuracy of results.

Descriptive Statistics: Clinico-demographic Factors

Data from a total of 255 patients were analysed. Table I shows the statistics for the clinic-demographic factors of the patients.

Gender, Ethnicity, Age Group and Past Medical Conditions

The majority of burn victims were males (n = 160, 62.7%). The breakdown of burn victims by ethnicity are as follows: Malay (n = 212, 83.1%), Chinese (n = 21, 8.2%), Indian (n = 14, 5.5%), others (n = 8, 3.1%). Burn victims were categorised into four different age groups: Infants < 1 years old (n = 62, 24.3%); toddlers aged 1 to 2.99 years (n = 110, 43.1%); pre-schooler aged 3 to 6.99 years (n = 47, 18.4%) and school going aged 7 to 12 years (n = 36, 14.1%). Only 12 patients were noted to have pre-existing medical condition(s), which included Tetralogy of Fallot (n = 1), epilepsy (n = 1), G6PD (n = 2), bronchial asthma (n = 3), unspecified congenital heart disease (n = 1), neonatal jaundice (n = 1), drug allergies (n = 3).

Mechanism of Burns, Location of Burns and Extent of Burns

Scalds were the commonest cause of injury (n = 207, 81.5%) followed by direct flame (n = 27, 10.6%) and contact burns (n = 12, 4.7%). The most common description leading to the scalding episodes describes the behaviour of the child reaching out and pulling onto various objects, such as kettle wires, tablecloths or containers with scald agents. Direct flame burns usually occurred as a result of accidental child contact with burning rubbish or child's play with lighter and/or petrol. Most of the burns occurred indoors (n = 199, 86.9%), while the rest of the burns occurred outdoors. The extent of burns sustained were divided based on their TBSA into the following groups: TBSA 0 to 10% (n = 189, 75.3%); TBSA 10 to 20% (n = 57, 22.7%) and TBSA > 20% (n = 5, 2%). The highest TBSA sustained in a child was 36%.

Patterns of Burns Mechanism in Age Groups

This is highlighted in Figure 1. In the infant group, scald burns represented 95.2% (n = 59) of burn injuries and contact burns represented 4.8% of burn injuries (n = 3). The percentage of scald burns remained at 92.7% in the toddler age group (n = 101), with direct flame burns at 2.8% (n = 3), contact burns are 2.8% (n = 3) and other burns at 1.7% (n = 2). In the pre-school age group, scald burns decreased to

68.1% (n = 32), direct flame burns increased to 25.6% (n = 12), contact burns at 4.2% (n = 2) and other burns at 2.1% (n = 1). In the school age children, scald burns decreased to 41.7% (n = 15), direct flame burns increased to 33.3% (n = 12), contact burns represented 11.1% (n = 4) and other burns represented 13.9% (n = 5).

Provision of First Aid

Half of the patients who sustained burn injuries did not receive any first aid (n = 114, 50.4%). Only one-third of the patients had their injuries under running tap water for a variable duration of time (n = 76, 33.6%). Alternative agents used by caregivers included toothpaste, aloe vera, traditional oil, ointments, soy sauce and cream. One caregiver even placed flour onto the child's wound, while another used egg white as first aid.

Descriptive Statistics: Outcomes

Table II shows the statistics for the various outcomes in our study population.

Duration of hospitalisation

This data was synthesised from a total of 236 patients. The median length of hospitalisation was 4 days (IQR = 8 days). Using 7 days as a cut-off point, one-third of the patients experienced prolonged hospitalisation (n = 80, 33.6%).

Wound cultures

Out of the 255 patients, wound cultures were done on 48 patients. Out of the 48 wound swabs, 24 were positive for organisms. There were nine patients who had multiple organisms cultured from their wounds. A total of four patients cultured drug-resistant organisms (three cases of MRSA, one case of ESBL Escherichia coli) The most common organism cultured was *Staphylococcus aureus* (n = 17). Other organisms include: *Enterococcus sp* (n = 6), *Pseudomonas sp* (n = 3), *Streptococcus sp* (n = 2), E coli (n = 1), *Acinetobacter baumannii* (n = 1), *Enterobacter sp* (n = 1).

Blood culture

Blood cultures were done on 38 patients, of which only four patients had positive results. Two of the patients who were admitted to ICU had consistent organisms cultured from both their blood and wound samples. The first patient sustained TBSA of 36% and had MRSA cultured; whereas the second patient sustained TBSA of 18% and had methicillin-sensitive *Staphylococcus aureus* (MSSA) cultured. The other two patients had the following organisms in the blood culture: *Elizabethkingia meningoseptica* in one patient and combination of *Micrococcus sp.* and *Enterococcus sp.* in the other patient. All the four patients sustained burn injuries from the scalding mechanism.

Wound debridement and blood product transfusions

Approximately one-fifth of the patients required surgical wound debridement (n = 45, 17.6%) whereas only a small portion of the patients required blood product transfusion (n = 19, 7.5%).

ICU admissions and mortality

A total of eight (3.1%) patients required ICU admission for the following reasons: four due to extensive TBSA > 15%, two due to bacteraemia; one due to corneal abrasion; one due to shock requiring central venous line insertion and albumin infusion. The patient who sustained a TBSA of 36% and MRSA bacteraemia was the only patient who required intubation in our study and was intubated for a total period of 18 days. There were no mortalities recorded among the subjects within the study period.

Factors Associated with Prolonged Hospitalisation

The main parameter utilised as the indicator of poor outcome in this study is prolonged hospitalisation. A Chi-squared test for independence (with Yates' Continuity Correction) indicated that the paediatric burn patients with TBSA > 10% are 12.4 times more likely to experience prolonged hospitalisation (OR, 12.46 [95% CI 5.96 - 26.05]; p = <0.001). In addition, children aged more than 3 years (pre-schooler and school going age children) are 2.4 times more likely to experience prolonged hospitalisation compared to infants and toddlers (OR, 2.37 [95% CI 1.34 - 4.19]; p = 0.004). Patients with non-scald burns are also associated with 2.4 times increase in odds of experiencing prolonged hospitalisation compared to scald burns (OR, 2.46 [95% CI 1.24 - 4.89]; p = 0.015).

Given that scalding was the most common mechanism of injury, our team performed further analysis if there were any significant differences in outcomes from scalding from different types of liquid. The scalding mechanism was divided into two categories: plain water scalds and scalds from other liquids (curry, oil, etc). There was no significant association between type of scald fluids and prolonged hospitalisation (OR, 1.00 [95% CI 0.53 - 1.90]; p = 1.000). Other factors such as gender and ethnicity were also not significantly associated with increase in risk of prolonged hospitalisation.

Direct logistics regression was performed to assess the impact of the individual factors on the likelihood that paediatric burn patients would experience prolonged hospitalisation. The model contained three independent variables (age greater than 3, TBSA > 10% and non-scald burns). The full model containing all predictors was statistically significant (p <0.001), indicating that the model was able to distinguish between those who experience prolonged hospitalisation versus those who did not experience prolonged hospitalisation. The model as a whole explained between 24.9% (Cox and Snell R square) and 34.5% (Nagelkerke R squared) of variance in hospitalisation duration, and correctly classified 78.8% of cases. Only two of the three independent variables made a unique statistically significant contribution to the model (TBSA > 10%, non-scald burns). The strongest predictor of prolonged hospitalisation was TBSA > 10% where patients were 13 times more likely to experience prolonged hospitalization than those with TBSA 10% or less, controlling for all other factors in the model (Adjusted OR 13.45 [95% CI 6.25 - 28.96]; p = < 0.001). Patients with TBSA > 10% are associated with higher percentage of antibiotics use (67.7% vs 20.6%), positive wound cultures (58.3% vs 41.7%), bacteraemia (13% vs 6.7%), blood product transfusions (25.8% vs 1.6%), wound debridement (38.7% vs 10.6%) and ICU admission (12.9% vs 0%) compared to patients with TBSA 10% or less, as outlined in Supplementary Table I. Patients who sustained non-scald

Table I: Patient characteristics

Clinico-demographic factors		n (%)
Sex	Male	160 (62.7%)
	Female	95 (37.3%)
Ethnicity	Malay	212 (83.1%)
	Chinese	21 (8.2%)
	Indian	14 (5.5%)
	Others	8 (3.1%)
Age group	Infants (< 1 years old)	62 (24.3%)
	Toddlers (1–2.99 years old)	110 (43.1%)
	Pre-schooler (3–6.99 years old)	47 (18.4%)
	School going (7–12 years old)	36 (14.1%)
Mechanism of burns	Scald	207 (81.5%)
	Direct flames	27 (10.6%)
	Contact	12 (4.7%)
	Others	8 (3.2%)
	Missing data	1
Type of scald fluids	Plain water	133 (64.3%)
	Others	74 (35.2%)
Location of burns	Indoors	199 (86.9%)
	Outdoors	30 (13.1%)
	Missing data	26
Extent of burns (TBSA)	0 – 10%	189 (75.3%)
	10.1 – 20%	57 (22.7%)
	> 20%	5 (2%)
	Missing data	4
Provision of first aid	Not given	114 (50.4%)
	Running water	76 (33.6%)
	Toothpaste	15 (6.6%)
	Aloe vera	3 (1.3%)
	Others	18 (7.9%)
	Missing data	29

Table II: Outcomes of paediatric burn patients between 2016 – 2018

Outcomes		n (%)
Duration of hospitalisation	Prolonged (> 7 days)	80 (33.6%)
	Not prolonged (≤ 7 days)	156 (66.4%)
Provision of antibiotics	Yes	82 (32.2%)
	No	173 (67.8%)
Results of wound culture	No growth	24 (9.4%)
	Positive	24 (9.4%)
	Not done	207 (81.2%)
Results of blood culture	No growth	34 (13.3%)
	Positive	4 (1.6%)
	Not done	217 (85.1%)
Need for wound debridement	Yes	45 (17.6%)
	No	210 (82.4%)
Need for blood products	Yes	19 (7.5%)
	No	236 (92.5%)
Need for ICU admission	Yes	8 (3.1%)
	No	247 (96.9%)
Mortality	Alive	255 (100%)
	Deceased	0 (0%)

burns were 2.7 times more likely to experience prolonged hospitalisation compared to scald burns (adjusted OR, 2.70 [95% CI 1.12 - 6.50]; $p = 0.027$).

