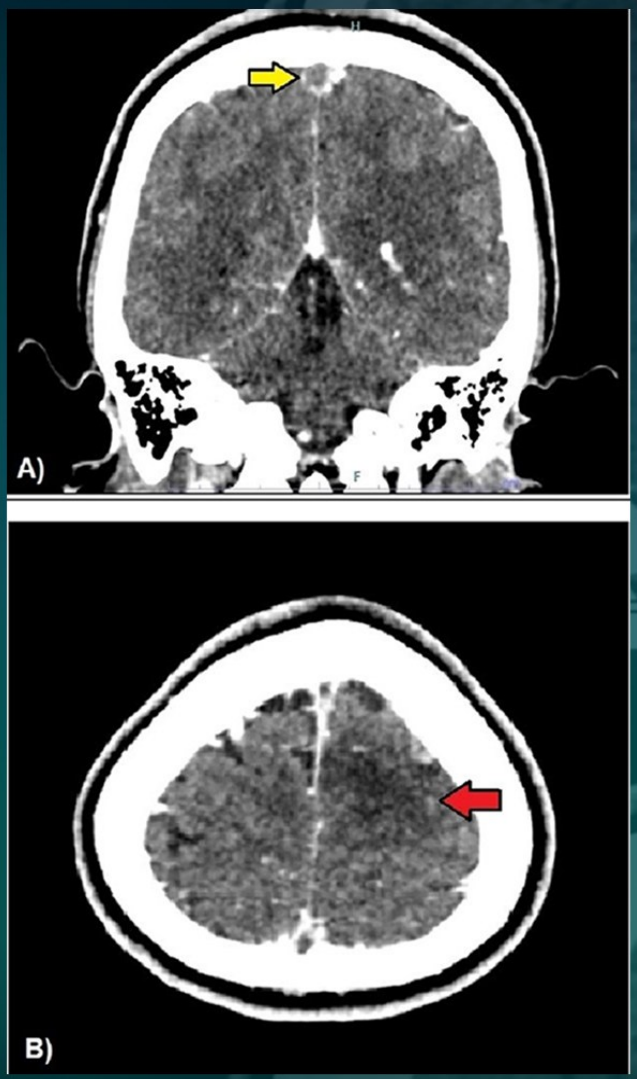
IMJM

VOLUME 25 NO 2
APRIL 2025 ISSUE
IIUM MEDICAL JOURNAL MALAYSIA

ISSN : 1823-4631
E-ISSN : 2735-2285

www.imjm.my



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IMJM
IIUM MEDICAL JOURNAL MALAYSIA
Volume 24, Issue 2, April 2025
https://doi.org/10.31436/imjm.v24i02

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IIUM MEDICAL JOURNAL MALAYSIA
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CASE REPORT

EDITORIAL

Volume 24 Number 2, April 2025

Ensuring Our Children Can Hear: Are We Doing Enough?

Hearing loss is one of the most common congenital conditions worldwide, yet it remains underrecognized and often neglected. According to the World Health Organization (WHO) 2021 report, an estimated 34 million children globally experience disabling hearing loss. In the United States, congenital deafness occurs in 2 to 3 per 1,000 live births, with an even higher prevalence among Neonatal Intensive Care Unit (NICU) admissions[1]. A study by the Ministry of Health Malaysia (MOH) reported a prevalence of 11 per 1,000 live births over a two-year period (2013–2014), highlighting the significance of this issue[2].

The Importance of Early Detection

Hearing plays a crucial role in a child's speech, language, cognitive, and social development. Neonatal hearing screening (NHS) facilitates early detection, allowing timely intervention that can profoundly impact a child's future. Research has shown that the critical period for auditory and speech-language development occurs within the first few years of life. Infants diagnosed with hearing impairment can receive habilitation with hearing aids as early as three months of age. For severe to profound hearing loss, cochlear implantation is an option as early as one year old. Missing this critical window can lead to long-term consequences, including speech and language delays, reduced academic performance, and limited employment opportunities in adulthood.

Expanding Coverage and Accessibility

Neonatal hearing screening can be either universal (UNHS) or targeted at high-risk infants (HRNHS). UNHS is considered the gold standard as nearly 50% of infants with hearing loss do not present with identifiable risk factors at birth. Limiting screening to high-risk groups risks missing a substantial number of affected infants. The American Academy of Paediatrics (AAP) supports universal hearing detection in infants before three months of age, emphasizing its importance in early intervention programs.

In Malaysia, neonatal hearing screening has been progressively implemented. Hospital Universiti Sains Malaysia (HUSM) initiated UNHS as early as 2003, followed by Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM, now Hospital Canselor Tuanku Mukhriz) in the early 2000s. The MOH launched its own program later, focusing initially on high-risk neonatal screening in 26 hospitals before expanding UNHS to seven hospitals by 2013. However, in some institutions, such as Sultan Ahmad Shah Medical Centre at IIUM (SASMEC@IIUM), plans for UNHS initiated in 2022 have yet to be fully realized, with only HRNHS currently in place.

Internationally, the implementation of UNHS has been more robust. In the United States, screening is mandatory in all 50 states, following the enactment of the Early Hearing Detection and Intervention (EHDI) Act in 2017. Singapore has successfully mandated UNHS since 2002, achieving a remarkable 99% coverage across all hospitals. These examples underscore the importance of strong governmental policies and funding to sustain universal screening initiatives.

Challenges and the Way Forward

Despite progress, significant barriers remain in Malaysia's neonatal hearing screening efforts. Studies indicate that some hospitals have discontinued UNHS due to funding constraints and equipment shortages[2]. Otoacoustic emission (OAE) and automated auditory brainstem response (AABR) devices, essential for screening, require frequent maintenance and replacement. Ensuring a dedicated federal budget for neonatal hearing screening is crucial.

Moreover, trained personnel are vital for an effective screening program. While the process is automated and time-efficient, tasking overburdened nurses with additional responsibilities may not be ideal. Instead, specially trained hearing screening personnel should be

employed, with audiologists providing oversight and expertise.

Beyond screening, follow-up care remains a major challenge. Many infants who fail initial screening do not return for further assessment, often due to logistical difficulties or lack of parental awareness. Implementing an electronic tracking system accessible nationwide could improve follow-up rates. Studies have found that families often relocate postpartum, making it difficult to track patients. In states like Kelantan, where newborns require identity cards for property eligibility, integrating hearing test data into official records may facilitate better follow-up adherence.

Raising Awareness and Education

Lack of awareness among healthcare professionals and the public further impedes the success of neonatal hearing screening programs. Recent research from SASMEC@IIUM in 2024 demonstrated that targeted educational interventions significantly improve healthcare professionals' knowledge and attitudes toward UNHS. Among medical specialties, otolaryngology (ORL) staff exhibited the highest awareness, likely due to their direct involvement in the field. Other studies across Malaysia have echoed similar findings, reinforcing the need for continuous medical education.

Equally important is parental awareness. Many parents remain uninformed about the impact of untreated hearing loss and the necessity of follow-up care[3]. Healthcare providers must actively educate parents on the importance of neonatal screening and available intervention options. Public health campaigns, including mass media outreach and advertisements, can further enhance awareness and reduce stigma surrounding hearing aids and cochlear implants.

The inclusion of hearing health in medical and nursing school curricula is another crucial step. Additionally, integrating hearing awareness topics into primary and secondary school education could foster long-term awareness and proactive attitudes toward hearing health.

Conclusion: Are We Doing Enough?

While neonatal hearing screening has advanced significantly worldwide, challenges remain in accessibility, funding, follow-up care, and awareness. Stronger governmental policies, sustained funding, and widespread education are essential to ensuring that all children receive early hearing screening, diagnosis, and intervention. Malaysia must strive to follow the example of countries with successful UNHS programs, ensuring that no child is left behind due to undetected hearing loss.

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REVIEW ARTICLE

Method for Measuring Speech Enhancement of Electronic Hearing Protection Device: A Systematic Review

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ABSTRACT

The usage of electronic hearing protection devices (e-HPDs) among industrial workers has been introduced among others, to allow more effective communication in noisy environments. The effectiveness of the speech enhancement element of e-HPDs thus needs to be assessed. To date, no standardized speech enhancement assessment method is available. This systematic review aimed to compile and synthesize available information in the literature on speech perception test method of e-HPDs while also assessing the quality of the selected studies. The Cochrane methodology was used, with the findings documented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and checklist. The International Prospective Register of Systematic Reviews (PROSPERO) was utilized to register this systematic review, with the CRD number assigned as CRD42024526086. Five electronic databases were explored: PubMed, ProQuest, IEEE, Scopus, and ScienceDirect. The quality appraisal was conducted based on Effective Public Health Practice Project (EPHPP) tool. In total ten studies were reviewed, utilizing several speech tests including Hearing in Noise Test (HINT), Speech Recognition in Noise Test (SPRINT), Callsign Acquisition Test (CAT), Modified Rhyme Test (MRT), Quick Speech in Noise Test (QuickSIN), Dutch Monosyllabic Speech Test and Mandarin Disyllabic Word Discrimination Test (WDT) to evaluate speech enhancement capabilities in e-HPDs. In conclusion, speech tests are essential for assessing how well e-HPDs perform enhancing speech in noisy environments. HINT has the strongest quality compared to other speech test for e-HPDs assessment. HINT or its modifications can subsequently be considered in the anticipated standardized speech perception test method of e-HPDs tests worldwide.

Keywords
Speech Assessment, Speech Test, Electronic Hearing Protection Device, Noise, Worker

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Received: 16th May 2024; Accepted: 19th August 2024

Doi: https://doi.org/10.31436/imjm.v24i02.2617

INTRODUCTION

Speech intelligibility assessment is a crucial aspect of assessing communication, serving to demonstrate the clinical benefits or outcomes of hearing interventions such as cochlear implants[1] and hearing aids.[2] It is also important in occupational audiology, aiding in the quantification of noise-induced hearing loss's impact on speech perception. Several studies have highlighted how speech intelligibility assessment can reveal the unmet needs associated with passive hearing protection devices (HPDs). These studies found that workers wearing passive HPDs often exhibit poor speech perception compared to those without protection.[3,4] This was also proved in one study which stated that the passive mode in hearing protection device led to a decrease in speech recognition performance by 25-30 percent compared to unprotected listening.[3] This was affirmed by a similar study that revealed how two passive HPDs (Peltor & Nacre) reduced speech recognition performance by 27–29 percent and 17–25 percent respectively compared to unprotected listening.[5] Passive hearing protection device is defined as a hearing protection device without the use of dynamic, mechanical elements such as valves or reactive ports or electronic circuitry such as active noise cancellation or electronically modulated signal pass-through technology.[6]

This reduction may cause workers to remove their HPDs to hear speech; a common occurrence proved by a study done in Malaysia which documented 25 percent of sawmill workers felt that HPDs created a barrier during communication,[7] thus forcing them to remove the HPDs temporarily which potentially results in noise-induced hearing loss (NIHL). To address these challenges, electronic hearing protection devices (e-HPDs) were introduced to mitigate communication barriers by allowing workers to hear speech while protecting their hearing. e-HPD is defined as devices that involved electronics components and digital signal processing that aimed to maintain good situational awareness while protecting against hazardous or loud noise.[8] Typically, the feature that is mostly incorporated in an e-HPDs is automatic noise reduction (ANR), which increases protection through the reduction of high noise levels, or phase-cancellation technology, which introduces antiphase noise. In contrast, speech is amplified and filtered at spectrum frequencies between 125 Hz and 8000 Hz by means of a level-dependent function, which continuously monitors the surrounding noise level to determine how much sound can pass through.[8]

Despite the gazettement of hearing protector implementation in laws and legislation[9], reluctance among workers to wear hearing protectors continuously persists due to various reasons, including attenuation of conversational signals, discomfort, and communication difficulties. Such reluctance can jeopardize critical communications, particularly in hazardous environments, where workers may need to respond to warning signals or interact with colleagues or supervisors.[10]

To alleviate these challenges, e-HPDs offer a promising solution. They facilitate more effective communication in noisy environments and help reduce instances where HPDs are removed. However, the suitability of existing speech intelligibility assessment methods for evaluating e-HPDs performance in industrial settings remains unclear because there are various types of speech test methods used to assess the e-HPD depending on their needs and interests. The wide variety of industrial noises also contribute to the none availability of a uniform standard to properly evaluate the speech enhancement component of an e-HPD due to the scarcity of assessing method. The authors thus felt that a systematic review looking into all previous methods that has been utilized to assess e-HPDs particularly those which also include not just the attenuation of noise but also the speech enhancement component was timely and much needed to ensure that workers that needed this type of protection gets what is expected. This is especially true in workers that need to hear speech conversation well during work as one study states that the passive protection led to a decrease in speech recognition performance by 25-30 percent compared to unprotected listening.[3]

This systematic review was retrospective in nature, conducted according to the Cochrane methodology13 where it involves defining the objectives through population, intervention, comparison, outcome (PICO), searching, screening, appraisal, analysis and reporting.

Registration

The International Prospective Register of Systematic Reviews (PROSPERO)14 of Cochrane Collaboration was used where the review was reported. The PROSPERO registration number was CRD42024526086.

Literature Searching

PubMed, ProQuest, IEEE, Scopus, and ScienceDirect were used to look for relevant papers published in December 2022. The above databases were chosen to cover all disciplines of biomedicine, biological sciences, medicine, general, engineering, computer & communication technology, and human sciences. The search was limited to the earlier fifteen years [2008-2023]. The search key consisted of ("active hearing protection device" OR "active hearing protector" OR "active personal hearing protection device" OR "active personal hearing protection" OR "active personal hearing protector" OR "active level-dependent hearing protection" OR "active level-dependent hearing protector" OR "electronic hearing protection device" OR "electronic hearing protection" OR "electronic hearing protector" OR "electronic personal hearing protection device" OR "electronic personal hearing protection" OR "electronic personal hearing protector" OR "electronic

level-dependent hearing protection" OR "electronic level-dependent hearing protector") AND ("speech intelligibility" OR "speech enhancement" OR "speech perception" OR "speech recognition" OR "speech test").

The process applied the inclusion criteria of articles for systematic review and meta-analysis combined a strategy using population, intervention, control, and outcomes measures (PICO). The PICO details are displayed in Table I. Publications were accepted for inclusion if they included the keywords and phrases, as well as a general description of the speech test procedures used to evaluate electronic hearing protection devices. All quantitative and qualitative research were included. Only publications in the English language will be selected and only research that utilized electronic hearing protection devices were included. Papers with conventional hearing protection devices alone were excluded.

Table I: Inclusion criteria using Population, Intervention, Control, Outcomes (PICO) Strategy

PARAMETER	INCLUSION CRITERIA
Population	Adults 18 years or older with and without hearing loss
Intervention	Use of e-HPDs equipped with speech perception test methods
Control	Non e-HPDs or no hearing protection
Outcomes	Speech test used with the speech perception percentage (i.e., signal to noise ratio, speech recognition, percent correct)

Citation Management

All citations were imported into the Mendeley software, and all the duplicates of duplications were removed before the title and abstract relevance screening.

Screening

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 statement[15] is applied for the screening process. Two levels of screening was conducted with two reviewers audiological knowledge with certified from accredited university. The first level of screening is based on the title and the abstracts of the articles while the second level of screening was based on the full articles. The following eligibility criteria were utilized to screen the articles. This process was recorded in an excel workbook.

Title and Abstract Relevance Screening

Only the title and abstract of citations were examined at the first level to ensure effective time management in situations when resources may be squandered by getting articles that did not match the minimum inclusion criteria. For relevance screening, the researchers used spreadsheets to create the title and abstract. The researchers separately reviewed the title and abstract of each citation. Any disagreements were resolved among the researchers through regular discussion. The principal author then read the full texts of the remaining articles and summarised them for discussion with the team later. The full-text journal articles were discussed among the researchers before the data was extracted.

Quality Assessment

The study quality was evaluated using the Effective Public Health Practice Project (EPHPP) critical appraisal tool. This process includes grading each article as strong, moderate or weak based on the following components: (1) Selection bias, (2) Study design. (3) Confounders, (4) Blinding, (5) Data collection methods, and (6) Withdrawal and drop-outs. A score of 1 applied if the study was "strong", a score of 2 for "moderate", and 3 for "weak". According to the following acceptance criteria, the decision to grade the global score for each paper was strong if it had no weak attributes, moderate if one weak attribute and weak if two or more weak attributes.[16,17]

Data synthesis

The data contained in the selected articles were extracted and synthesized based on PICO: (1) population (number, age, sex, hearing threshold); (2) interventions and control (types and brands of personal hearing protector used); (3) outcomes (type of speech test used with the speech perception percentage (i.e., signal to noise ratio, speech recognition, percent correct).

RESULTS

Article Selection

A total number of 166 articles and abstracts were initially selected from the search. Figure I shows the number of articles that were screened and assessed for eligibility. Then, 46 duplicate articles were eliminated. In the next stage 75 of the remaining 120 papers were rejected because they did not match the inclusion requirements. The writers reviewed the remaining 45 publications for eligibility, and 35 were found unfit based on certain criteria. Six papers were further excluded because they did not utilize electronic personal hearing protector device in their studies, while 22 papers were removed as the speech assessment test method of e-HPDs were not discussed in those studies. Additionally, three papers that were not in full articles and three old publications that were more than 15 years earlier were excluded respectively. One publication that was not in English language, but in German in 1994 was removed from the final review. The attempt to translate the paper was not successful because it was an old publication. Finally, the remaining ten articles were deemed relevant for this final systematic review.

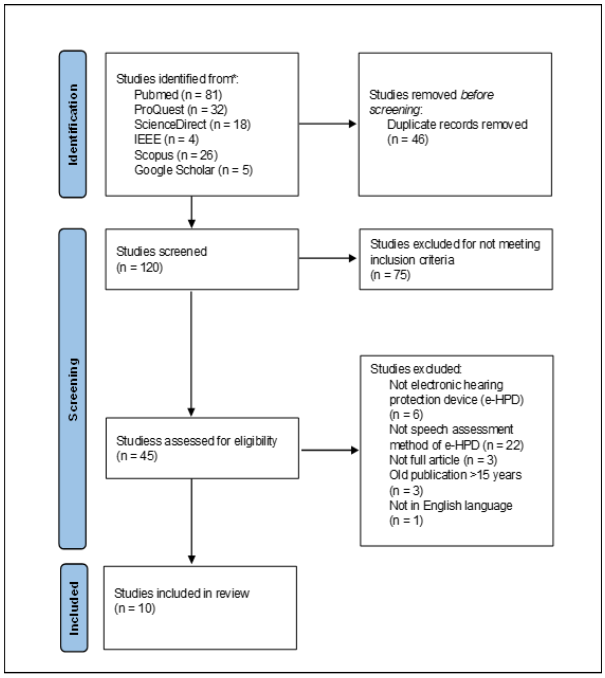

Figure 1. PRISMA flow chart of the article search and selection

Study Quality Scores

Table II shows the quality appraisal scores for the ten selected studies. Two studies were scored as strong as they did not have any weak scores across the quality appraisal criteria and two studies were scored as weak and both had poor quality due to the withdrawals and double blinding were not described in the articles. Meanwhile the rest of the articles were scored as moderate as they had 1 weak criterion in which the double blinding process was not described in those articles.

Table II: Quality appraisal scores for the ten articles included in the review.

Articles	Quality Appraisal Criteria						Global Score
	Participant Selection Bias	Study Design	Confounding variables	Double blinding	Data collection	Withdrawals	
Giguère, Laroche, and Vaillancourt (2015)[12]	2	1	2	2	1	1	1
Byrne and Palmer, (2012)[21]	2	1	2	3	1	1	2
Giguère, Laroche, and Vaillancourt, (2012)[3]	2	1	2	2	1	1	1
Brown et al., (2015)[19]	2	1	2	3	1	1	2
Brammer, Yu and Tufts, (2014)[22]	2	1	2	3	1	1	2
Smalt et al., (2019)[23]	2	1	2	3	1	1	2
Hung Lin et al., (2006)[24]	2	1	2	3	1	1	2
Nakashima and McDavid, (2018)[18]	2	1	2	3	1	1	2
Bockstael, Coensel and Bottekdooren, (2011)[20]	2	1	2	3	1	3	3
Hiselius, Edvall and Reimers, (2015)[4]	2	1	2	3	1	3	3

*1 is strong, 2 is moderate and 3 is weak

The Findings Based on PICO on the Speech Perception Test Method of Electronic Hearing Protection Devices

Population

The summarized results of the reviewed studies according to the PICO criteria are displayed in Table III. Six studies adopted normal hearing subjects and the other four studies recruited both normal hearing and hearing loss participants. Only one study classified the participants into 4 categories of hearing status (1) normal,

(2) slight-to-mild, (3) mild-to-moderate, and (4) moderate -to-severe.[5]

Intervention and Controls

All the studies included electronic hearing protection devices or protection devices with electronic elements in their speech test. Four studies utilized only electronic HPD in their research in which two studies combined electronic earmuffs and earplugs[5,18], one study utilized electronic earmuffs only[3], and one study did not state the type of e-HPD used.[4] Four other studies adopted both electronic and conventional HPDs (work as passive only) in their speech test in which two studies used earplugs category only[19,20], one study used earmuffs category only[21] and one study did not state both types of HPD or e-HPD used.[23] The remaining two studies utilized proof-of-concept devices and headsets with electronic features.[22,24]

Outcomes

Speech Test Methods for e-HPD

In the final reviewed articles, varieties of the speech perception test methods for electronic hearing protection devices (e-HPD) were adopted in their studies. The most utilized method is Hearing-in-Noise Test (HINT) (3 articles, 30%)[3,5,21], followed by Modified Ryhme Test (MRT) (2 studies, 20%).[22,23] The remaining five articles[4,19,20,24] individually utilized different methods which are Callsign Acquisition Test (CAT), Modified QuickSIN test, Dutch monosyllabic speech test, Mandarin Disyllabic Word Discrimination Test (WDT), and Speech Recognition in Noise Test (SPRINT) respectively. The details of the speech perception test methods of e-HPD were classified as shown in Table III.

The Outcome Measure of the Speech Test

Most of the studies measured percent word recognition score (WRS) in their speech test outcome.[3,5,22,24] Two studies considered speech recognition scores in absolute as their outcome measure.[18,20] The remaining four studies assessed different outcome measures based on the type of speech test used in which speech recognition threshold[4], mean QuickSIN score[19], MRT percent correct[16] and lastly, correct percentage of HINT test score.[21]

DISCUSSION

Meta Analyses

The researcher actually intended to conduct the meta-analyses; however, this was not possible as there are insufficient studies related to the speech perception test method of e-HPDs in the body of knowledge. Only ten studies were available for discussion. Additionally, all the studies included had different methodologies like different sample sizes recruited, type of speech tests used some using HINT, MRT, CAT, SPRINT, and more. There was also unstandardized type of e-HPDs used as well as the outcome measures etc that made it impossible to proceed with the meta-analyses. The alternative syntheses used is narrative synthesis.

Speech Test

From the included studies in this review, most of the researchers used Hearing-in-Noise Test (HINT) for the speech perception test of the e-HPDs. It is mostly used due to the nature of the HINT test that can be developed and adapted to other languages to provide comparable measurements of speech intelligibility in noise for each language.[25] Various HINT test has already been developed for other languages such as Malay[26], Mandarin27, Danish28, American English[29], Brazilian Portuguese[30], Cantonese[31], Korean[32], Spanish[33], Norwegian[34], Turkish[35], Castilian[36], Canadian French[37], Japanese[38], Bulgarian[39] and many others. Based on the location of the studies conducted, it is preferable to use the language of the speech test respective to the mother language of the local population as the ability to perceive speech in noisy environments is affected by the level of proficiency in a non-native language. This is also to make sure the reliability of the speech test itself.[40] Apart from that, HINT was claimed to adopt phonetically balance elements in its wordlists that is commonly used in intelligibility testing.

Table III: The Findings of The Systematic Review on the E-HPD Speech Test Methods Based On PICO

Author(s); date; study location	Participants	Type and brand of e-HPD used	Mode of testing	Speech test used	Outcome measures	Main Findings
Giguère, Laroche, and Vaillancourt, 2015[5], Canada	Forty-five adults aged from age 23 to 81 years old (24 males and 21 females). Participants were divided into four groups: normal hearing (n=12), minor to mild hearing loss (n=12), mild to moderate hearing loss (n=12), and moderate to severe hearing loss (n=9).	[1] One level-dependent earmuff: Peltor® PowerCom Plus™ (muffs) *Active SR1-SR5 *NRR 25dB [2] One level dependent earplug: Nacre QuietPro (earplugs) *Active (TT2-TT11) *Passive (TT1- 29dB NRR)	[1] Unprotected [2] Passive attenuation [3] Active (low gain) [4] Active (high gain) Low and high gain quantitatively measured using manikin"	Hearing-in-Noise Test (HINT).	Speech recognition (% word recognition).	Participants with normal hearing exhibited minimal effect, however those with the most hearing loss showed significant reductions in scores as compared to unprotected listening. At both low and high gain pass-through levels, activating the devices' level-dependent mode produced significant speech recognition gains over the passive mode.
Byrne and Palmer, 2012[21], United Stated	15 adults with normal hearing (aged 21 to 60 years)	[1] One electronic earmuff: MineEars electronic earmuffs. (ProEars, Westcliffe, CO, USA). [2] One passive earmuff: Bilsom model 847 (Sperian Hearing Protection, San Diego, CA, USA).	[1] Passive muff [2] Active off, low gain, and high gain	Hearing-in-Noise Test (HINT).	Correct percentage of HINT test score (%)	The repeated-measures ANOVA findings revealed a significant main effect for the SNR condition [F (2,28)=1014.50, p 0.0001]. The highest scores were obtained when the SNR was +5 dB, while the lowest values were obtained when the SNR was -5 dB. The earmuff condition also had a significant main effect [F (3,42) = 57.19, p 0.0001]. The interaction effect was also significant [F (6,84) = 6.94, p 0.0001].
Giguère, Laroche, and Vaillancourt, 2012[3], Canada	Twenty-two subjects (combination of hearing status)	One electronic earmuff: Peltor Powercom Plus (muff) *NRR 25dB *At full gain, limit at 87dBA	[1] Unprotected [2] Passive attenuation [3] Active (low gain) [4] Active (high gain)	Hearing-in-Noise Test (HINT).	Speech recognition (% word recognition).	The passive mode with surround off led to a decrease in performance by 25-30% compared to unprotected listening, while the active modes yielded a benefit of 11-15% and 23-24% at surround setting 1 (low gain) and surround setting 4 (high gain) respectively.
Brown et al., 2015[19], United States	Ten normal hearing male adults (mean age: 29.5 years)	A proof-of-concept device	[1] Conventional passive HPD [2] Active HPD with subband ANC and no communication signal processing [3] Active HPD with subband ANC and communication channel gain processing.	Modified Rhyme Test (MRT).	Word recognition score (%)	Follow-up pair-wise tests revealed that Combat Arms (t9 = 3.00, p=0.015) and Hybrid (t9 = 3.53, p=0.006) performance was significantly worse than Control (p=0.595), while EB15 performance was very similar to Control (p=0.595) and better than Combat Arms (t9 = 2.41, p= 0.039) or Hybrid (t9 = 3.17, p=0.011). Thus, the EB15 performed the best voice recognition among the three HPDs tested in the speech-in-noise task, despite the fact that mean scores for all conditions were higher than 25, with more than 80% correct.
Brammer, Yu and Tufts, 2014[22], United States	Six subjects normal hearing (4 male and 2 female) with mean age of 29.5 ± 8.5 yrs. Subjects are Native American English	[1] Two actives electronic [2] Two passive Brands were not stated	[1] Open ear [2] Passive A [3] Passive B [4] Active A [5] Active B	Modified Rhyme Test (MRT).	MRT percent correct score (%)	For the environmental noises used in this work, subband speech SNR control paired with subband ANC enhanced word scores more than subband ANC alone and improved word score consistency among participants.
Smalt et al., 2019[23], United States	Thirteen adults with normal hearing (excluding one) with an average age of 31 years.	Four earplugs: [1] Etymotic EB15 (active) [2] Active prototype [3] 3M Combat arms (passive) [4] ShotShields passive prototype	[1] Control (open) [2] Active hpd [3] Active prototype [4] Passive hpd [5] Passive prototype	Modified version of QuickSIN test.	Mean QuickSIN score (out of 30 words)	There was an effect of HPD (F [4,48] = 3.716; p = 0.010) and a noise level effect (F [2,24] = 1737; p=2 1016). There was no effect of HPD or noise level on MRT performance. A pairwise T-test with Bonferroni-Holm correction for multiple comparisons revealed that Active A and Active B were the only HPD pairs with significant differences in MRT performance (p = 0.017).
Hung Lin et al., 2006[24], Taiwan	Thirty normal hearing subjects aged of 19-30 years old (15 men and 15 women)	Feedback Adaptive Active Noise Cancellation (FBAANC) headset	1) With headsets 2) without headsets	Mandarin Disyllabic word discriminatio n test (WDT).	Word recognition score	The mean WDT score is the average of the first six lists on the same SNR. When the SNR was more than -10dB, the mean WDT score was greater than 80%. However, the score with the FbAANC headset was 6 to 8% lower than the score without the FbAANC headset on the SNR of -5 and 0 dB. However, when the SNR was less than -10dB, the score with the FbAANC headset was 13 to 32% higher than without the FbAANC headset.
Nakashima and McDavid, 2018[18], Canada	Eighteen participants ages 20-54 yrs old (15 males and 3 females). 16 normal hearing and 2 have hearing loss at 40dBHL at 6/8kHz	[1] One electronic earmuff 3M Peltor Tactical 6-S (muff) *max level of 82 dBSPL [2] One electronic earplug (Invisio V60 and X5 headsets)	1) Unprotected 2) Active earmuff 3) Active earplug	Speech Recognition in Noise Test (SPRINT).	Number of correctly repeated words (out of 50 numbers)	The conventional SPRINT settings yielded average scores ranging from 41 to 44 out of 50, while the SHL SPRINT conditions yielded scores ranging from 20 to 34 out of 50. A two-way ANOVA on the results revealed significance for the ear condition (F=34.7, p 0.001) and SPRINT condition (F =1077, p 0.001), mas well as their interaction (F=27.3, p 0.001). Unprotected ear and earplug (EP) and unprotected and earmuff (EM) pairwise comparisons were significant (p 0.001 for both). There was no discernible difference between EP and EM circumstances.
Bockstael, Coensel and Bottekdooren, 2011[20], Belgium	60 normal-hearing subjects (30 males and 30 females) with average age of 27.6 years old. They are native Dutch speakers.	[1] One acrylic passive earplug (25NRR) [2] One active custom-made earplug [3] One active form earplug	[1] Unoccluded [2] Active min [3] Active max [4] Active foam [5] Passive earplug	Dutch monosyllabic speech test.	Speech recognition score (absolute)	The interaction effects between sound environment and subject [F (236, 647) =1.2; p=0.032], listening condition and subject [F (162, 647) =1.3; p=0.009], and sound environment and listening condition [F (12, 647) =77.7; p0.0001] are all significant (=0.05). If the amplification is set low enough, active custom-made protectors look to be a better option.
Hiselius, Edvall and Reimers, 2015[4], Sweden	Thirty-one normal hearing subjects	Three electronic HPDs. Brand not stated	Three e-HPDs in 2 noises each (3x2)	Callsign Acquisition Test (CAT)	Speech Recognition Threshold (SRT)	Passive HPDs with low attenuation are expected to have a negligible effect on speech intelligibility in noise, whereas an electronic HPD with a level-dependent function has the potential to improve intelligibility.

The Quality Score of the Study

Tool Utilized

Effective Public Health Practice Project Quality Assessment Tool was utilised for this study instead of other quality assessment tool specifically the Cochrane Collaboration Risk of Bias Tool (CCRBT). EPHPP was selected as this is a more generic tool that can be used to assess various types of study designs, including RCTs, observational studies, and before-and-after studies compared to CCRBT that specifically designed for assessing randomized controlled trials (RCTs). It evaluates risks of bias in depth across several domains. As this study is interested in a holistic view of study quality, the EPHPP was chosen to assess broader methodological quality, which includes but is not limited to bias meanwhile CCRBT focuses specifically on the risk of bias. More importantly, EPHPP can be scored based on objective guideline meanwhile CCRBT was scored subjectively. Thus, EPHPP is easier to be used and applied across different types of studies with less intensive training compared to CCRBT. The latter may require more training and expertise to apply effectively, as it requires detailed judgments about bias that are often not straightforward. In addition, EPHPP is flexible and has better inter-rater reliability compared to CCRBT.[17]

Quality Scores

Among ten available speech tests for e-HPD assessment, the articles that utilized HINT in their speech perception test have the strongest quality, as six aspects of elements in which participant selection, study design, confounding variables, double blinding, data collection, and withdrawals information have been clearly stated in those studies. The high-quality appraisal scores indicate that studies using HINT typically adhere to rigorous methodological standards, which enhances the reliability and validity of their findings. Additionally, because HINT was already adapted to multiple languages, it is widely used around the world. Both the reliability of the studies and the test's adaptability contribute to its popularity and acceptance as a preferred method for assessing speech perception. Two articles that were categorized as weak due to the unclear description on the blinding and withdrawal elements were still be included in this study as the researcher just wanted to explore all the available speech test method for e-HPDs.