DISCUSSION

There remains a lack of universal definition on the age cut-off point for being considered a child. The cut-off points range between 9 to 20 years of age. Our study provides data for patients aged 12 years and below as this was the criteria for paediatrics surgical ward admission for our centre. This cut-off point is consistent with studies previously performed in the Southeast Asian region.[9-11]

Male children accounted for roughly two-thirds of the overall admission, which can be attributed to their risk-taking behaviour.[2] It is not surprising that Malay children accounted for the majority of admissions, as Malays are the ethnic majority in the catchment area. The categorisation of children into various age groups was based on the child's level of education, which age ranges consistent with classification from previous studies to allow ease of data

Table III: Factors associated with prolonged length of hospitalisation

Variables	n (%)	Prolonged hospitalisation > 7 days		Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
		Yes	No				
Gender (N = 236)							
Males	146 (62.9%)	51 (34.9%)	95 (65.1%)	1.13 (0.65 – 1.97)	0.775		
Females	90 (38.1%)	29 (32.2%)	61 (67.8%)	Ref	-		
Ethnicity (N = 236)							
Malay	198 (83.9%)	68 (34.3%)	130 (65.7%)	1.13 (0.54 – 2.39)	0.887		
Non-Malay	38 (16.1%)	12 (31.6%)	26 (68.4%)	Ref	-		
Age (N = 236)							
> 3	76 (32.2%)	36 (47.4%)	40 (52.6%)	2.37 (1.34 – 4.19)	0.004	1.63 (0.79 – 3.40)	0.189
≤ 3	160 (67.8%)	44 (27.5%)	116 (72.5%)	Ref	-		
Burns mechanism (N = 235)							
Non - scalds	41 (17.4%)	21 (51.2%)	20 (48.8%)	2.462 (1.24 – 4.89)	0.015	2.70 (1.12 – 6.50)	0.027
Scalds	194 (82.6%)	58 (29.9%)	136 (70.1%)	Ref	-		
Scald injuries (N = 193)							
Plain water	123 (63.7%)	37 (30.1%)	86 (69.9%)	1.00 (0.53 – 1.90)	1.000		
Non-plain water	70 (36.3%)	21 (30.0%)	49 (70.0%)	Ref	-		
Delayed presentation (N = 156)							
> 2 hours	52 (33.3%)	16 (30.8%)	36 (69.2%)	0.77 (0.38 – 1.57)	0.592		
< 2 hours	104 (66.7%)	38 (36.5%)	66 (63.5%)	Ref	-		
TBSA (N = 232)							
> 10%	52 (22.4%)	40 (76.9%)	12 (23.1%)	12.5 (5.96 – 26 .05)	< 0.001	13.45 (6.25 – 28.96)	<0.001
10% or less	180 (77.6%)	38 (21.1%)	142 (78.9%)	Ref	-		

*p values presented are extracted from the Yates Continuity Correction as it is a 2 x 2 table

Supplementary Table I: Extent of burns (TBSA) vs outcomes

Outcomes	TBSA 10% or less, n (%)	TBSA > 10%, n (%)
Provision of antibiotics		
Yes	39 (20.6%)	42 (67.7%)
No	150 (79.4%)	20 (32.3%)
Wound culture		
Not done	165 (87.3%)	38 (61.3%)
Done	24 (12.7%)	24 (38.7%)
Positive	10 (41.7%)	14 (58.3%)
No growth	14 (58.3%)	10 (41.7%)
Blood culture		
Not done	174 (92.1%)	39 (62.9%)
Done	15 (7.9%)	23 (37.1%)
Positive	1 (6.7%)	3 (13.0%)
No growth	14 (93.3%)	20 (87.0%)
Blood transfusion		
Yes	3 (1.6%)	16 (25.8%)
No	186 (98.4%)	46 (74.2%)
Wound debridement		
Yes	20 (10.6%)	24 (38.7%)
No	169 (89.4%)	38 (61.3%)
ICU admission		
Yes	-	8 (12.9%)
No	189 (100%)	54 (87.1%)

*N = 251

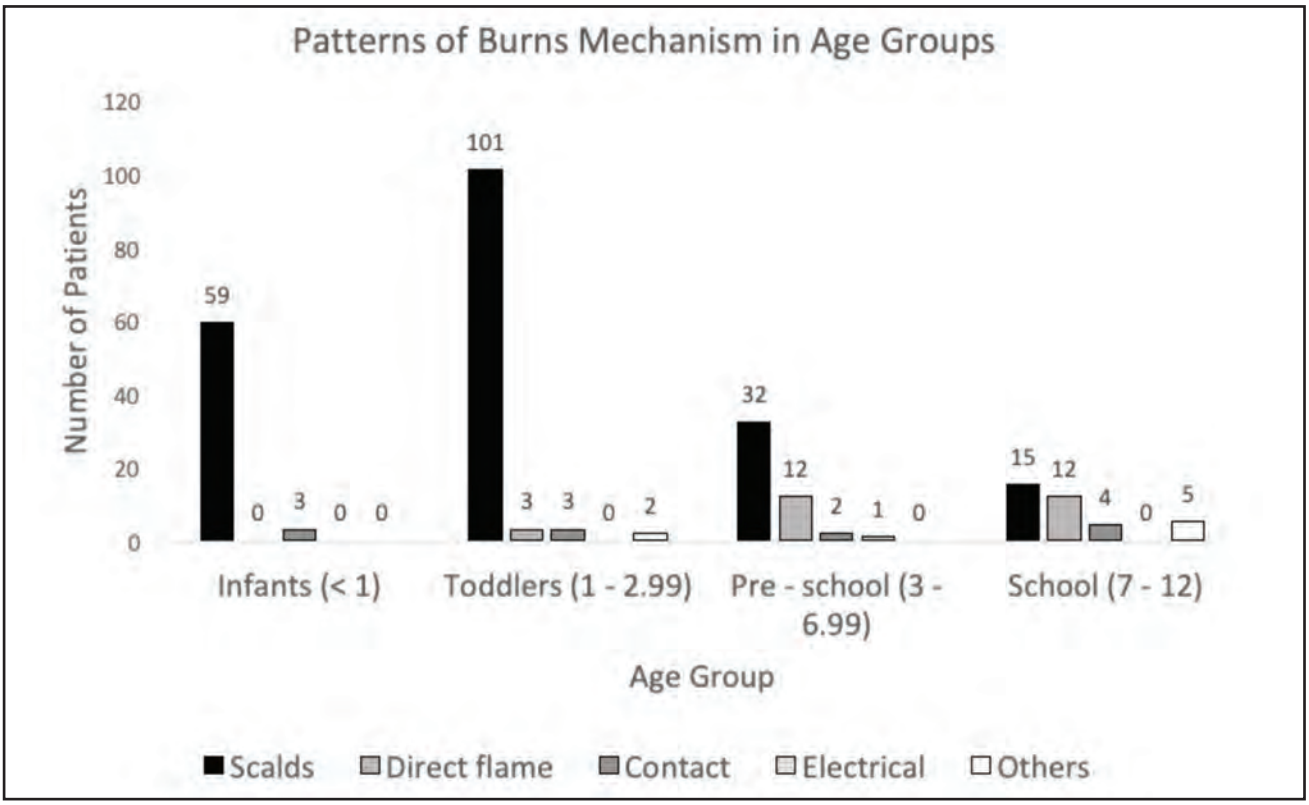

Fig. 1: Patterns of burns mechanism in age groups.

comparison.[7,11-13] Our study found that toddlers (aged 1–2.99 years) were the most vulnerable age group as they represented the highest number of admissions.

Various data uncovered in this study would be crucial in the development of an effective burn prevention campaign. Our data confirms that scalding remains the main mechanism of burns injury among young children, with most injuries occurring at home.[2,14] This is related to the normal developmental stages of the children, as most of them start to reach for objects and crawl by the age of 6 months followed by becoming fully mobile by the age of 18 months.[15] This tendency for young children to reach out and pull onto objects that cause scalding episodes are crucial intervention points for injury prevention by caregivers. It is also interesting to note that children become more prone to direct flame burns as they approach the school age group. This trend was observed in other studies worldwide and was attributed to fires from children's play.[15,16] Drawing upon paediatric burn prevention measures employed worldwide, examples of prevention strategies to reduce scald and flame burns that are relevant to the local population include short radio messages on burns prevention, raising height of cooking surfaces, safe storage of flammable substances, guarding of open fires and home visits with counselling on home hazards.[17] The introduction of "Child Safe Home" concept with online information disseminated in the local language may be considered.

It is also evident that there is a lack of awareness on the appropriate provision of first aid for burns as only one-third of the children had their wounds under running water post-injury. It is unclear if other alternatives, such as toothpaste, soy sauce and egg white, placed on the wound may potentially aggravate or contaminate the wound further leading to poorer outcomes. However, numerous studies below have proven the effectiveness of immediate running water lavage for burn injuries. Large scale data from the New South Wales Agency for Clinical Innovation State-wide Burn Injury Service showed initial treatment with running water up to 20 minutes was associated with reduction in burn wound depth, wound healing time and graft area requirements.[18] The seven-year study in Taiwan on over 12,000 patients demonstrated proper first aid resulted in a reduction in length of stay for burns with TBSA less than 30%.[19] A small study in Nigeria observed that burn patients who received water lavage as first aid had a 50% reduction in the development of complications compared to those who did not received it (35.3% vs 18.4%).[20] Overall, this highlights the utmost importance of emphasising adequate first aid with at least 20 minutes of running water in any burns prevention campaign. Additional first aid strategies include immediate removal of child from burn source and prevention of hypothermia by wrapping unaffected areas of child in clean dry blankets prior to arrival of the emergency medical services team.[21]

The majority of the paediatric patients (75.3%) who were admitted had TBSA < 10%. This was consistent with various local and international data.[7,11,12,22,23] Comparing our data with the data presented in 1995 by Ibrahim et al based on a tertiary burn referral in the capital city of Kuala Lumpur,

Malaysia, we found that there is a significant reduction in proportion of patients requiring hospitalisation greater than 7days (33.6% in our study vs 49% in Ibrahim et al's study). This improvement in outcome is thought to be attributed to recent advancements in management of paediatric burns and improvements in healthcare infrastructure throughout the years.[24]

Our study also provided some preliminary data on the local bacteriological profile of burn wounds in children. *S. aureus* remains the predominant organism cultured from wounds of our study patients, which was consistent with data from the study by Ibrahim et. al.[7] This is in contrast to studies in Turkey and Iran, where coagulase-negative Staphylococcus sp. was shown to be the main organism.[23,25] In a study conducted in India, Acinetobacter baumannii was presented as the main organism cultured from paediatric burn wounds.[26] This variability in reported organisms suggests that bacteriological profiles of pathogens vary between region to region. The trend in adult burn patients is more predictable, with *S. aureus* and Pseudomonas aeruginosa being the two most common pathogens isolated from overall burn wound samples; whereas Acinetobacter baumannii, MRSA and Pseudomonas aeruginosa were the common organisms cultured from wounds of severe burn victims.[27] 31 It is unclear if this bacteriological trend is similar in paediatric burns. Hence, the data provided by our study may suggest S. aureus as the most common organism implicated in local paediatric burn wound infections. However, this remains to be proven in future studies given that only 48 patients in our study had wound swabs sent for cultures and the possibility of *S. aureus* being a contaminant rather than an infective organism as it is a common skin commensal.

Generally, the mortality rates in paediatric burn patients are rather low worldwide. In Malaysia, Ibrahim et al recorded 1% mortality rate in 1995, whereas a 3-year study conducted between 2016 to 2018 at the Malacca Hospital did not record any deaths.[7,8] Data from Singapore suggested mortality rates of 0.28 to 0.4%, and studies in China and Saudi Arabia provided rates of 0.24% and 0.76% respectively.[10,11,13,16] In a study, which analysed 57 years of paediatric burns data from a single centre in South Australia, it was found that all the children with TBSA < 40% survived, whereas those with TBSA > 40% had a mortality rate of 34%.[32] It is worth noting that studies which included older children up to 18 years of age recorded a higher mortality rate.[26] This could be due to older children having higher risk of sustaining severe burns, especially from flame injuries, where flame injuries were observed to be significant predictors of mortality in numerous studies.[33,34] We were unable to provide the accurate mortality rate for paediatric burns at our centre as none of our patients died during the course of this study.

TBSA > 10% and non-scald burns are the two strongest predictors for prolonged hospitalisation based on data from our study. This corresponds to data presented in known literature on the influence of these two factors on other measures of poor outcomes, such as increased risk of infections and mortality.[26,33-37] This information would be useful in guiding clinicians to triage paediatric burn patients' presentations, provide rapid care and close monitoring for those with TBSA > 10% and non-scald burns. Burn depth is also important in the initial assessment process given that deeper wounds carry higher risk of complications and may require surgical intervention. However, there remains inaccuracies in burn depth approximation even in large experienced burn centres.[21] Hence, it may be more practical for centres to adopt TBSA measurements in favour of burn depth evaluation to guide initial triaging protocols and resuscitative efforts with fluid therapy.

Due to the retrospective nature of our study, there were some limitations such as an inadequate account of additional sociodemographic variables (e. g., family size and income group), clinical data such as burn depth and long-term complications such as scarring and psychological trauma. As this study was based on hospitalised children, the findings may be less applicable to children with milder burns injuries treated in an outpatient setting. This study was conducted on subject prior to COVID-19 pandemic when there were likely changes to the demographics and management approaches adopted by healthcare systems.[38,39] Nevertheless, as we emerged from the COVID-19 pandemic, the study findings are likely relevant to the current post-pandemic population.

CONCLUSIONS

The findings mentioned above provide a recent update on the epidemiology and outcomes of paediatric burn cases based on a single tertiary centre in Malaysia in the pre-COVID-19 era. Data collected on the demography of paediatric burns patients would contribute to the identification of at-risk populations, development of effective prevention strategies and inform clinical practice and research in the future.

AUTHOR CONTRIBUTIONS

C.X.L, R.Z.M.L, S.Y.Q and C.F.N performed the relevant literature search, conceived and designed this retrospective study. Y.Q.K, X.S.L and C.X.L organised rigorous data collection and critical data analysis. C.X.L, Y.Q.K and X.S.L performed the manuscript writing. R.Z.M.L, S.Y.Q, and C.F.N provided conceptualisation, technical support, and proofreading. All authors have read and agreed to all the information and conclusions in the submitted version of the manuscript.

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DECLARATION OF INTERESTS

The authors declare that there is no conflict of interest.

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Current management of appendicular mas - a narrative review

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ABSTRACT

Appendicular mass is considered as one of the complications of acute appendicitis but there is no consensus on the optimal management of this condition. The management of this condition has always been conservative management with interval appendectomy as popularized by Oschner and Sheerin. The need for interval appendectomy has now been questioned, and an emerging trend has been early appendectomy by laparoscopic method. There are no guidelines on the management of appendicular mass and treatment is decided by the surgeon. We have conducted a narrative review to investigate what is the current practice in the management of appendicular mass.

KEYWORDS:
Appendicular mass, appendicular phlegmon, appendicular lump, interval appendectomy

INTRODUCTION

Acute appendicitis is one of the most common acute abdominal conditions that is seen in surgical practice and appendicular mass accounts for up to 10% of cases. The pathological spectrum can range from Phlegmon to abscess formation. The appendicular mass is composed of the inflamed appendix, omentum and bowel loops, and it forms after about 24 to 48 hours after the initial symptoms. This is a protective mechanism to prevent the spread of infection. The treatment of appendicular mass has been debated over the past 80 years. The diagnosis of appendicular mass is made clinically, but ultrasonography is the most popular investigation of choice, although computerized tomography (CT), is more sensitive. The presentation is more acute in children, whereas in the adults the mass tends to take longer to form.[1]

The management of appendicular mass can be divided into three treatment approaches 1) Conservative management with broad spectrum antibiotics and intravenous fluids followed by interval appendectomy in 6 - 8 weeks. This was proposed by Oschner and Sheeren in 1901 and is the most popular treatment option for appendicular mass and is widely practiced worldwide. 2) Conservative management without interval appendectomy, as this option is proposed due to low infection rates and low recurrence rates and hence there is no need for interval appendectomy. For patients above the age of 40, follow up treatment with investigations like colonoscopy and computerized tomography (CT) is required. 3) Immediate appendectomy which is emerging as an alternative treatment option, and this option eliminates the risk of recurrence and the need for interval appendectomy. The operative options are open appendectomy and laparoscopic appendectomy. Open appendectomy was the treatment of choice, but laparoscopic appendectomy is emerging as an alternative treatment option due to decreased post operative pain, early recovery, and earlier discharge to home. Currently conservative treatment of appendicular mass is the most favored by most surgeons. However, the pressing question is the need for interval appendectomy after conservative treatment, as there is a growing trend to opt against interval appendectomy. The argument for this is the low rate of recurrent infection and the early return to work.[2,3]

MATERIALS AND METHODS

Currently there is no uniform consensus on the management of appendicular mass, and we have conducted this review article to investigate the various management options. We conducted a literature review using PUBMED, Cochrane database of clinical reviews and Google scholar looking for clinical trial, observational studies, cohort studies systemic reviews, and meta-analysis from 1990 to 2022.We used the following keywords, “Appendicular Mass”, “Appendicular Phlegmon”, “Appendicular Lump”, “Interval Appendectomy “and, “Complicated Appendectomy”. All articles were in English language only. Further articles were obtained by manual cross referencing of the literature. Case reports and studies with less than 10 patients and editorials were excluded.

DISCUSSION

Conservative management followed by interval appendectomy.

Oschner and Sherren proposed this management for appendicular mass in 1901, during the era of limited antibiotics and imaging technologies. This approach involved keeping the patient nil by mouth and starting intravenous antibiotics and measuring the size of the appendicular mass. This treatment is continued for 24 to 48 hours, and it involves monitoring of the vital signs.[2] This method removes the risk of complications that can occur during the acute phase of surgery and interval appendectomy eliminates the risk of recurrence.[3] Interval appendectomy will help to give a histological diagnosis and to prevent recurrence. The complication rates from interval appendectomy are low.[4]

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Table I: Table of contents of the retrospective studies

Olsen et al	Systematic review	3,772 patients	70 to 80% success rate	Most of the studies were retrospective in nature
Van Amstel et al	Meta-analysis	1,355 patients	12% complication in conservative group	Most of the studies were retrospective in nature
Gillick et al	Retrospective study	427 patients	85% success rate	Retrospective in nature
Ravichandran et al	Prospective study	116 patients	Decreased wound infection rates	Low patient load
Demetrashvilli et al	Retrospective study	48 patients	Complication rates were the same in both groups	Retrospective in nature
Kim et al	Retrospective study	76 patients	Outcomes and complications were the same in both groups	Retrospective in nature

Table II: Table of contents of the studies for conservative treatment

Fugazolla et al	Meta-analysis	1,288 patients	90% success rate for conservative treatment.15% recurrence rate	Most studies were retrospective in nature
Anderson et al	Meta-analysis	59,488 patients	93%success rate with 10%recurrence rate	Most of the studies were retrospective in nature
Demetashivilli et al	Prospective cohort study	74 patients	High success rate for conservative treatment	Low patient numbers
Yilmt et al	Retrospective study	126 patients	Lower morbidity and infection rate	Retrospective study in nature

Table III: Table of contents for studies that favor early appendectomy

Khan et al	Randomized control trials	300 patients	5-8% complication rate	Low patient numbers
Arshad et al	Comparative study	176 patients	Low wound infection rate	Low patient numbers
Das et al	Retrospective study	112 patients	Low wound infection rate	Retrospective in nature
Pathan et al	Prospective study	100 patients	Reduced infection rate	Low patient numbers
Ishar et al	Observational study	60 patients	Reduced mean hospital stay at 4 days	Low patient numbers
El-sood et al	Retrospective study	40 patients	Reduced mean hospital stay	Low patient numbers
Kumar et al	Prospective study	50 patients	Reduced mean hospital stay	Low patient numbers

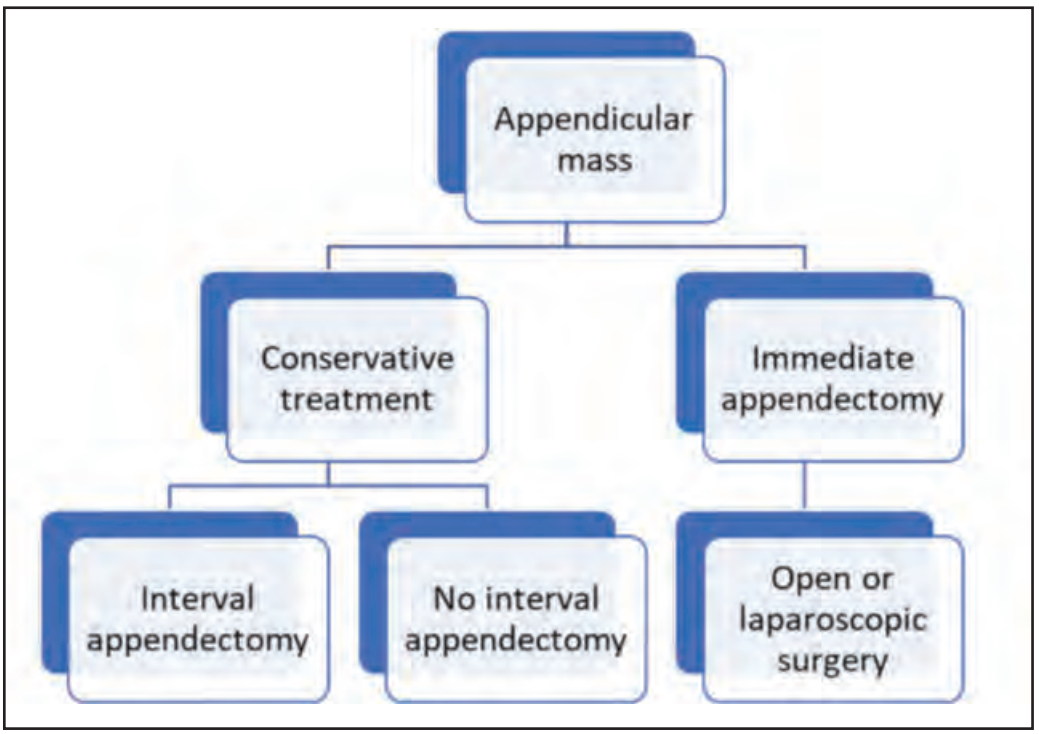

Fig. 1: Flow chart for the management of appendicular mass.

A retrospective study by Koirala et al evaluated conservative therapy for appendicular mass where 173 patients were treated. Of this number, 10 patients developed complications that required emergency appendectomy, but the rest were managed conservatively. Only 35 patients returned for interval appendectomy. Bhandari et al in their study of 75 patients with appendicular mass were managed conservatively and only five patients developed appendicular abscess, but only 13 patients came back for interval appendectomy. Although these were retrospective studies, it showed the success of conservative treatment but highlighted the problem of patient's attendance for interval appendectomy. Further retrospective studies by Gillick and demetrashvili also showed the benefit of conservative treatment in the management of appendicular.[5–7]

In a prospective study by Elsaady, a total of 169 cases of appendicular mass 121 patients were treated conservatively. Of this total 106 were successfully treated and treatment failure was seen in 15 cases. This showed that the conservative method with interval appendectomy was an effective and safe treatment method. This was also confirmed by a prospective study by Ravichandran et al and ahmed et al which showed the success of conservative treatment followed by interval appendectomy.[8–10]

A systemic review by Olsen et al reviewed the literature in 48 studies and a total of 3,772 patients and they concluded that conservative management of appendicular mass was safe and associated with a Success rate of 80%-90% and there were no major complications. Another systemic review by Teixeira et al also concluded that conservative management of appendicular mass was safe and the risk of detecting neoplasms of the appendix was low.[11,12]

A meta-analysis by van Amstel, which included 14 studies and 1355 patients, for which 1022 were treated with conservative therapy and 333 underwent emergency appendectomy, complications were seen in 12.2% of the conservative therapy group and 25.5% in the emergency appendectomy group. The most common complication was wound infection. This showed that conservative therapy followed by interval appendectomy should be the treatment of choice for appendicular mass but the drawback from this meta-analysis was that the majority of the studies were small retrospective studies.[13]

An audit by Ahmed et al in the mid trent region in the United Kingdom, concluded that 75% of surgeons there conducted conservative therapy with interval appendectomy on patients with appendicular mass and that there was no present protocol for the treatment of appendicular mass.[14]

Another survey of hospitals in the south coast of the United Kingdom showed the diverse practice in the management of appendicular mass, where senior surgeons would manage these patients conservatively, but surgical registrars were more inclined to perform interval appendectomy.[15]

Kim et al did a retrospective analysis on 76 patients who were diagnosed with appendicular mass, 48 underwent conservative therapy followed by interval appendectomy and 28 underwent emergency appendectomy, the recurrence rate was low and the outcomes after surgery were the same in all the groups hence conservative therapy followed by interval appendectomy is still the primary choice of therapy for appendicular mass, but the choice of therapy will usually be decided by the surgeon.[16]

Garba et al., conducted a review on the treatment approaches for the management of appendicular mass and concluded that conservative management followed by interval appendectomy is still the primary treatment of choice for the management of appendicular mass and follow-up of patients are essential while waiting for interval appendectomy.[17] Simillis et al conducted a meta-analysis comparing conservative therapy versus immediate appendectomy on the treatment of appendicular mass,[21] studies were included, and the conclusion was that conservative therapy followed by interval appendectomy was associated with decreased wound complication ,abscess formation and intestinal obstruction. The duration of hospital stay was also the same between the groups.[18]

The European Association of Emergency Surgeons consensus development conference 2015 still recommends conservative management followed by interval appendectomy in the management of appendicular mass. Interval appendectomy is done to reduce the chance of recurrence and to not miss any under lying malignancy.[19] The World Society of Emergency Surgeons Jerusalem guidelines also recommends conservative treatment as the initially therapy of appendicular mass in the event of non-availability of laparoscopic surgery.[20]

Most of the studies that were done on conservative management of appendicular mass with interval appendectomy were retrospective in nature and this influenced the outcomes of wound infection and recurrence rate. An area of issue is the number of patients who are lost to follow- up and hence did not come for interval appendectomy. The number of patients in most of the studies was rather low in number. For future research it is hoped that randomized control trials can be used to investigate the conservative management of appendicular mass, but sample size may be a problem.