CONCLUSION

In summary, speech tests play a crucial role in evaluating the performance of e-HPDs in ensuring their effectiveness in enhancing speech perception in noisy environments. Each speech test for e-HPD assessment has its advantages and disadvantages. The choice of tests used depends on factors such as language compatibility, ease of administration, reliability, and validity, with researchers selecting the most appropriate test for their specific study objectives. This review found that studies using HINT showed the strongest quality scores compared to other speech tests and should thus be utilized and adopted in future standardized speech perception test method of e-HPDs worldwide. Based on this review, the authors would also like to suggest future studies that compare and assess speech tests to determine the most appropriate speech test in e-HPDs assessment, as currently, no such experiments have been conducted. This will surely expedite the development of a much-anticipated standardized assessment of speech-enhancing element of e-HPDs specifically and hearing protection devices in general.

FUNDINGS

This study was funded by Ministry of Science, Technology, and Innovation (MOSTI). There are no conflicts of interest, financial, or otherwise.)

CONFLICT OF INTEREST

There are no known conflicting financial or non-financial interests among the authors that could have influenced the conclusions presented in this study.

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NARRATIVE REVIEW

Intestinal Barrier Integrity: The Essential Role of Neuropeptides and Their Implications in the Pathogenesis of Gastrointestinal Diseases

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ABSTRACT

The intestinal barrier relies on tight junctions and proteins including claudins, occludins, and zonula occludens, helping to seal the epithelial cell gaps and hence controlling permeability. When tight junctions are disrupted, intestinal permeability increases, a condition recognised as "leaky gut." This condition is linked to gastrointestinal (GI) disorders including inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). Neuropeptides are crucial in modulating the tight junctions' integrity within the GI epithelial barrier. This review focuses on neuropeptide Y, vasoactive intestinal peptide, cholecystokinin, and substance P in regulating intestinal barrier integrity. Studies included in this narrative review were selected based on their relevance to the topic, identified through searches in databases such as Google Scholar, PubMed, and Mendeley using relevant keywords. Understanding the mechanisms of these neuropeptides may provide pathophysiological insights and potential treatment strategies for restoring intestinal barrier integrity in GI disorders.

Keywords
Intestinal barrier, neuropeptide Y, vasoactive intestinal peptide, cholecystokinin, substance P

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Received: 21st October 2024; Accepted: 25th February 2025

Doi: https://doi.org/10.31436/imjm.v24i02.2712

INTRODUCTION

The gastrointestinal tract (GIT) is a complex system essential for absorbing water and electrolytes to maintain fluid balance while efficiently processing and eliminating waste products. This process is carried out by a series of specialised organs which span between the mouth and the anus, each fulfilling a distinct role. The GIT also hosts a diverse microbiota that plays an integral part in maintaining digestive health.[1] Central to the function of the GIT is the intestinal barrier, a critical structure that divides the body's internal environment from the gut lumen.

The mucosal barrier of the GIT consists of three distinct layers: an outermost layer contains mucus, gut microbiota, and defense proteins such as secretory immunoglobulin and antimicrobial peptides. The middle layer is formed by intestinal epithelial cells, connected by junctional proteins such as tight and adherens junctions.[2] The innermost layer, the lamina propria, houses connective tissues, blood vessels, and immune cells. The principal role of this barrier is to selectively assimilate nutrients and other essential substances from the lumen while effectively blocking harmful foreign materials, food particles, microorganisms, and their byproducts from entering the body.[1]

The expansive surface area and high energy demands highlight the vital role of the GIT in nutrient absorption and safeguarding against harmful substances and pathogens.[2] This protective function is largely supported by tight junction proteins (TJPs) localised near the apical region of the epithelium between adjacent cells. These TJPs consist of dynamic structures comprised of at least 20 transmembrane proteins that continuously interact with their components to regulate the effectiveness of the gut barrier.[3] The key transmembrane proteins, including claudin, occludin, zonula occludens-1 (ZO-1), and cingulin, are necessary for sustaining the structural integrity and biological functions of intestinal epithelial cells.

An optimally functioning intestinal barrier is necessary for maintaining gut health. A dysregulated intestinal barrier is believed to contribute to various diseases, including GI disorders, and extend beyond the gut through interactions across the gut-brain axis.[4] The gut-brain axis is a bidirectional communication network involving neural, hormonal, immune, and microbiota pathways.[4] When this barrier function is compromised, it leads to amplified intestinal permeability called "leaky gut". This condition allows harmful substances such as toxins, bacteria, and other foreign molecules, which are normally restricted, to be excessively absorbed into the systemic vascular system.[5] It then triggers cascades of systemic effects that lead to extra-intestinal disorders, including metabolic disorders such as diabetes and obesity, neurodegeneration and neuropsychiatric conditions like depression and anxiety, as well as altered immune responses that may trigger inflammatory diseases.[2] A dysregulated intestinal barrier is believed to contribute to neurodegenerative and psychiatric disorders through interactions across the gut-brain axis.[45] These effects arise through mechanisms involving altered gut microbiota, disrupted intestinal barrier function, and changes in neuropeptide signalling pathways within the gut-brain axis.[2]

Neuropeptides such as ghrelin, glucagon-like peptides, neuropeptide Y (NPY), vasoactive intestinal peptide (VIP), cholecystokinin (CCK), and substance P (SP) play an important role in regulating gut health.[6] Current research highlights the role of neuropeptides in facilitating communication between the gut microbiota and the host along this axis. These neuropeptides are secreted not only by neurons in both central and peripheral but also by the GIT, establishing an important bridge between the gut and the brain. Moreover, these peptides are essential to uphold the integrity of the intestinal barrier, which is vital for overall gastrointestinal health.[7] This review will emphasise the role of different neuropeptides, including NPY, VIP, CCK, and SP in regulating intestinal barrier integrity and their associated roles in disease pathogenesis. This narrative review incorporates studies considered relevant to the topic, identified through searches on Google Scholar, PubMed and Mendeley using keywords including "intestinal barrier", "neuropeptides", "gut-brain axis", and "intestinal permeability".

INVOLVEMENT OF GUT NEUROPEPTIDES IN INTESTINAL BARRIER INTEGRITY

Neuropeptide Y (NPY)

NPY is a 36-amino acid neuropeptide widely distributed throughout the body, including the central and peripheral nervous systems, and in organs associated with the cardiovascular, gastrointestinal, and genitourinary systems.[8] It is primarily expressed in the hypothalamus, playing a crucial role in responding to peripheral metabolic signals, thereby regulating food consumption and energy metabolism.[9] In the peripheral nervous system, it works with norepinephrine and adenosine triphosphate to modulate cardiovascular and other physiological functions.[8,9] Numerous studies highlight NPY's critical role in the GIT, particularly in regulating gastrointestinal motility through its effects on smooth muscle contractions, as well as mediating vasoconstriction in the gastrointestinal blood vessels.[10]

Additionally, NPY influences intestinal barrier permeability, contributing to the maintenance of the gut barrier function through various mechanisms.[8] The intestinal epithelium, which lines the small intestine, consists of structures such as the brush border, crypts, villi, and a basolateral plasma membrane.[2] This epithelium facilitates nutrient absorption and serves as a critical physical and biological barrier.[11] TJPs, such as occludins, claudins, and zonula occludens, are vital for preserving the integrity of the epithelial barrier by sealing the paracellular space between adjacent epithelial cells. This prevents the intrusion of external substances such as microorganisms, antigens, and xenobiotics.[2]

There is a significant connection between NPY and the regulation of TJPs. Claudin-2 which primarily serves as a marker of a leaky gut barrier, functions as the transmembrane protein responsible for channel formation, that allows the transport of small ions and water.[12] One study demonstrated that NPY increases epithelial monolayer permeability by upregulating the expression of claudin-2 through the phosphatidylinositol-

3-kinase (PI3K) pathway. In an experiment using colonic tissue cultures from the wild type and NPY knockdown mice, NPY was found to enhance epithelial permeability while NPY knockdown was demonstrated to improve intestinal integrity.[13]

Further evidence comes from another study, which found that overexpression of NPY leads to disrupted intestinal homeostasis, compromised barrier integrity, increased intestinal permeability, and elevated serum levels of inflammatory cytokines in the samples of ovariectomized rats.[14] These pathological changes are reversed by the NPY receptor antagonist (BIBO3304), implicating the involvement of NPY in the pathophysiology of leaky gut. Collectively, these findings underscore NPY's essential role in preserving intestinal permeability function, with its dysregulation potentially contributing to the development of intestinal disorders.

Vasoactive Intestinal Peptide (VIP)

VIP belongs to the secretin-glucagon peptide family and is a 28-amino acid peptide secreted through the proteolytic cleavage of its precursor, preproVIP195, a 170 -amino acid protein. VIP exerts diverse roles in both physiological and pathological conditions, affecting the growth, development, and regulation of epithelial, neuronal, and endocrine cells.[15] VIP is present in mast cells and lymphoid cells, with primary localisation in the neurons of the GIT.[16] In the gastrointestinal system, VIP serves various functions, including stimulating growth, regulating intestinal blood flow, controlling gut motility, relaxing sphincters, managing secretion activities, and modulating intestinal inflammatory response.[1]

Extensive research has highlighted the protective role of VIP in maintaining intestinal barrier integrity. It prevents increased intestinal permeability by enhancing TJPs.[17] Intestinal permeability is controlled by TJPs located between intestinal epithelial cells at the uppermost part of the intestinal epithelium.[17] Moreover, immunoreactive claudin-3 was observed within the intestinal crypts during necrotizing enterocolitis (NEC), and administration of VIP helped preserve the distribution and expression of TJPs.[18] The expression of claudin-3 was markedly elevated in the NEC+VIP group in juxtaposition with the solitary NEC group, suggesting that exogenous delivery of VIP reduces tight junction impairment.

Despite its protective roles in the barrier function, VIP is also implicated in the pathology of IBS, with studies showing that IBS patients exhibit significantly higher plasma levels of VIP compared to healthy controls.[19] Additionally, a separate study revealed that irregular food intake impairs barrier functions and causes dysbiosis, contributing to metabolic imbalance. This disruption is linked to chronic activation of VIP-producing neurons, suggesting the potential use of VPAC2 inhibitors to enhance barrier function.[20] These findings suggest that while VIP typically supports gut health via maintaining intestinal barrier function, its protective role may also be overwhelmed by other factors such as inflammation and altered microbial composition. In addition, elevated levels may represent a compensatory mechanism, underscoring its complex role in the disease's pathology.[21] Further investigations are required to understand the apparent contradiction between VIP's protective roles and its increased levels in IBS for better understanding of underlying mechanisms involved in the disease pathogenesis.

Cholecystokinin (CCK)

CCK is a hormone released by the gut endocrine cells that facilitates bile secretion from the gallbladder into the small intestine. CCK is synthesized from a 115-amino acid precursor molecule that undergoes various modifications to generate several isoforms ranging from 4 to 58 amino acids.[22] The main fragments present in the human body include CCK-58, CCK-22, CCK-33, and CCK-8. Of these, CCK-8 is the smallest active form and is recognised as a potent neurotransmitter.[23] Notably, CCK-8 has remained largely unchanged across species, retaining its biological functions through interaction with its receptors present in both the central nervous system (CNS) and GIT.[22]

CCK regulates GIT motor functions by inhibiting gastric emptying and stimulating gut motility. It induces smooth muscle contraction in the gallbladder and GIT while also

enhancing glandular excretion in the liver, pancreas, small intestine, and other organs.[23] CCK has been demonstrated to protect the colonic mucosal barrier by regulating TJPs and preventing damage in sepsis.[24] Intervention with CCK supports the integrity of the intestinal barrier by preventing excessive permeability and inhibiting the translocation of bacteria from the gut into the bloodstream. This protective function is vital in safeguarding the body from complications associated with a condition termed endotoxemia.

Substance P (SP)

SP is an excitatory neurotransmitter composed of 11 amino acids, produced by motor neurons in the central and peripheral nervous systems as well as in immune cells.[25] It belongs to the tachykinin (TAC) peptide hormone family, which is encoded by the TAC1 gene. SP serves dual functions as a neurotransmitter and a neuromodulator, with its highest concentration found in the mucosa of the GIT and its lower concentration in the lamina propria of the intestinal muscular membrane. In addition to its involvement in gastrointestinal inflammation, SP also affects the musculoskeletal and respiratory systems.[26] As a pro-inflammatory chemical messenger, SP is frequently activated during intestinal inflammation, contributing to altered gut motility.[26]

The significance of SP in gastrointestinal function is highlighted by research showing that patients experiencing constipation exhibited abnormal neurotransmitter levels, including a deficiency of SP, in the muscular layer of the intestinal walls.[27] Evidence suggests that SP may also influence intestinal activity through broad-spectrum action on the cationic transport channel in Cajal's interstitial cells, which is mediated by the release of intracellular calcium ions triggered by the stimulation of tachykinin NK1 receptors.[28] This interaction influences multiple processes beyond gastrointestinal motility, including secretion from glands, vascular membrane permeability, and pain responsiveness.

Besides its role in regulating gut motility, recent findings suggest that SP can enhance epithelial cell expansion and exert an apoptosis-inhibiting effect at injury sites in the colon by interacting with its high receptor affinity neurokinin-1 receptor, NK-1R.[29] In terms of TJPs, SP accelerates intestinal healing by increasing the expression rate of ZO-1.[30] SP has also been shown to protect against sodium lauryl sulphate (SLS)-induced toxicity by sustaining the expression of E-cadherin at adherens junctions and providing anti-inflammatory effects.[31]

On the flip side, excessive expression of SP can disrupt normal gastrointestinal function. In a related case study, elevated serum levels of SP were observed in infants with acute intussusception, a condition characterised by a section of the intestine folding into another segment. This primarily occurs in the small bowel, while isolated cases involving only the large bowel are relatively rare.[32] The involvement of neuropeptides in the integrity of the intestinal barrier was summarised in **Table I** and illustrated in Figure 1.

Table I: Roles of Neuropeptides in Intestinal Barrier Integrity

Neuropeptides	Roles in Intestinal Barrier Integrity	Mechanisms	Study
NPY	Increases permeability	Upregulates claudin-2 expression via PI3K pathway	11–13
VIP	Enhances tight junction proteins but may disrupt barrier at high levels	Improves claudin-3 expression; protective against NEC	17–20
CCK	Regulates motility and protects barrier integrity	Enhances tight junction proteins; exhibits anti-inflammatory	24
SP	Promotes healing and tight junction maintenance but disrupts function at excess levels	Enhances ZO-1 expression, maintains E-cadherin	27–32

Abbreviations: CCK, cholecystokinin; NEC, necrotizing enterocolitis; NPY, neuropeptide Y; PI3K, phosphatidylinositol-3-kinase; SP, substance P; VIP, vasoactive intestinal peptide; ZO-1, zonula occludens-1

INVOLVEMENT OF GUT NEUROPEPTIDES IN GASTROINTESTINAL DISEASES AND DISORDERS

Irritable Bowel Syndrome (IBS)

IBS is a chronic GI disorder defined by disturbances in the complex brain-gut axis. Patients typically experience abdominal pain along with alterations in faeces consistency, immune response initiation, dysregulated intestinal motility, augmented intestinal barrier permeability, and enhanced vulnerability to psychosocial stressors.[33] Globally, IBS affects approximately 11.2% of the populace, making it the most prevalent functional gastrointestinal disorder.[34] Although the well-defined aetiology of IBS continues to be elusive, it is postulated to

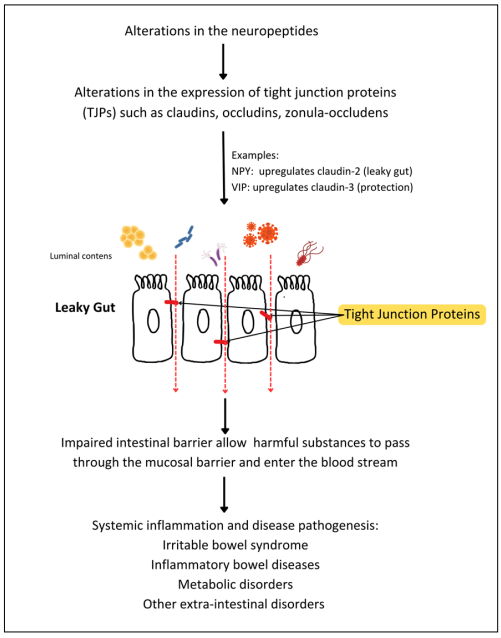

Figure I: The association between the gut-brain axis dysregulation and neuropeptide alterations in leaky gut and gastrointestinal disorders.

involve a complex interplay of various contributing factors. Dysfunction of the brain-gut axis is growingly acknowledged as a significant factor in the development of IBS.

Neuropeptides exacerbate intestinal barrier dysfunction, a critical component of IBS pathology. Research revealed significant alteration in the blood levels of neuropeptides, including SP and NPY, in different diarrhoea-predominant IBS rat models in comparison to the normal reference group. In the context of IBS, elevated SP levels indicate an increased perception of intestinal pain and visceral hypersensitivity, while reduced NPY levels suggest dysregulation of the stress response and an imbalance in gut homeostasis.[35] Similarly, increased SP and decreased NPY were reported in a retrospective cohort study involving IBS patients and in an animal study using IBS mouse models.[36,37] In contrast, a cross-sectional study reported higher NPY levels in IBS patients as opposed to healthy control subjects.[38] Differences in the physiological response to stress or inflammation among IBS patients might contribute to these contrasting findings.

The expression of VIP is reportedly elevated in IBS, as presented in an animal study using specific pathogen-free Sprague-Dawley rats and in a clinical study.[19,39] This points to the fact that increased VIP levels may contribute to the pathophysiology of IBS by influencing gastrointestinal motility and sensitivity. Conversely, another reported decreased VIP expression in IBS constipation patients, indicating that VIP expression may not consistently increase in IBS across different experimental conditions or models.[40] These discrepancies underscore the complexity of neuropeptide regulation in IBS and highlight the need for further research to clarify the role of VIP in this disorder.

A randomised comparative trial observed that IBS patients exhibited higher levels of cholecystokinin (CCK) than healthy individuals, with increased levels associated with constipation, while NPY levels were undetectable.[41] Additionally, a case study also indicated elevated CCK levels in IBS patients.[40] This study found direct correlations between CCK levels in both the mucosa and plasma and various pain metrics, including pain intensity, symptoms, and frequency. Conversely, the levels of CCK measured before meals were substantially reduced in individuals with IBS compared to controls. While baseline pre-prandial CCK levels in IBS patients were quite low, they surged nearly fourfold after eating. This suggests that IBS patients may respond differently to meals, potentially contributing to their symptoms and digestive issues.[40]

Inflammatory Bowel Disorders (IBD)

IBD is a recurring disorder of the digestive tract that progresses over time and is characterized by abnormal and persistent inflammation. It incorporates two major types: Crohn's disease and ulcerative colitis.[42] As indicated by the Global Burden of Disease Study, the IBD prevalence continues to rise, with an estimated 4.9 million cases worldwide in 2019.[43] Most IBD cases are diagnosed between the ages of 15 and 35 years old, with approximately 25–30% of patients under 20 years old diagnosed with Crohn's disease, while one-fifth are diagnosed with ulcerative colitis.[44] A significant factor in the development of IBD is a disproportionate immune reaction against microbes and disrupted gut microbiota in genetically susceptible individuals. IBD is associated with the integrity of the intestinal barrier, particularly the TJPs. Although IBD is classified as an idiopathic disorder,

numerous studies suggest that maintaining intestinal barrier integrity is vital to prevent its development. A compromised intestinal barrier leads to increased intestinal permeability, allowing the translocation of bacteria and toxins, which can trigger a series of immune and inflammatory responses. Alterations in TJPs are also observed in IBD. For instance, claudin-2, a tight junction protein essential for forming water channels in the space between cells, is often highly expressed in leaky epithelial tissues and enhanced in IBD. This excess of claudin-2 contributes to heightened intestinal permeability and worsens the inflammatory response associated with the disease.[45,46]

NPY acts as a pro-inflammatory molecule in IBD. In animal studies, NPY has been shown to increase epithelial permeability by activating the PI3-K pathway, leading to the intensified expression of claudin-2. This increased claudin-2 expression can compromise intestinal barrier integrity and potentially contribute to the onset and development of IBD.[14] Clinical studies using sigmoid colon biopsies further support these findings, showing elevated NPY expression in patients diagnosed with IBD.[47] Nevertheless, CCK has shown promise in reducing the inflammatory response in the compromised intestine while also enhancing the integrity of the intestinal epithelial barrier. *In vivo* studies suggest that CCK may effectively treat IBD due to its anti-inflammatory characteristics and its role in maintaining intestinal barrier function.[48,49]

The neuromodulator VIP is recognised for stimulating vasodilation of the intestinal barrier and has also been implicated in the progression of IBD. An animal study revealed significantly elevated VIP expression in dogs with severe IBD.[50] Similarly, a clinical study reported significantly intensified VIP levels in the plasma of those diagnosed with Crohn's disease and ulcerative colitis compared to controls.[51] A similar pattern is observed with SP, where another research found elevated serum levels and enhanced density of SP immunoreactive fibres in the lamina propria of IBD patients.[26] Furthermore, SP stimulates the expression of inflammation-associated cytokine mRNA and the excretion of inflammation-associated cytokines in mesenteric preadipocytes derived from individuals suffering from IBD.[52]

Table II highlights changes in the levels of neuropeptides and their roles in GI diseases such as IBS and IBD. The inconsistencies in results could be attributed to several reasons such as differences in experimental models, study duration, and variations in measurement techniques.[38,53] Further studies employing similar study populations, larger sample sizes, and standardized measurement protocols are warranted to address these discrepancies and to provide more relevant findings.

Table II: Roles of Neuropeptides in Gastrointestinal Disorders

GIT Diseases	Mechanisms	Pathogenesis	Study
IBS	Altered in IBS; SP associated with pain, NPY with stress response	Elevated SP, reduced NPY in IBS though some studies show higher NPY levels in IBS	[24,35,37–39]
IBD	NPY increases permeability; SP and VIP contribute to inflammation	NPY, VIP, and SP levels elevated in IBD, with roles in enhancing permeability and cytokine production.	[16,41–50]

Therapeutic Implications for GI Diseases

Understanding the underlying roles of each neuropeptide in modulating intestinal barrier function potentially offers prospective directions for clinical applications for GI disorders like IBS and IBD. For instance, the use of NPY receptor antagonists to block NPY signalling, NPY gene transcription inhibitors to reduce NPY transcription, and anorexigenic hormone analogues to reduce NPY-induced food intake are among potential strategies which target the NPY pathways.[8] Additionally, VIP and NPY are being explored for their roles in IBS and IBD, where VIP modulation can promote colonic crypt cell migration, proliferation, and repair, while NPY helps in tissue homeostasis.[15,54] NPY are also implicated in inflammation -induced tumorigenesis by modulating epithelial cell proliferation, survival, and apoptosis, through miRNA-dependent mechanisms, which may influence cancer progression.[13] These findings highlight the broad potential of neuropeptides in treating both GI and systematic conditions.

CONCLUSION

In conclusion, neuropeptides including NPY, VIP, CCK, and SP play a vital role in supporting the barrier function of the intestinal epithelium, and abnormalities in these peptides may contribute to the pathogenesis of diseases including IBD and IBS. The insights gained from this review may inform therapeutic strategies, such as developing neuropeptide analogs to restore intestinal barrier integrity by targeting pathways mediated by neuropeptides. Future studies should aim to test neuropeptide mechanisms in diverse populations or explore their roles beyond gut health including the gut-brain axis.

CONFLICT OF INTEREST

The authors declare no conflict of interest concerning this manuscript.

ACKNOWLEDGMENT

The authors wish to acknowledge the financial support from the Ministry of Higher Education Malaysia via the Fundamental Research Grant Scheme (FRGS/1/2023/SKK10/USM/02/9).

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REVIEW ARTICLE

Determinants of Road Traffic Accident Among Elderly in Malaysia: A Scoping Review

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ABSTRACT

Malaysia is transitioning into an aged nation, with 15% of its population projected to be 60 years or older by 2030. This demographic shift is expected to increase the number of elderly road users, yet road conditions remain inadequate for their needs, and preventive measures for road traffic accidents (RTAs) are still underdeveloped. There is limited understanding of how physiological, cognitive, and environmental factors contribute to RTAs among the elderly in Malaysia. This scoping review aims to explore existing literature on the factors influencing RTAs in this demographic. The review follows the PRISMA-ScR reporting guidelines and includes peer-reviewed studies published in English from 2012 to 2022. A total of 15 studies were identified, and the findings are categorized into four domains: medical conditions, physical capability, driving nature, and environmental factors. Key determinants include cognitive impairment, medical illnesses, visual impairment, depression, and adverse medication effects (medical conditions); poor physical strength and flexibility, and fatigability (physical capability); long driving hours or distance, driving alone, and poor ergonomics (driving nature); and poor road condition and visibility, road complexity, reckless behaviour of other road users, and poorly maintained or old vehicles (environmental factors). These determinants are crucial in informing RTAs prevention strategies and guiding public health interventions for the elderly. However, the limited number of studies highlights the need for further research in this area to better support the safety of elderly road users.

Keywords
Determinants, road traffic accident, elderly, Malaysia

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Received: 4th January 2024; Accepted: 3rd February 2025

Doi: https://doi.org/10.31436/imjm.v24i02.2483

INTRODUCTION

Malaysia is undergoing a demographic shift toward an aging society, with individuals aged 60 and above-classified as elderly by the United Nations-now comprising more than 7% of the total population.[1] According to the National Health Policy for Older Persons, the country is projected to attain the status of an aged nation by 2030, when 15% of the population will be 60 years or older.[2] This demographic trend has led to an increase in elderly road users, who participate in various modes of transportation, such as walking, cycling, riding motorcycles, and driving. Among these, driving remains the preferred mode of transport for the elderly due to its convenience and the limited availability of public transportation.[3,4] Elderly individuals often drive to fulfil essential daily needs such as grocery shopping, healthcare appointments, and social activities.[5]

The incidence of road traffic accidents (RTAs) in Malaysia has steadily risen by 5% annually, with 598,635 RTAs recorded in 2024.[6] Data from the Ministry of Transport (2018) highlights that drivers aged 50 and above contribute to 32% of RTAs in the country. Although elderly drivers often have extensive driving experience, age-related declines in physical and cognitive abilities can impair their driving performance, making them more vulnerable to accidents. Factors such as slower reaction times, diminished vision, and challenges in navigating complex traffic conditions-narrow roads, sharp turns, heavy traffic, and adverse weather-heighten the risk for elderly drivers.[7] Furthermore, rapid urbanization and inadequate infrastructure planning increase the dangers for elderly pedestrians, exacerbating their susceptibility to road accidents in Malaysia's changing urban landscape.[8]

Amid this rising concern, the safety of elderly road users has become a topic of national debate. Critics argue that elderly drivers pose significant risks due to their declining ability to respond quickly to hazardous situations, potentially endangering both themselves and other road users.[9] On the other hand, many advocate for solutions that allow elderly individuals to remain active and independent, emphasizing their right to mobility.[10] Proposals such as periodic medical and cognitive assessments during license renewals have been suggested to ensure that elderly drivers remain fit to drive. However, these measures are still under discussion, and no formal policies have been implemented, reflecting the ongoing debate about balancing road safety with the independence of elderly road users in Malaysia.

Although some countries have implemented specific regulations for elderly drivers, Malaysia's current measures to mitigate RTAs among this demographic remain inadequate. Elderly individuals involved in RTAs face additional challenges due to their slower recovery rates and preexisting health conditions, often resulting in extended hospital stays, increased medical costs, and higher mortality rates.[11] Current prevention strategies tend to focus on younger populations, leaving a significant gap in infrastructure, research, and policy development tailored to the unique needs of elderly road users.

Despite the growing recognition of RTAs among elderly road users in Malaysia, there remains a significant gap in understanding the specific circumstances under which these incidents occur and the mechanisms by which elderly individuals are involved in such accidents. Limited research has been conducted to explore the factors contributing to their vulnerability, including the common situational contexts, such as the types of roads, traffic conditions, or behaviours leading to accidents. Furthermore, there is insufficient data on how physiological, cognitive, and environmental factors interact to increase the likelihood of RTAs among elderly road users. This gap in knowledge hampers the development of comprehensive, evidence-based interventions aimed at reducing the risks faced by this demographic on the road.

This paper seeks to address these gaps by critically examining the existing literature on the determinants of RTAs among the elderly in Malaysia. Thus, this scoping review aims to identify and determine the risk factors associated with road traffic accidents among elderly road users in Malaysia. The findings are expected to inform future prevention and mitigation strategies that are specifically designed to meet the needs of this growing demographic. Despite the rising incidence of RTAs in Malaysia, progress in targeted prevention efforts has been limited, highlighting the urgency for a more focused and informed approach.

METHODOLOGY

The scoping review has been conducted based on the six-stage framework for reviews developed by Arksey and O'Malley (2005) and a modified method used by Colquhoun et al. (2014).[12,13] This process involves identifying the research question, identifying relevant studies, selecting the studies, charting the data, collating, summarizing, and reporting results and ongoing consultation with stakeholders. This review was presented in accordance with the PRISMA Extension for Scoping Reviews reporting guidelines.[14] Our research team were involved in all steps of this review and the results were discussed.

Eligibility criteria

The inclusion criteria were: (a) Research studies referring to the risk factors or determinants of RTAs involving elderly road users, whether as pedestrians, cyclists, or using other forms of land transport; (b) Published in English languages; (c) Published between year 2012 and 2022, and; (d) Quantitative, qualitative, mixed methods, guidelines or reports guideline articles. The literature search was cross-referenced with references of the included studies. Records retrieved that did not meet these criteria were excluded.

Information sources and search strategies

To identify potentially relevant document, the following databases were searched from 2012 to 2022: Springer, Scopus, Science Direct, Web of Science, and Taylor & Francis. The search strategy incorporated both Medical

Subject Headings (MeSH) terms and free-text keywords, with refinements made through team discussions. Truncation and wildcard parameters including Boolean connectors "AND/OR" techniques were applied to ensure that the search focused on the specific key terms. See Appendix 1 for the full search strategy and a detailed search narrative.

The final search results were exported into Mendeley Reference Management Software and duplicates were removed.

Selection of the articles, data charting and data item

The first author performed an initial sorting of the articles and only kept those meeting the inclusion criteria. Subsequently, the other two authors worked in pairs and evaluated titles, abstracts and full texts of all potentially relevant publications. A data-charting form was jointly developed by the research team to determine which variables to extract. Two authors independently charted the data, discussed the results and continuously updated the form in an iterative process. The articles were summarised according to the following information: Year, country, study design, database resource, type of vehicle involved and the study's location.

Synthesis of results

The findings from each paper were extracted by the reviewers for summary and comparison purposes. Data were subjected to a narrative synthesis with the findings presented as a narrative summary organised into themes. In relation to our scoping review aim, information regarding the determinants or risk factors of RTAs involving elderly were extracted. Commonalities and patterns in the extracted data were summarised using the descriptive-analytical method.

RESULTS

Selection of sources of evidence

We initially identified 1,578 records through database searches. After removing 255 duplicates, 1,323 articles remained for screening based on their titles and abstracts, following our inclusion and exclusion criteria. This process narrowed the selection to 151 articles, but after full-text review, 136 were excluded for not meeting the criteria for defining elderly or focusing on the determinants of RTAs. Ultimately, 15 articles were selected for comprehensive synthesis. The study selection process was shown in Figure 1.

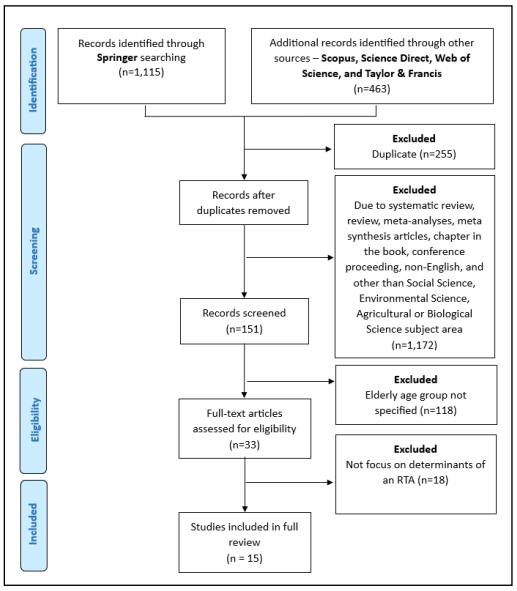

Figure 1: Search strategy for eligible articles

Characteristics of sources evidence

All selected studies were involving elderly in Malaysia and published in past eleven years, between year 2012 and 2022. Out of 15 articles, one (6.7%) article published respectively in year 2021, 2018, 2017, and 2012, four (26.7%) articles in 2020, three (20.0%) articles in 2019, and two (13.3%) articles respectively in 2016 and 2014. According to study design, 11 (73.3%) studies adopting cross-sectional, while two (13.3%) used qualitative method, one (6.7%) applied case-control and another one (6.7%) applied experimental study. Most (93.3%) studies were based on the primary data and only one (6.7%) study utilised secondary data. There are four types of vehicles studied in the selected articles, which were car, motorcycle, bus and pedestrian. Six (40.0%) studies analysed only car, four (26.7%) studies on car and motorcycle, two (13.3%) studies involve car, motorcycle and pedestrian, one (6.7%) study on both car and pedestrian, one (6.7%) study only on bus and the other one study (6.7%) among pedestrians. The study period ranged from three months to three years. The summary of the characteristics of the selected articles were presented

in Table 1. The details of the selected articles according to authors' name, year of publication, the title, study design applied, type and source of the data, sample size, vehicle type and study period were shown in Table 2.