Conservative management without interval appendectomy

There are some in the surgical fraternity who oppose interval appendectomy as they point out that the rate of recurrence attacks is low and the complication rates from interval appendectomy are not low. A study by Noori et al, on 65 patients with appendicular mass who underwent conservative management with no interval appendectomy, the rate of recurrence was 10% and wound infection was seen in 4% of the cases. Hence upon completion of conservative management, interval appendectomy is not necessary as the recurrence rate is low.[21]

Demetrashivili et al also had conducted a cohort study on 74 patients with appendicular mass, where 47 had undergone conservative therapy and 27 underwent immediate appendectomy, and there were no significant differences in

the treatment for both groups, hence conservative treatment without interval appendectomy was still the preferred treatment of choice. Patients who present with recurrence can be operated and Computerised Tomography and colonoscopy can be done to investigate patients who present with recurrence.[22]

Yilmaz et al in his retrospective study on 126 patients with appendicular mass were divided into two groups one was managed with appendectomy and another group with conservative therapy alone.43 underwent appendectomy and 72 underwent conservative therapy, the morbidity and infection rate was higher in the appendectomy group .Based on this study conservative appendectomy without interval appendectomy should be the treatment of choice and patients with recurrence can be followed up by investigations like colonoscopy and computed tomography. The drawback of this study was the fact that it was retrospective in nature.[23] Panahi et al in his study did a literature search on the best management option of appendicular mass, and after filtration a total of 5 papers were identified to provide the best evidence. Based on this, conservative management without interval appendectomy was considered the best treatment option for appendicular mass and to prevent recurrence, patients should be followed up with investigations like colonoscopy and imaging like ultrasound or computed tomography. Meshikhes also looked in the literature and concluded that interval appendectomy can be safely excluded, and that recurrence can be managed by laparoscopic appendectomy. Quartey investigated the need for interval appendectomy and concluded that it was not necessary and that concluded that recurrence can be investigated by colonoscopy or computerized tomography.[24–26]

Malik et al conducted a retrospective study on 220 patients with conservative management and 213 patients were treated successfully, the recurrence rate was 13% with a median follow up of 6 months. He concluded that interval appendectomy was not necessarily due to the low recurrence rates. Another retrospective study by Tingstedt also confirmed this.[27,28]

In a meta-analysis done by Anderson et al, which investigated the conservative management of appendicular lump and upon successful treatment interval appendectomy was not indicated. There was a success rate of 93% but percutaneous drainage of abscess was seen in 20% of cases. The risk of recurrence was seen in less than 10% of cases and was also associated with a risk of missing other diagnosis like malignancy or Crohn 's disease in about 2% of cases. Follow-up of patients above the age of 40 was suggested with colonoscopy and Computed Tomography to not miss other diagnosis.[29]

A meta-analysis by Fugazolla et al on 14 studies with 1288 patients, where 622 were treated with conservative management and 666 with appendectomy, the success rate was 90% and the recurrence rate was 15.4%. This showed that conservative therapy should be the treatment of choice for patients with appendicular mass.[30]

The drawback from these studies was that most of them were retrospective in nature and due to the low recurrence rate and post operative infection rates the need of interval appendectomy was questioned. With better investigations like computerized tomography and colonoscopy, the need for interval appendectomy is being questioned. For future research, more randomized control trials should be conducted in the conservative management of appendicular mass and more prospective studies should be done, with better sample size.

Immediate appendectomy either by open or laparoscopic method

There are surgeons who advocate for immediate appendectomy for patients who present with an appendicular mass, as this approach excludes the need for readmission, cures the condition and reaches a definitive diagnosis. A prospective study by Bahram on 46 patients with appendicular mass who were subjected to immediate appendectomy. The infection rates were 8% and the mean hospital stay was 3 days. This showed that immediate appendectomy was feasible and safe in the management of appendicular mass.[31]

Ali et al in his literature review, stated that emergency appendectomy in the management of appendicular mass is emerging as an alternative treatment than conservative management. It is safe and cost- effective and reduces hospital stay.[32]

Khan et al conducted randomized control trials on 300 patients with appendicular mass,150 had undergone immediate appendectomy and 150 conservative treatments. The wound infection rates among the groups were 5% and 8% respectively and the frequency of intra-abdominal abscess was less than 2%. This study concluded that immediate appendectomy was more effective option in the management of appendicular mass.[33]

Arshad et al in his comparative study on 176 patients of appendicular mass ,88 patients underwent immediate appendectomy and 88 underwent conservative treatment. The wound infection rate was higher in the immediate appendectomy group but the stay in hospital was less than in the conservative treatment group, but the rate was not high to exclude immediate appendectomy. Immediate appendectomy in the treatment of appendicular mass is a safe and effective treatment option.[34]

Das et al conducted a retrospective analysis on 112 patients of appendicular mass who were divided into 56 patients who underwent immediate appendectomy and 56 underwent conservative treatment. The length of hospital stay was less in the appendectomy group. They were discharged home sooner than the group that underwent conservative treatment. Early appendectomy is curative, cost- effective and reduces hospital stay in the management of appendicular mass. This was also confirmed by obaidi et al who came with the same conclusions in his study.[35,36]

Tiwary et al in their study of 54 patients with appendicular mass were divided into 2 groups of 27 patients each who

underwent immediate appendectomy and conservative treatment. The infection rates were the same in both groups but the stay in hospital was shorter in the appendectomy group. Early appendectomy is better in the treatment of appendicular mass as it is associated with shorter stay and reduced cost and eliminates the need for a second admission.[37]

Pathan et al in his prospective observational study of 100 patients of appendicular mass also noted that the length of hospital stay was reduced in the immediate appendectomy group. It was also associated with faster return to work and low economic burden. This conclusion was also observed by Israr in his observational study that immediate appendectomy was safe and effective.[38,39]

Laparoscopic appendectomy has been emerging as an alternative to the management of appendicular mass. Several retrospective studies were done on the role of laparoscopic appendectomy in the management of appendicular mass. The mean operation time was longer but the use of postoperative analgesia and the stay in the hospital was reduced. The advantage of laparoscopic appendectomy was adequate access and visualisation of the peritoneum, lower risk of adhesion and faster mobility. Hence laparoscopic appendectomy is a feasible option in the management of appendicular mass.[40–44]

The World Society of Emergency Surgeons Jerusalem guidelines of 2020 recommended that in the management of appendicular mass, laparoscopic surgery is a safe and feasible treatment option if it is done in experienced hands. It is associated with fewer admissions and fewer additional interventions.[21]

The drawback of most of these studies is that they are retrospective in nature with small sample sizes. There were also concerns that acute appendicitis is an emergency procedure and most of the appendectomies were performed by junior specialists and registrars which could account for the higher post operative wound infection rates. Most of the studies that used laparoscopic appendectomy in the management of appendicular used senior surgeons who had experience in laparoscopic surgery, and this could account for the better outcomes. It is hoped that future randomized control trials can be conducted in terms of the use of laparoscopic appendectomy in the management of appendicular mass.

CONCLUSION

Based on the available evidence, the management of appendicular mass should be done with immediate appendectomy and laparoscopic appendectomy should be the surgery of choice. If facilities for laparoscopic appendectomy are not available then conservative treatment should be done for the patient and for patients above the age of 40 years, they can be followed by computerised tomography and colonoscopy. Interval appendectomy is not required, and it is only indicated for patients who present with recurrent symptoms.

CONFLICT OF INTEREST

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

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A 10-year systematic review and meta-analysis of determinants of postpartum depression in the Association of Southeast Asian Nations countries

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ABSTRACT

Introduction: Postpartum depression (PPD) is a mental and emotional condition that can affect women during their first postnatal year and concern globally. This study aimed to determine the overall prevalence and determinants of postpartum depression (PPD) in Association of Southeast Asian Nations (ASEAN) countries.

Materials and Methods: A systematic search of observational studies conducted in ASEAN countries between 1 January 2010 and 31 December 2020 was performed in the Medline, PubMed and Google Scholar databases. The quality of studies was evaluated based on The Joanna Briggs Institute Checklist. The analysis was performed with Review Manager software version 5.4. Meta-analysis of the estimates from primary studies was conducted by adjusting for possible publication bias and heterogeneity.

Results: Twenty-five studies including 19924 postnatal mothers were included in this review. The pooled prevalence of PPD is 22.32% (95% CI: 18.48, 26.17). Thailand has the highest prevalence of PPD with a pooled prevalence of 74.1% (95% CI: 64.79, 83.41). The prevalence of PPD was highest when the assessment for PPD was conducted up to 6 weeks postpartum with a pooled prevalence of 25.24% (95% CI: 14.08, 36.41). The identified determinants of PPD were unplanned pregnancy, term pregnancy, lack of family support and physical violence. There were limited studies done and high heterogeneity in terms of quality, methodology, culture, screening method and time of PPD measurement.

Conclusions: Approximately one in five postpartum women in ASEAN countries had PPD. The risk factor that lowers the risk of PPD is unplanned and term pregnancies, while women with a lack of family support and experienced physical violence increase the risk of PPD. Robust prevalence studies are needed to assess the magnitude of this problem in ASEAN countries.

KEYWORDS:
Postnatal depression, postpartum depression, ASEAN countries, risk of postpartum depression

INTRODUCTION

Postpartum depression (PPD) is a mental and emotional condition that can affect women during their first postnatal year and is a concern globally.[1] It involves the woman herself and the family institution and, subsequently, the economy of the family itself.[2] PPD is often overlooked and causes morbidity to new mothers and their families. PPD is defined as a major depressive episode 'with peripartum onset if the onset of mood symptoms occurs during pregnancy or within four weeks following deliveries' based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). Multiple studies and clinical practices define PPD as occurring within 4 weeks after childbirth, 3 months, 6 months or up to 12 months after delivery.

A recent systematic review and meta-analysis by Abel et al.[3] on 58 studies conducted between 2007 and 2017 reported that the PPD prevalence ranged between 18.2% and 25.6%. They also highlighted that the prevalence was higher in low-income countries, with a pooled prevalence of 25.8%, compared to middle-income countries, which was 20.7%. Wang et al.[4] conducted a systematic review and meta-analysis among 565 studies involving 1,236 365 women from inception and July 2021 found that the global prevalence of PPD is 17.22% (95% CI: 16.00, 18.51). They reported that South Africa has the highest prevalence, which is 39.96%.

The literature on PPD revealed several risk factors that can contribute to women's PPD. The risk factors are different among the developed and developing countries. It can be divided into socio-demographic categories, marital and pregnancy factors and psychosocial factors. The examples of socio-demographic factors are unintended or birth[5–7], occupation and marital status[8] and low socio-economic and education status.[6,9,10] For marital and pregnancy factors such as intimate partner violence,[11] domestic violence[5,12,13] psychosocial factors identified were partner conflict, perfectionism, lack of family and parental support, reduced social support,[6,10,14] and depression during pregnancy or history of depression before pregnancy.[5,10]

ASEAN countries comprise an intergovernmental organisation of 10 Southeast Asian countries: Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand and Vietnam. The most

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striking characteristic of ASEAN countries is that it has a wide diversity of socio-cultural, hence different socio-economic statuses. We find many studies related to PPD in developed and other developing countries but very limited studies related to ASEAN countries. This can be due to a lack of exposure and intervention about PPD in women.

Therefore, in this systematic review and meta-analyses, we aimed to estimate the overall prevalence of PPD and its determinants in ASEAN countries. Findings from this study will be used to identify the need for early screening and detection, encourage the development of an intervention to reduce its occurrence and support women with PPD.

MATERIALS AND METHODS

A systematic review and meta-analysis of studies were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.15 The protocol for this systematic review and meta-analysis has been registered in the PROSPERO (Protocol No. CRD42021234127), and the protocol includes only the determinants of PPD in ASEAN countries. The inclusion criteria are studies conducted in ASEAN countries that report the prevalence and determinants of PPD over 10 years from 1st January 2010 to 31st December 2020. Studies with cross-sectional, case–control and cohort designs published in English were included. Case series/reports, conference papers, proceedings, articles available only in abstract form, editorial reviews, letters of communication, commentaries and qualitative studies were excluded.

A systematic search was performed in the Medline (PubMed) and Google Scholar databases for articles between 1st January 2010 and 31st December 2020. The investigation was done using the Medical Subject Headings (MeSH) search terms: 'determinants,' 'risk factors,' 'postnatal depression,' 'perinatal depression,' 'maternal depression' and 'maternal blues'. Reference lists of included citations were cross-checked to find additional potentially eligible studies.

All records identified by our search strategy were exported to EndNote X8 software. Duplicate articles were removed. Two independent reviewers screened the titles and abstracts of the identified themes. The full texts of eligible studies were obtained and read thoroughly to assess their suitability. In a conflict between the two reviewers, a consensus discussion was held, and a third reviewer was consulted.

The data were extracted into Microsoft Excel. This included first author, year of publication, study location, study design, setting, study population, sample size, PPD definition, risk factors and data for the calculation of effect estimates. Data for risk factors included physical and biological, psychological, obstetric, paediatrics, socio-demographic and cultural factors.

A critical appraisal was done to assess the data quality using the Joanna Briggs Institute Meta-Analysis for cross-sectional, case–control and cohort studies (Aromataris and Munn, 2020). The risk of bias was considered low when more than 70% of the answers were 'yes,' moderate when 50–69% of the responses were 'yes' and high when up to 0%–49% of the answers were 'yes.' The risk factors were reported as an odds ratio with a 95% confidence interval. The analysis was performed with Review Manager software version 5.4 (Nordic Cochrane Centre). We used a random-effects model to pool data. The I2 statistic was used to assess heterogeneity and use the guide as outlined: 0%–40% might not be necessary; 30%–60% may represent moderate heterogeneity; 50%–90% may represent substantial heterogeneity and 75%–100% would be considerable heterogeneity; 50%–90% may represent significant heterogeneity 17Subgroup analysis was performed based on ASEAN countries and the time of assessment of the study design. Funnel plots were used to assess the publication bias.

RESULTS

Characteristics of the Included Studies

A total of 7609 articles were retrieved through an electronic search, of which 7559 were eligible for assessment after removing ten duplicate records. Of the 7559 articles screened for eligibility, 7250 were excluded. A total of 349 articles underwent full-text evaluation for eligibility, of which 312 were excluded because articleswere not from ASEAN countries (n = 293) but only prenatal depression (n = 19). In this review, 37 articles underwent quality assessment, of which 25 articles with low risk of bias were included in the final analysis, as shown in Fig 1, whereas four studies with a moderate risk of bias and six studies with a high risk of bias were excluded.

Table I shows 25 studies included in this review: Malaysia (n = 4),[11,16–18] Singapore (n = 3),[19–21] Thailand (n = 5),[14,22–25] Indonesia (n = 6),26–31, Vietnam (n = 5),32–36, Philippines (n = 1)8 and Laos (n = 1)37. Fifteen studies were cross-sectional,[8,11,14,16,22,23,26,28–32,34,36,37] two were case–control,[19,24] and eight were cohort studies.[17,18,20,21,25,27,33,35] According to the data, the smallest sample size was 31 women, and the largest was 6636 women. The majority of the included studies used Edinburgh Postnatal Depression Scale (EPDS), which is 21 studies out of 25.[8,11,14,17,18,20,21,23–31,33–37] From this, nine studies using cut-off points ≥12,[11,14,17,18,23,28,30,34,36] seven studies using cut-off points ≥10,[8,21,25,26,29,35,37] two studies using cut-off point ≥13,[20,27] one study using cut-off point ≥433 and ≥1124, respectively, and one study not explicitly mentioned the cut-off point.[31] Other than that, four studies using different types of measures of PPD, which are Mini International Neuropsychiatric Interview (MINI),[16] The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV),[19] Center for Epidemiological Studies Depression Scale (CES-D)22 and Case-Finding Instruments for Depression.[32]

Prevalence of PPD in ASEAN Countries

A total of 25 studies were included, with a total of 19,924 samples size. The pooled prevalence of PPD was 22.32% (95% CI: 18.48, 26.17). Figures 2 and 3 show a funnel plot. A subgroup analysis based on countries was performed in Figure 4. Thailand showed the highest pooled prevalence of women with PPD, which is 74.10% (95% CI: 64.79, 83.41). This is because the study[22] was done among a particular group population of women with human immunodeficiency virus and a small sample size of 85 mothers. Apart from that, a limited number of studies are available, such as Laos[37] and The Philippines.[8]

Table I: Summary of research articles included in systematic review and meta-analysis for PPD in ASEAN countries

No.	Author	Study area (Region)	Study design	Sample Size	Measures of PPD	Prevalence of PPD (%)	Time of assessment	Factors associated with PPD
1	Zainal et al.[16]	Malaysia	Cross-sectional	411	MINI	6.8	6–8 weeks postpartum	- Housewife - Caesarian section - Previous history of depression - Non-exclusive breastfeeding
2	Yusuff et al.[17]	Malaysia	Cohort	2072	EPDS	14.3	1, 3 and 6 months postpartum	- Women depressed during pregnancy - Women with consistent worries of newborn
3	Norhayati et al.[18]	Malaysia	Cohort	742	EPDS	4.8 2.1	1 and 6 months postpartum 1 and 6 months postpartum	- Mother with SMM - Mother without SMM
4	Ahmad et al.[11]	Malaysia	Cross-sectional	6639	EPDS	4.4	6–16 weeks postpartum	- Exposed to intimate partner violence - Emotional violence - Unplanned pregnancy - Lack of family support during confinement - Partner's use of alcohol - Being from household with a low income
5	Suhitharan et al.[19]	Singapore	Case–control	744	DSM-IV	12.9	4–8 weeks postpartum	- Absence of labour epidural analgesia - Increasing age - Family history of depression - History of depression - Previous history of PPD
6	Tham et al.[24]	Singapore	Cohort	1247	EPDS	20.1	3 months postpartum	- Borderline high depressive/ anxiety symptoms - Poor subjective sleep quality during pregnancy
7	Teo et al.[20]	Singapore	Cohort	1249	EPDS	9.8	1 month postpartum	- Traditional-Indian-Confinement diet associated with less PPD symptoms
8	Ross et al.[22]	Thailand	Cross-sectional	85	CES-D	74.1	6 weeks postpartum	- Low self-esteem - Infant health status - Low education level
9	Panyayong et al.[23]	Thailand	Cross-sectional	1731	EPDS	8.4	12 months postpartum	- Maternal health - Marital conflict - Economic burden - Stressful life events - Previous depression
10	Roomruangwong et al.[24]	Thailand	Case–control	313	EPDS	16.9	4–6 weeks postpartum	- History of lifetime major depression & PPD - History of depression during pregnancy - Multiparity - Unwanted pregnancy - Childcare stress - Premenstrual syndrome - Pain symptoms during early purperium - Use of caffein during pregnancy - Baby feeding problem
11	Hassert et al.[14]	Thailand	Cross-sectional	225	EPDS	36.0	12 months postpartum	- Partner conflict - Perfectionism
12	Phoosuwan et al.[25]	Thailand	Cohort	449	EPDS	47	1 and 3 months postpartum	- Low income - Limited social support - Low psychological well being

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Table I: Summary of research articles included in systematic review and meta-analysis for PPD in ASEAN countries

No.	Author	Study area (Region)	Study design	Sample Size	Measures of PPD	Prevalence of PPD (%)	Time of assessment	Factors associated with PPD
13	Dira et al.[26]	Indonesia	Cross-sectional	44	EPDS	20.5	2 months postpartum	- Low maternal education - Primiparity - Maternal age <23 years old - Have a history of children death - Unwanted pregnancy
14	Nurbaeti et al.[27]	Indonesia	Cohort	283	EPDS	18.37 15.19 26.15	1 month postpartum 2 months postpartum 3 months postpartum	- Childcare stress - Marital satisfaction - Life stress - Non acceptance of baby gender
15	Putriarsih et al, 2018	Indonesia	Cross-sectional	200	EPDS	18.5	2–6 weeks postpartum	- Labor complication - Unwanted pregnancy - Low family income
16	Nurbaeti et al.[28]	Indonesia	Cross-sectional	166	EPDS	19.88	6 weeks postpartum	- Stressful life events - Childcare stress - Marital satisfaction
17	Usnawati et al.[31]	Indonesia	Cross-sectional	100	EPDS	49.0	12 months postpartum	- Smaller parity - Working mother - Lower husband support
18	Putra et al.[30]	Indonesia	Cross-sectional	31	EPDS	32.3	12 months postpartum	- Maternal age of postpartum
19	Suzuki et al.[32]	Vietnam	Cross-sectional	300	Case-Finding Instruments for Depression	23.1	3 months postpartum	- Parental and familial conflict - Recent moving - Lack of confidence in childrearing - Less relaxed feeing toward the child
20	Fisher et al.[33]	Vietnam	Cohort	497	EPDS	0.9 2.4	8 weeks postpartum 6 months postpartum	- Exposure to either lifetime or perinatal IPV (emotional abuse, physical and sexual violence
21	Murray et al.[34]	Vietnam	Cross-sectional	431	EPDS	18.1	6 months postpartum	- Poverty - Food insecurity - Being frightened of family members - Intimate partner violence
22	Tho Tran et al.[35]	Vietnam	Cohort	1274	EPDS	8.2	12 weeks postpartum	- Women exposed to emotional violence - Type of employment - Lack of family support after delivery - Lower level of education - Husband preference for a specific sex of child - Presence of mental disorder - Depression during pregnancy
23	Do et al, 2018	Vietnam	Cross-sectional	116	EPDS	27.6	< 1 year postpartum	- Low level of education - Being the first-time mothers - Dissatisfaction about family - Limited communication and interaction with others
24	Labrague et al.[8]	Philippines	Cross-sectional	165	EPDS	16.4	6 weeks postpartum	- Occupation - Marital status
25	Souphalak et al, 2020	Laos Laos	Cross-sectional	428	EPDS	31.8	6-8 weeks postpartum	- Unintended pregnancy - Low birth satisfaction - Depression during pregnancy

Note: PPD = postpartum depression, MINI: Mini International Neuropsychiatric Interview, EPDS: Edinburg Postnatal Depression Scale, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition, CES-D: Center for Epidemiological Studies Depression Scale, IPV: Intimate partner violence

Table II: Summary of risk factors included in systematic review and meta-analysis for PPD in ASEAN countries