Table 1: Characteristics of selected articles *(n=15)*

Characteristics	*n* (%)
Study design	
Cross-sectional	11 (73.3%)
Qualitative	2 (13.3%)
Case-control	1 (6.7%)
Experimental	1 (6.7%)
Type of data	
Primary	14 (93.3%)
Secondary	1 (6.7%)
Vehicle type analysed	
Car	6 (40.0%)
Car & motorcycle	4 (26.6%)
Car, motorcycle & pedestrian	2 (13.3%)
Car & pedestrian	1 (6.7%)
Pedestrian	1 (6.7%)
Bus	1 (6.7%)

Determinants of RTAs among elderly in selected articles

The determinants of RTAs among elderly were categorised into four domains, which were medical condition, discussed in eight (50.0%) articles; physical capability in eight (50.0%) articles; driving nature in three (18.8%) articles; and environment in nine (56.3%) articles. The summary of these determinants was shown in Table 3.

Medical condition

Five key themes emerged regarding medical conditions as determinants of RTAs among the elderly. Cognitive impairment was the most prominent theme, followed by medical illnesses, visual impairment, depression, and the adverse effects of medication. Cognition refers to intellectual functions requiring mental processes such as thought, experience, and sensory input.[15] A study conducted in Peninsular Malaysia reported that 47.2% of 212 elderly participants experienced chronic insomnia.[16] Those affected were more likely to drive while feeling sleepy (OR 1.12, p=0.032, 95% CI: 1.01-1.125), and one in five reported falling asleep while driving (OR 1.07, p=0.016, 95% CI: 1.01-1.14). Another study involving 500 elderly individuals found that 51% of motorcycle riders and 26% of car drivers had been involved in RTAs

Table 2: Details on characteristics of selected articles (n=15)

Author(s) (Year)	Research Title	Study Design	Type & Source of Data	Sample size (*n*)	Vehicle Type	Study period
Rahman *et al.* (2021)	Comparison of driving difficulty between bilateral cataract and non-cataract elderly drivers in Malaysia	Case-control study	Primary data (interview & questionnaires) in Malacca	61	Car	3 months (Oct. – Nov. 2017)
Ang *et al.* (2020)	The influence of spouses and their driving roles in self-regulation	Qualitative study	Primary data (semi-structured & guided interviews) in Selangor & Kedah	11	Car	1 year & 6 months (Jan. 2017 – Apr. 2018)
Qandeel & Jehom (2020)	Patterns of living environment among itinerant elderly community in Malaysia	Qualitative study	Primary data (semi-structured interviews) in Kuala Lumpur	14	Car & pedestrian	1 year (2018 – 2019)
Rosli *et al.* (2020)	Driving behaviour of elderly drivers in Malaysia	Cross-sectional study	Primary data (observation & self -administered questionnaires) in Johor	240	Car	1 year (2015 – 2016)
Zuwairy *et al.* (2020)	Road traffic accidents: A descriptive study of commuting injury among healthcare workers in Malaysia	Cross-sectional study	Secondary data (MOH, Malaysia) in Malaysia	113	Car, motorcycle & pedestrian	3 years (2014 - 2016)
Ang *et al.* (2019)	Self-regulatory driving and riding practices amongst older adults in Malaysia	Cross-sectional study	Primary data (self-administered questionnaires) in Selangor & Kedah	637	Car & motorcycle	2 years (2016 – 2018)
Ang *et al.* (2019a)	The Malay Manchester driver behaviour questionnaire: A cross-sectional study of geriatric population in Malaysia	Cross-sectional study	Primary data (questionnaires) in Selangor & Kedah	500	Car & motorcycle	2 years (2016-2018)
Anuar *et al.* (2019)	Senior driver performance on airport road access wayfinding design	Experimental study	Primary data in Kedah	64	Car	1 year (2018)
Majid *et al.* (2018)	Assessment on sitting posture relation to risk factors by using chi-square test among elderly taxi drivers in Peninsular Malaysia	Cross-sectional study	Primary data (self-administered questionnaires) in Peninsular Malaysia	500	Car	1 year (2016)
Hong *et al.* (2017)	Significant factors for Malaysian older drivers or riders to give up their keys	Cross-sectional study	Primary data (rigid & structured questionnaires) in Johor	105	Car & motorcycle	1 year (2015)
Al-bargi *et al.* (2016)	Crossing behaviour of pedestrians along urban streets in Malaysia	Cross-sectional study	Primary data (observation & self -administered questionnaire) in Kuala Lumpur	448	Pedestrian	1 year (2014)
Razali *et al.* (2016)	Sleep quality and psychosocial correlates among elderly attendees of an urban primary care centre in Malaysia	Cross-sectional study	Primary data (structured questionnaires) in Klang Valley	123	Car & motorcycle	1 years (2014)
Mahdi *et al.* (2014)	Risk factors for near miss incident among long distance bus drivers in Malaysia	Cross-sectional study	Primary data (questionnaires) in East Coast Malaysia	517	Bus	1 years (2013)
Sukor *et al.* (2014)	Mobility of the elderly at rural area factors affecting the activity trips and mode choice	Cross-sectional study	Primary data (self-administered questionnaires) in Johor	242	Car, Motorcycle & Pedestrian	1 year (2012)
Zailinawati *et al.* (2012)	Prevalence of insomnia and its impact on daily function amongst Malaysian primary care patients	Cross-sectional study	Primary data (self-administered questionnaires) in Peninsular Malaysia	212	Car	1 year (2007)

over the past five years, primarily due to difficulties in attention and concentration.[15]

Elderly with dementia also face significant challenges in vehicle handling and navigating familiar routes, which is associated with a heightened risk of RTAs (OR 13.89, p=0.035, 95% CI: 1.33-144.59).[17] Advancing age is also linked to the onset of medical conditions that impair driving ability. A study by Ang et al. (2019) involving 647 elderly individuals found that the majority were diagnosed with at least one comorbidity, with 67% of drivers and 70% of riders affected.[17] Car drivers with a history of stroke had significantly higher odds of RTAs (OR 4.09, *p*=0.033, 95% CI: 1.09-15.40), while motorcycle riders with diabetes also exhibited a higher risk (OR 2.72, p<0.001, 95% CI: 1.39-5.32). Arthritis was found to increase the odds of RTAs for both drivers and riders (OR 2.32, p=0.041, 95% CI: 1.20-4.66).

Visual impairments caused by medical conditions can significantly compromise the driving abilities of elderly individuals, affecting their safety and performance on the road. A study in Malacca reported that elderly individuals with cataracts faced significantly greater difficulty driving in rainy conditions (p=0.034), at night (p=0.005), and during traffic congestion (p=0.013) compared to those without cataracts.[18] Depression and medication side effects were also identified as important determinants. Elderly drivers and riders experiencing depression had higher odds of RTAs (OR 1.84, p<0.001, 95% CI: 1.18-2.89) due to more frequent aberrant driving behaviours and lapses.[17] Additionally, a study in Johor found that 57.9% of elderly drivers were taking medications for various health conditions, with many reporting that newly prescribed medications caused dizziness, drowsiness, and delayed reaction times when interpreting road signs or manoeuvring the vehicle.[19] This condition often diminished their confidence while driving, particularly during peak traffic hours, thereby increasing their risk of RTAs.[20]

Physical capability

Two key themes emerged regarding physical capability as determinants of RTAs among the elderly: reduced physical strength and flexibility, and increased susceptibility to fatigue. A qualitative study among elderly drivers highlighted poor hand grip strength and lower limb weakness as factors leading to delayed reactions and an increased risk of RTAs.[21] Additionally, 58.2% of elderly drivers with a history of RTAs reported that poor joint flexibility and muscle weakness were contributing factors.[17] Musculoskeletal problems also made driving in tight spaces, navigating corners, making U-turns, and responding to dangerous situations challenging for 68.5% of elderly drivers.[19,20] Moreover, elderly pedestrians were found to be the slowest when crossing heavy traffic roads.[22]

In terms of commuting-related injuries, senior workers had the highest incidence of RTAs, with 28.2 per 100,000 compared to 15.3 per 100,000 in other age groups. This heightened risk was attributed to increased susceptibility to fatigue from prolonged working hours and long-distance commuting.[23] Furthermore, a study revealed that 20.5% of elderly workers experienced microsleep while driving or riding after work due to fatigue.[24]

Driving nature

Three key themes emerged regarding the nature of driving as determinants of RTAs among the elderly: long hours or distance driving, poor ergonomics, and driving alone. Long-distance driving was the most commonly discussed theme. A qualitative study found that elderly drivers experienced navigation difficulties after prolonged driving distances or extended periods in traffic jams.[21] Additionally, 75.8% of 120 elderly taxi drivers reported driving more than 250 kilometers per week, with 60.4% attributing their fatigue to long-distance driving.[25] A similar study among bus drivers revealed that older drivers exhibited significantly reduced attention and concentration after four hours of driving compared to younger age groups.[26]

Furthermore, driving alone and poor ergonomics were identified as contributing factors. Elderly drivers expressed greater confidence when driving long distances with a spouse or companion, as they believed their presence enhanced alertness and reduced the risk of

RTAs.[21] In another study of elderly taxi drivers, 33.3% reported discomfort due to seat design, with 92.5% experiencing back pain and lower extremity discomfort. Moreover, 84.2% of elderly taxi drivers believed that poor seat ergonomics increased their risk of RTAs.[25]

Environment

Three key environmental factors were identified as determinants of RTAs among the elderly: poor road conditions and visibility, reckless road users, and poorly maintained or older vehicles. Among these, poor road conditions and visibility were the most commonly discussed. A simulated study by Anuar et al. (2019) found that inadequate signage and excessive roadside advertisements increased confusion among elderly drivers, leading to a significantly higher risk of RTAs compared to younger drivers (mean: 1.67, SD: 0.82 versus mean: 0.75, SD: 0.96).[27] Additionally, a rural area study in Johor reported that 36.5% of 241 elderly riders experienced an RTAs in the past year, with 88.0% attributing the accidents to poor road conditions, such as inadequate night lighting and potholes.[18,28] Furthermore, the complexity of urban road environments, marked by road junctions, flyovers, and numerous traffic signs, further diminishes focus and attention among elderly drivers, thereby heightening their risk of RTAs.[27]

Reckless road users were also identified as a major risk factor for elderly drivers. Qualitative research found that elderly drivers were more susceptible to RTAs due to delayed reactions when encountering reckless drivers.[21] A similar study among elderly pedestrian in Kuala Lumpur also has poor confidence in road crossing due to reckless motorist.[22,29] Additionally, 44.4% of RTAs involving elderly drivers were attributed to distractions caused by other road users, including reckless motorists.[19] Furthermore, a significant proportion of elderly taxi drivers (56.7%) were found to be operating vehicles over 10 years old, which lacked modern safety features and presented challenges in maneuvering.[25]

Table 3: Distribution of RTAs determinants among elderly in Malaysia in selected articles

Author(s) (Year)	Medical Condition					Physical Capability		Driving Nature			Environment			
	Cognitive impairments	Medical illness	Visual impairments	Depression	Adverse medication effect	Poor physical strength & flexibility	Fatigability	Long hours or distance	Driving alone	Poor ergonomics	Poor road condition & visibility	Road complexity	Reckless behaviour of other road users	Poorly maintained or old vehicles
Rahman *et al.* (2021)			✓								✓			
Ang *et al.* (2020)						✓		✓	✓				✓	
Qandeel & Jehom (2020)													✓	
Rosli *et al.* (2020)					✓	✓							✓	
Zuwairy *et al.* (2020)							✓							
Anuar *et al.* (2019)											✓	✓		
Ang *et al.* (2019)	✓	✓	✓	✓		✓								
Ang *et al.* (2019a)	✓													
Majid *et al.* (2018)								✓		✓				✓
Hong *et al.* (2017)	✓	✓				✓								
Al-bargi *et al.* (2016)						✓					✓		✓	
Razali *et al.* (2016)							✓							
Mahdi *et al.* (2014)	✓						✓	✓						
Sukor *et al.* (2014)											✓		✓	
Zailinawati *et al.* (2012)	✓	✓		✓	✓									

DISCUSSION

The rapid industrialization of Malaysia, along with the development of an advanced transportation network and diverse modes of transport, has undoubtedly improved the quality of life for the elderly population. These advancements have made transportation more accessible; however, they have also contributed to an increased risk of RTAs, rising healthcare costs, and the loss of productive lives.[30] The growing number of elderly individuals as active road users across various transport modes-such as driving, walking, and cycling-has amplified their involvement in RTAs.

Despite this, efforts to comprehensively understand the determinants of RTAs among the elderly in Malaysia remain limited. A review of the literature from 2012 to 2022 identified only 15 relevant studies, indicating either a lack of research focus in this area or a genuine scarcity of published work. This gap highlights the urgent need for more focused investigations into the factors contributing to RTAs among elderly road users. A meta-

analysis study on the global epidemiology of RTAs among the elderly highlighted the insufficient number of studies despite the notable prevalence and fatality.[30] Furthermore, developing and low-income countries face limited research due to capacity constraints, under-reporting, and poor coordination between agencies, making the formulation of appropriate interventions and strategies to address the issue challenging.[31]

The determinants of RTAs were categorized into four domains-medical condition, physical capability, driving nature, and environment-to systematically address the complex factors that contribute to accident risk. This structured classification enables a clearer understanding of how various aspects of an elderly individual's health, behaviours, and external conditions interact to influence their involvement in RTAs. By organizing these factors, it allows for a more targeted and comprehensive approach to addressing the specific vulnerabilities of elderly road users, facilitating the design of interventions tailored to their unique needs.

Within the medical condition domain, cognitive impairment emerged as a predominant theme. Cognitive functions, including attention, memory, and executive processes, typically deteriorate with advancing age, adversely affecting driving performance. Older drivers may experience challenges in processing complex traffic scenarios, which can increase the likelihood of collisions. Additionally, they are more prone to misjudging traffic gaps, potentially resulting in hazardous driving conditions.[32] In addition to cognitive decline, older adults frequently experience medical conditions such as metabolic or endocrine disorders, delirium, dementia, and Alzheimer's disease, all of which further elevate their risk of RTAs. A study conducted in Sweden revealed that elderly individuals with diabetes or a history of mild stroke face a significantly increased risk of RTAs.[33] Similar findings have been reported in studies from Malaysia and other countries, underscoring the global relevance of these health factors in contributing to driving hazards among older populations.[19,34–37] This condition damages blood vessels, reduces blood flow to the brain and lead to slower reaction times, difficulty concentrating, and impaired decision-making, thus increasing the risk of RTAs.[38]

Dementia impairs critical cognitive functions such as judgment, decision-making, and reaction time, diminishing the ability of drivers to effectively respond to dynamic road conditions or emergencies. Furthermore, dementia affects spatial awareness, making it difficult for individuals to accurately judge distances, and can lead to emotional instability, resulting in erratic driving behaviors.[39] These combined cognitive deficits significantly increase the risk of road traffic accidents (RTAs) among individuals with dementia. Adverse effects of medications, including nerve disturbances, gastrointestinal discomfort, and drowsiness, are commonly experienced by elderly individuals. These side effects can impair concentration and alertness, thereby increasing the risk of road traffic accidents (RTAs) by reducing their ability to react promptly and appropriately to driving conditions.[40]

Reduced mobility and flexibility further hinder older adults' ability to execute essential driving manoeuvres. Limitations such as decreased neck rotation, which impairs their ability to check blind spots, and slower reaction times in emergency situations, exacerbate the challenges they face on the road.[41] These physical declines contribute to the overall increased risk of accidents in this age group. Similar findings were reported in Germany, where elderly individuals experienced difficulties stepping over curbs due to sarcopenia.[42] In Japan, muscle degeneration and challenges with stepping over curbs were also linked to increased RTA risk among elderly pedestrians.[43] Additionally, fatiguability, particularly following prolonged driving, was found to be a significant contributor to RTAs in China, even among non-comorbid elderly individuals.[44,45] In contrast, younger drivers were able to maintain attention during long driving periods by employing strategies such as consuming caffeinated beverages and listening to music.[46]

Within the driving nature domain, factors such as driving in long hours or distances, poor attention and concentration after extended periods of driving also

related with poor coping mechanism to maintain their focus. Younger drivers are better at maintaining their attention by taking caffeinated drinks and listening to music.[46] Vehicle ergonomics, including seat and steering design, as well as sitting position, are generally not tailored for the specific needs of elderly drivers. Age-related issues such as reduced flexibility and joint stiffness make it difficult for older adults to adapt to standard vehicle designs, leading to discomfort and fatigue during driving.[47,48] Additionally, while having a companion or spouse may reduce the likelihood of accidents, this benefit is uncertain, as elderly companions often face similar cognitive and attention challenges.[49] Many elderly individuals drive vehicles over 10 years old, lacking modern safety features, as seen in a German study where 75.5% reported using such cars, increasing their risk of RTAs.[50]

A study on Malaysian federal roads found that poor road conditions, such as potholes, can lead to sudden loss of vehicle control, particularly among elderly drivers.[51] Furthermore, poor lighting exacerbates the already diminished night vision common in older adults, delaying their ability to recognize hazards in time. Additionally, uneven or poorly marked roads can confuse elderly drivers, who often face challenges with spatial awareness and slower reaction times, thereby increasing their susceptibility to road traffic accidents. Additionally, reckless behaviour by other road users, such as motorists making sudden lane changes, can startle elderly drivers and provoke impulsive reactions, which may lead to road traffic accidents.[52]

LIMITATION

The search focused on English-language studies in five databases, excluding articles in other languages due to translation limitations. Future reviews are advised to include Malay or other languages and expand the search across more databases for a comprehensive view. The current review covers articles from 2012 onward, potentially limiting insights. Most of the selected articles utilized cross-sectional study designs, providing recent population-based data. However, this approach often lacks the depth required to comprehensively analyse the underlying determinants of RTAs in this demographic. Important factors such as elderly road users' knowledge and awareness of road safety, their preventive practices, and the influence of local cultural contexts were insufficiently examined in the reviewed studies.

CONCLUSION

This scoping review offers an overview of the existing scientific literature on road traffic accidents (RTAs) involving the elderly in Malaysia. It highlights key determinants grouped into four domains—medical conditions, physical capability, driving nature, and environmental factors—that contribute to RTAs in this population. Addressing these determinants is crucial for policymakers and stakeholders to implement effective interventions aimed at ensuring the safety of elderly road users. As Malaysia approaches an aged-nation status by 2030, such measures are essential to accommodate the growing elderly population and reduce their vulnerability to RTAs.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ACKNOWLEDGEMENT

The authors would like to express gratitude to Department of Community Medicine, Health Campus, Universiti Sains Malaysia for supporting this study.

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ORIGINAL ARTICLE

Mapping the Landscape: Malaysian Muslim Women's Insights on Human Milk Banking Through the Islamic Lens

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ABSTRACT

INTRODUCTION: Donated human milk in human milk bank (HMB) is healthier for preterm babies compared to formula milk. In 2022, Halimatussaadiah milk bank was established in Pahang, Malaysia. The objective of this study was to determine the knowledge, attitudes, and behaviours of Malaysian Muslim mothers towards HMB and its Islamic perspectives. **MATERIALS AND METHODS:** From July 2021 to January 2023, a Pahang state multicentred cross-sectional study was carried out at Sultan Ahmad Shah Medical Centre, Hospital Tengku Ampuan Afzan, and Hospital Sultan Haji Ahmad Shah. 793 Muslim Malaysian women who had delivered and breastfed at least one child before, completed validated self-administered Google Form questionnaires, encompassing knowledge, attitude, and behaviour towards HMB. **RESULTS:** The participants, averaging 32.67 years old, were mostly well-educated with an average of 2 children and a monthly household income of approximately MYR 4,500.00. 62.3% recognized HMB as a crucial element for the wellbeing of premature infants. Strong support for Shariah-compliant HMB was evident, with 64.3% advocating for donor-recipient identity disclosure. 34.9% were open to their babies receiving milk from multiple donors, although opinions were divided on accepting milk from non-Muslim women in life-threatening situations, and their willingness to donate breastmilk, both to known and unknown babies. Out of 793 women, only 1.3% had donated their breast milk to HMB. Yet, 45.6% were willing to volunteer and give their milk to a Shariah compliant HMB. **CONCLUSION**: Generally, Malaysian Muslim women in Pahang showed a strong acceptance to the establishment of HMB provided that religious concerns were appropriately addressed.

Keywords
Human milk bank, Malaysia, Muslim, Knowledge, Attitude

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Received: 2nd April 2024; Accepted: 6th November 2024

Doi: https://doi.org/10.31436/imjm.v24i02.2559

INTRODUCTION

The health benefits of breastfeeding and breastmilk are well-established, offering protection against infections, atopy, and cardiovascular diseases, as well as promoting positive neurodevelopmental outcomes and reducing the risk of various disorders.[1] Research has shown that breastfed newborns, especially preterm infants, experience lower incidences of necrotizing enterocolitis (NEC) and sepsis, along with improved neurodevelopment compared to those fed with formula milk.[2] Although formula milk attempts to replicate breastmilk, it lacks essential immune components and has been linked to higher risks of obesity, diabetes, and cardiovascular disease later in life. Consequently, donor breastmilk is generally preferred over formula,[3] bringing the practice of human milk donation to increased prominence.

In Muslim communities, the establishment of Shariah-compliant human milk bank (HMB) has gained attention, with studies from Turkey demonstrating strong support from both Muslim mothers and religious scholars.[4–6] The concept of Shariah-compliant milk bank is particularly significant as it adheres to Islamic guidelines, which emphasize the importance of milk kinship and religious compliance in breastfeeding and milk donation practices. Despite the introduction of donor human milk for preterm infants in countries like Kuwait and Malaysia,[7,8]

the attitudes of Malaysian Muslim mothers toward these banks, along with their religious concerns, remain largely unexplored.

In 2020, Sultan Ahmad Shah Medical Centre at the International Islamic University Malaysia (SASMEC@IIUM) established a Shariah compliant HMB, marking a significant step towards addressing the needs of preterm infants while adhering to Islamic principles. Shariah compliant HMB ensures that infants receive milk from the same donor to avoid the formation of unintended milk kinship. Additionally, they facilitate the introduction of the donor's family to the recipient's family, thereby aligning with Islamic teachings and minimizing religious controversies

However, there was a notable lack of research focused on promoting awareness of the benefits of such milk banks within the local community. A cross-sectional study in 2021 conducted in Malaysia, involving 269 Muslim and 91 non-Muslim mothers, revealed that 67.8% of respondents supported the establishment of human milk banks in the country.[9] Yet, the specific views of Muslim Malaysian mothers regarding the importance, significance, and challenges of Shariah-compliant milk banks have not been adequately studied.

To our knowledge, this was the first large-scale study in Malaysia addressing the concept of Shariah-compliant milk banks among Malaysian Muslim mothers. The study aimed to determine the knowledge, attitudes, and behaviours of Malaysian Muslim mothers towards HMB and its Islamic perspectives.

MATERIALS AND METHODS

From July 2021 to January 2023, a Pahang state level multicentred cross-sectional study was carried out at the Sultan Ahmad Shah Medical Centre (SASMEC @ IIUM, Kuantan), Hospital Tengku Ampuan Afzan (HTAA, Kuantan), and Hospital Sultan Haji Ahmad Shah (HOSHAS, Temerloh). All Muslim Malaysian women over the age of 18 who provided consent and could communicate in Malay or English were recruited using simple random sampling from the outpatient clinic, Department of Obstetrics and Gynaecology of the respective hospitals. One of the aims of including pregnant women in this research was to reduce the waiting time of breastmilk donors screening. Participants who were primigravid or nulliparous were excluded from the study, as this study was a part of a larger primary investigation assessing the knowledge, attitudes, and behaviours of Malaysian Muslim mothers regarding breastfeeding, wet-nursing, milk kinship and HMB in Pahang, Malaysia. Individuals without prior breastfeeding experience were not included in the sample.

A single proportion formula was employed to estimate the sample size.[10] With a power of 80%, an expected proportion of 45% mothers with good acceptance of Shariah compliant HMB responding positively,[11] and a population size of 2400 in SASMEC@ IIUM, HTAA, and HOSHAS, the study sample size is 850 after accounting for a 20% attrition rate.

Sociodemographic data such as age, parity, education level, and total monthly household income were collected. Parity was defined as the number of pregnancies that reached 20+0 weeks of gestation or beyond, independent of the number of foetuses or outcomes (ACOG, 2014). Education was divided into primary, secondary, and higher levels (ISCED, 2011). Shariah compliant HMB was the milk bank which operated in accordance with Shariah rulings.

Study instrument

A self-administered questionnaire was used to measure knowledge, attitudes, and behaviours of participants towards human milk bank (HMB) and the Islamic perspective. The self-administered closed-ended questionnaire was developed by "adapt-and-adopt" method from literature review through the studies conducted in Turkey and Malaysia to assess knowledge, attitudes, and behaviours of Muslim women and religious scholars on human milk banking.[4–6,11] Generally, the questionnaire comprised three domains: i) knowledge, ii) attitudes, and iii) behaviours towards human milk banking.

There were 10 items in knowledge, and attitudes domains respectively, and 6 items in behaviours domain. The items in knowledge domain consisted of closed ended multiple choice questions including correct answers, distractors or incorrect answers and the option *"I do not know"* to reduce the chances of guessing. The items in attitude contained five-point Likert scale (strongly agree, agree, neutral, disagree, strongly disagree). The content was validated by obstetrician, neonatologist, family medicine specialist, specialist nurse, and nutritionist. Face validity was conducted by pre-testing in a similar study population demographic in SASMEC@IIUM. Cronbach's Alpha of 0.823 was obtained, indicating good internal consistency and reliability for the questionnaire

Data analysis

Statistical analysis was performed using IBM SPSS version 21. Descriptive statistics of frequency (%) and mean (standard deviation) were used to describe sociodemographic factors and variables related to knowledge, attitude, and behaviours.

RESULTS

A total of 850 participants responded to a web-based self-administered questionnaires. However, 793 responses were included in data analysis after excluding missing data, which corresponded to 93% completion rate of the questionnaires. Table 1 provides the summary of the sociodemographic characteristics of the participants.

Table 1 Sociodemographic characteristics of study participants

Sociodemographic characteristics	Mean ± SD
Age (Year)	32.67 ± 4.67
Number of children	2.15 ± 1.21
Income (Ringgit)	4548.25 ± 5877.56
Education	
Primary	14 (1.8)*
Secondary	276 (34.8)*
Higher	503 (63.4)*

*Frequency N (%)

Table 2 illustrates the knowledge of Malaysian Muslim mothers in HMB, where 62.3% of participants understood the primary purpose of HMB is to provide safe breast milk to premature infants. Support for Shariah compliant HMB was high, with 64.3% agreeing that donors and recipients should know each other's identities to avoid unintended milk kinship. About 69.1% believed HMB were established to preserve life, while 48.4% were aware of disease transmission risks. Social media played a significant role in informing 50.2% of participants. Most (50.7%) favoured dual oversight by religious and medical authorities, showing positive perceptions of Shariah compliant HMB.

Table 2 Knowledge of Malaysian Muslim mothers in human milk bank

	Frequency (n)	Percentage
1. Human milk bank is primarily needed to		
A. provide safe breastmilk to the ill premature babies	494	62.3
B. feed the healthy babies of healthy mothers	115	14.5
C. earn extra money by milk donation	10	1.3
D. I don't know	174	21.9
2. The milk in human milk bank is pasteurised.		
A. Yes	417	526
B. No	80	10.1
C. I don't know	256	37.3
3. In Shariah compliant milk bank, a single recipient (baby) is fed by milk collected		
A. Yes	357	45.0
B. No	92	11.6
C. I don't know	344	43.4
4. In Shariah compliant milk bank, the institution has the responsibility of informing both donors and recipients of each other's identities to prevent marriage of milk		
A. Yes	510	64.3
B. No	39	4.9
C. I don't know	244	30.8
5. Shariah compliant human milk bank is established to preserve life.		
A. Yes	548	69.1
B. No	25	3.2
C. I don't know	220	27.7
6. If you have ever heard about milk bank, from where did you hear about it?		
A. Friends	64	11.8
B. Social media	273	50.2
C. Other sources	207	38
7. Infectious diseases can be transmitted from donors to recipient.		
A. Yes	384	48.4
B. No	130	16.4
C. I don't know	279	35.2
8. Standard operating procedures of Shariah compliant human milk banks aim for protecting lineage.		
A. Yes	488	61.5
B. No	37	4.7
C. I don't know	268	33.8
9. Who should monitor the Shariah compliant milk bank?		
A. Religious authorities	60	7.6
B. Hospital administrators	103	13.0
C. Both	402	50.7
D. I don't know	228	28.8
10. Milk bank in Islam is allowed for		
A. *Daruriyyah* (necessity)	390	49.2
B. *Hajiyyah* (complement)	56	7.1
C. *Tahsiniyyah* (refinement)	53	6.7
D. I don't know	294	37.1

Table 2 Knowledge of Malaysian Muslim mothers in human milk bank

	Frequency (n)	Percentage (%)
1. Human milk bank is primarily needed to		
A. provide safe breastmilk to the ill premature babies	494	62.3
B. feed the healthy babies of healthy mothers	115	14.5
C. earn extra money by milk donation	10	1.3
D. I don't know	174	21.9
2. The milk in human milk bank is pasteurised.		
A. Yes	417	52.6
B. No	80	10.1
C. I don't know	256	37.3
3. In Shariah compliant milk bank, a single recipient (baby) is fed by milk collected from a woman only.		
A. Yes	357	45.0
B. No	92	11.6
C. I don't know	344	43.4
4. In Shariah compliant milk bank, the institution has the responsibility of informing both donors and recipients of each other's identities to prevent marriage of milk brothersand sisters.		
A. Yes	510	64.3
B. No	39	4.9
C. I don't know	244	30.8
5. Shariah compliant human milk bank is established to preserve life.		
A. Yes	548	69.1
B. No	25	3.2
C. I don't know	220	27.7
6. If you have ever heard about milk bank, from where did you hear about it?		
A. Friends	64	11.8
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C. Other sources	207	38
7. Infectious diseases can be transmitted from donors to recipient.		
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D. I don't know	294	37.1

In Table 3 which illustrates the attitude of Malaysian Muslim mothers towards HMB, 34.9% expressed their approval for their babies to receive milk from various donors, indicating an openness to utilizing multiple sources of breastmilk if necessary. Opinions among participants varied on the acceptability of using milk from non-Muslim women in life-saving situations, with 27.6% in agreement and 42.6% in disagreement or strong disagreement. A considerable number of mothers expressed their willingness to donate breastmilk, both to babies they know personally (57%) and to babies they do not know (31.4%). The majority (73.6%) held the view that pasteurization in HMB would not diminish the quality of breastmilk, reflecting confidence in the safety measures employed during milk processing. There was a consensus (40.9%) that all nursing mothers should be informed about, and encouraged to contribute to the milk bank, indicating a positive attitude toward promoting milk donation. 86.9% respondents believed that donors and recipients should be acquainted to prevent the marriage of milk siblings, highlighting a preference for transparency and potential social connections in the donation process.

Table 3 Attitude of Malaysian Muslim mothers towards human milk bank

	Frequency (n)	Percentage (%)
1. If my baby is premature and my milk is insufficient for my baby, I am willing to feed my baby with milk donated by women whom I know personally.		
A. Strongly agree	96	12.1
B. Agree	342	43.1
C. Neutral	162	20.4
D. Disagree	173	21.8
E. Strongly disagree	20	2.5
2. If my baby is premature and my milk is insufficient for my baby, I am willing to feed my baby with milk donated by women whom I do not know personally.		
A. Strongly agree	24	3.0
B. Agree	152	19.2
C. Neutral	198	25.0
D. Disagree	328	41.4
E. Strongly disagree	91	11.5
3. I think all donor mothers should have infection screening before donation process.		
A. Strongly agree	386	48.7
B. Agree	335	42.2
C. Neutral	44	5.5
D. Disagree	19	2.4
E. Strongly disagree	9	1.1
4. I will consent for my baby to receive donated milk from different donors.		
A. Strongly agree	33	4.2
B. Agree	85	10.7
C. Neutral	194	24.5
D. Disagree	358	45.1
E. Strongly disagree	123	15.5
5. I think it is acceptable to feed the baby by the milk of non-Muslim women in lifesaving circumstances.		
A. Strongly agree	33	4.2
B. Agree	189	23.8
C. Neutral	233	29.4
D. Disagree	260	32.8
E. Strongly disagree	78	9.8
6. If my breastmilk is in excess, I would like to give my breastmilk to other babies whom I know.		
A. Strongly agree	88	11.1
B. Agree	364	45.9
C. Neutral	207	26.1
D. Disagree	117	14.8
E. Strongly disagree	17	2.1
7.If my breastmilk is in excess, I would like to give my breastmilk to other babies whom I donot know.		
A. Strongly agree	50	6.3
B. Agree	199	25.1
C. Neutral	248	31.3
D. Disagree	243	30.6
E. Strongly disagree	53	6.7

In Table 4 which illustrates the behaviours of Malaysian Muslim mothers towards HMB, out of 793 women, only 1.3% had donated their breast milk to HMB. Yet, 45.6% are willing to volunteer and give their milk to a Shariah-compliant milk bank, indicating they have a positive attitude toward contributing to places that follow specific religious principles. 98.6% of respondents were not interested in getting money for giving their milk to HMB. This showed their enthusiasm to help without expecting payment. Many participants (35.2%) were ready to collect and send their breast milk to HMB by themselves, which shows they were dedicated and wanted to be personally involved. Nevertheless, some participants (30.4%) wanted help sending their breast milk to HMB, suggesting that it might be difficult for them to contribute without assistance. Most respondents (70.7%) thought deciding to donate breast milk should be a joint decision with their spouse, while 22.7% believed it should be their decision alone.