Variables	Number of studies
Physical and biological factors	
Gestational diabetes in pregnancy	2
Hypertension in pregnancy	2
Health of the mothers	3
Psychological factor	
History of family death	2
Lack of family support	4
Little family attachment	3
Spouse assistance for child-rearing	4
Physical violence	2
Obstetric and paediatric factor	
Unplanned pregnancy	7
Term pregnancy	4
Low birth weight	3
Types of delivery	5
Labour difficulty	3
Parity	5
Breastfeeding	4
Socio-demographic factor	
Mother age	10
Mother education level	10
Marital status	4
Occupation of the mothers	8
Economic burden	3
Type of family	2
Urban area	2
Cultural factor	
Gender preferences	3

Factors Affecting PPD

A total of 25 studies reported risk factors for PPD. Similar factors were searched for in each study. The selected studies identified 23 risk factors, which were then divided into five groups as shown in Table II: (1) Physical and biological factors which include gestational diabetes in pregnancy,[19,36] hypertension in pregnancy,[19,36] health of the mothers;[19,23,32] (2) Psychological factor such as history of family death,[8,36] lack of family support,[17,23,24,35] little family attachment,[8,23,36] spouse assistance for child rearing,[8,17,23,31] physical violence;[23,35] (3) Obstetric and paediatric factor which were unplanned pregnancy,[8,16,17,19,23,24,37] term pregnancy,[8,23,35,37] low birth weight,[8,32,37] types of delivery,[8,16,17,19,37] labour difficulty,[8,19,37] parity[8,16,31,36,37] and breastfeeding;[8,16,23,36] (4) Socio-demographic factor which were mother age,[8,16,17,23,26,30,31,35–37] mother education level,[8,17,19,26,30–32,35–37] marital status,[8,19,23,37] occupational status of the mother,[817,19,30–32,35,37] economic burden,[23,32,37] type of family,[8,36] urban area[36,37] and (5) cultural factor which include gender preferences.[8,17,37]

In the meta-analyses, four factors were significantly associated with PPD, as shown in Figures 6–9. There was an unplanned pregnancy, term pregnancy, poor family support and physical violence. Seven studies[8,16,1719,23,24,37] with 5864 women were included to analyse the relationship between unplanned pregnancy and PPD. The pooled result showed that women with unplanned pregnancies had a lower risk of PPD with an odd of 0.69 compared to women with planned pregnancies (OR: 0.69, 95% CI: 0.53, 0.91). In comparison, four studies[8,23,35,37] with a total of 3598 women were included in this analysis for the association of term pregnancy with PPD. The pooled analysis showed that women with term pregnancy had a lower risk of PPD with an odds of 0.55 compared to women with preterm pregnancy (OR: 0.55, 95% CI: 0.40, 0.74). For the association of family support and PPD, four studies[17,23,24,35] were included for analysis, with a total of 5390 women involved. The pooled result showed that women lacking family support had a higher risk of PPD with odds of 5.10 compared to women with good family support (OR: 5.10, 95% CI: 1.95, 13.38). Meanwhile, two studies[23,35] were included with a total of 3005 women to assess the association between physical violence and PPD, which showed that women who experienced physical violence had a higher risk of PPD with the odds of 2.16 compared to women without (OR: 2.16, 95% CI:1.56, 2.99).

DISCUSSION

In this study, we found that the pooled prevalence of PPD in ASEAN countries was 22.32%, comparable with middle-income countries, which were 20.8%;[3] but lower than Middle East countries, which were 27%.[6] The prevalence of PPD in ASEAN countries was higher than the recently reported global prevalence estimates of 17.22%.[4] This estimated prevalence could be related to the limited number of research available in ASEAN countries and the fact that most ASEAN countries are from middle- and low-income countries.

Besides that, the pooled prevalence based on the subgroup analysis of the time of assessment showed a higher prevalence in the first 6 weeks of postpartum, which was 25.24%. This is slightly similar to the study3 whereby the prevalence of PPD was higher in the first ten weeks of postpartum. This is possibly due to women's attempts to

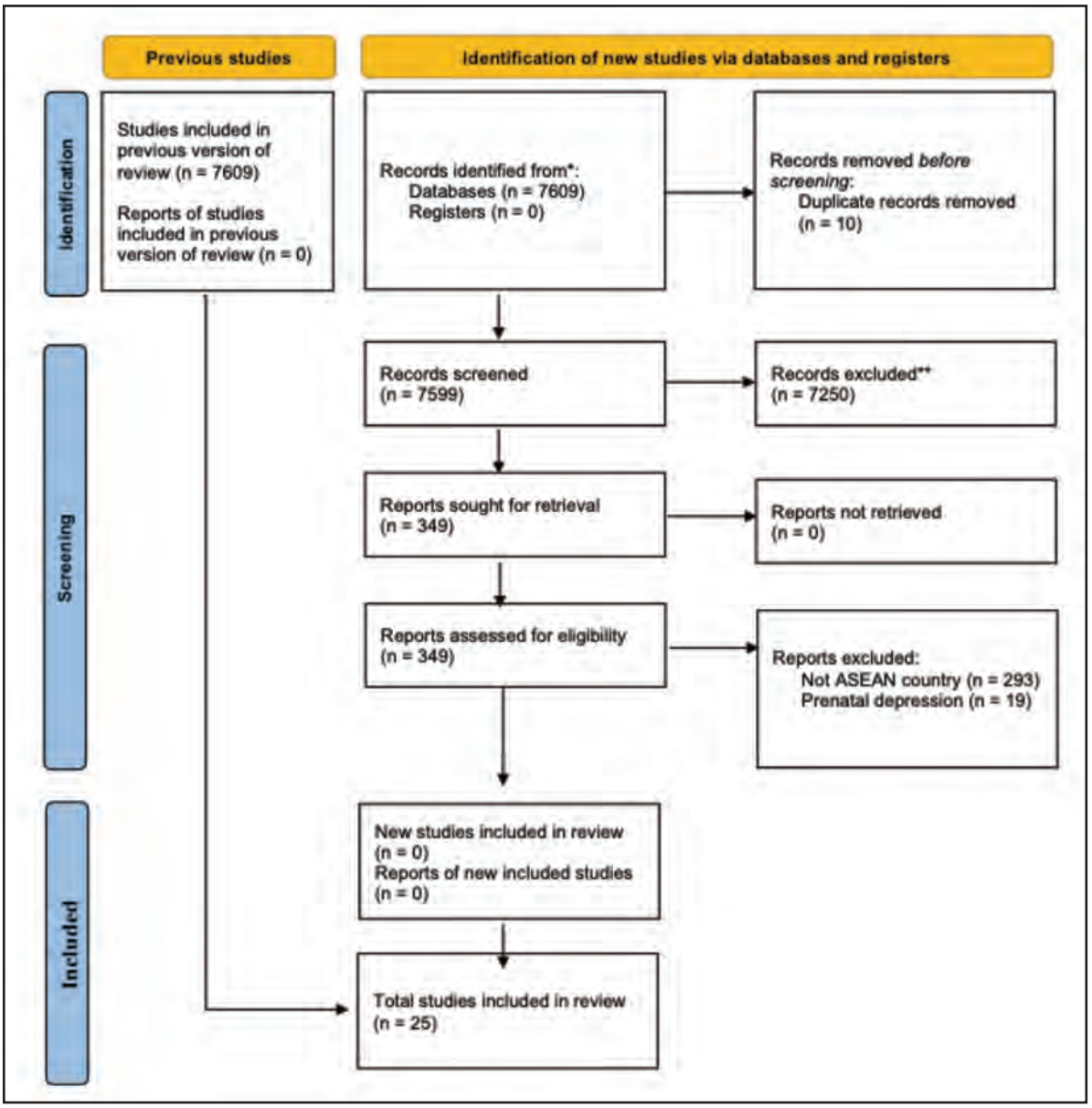

Fig. 1: PRISMA flow diagram.

adjust for babysitting and transition into motherhood. Other than that, the possibility of hormone dysregulation following childbirth also contributes to the depression.[3]

From our study, we found four significant risk factors associated with PPD. There were unplanned pregnancy, term pregnancy, poor family support and physical violence. According to current study findings, women experiencing physical violence and lack or poor family support were at increased risk of PPD. In this situation, usually after delivery, the mother will go through a new phase and transition whereby the mother needs support from the family to help, teach and manage the newborn. Hence, if they had a lack of support from family members or experienced physical violence, it could aggravate women's condition and contribute to PPD. These findings were similar to various systematic reviews/meta-analysis as described below.[3,38–40]

According to a systematic review and meta-analysis on PPD and its association with adverse infant health outcomes in low- and middle-income countries,[3] a mother's stress and depression symptoms could be worsened by a lack of social support because it affects the mother's self-confidence. Sawyer et al.[38] highlighted in a systematic review of postnatal psychological well-being in Africa that women who have poor support and marital/family conflict were associated with depression. Domestic violence has been associated with perinatal mental disorders, including antenatal and PPD.[39] A systematic review and meta-analysis on domestic violence and perinatal mental disorders[39] highlighted that women with PPD reported a high prevalence and risk for intimate partner violence during the lifetime (OR 2.9, 95% CI 1.8–4.8), during the past year (OR 2.8, 95% CI 1.7–4.6) and during pregnancy (OR 4.4, 95% CI 2.9–6.5). These findings are consistent with our results that demonstrated poor family support and intimate physical violence was associated with PPD.

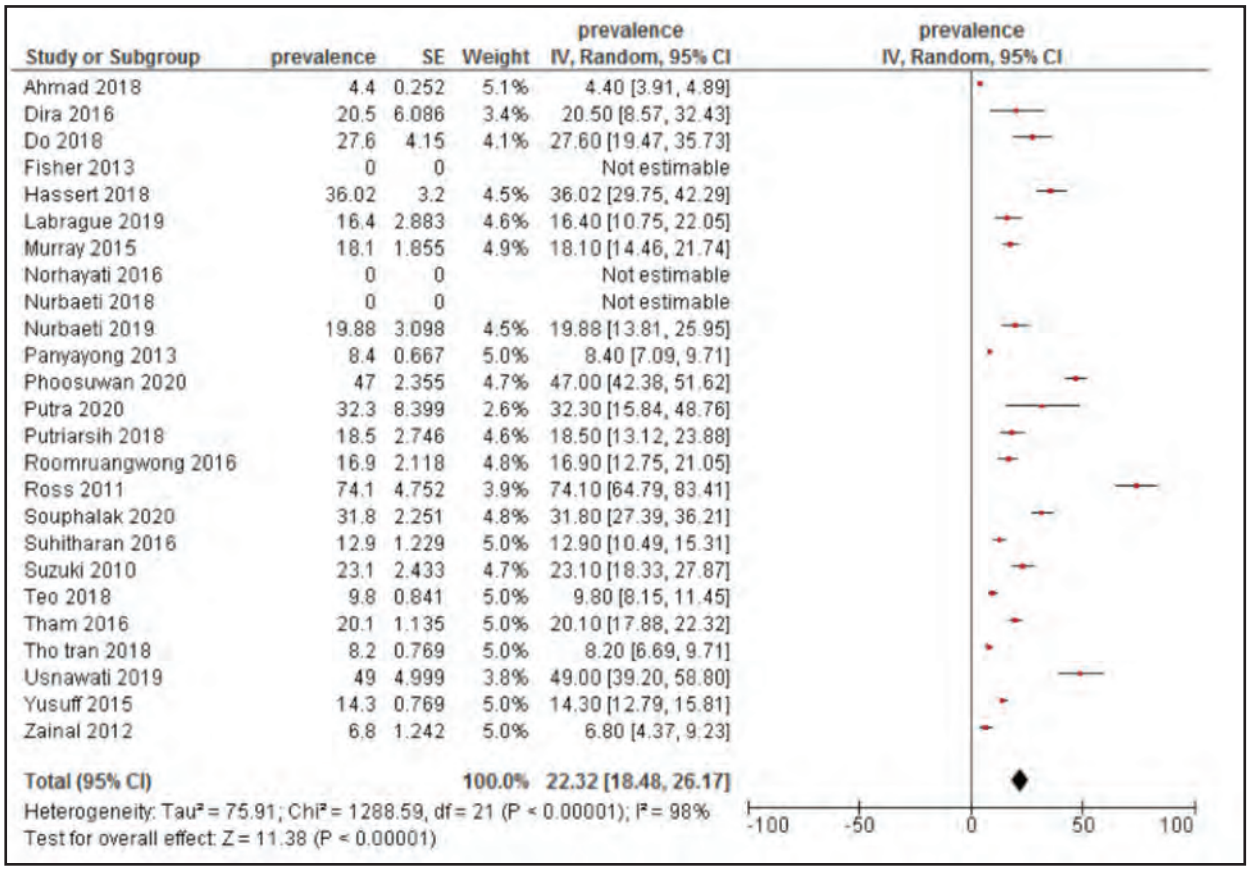

Fig. 2: Forest plot of the prevalence of PPD in ASEAN countries.

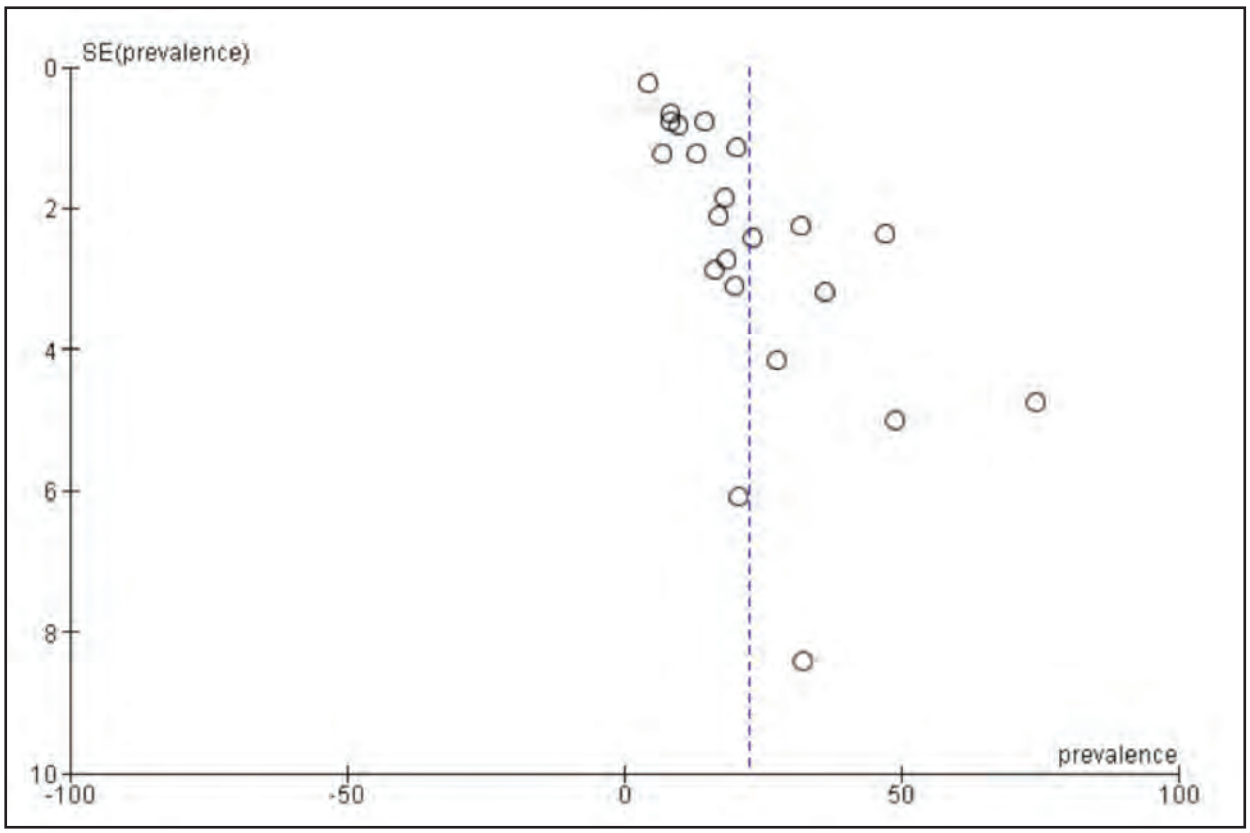

Fig. 3: Funnel plot for assessing publication bias.

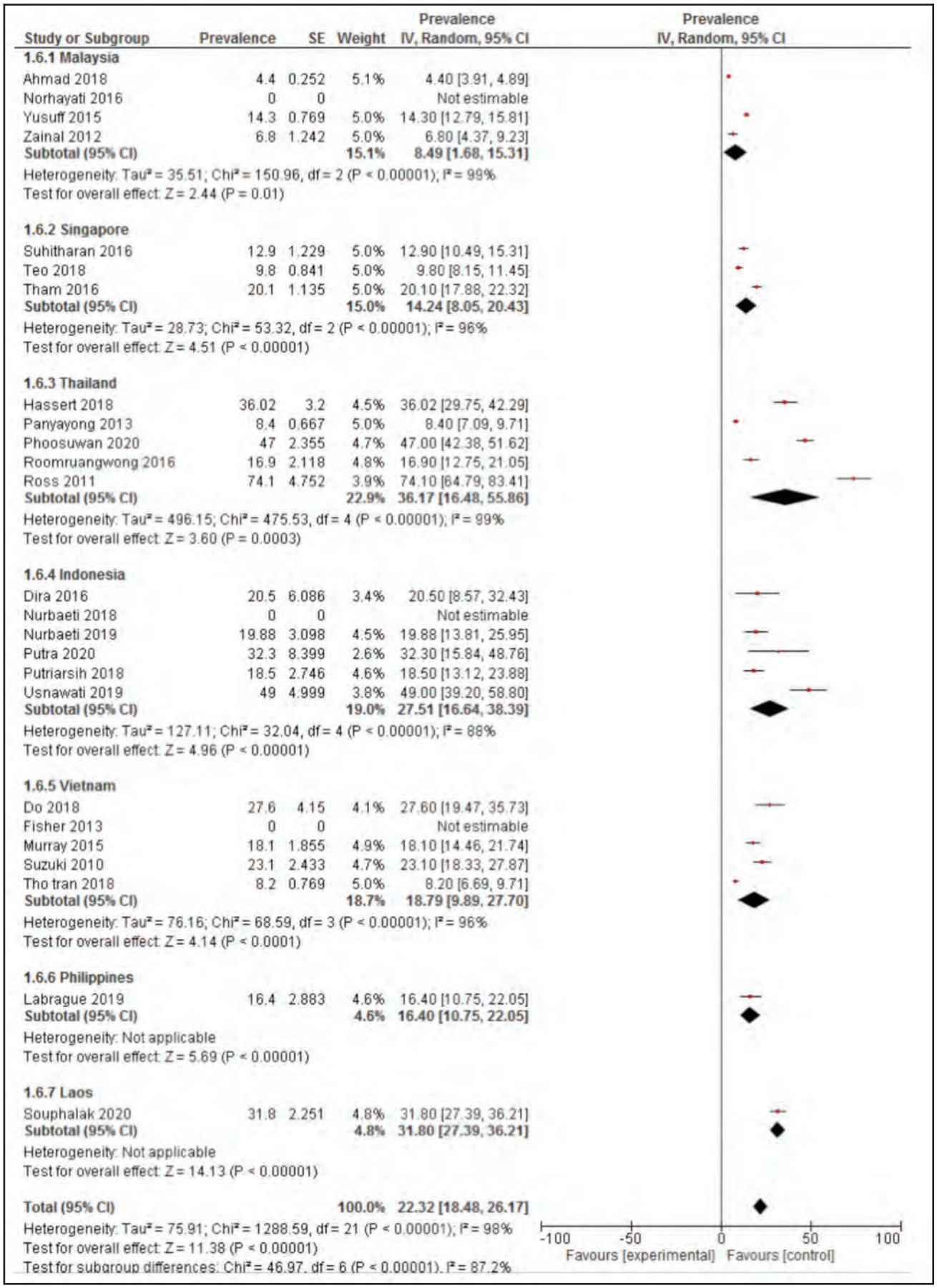

Fig. 4: Forest plot of a subgroup based on the countries for PPD.

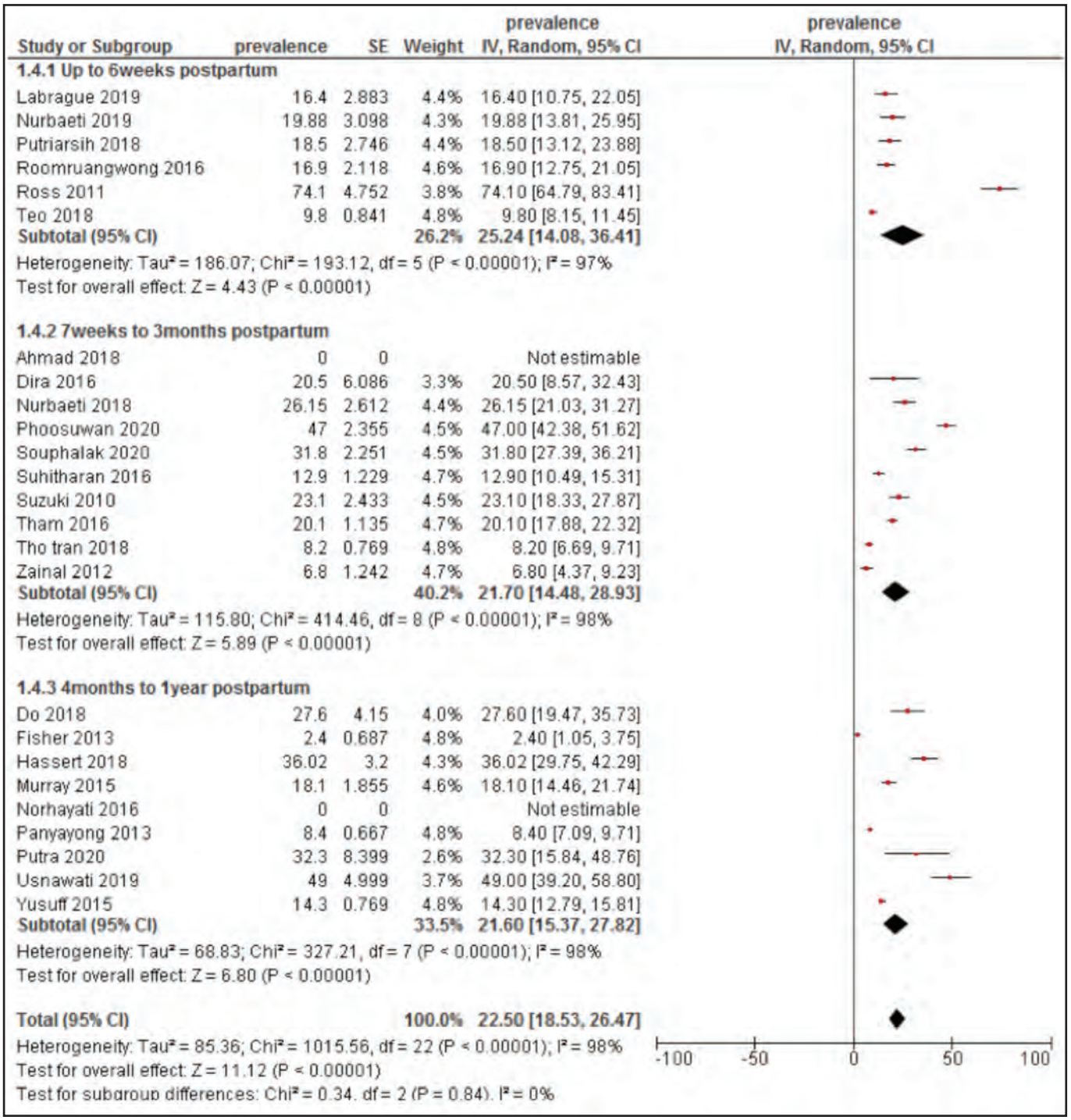

Fig. 5: Forest plot of the subgroup analysis based at different assessment time points for PPD.