Table 4 Behaviours of Malaysian Muslim mothers towards human milk bank

	Frequency (n)	Percentage (%)
1. Have you ever donated your breastmilk to milk bank to feed those babies who need human milk for nutrition?		
A. Yes	10	1.3
B. No	783	98.7
2. Do you wish to get payment if you donate your milk to the milk bank?		
A. Yes	11	1.4
B. No	782	98.6
3. Are you willing to collect your breastmilk and send yourself to the milk bank?		
A. Yes	279	35.2
B. No	514	64.8
4. Do you need someone to send your expressed breastmilk to the milk bank?		
A. Yes	241	30.4
B. No	552	69.6
5. Who should decide to donate your breastmilk?		
A. Myself	180	22.7
B. Husband	52	6.6
C. Both	561	70.7
6. Would you like to volunteer to donate milk to Shariah compliant milk bank?		
A. Yes	362	45.6
B. No	431	54.4

DISCUSSION

The dynamic nature of human milk and its health benefits

Human milk, the biological norm for infant nutrition, contains diverse bioactive compounds that promotes numerous health benefits. From colostrum to late lactation, its composition varies, offering protection against infection and inflammation, while its dynamic nature supports infant development.[12] Additionally, the study involving 207 premature infants demonstrated that an exclusively human milk diet led to significantly lower rates of necrotizing enterocolitis (NEC) and reduced need for surgical intervention compared to a bovine milk-based fortifier.[10] As the practice of feeding infants with expressed human milk grows, it provides a potential fail-safe for mothers to share their unique bacterial imprint with their infants, regardless of the delivery method or timing.[13]

Motivations for milk donation in non-Muslim communities

In the context of milk donation in non-Muslim communities, a French study of 214 mothers found that 75% were motivated to donate milk to help others, 25% to support premature neonatal care, and 30% due to ample supply.[14] Similarly, a 2018 survey of 489 Chinese nursing women showed 76.7% were willing to donate despite limited understanding.[15] Another cross- sectional study in 2019 with 1078 mothers in Wuhan, China, found 75.3% supporting HMB establishment, 81.3% favouring donating breast milk, and 38.3% supporting accepting donor milk.[16] Meanwhile, a KwaZulu-Natal study reported that 52.7% of 148 participants were likely to donate breast milk, influenced by well-informed staff, sufficient milk production, and support from family, friends, or partners.[17]

Challenges and reservations regarding milk donation

Nonetheless, perception of milk donation is not without challenges. In a study involving 100 postnatal mothers in an Indian tertiary care centre, positive perceptions of HMB were evident, with 89% recognizing the life-saving potential of human milk donation and 95% acknowledging its nutritional completeness for infant development.[18] However, reservations were present, as 19 participants preferred donating milk only to family and friends, contrary to the disagreement of 81% of respondents. Additionally, 28 women expressed concerns about the adequacy of their milk for their own infants if donated to others, indicating apprehensions regarding resource allocation. In a study in Punjab, India, with 200 parous women, 66.5% had a neutral attitude towards HMB, with an overall mean attitude score of 28.8 ± 5.87, suggesting a largely neutral view due to the newness of the

concept.[19] A study in Michigan, United States, involving 73 mothers found that the majority (89%, n=59) preferred formula to donor human milk (11%, n=7) for their infants.[20] In cases where donor human milk was the sole option, participants preferred acquiring it from a relative or friend (60%, n=40) over a milk bank (40%, n=26).[20]

Cultural and religious concerns about anonymous milk donation in Muslim communities

The Western-style milk bank model, which utilizes pooled donor milk while keeping the identities of donors and recipients anonymous, raises concerns within Muslim communities. In Islamic law, marriage between individuals who share a milk relationship-either with a milk mother or milk siblings-is prohibited, creating religious and cultural objections to anonymous milk donation. Consequently, such milk banks have faced resistance in these communities.

Diverse attitudes toward HMB in Muslim countries

There is a mixed reaction towards the establishment of HMB in Muslim countries. In a survey of 401 religious officers from Turkey,[5] 63.3% supported the use of donor human milk when the mother's milk was unavailable. Regarding religious sensitivity, 71.3% preferred a restricted arrangement limiting recipients from pooled donations. Only 1.7% supported Western-style milk banks in Turkey. This reflects the majority's preference for restricted pooling due to cultural and religious concerns. Over the years, there has been a notable shift in the perception of Turkish women regarding human milk banks and milk donation. In 2009, a study with 350 married women showed that 64.0% were willing to donate their milk, while 36.3% considered it a religious issue.[4] However, in 2014, a study involving 240 Turkish women indicated a change in perspective. Only 22.9% supported the establishment of milk banks, and among them, 19.1% expressed a willingness to donate. The primary concern for 76.8% was potential marriages between milk siblings.[6] In a more recent survey in 2022 with 271 Turkish women, the willingness to donate breast milk increased to 57.9%. However, the readiness to use donor milk for their newborns was lower at 27.7%, with concerns including religious issues, fear of infectious disease transmission, and distrust of strangers. Positive attitudes were associated with the perceived importance of breastfeeding and religious beliefs.[21] In a 2021 survey at North Syrian hospitals with 536 participants, 47.2% favoured establishing a milk bank, with 81.3% willing to use it if they were unable to breastfeed. Religious reasons were cited by 49.4% opposing milk banks.[22] Meanwhile, a Bangladesh study found 108 of 121 mothers willing to donate to a HMB, with 71.9% open to obtaining milk from an HMB if needed. Yet, 28% would not accept milk from an HMB, and 8.3% found HMBs incompatible with Islamic beliefs. Most (99.2%) lacked awareness of HMB practices in Bangladesh.[23] Both studies highlighted diverse attitudes and factors influencing perceptions of milk banks in different cultural contexts.[22,23]

The rise of Shariah compliant HMB in Malaysia

To address these concerns while preserving the health benefits of human milk, countries like Kuwait and Malaysia[7,8] had introduced the ideology of Shariah compliant milk banks. A case series in Kuwait highlighted the benefits of donated human milk for six premature infants born at 26-28 weeks, weighing 705-1000 grams.[7] Initial total parenteral nutrition provided essential nutrients for 11-21 days, and subsequent breastfeeding supplemented with donated milk between 19-41 days. The infants were discharged with weights between 1810-1940 grams, indicating positive growth. Following that, a human milk donation initiative has been launched at the Duchess of Kent Hospital in Sandakan, Sabah, Malaysia, as an Islamic-based alternative to traditional human milk banks. The trial, which ran from January 2009- December 2010, included 48 infants who received donor breast milk. Of these, 42 were in the special care nursery and six were on the paediatric ward. Majority of donors (88%) and recipients (77%) identified as Muslim. Furthermore, 60% of the newborns who received donated human milk were preterm. Tragically, two newborns died as a result of prematurity complications.[8] The Shariah compliant HMB in Malaysia was established at Sultan Ahmad Shah Medical Centre (SASMEC@IIUM), Kuantan in 2022, named Halimatussaadia Mother's Milk Centre (HMMC). Its development began in 2019, receiving approval in 2020, with its first donor in 2021. It was Malaysia's first

Shariah compliant HMB, created to meet Islamic guidelines regarding milk kinship.

Support for Shariah compliant HMB among Malaysian Muslim women

In our study, Malaysian Muslim women strongly supported Shariah-compliant HMB, with 64.3% favouring identity disclosure to prevent unintended familial relationships. Additionally, 48.4% acknowledged the potential for infectious disease transmission from donors. Participants advocated dual oversight, with 50.7% supporting monitoring by religious authorities and hospital administrators. Regarding permissibility in Islam, 49.2% considered it allowed for necessity *(Daruriyyah)*. Among Muslim Malaysian women in Pahang state of Malaysia, a notable portion expressed willingness to donate breast milk to known (57%) and unknown (31.4%) babies. A consensus (40.9%) favoured informing and encouraging all nursing mothers to contribute to the milk bank, reflecting a positive attitude toward milk donation. While only 1.3% had donated milk to HMB, 45.6% were willing to volunteer at a Shariah-compliant milk bank without expecting payment (98.6%).

Awareness and perceptions of pasteurization in HMB

Pasteurized donor milk is now routinely administered to high-risk infants, and most mothers in the United States extract and freeze their milk at some time during lactation for future infant feedings. However, heat treatment degrades many milk proteins, and freeze-thaw cycles may result in reduced bioactivity.[12] While pasteurization alters various components in donor milk, clinical studies showed that many beneficial characteristics remain following this treatment, making pasteurized donor milk a viable option when a mother's own milk is unavailable.[24] In our study, over half (52.6%) were aware of milk pasteurization in HMB, indicating understanding of safety measures in processing. The majority (73.6%) believed pasteurization would not diminish milk quality.

Decision-making and perspectives on milk donation in Malaysia

In our research, a significant number (35.2%) were ready to collect and send milk independently, while 30.4% preferred assistance from HMB. Regarding decision-making, 70.7% believed donating should be a joint decision with their spouse, and 22.7% felt it should be an individual decision. Opinions on accepting milk from non-Muslim women varied, with 27.6% in agreement and 42.6% in disagreement.

Strength and limitation of the study

The study strength lies in its use of a validated questionnaire to assess breastfeeding knowledge, attitudes, and behaviours among pregnant Muslim women. Random selection and a larger study population enhanced generalizability and statistical robustness. It uniquely explored Malaysian Muslim mothers' views on HMB, highlighting religious and personal concerns. However, limitations included the absence of construct validation and failure to assess willingness to establish milk kinship through donation. Despite those, the study made a significant contribution, encouraging further research into HMB in Malaysia.

CONCLUSION

The study emphasized the robust approval of Malaysian Muslim mothers for the creation of a Shariah-compliant HMB to safeguard the lives of premature infants. Nonetheless, there was a strong sentiment among women that the matter of milk kinship needs proper attention and promotion of HMB by Muslim religious scholars and healthcare professionals.

FUNDING

This study was supported by a research grant from the Sultan Ahmad Shah Medical Centre at International Islamic University Malaysia (SASMEC@IIUM).

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Prevalence of Premature Ejaculation and Its Associated Factors Among Men Attending Government Health Clinics in Kuantan, Pahang

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ABSTRACT

INTRODUCTION: Premature ejaculation (PE) is a common sexual dysfunction affecting men globally, often underdiagnosed and under-treated. Its prevalence varies across different sociocultural and geographical settings. The objective of this study is to determine the prevalence of PE and its associated factors among men attending government health clinics in Kuantan, Pahang, Malaysia. **MATERIALS AND METHODS:** A six-month cross-sectional study was conducted from April 2023 to September 2023 at twelve health clinics. The respondents who were selected were sexually active men over the age of 18 years. Those with psychiatric illness or illiteracy were excluded. Data were collected using the validated Malay version of the Premature Ejaculation Diagnostic Test (PEDT) and the Depression, Anxiety, and Stress Scale (DASS-21). PE was defined as a PEDT score above 9. Descriptive analysis and simple and multiple logistic regression were performed using SPSS. **RESULTS**: Out of 300 eligible men, 287 responded (95.7% response rate). The prevalence of PE was 32.4% (n=93), with 17.8% (n=5) classified as probable PE and 14.6% (n=42) as PE. Multiple logistic regression showed PE were significantly associated with stress [AOR (95% CI): 3.83 (1.33–11.00); p-value=0.013] and anxiety [AOR (95% CI): 2.60 (1.29–5.25); p-value=0.008]. **CONCLUSION:** The study revealed a high prevalence of PE among men and potentially linked to stress and anxiety. Raising awareness among the public and healthcare providers can improve detection rates in primary care. Therefore, routine PE screening is recommended for men attending health clinics, and such measures would facilitate early diagnosis and treatment.

Keywords
Sexual Dysfunctions, Premature Ejaculation, Stress, Anxiety

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Received: 17th July 2024; Accepted: 28th August 2024

Doi: https://doi.org/10.31436/imjm.v24i02.2650

INTRODUCTION

Premature ejaculation (PE) is common male sexual dysfunctions characterised as a condition where ejaculation occurs within approximately one minute duration of vaginal penetration and before the individual desires it; and these symptoms must persist for at least six months appear on nearly all occasions of sexual activity. Additionally, the condition must cause significant distress to the individual, and the dysfunction cannot be explained by any another mental disorder, relationship issues, other stressors, or substances/medications.[1]

Globally, the prevalence of PE ranges from 4.7% to 58%, with varying prevalence in different geographical areas.[2–9] A few studies done in Malaysia showed that the prevalence of PE ranges from 21.4% to 40.6%.[10–15] Despite its high prevalence, PE remains underdiagnosed due to various factors, such as lack of widespread awareness among men, cultural beliefs, emotional embarrassment, and societal taboos.[16] These variations highlight the influence of sociocultural factors on PE prevalence.

PE is a complex condition influenced by different demographic, psychological, and clinical factors. Only few studies have shown that PE is more prevalent among older males.[5,6] Ethnicity also plays a significant role, with

studies in Malaysia indicating a higher prevalence among Indian men and varying rates across different regions globally.[4,15] Education level impacts PE, with lower education levels being associated with higher prevalence. Additionally, economic factors such as low monthly income and financial problems, further influence sexual health.[14] Psychological factors, including anxiety and depression, are significantly linked to PE.[5,10,11,13,17] Smoking is also associated with an increased risk of PE, likely due to the negative impact on vascular health.[5,13] Clinical conditions like higher body mass index, type 2 diabetes mellitus, hypertension, hyperthyroidism, stroke, traumatic brain injury, epilepsy, chronic prostatitis, and varicocele are all associated with increased in the prevalence of PE.[14,18–20] This multifaceted aetiology underscores the importance of the need of a comprehensive approach to diagnosing and managing PE in clinical practice.

Various studies have investigated the prevalence of PE across different regions and populations in Malaysia.[10–13,15] A study conducted in Kuantan measured PE associated with the quality of life.[14] However, there is a lack of studies in the assessment of the psychological factors related to PE in Kuantan. Hence, this study specifically addresses this gap by focusing on the psychological factors related to PE, different from previous studies. PE is an important issue sexual health among men that should not be ignored, as it is often underdiagnosed and undertreated. Therefore, this research aims to measure the prevalence of PE and its associated factors among males attending government health clinics in Kuantan, Pahang, Malaysia.

MATERIALS AND METHODS

Study design and population

A six-month cross-sectional study was conducted in all the 12 government health clinics situated in Kuantan from April to September 2023. The sample size of male subjects was calculated based on the prevalence of PE in Kelantan and added with a 10% non-response rate. The final estimated sample size was 300 men.[12] Male clinic attendees of age above 18 years, who were able to comprehend the Malay language, married, and sexually active for the last six months were included. Those who were illiterate, diagnosed with any psychiatric illness or mentally retarded were excluded. All male patients who attended the respective clinic on the day of data collection were selected through simple random sampling. Patients who met the inclusion criteria were recruited at the registration counter, while those who declined to participate were considered part of the non-response rate. Respondents were requested to sign an informed consent form upon consenting to participate. Assurance of confidentiality was provided to all participants.

Data collection

A self-administered questionnaire consisting of three sections: section A: sociodemographic and medical illness consist of age, race, working status, education level, occupation, monthly income, frequency of sexual intercourse, family member with similar symptoms, smoking status, diabetes mellitus and hypertension; section B assessed the psychological status by using the Depression Anxiety Stress Scale (DASS-21); section C is to screen for PE by using the Premature Ejaculate Diagnostic Test (PEDT).

Malay version Premature Ejaculation Diagnostic Tools (PEDT)

The PEDT questionnaire had a Cronbach's alpha coefficient of 0.86 for Malay, demonstrating good test-retest reliability, high sensitivity, and specificity.[14,21] This instrument comprises five items across five domains. The total PEDT score ranges from 0 to 20. A score of ≤8 indicates no PE; scores of 9 to 10 probable PE and ≥11 indicate confirmed PE.

Malay version 21-item Depression Anxiety Stress Scale (DASS-21)

The DASS-21 Malay Version demonstrated satisfactory internal reliability with Cronbach's alpha coefficients of 0.75, 0.74, and 0.79 for depression, anxiety, and stress, respectively.[22] Responses were recorded on a 4-point scale, ranging from 0 (indicating the statement did not apply at all) to 3 (indicating the statement applied to the participant very much or most of the time). Subscale scores varied from 0 to 21 and were classified into

normal, mild, moderate, severe, and extremely severe.

Data analysis

SPSS 29.0 software was used to analyse the data. The continuous data were normally distributed; hence, mean and standard deviation were used. Furthermore, descriptive statistics for categorical data employ frequency and percentage. The prevalence and severity of PE were calculated in percentages with a 95% confidence interval (CI). The relationship between PE and other variables, such as sociodemographic profile, medical illness, behavioural, and psychological factors, was analysed using simple logistic regression. A multiple logistic regression model using the Enter method was used to determine the factors associated with PE. All significant variables of known clinical relevance ($p<0.25$) were included in the multivariate logistic regression.[23] The final model showed a significant value ($P<0.05$), considered a statistically significant associated factor for PE.

RESULTS

Sociodemographic data

A total of 287 men responded, with a response rate of 95.7%. Table I shows the sociodemographic data of the subjects. The mean age was 40.4 (±10.5), ranging from 18 to 70 years. The vast majority were Malays, accounting for 93.0% of the total, with non-Malays making up the remaining 7%. More than half of the respondents had secondary education (53.0%), and 41.5% had university or college education. Most were employed (92.7%), and about two-thirds were in the low-income category (B40) (73.5%). Non-smokers and smokers were nearly equal in numbers, at 41.3% and 40.1%, respectively. Around 63.4% reported having sexual intercourse 2-4 times per week, and 95.1% did not have a family member with similar symptoms. The mean BMI was 27.21 (±6.21). A substantial proportion of respondents had DM (78.0%) and hypertension (73.9%). Surprisingly, more than half of the people who participated in the survey did not experience any symptoms of stress (90.2%), anxiety (76.3%), or depression (86.8%).

Table I: Sociodemographic and Clinical Characteristics of Respondents

Variables	Characteristics	n	(%)	Mean (SD)
Age (years)		-	-	40.4 (10.5)
Ethnicity	Malay	267	93.0	
	Non-Malay	20	7.0	
Education Level	Primary School	16	5.5	
	Secondary School	152	53.0	
	College/ University	119	41.5	
Working Status	Unemployed	21	7.3	
	Employed	266	92.7	
Monthly Household Income	B40: < RM 4850	211	73.5	
	M40: RM 4850 - 10959	70	24.4	
	T20: ≥ RM 10960	6	2.1	
Frequency of Sexual Intercourse	≤ 1 time/ week	81	28.2	
	2 - 4 times/ week	182	63.4	
	≥ 5 times/ week	24	8.4	
Family Member has similar symptoms	No	273	95.1	
	Yes	14	4.9	
Smoking Status	Non-smoker	127	44.3	
	Ex-smoker	45	15.7	
	Smoker	115	40.0	
Body Mass Index		-	-	27.41 (6.21)
Diabetes Mellitus	No	224	78	
	Yes	63	22	
Hypertension	No	212	73.9	
	Yes	75	26.1	
Stress	No	259	90.2	
	Yes	28	9.8	
Anxiety	No	219	76.3	
	Yes	68	23.7	
Depression	No	249	86.8	
	Yes	38	13.2	

Prevalence of premature ejaculation and severity

Figure 1 shows that 32.4% of male respondents had PE, in which the total value was derived by summating PE and probable PE. Looking into the severity domain, the results showed that 17.8% of men reported having probable PE, and 14.6% had PE, as shown in Table II.

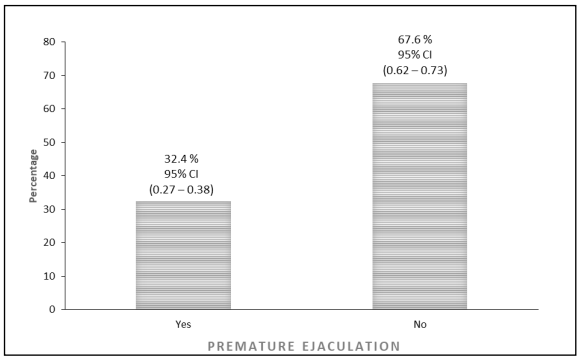

Figure 1: Prevalence of Premature Ejaculation

Table II: Severity of Premature Ejaculation

Severity	n (%)	95% CI
Normal	194 (67.6)	0.62 – 0.73
Probable Premature Ejaculation	51 (17.8)	0.14 – 0.23
Premature Ejaculation	42 (14.6)	0.11 – 0.19

Associated factors

Table III displays the results of simple and multiple logistic regression. From simple logistic regression, the associations with PE include higher body mass index (OR=1.07, 95% CI 1.02–1.11), diabetes mellitus (OR=2.53, 95% CI 1.43–4.49), hypertension (OR=1.71, 95% CI 0.99–2.94), stress (OR=9.71, 95% CI 3.78–24.93), anxiety (OR=5.32, 95% CI 2.98–9.51), and depression (OR=5.12, 95% CI 2.48–10.58). However, no significant correlation was found between PE and factors such as age, ethnicity, education level, employment status, household income, family history of PE, and smoking status.

According to Table III, two factors significantly increased the likelihood of PE which is stress and anxiety. Individuals who were stressed were nearly four times more likely to report PE (OR=3.83, 95% CI 1.33–11.00) than those without PE. Additionally, individuals with anxiety were twice as likely to develop PE (OR=2.6, 95% CI 1.29–5.24). Although other factors were linked to an increased risk of PE, these associations were not statistically significant in this study.

Table III: Associated factors for premature ejaculation

Variables	Simple Logistic Regression			Multiple Logistic Regression		
	Wald[a]	p-value[b]	Crude OR[c] (95% CI)[d]	Wald[a]	p-value[e]	Adjusted OR[f] (95% CI)[e]
Age	0.62	0.43	0.99 (0.98 – 1.01)	-	-	-
Ethnicity						
Non-Malay (ref.)						
Malay	0.06	0.81	1.13 (0.42 – 3.04)	-	-	-
Education Level						
Primary School (ref.)				-	-	-
Secondary School	0.04	0.83	0.89 (0.31 – 2.59)			
College/ University	0.53	0.47	0.67 (0.23 – 1.98)	-	-	-
Working Status						
Unemployed (ref.)				-	-	-
Employed	0.01	0.93	0.96 (0.37 – 2.45)			
Monthly Household Income				-	-	-
B40 (ref.)				-	-	-
M40	0.02	0.90	0.96 (0.54 – 1.72)			
T20	0.80	0.37	2.10 (0.41– 10.69)			
Frequency of Sexual Intercourse						
≤ 1 time/ week (ref.)						
2 - 4 times/ week	0.53	0.47	0.82 (0.47–1.41)	0.33	0.57	1.21 (0.64–2.29)
≥ 5 times/ week	3.30	0.06	0.34 (0.11–1.09)	0.19	0.66	0.76 (0.21–2.66)
Family Member						
No (ref.)				-	-	-
Yes	0.10	0.75	0.83 (0.25 – 2.71)			
Smoking Status						
Non-smoker (ref.)				-	-	-
Ex-smoker	0.02	0.88	1.06 (0.51– 2.21)	-	-	-
Smoker	0.90	0.34	1.30 (0.76– 2.22)			
Body Mass Index	9.29	0.002*	1.07 (1.02–1.11)	1.64	0.20	1.03 (0.98–1.08)
Diabetes Mellitus						
No (ref.)						
Yes	10.05	0.002*	2.53 (1.43– 4.49)	1.97	0.16	1.63 (0.82–3.24)
Hypertension						
No (ref.)						
Yes	3.66	0.056*	1.71 (0.99– 2.94)	0.16	0.69	1.14 (0.59–2.22)
Stress						
No (ref.)						
Yes	22.32	<0.001*	9.71 (3.78– 24.93)	6.21	0.013*	3.83 (1.33 – 11.00)
Anxiety						
No (ref.)						
Yes	31.82	<0.001*	5.32 (2.98– 9.51)	7.11	0.008*	2.6 (1.29–5.24)
Depression						
No (ref.)						
Yes	19.44	<0.001*	5.12 (2.48–10.58)	2.47	0.12	2.04 (0.84–4.98)

[a]Wald statistic; [b]p-value of Simple Logistic Regression; [c] Crude odd ratio; [d] Confidence Interval; e p-value of Multiple Logistic Regression; [f] Adjusted odd ratio; *significant at p-value less than 0.05. The model of Nagelkerkr R square for this study was 0.236. This implies that only 24% of the variation in this study was explained in this model.

DISCUSSION AND CONCLUSION

Prevalence of premature ejaculation and severity

The study's results found that 32.4% of the respondents reported ranging from 21.4 to 33.9% experiencing PE, which closely matches the previous prevalence of PE in Malaysia,.[10–12,14] Our result closely matches a study conducted at Jaya Gading Health Clinic with 15.8% and 18.1%, respectively, for probable PE and PE.[14] However, a study done at the University Malaya Medical Centre (UMMC) with 207 respondents revealed the highest prevalence reported in Malaysia at 40.6%, which may be attributed to better awareness and reporting in the West coast region of peninsular Malaysia compared to the East Coast, where cultural factors such as embarrassment and taboos are more common.[15]

From a global perspective, PE prevalence varies across countries, but the widespread use of the PEDT allows for

more reliable comparisons across studies. Our findings are consistent with prevalence rates reported in Asia, with 37.7%, 32.5%, and 26.67% in China, South Korea, and Egypt, respectively.[6,7,19] Global research reveals that the PE prevalence in our study is similar with a study conducted in Somalia, which reported 12% for probable PE and 25% for PE.[2] In contrast to our findings, a Vietnamese study on male partners in infertile couples revealed a lower prevalence of probable PE and PE with rates of 7.1% and 4.7%, respectively.[3] These variations emphasise diverse factors such as ethnicity, sociocultural and distinct geographical regions that may influence the prevalence of PE in different countries and areas.

Significant discrepancies in PE prevalence are observed in studies using different diagnostic tools. For instance, in Malaysia, two studies reported PE prevalence rates of 22.3% and 25% using the Intravaginal Ejaculatory Latency Time (IELT) and the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), respectively.[10,11] A recent study in Germany utilising the Sexual Complaints Screener for Men (SCS-M) found a much lower PE prevalence of 5.2%.[9] A literature review has highlighted that PE is predominantly identified as a major sexual dysfunction among young adult males. This finding could potentially account for the observed lower prevalence as this study focused on men aged 50 years and above.[4] Additionally, two studies in China using the IELT reported a substantial increase in PE prevalence in the same province, rising from 10% to 60% over five years.[5,8] This higher rate may be linked to the recent COVID-19 pandemic, which affected psychological, social, and physical health, potentially influencing sexual health and behaviours. Despite these observations, research on the COVID-19-PE link is limited. Using varying diagnostic tools, such as IELT, DSM-5, and SCS-M, contributes to inconsistent results, hindering direct comparisons.

Associated factors

Two variables, anxiety and stress, were shown to have a significant association with PE. Our study shows that stressed individuals are nearly four times more likely to experience PE. One study conducted in Vietnam explored the relationship between stress and PE among infertility couples, revealing a positive correlation between stress and PE. This suggests a link between higher levels of stress and PE. Nevertheless, their findings may have been influenced by their sample population, which consisted of males from infertile couples.[17]

Various instruments of study were employed from local and global studies, but none specifically assessed stress as a psychological factor. The inconsistent findings on the link between stress and PE in various studies are due to the lack of standardised tools to assess stress in men. Earlier Malaysian studies used the Hospital Anxiety and Depression Scale (HADs) to evaluate the psychological aspects linked to PE. However, these studies did not measure the stress factor.[10,11] Whereby, worldwide studies primarily focus on anxiety and depression with different tools such as the Patient Health Questionnaire (PHQ-2 & PHQ-9), Generalised Anxiety Disorder (GAD-2 and GAD-7), and HADs, failing to capture the full spectrum of stress experiences.[5,8,9]

Our study reveals a significant association between anxiety and PE, showing that individuals with anxiety are more than twice as likely to experience PE compared to those without anxiety. Our finding is consistent with a previous Malaysian study, which reported a 2.83-fold likelihood of developing anxiety in men with PE.[10] Similar associations have been observed in global studies from Vietnam and China, which identified strong correlations between anxiety and PE using PEDT with DASS-21 and PEDT with GAD-7.[8,17] These findings indicate strong correlations between anxiety and PE even when different tools are used to measure anxiety. A study in China differentiated between lifelong PE (LPE) and acquired PE (APE), finding a weaker link between LPE and our findings closely align with APE, demonstrating that men with PE are nearly three times more likely to develop anxiety.[5] This indicates that anxiety is often linked to APE, explaining why APE has a higher likelihood than LPE.

Determining whether PE precedes stress and anxiety or *vice versa* is complex, as the relationship is likely bidirectional. This may explain why anti-anxiety medications (SSRIs) that regulate serotonin are effective in treating PE.[24] A study in China suggests that men with PE often develop anxiety due to the distress and embarrassment associated with their condition. (5) However, it is plausible that anxiety often precedes PE, but once PE occurs, it can further increase anxiety, leading to a vicious cycle.[17]

STRENGTHS AND LIMITATIONS

The strength of this study lies in its comprehensive representation of men attending government health clinics in Kuantan. By adopting an improvised method from a study at Jaya Gading Health Clinic, it used simple random sampling across all twelve clinics to represent the male population. Furthermore, this study examined PE with psychological factors, underscoring the necessity for primary care providers to implement proactive screening strategies for PE, even in the absence of symptoms, to ensure early detection and treatment.

The study, however, has several limitations. The reliance on self-reported data may introduce recall bias, and the cross-sectional design limits the ability to establish causality for PE. Future research should perhaps include populations from diverse ethnicity and conducting comprehensive assessments for potential confounding variables and relationship satisfaction. Furthermore, the questionnaire we employed is a screening tool for PE, which may limit its ability to distinguish between LPE and APE effectively.

CONCLUSION

This study found a high prevalence of PE among men attending government health clinics in Kuantan, Pahang, with significant associations between stress and anxiety. Raising awareness among the public and healthcare providers is crucial for improving detection rates in primary care. Utilising screening tools like PEDT and DASS-21 can effectively identify men with undisclosed sexual health problems, facilitating early diagnosis and treatment.

CONFLICT OF INTEREST

The author discloses that they do not have any conflicts of interest.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

This study obtained approval from the Department of Family Medicine and Kulliyyah Research Committee (KRC) of Kulliyyah of Medicine, International Islamic University Malaysia (IIUM) on 20th June 2022 with Research ID: 880. Furthermore, this study was registered with the National Medical Research Register (NMRR) and obtained approval from the Medical Research and Ethics Committee (MREC) with ID: NMRR ID-23-00266-YMV (IIR).

ACKNOWLEDGEMENT

The researchers express their profound appreciation to the Director General of the Ministry of Health Malaysia for authorising the publication of this manuscript. Special thanks to the Pahang State Health Department and Kuantan District Health Office for allowing me to use government health clinics for data collection. Thank you to the staff for their cooperation and assistance in ensuring smooth data collection.

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ORIGINAL ARTICLE

The Association Between Marital Satisfaction, Depression, and Sexual Dysfunction Scores among Women at Six Months Postpartum in Kelantan, Malaysia

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ABSTRACT

INTRODUCTION: Female sexual dysfunction (FSD) can significantly impact the quality of sexual relationships, potentially leading to marital dissatisfaction and depression if it occurs postnatally. However, there is limited research investigating FSD, marital satisfaction, and postnatal depression (PND) in Malaysia. This study aimed to determine the association between FSD scores with marital satisfaction scores and depression scores among postpartum women in Kota Bharu, Kelantan. **MATERIALS AND METHODS:** A cross-sectional study was conducted among 429 women at 6 months postpartum in four primary healthcare clinics in Kota Bharu district. They were required to answer the Malay Version of the Female Sexual Function Index-6 (MVFSFI-6), Golombok Rust Inventory of Marital State (MV-GRIMS), and the Edinburgh Postnatal Depression Scale (MV-EDPS). The data was analysed using multiple linear regression. **RESULTS:** At six months postpartum, 52.5% were at risk of sexual dysfunction, 55.0% at risk of marital dissatisfaction, and 18.2% at risk of PND. The associations between FSD scores and marital dissatisfaction scores, as well as FSD scores and PND scores, were significant. **CONCLUSION:** Experiencing of FSD could heighten the risks of marital dissatisfaction and depression in postpartum women. Thus, healthcare providers should holistically assess sexual issues in postpartum women and refer them for early diagnosis and treatment to prevent adverse outcomes.

Keywords
Depression, female sexual dysfunction, Female Sexual Function Index-6, marital dissatisfaction, postpartum women.

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Received: 17th July 2024; Accepted: 28th August 2024

Doi: https://doi.org/10.31436/imjm.v24i02.2610

INTRODUCTION

Women's sexual health is a crucial aspect of their well-being, influenced by numerous factors. Following childbirth, biological, psychological, and social changes can significantly affect sexual health.[1] The extent of sexual morbidity and its impact post-delivery has been explored in a limited number of studies among select samples of postpartum women. During the postnatal period, women's sexual function may be compromised by factors such as trauma to the reproductive organs, vaginal bleeding, constraints of newborn care, lethargy, body shape changes, and physical discomfort, including breast tenderness.[2] Despite these challenges, postpartum sexual function is often overlooked by healthcare providers. Studies indicate that rates of sexual dysfunction (SD) vary from 41-83% in the first three months following childbirth, decreasing to 64% at six months postpartum.[3,4] However, discussing sexuality remains taboo in Asian countries, particularly in Malaysia, which significantly impacts women's lives.[5,6]

Marital satisfaction defined as objective feelings of contentment, satisfaction and pleasure experienced by married couple when all aspects are considered in their lives.[7] A sexual relation is an important element in constancy and successful of family foundation. The marital satisfaction is influenced by many factors such as safe and pleasurable sexual relationship is mentioned to be one of the most important factors. SD may affect the sexual relationship and eventually marital dissatisfaction.[8,9] According to a study, married women without children have better sexual satisfaction and higher marital satisfaction than women who have experienced childbirth, this possibly due to reduced physical and emotional strain.[9] Marital dissatisfactions in turn lead to

marital instability and divorce.[10]

Depression is another major health concern after childbirth. Postnatal depression (PND) can develop at any time during the first year of postpartum. It has negative consequences on women health, the development of her children and family harmony.[9] Previous review found that the prevalence of PND in Asian countries ranged from 3.5-63.3%.[11] In Malaysia, the prevalence of PND is 6.8-14.3% within the first 6 months postpartum.[12,13] Other systematic review showed that various risk factors such as unplanned pregnancy, domestic violence, low social support, previous history of depression and poor marital relationship are significantly associated with PND.[14] In addition, it was reported that women who have sexual problems after childbirth may experience higher risk of PND symptoms or other mental problems.[15] However, there is a limited study investigating the SD and PND women and there is no study on this issue in Malaysia.

Research indicates some association between female sexual dysfunction (FSD), marital satisfaction and PND. A study found strong negative association between SD and PND scores.[16] Similarly, an inverse relationship was observed between marital satisfaction and PND.[17] Recognising the importance of women health and the need to integrate sexual health issues into primary healthcare, it is clear the interconnected issues of FSD, marital dissatisfaction and depression have a profound impact on women's overall well-being and quality of life. Therefore, this study was conducted to investigate the association between sexual dysfunction (SD) with marital dissatisfaction and depression in postpartum women in Kelantan, Malaysia.

MATERIALS AND METHODS

429 women at six months postpartum participated in this cross-sectional study. Data was collected from February-November 2019. Participants were selected from four primary healthcare clinics with Family Medicine Specialists (FMS) in Kota Bharu, Kelantan, Malaysia, namely i) Klinik Kesihatan Bandar Kota Bharu, ii) Klinik Kesihatan Pengkalan Chepa, iii) Klinik Kesihatan Wakaf Che Yeh, and iv) Klinik Kesihatan Ketereh. Each Maternal and Child Health (MCH) clinic was estimated to follow up approximately 50-60 new postnatal mothers each month. Non-proportionate systematic random sampling in a 1:2 ratio, based on attendance at each MCH clinic, was used.

Population and sample size

The study involved women aged 18 years old and above, who had delivered a single full-term child, married, and cohabiting with a sexually active partner. Exclusions comprised women with psychiatric disorders, pregnant women, non-Malaysians, and those who had not resumed sexual activity post-delivery, as their responses could reflect non-engagement in sexual activity rather than dysfunction, potentially introducing bias. Additionally, the Malay version of the Female Sexual Function Index-6 is validated specifically for sexually active women. None of the participants reported abstaining from sexual intercourse at six months.

The sample size to determine the association between marital satisfaction scores, female sexual dysfunction (FSD) scores, and depression scores among women at six months postpartum in Kota Bharu, Kelantan, should ideally be calculated using linear regression. However, due to limited information, it was not feasible to perform the calculation for this objective. Instead, as this study is part of a larger research project on FSD among postpartum women,[18] the sample size was determined using the single proportion formula with an α of 0.05 and a power of 0.8. This calculation was based on a study by De Lima Holanda et al.,[19] which reported a prevalence of sexual dysfunction (SD) of 43.5% among women at six months postpartum. The required sample size for the study was 416 women at six months postpartum. Accounting for a 20% non-response rate, the final calculated sample size was adjusted to 453 participants.

Research tools

The participants answered 4 types of questionnaires after consented for the study, namely i) participants' Performa, ii) Malay version Female Sexual Function Index-6 (MVFSFI-6); iii) Malay version Golombok Rust Inventory

of Marital State (MV-GRIMS), and iv) Malay version Edinburgh postnatal depression scale (MV-EPDS). The information about these questionnaires is as elaborated below.

Questionnaire i: Participants' Performa

The questionnaire gathers socio-demographic details like age, education, job, and income, alongside clinical information like number of children, delivery method, breastfeeding, and medical history. It also explores marital and sexual aspects such as spouse's age, marriage duration, resumption of sexual activity post-delivery, and sexual frequency.

Questionnaire ii: Female Sexual Function Index-6 – a validated Malay version (MVFSFI-6)

The FSFI-6, a validated questionnaire, assesses women's sexual function over the past four weeks, offering a simpler version of the FSFI-19. A score of ≤ 19 indicates Female Sexual Dysfunction (FSD), with sensitivity and specificity of 0.93 and 0.94, respectively. Its Cronbach's alpha coefficient is 0.789.[20] The Malay-translated version (MVFSFI-6) demonstrated high reliability (Cronbach's alpha of 0.9314) in a study involving breast cancer patients.[21] This tool proves useful for research and outpatient consultations in identifying FSD efficiently. See Table 1 for FSFI-6 domains, items, and score range.

Questionnaire iii: Golombok Rust Inventory of Marital State-A validated Malay version (MV-GRIMS)

The GRIMS questionnaire evaluates marital relationships with 28 items across four domains: i) Satisfaction, ii) Communication, iii) Shared interests, and iv) trust and respect. Respondents rate items on a 4-point Likert scale. Positive score includes Items: 3, 6, 7, 8, 11, 13, 16, 18, 19, 21, 23, 24, 26, and 27, while negative score includes Items 1, 2, 4, 5, 9, 10, 12, 14, 15, 17, 20, 22, 25, and 28. Total scores range from 0-84, with higher scores indicating increased marital dissatisfaction. A score of 34 or higher suggests significant marital issues. The MV-GRIMS shows excellent internal consistency (Cronbach's alpha: 0.43 to 1.00) and high test-retest reliability (ICC ≥ 0.51). It also demonstrates high sensitivity and specificity.[22]

Table 1: Score range of Female Sexual Function Index-6 domain

Sexual Function Domain Description of Item	Score range
Desire	
Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?	1-5
Arousal	
Over the past 4 weeks, how would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?	0-5
Lubrication	
Over the past 4 weeks, how often did you become lubricated ("wet") during sexual activity or intercourse?	0-5
Orgasm	
Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?	0-5
Pain	
Over the past 4 weeks, how often did you experience discomfort or pain during vaginal penetration?	0-5
Satisfaction	
Over the past 4 weeks, how satisfied have you been with your overall sexual life?	1-5
Total	2-30

The GRIMS questionnaire evaluates marital relationships with 28 items across four domains: i) Satisfaction, ii) Communication, iii) Shared interests, and iv) trust and respect. Respondents rate items on a 4-point Likert scale. Positive score includes Items: 3, 6, 7, 8, 11, 13, 16, 18, 19, 21, 23, 24, 26, and 27, while negative score includes Items 1, 2, 4, 5, 9, 10, 12, 14, 15, 17, 20, 22, 25, and 28. Total scores range from 0-84, with higher scores indicating increased marital dissatisfaction. A score of 34 or higher suggests significant marital issues. The MV-GRIMS shows excellent internal consistency (Cronbach's alpha: 0.43 to 1.00) and high test-retest reliability (ICC ≥ 0.51). It also demonstrates high sensitivity and specificity.[22]

Questionnaire iv: Edinburgh Postnatal Depression Scale – a validated Malay version (MV-EPDS)

The EPDS, developed by Cox et al. in 1987, is a self-administered survey consisting of ten statements related to depression symptoms.[23] Responses are recorded on a Likert-style scale ranging from 0-3, with total scores ranging from 0-30. A threshold score of 12/13 indicates likely depression, with a sensitivity of 86.0% and specificity of 78.0%. The Malay version (MV-EPDS), established through back-translation, is a reliable screening tool for postnatal depression (PND). A threshold score of ≥12 indicates depression risk, with a

sensitivity of 72.7% and specificity of 92.6%.[24]

Data collection

The study used non-proportional systematic random sampling in the ratio 1:2, which was based on attendance at each Maternal and Child Health Care Unit in primary healthcare clinics. The study only included participants who met the eligibility criteria. Prior to the study, women were informed about the details and purpose of the research and were asked if they would like to participate. If they agreed to participate, written consent was obtained. The participants were then given self-administered questionnaires as described above which took approximately 20-30 minutes to complete. Participants were also reassured of their confidentiality.

Those who tested positive for postpartum depression on the questionnaire received prompt notification of their results. Those who were keen on management were referred to a psychiatrist, while those who did not were given the contact information for the psychiatric clinic.

Data analysis

The SPSS software version 26.0 was utilized to analyse the data. Descriptive analysis was employed to characterize the categorical variables (frequency and percentage) and numerical variables (mean and standard deviation). To examine the association between marital satisfaction score and FSD score as well as depression score in postpartum women, simple and multiple linear regression confirmatory analyses were conducted. The FSFI-6 score was treated as the independent variable while the GRIMS and EDPS scores as the dependent variable, with adjustments made for household income. The factors were considered statistically significant when the p-value was below 0.05.

RESULTS

453 women who attended the respective clinics were invited to participate. However, 24 women were excluded due to refusal to participate or incomplete questionnaires. The response rate for this study was 95%, with a total of 429 subjects. Some parts of the study findings with different aims have been published by Ng et al., 2023.[18]

Sociodemographic data

The socio-demographic characteristic of the participants is summarised in Table 2. The mean age of the participants was 30.9 (SD 5.55) years old with 50.1% above 30 years old. Two thirds (61.8%) had total monthly household income of less than MYR 3000. More than half (53.4%) had secondary school education and were housewives (54.8%). Most women were multiparous with a mean of having 2 children, and majority (88.6%) breastfed their babies.

Most women (97%) did not have a chronic medical condition, and a significant proportion (79%) continued to practice confinement. The husbands' mean (SD) age was 4 years older than their wives, the duration of marriage was 6.7±5.0 years, and sexual activity was resumed at mean of after three months postpartum. About 50% had sexual intercourse once a week and for some more.

Table 2: Sociodemographic data of included postpartum women (n=429)

Variables	n (%)
Socio-demographic Data	
Age in years	30.9(5.55)*
Educational level	
Nil or primary	11(2.6)
Secondary	229(53.4)
Tertiary	189(44.1)
Job	
Home maker	235(54.8)
Self-employed	54(12.6)
Government servants/ private workers	140(32.6)
Monthly household income in MYR	2654.5(1918.2)*
Past Obstetric History	
Number of children	2.4(1.39)*
Mode of delivery	
Vaginal delivery with intact perineum	49(11.4)
Vaginal delivery with tear/ episiotomy/ instrumental delivery	306(71.3)
Caesarean section	74(17.2)
Parity	
Primiparous	137(31.9)
Multiparous	292(68.1)
Breastfeeding history	
Not at all	49(11.4)
Yes (partial and exclusive)	380(88.6)
Confinement practises	
Yes	339(79)
No	90(21)
Chronic medical illness during pregnancy	
Yes	13(3.0)
No	416(97.0)
Marital And Sexual Profile	
Spouse's age in years	33.9(6.5)*
Duration of marriage in years	6.7(5.0)*
Resumption of sexual intercourse in weeks	12.9(3.4)*
Frequency of sexual intercourse	
Once or more in a week	235(54.8)
Once every two weeks	127(29.6)
Once a month	67(15.6)

*Mean (SD)

52.4% of the respondents had positive results for FSD. The mean (SD) for the FSD, GRIMS and EPDS scores were 19.4±3.62, 32.3±6.91 and 7.3±4.81 respectively. More than half of the women were at risk for marital dissatisfaction and about 20% having risk for PND. (See Table 3)

Table 3: Findings from questionnaires of Female Sexual Function Index (FSFI), Golombok Rust Inventory of Marital State (GRIMS), and Edinburgh Postnatal Depression Scale (EPDS)

Variables	n %
FSFI	19.41(3.62)*
FSD	
Yes	225(52.4%)
No	204(47.6%)
GRIMS	32.31(6.91)*
Marital dissatisfaction	
Yes	236(55.0%)
No	193(45.0%)
EDPS	7.37(4.81)*
Postnatal depression	
Yes	78 (18.2%)
No	351 (81.8%)

*Mean (SD)

The association between female sexual dysfunction (FSD) score with marital satisfaction score and postnatal depression score using multiple linear regression analysis

Multiple linear regression analysis revealed a significant negative association between female sexual dysfunction (FSD) score and marital satisfaction (β=-0.368, 95% CI:-0.546 to -0.191, p<0.001) after adjusting for household income. The model, which accounted for 4.8% of the variance in marital satisfaction, suggests that FSD contributes to lower marital satisfaction.

Multiple linear regression analysis demonstrated a significant negative association between FSD score and postnatal depression score (β=-0.238, 95% CI:-0.362 to -0.114, p<0.001) after adjusting for household income. The model, which explained 3.2% of the variance in postnatal depression, indicates that FSD is associated with increased risk of postnatal depression.

These findings also suggest that while FSD has a measurable impact on marital satisfaction and postnatal depression, other factors not included in the model likely play a larger role in explaining marital satisfaction and postnatal depression.

DISCUSSION

In the present study, 52.4% of the women experienced sexual dysfunction (SD), a finding consistent with other studies.[25,26] However, another study in Malaysia reported a lower (35.5%) prevalence of FSD among postpartum women, likely due to differences in postpartum duration and the questionnaire used.[27] Possible factors contributing to FSD during the postpartum period include hormonal and physical changes which reduce sexual desire, arousal, and lubrication; psychological and emotional changes; relationship dynamics; lack of support; cultural expectations; lactation-related factors; and clinical and medical conditions.[28] These findings emphasize the importance of recognizing and addressing the prevalence of sexual dysfunction in postpartum women, ensuring that healthcare professionals do not neglect or overlook this critical aspect of maternal health.

In addition, 55.0% of the women reported marital dissatisfaction. The result is higher than rates reported in other countries such as Australia (37.2%), Nigeria (39.5%) and Saudi Arabia (39.5%).[15,29,30] This discrepancy may stem from the use of different research tools to assess marital satisfaction (e.g., Relationship Assessment Scale, Couples Satisfaction Index, Index of Marital Satisfaction) and variations in sociodemographic backgrounds, cultural norms, and support systems. The findings also contribute in highlighting the substantial prevalence of marital dissatisfaction within our study population and emphasising the need to consider contextual factors when interpreting marital satisfaction globally. For instance, cultural expectations, family dynamics, and access to social support may influence how individuals perceive and report relationship satisfaction.

Further comparison with existing studies revealed that the timing of postpartum assessment plays a significant role in marital satisfaction. While our study identified that more than half of women were at risk for marital

dissatisfaction at 6 months postpartum, a study in Australia found that postpartum women within the first 5 months after childbirth were more affected by dissatisfaction compared to those 6-12 months postpartum.[15] This aligns with findings by Doss et al. (2009), who reported that relationship satisfaction was significantly lower in the early months after childbirth, adversely affecting couples' relationships.[31] These observations highlight the critical need for interventions during the early postpartum period, including at 6 months postpartum period, to mitigate marital dissatisfaction and promote family well-being.

The transition to motherhood is a significant life event marked by fundamental changes for a substantial number of individuals. This is supported by a meta-analysis showed that the significantly decrease of marital satisfaction up to 1 year postpartum for women.[32,33] Another study even showed the marital dissatisfaction continues up to the second year postpartum.[34] A variety of factors could contribute to a decline in marital satisfaction, including the transition from a marriage of spouses without children to a system of parents with a child, the stress caused by childcare, reduced postpartum communication and responsiveness, and multiple activities performed at once.[33]

The postpartum period is a time when women, particularly those in stressful situations, are at a heightened risk of developing mental health problems. Our findings highlight that the prevalence of postnatal depression remains high at approximately 18.2% at six months postpartum. This finding aligns with a study conducted in the same district in 2006, which reported a prevalence of 20.7% PND at 4–6 weeks postpartum, as well as in the recent global analysis where PND prevalence was 17.2% worldwide.[35,36] The rate in the current study (18.2%) is higher than that reported in two previous studies in Kuala Lumpur and Sabah, which was 14.3%.[37,38] This may be due to Kelantan, the state where this study was conducted, has the lowest household monthly income in Malaysia.[39] Indeed, many studies have reported that low household income increases the risk of PND in developing countries.[36,40] Azidah et al (2006) noted that the factors contributing to PND were having depressive symptoms at the end of pregnancy and early postpartum period, worry about their babies, use of traditional medication, and traditional massage.[35] Findings from current study emphasized the proportion and possible influence of sociocultural and economic factors, such as household income, family support and postnatal practices, on mental health outcomes during the postpartum period. This underscores the need for focus history taking, targeted possible reasons, and support systems that address financial stressors and provide mental health resources, particularly in economically disadvantaged area, to reduce the burden of postnatal depression in Kelantan.

The association between marital satisfaction score and female sexual dysfunction score among women at 6 months postpartum

Marital satisfaction is one of the important concepts used to assess happiness and stability in a marriage. We investigated whether sexual problems can affect the relationship issue such as marital satisfaction. The findings from this study showed that female sexual dysfunction (FSD) is associated with marital dissatisfaction. The lower the FSFI-6 score, the higher the score of GRIMS score. The female sexual index score is useful for predicting GRIMS score. While FSFI-6 score is a significant predictor of marital satisfaction, the R^2 value emphasises that it accounts for only a small fraction of the variability, indicating a complex interplay of other contributing factors that need to be further researched. Sexual functioning is one of the issues. Many studies reported significant relationship between sexual satisfaction and marital satisfaction.[15,40,41] Sexual satisfactions can act as a compensatory factor for the negative impact of poor communication on marital satisfaction, even for couples who struggle with communication difficulties in their relationship.[42] The findings encourage healthcare providers to address both sexual health including sexual functioning screening, marital satisfaction and relationship dynamics in consulting their postpartum patients.

Couples distressed about their sexual relationship may not engage in problem solving discussion because sexual dysfunction is a sensitive topic. Yet, not discussing the sexual problem may exacerbate the strain on their relationship. Further longitudinal study is needed to explore the marital satisfaction with sexual problem from pre-pregnancy until after childbirth.

Association postpartum depression score with female sexual dysfunction score among women at 6 months postpartum

The result of the current research demonstrates an association between sexual dysfunction and postnatal depression (PND), despite the low R^2 value (indicating a complex interplay of other contributing factors occurs). This finding is consistent with results from other studies.[42,43] When FSFI-6 scores increase by 1 unit, the EDPS scores decrease by 0.238 unit. Hence, a lower FSFI-6 score, indicates a higher risk of sexual dysfunction, therefore the risk of PND increases. According to Glazener and colleagues, PND is associated with women's loss of sexual desire after childbirth. Depression was also associated with a lower frequency of intercourse, and fatigue negatively affects women's sexual functioning at 12 weeks postpartum.[43] A study by Elliott and Watson (1985) noted that the relationship between PND and women's decreased sexual interest, enjoyment, frequency, and satisfaction by 6 months postpartum which became more significant between 9-12 months postpartum.[42] Ignorance of sexual issues in postpartum women leads to negative long-term effect. The risk of depression symptoms was 2.5 times greater in women with sexual dysfunction and 3.7 times greater in women with relationship dissatisfaction.[23]

A prospective cohort study showed that 1 in 5 women complained of deterioration in sexual life and depression anxiety symptoms after childbirth. The depressive symptoms are associated with a decline in sexual life up to 18 months postpartum.[44] Another study showed women with depression had significant reduction in arousal, orgasm, and satisfaction than non-depressed women, suggesting more problematic sexual functioning.[45] However, women with sexual dysfunction had a 1.62-fold risk for depressive symptoms during the entire 24 months after childbirth than women without sexual dysfunction. Risk factors for depressive symptoms were a higher pain score, a medical condition, and severe perineal laceration.[46] A systematic review revealed presence of bidirectional association between sexual dysfunction and depression.[47]

Findings from the current study also contribute to the broader understanding of the complex relationship between sexual dysfunction (SD) and PND by providing additional evidence of how sexual health directly influences mental well-being in the postpartum period. By quantifying the association between SD and depression, this study highlights the importance of addressing sexual health as part of comprehensive postpartum care. The recognition of this relationship can inform healthcare practitioners and encourage early interventions to prevent the long-term consequences of untreated SD and PND.

LIMITATION

The research was carried out in 4 primary healthcare centres located in Kelantan. Majority of the participants were Malay ethnicity; hence findings cannot be generalized to the population of Malaysia with different ethnicities.

The cross-sectional design of this study cannot establish a cause-and-effect relationship between sexual dysfunction (SD), marital satisfaction, and postpartum depression (PND). Future longitudinal studies may provide stronger evidence to understand the underlying relationship identified in this study.

Although sexuality and mental health issues are often viewed as taboo and stigmatized, the usage of a self-administered questionnaire may encourage participants to provide more truthful and dependable responses.

CONCLUSION

In this study, approximately over 50% were 6 months postpartum and at risk to experiencing sexual dysfunction (SD) and marital dissatisfaction. 20% were at risk of

developing postnatal depression (PND). The frequency of SD may increase the risk of marital dissatisfaction and depression in postpartum women. Therefore, health care providers should have holistically assessment for sexual problems in postpartum women and they can refer women for early diagnosis and treatment to prevent negative consequences.

ACKNOWLEDGMENTS

We would like to thank all the women who participated in this study and had given the time to share their experiences.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

The ethical board approval has been granted by The Research and Ethics Committee of USM (USM/ JEPeM/18080359) as well as the Medical Research Ethics Committee of the Ministry of Health Malaysia (NMRR-18-2551-43304).

This study was funded by Tabung Insentif Pembangunan Pengajian Siswazah (TIPPS) from School of Medical Sciences, USM

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ORIGINAL ARTICLE

Addressing Mental Health Challenges: A Community-Based Survey on Depression, OCD, Eating Disorders, and Psychosis Risk Among 18-44-year-olds in India

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ABSTRACT

INTRODUCTION: Mental health is a complex issue with high prevalence but poor health facilities and health-seeking behaviour. The age group of 18-44-year-olds is socio-economically crucial, however, their mental health is largely neglected. This research was conducted to study mental health problems among the 18–44-year-old age group. **MATERIALS AND METHODS**: This cross-sectional study was conducted among 1700 participants, aged 18-44 years old, from the urban and rural areas of Sangli district (Maharashtra state), India, using stratified random sampling. All ethical considerations were adhered to during data collection. Pre-validated tools namely, WHO-5 Well-Being Index, OCI-R, CAPE, etc., were used in data collection interviews. Statistical analysis was done using frequency (%) and the chi-squared test. **RESULTS**: The highest number of participants were positive for symptoms of obsessive-compulsive disorder (OCD) (n=336, 19.8%), followed by depression (n=326,19.2%), a high risk of psychosis (n=164, 9.6%) and an eating disorder (n=144, 8.5%). The area of residence (urban/ rural) was associated with these mental illnesses. Depression was not significantly associated with any socio-demographic factors. OCD was significantly higher in participants from rural area, females, illiterates, and belonging to socioeconomic class III. Eating disorders were associated with rural areas, widowed status, and illiteracy. Psychosis risk was significantly higher in males, rural areas, joint families, and widower status. **CONCLUSIONS:** A very high proportion of 18-44-year-olds suffer or are at risk of various mental health conditions, requiring the development of targeted preventive and curative services. Rural areas should receive sufficient attention regarding mental health services.

Keywords
Mental Health; Mental Health Services; Age group; Depressive Disorder; India

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Received: 19th August 2024; Accepted: 25th Jan 2025

Doi: https://doi.org/10.31436/imjm.v24i02.2677

INTRODUCTION

People are in a state of mental well-being when they can successfully manage the challenges and stresses of day-to-day life and contribute positively to society.[1] Mental health issues have escalated into a significant public health challenge, with a staggering estimate of over one billion people affected. This alarming trend, an increasing prevalence over the last few decades, underscores the urgent need for intervention.[2] COVID-19 exacerbated various mental health conditions like stress, anxiety, depressive disorders, suicide ideation, anxiety disorders, and alcohol use.[3,4]

Depression, obsessive-compulsive disorder (OCD), eating disorders, psychosis, etc., are some of the most critical mental health issues. Globally in 2019, depression impacts around 260 million people, with symptoms like loss of interest in activities, poor concentration, and low self-esteem. It could lead to suicide ideation. OCD leads to unwanted thoughts or unwanted repetitive behaviours which hamper the functioning of a person. In 2019, eating disorders experienced by 14 million people, are often paired with anxiety about one's body and significantly increase the risk of substance abuse and suicidal ideation. Psychotic conditions, especially schizophrenia, affect approximately 24 million people and impair their perception and behaviour, resulting in symptoms like hallucinations, delusions, and reduced cognitive functioning.[1]

Mental health in India is a complex subject. There is a

significant burden of mental health issues, the most common being depression, anxiety, substance abuse, and psychosis. The number of individuals experiencing mental health struggles has significantly increased over the past few years. These issues can impact an individual's day-to-day functioning, thus reducing one's productivity, resulting in family strain and, ultimately, the nation's economy. The government and the overall health sector have realized the importance of addressing the issue, and steps have been initiated to provide mental health care. But the demand-supply gap is still enormous.[5] This is further complicated by the stigma surrounding mental health issues and lack of awareness, creating a problematic barrier for help-seeking among the people.[6] Community health workers are required to contribute to this challenge.

Management of health issues begins with understanding the extent of the problem. In India, a mental health survey was conducted in 2015-2016 on 39,532 individuals in 12 states. Findings revealed an overall lifetime prevalence of mental health issues at 13.9%. There were significant interstate variations of these morbidities and the availability of mental health services. Within states, the variation within different geographic and economic regions was staggering.[7] This highlights the need for the availability of local data and partial decentralization in the planning of health services to have the requisite impact on mental health care.

The 18–44-year-old age group is often considered a driver of socio-cultural-economic change. This demographic has a significant impact due to their participation in higher education and contribution to the workforce, especially manual and physically challenging labour. They are at the forefront of innovation and entrepreneurial activities. Similarly, this age group is commonly associated with marriage, childbirth, and transmitting ideas and values to future generations.[8] However, the national suicide statistics show a grim reality of the highest suicide rates among the age group of 18-30-year-olds followed by 30-44-year-olds.[9] Hence, understanding the prevalence of mental health issues in this age group and planning for prevention and management is very important.

As discussed earlier, the availability of local data and decentralization of planning is essential for preventing and managing mental health issues. However, there is an overall scarcity of data, especially from the study area. Whatever data is available is among specific college-going students or senior population.[10,11] Hence, the purpose of this research was to study the prevalence of various crucial mental health issues like depressive disorders, OCD, eating disorders, and psychotic symptoms among the participants of the 18-44-year-old age group in the Sangli district (Maharashtra state), India. It is hoped the study will have some impact on practical, theoretical, social, and research domains. The research aims to fill the gap in current knowledge regarding the extent of the presence of depression, obsessive-compulsive disorder (OCD), eating disorders, and psychotic symptoms in the study area. Findings could be applied in education, healthcare, and community programs, leading to enhanced mental health education, targeted interventions, and community initiatives. Future studies could explore this problem in greater depth propelling societal change, hence improving mental health outcomes.

MATERIALS AND METHODS

This cross-sectional study was conducted in Sangli district (Maharashtra state), India. According to the 2011 census, the district's population was 28,22,143, with 39.3% of the population being 18-44 years old. The calculated sample size (99.99% confidence level, 5% margin of error) was 1444 @ 1500. With 10% buffer, the sample size was 1650 and rounded to 1700. As the rural proportion of the population in Sangli district was 74.47%, it was decided to include 1266 rural and 434 urban samples.[12]

Data was collected using stratified random sampling. Stratification was done as urban and rural samples. All the urban wards (divisions) from the Sangli urban area were listed as urban samples, and all the villages from the Sangli district were listed as rural samples. A single ward from the Sangli urban area and a village from the list were randomly selected using simple random sampling. To collect actual samples, every fifth house in the chosen location was approached for data collection. All the eligible and consenting individuals from the house present at the time of data collection were recruited as study

participants. If a home was locked or people were ineligible/non-consenting, the immediate next house was involved. Data was collected until the requisite sample size was fulfilled. The study was conducted for 3 years until 2015.

It is practically impossible to include screening for every mental health problem in this research. Hence, after considering the most common mental health problems in previous surveys and the feasibility of data collection, it was decided to include depression, OCD, eating disorders and psychotic symptoms in this study.[7] The study tool was a scheduled structured interview. The first part consisted of questions regarding sociodemographic characteristics like age, gender, education, etc. The next consisted of validated, reliable tools for screening various mental health issues namely; i) depression: WHO-5 Well-Being Index,[13] ii) OCD: Obsessive-Compulsive Inventory -Revised (OCI-R),[14] **iii) e**ating disorders: Eating attitude test,[15] iv) detection of individuals with a high risk of psychosis: Community Assessment of Psychic Experiences (CAPE).[16]

It is important to note that the current research was a community screening study, and the persons identified positively by any of the above tools do not necessarily suffer from that disease. The positive outcome only suggests that the person exhibits some symptoms of that disease. The principal author undertook three weeks of training in the Department of Psychiatry at the same medical college and prior to data collection.

The Institutional Ethics Committee (IEC) approval was obtained and adhered to regarding consent, privacy or anonymity, and various other aspects. For people undergoing psychiatric treatment, consent was also taken from their legal caretakers. The inclusion criteria were age 18-44-year-old and present during data collection. The exclusion criteria were non-consenting or debilitated persons and language, physical, or other barriers hampering the data collection.

Microsoft Excel and IBM SPSS were used for data compilation and analysis. Descriptive statistics and chi-squared tests were used to study the associations of various sociodemographic factors with mental health conditions.

RESULTS

The sociodemographic characteristic of 1700 participants is shown in Table I, whilst Figure I illustrates the proportion of participants with mental health problems.

Table I: Sociodemographic characteristics of the study participants

Sociodemographic characteristics		Residence		Total
		Rural	Urban	
Gender	Male	695 (54.9%)	220 (50.7%)	915 (53.8%)
	Female	571 (45.1%)	214 (49.3%)	785 (46.2%)
Age Group (in years)	18-30	833 (65.8%)	226 (52.1%)	1059 (62.3%)
	31-44	433 (34.2%)	208 (47.9%)	641 (37.7%)
Type of family	Nuclear	289 (22.8%)	98 (22.6%)	387 (22.8%)
	Joint	977 (77.2%)	336 (77.4%)	1313 (77.2%)
Occupation	Skilled	568 (44.9%)	188 (43.3%)	756 (44.5%)
	Unskilled	326 (25.7%)	148 (34.1%)	474 (27.9%)
	Business	242 (19.1%)	68 (15.7%)	310 (18.2%)
	Professional	130 (10.3%)	30 (6.9%)	160 (9.4%)
Marital Status	Married	872 (68.9%)	361 (83.2%)	1233 (72.5%)
	Unmarried	362 (28.6%)	63 (14.5%)	425 (25%)
	Divorce	13 (1%)	4 (0.9%)	17 (1%)
	Widow	19 (1.5%)	6 (1.4%)	25 (1.5%)
Education	Illiterate	112 (8.9%)	31 (7.1%)	143 (8.4%)
	Primary	201 (15.9%)	94 (21.7%)	295 (17.4%)
	Secondary	546 (43.1%)	150 (34.5%)	696 (40.9%)
	Graduate	328 (25.9%)	114 (26.3%)	442 (26%)
	Postgraduate	79 (6.2%)	45 (10.4%)	124 (7.3%)
Socioeconomic classification (Updated B. G. Prasad's classification)	Class-I	43 (3.4%)	10 (2.3%)	53 (3.1%)
	Class-II	693 (54.7%)	298 (68.7%)	991 (58.3%)
	Class-III	334 (26.4%)	85 (19.8%)	419 (24.7%)
	Class-IV	196 (15.5%)	41 (9.2%)	237 (13.9%)
Total		**1266 (74.5%)**	**434 (25.5%)**	**1700 (100%)**

The highest proportion of participants were positive for symptoms of OCD, (19.8%), followed by depression, (19.2%). The association of mental health problems with various sociodemographic characteristics is shown in Table II.