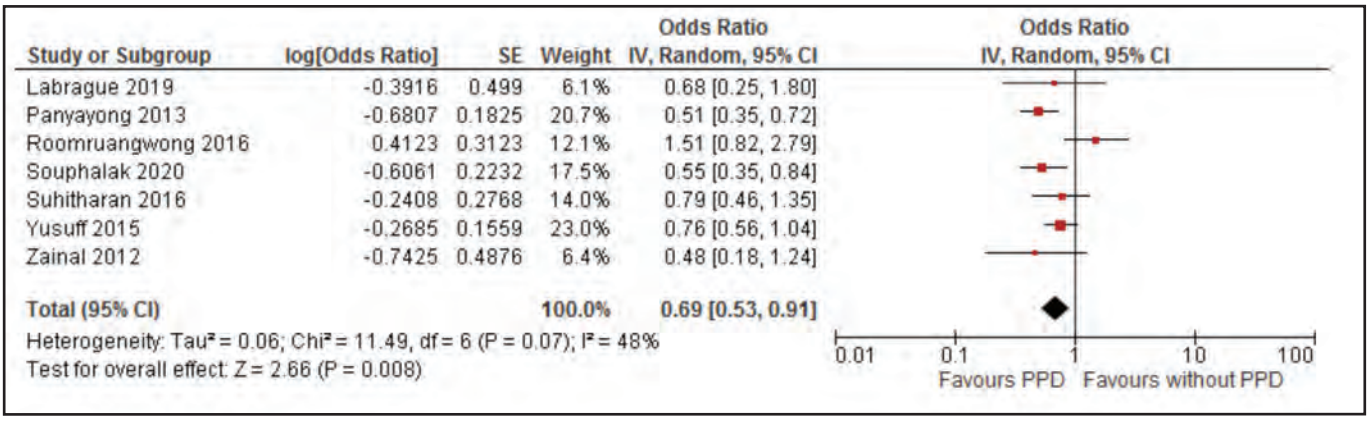

Fig. 6: Forest plot for association between unplanned pregnancy and PPD.

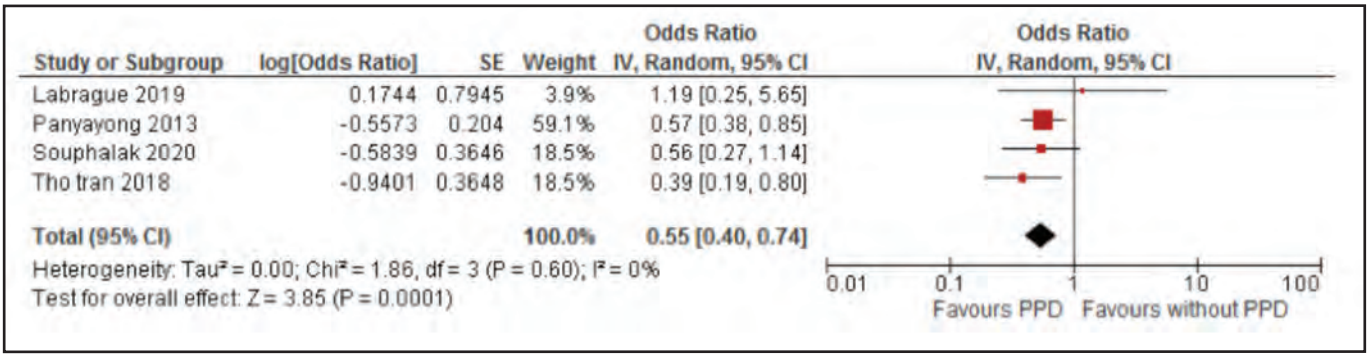

Fig. 7: Forest plot for association between term pregnancy and PPD.

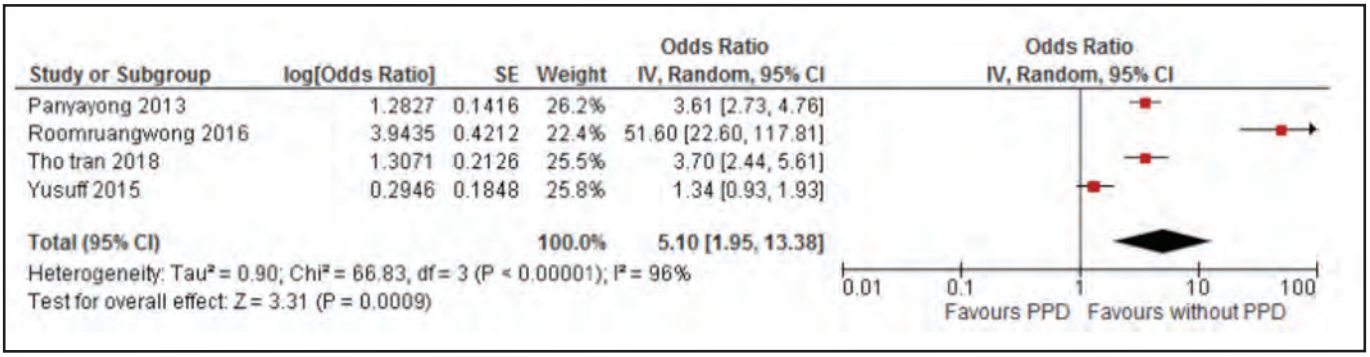

Fig. 8: Forest plot for association between poor family support and PPD.

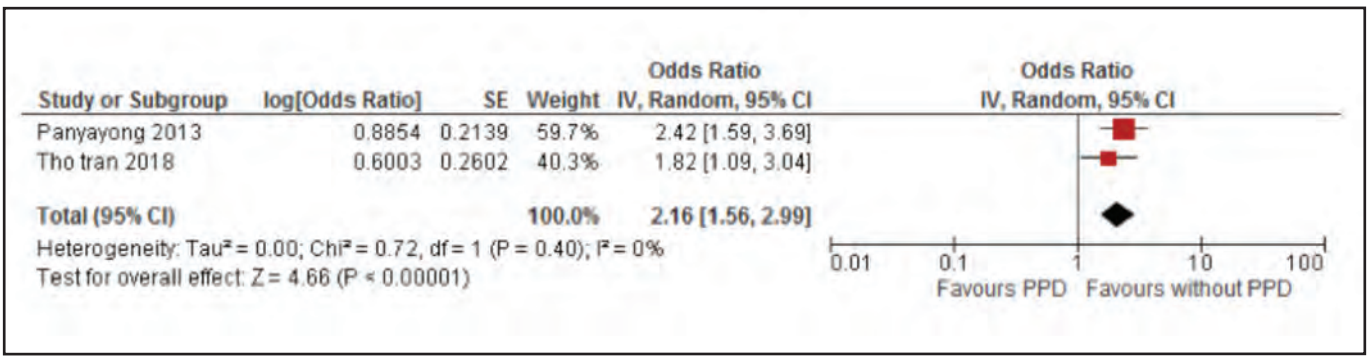

Fig. 9: Forest plot for association between physical violence and PPD.

For unplanned and preterm pregnancies, our study showed a lower risk of PPD and was in contrast with other studies,[3,4,40] whereby these risk factors favour PPD. This is probably due to the minimal study from ASEAN countries, different tools in PPD assessment method, a wide range of PPD assessment time, greater variety of sample size and cultural and background factors.

Based on the measurement tools used for diagnosis of PPD, about 84% of included studies used EPDS, whereas 16% used different diagnostic tools: MINI, DSM-IV, CES-D and Case-Finding Instruments for Depression. Out of 84%, eight studies[11,17,18,24,25,33,35,36] used validated EPDS, five studies[14,27,28,34,37] used back-to-back translation and another eight studies[8,20,21,23,26,29–31] not mentioned about validation of EPDS. All this has a significant impact on the result because of the considerable disparities, and the result is difficult to interpret. Furthermore, different cut-off points for EPDS also significantly impacted the result. According to Levis et al.[40] a cut-off value of 11 or higher showed maximised sensitivity and specificity, and 12 of the included studies[11,14,17,18,20,23,24,27,28,30,34,36] using cut-off point ≥11.

More research on PPD would be beneficial in identifying postnatal depression in mothers as soon as possible after giving birth and acting immediately to prevent morbidity, death, disabilities and negative impacts on the child's future development. This is especially crucial for the development of maternal health care in ASEAN countries. Aside from that, this research is limited to papers published in English and limited studies about PPD in ASEAN countries.

CONCLUSION

The prevalence of PPD in ASEAN countries was 22.32%. Unplanned and term pregnancies lower the risk of PPD, while poor family support and women who have experienced physical violence increase the risk of PPD. This review also found a very limited study among ASEAN countries and a scarcity of high-quality studies in ASEAN that can be used to generate generalisability evidence. More studies are needed to assess this problem's magnitude and plan a proper intervention program. Apart from that, the findings can be used to identify the need for early detection, encourage the development of an intervention to reduce its occurrence and support mothers with PPD.

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Nanoparticles produced from propolis extract: Their applications in medicine, why not?

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Dear Editor,

As we know, propolis is a natural resinous material produced by bees from various plants. This material is used to seal and line the beehives. The quality of propolis depends on chemical compositions, geographical region and botanical origin. Propolis contains resin, wax, essential oil, pollen, minerals, phenolic acid, flavonoids, terpenes, aromatic aldehydes, alcohols, fatty acids and stilbenes. It has many benefits for human health, for instance, antioxidant, antimicrobial, antiproliferative, antitumoral, anti-inflammatory and immunomodulatory capacity. Currently, there are many types of products made from propolis, including tablets, liquids and capsules but they are quite expensive in Vietnam (15–20 USD/120 capsules). Customers can use either the original propolis or propolis extract depending on the application. In Vietnam, beekeepers are not very interested in propolis due to the low yield (approximately 0.2 kg/herd/year).

The biggest problem for propolis is its low solubility in water and poor bioavailability. Therefore, scientists must use organic solvents (acetone, ethanol, etc.) to extract the bioactive compounds. In addition, to resolve these problems, many previous studies pointed out that nanoparticles (NPs) produced from propolis extract could be used as drug delivery systems to facilitate drug absorption and are relatively safe (low toxicity) and compatible with the human body.1 Propolis extract NPs could improve the biological activities compared to the control. In fact, there are many ways to encapsulate propolis, for instance, lipid NPs, polymeric NPs, and inorganic NPs with various diameters.

In general, all studies about propolis extract NPs are very interesting; however, they only have focused on the antiproliferative, antimicrobial, immunomodulatory activities, cytotoxicity and phytochemical profiles. Those are highlights of medicine, but it is a pity that these experiments were performed in vitro.[1] In my opinion, there are some major issues that need to be resolved when researching the human body. Firstly, the interaction of unintended NPs and immune cells may create some molecular responses that negatively affect human health, stimulate infectious diseases, induce autoimmune disorders and promote cancer development.[2] Secondly, plant extract NPs can be undetected by the immune system.[3] Lastly, the data on the toxicity of plant extract NPs (both carriers and phytochemical components of extract from plants) are inadequate. So, the impact of nanoparticles on the immune system is still a grey zone. Determination of the toxicity of propolis extract NPs and evaluation of their interaction with the human immune system are quite necessary. Based on the issues mentioned above, the applications of propolis extract NPs in the human body are huge challenges for the medical field and nanotechnology, however, future studies are necessary for in vivo models. Therefore, the perspective being proposed in this study is indeed feasible. Although the development of nanomedicine is still a long way off, it looks bright and may attain great achievements in the future. For NPs produced from propolis extract, I believe that there are many exciting things to discover with this nanomaterial and they are surely advantageous for human health, at least for in vitro experiments.

CONFLICT OF INTEREST

None.

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