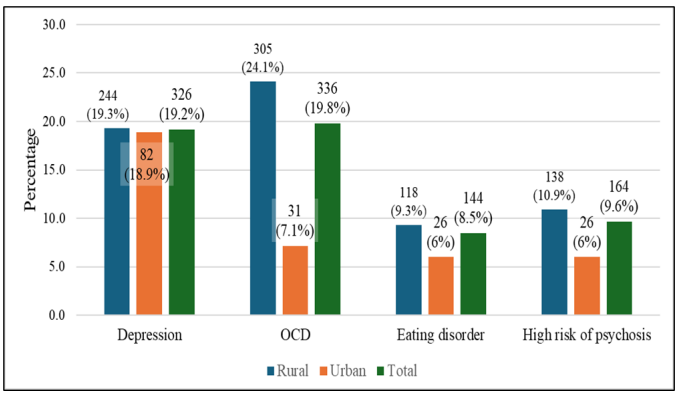

Figure 1: Participants screened positive for mental health problems

Table II: Association of mental health problems with various sociodemographic characteristics

Sociodemographic characters		Depression	OCD	Eating Disorder	High risk of Psychosis
Gender	Male	184 (20.1%)	158 (17.3%)	79 (8.6%)	106 (11.6%)
	Female	142 (18.1%)	178 (22.7%)	65 (8.3%)	58 (7.4%)
		χ^2 =1.1125, P=0.29	χ^2 =7.7905, P=0.005*	χ^2 =0.068, P=0.79	χ^2 =8.5, P=0.003*
Age Group (years)	18-30	206 (19.5%)	202 (19.1%)	93 (8.8%)	105 (9.9%)
	31-44	120 (18.7%)	134 (20.9%)	51 (8%)	59 (9.2%)
		χ^2 = 0.1379, P=0.71	χ^2 = 0.8435, P=0.36	χ^2 = 0.351, P=0.55	χ^2 = 0.231, P=0.63
Residence	Rural	244 (19.3%)	305 (24.1%)	118 (9.3%)	138 (10.9%)
	Urban	82 (18.9%)	31 (7.1%)	26 (6%)	26 (6%)
		χ^2 = 0.03, P=0.86	χ^2 = 58.547, P=0.000*	χ^2 = 4.622, P=0.032*	χ^2 =8.938, P= 0.003*
Type of family	Joint	240 (18.3%)	259 (19.7%)	117 (8.9%)	139 (10.6%)
	Nuclear	86 (22.2%)	77 (19.9%)	27 (7%)	25 (6.5%)
		χ^2 = 2.999, P=0.08	χ^2 = 0.0055, P=0.94	χ^2 = 1.44, P=0.23	χ^2 = 5.839, P= 0.016*
Occupation	Skilled	158 (20.9%)	152 (20.1%)	67 (8.9%)	73 (9.7%)
	Unskilled	80 (16.9%)	89 (18.8%)	36 (7.6%)	38 (8%)
	Business	57 (18.4%)	62 (20%)	23 (7.4%)	32 (10.3%)
	Professional	31 (19.4%)	33 (20.6%)	18 (11.3%)	21 (13.1%)
		χ^2 = 3.1929, P=0.36	χ^2 = 0.43, P=0.93	χ^2 = 2.66, P=0.45	χ^2 = 3.828, P=0.28
Marital Status	Married	222 (18%)	243 (19.7%)	89 (7.2%)	105 (8.5%)
	Unmarried	94 (22.1%)	81 (19.1%)	49 (11.5%)	55 (12.9%)
	Divorce	2 (11.8%)	2 (11.8%)	1 (5.9%)	0 (0%)
	Widow	8 (32%)	10 (40%)	5 (20%)	4 (16%)
		χ^2_{Yates} = 5.313, P=0.15	χ^2_{Yates} = 5.609, P=0.13	χ^2_{Yates} = 10.008, P=0.02*	Fisher's exact test = 8.023, P=0.05*
Education	Illiterate	36 (25.2%)	33 (23.1%)	24 (16.8%)	18 (12.6%)
	Primary	53 (18%)	49 (16.6%)	25 (8.5%)	35 (11.9%)
	Secondary	128 (18.4%)	152 (21.8%)	59 (8.5%)	61 (8.8%)
	Graduate	94 (21.3%)	92 (20.8%)	29 (6.6%)	39 (8.8%)
	Postgraduate	15 (12.1%)	10 (8.1%)	7 (5.6%)	11 (8.9%)
		χ^2 = 9.132, P=0.057	χ^2 = 15.74, P=0.003*	χ^2 = 16.1, P=0.003*	χ^2 = 4.134, P=0.39
Socio-economic classification	Class I	12 (22.6%)	9 (17%)	4 (7.5%)	2 (3.8%)
	Class II	173 (17.5%)	161 (16.2%)	80 (8.1%)	101 (10.2%)
	Class III	94 (22.4%)	123 (29.4%)	40 (9.5%)	39 (9.3%)
	Class IV	47 (19.8%)	43 (18.1%)	20 (8.4%)	22 (9.3%)
		χ^2 = 5.236, P=0.16	χ^2 = 32.69, P=0.000*	χ^2 = 0.887, P=0.83	χ^2_{Yates} = 1.785, P=0.62
Total		**326 (19.2%)**	**336 (19.8%)**	**144 (8.5%)**	**164 (9.6%)**

**significant*

Depression was associated with socioeconomic status, with the highest percentage of Class-I who had signs of depression. OCD was associated with gender, residence, education, and socioeconomic classification. The association of eating disorders with residence, marital status and education was statistically significant. The high risk of psychosis was associated with gender, residence, type of family, and marital status.

The present research also further analysed the rural-urban distribution of mental health problems and their association with various sociodemographic factors. Most of these associations were not significant. Table III shows the sociodemographic factors that had a statistically significant association with the rural-urban distribution of depression and OCD. The rural-urban distribution of eating disorders and high risk of psychosis were not associated with any sociodemographic factor.

Table III: Urban-rural distribution of depression & obsessive-compulsive disorder (OCD) and the associated sociodemographic factors

DEPRESSION				
Sociodemographic characters		**Rural**	**Urban**	**Total**
Marital Status	Married	154 (63.1%)	68 (82.9%)	222 (68.1%)
	Unmarried	82 (33.6%)	12 (14.6%)	94 (28.8%)
	Divorce	2 (0.8%)	0 (0%)	2 (0.6%)
	Window	6 (2.5%)	2 (2.4%)	8 (2.5%)
	Fisher's exact test=12.221, p=0.003			
Socioeconomic Status	Class I	9 (3.7%)	3 (3.7%)	12 (3.7%)
	Class II	117 (47.9%)	56 (68.3%)	173 (53.1%)
	Class III	77 (31.6%)	17 (20.7%)	94 (28.8%)
	Class IV	41 (16.8%)	6 (7.3%)	47 (14.4%)
	χ^2 = 11.111, p=0.011			
Total		**244 (100%)**	**82 (100%)**	**326 (100%)**
OBSESSIVE - COMPULSIVE DISORDERS				
Age Group	18-30	191 (62.6%)	11 (35.5%)	202 (60.1%)
	31-44	114 (37.4%)	20 (64.5%)	134 (39.9%)
	χ^2 =8.644, p=0.003			
Total		**305 (100%)**	**31 (100%)**	**336 (100%)**

DISCUSSION

In this current research, most persons approached in rural areas were willing to participate. However, many from urban areas were apprehensive or sceptical about this mental health survey.

About 19% of participants were screened positive for depression, with no significant rural-urban difference. Similarly, it was not associated with gender, education, occupation, marital status, and type of family. However, based on the descriptive statistics, it was observed that a higher percentage of widowed persons, persons living in nuclear families, persons with skilled labour or professionals, and illiterates were depressed. Depression was not associated with socioeconomic status, but a higher proportion of persons belonging to Class–I was depressed. The rural-urban distribution of depression was significantly associated with marital status and socioeconomic status. A community survey was

conducted in Al-Qunfudah governorate, Saudi Arabia[17] which observed the prevalence of depression in the age group of 18-40-year-olds at 70.3%. This prevalence was over 300% higher than current study. This variation in the prevalence of depression could be attributed to sociocultural differences in the study population. However, both studies observed an increased prevalence of depression among less educated and single persons. In a Nigerian study, the prevalence of depression was observed at 5.2%, with the rural population being more impacted than the urban.[18] Sociocultural differences could explain the lower prevalence of depression in their study compared to our findings. However, in that study, prevalence trend among rural residents compared to urban counterparts mimics the findings of the current research. In a study conducted among rural adult women from Puducherry, India, the prevalence of depression was 15%, whereby it was identified that fewer years of education and being separated/widowed as risk factors for depression.[19] In the current study, 18.1% of women had depression, with a higher proportion of them being illiterate and widowed. The current research looks into 18-44-year-olds; hence the prevalence of depression varies from the India's National Mental Health Survey (NMHS) (2015-16), which stated that prevalence of depressive disorders in 18-29-year-olds, 30-39-year-olds, and 40-49-year-olds were 1.6%, 2.6%, and 3.6% respectively. Depression was higher in rural areas as compared to cities with less than 1 million population. Similarly, it was higher among illiterates, widowed, and lowest earning sections of people.[20] The prevalence observed was much lower than the current findings. The India NMHS used the Mini International Neuropsychiatric Interview (MINI) schedule V.6 as a diagnostic tool to assessed depression. In contrast, in the current study, the WHO-5 Well-Being Index, was used as a screening tool. Hence, the outcomes from both these tools are different, and the current research is expected to have a higher prevalence. However, the trends of the distribution of depression according to sociodemographic attributes are similar in both studies.

It is important to note that in the current study, the presence of OCD does not mean that the person was suffering from OCD; it means the person exhibits some symptoms of OCD. In the current study, the presence of OCD symptoms, was the most reported mental health problem, (19.8%). However, a substantially higher proportion of rural participants (24.1%) had reported OCD as compared to urban participants (7.1%). This difference was statistically significant. OCD was significantly higher in females, illiterates, and those belonging to socioeconomic Class III. In a study from Saudi Arabia, the lifetime prevalence of OCD was observed at 4.2%.[21] Females were at greater odds for lifetime OCD. This prevalence was lower than the current study, as the diagnostic tool used, CIDI 3.0, has better specificity than the OCI-R which was used in the current study. However, the pattern of female preponderance observed in the current study and past research is similar.

In the current research, eating disorders was noted in 8.5% of participants, and statistically significant amongst rural-urban participants, with a higher proportion of rural participants. Similarly patterns for marital status (highest proportion among widowed persons) and education (highest among illiterates). Studies from Indian have found the prevalence of eating disorders at between 25.2-35%.[22,23] However, these studies were conducted among specific groups, such as college students, and not the community, hence comparing their findings with current research will be inaccurate.

Over 9% of participants had a high risk of psychosis. Its association was statistically significant with gender (higher in males), residence (higher in rural areas), type of family (higher in joint family members), and marital status (higher in widowed). In a study among Chinese students, 51.4% of adolescents reported at least one psychotic-like experience.[24] However, these findings during the COVID -19 pandemic are not comparable with current research findings.

CONCLUSION

A substantial proportion of India's 18-44-year-old age group are at risk of mental health problems. The rural population is equally vulnerable to these issues. There is a need for a robust strategy and execution of preventive and curative mental health services targeted at the 18-44-

year-old age group, especially in rural areas. This age group is the backbone of India's economic and social development and must be supported to foster prosperity.

Findings from this research have practical implications for designing and implementing mental health services, especially locally. These should include educational campaigns to raise awareness, early detection initiatives to identify at-risk individuals, and accessible mental health services in urban and rural areas. Training primary healthcare workers to recognize and manage mental health disorders can enhance early intervention and support for affected individuals.

Future research should focus on prospective studies to track the mental health outcomes and effectiveness of mental health services. Researchers should also examine the impact of cultural, socioeconomic, and environmental factors on mental health to develop more tailored and effective interventions. Similarly, the studies should expand to include broader geographic conditions.

LIMITATIONS

The research was a cross-sectional design; hence it was not able to suggest and test effective implantation strategies. Secondly, data was self-reported, hence respondent bias like social desirability and recall bias cannot be avoided. The sample may not fully represent the entire 18–44-year-old population in India, particularly regarding regional, cultural, and socioeconomic diversity. This may affect the generalizability of the findings.

Future research should address these limitations by employing longitudinal designs, multi-centric data collection, corroborating self-reported information using multiple sources, using diagnostic tools following the screening, and ensuring diverse and representative sampling.

ACKNOWLEDGEMENT

We thank ASHA (Accredited Social Health Activists) and Anganwadi workers from the study area for assisting with data collection.

CONFLICT OF INTEREST

The principal author funded this study, and there is no conflict of interest to declare.

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ORIGINAL ARTICLE

Factors Related to Parental Perceptions and Awareness of Adolescent Cyberbullying in Selangor, Malaysia

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ABSTRACT

INTRODUCTION: The rise of digital technology has heightened concerns about adolescent cyberbullying, emphasising the importance of parental perceptions and awareness. This study assessed parental perceptions and awareness of adolescent cyberbullying and identified associated factors among secondary school parents in Selangor, Malaysia. **MATERIALS AND METHODS**: A cross-sectional study was conducted from June-September 2023 involving 522 parents, selected through multistage cluster sampling. Data were collected using the validated 33-item Parental Perception and Awareness of Cyberbullying Questionnaire (KEPS-I). Multiple linear regression analyses identified associated factors. **RESULTS:** The overall mean score for parental perceptions and awareness was 3.96 (SD=0.44). Parents demonstrated the highest awareness in cyberbullying prevention strategies but scored lowest in knowledge of internet and social media platforms. Younger parents exhibited greater awareness, likely due to their familiarity with digital technology (adjusted b=-0.475, P<0.001). Parents who used the internet daily were also more aware (adjusted b=5.670, P=0.041), while non-Bumiputera parents showed lower scores, reflecting gaps in digital literacy or access to information (adjusted b=-3.035, P=0.037). Only 2.5% of parents reported their child's experience with cyberbullying, indicating possible underreporting. **CONCLUSION:** Gaps in digital literacy, particularly among older and non-Bumiputera parents, highlight the need for targeted educational initiatives and school policies to improve parental awareness and intervention strategies. Future research should evaluate digital literacy programs and explore adolescent perspectives to better address underreporting and strengthen prevention efforts.

Keywords
Cyberbullying, Parental Awareness, Parental Perception, Adolescents, Selangor

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Received: 17th September 2024; Accepted: 26th December 2024

Doi: https://doi.org/10.31436/imjm.v24i02.2701

INTRODUCTION

In the digital age, adolescents' use of the internet and social media has surged, providing unprecedented opportunities for education, communication, and social interaction. However, this connectivity also brings significant risks, including cyberbullying, which poses severe threats to the mental health and well-being of young users. Cyberbullying, defined as deliberate and repeated online aggression via digital devices, affects adolescents globally, often leaving victims with long-lasting emotional and psychological scars.[1,2] Prevalence studies report global rates of cyberbullying victimisation ranging from 14.6-52.2%, with perpetration rates between 6.3-32%.[3] In Malaysia, the issue is equally concerning, with the country holding the second-highest youth cyberbullying rate in Asia.[4]

A study in Selangor found that 13.3% of secondary school students had experienced cyberbullying, predominantly through instant messaging.[5] Adolescents are particularly vulnerable due to their heavy engagement with social media and digital platforms, which increases their exposure to online risks.[6,7] This reliance on digital communication tools is particularly pronounced during middle adolescence, a period marked by heightened social connectivity.[8,9] The COVID-19 pandemic further exacerbated the issue, with virtual learning environments intensifying exposure to online harassment.[9,10]

Parents play a crucial role in safeguarding adolescents from cyberbullying. However, research shows that many parents lack awareness of their children's online activities

and the associated risks.[11,12] For instance, in the United States, 95% of adolescents aged 13-17 years old have access to smartphones, with a growing prevalence of daily internet usage.[13] Alarmingly, studies report that 35.9% of parents never monitor their children's online activities, 51.9% do not supervise social media usage, and 43.6% fail to educate their children on safe internet practices.[14] This limited parental involvement may be attributed to factors such as permissive parenting styles and difficulties in keeping pace with the rapidly evolving digital landscape.[11,15]

Globally, similar trends have been observed, with cultural and systemic differences further influencing how parents perceive and respond to cyberbullying risks. For example, in Israel, parents were found to be aware of the psychological and legal implications of cyberbullying, yet their knowledge often remained superficial, typically derived from media rather than communication with their children, leading to significant gaps in effective intervention.[16] In Saudi Arabia, parents recognised the harmful effects of cyberbullying and stressed the importance of internet monitoring but often relied on schools and stricter laws to address the issue, reflecting a reactive approach.[17] Similarly, in Canada, many parents underestimated their children's involvement in cyberbullying, either as victims or perpetrators, due to their limited familiarity with newer digital platforms.[15] These findings highlight a global gap in parental awareness, shaped by cultural and systemic factors, which underscores the need for localised research to address specific contextual challenges.

Despite the growing prevalence of cyberbullying, Malaysian research predominantly focuses on adolescents, with limited attention to parental perspective.[18–20] Alarmingly, previous studies suggest that parents often underestimate the seriousness of cyberbullying and its potential impact.[11,21] To date, only one study in Malaysia has examined parents' knowledge, attitudes, and perceptions of cyberbullying, underscoring a critical gap in the literature.[22]

This study aims to address these gaps by evaluating parental perceptions and awareness of adolescent cyberbullying in Selangor and identifying associated sociodemographic and child-related factors. It is hypothesised that these factors significantly influence parental perceptions and awareness of cyberbullying.

MATERIALS AND METHOD

Study Design and Sampling Method

This cross-sectional study was conducted from June-September 2023 among parents of secondary school students in Selangor, Malaysia. A multistage cluster sampling method was employed to select participants. The sampling process began with the random selection of four districts from Selangor's nine districts, ensuring representation of both urban and rural areas to enhance generalizability. Within each district, two national secondary schools were randomly chosen, followed by a random selection of two classes from each school. All parents of students in these classes were invited to participate. Parents were included if their children were present in school during data collection. Exclusion criteria included parents who were illiterate or unable to understand the Malay language, as the questionnaire was administered in Malay.

Ethical approval was obtained from the Human Research Ethics Committee, Universiti Sains Malaysia (reference number: USM/JEPeM/KK/23010098), and the study was registered with the National Medical Research Register (reference number: NMRR ID-23-005530N7H). School principals provided permission, and participants gave informed consent, with confidentiality strictly maintained.

Study Sample Size

The sample size was calculated using G*Power software,[23] considering a medium effect size (0.15), Type 1 error rate of 0.05, and a power of 0.80 with 15 predictors. Accounting for a 30% non-response rate and the design effects of cluster sampling, resulting in a required sample size of 605. A total of 605 parents were recruited, with 522 providing complete and usable responses, yielding a response rate of 88%.

Study Instruments

Data were collected using a self-administered questionnaire in two sections. The first section gathered sociodemographic data of participants and their children, including variables such as online behaviour, history of cyberbullying victimisation, and parent-child relationship quality.

The second section utilised the validated Malay version of the Parental Perception and Awareness on Cyberbullying Questionnaire (KEPS-I).[24] The validation process involved 270 parents or caregivers with school-going children, aged between 20-60 year old, from primary and secondary schools. The questionnaire underwent exploratory and confirmatory factor analyses to establish construct validity. It demonstrated acceptable factor loadings exceeding 0.40 and strong internal consistency reliability, with Cronbach's alpha values ranging from 0.894 to 0.939.[24]

The KEPS-I comprises 33 items across five domains: i) perceptions and effects of cyberbullying, ii) perceptions of preventive measures, iii) family practices related to internet usage, iv) internet and social media knowledge, and v) knowledge acquisition regarding cyberbullying. Responses were recorded on a five-point Likert scale, ranging from "strongly disagree" (1) to "strongly agree" (5), with higher scores indicating greater perception and awareness of cyberbullying.

Data Collection

Data collection was conducted in collaboration with school counsellors, who distributed questionnaires to students for delivery to their parents. Parents returned completed questionnaires in sealed envelopes within a week, which were retrieved by the researcher. Contact information for the primary researcher was included to address any inquiries from the participants. Each questionnaire was assigned a unique reference number to ensure anonymity and confidentiality.

Statistical Analysis

Data were analysed using IBM SPSS version 26.0. Descriptive statistics summarised the participants' sociodemographic characteristics and KEPS-I scores. Simple and multiple linear regression analyses assessed the association between sociodemographic factors and cyberbullying awareness, with a p-value of less than 0.05 considered statistically significant. Results included adjusted β coefficients, confidence intervals, and t-statistics.

In this study, 'daily internet and social media use' referred to parents' consistent engagement with digital platforms, such as social media, web browsing, or messaging applications, on a daily basis, irrespective of duration. 'Perceived closeness in parent-adolescent relationships' was defined as the parents' subjective evaluation of their emotional connection with their child, which included components such as trust, communication, and support.

Certain variables were re-coded during the analysis due to low response rates for specific categories. For instance, ethnicity was simplified into two groups: 'Bumiputera' (coded as '0'_ comprising Malay and Indigenous groups, and 'Non-Bumiputera' (coded as '1') including Chinese and Indian ethnicities. Marital status was re-categorised into 'one-parent' households (coded as '0') for divorced or widowed participants, and 'two-parent' households (coded as '1') for married participants. Educational level was grouped into 'lower education level' (coded as '0') for parents with primary or secondary school qualifications, and 'higher education level' (coded as '1') for those with college or university education. Similarly, monthly household income was dichotomised into 'lower-income' (coded as '1') for parents earning less than RM 4,850, and 'higher-income' (coded as '0') for those falling within the middle 40% (M40) or top 20% (T20) income groups earning RM 4,850 and above.

RESULTS

Participant Characteristics

The mean age of the participants was 45.74 (SD 5.23) years old, and the majority were female (61.3%). Most participants identified as Malay (74.2%), were married (94.1%) and reported being employed (82.6%). A majority (67.0%) had attained a college or university education. Additionally, 94.8% of the parents reported using the

internet and social media daily. Detailed demographic characteristics of the participants and their children are presented in Table I.

Table I: Sociodemographic characteristics of participants and their children (n=522)

Variables	n (%)
Parental factors	
Age (years)	45.74 (5.23)*
Sex	
Male	202 (38.7)
Female	320 (61.3)
Ethnicity	
Malay	387 (74.2)
Chinese	67 (12.9)
Indian	56 (10.7)
Others	12 (2.3)
Marital status	
Divorced	21 (4.0)
Widow	10 (1.9)
Married	491 (94.1)
Number of children	
Two and more	495 (94.8)
One	27 (5.2)
Highest formal education	
Primary school	3 (0.6)
Secondary school	169 (32.4)
College / University	350 (67.0)
Employment Status	
Employed	431 (82.6)
Unemployed	91 (17.4)
Monthly household income	
≥RM10960 (T20)	142 (27.2)
RM4850 to RM10959 (M40)	187 (35.8)
<RM4850 (B40)	193 (37.0)
Use internet and social media daily	
No	27 (5.2)
Yes	495 (94.8)
History of cyberbullying victimisation	
No	491 (94.1)
Yes	31 (5.9)
Perceived close parent-adolescent relationship	
No	10 (1.9)
Yes	512 (98.1)
Children's factors	
Age (years)	
16	253 (48.5)*
14	269 (51.5)*
Sex	
Male	268 (51.3)
Female	254 (48.7)
Disability	
No	503 (96.4)
Yes	19 (3.6)
Experience cyberbullying victimisation (reported by parents)	
No	509 (97.5)
Yes	13 (2.5)

*mean(SD)

Parental Perceptions and Awareness of Cyberbullying

The overall mean score for parental perceptions and awareness of cyberbullying was 3.96 (SD=0.44). Among the five domains assessed, parents scored the highest in perceptions of preventive measures against cyberbullying [mean=4.40 (0.47)] and the lowest in knowledge of the internet and social media [mean=3.61 (0.66)]. Table II shows the mean scores for each domain of the KEPS-I questionnaire.

Table II: Mean score for parental perceptions and awareness of cyberbullying (n=522)

Measure	Mean (SD)
Perceptions and extent of cyberbullying	4.20 (0.51)
Perceptions of preventive measure of cyberbullying	4.40 (0.47)
Family practice on using the Internet	3.90 (0.68)
Level of knowledge on the internet and social media	3.61 (0.66)
Acquisition of knowledge about cyberbullying	3.66 (0.60)
Total mean score for KEPS-I	**3.96 (0.44)**

Note: SD=standard deviation

Factors Associated with Cyberbullying Awareness

The multiple linear regression analysis identified several significant predictors of cyberbullying perceptions and awareness among parents: age, ethnicity, and daily internet and social media use. Parental age was inversely associated with awareness scores, with each one-year increase in age resulting in a decrease of 0.475 in the awareness score (95% CI:-0.704,-0.246; P<0.001). Parents of Non-Bumiputera ethnicity had significantly lower awareness scores compared to Bumiputera parents (Adjusted b=-3.035; 95% CI:-5.893, -0.177; P=0.037). Conversely, parents who reported daily use of the internet and social media exhibited higher awareness scores (Adjusted b=5.670; 95% CI:0.244, 11.115; P=0.041).

The final regression model satisfied all assumptions for multiple linear regression, including linearity, normality of residuals, and homoscedasticity. No significant interactions were identified among the independent variables, and multicollinearity was not detected. Consistent results were obtained using forward, backward, and stepwise selection methods. Table III shows the details of the analysis.

DISCUSSION

This study explored parental perceptions and awareness of cyberbullying, revealing a mean KEPS-I score of 3.96 (SD = 0.44). Although the KEPS-I tool is unique to this study, comparisons can be drawn with previous research

Table III: Simple and multiple linear regression of factors related to perceptions and awareness of cyberbullying score among parents (N=522)

Variables	Simple linear regression		Multiple linear regression		
	Crude b (95% CI)	P-value	Adjusted b (95% CI)	T-stat	P-value
Parental factors					
Age	-0.509 (-0.738, -0.279)	<0.001	-0.475 (-0.704, -0.246)	-4.069	<0.001
Sex					
Male	1				
Female	3.149 (0.655, 5.644)	0.013	2.252 (-0.222, 4.726)	1.789	0.074
Ethnicity					
Bumiputera	1				
Non-Bumiputera	-4.145 (-7.003, -1.288)	0.005	-3.035 (-5.893, -0.177)	-2.086	0.037
Marital status					
One-parent	1				
Two-parent	0.441 (-4.729, 5.612)	0.867			
Number of children					
Two and more	1				
One	0.355 (-5.163, 5.873)	0.900			
Highest formal education					
Lower education level	1				
Higher education level	1.768 (-0.828, 4.363)	0.182	0.723 (-1.872, 3.319)	0.547	0.584
Employment status					
Employed	1				
Unemployed	1.596 (-1.623, 4.814)	0.331			
Monthly household income					
Higher-income	1				
Lower-income	-1.277 (-3.806, 1.252)	0.322			
Use internet and social media daily					
No	1				
Yes	6.871 (1.384, 12.357)	0.014	5.670 (0.244, 11.115)	2.046	0.041
History of cyberbullying victimisation					
No	1				
Yes	-2.122 (-7.289, 3.046)	0.420	-2.207 (-7.381, 2.966)	-0.838	0.402
Perceived close parent-adolescent relationship					
No	1				
Yes	5.034 (-3.871, 13.939)	0.267	6.713 (-2.013, 15.439)	1.511	0.131
Children's factors					
Age					
16 years old	1				
14 years old	1.968 (-0.471, 4.408)	0.114	1.037 (-1.441, 3.516)	0.822	0.411
Sex					
Male	1				
Female	-1.161 (-3.604, 1.283)	0.351			
Diagnosed with any form of disability					
No	1				
Yes	-1.421 (-7.945, 5.103)	0.669			
Experience cyberbullying victimisation					
No	1				
Yes	-4.780 (-12.611, 3.052)	0.231	-4.653 (-12.291, 2.986)	-1.197	0.232

Note: CI=confidence interval; R2=5.4%; forward/backward/stepwise multiple linear regression applied; model assumptions are fulfilled; no interactions among independent variables; no multicollinearity detected

using different methodologies. For example, Clarke[25] utilising the Parents' Perception and Awareness of Cyberbullying (PPAC) scale, found that parental beliefs and practices regarding cyberbullying were moderate. Despite differences in tools and study designs, the findings from both studies highlight similar patterns of parental engagement in addressing cyberbullying. Specifically, Clarke observed strong parental confidence in prevention strategies, which aligns with the high scores in the preventive measure domain in this study.

The results emphasised the importance of media platforms in raising awareness and preventing cyberbullying. Parents strongly agreed that the media should play a role in prevention efforts, underscoring the impact of media-driven educational campaigns. Previous studies support this finding; for instance, Vranda[26] highlighted how print media fosters public awareness by reporting incidents of cyberbullying and its societal consequences. Similarly, social media campaigns can quickly disseminate preventive messages, promote positive online behaviour, and advocate for robust policies and laws.[27] Traditional media such as radio and television were also significant sources of parental knowledge about cyberbullying, as reported by Nazmul et al.[22] These findings suggest that leveraging both digital and traditional media is critical in educating parents, particularly those less familiar with digital platforms, to promote collective action against cyberbullying.

Parental involvement emerged as another key theme in this study, reinforcing findings from prior research. Active parental engagement, characterised by nurturing and supportive behaviours, fosters open communication between parents and adolescents. Studies have shown that such involvement reduces problematic internet use and encourages disclosure of online experiences.[28,29] Additionally, parents' responsiveness and monitoring strategies significantly decrease bullying behaviours.[30] However, prior studies, including Cassidy et al.[31] suggest that many educators perceive parents as lacking awareness of their children's online activities, which may undermine efforts to address cyberbullying effectively. These insights highlight the importance of strengthening parental

oversight and promoting collaborative interventions involving parents, schools, and policymakers.

Interestingly, the lowest KEPS-I scores were observed in the "Knowledge on the internet and social media" domain, particularly concerning newer platforms like Snapchat and WeChat. These findings are consistent with prior research indicating that parents are often more familiar with older technologies while lacking an understanding of newer platforms.[15,32] This generational gap underscores the need for targeted educational programs to enhance parents' digital literacy and ability to address cyberbullying effectively.

Three key factors significantly influenced parental perceptions and awareness of cyberbullying. First, parental age was inversely associated with awareness, with younger parents scoring higher. This aligns with previous research indicating that younger parents are more adept with digital technologies and online risks.[22,33] Older parents, on the other hand, may face challenges in adapting to newer technologies, which can create a digital divide that hinders effective communication with their children about online safety.[34] Bridging this gap through targeted interventions to improve technological literacy among older parents may enhance their awareness and ability to address cyberbullying.

Second, ethnicity played a significant role, with Non-Bumiputera parents scoring lower than Bumiputera parents. Cultural differences in community resources and support systems may account for these variations.[35] For instance, Bumiputera communities may have stronger networks that facilitate education on cyberbullying, while Non-Bumiputera groups may face barriers to accessing similar resources. Addressing these disparities through culturally sensitive interventions is crucial for improving awareness across all ethnic groups.

Finally, daily internet and social media use was positively associated with awareness, indicating that parents who are regularly engaged with digital platforms are better equipped to recognise and address cyberbullying risks.[36] Encouraging parents to increase their familiarity with online environments may further enhance their ability to support their children in navigating these spaces.

A relatively low percentage of parents in this study reported their child's experience with cyberbullying, which may reflect underreporting or lack of awareness. Previous research indicates that 52% of Malaysian adolescents have reported experiences of online victimisation,[37] while 21% of American parents acknowledged that adolescents aged 12-17 years old had experienced cyberbullying.[38] This discrepancy suggests that many parents may remain unaware of their children's experiences, likely due to limited communication or the concealed nature of cyberbullying. Adolescents often refrain from disclosing such incidents to adults out of fear that doing so might result in restricted internet access, heightened parental monitoring, or reduced autonomy in their digital activities.[39,40] Consequently, the low prevalence of reported cyberbullying victimisation in this study sample may have constrained the ability to identify significant associations in the analysis.

This study has several limitations. The reliance on self-reported data introduces the potential for biases, including social desirability bias and recall bias. To address this limitation, the study ensured that responses were anonymous and confidential to encourage parents to answer honestly Additionally, the cross-sectional design limits the ability to establish causal relationships between variables. Sampling-related limitations, such as potential response bias due to non-response or exclusion of illiterate parents, may also affect the generalizability of the findings.

Future research could address these limitations by adopting longitudinal designs to explore changes in parental awareness over time. Studies could also examine factors such as parental mental health, family dynamics, and exposure to media reports on cyberbullying, which may influence awareness. Incorporating adolescents' perspectives would provide a more comprehensive understanding of the discrepancies in cyberbullying reporting and victimisation. Furthermore, intervention studies targeting older parents and culturally diverse groups could offer valuable insights into strategies for improving cyberbullying awareness.

CONCLUSION

This study highlights the factors influencing parental perceptions and awareness of cyberbullying in Malaysia, revealing significant associations with parental age, ethnicity, and daily internet and social media use. The findings underscore the critical role of younger parents and those more engaged with online platforms in recognising cyberbullying risks, while also identifying disparities in awareness among different ethnic groups. These insights contribute to a deeper understanding of parental engagement in the digital safety of adolescents.

To enhance the practical impact, these findings could guide the development of targeted school policies and parental education programs in Malaysia. Schools could implement awareness campaigns tailored to bridge the generational and cultural gaps in cyberbullying knowledge, equipping parents with the skills needed to monitor and support their children's online activities effectively. Furthermore, integrating cyberbullying education into school-parent engagement activities, such as workshops or digital safety seminars, could strengthen collaboration between parents, educators, and policymakers.

Future research should explore adolescent perspectives to address discrepancies in reported cyberbullying victimisation and evaluate the effectiveness of interventions designed to improve parental awareness. By addressing these gaps, stakeholders can create a more cohesive and informed approach to preventing and managing cyberbullying in Malaysia.

FUNDING

This study was supported by a postgraduate development incentive grant from Universiti Sains Malaysia.

CONFLICT OF INTEREST

None

ACKNOWLEDGEMENT

Many thanks to the school principals and teachers for their cooperation and assistance in facilitating the data collection process at their respective institutions.

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ORIGINAL ARTICLE

The Malay Version of the Theory of Planned Behaviour Questionnaire on the Intention of Pre-Pregnancy Care Services Utilisation: A Validation Study

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ABSTRACT

INTRODUCTION: This study aims to translate and adapt the Theory of Planned Behaviour questionnaire on intention of pre-pregnancy care services utilisation (IPCSU) from English to Malay and determine its validity and reliability. **MATERIALS AND METHODS**: This was a cross-sectional validation study conducted at UiTM Shah Alam, Selangor, Malaysia from October to December 2022 among 145 unmarried female undergraduate students aged 18 to 25 years who could speak and understand written Malay. Participants were excluded if they were currently pregnant or had been pregnant in the past. Convenience sampling was employed for participant selection. The English version of the 25-item IPCSU questionnaire was subjected to translation, adaptation, content validation, and face validation, ; followed by field testing to create the Malay version. Psychometric analysis was performed using exploratory factor analysis, internal consistency, and test-retest reliability. **RESULTS:** A total of 145 participants (91% response rate) were recruited, with 89.7% being Malay and a mean age of 21.7 years (±SD 1.6). The scale-level content validity index/average (0.98) and scale-level face validity index/average (0.88) were acceptable. Exploratory factor analysis found that the Malay version of IPCSU had four conceptually equivalent domains, with four items removed due to a low inter-item correlation matrix. The construct validity achieved an acceptable factor loading for each construct (0.47 to 0.80). The overall Cronbach's alpha was 0.95, indicating excellent internal consistency, and the intraclass-correlation coefficient values ranged from 0.46 to 0.86, indicating moderate to excellent reproducibility. **CONCLUSION:** The Malay version of the IPCSU questionnaire is valid, reliable, and stable over time.

Keywords
Theory of Planned Behaviour, Validity and Reliability, Preconception care, Pre-pregnancy care

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Received: 4th April 2024; Accepted: 28th October 2024

Doi: https://doi.org/10.31436/imjm.v24i02.2569

INTRODUCTION

Pre-pregnancy care (PPC) provides biomedical, behavioural, and social health interventions to women and couples before conception. The goal is to enhance their health condition and minimise factors that might lead to poor maternal and child health outcomes.[1]

A growing body of evidence supports the effectiveness of PPC as an intervention to reduce maternal and perinatal mortality and morbidity. For instance, a systematic review and meta-analysis study demonstrated the beneficial impact of PPC on maternal and infant health, particularly in women with specific risk factors such as diabetes and hypertensive disorders.[2] Furthermore, PPC was associated with reduced risk of maternal and neonatal complications.[3]

However, despite this evidence, the prevalence of PPC services utilisation is low worldwide. For example, countries such as China (42%), the United States (36%), and Ethiopia (14.5%) shows a different level of PPC services utilisation, and in Iran, more than 50% of women do not engage with PPC.[4-7] The situation in Malaysia is quite similar, as evidenced by studies conducted in different regions, such as Kedah, Perak, and Bachok. [8-10]

Most studies on using PPC services mainly focused on women who are married or pregnant women with comorbidities. However, PPC should also be emphasised in healthy young adults including those who are unmarried or not pregnant. Therefore, the prevalence of the intention of PPC services utilisation in this population has yet to be discovered. We selected the Theory of Planned Behavior (TPB) to assess intention. This model effectively understands the relationship between intention and behaviours.[11] According to Ajzen's theory, a person's behaviour is determined by his or her intentions, which are determined by attitude, subjective norms and perceived behavioural control.[12]

A research gap exists in this context, as local studies have yet to report the intention of PPC service utilisation using a Malay-validated TPB questionnaire. Hence, there is a need to validate the tools. We aimed to translate and adapt the TPB questionnaire on the intention of PPC services utilisation (IPCSU) from English to Malay language and to determine the validity and reliability of the tool among female undergraduate students of Universiti Teknologi MARA (UiTM) Shah Alam.

Material and Methods

Study design and setting

This was a cross-sectional questionnaire translation and validation study conducted in three phases. Phase 1: Back-to-back translation, adaptation, and content validation of the IPCSU questionnaire from English into the Malay language; Phase 2: face validation of the Malay version of IPCSU questionnaire and phase 3: field testing and psychometric analysis of the questionnaire.

Instrument

Limited tools are available for measuring the intention of PPC services utilisation based on the TPB constructs. These tools include extended questionnaires with 61 and 51 items, respectively[13,14] and a shorter version with 25 items.[15]

Hence, the decision was made to validate the shorter version of the questionnaire because it is simpler with fewer items, and its psychometric properties are comparable to the extended version. This questionnaire was validated in Iran containing the TPB construct, which has 25 items within four domains with ten items in attitude, seven in subjective norms, five in perceived behaviour control and three in behavioural intentions domains. A five-point Likert scale (ranging from 1=totally disagree to 5=totally agree) was used for each item. Higher scores indicate a more positive attitude, subjective norms, and perceived behavior control toward PPC, as well as a stronger intention to use PPC services. The Cronbach's alpha was 0.75, 0.68, 0.77, and 0.76, respectively, and the entire tool was 0.72.[15]

Phase 1: Back-to-back translation, adaptation, and content validation

The English version of the IPCSU questionnaire was translated into Malay using international guidelines for cross-cultural adaptation to ensure the quality of the translated version and its consistency of meaning to the original version.[16] Firstly, the forward translation from English to Malay language was performed independently by two bilingual translators - an expert in linguistics and a public health medicine specialist. This was followed by a back-translation from Malay to English by another two bilingual translators who were unaware of the English version of the questionnaire. Each translator produces a report independently. The process involved addressing inconsistencies in forward and backward translations, followed by cross-cultural adaptation. This synthesis also entailed selecting easily comprehensible Malay words and culturally appropriate phrases for adaptation into Malaysian culture.

Next, a content validation was conducted by six experts (consisting of primary care medicine, public health medicine, and obstetrics and gynaecology specialists) to assess the relevance of the items in the questionnaire and provide a critical review. The content validity index (CVI) was used to determine the content validity. The CVI assesses the relevance of each item to the domain, which is item-level content validity index (I-CVI) and scale-level content validity index (S-CVI).[17] They need to evaluate each item by rating on a 4-point Likert scale in terms of the degree of relevance (1=not relevant to 4=very

relevant), clarity (1=not clear to 4=very clear), and essentiality (1=unnecessary to 4=essential). The CVI was computed by calculating the scale average. Feedback and suggestions provided by the experts were incorporated to refine the questionnaire. Changes were made to the original questionnaire to suit the study's objectives, local language, and culture. At the end of Phase 1, a preliminary Malay version of the IPCSU questionnaire was produced.

Phase 2: Face validation

The preliminary Malay version of the IPCSU questionnaire went through a process of face validation on the target population by convenience sampling. It was pre-tested on 30 eligible students according to the inclusion and exclusion criteria. The inclusion criteria included unmarried female undergraduate students from UiTM Shah Alam aged 18-25 who could speak and understand the written Malay language. Participants who were currently pregnant or had been pregnant in the past were excluded from the study, as were those who did not provide informed consent. The face validity index (FVI) was used to determine the face validity, which can be quantified as item-level face validity index (I-FVI) and scale-level face validity index (F-CVI).[18] The face validation was conducted to assess their understanding of the questionnaire's wording, content, and overall structure. They were required to rate each item according to the 4-point Likert scale in terms of degree of clarity and comprehensibility (1=not clear and not understandable to 4=very clear and understandable). The FVI was computed by calculating the scale average. Correction and fine-tuning of the preliminary Malay version of the IPCSU questionnaire by the research team was done based on the respondent's feedback. This revised Malay version of the IPCSU questionnaire went through a second face validation by another 30 students from UiTM Shah Alam. The feedback indicated that the questionnaire was satisfactory, and no further amendments were required. The content and face-validated Malay version of the IPCSU questionnaire was ready for field testing.

Phase 3: Field testing and psychometric analysis

The Malay version of the IPCSU questionnaire was field-tested on students from the same setting from October to December 2022. The same inclusion and exclusion criteria were applied to select the participants. Respondents who participated in Phase 2 and Phase 3 were mutually exclusive, as those who participated in Phase 2 were not re-selected for Phase 3 of this study. The sample size for this field testing was calculated using the subject-to-item ratio. Pallant recommended a minimum sample size according to the subject item ratio 5:1.[19] The Malay version of the IPCSU questionnaire contains 25 items. Therefore, the minimum required sample estimated was 125 participants. By considering 20% of non-responders and the non-eligibility rate, this study aimed to approach 150 participants. Convenience sampling was used to recruit the respondents. Participants were briefed face to face, and clear instructions were given on completing the questionnaires. A link for the online self-administered Malay version of the IPCSU questionnaire via Google Form was sent through a WhatsApp group. The respondents were required to give consent by selecting the "yes" option before starting the survey. The questionnaire used a proxy identifier instead of personal details to ensure the confidentiality and anonymity of the respondents. All questions were set as "required" to be answered prior to submission to avoid missing data. After two weeks, 30 participants from previously recruited participants were contacted to complete the same questionnaire for test-retest reliability analysis. The selection was based on logistic reasons.

Permission to use and translate the original TPB questionnaire on intention of PPC services utilisation into Malay was obtained from the corresponding author from Arak University of Medical Sciences, Arak, Iran.[15] The Universiti Teknologi MARA (UiTM) Research Ethics Committee has approved this study [reference:600-RMI (5/1/6)].

Statistical analysis

Data entry and statistical analysis were performed using IBM SPSS Statistics Version 25. During data entry, the

Likert Scale responses for negatively phrased questions were reversed. In the descriptive analysis, categorical variables were presented as frequency and percentages. Mean and standard deviation (SD) were reported for normally distributed continuous data.

The construct validity of the Malay version of the IPCSU questionnaire was assessed using exploratory factor analysis (EFA). There are three main steps in conducting EFA: determining the data's suitability, factor extraction, and factor rotation.[20] The suitability of data was assessed by checking the correlation coefficient among items in the correlation matrix, the Keiser-Meyer-Olkin Sampling Adequacy Test (KMO) and Bartlett's Test of Sphericity. Correlation coefficient values ranging from 0.30 to 0.90, a significant KMO value of ≥0.06 and Bartlett's Test of Sphericity with a p-value <0.05 are considered suitable for factor analysis. Principal component analysis (PCA) was used for factor extraction. Kaiser criterion (eigenvalue >1), cumulative percent of variance extracted, and Scree test were done to decide which factors to retain.[20] The orthogonal (varimax) rotation technique was performed for factor rotation, and communalities values should be greater than 0.40.[21] Factor loading was set at 0.45 according to sample size.[21,25]

The reliability of the finalised Malay version of the IPCSU questionnaire was assessed using Cronbach's alpha coefficient as a measure of internal consistency to determine the extent to which all items in a test measure the same concept. Internal consistency is "the degree of interrelatedness among the items".[26] This was done for the entire instrument and the different domains. Cronbach's alpha >0.7 suggests adequate internal consistency.[21] Corrected item-total correlation was also performed, and the effect of removing an item on Cronbach's alpha was also determined. Intraclass correlation coefficients (ICC) were used to assess the test-retest reliability of the questionnaire. Values >0.9 indicate excellent reliability, 0.75–0.90 indicate good reliability, 0.5–0.75 indicate moderate reliability, and <0.5 indicate poor reliability.[27]

RESULTS

Cross-cultural adaptation, content validity and face validity index

Table I shows the cross-cultural adaptation, content validity and face validity of the Malay version of the IPCSU questionnaire. Several changes were made to the original questionnaire to suit the study's objectives, local language, and culture in phase 1 and phase 2 of this study. The I-CVI was between 0.83 – 1, with an S-CVI/Ave of 0.98, indicating an acceptable CVI value.[17] The I-FVI was between 0.70 – 1 with an S-FVI/Ave of 0.88. FVI of at least 0.80 indicates an acceptable value.[18] There were five items with I-FVI below the cut-off value of 0.80. Thus, these items were revised to increase clarity for better understanding.

Descriptive analysis

A total of 150 respondents were approached; however, five did not fulfil the inclusion or exclusion criteria, resulting in a response rate of 91%. Consequently, 145 completed questionnaires were analysed. Most respondents were Malay (89.7%), with a mean age of 21.7 years (±SD 1.6). The sociodemographic characteristics of the participants are presented in Table II.

EFA and reliability analysis

We employed EFA to validate the underlying factor structure of the Malay version of the IPCSU questionnaire and to ensure its construct validity in the Malaysian context. EFA is a statistical technique used to identify the underlying structure of a set of variables. It does this by grouping variables that are correlated with each other and then identifying the factors that these groups of variables represent.

In our analysis, most of the correlation coefficient values among items in the correlation matrix were above 0.3, which are considered acceptable. However, we identified four items with very low inter-item correlations <0.3: two from the attitude domain and two from the subjective norms domain. Following standard practice for

Table I: The cross-cultural adaptation, content validity and face validity of the Malay version of IPCSU

TPB Construct	Item	English Version	Synthesis Changes	I-CVI of Experts (n=6)	I-FVI of Respondents (n=30)
Attitude	A1	I believe that I need to have a pre-pregnancy care checkup before I get pregnant.		1	0.90
	A2	I believe that even by reducing alcohol consumption and smoking, it cannot assure a complete healthy baby.	Order of item was rearranged to A3.	0.83	0.97
	A3	I believe that maternal nutrition before pregnancy has an effect on fetal health.	Order of item was rearranged to A2.	1	0.87
	A4	I believe that genetic counselling for hereditary diseases can cause stress to prospective parents. Therefore, I feel it is better not to pursue it.	Add "hereditary diseases" and add "prospective" from "I believe that genetic counselling is stressful for parents, so it is better not to do it".	1	0.73
	A5	There are some vaccines that should be taken before pregnancy because if taken during pregnancy, they can have harmful effects on the fetus.	Rephrased to enhance clarity from "Some vaccines are best given before pregnancy because of the bad effects on the fetus".	1	0.80
	A6	I believe that having pre-pregnancy counselling will bring benefits to the future health of my baby.		1	0.97
	A7	I believe that pre-pregnancy care can reduce the additional costs of treatment in the future.		1	0.70
	A8	I believe that by having pre-pregnancy care in the future, I can prevent pregnancy complications (miscarriage, preterm birth, etc.).		1	0.93
	A9	I disagree with pre-pregnancy care because I have never seen an unwanted pregnancy complication in my family or friends.	Rephrased to enhance clarity from "I disagree with filing a pre-pregnancy care because I have never seen an unwanted pregnancy complication in my family or friends".	1	0.70
	A10	In my opinion, pre-pregnancy care should be provided for women with medical condition.		1	0.90
Subjective Norms	SN1	I will do pre-pregnancy care if requested by the staff of health centers.		1	0.93
	SN2	I will do pre-pregnancy care because my friends had opened a maternal health record book.	Rephrased to enhance clarity from "I will do it because my friends had opened a pregnancy record book".	0.83	0.73
	SN3	I will make plans for the pre-pregnancy care if my spouse asks to.	Change husband to spouse.	1	0.90
	SN4	In my opinion Internet and the mass media (television, radio, etc.) have an important role in behaviour that promote pre-pregnancy care.		1	0.87
	SN5	The dissatisfaction of my family and spouse can hinder me from receiving pre-pregnancy care.	Rephrased to enhance clarity from "The dissatisfaction of my family and spouse can prevent me from receiving pre-pregnancy care".	0.83	0.70
	SN6	If the doctor recommends pre-pregnancy care, I will do it.		1	1
	SN7	When attending pre-pregnancy care, I will follow the recommendations of the health center staff.		1	1
Perceived Behavioral Control	PBC1	I can make plans for pre-pregnancy care even if my family disagrees.		1	0.87
	PBC2	I will do pre-pregnancy care despite my busy schedule.		1	0.90
	PBC3	I am sure that I can control high-risk behaviors (such as sedentary lifestyle, obesity, smoking or excessive alcohol intake) before pregnancy.		1	0.83
	PBC4	I will do pre-pregnancy care even the required tests (such as tests to detect genetic diseases) are expensive for me.	Add example of test.	1	0.83
	PBC5	If necessary, I certainly will do pre-pregnancy care.		1	0.90
Behavioural Intention	BI1	I will see a doctor for treatment before pregnancy if I have any diseases.		1	0.93
	BI2	I will reduce high-risk behaviors (such as sedentary lifestyle, obesity, smoking or excessive alcohol intake) before pregnancy.	Rearrange the word order.	1	0.93
	BI3	I will do pre-pregnancy care to ensure the health of my future baby.		1	0.93
			S-CVI/Ave	0.98	-
			S-FVI/Ave	-	0.88

Note: I-CVI = Item-level content validity index; I-FVI = Item-level face validity index, S-CVI/Ave = Scale-level content validity index based on the average method; S-FVI/ Ave = Scale-level face validity index based on the average method

Table II: Sociodemographic characteristics of respondents (n=145)

Variables		Total Freq, n (%)	Mean (SD)
Age			21.7 (1.61)
Ethnicity	Malay	130 (89.7%)	
	Bumiputera (Sabah/ Sarawak)	15 (10.3%)	
Income	B40	96 (66.2%)	
	Non-B40	49 (33.8%)	
Chronic disease status	No	128 (88.3%)	
	Yes	17 (11.7%)	
Genetic disease status	No	132 (91.0%)	
	Yes	13 (9.0%)	
Intention to get married	≤ 5 years	49 (33.8%)	
	> 5 years	96 (66.2%)	

determining item removal, we removed these items to ensure a robust factor structure. This threshold indicates a minimum level of relationship between items necessary for meaningful factor formation.[20]

The suitability of our data for factor analysis was strongly supported by a KMO value of 0.92 and a significant Bartlett's test ($p<0.001$). The KMO value is above the recommended 0.6, which suggests excellent sampling adequacy, while the significant Bartlett's test confirms the presence of correlations in our data matrix, indicating the sample is suitable for factor analysis.[21] After removing the four items with low inter-item correlations, 21 items were retained for the EFA.

We then performed EFA using PCA for factor extraction and varimax rotation, initially applying a minimum factor loading criterion of 0.45. This analysis resulted in a total questionnaire variance of 68.8%. We chose PCA for its efficiency in reducing data dimensionality while retaining maximum variance, and selected varimax rotation to maximize the dispersion of loadings within factors, producing a simpler, more interpretable solution. This combination is widely used in psychometric research.[22-24]

The Kaiser's criterion suggested three factors should be retained, as three factors had eigenvalues exceeding 1.0. However, the elbow of the Scree plot occurred at factor 5, suggesting that four factors should be retained.[25] Faced with this discrepancy, we carefully considered both statistical indicators and conceptual relevance. Ultimately, four factors were deemed the most conceptually appropriate for the Malay version of the IPCSU questionnaire, aligning with the underlying Theory of Planned Behavior framework, ensuring that the factor structure meaningfully represents the constructs of attitude, subjective norms, perceived behavioral control, and behavioral intention. Consequently, we reanalyzed the data by fixing the number of factors at four. The result shows that initial eigenvalues were greater than 1, and the cumulative percent of variance explained was 73.4%. All communalities on the scale were above 0.40, indicating an acceptable level. 21 Furthermore, all items demonstrated factor loadings greater than 0.45, meeting our predetermined criteria.

We set a minimum factor loading of 0.45, which is considered meaningful for our sample size of 145. This threshold ensures that each item contributes substantially to its respective factor. One item, PBC5, cross-loaded into factors 2 and 3 with values of 0.543 and 0.590, respectively. After careful consideration, we retained this item in Factor 3 as it fits better conceptually within this factor, maintaining the integrity of the TPB framework. This decision balanced statistical results with theoretical considerations. Table III provides a comprehensive overview of the EFA results for the Malay version of the IPCSU questionnaire, illustrating the factor structure and item loadings.

Table IV shows the item-total reliability analysis and Cronbach's alpha for each domain. The corrected item-total correlations ranged from 0.46 to 0.93, indicating moderate to strong correlations of the individual items to the sum scale of the questionnaire.[28] These values indicate the strength of association between individual items and the overall scale which suggest that each item contributes meaningfully to the measurement of the intended construct while not being redundant. Cronbach's alpha values above 0.70 are generally considered acceptable, indicating good internal consistency. Our values ranging from 0.88 to 0.95 for individual domains and 0.95 for the overall scale demonstrate excellent internal consistency, suggesting that the items within each domain and across the entire questionnaire are measuring the same underlying construct.[21] The deletion of any items

in the scale would not have improved Cronbach's alpha of the scale. We conducted test-retest reliability analysis with a two-week interval on a subset of 30 participants. ICC values ranged from 0.46 to 0.86, indicating moderate to excellent reproducibility. These results demonstrate the stability of the questionnaire over time, a crucial aspect of reliability in psychometric instruments.[27]

Therefore, our psychometric analysis demonstrates that the final Malay version of the IPCSU questionnaire consisting of 21 items is valid and reliable. The four-factor structure aligns with the TPB framework, and the high internal consistency and test-retest reliability indicate a stable measurement tool suitable for assessing intention to use pre-pregnancy care services in the Malaysian context.

Table III: Exploratory factor analysis of the Malay version of IPCSU

TPB Construct	Item	Factor loadings			
		1	2	3	4
Attitude	A1	0.544			
	A2	0.667			
	A3	0.528			
	A5	0.669			
	A6	0.693			
	A7	0.765			
	A8	0.701			
	A10	0.631			
Subjective Norms	SN1		0.763		
	SN3		0.469		
	SN4		0.686		
	SN6		0.802		
	SN7		0.774		
Perceived Behavioral Control	PBC1			0.720	
	PBC2			0.789	
	PBC3			0.744	
	PBC4			0.766	
	PBC5		0.543	0.590	
Behavioural Intention	BI1				0.785
	BI2				0.800
	BI3				0.795

DISCUSSION

This study aims to translate, adapt and validate the TPB questionnaire on IPCSU for use in the Malaysian context. Our results demonstrate that the Malay version of the IPCSU questionnaire exhibits strong psychometric properties. The translation and adaptation process involved careful item swapping, deletion, and rephrasing to ensure cultural appropriateness for the Malaysian context. For instance, we refined item A4 on genetic counseling to enhance clarity. Despite these

Table IV: Psychometrics of the Malay version of IPCSU

TPB Construct	Item	Cronbach's alpha	Corrected item-total correlation	Cronbach's Alpha if Item Deleted
Attitude		0.88		
	A1		.686	.864
	A2		.706	.863
	A3		.459	.891
	A5		.604	.872
	A6		.774	.855
	A7		.727	.859
	A8		.733	.859
	A10		.601	.873
Subjective Norms		0.93		
	SN1		.929	.900
	SN3		.634	.955
	SN4		.756	.932
	SN6		.904	.904
	SN7		.929	.900
Perceived Behavioral Control		0.90		
	PBC1		.745	.886
	PBC2		.847	.865
	PBC3		.655	.909
	PBC4		.810	.872
	PBC5		.766	.882
Behavioural Intention		0.95		
	BI1		.857	.946
	BI2		.899	.914
	BI3		.909	.906

modifications, our EFA revealed a structure that aligns well with other adapted TPB questionnaires in different health domains. However, the strength of item loadings and inter-item correlations may differ from those reported in other countries' versions, likely reflecting subtle cultural interpretations of the constructs. [29-31] This observation aligns with findings from other cross-cultural adaptations of TPB instruments, where linguistic and cultural variations often lead to slight differences in psychometric properties while maintaining overall validity and reliability.

Our EFA findings extracted four factors: attitude, subjective norms, perceived behavioural control and behavioural intention, which aligned with the TPB theoretical framework.[12] While the original questionnaire contained 25 items, [15] our Malay version of the IPCSU questionnaire retained 21 items distributed across these four domains: attitude (8 items), subjective norms (5 items), perceived behavioral control (5 items), and

behavioral intention (3 items). This distribution maintains adequate representation of each construct, hence preserving the questionnaire's theoretical integrity. The reduction in items aims to improve response rates and data quality while still capturing the essential elements of the TPB.

Four items (A4 and A9 from the attitude domain; SN2 and SN5 from the subjective norms domain) were removed due to a very low inter-item correlation matrix <0.3, which is unsuitable for factor analysis.

Items with inter-item correlations below 0.3 were removed as they do not contribute meaningfully to factor formation. Low correlations indicate that these items are not measuring the same underlying construct as other items in their domain, potentially introducing inconsistency or measurement error. It also indicates a weak relationship between the variables and prevents factor formation.[20] This means that the participants are not able to discriminate between the items, and the item is not effectively measuring the intended domain. Therefore, the literature suggests that the correlation coefficient should be at least 0.3 and that variables with lower correlations should be excluded from the factor analysis.[21] While removing items could potentially narrow the scope of measurement, our careful selection process ensured that the remaining items still fully represent the TPB constructs. The improved internal consistency (Cronbach's alpha of 0.95) suggests that the removal of these items may have actually enhanced the questionnaire's construct validity by creating a more cohesive set of items.

An acceptable factor loading is based on the number of participants.[21] Hence, a cut-off value of 0.45 was set. This threshold is appropriate for our sample size of 145, as Hair et al. suggest that for a sample size of 150, factor loadings of 0.45 and above are significant. All remaining items had factor loading values ranging from 0.47 to 0.80. One item (PBC5) was noted to have cross-loading into a factor other than the original. It loads into factor 2 and 3 with the values of 0.543 and 0.590. This item was retained in factor 3 as they fit better conceptually in this factor and have higher factor loading. In addition, this item is likely representing a key aspect of PBC and removing it could compromise the construct's measurement. The cross-loading may reflect the interrelated nature of TPB components in the context of PPC intentions, possibly due to the different settings of the study population. While this cross-loading presents some interpretative challenges, retaining PBC5 in factor 3 may provide the best balance between statistical results and theoretical considerations, ensuring our adapted questionnaire fully captures the complexity of PPC decision-making in the Malaysian context.

Overall, our Malay version showed higher internal consistency, (Cronbach's alpha=0.95) compared to the original (0.72), a significant improvement attributable to several factors.[15] The differences in internal consistency could also be due to variations in participants' sociodemographic characteristics between our study and the original. Our adapted questionnaire was likely better tailored to the cultural context of our participants, making the items more relevant and relatable. We also conducted two rounds of face validation, revising the questionnaire based on initial feedback before a second validation, likely enhancing item clarity and relatability. Through rigorous translation and validation, including the removal of poorly performing items, we retained only the most relevant and well-understood questions. While similar reliability improvements have been observed in other cross-cultural TPB questionnaire adaptations, our two-stage face validation process may have particularly contributed to the substantial increase in internal consistency.

This study is the first to translate and validate the TPB questionnaire on IPCSU from English to Malay. However, it has several limitations. First, although the subject-to-item ratio of 5:1 was adequate for factor analysis in this study, a larger sample size of at least 300 participants would reduce the margin of error, leading to more stable solutions. Future studies should aim for a larger, more diverse sample to improve generalisability. We recommend employing random sampling across different regions of Malaysia, including participants from various ethnic backgrounds, education levels, and age groups. Second, this study was conducted in a local university with a predominantly Malay population and

uniform education level, limiting generalisability. To address this, future research should consider multi-site studies across different universities and community settings. Furthermore, the questionnaire is currently only useful for those who understand Malay. We suggest translating and validating the questionnaire in other major languages spoken in Malaysia, such as Mandarin and Tamil, employing rigorous back-translation techniques to ensure equivalence across language versions. Third, the convenience sampling method may have introduced sampling bias. To mitigate this in future studies, researchers should consider using mixed-methods approaches, to better understand how different cultural and linguistic groups interpret and respond to the questionnaire items. Additionally, to further enhance the questionnaire's validity, we recommend conducting confirmatory factor analysis with a new sample to verify the factor structure and testing the questionnaire's predictive validity by assessing actual PPC utilisation in various settings.

CONCLUSION

The finalised Malay version of the IPCSU questionnaire is valid, reliable, and stable over time. This tool can measure the intention to use PPC services among young female adults in the reproductive age group. Intervention strategies can then be developed and targeted, particularly toward those with low intention of PPC services utilisation.

ACKNOWLEDGEMENTS

We want to acknowledge the translators and panel experts involved in this study for their participation, contribution, and dedication in this study as well as the author of the original TPB questionnaire on intention of preconception care services utilisation for allowing us to translate and validate this questionnaire. Finally, the authors would also like to extend our gratitude to the respondents for their willingness to participate in this study.

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ORIGINAL ARTICLE

Panax Ginseng for Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

INTRODUCTION: Panax ginseng is a traditional Chinese medicine used for chronic obstructive pulmonary disease (COPD). The study assessed Panax ginseng's advantages for patients with COPD. **MATERIAL AND METHOD:** PRISMA guidelines were used based on the PICOS model. A systematic search of PubMed/Medline and the Cochrane Library was conducted till March 2022. I2 statistic and random effects model was employed to assess heterogeneity, and GRADE assessment was used to evaluate the quality of outcomes. **RESULTS:** Four trials involving 469 participants were included. Panax ginseng had no significant effects in reducing the frequency of COPD exacerbations (p=0.08) or improve FEV1 (p=0.22), FEV1 (p=0.28), FVC (p=0.20), FVC (p=0.79), and FEV1/FVC ratio (p=0.06) as compared to the placebo. No effects on the mental health-related quality of life (p=0.94), physical health-related quality of life (p=0.92), and respiratory health-related quality of life (p=0.29) were observed. The severity of COPD (p=0.64) was also not affected. Adverse effects documented by Panax ginseng, including insomnia (p=0.15), epistaxis (p=0.69), respiratory tract infection (p=0.83), and white blood cells (p=0.33), were insignificant compared with placebo. **CONCLUSIONS:** There is low to moderate certainty of evidence that Panax ginseng improves exacerbation or lung functions in COPD patients. Thus, more high-quality double-blind RCTs are required to establish its clinical effectiveness, and at present, Panax ginseng should not be considered a substitute for conventional COPD treatment.

Keywords
Panax ginseng; COPD; traditional medicine

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Received: 13th February 2024; Accepted: 25th February 2025

Doi: https://doi.org/10.31436/imjm.v24i02.2391

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable lung condition that affects millions worldwide and is currently the third leading cause of death, responsible for over 3 million deaths annually.[1] People have been affected by this disease all around the world, and most countries have experienced major social and economic hardships as a result.[2] Currently, due to the growing number of senior citizens, the number of COPD patients is anticipated to be higher.[3]

Respiratory symptoms in COPD patients are breathlessness and chronic cough with or without sputum production.[2] In stable COPD patients, medications are prescribed depending on the stage of the disease and limitation of airflow based on spirometry. Medications such as long-acting beta-2 adrenoceptor agonists (LABA) and long-acting muscarinic receptor antagonists (LAMA) can be administered individually or in combination (LAMA). Inhaled corticosteroids (ICS) are also given with LABAs/LAMAs, usually at a later stage.[4] Despite the availability of treatments like LABAs and LAMAs, many COPD patients seek complementary therapies such as Panax ginseng. However, the evidence regarding its efficacy for COPD remains unclear, prompting this systematic review.

Panax ginseng, commonly used in traditional Chinese and Korean medicine, has shown promise due to its anti-inflammatory and antioxidant properties, which could theoretically benefit COPD patients.[5] Since "Panax" means "cure all" in Greek, there are numerous ways to use ginseng to treat and cure various medical issues. It is also famous in Western countries as part of

complementary medicine and alternative therapies.[5] Panax ginseng is known as Korean ginseng or renshen.[6] Panax ginseng can be consumed in various forms, including capsules, tablets, extracts, and teas.[5]

The Panax ginseng used in our study contained ginseng extract capsule, G115. G115 was the first ginseng extract to be registered on the European market and to be standardised on a specified amount of ginsenosides.[7] Ginsenosides are the primary bioactive constituents of Panax ginseng.[8] In all four trials in this study, the G115 capsule was produced by the same supplier – Ginsana SA, Switzerland.[9–12] However, only two trials mentioned that one capsule of 100 mg of ginseng (G115) containing 4 mg ginsenosides.[9,10] One study mentioned that Panax ginseng used contained 4% ginsenosides.[11] One study did not mention the content of ginsenosides in the Ginseng capsule.[12] Although all four trials used G115 capsules, only two reported the standard ginsenoside content, highlighting a need for more consistent reporting in future studies. This systematic review aims to evaluate whether Panax ginseng G115 can effectively reduce COPD exacerbations and improve lung function, potentially offering a complementary approach to existing pharmacological treatments.

The mechanism underlying the effects of ginseng in treating COPD are thought to be related to multiple pathways. Panax ginseng's primary bioactive compounds, ginsenosides, are known to reduce oxidative stress and inflammation, both key contributors to COPD pathogenesis.[4,13] Glutathione and superoxide dismutase are two examples of anti-oxidative enzymes and antioxidants that are increased in response to Panax ginseng and ginsenosides.[13] By increasing antioxidants like glutathione and inhibiting inflammatory cytokine production, ginsenosides may improve lung function and reduce exacerbations.

Second, ginseng has the potential benefit of reducing inflammation, an important factor in COPD which are regarded to be important component in COPD. Ginseng's effect might be related to, which is involved in various inflammation and immune regulation. Ginsenoside inhibits the pathway that related to lung inflammation and reduction of cytokine production leading to the inflammatory response. Thus, the inhibitory potential of ginsenosides can contribute to their in vivo lung anti-inflammatory action which can be effective against lung inflammatory diseases such as bronchitis and COPD.[14] Apart from anti-inflammatory effects, ginsenosides also provide a range of health benefits, including antiallergy and anticancer properties.[15] It also has been shown to benefit several numbers of health conditions, as evidenced by a systemic review such as erectile dysfunction,[16] diabetes,[17] and fatigue.[18]

This review focuses on the studies of Panax ginseng G115 on the COPD patient. Given the limitations and side effects associated with standard COPD medications, Panax ginseng offers an attractive alternative or adjunctive treatment, particularly for those seeking natural or complementary therapies.

MATERIALS AND METHODS

Our protocol was registered in PROSPERO (CRD42022308128) to ensure transparency and minimize bias in the systematic review and meta-analysis process. A systematic review and meta-analysis were chosen to consolidate existing evidence and quantitatively assess the effectiveness of Panax ginseng in COPD, providing a robust conclusion based on aggregated RCT data. In this paper, a systemic review and meta-analysis of RCTs comparing Panax ginseng preparations as an intervention with a placebo toward patients with COPD are conducted. The research was conducted based on the standards provided by PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analyses) guidelines.

Literature Searching Strategies

MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and Epistemonikos were used to search for RCTs and controlled clinical trials involving these patients. The search included the terms 'Panax ginseng,' 'COPD,' and 'COAD' combined with Boolean operators such as 'AND' and 'OR' to refine the search results. The reference lists of RCTs that had been identified were checked to locate unpublished trials or

trials that were not found via electronic searches. In addition, the reference lists of the included RCTs were checked to locate any unpublished trials or studies that might not have been indexed in the electronic databases, ensuring a comprehensive literature search. The ongoing trials were searched through the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/ and www.clinicaltrials.gov).

Inclusion and Exclusion Criteria

The study population comprised adults who were diagnosed with COPD. In contrast to a placebo, Panax ginseng was included in any dosage and duration to capture the broad scope of its use in COPD management, though this may introduce heterogeneity, which was accounted for in subgroup analyses.

The primary outcomes were frequency of COPD exacerbations, duration of COPD exacerbations, and lung function test, whereas the secondary outcomes were quality of life; severity of COPD; the number of use relief medication; adverse events such as insomnia, dizziness, and epistaxis; and blood parameters such as white blood cells; and renal and liver functions. Quality of life was assessed using validated instruments such as the St. George's Respiratory Questionnaire (SGRQ) or COPD Assessment Test (CAT). Both blinded and open-label studies were included.

Quality assessment

The titles and abstracts from the searches were scanned, and full-text articles were obtained. The reviewers assessed the eligibility criteria of the RCTs to be included in this study. The justifications for exclusion were stated, and assessments were done independently. For example, studies were excluded if they lacked a placebo-controlled comparison or if the intervention did not solely include Panax ginseng. If clarification was necessary, the authors were contacted.

The data were extracted independently, which included characteristics of the trials (study setting), the participant's characteristics (age, sex, and ethnicity), the method used for the trials (number of participants randomized and analysed and the duration of follow-up), description of the intervention, and the study outcomes. The risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, selectivity of outcome reporting, and other bias.[19]

Any disagreements between reviewers were resolved through discussion, and if consensus could not be reached, a third reviewer was consulted to ensure unbiased selection. Using a GRADE approach, the researchers assessed the quality of the evidence in the systemic reviews and the strength of the recommendations. Based on the GRADE methodology,[20] we assessed the quality of evidence for risk of bias, inconsistency, indirectness, imprecision, and publication bias for both the primary and secondary outcomes, which were rated as very low, low, moderate, or high.

Statistical Analyses

Review Manager 5.4 was used due to its comprehensive tools for conducting meta-analyses of clinical trials and generating forest plots to visualize treatment effects.

The level of heterogeneity was evaluated. The obvious heterogeneity at face value by comparing populations, settings, interventions, and outcomes was assessed. Next, we used the I2 statistic to evaluate statistical heterogeneity.[19] Thresholds for interpreting the I2 statistic might be deceptive because the importance of inconsistency varies on a range of factors. The heterogeneity can be classified as follows: 0%–40% represented not important; 30%–60%, moderate heterogeneity; 50%–90%, substantial heterogeneity; and 75%–100%, considerable heterogeneity.[19] High heterogeneity (e.g., I2 >75%) indicates substantial differences across studies, which may limit the reliability of pooled estimates and necessitates cautious interpretation of overall results.

We assessed the presence of heterogeneity in two steps. First, we assessed obvious heterogeneity at face value by

comparing populations, settings, interventions, and outcomes. Second, we evaluated statistical heterogeneity using the I^2 statistic.[19] Risk ratios and absolute risk reduction are used to calculate the treatment effect for dichotomous outcomes. Meanwhile, mean differences (MDs) with 95% confidence intervals (CIs) were used for continuous outcomes. In this study, subgroup analyses by dosage and duration were conducted to identify specific contexts in which Panax ginseng might be more effective. These analyses help to account for heterogeneity and reveal dosage-specific effects.

We checked included trials for a unit of analysis errors. Unit of analysis errors can lead to inflated significance levels. Unit of analysis errors can occur when trials randomized participants to intervention or control groups in clusters, but analysed the results using the total number of individual participants. Adjustments were made to ensure the integrity of statistical outcomes, using the mean cluster size and intracluster correlation coefficient.[19] We contacted the original trial authors to request missing or inadequately reported data. We performed analyses on the available data in case missing data are not available. To investigate the impact of risk of bias for sequence generation and allocation concealment of included studies, we performed a sensitivity analysis. Funnel plots were to be assessed for asymmetry as an indicator of possible publication bias, with significant asymmetry suggesting the likelihood of underreported or overrepresented results.

RESULTS

Results of the Search

A total of 178 records were identified through database and other searches, and after duplicate removal, 140 unique records were screened. Figure 1 outlines the selection process for the included studies, including reasons for exclusion at each stage, leading to the final inclusion of four trials.

Trials were excluded because it was a protocol [21] and did not have the outcome of interest.[22] Consequently, four trials are included, and two trials are disregarded from the review.

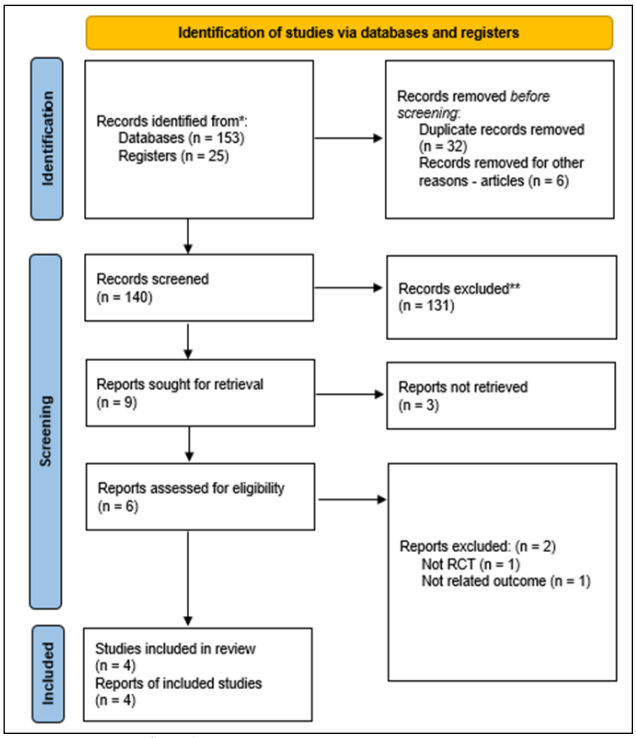

Figure 1: PRISMA flow chart.

Table I: Characteristics of included studies.

Reference	Country	Participants	COPD severity	Duration of intervention	Intervention /Dosage	Control
[10]	China	Intervention: 100 Control: 100	Moderate to very severe using GOLD Guidelines as FEV_1/ FVC less than 0.7 and FEV_1 less than 80% predicted, confirmed by spirometry	24 weeks	anax ginseng capsule (G115®)/ 200mg twice daily	Placebo (lactose-based)
[9]	China Austral-ia	Intervention: 82 Control: 86	Moderate using GOLD Guidelines as FEV_1/ FVC less than 0.7 and FEV_1 greater than 50% and less than 80% predicted, confirmed by spirometry	24 weeks	Panax ginseng capsule (G115®)/ 100mg twice daily	Placebo (lactose-based)
[11]	China	Intervention: 4 Control: 5	Moderate to very severe using GOLD Guidelines as FEV_1/ FVC less than 0.7 and FEV_1 between 20% and 79%	4 weeks	Panax ginseng extract capsule (G115®)/ 200mg twice daily	Placebo (lactose-based)
[12]	Israel	Intervention: 51 Control: 41	Moderate as FEV_1 50 to 65% of predicted	12 weeks	Panax ginseng extract capsule/ 100mg twice daily	Placebo

Four trials, including 469 participants, assessed FEV_1 (Litres) and FVC (Litres), with treatment durations ranging from 4 to 24 weeks.[9–12] All trials declared funding from ginseng manufacturers.[9–12] Two trials were conducted in multicentre hospitals.[9,10] Two trials recruited participants from hospitals in China.[10,11] One trial recruited participants from hospitals in Australia and China [9] and one trial recruited participants from Israel.[12] One trial did not mention the setting from which the participants were recruited.[12] Two trials chose participants with moderate severity of COPD [10,11] and another two trials chose moderate to very severe severity of COPD for the participants.[9,12] Four trials included participants that were aged 40 years and above.[9–12]

Trial subjects were randomly divided into intervention and control groups. For two trials, the intervention was Panax ginseng total daily dose of 200 mg,[9,12] whereas the other two trials were using Panax ginseng total daily dose of 400mg.[10,11] The ginseng was administered orally in four trials.[9–12] The duration of the treatment was 24 weeks,[9,10] 12 weeks,[12] and four weeks.[11] Participants in the control groups were given a placebo. Three trials mentioned the lactose-based content of the placebo.[9–11] One trial did not mention the content of the placebo. [12] The participants in three trials were given symptomatic relief to be used when needed.[9,10] Two trials mentioned that participants could continue their usual COPD drugs according to COPD guidelines.[9,10]

One trial stated that respiratory drugs including long-acting anticholinergic or long-acting β2 agonists alone or in combination with glucocorticoids could be used throughout the study under the advice of the participants' respiratory physician.[11] One trial did not mention whether the standard treatment was given or not.[12] Almost all the outcomes in one trial were reported in mean change such as FEV_1, FEV_1%, FVC, FVC%, mental-related quality of life, physical-related quality of life, respiratory-related quality of life, the severity of COPD, and use of relief medication.[10] Considering that it was reported in one trial that it has no change in the baseline results of the post-intervention; therefore, the baseline results are used for the control group.[12] Table 1 summarizes the characteristics of the four trials.

PRIMARY OUTCOMES

The primary outcomes reported about frequency, duration of exacerbation of COPD, and lung function test. Three trials reported the frequency of COPD exacerbation.[9,10] One trial reported the duration of exacerbations.[10] Four trials reported FEV1 (Litres) and FVC (Litres).[9–12] Two trials reported outcomes about FEV_1% and FVC%.[9,10] Two trials reported FEV1/FVC.[11,12] Secondary outcomes were reported in four trials.[9–12] The mental-related quality of life was measured using a short-form health survey (SF-36) questionnaire in three trials.[9–11] The physical-related quality of life was measured using an SF-36 questionnaire in two trials [9,10] and 6-minute walking test in two trials.[10,11] Three trials measured outcomes using respiratory-related quality of life.[9–11] Respiratory-related quality of life was assessed using the St. Georges Respiratory Questionnaire. Three trials reported the severity of COPD[9–11] using the COPD Assessment Test (CAT).

Three trials reported the use of relief medication as an outcome.[9–11] Regarding adverse effects, two trials reported insomnia and epistaxis.[9,10] Three trials reported respiratory tract infection.[9–11]

Figure 2 summarizes bias indicators across studies, highlighting domains like allocation concealment and blinding, while Figure 3 details the risk of bias for individual studies. The details of these trials are found in the table of characteristics of included studies.

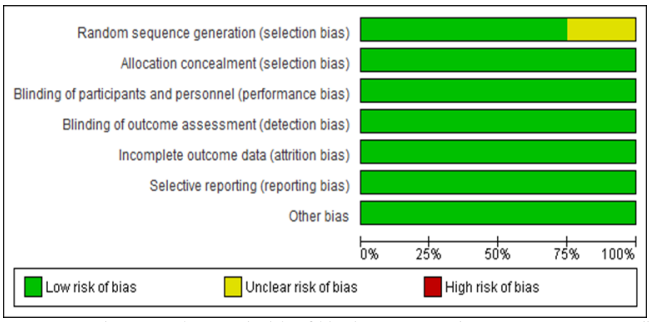

Figure 2: Judgements about each risk of bias item presented as percentages across all included studies.

Random sequence generation was low risk in three trials.[9–11] The trials randomized the participants using a computer-generated randomization code 1:1 ratio,[9,10] SPSS statistical software.[11] We judged random sequence generation as an unclear risk of bias when the method of

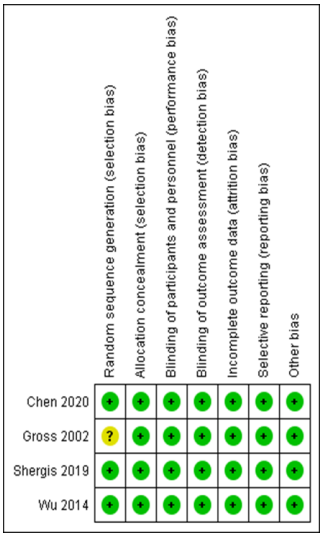

Figure 3: Judgments about each risk of bias item for each included study.

randomization was not reported.[12] Allocation concealment was low risk in four trials.[9–12] The trials concealed the randomization numbers in opaque envelopes. Blinding was low risk in the four trials.[9–12] The trials blinded the participants, personnel, and outcome assessment to group allocation. Incomplete outcome data was low risk in four trials.[9–12] Based on the data given in three trials, the missing data were balanced across the intervention and control groups.[9–11] One trial did not mention whether the missing data was balanced or not.[12] Three trials mentioned that the dropouts were due to participants who no longer wanted to participate.[9,10,12] Two trials stated missing data due to adverse effects.[9,10] Three trials mentioned missing data were due to loss of follow-up.[9–11] In three trials, missing data were balanced between intervention and control groups, accounting for approximately 5-10% of total participants. Sensitivity analyses indicated that excluding these data did not significantly affect the primary outcome measures. The use of intention-to-treat analysis minimizes potential biases from participant dropouts, thereby providing a more conservative estimate of treatment effects. Two trials carried out an intention-to -treat analysis in which the participants were analysed according to the groups that they were initially assigned.[9,10] Two trials analysed the participants by per-protocol analysis.[11,12] Four trials reported a low risk of bias for selective reporting.[9–12] The assessment indicated a low risk of bias across key domains, which supports the reliability of the findings, although inconsistency due to sample size variability and reporting issues remains a concern. All trials reported the outcomes as specified in their methods. We detected no other potential sources of bias.

As depicted in Figure 4, the confidence interval (MD-0.20, 95% CI -0.43 to 0.02) crosses zero, indicating that there is no significant difference between Panax ginseng and placebo in reducing COPD exacerbations. One trial had none of the participants experience an exacerbation during the study duration.[11]

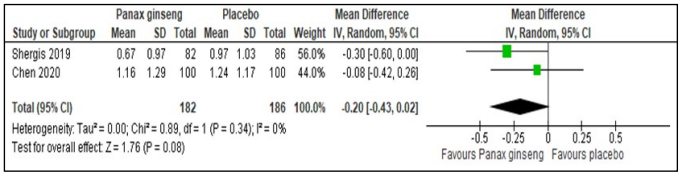

Figure 4: Forest plot for the outcome frequency of COPD exacerbations.[9,10]

Only one trial measured the duration of COPD exacerbations (MD -1.04 95% CI -1.89 to -0.19; one trial, 200 participants, low–quality evidence).[10] Panax ginseng showed no difference in FEV_1 compared to placebo (MD 0.11, 95% CI -0.06 to 0.27; I^2 statistic=74%; P=0.22; four trials, 469 participants, moderate–quality evidence)[9–12] (Table 2).

Subgroup analysis for FEV_1 by dosage was performed. Panax ginseng of 200 mg daily (MD 0.14, 95% CI -0.31 to 0.60; I^2 statistic=87%; P=0.54; two trials, 260 participants, low–quality evidence)[9,12] and 400 mg daily (MD 0.24, 95% CI -0.29 to 0.76; I^2 statistic=71%; P=0.37; two trials, 209 participants, low–quality evidence) [10,11] showed no difference compared to placebo. The subgroup analysis for FEV_1 by dosage revealed substantial heterogeneity (I^2=87%), suggesting that differences in study populations or intervention characteristics likely influenced these results. This limits the generalizability of the findings.

Panax ginseng showed no difference in FEV_1 compared to placebo (MD -2.21, 95% CI -6.24 to 1.81; I^2 statistic=82%; P=0.28; two trials, 368 participants, low–quality evidence).[9,10] Panax ginseng showed no difference in FVC compared to placebo (MD 0.20, 95% CI -0.11 to 0.51; I^2 statistic=83%; P=0.20; four trials, 469 participants, moderate – quality evidence)[9–12] (Table 2).

Table II: Summary of the findings, including GRADE quality assessment for comparison between Panax ginseng and placebo.

Panax ginseng compared to placebo for COPD COPD patient Intervention: Panax ginseng Comparison: placebo								
Outcome	**Anticipated Absolute Effects *(95% CI)**		**Study event rates (%)**		**Relative effect (95% CI)**	**No of Participants (Studies)**	**Certainty of the Evidence (Grade)**	**Comments**
	Risk with placebo	Risk with Panax ginseng	With placebo	With Panax ginseng				
Frequency of COPD exacer-bations	The mean of frequency of COPD exacerbations was 0	MD 0.2 lower (0.43 lower to 0.02 higher)	186	182	-	368 (2 RCTs)	⨁⨁⨁◯‡ Moderate	Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Imprecision: serious
FEV_1 (Litres)	The mean of FEV_1 (Litres) was 0	MD 0.11 higher (0.06 lower to 0.27 higher)	232	237	-	469 (4 RCTs)	⨁⨁⨁◯† Moderate	Risk of bias: not serious Inconsistency: serious Indirectness: not serious Imprecision: not serious
FVC (Litres)	The mean FVC (Litres) was 0	MD 0.2 higher (0.11 lower to 0.51 higher)	232	237	-	469 (4 RCTs)	⨁⨁⨁◯† Moderate	Risk of bias: not serious Inconsistency: serious Indirectness: not serious Imprecision: not serious
FEV_1/FVC (percentage)	The mean FEV_1/FVC (percentage) was 0	MD 0.07 higher (0 to 0.15 higher)	46	55	-	101 (2 RCTs)	⨁⨁⨁◯‡ Moderate	Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Imprecision: serious
Mental health related quality of life	The mean mental health related quality of life was 0	MD 0.04 higher (1.09 lower to 1.17 higher)	191	186	-	377 (3 RCTs)	⨁⨁⨁◯‡ Moderate	Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Imprecision: serious
Physical health related quality of life	The mean physical health related quality of life was 0	SMD 0.01 higher (0.22 lower to 0.25 higher)	291	286	-	577 (3 RCTs)	⨁⨁⨁⨁ High	Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Imprecision: not serious
Severity of COPD	The mean severity of COPD was 0	MD 0.24 higher (0.78 lower to 1.27 higher)	191	186	-	377 (3 RCTs)	⨁⨁⨁◯‡ Moderate	Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Imprecision: serious

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; MD: Mean difference; SMD: Standard mean difference
GRADE Working Group grades of evidence:
High certainty indicates we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty indicates we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty indicates our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. Very low certainty indicates we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect. ⨁⨁⨁ ◯ refers to Quality of the evidence (GRADE). †There is a presence of statistical inconsistency.
‡Downgraded due to large CIs from small sample size.

Subgroup analysis for FVC by dosage was performed. Panax ginseng 200 mg daily (MD 0.22, 95% CI -0.56 to 0.99; I^2 statistic=93%, P=0.58; two trials, 260 participants, low – quality evidence)[9,12] and 400 mg daily (MD 0.23, 95% CI -0.29 to 0.75; I^2 statistic=66%, P=0.39; two trials, 209 participants, low–quality evidence)[10,11] showed no difference compared to placebo. Panax ginseng showed no difference in FVC compared to placebo (MD 0.31, 95% CI -1.97 to 2.60; I^2 statistic=0%; P=0.79; two trials, 368 participants, moderate – quality evidence).[9,10]

Panax ginseng showed no difference in FEV1/FVC compared to placebo (MD 0.07, 95% CI -0.00 to 0.15; I^2 statistic=0%; P=0.06; two trials, 101 participants, moderate–quality evidence).[11,12] The lack of significant improvement in COPD outcomes suggests that Panax ginseng, as studied, may not effectively modulate key pathophysiological processes in COPD, such as airflow limitation or chronic inflammation, at the studied dosages and durations.

SECONDARY OUTCOMES

Panax ginseng showed no difference in the mental-related quality of life (MD 0.04, 95% CI -1.09 to 1.17; I^2 statistic=0%; P=0.94; three trials, 377 participants, moderate-quality evidence),[9–11] compared to placebo. Panax ginseng group showed no difference in the physical -related quality of life compared to the placebo (MD 0.01, 95% CI -0.22 to 0.25; I^2 statistic=41 %; P=0.92; three trials, 577 participants, high–quality evidence).[9–11] Panax ginseng group showed no difference in the respiratory-related quality of life compared to the placebo (MD -2.54, 95% CI -7.23 to 2.16; I^2 statistic=62%; P=0.29; three trials, 377 participants, low–quality evidence).[9–11] Panax ginseng group showed no difference in the severity of COPD compared to placebo (MD 0.24 95% CI -0.78 to 1.27; I^2 statistic=0%; P=0.64; three trials, 377 participants, moderate-quality evidence).[9–11] Panax ginseng showed no difference in the scoring as compared to placebo (MD 43.75, 95% CI -44.62 to 132.11; I^2 statistic=96%; P=0.33; three trials, 377 participants, low–quality evidence).[9,10] There was no difference in the number of participants with insomnia in the Panax ginseng group and placebo (MD 0.22, 95% CI 0.02 to 1.89; I^2 statistic=0%; P=0.15; two trials, 368 participants, moderate-quality evidence).[9,10] There was no difference in the number of participants with epistaxis in the Panax ginseng group and placebo. (MD 0.50, 95% CI 0.02 to 15.24; I^2 statistic = 61%; P = 0.69; two trials, 368 participants, low–quality evidence)[9,10] (Figure 18). There was no difference in the number of participants with respiratory tract infection in the Panax ginseng group and placebo (MD 1.11, 95% CI 0.43 to 2.91; I^2 statistic=57%; P=0.83; three trials, 377 participants, low–quality evidence).[9,10] Two trials were reported regarding leukocytosis. There was no significance difference in Panax ginseng and placebo (MD 1.92, 95% CI 0.52 to 7.15; I^2 statistic=0%; P=0.33; two trials, 368 participants, moderate–quality evidence).[9,10] Certainty was downgraded to moderate due to imprecision resulting from small sample sizes and wide confidence intervals, particularly affecting the mental and respiratory quality of life outcomes.

DISCUSSION

This review was designed to include all RCTs addressing the effectiveness of Panax ginseng for patients with COPD. The four identified trials formed a heterogeneous group addressing several comparisons and a variety of outcomes. This study shows that Panax ginseng use does not significantly reduce the frequency and duration of COPD exacerbations in patients with COPD. The values of lung function tests were not much improved by using Panax ginseng. There were no significant changes in quality of life, the severity of COPD, and the use of relief medication with the usage of Panax ginseng. Reporting of the adverse effects was limited to minor side effects, which included insomnia, dizziness, upper respiratory tract infections, epistaxis, and leucocytosis, which not significantly occur in Panax ginseng usage.

We performed a comprehensive and extensive literature review for assessing the effectiveness of Panax ginseng for patients with COPD. Our review evaluated the mono-preparation of Panax ginseng, with a different total dosage of the Panax ginseng, but was not able to show whether different dosages made difference in the outcomes. The control group is a placebo. The duration and doses of the

Panax ginseng were different in each trial, thereby limiting the applicability of the findings in this review. The adverse effects of the Panax ginseng have no difference as compared to the placebo in our review. A further consequence of the lack of a sufficient number of studies was that we could not conduct any of our pre-planned subgroups. These analyses, as well as potentially additional interesting subgroup analyses (e.g., according to the duration of Panax ginseng), can hopefully be considered in future updates of this review.

Generally, there was a low risk of bias in most of our included studies in the domains. There was an unclear risk of bias in assessment in random sequence generation in one trial because the method of randomization was not reported. This meta-analysis found that there was no evidence of selective reporting bias in all included studies, as all the trials reported the outcomes as specified in their methods. Otherwise, the attrition bias and performance bias were at low risk of bias in all the trials. For the GRADE criterion "imprecision," we had to downgrade the ratings in several cases if the optimal information criterion size was not met. We encountered high heterogeneity in the trials reporting FEV_1 and FVC; nevertheless, it cannot be explained by the different dosages. Using the GRADE approach, we, therefore, assessed the overall level of evidence contributing to this review as low to high quality.

We attempted to reduce publication bias by checking the reference lists of all related studies for further references and searching multiple databases. Despite the vigorous search of journal databases, we cannot be sure that we have extracted all trials relevant to our review. We were not able to construct a funnel plot for detecting bias due to insufficient trials.

Although Panax ginseng has demonstrated efficacy in conditions such as glucose control[23] and erectile dysfunction[16], its inability to significantly affect COPD outcomes may be attributed to the distinct pathophysiological mechanisms underlying COPD, which may not be as susceptible to ginseng's anti-inflammatory and antioxidant properties.[23]

Panax ginseng had no difference in causing adverse events which were also observed in the placebo group. General symptoms for adverse events such as insomnia, epistaxis, dizziness, dyspepsia, skin disorders, dried mouth, diarrhoea, headaches, hot flushes, chest discomfort, constipation, tachycardia, and anorexia were reported in both ginseng and placebo groups.[24] However, these were limited to systematic reviews without meta-analyses.

Implications for Clinical Practice

Nowadays, individuals with COPD around the world are turning to traditional Chinese medicine (TCM) as a supplemental or dietary supplement. According to a review, TCM benefits people with COPD by lowering their risk of exacerbations, improving lung function, their quality of life, and their ability to exercise.[25] Previous studies suggest that TCM combinations, rather than mono -preparations like Panax ginseng, may be more effective in improving COPD symptoms. According to this review, there was no difference between Panax ginseng and placebo for patients with COPD, but it is safe to take Panax ginseng as a medication. Future research should consider the role of Panax ginseng as part of multi-herb formulations, potentially enhancing its therapeutic effects.

CONCLUSION

In conclusion, safety profile of Panax ginseng has been demonstrated in this systematic review, concluding that Panax ginseng mono-preparations are rarely associated with adverse events. While Panax ginseng has shown no significant adverse events, it should be recommended only as an adjunctive treatment for COPD, particularly for patients interested in complementary medicine, and not as a replacement for standard therapies such as LABAs and LAMAs

However, the use of Panax ginseng in COPD patients did not give significant effects in improving exacerbation or improving the lung functions based on the evidence and the analysis in this review. Nevertheless, further high quality double blind RCT are required to establish the clinical effectiveness of Panax ginseng in treating COPD. Drawbacks of this review are that there is a lack of a sufficient number of studies to proceed with subgroups

analysis. Potentially additional interesting subgroup analyses (e.g., according to the duration of Panax ginseng), can hopefully be considered in future updates of this review. Future RCTs should standardize the dosage of Panax ginseng (e.g., 400 mg per day), extend treatment durations (e.g., 12-24 weeks), and focus on homogeneous COPD populations to reduce variability and increase the reliability of results.

Although Panax ginseng is rarely associated with adverse events, this review indicates that it does not significantly improve exacerbation rates or lung function in COPD patients, pointing to the need for more rigorous and larger trials before it can be recommended clinically.

FUNDING

This research received no external funding

CONFLICT OF INTEREST

The authors declared no conflict of interest.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

The study did not require ethical approval.

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ORIGINAL ARTICLE

A Follow Up Study on Lung Cancer Survival in the State Hospital in East Coast State of Pahang

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ABSTRACT

INTRODUCTION: There is lack of data of lung cancer survival in Malaysia. **MATERIAL AND METHODS:** This study was to determine the survival of lung cancer patients and factors affecting the survival in Kuantan, Pahang. A total of 170 lung cancer patients confirmed by histology from 1st January 2014 to 31 December 2017 were recruited in the study. Their demographic data, ECOG performance status, staging and treatment were recorded. Survival time was defined in weeks from the date of histological diagnosis made to the date of death of the patients. Kaplan-Meier curve was used to determine the median overall survival and log-rank test was used to test the survival differences between each subgroup. Multivariate analysis using COX regression was used to determine factors affecting its survival. **RESULTS**: The median age of the 170 patients was 63 years old, majority were males (74%) and smokers (64%). Adenocarcinoma (74.7%) was the most common histology followed by squamous cell carcinoma (18.8%). Almost all patient presented at the clinic at stage 3 or 4 (98%) but majority had ECOG 0-2 (64.3%). Median overall survival was 28.7 weeks. In the multivariate analysis, "supportive treatment" and "poor ECOG performance status" were independent predictors of death with the hazard ratio of 1.4 (95%CI 1.17 to 1.66) and 3.0 (95%CI 2.05 to 4.39) times respectively. **CONCLUSION**: Majority of lung cancer patients in Pahang presented with advanced disease with overall median survival of 28.7 weeks. Patients treated with supportive care and poor ECOG performance status were the two independent poor prognostic factors for survival.

Keywords
Lung cancer survival, HTAA, Pahang

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Received: 7th August 2024; Accepted: 30th December 2024

Doi: https://doi.org/10.31436/imjm.v24i02.2641

INTRODUCTION

According to World Health Organization, lung cancer is one of the commonest reported cancers worldwide with an incidence of 11.6% on top of highest reported mortality of 18.4% in year 2018.[1,5.13,24] In Malaysia, lung cancer is the third commonest cancer (10.2%) and has poorest median survival time of 6.63 months in year 2007-2011 compared to other cancers.[13,19,21] In Pahang, an east coast states, the median survival was significantly shorter at 4.5 months in year 2007-2010.[7] Only 14.8% of lung cancer patients survived 1 year after diagnosis compared to the national data of 35.5%[6,13] as majority of the patients presented at the clinics at late stages with poor functional status, or low Eastern Cooperation Oncology Group (ECOG) score. Some opted for conservative treatment without chemotherapy, and many were unable to afford targeted therapy due to financial constraints.[6]

The landscape of lung cancer management markedly changed in recent years with discoveries of oncogenes and new targeted therapy. Targeted therapy is advocated to patients who harboured activating driver mutation whereas patients without driver mutation but expressed high PDL-1, are treated with immunotherapy alone or with combination of chemotherapy. These targeted therapy and immunotherapy have been shown to prolong overall survival (OS).[2,7,14,15,18,19,23] This is evidenced by the growing number of patients receiving targeted therapy from 2014 to 2017 and therefore are expected to have better survival. However, lung cancer survival in Malaysia

is not well studied especially after the emergent of these novel lung cancer treatments. Therefore, this study was intended to measure the 1 year survival of and median overall survival of lung cancer patients in Hospital Tengku Ampuan Afzan (HTAA), Kuantan and to determine factors that affect lung cancer survival.

MATERIALS AND METHODS

This was a three-year retrospective cohort study carried out at HTAA, Pahang from January 2014 to December 2019. HTAA is a tertiary government hospital which provides lung cancer treatment in Pahang. Currently another University hospital is also providing lung cancer treatment in Pahang; the Sultan Ahmad Shah Medical Centre. This study received the approval of the Malaysian Research Ethical Committee.

The methodology of this study is shown in Figure 1. Details of-demography, patient characteristics, and disease characteristic of patients were retrieved from hospital administration records, clinic Records, Endoscopic suite, and Histopathology laboratory registries and transcribed into clinical record form (CRF). The outcome of the condition of the patients were recorded for at least 2 years from date of diagnosis and it was retrieved from HTAA administration records, whereas for the patients without outcome record in hospital, the death dates were retrieved from National Registry Department (NRD).

The detailed demographic data of the patients, occupation, smoking history, number of smoking in packs year unit, underlying lung disease, staging, ECOG performance status, treatment and treatment outcome was recorded. Non-smokers were defined as those who have smoked less than 100 cigarettes before the date of diagnosis. Smokers further divided into group of those smoked more than 15 packs year and less than 15 packs year. Staging was based on the 7th TNM clinical staging using computerized tomography (CT) of thorax and abdomen, CT of brain, bone scan or PET Positron Emission Tomography (PET) scan. Endobronchial Ultrasonography (EBUS) or thoracoscopy was also used to obtain histology and the staging. The performance status of the patients at presentation was classified according to the Eastern Cooperation Oncology Group (ECOG). Good ECOG performance was defined as ECOG performance status of 0 to 2 and poor ECOG was 3 to 4. The treatment of advanced lung cancer was divided into two groups: 1) Supportive care which included radiotherapy for symptomatic relief without treatment mentioned in no 2, and 2) definite treatment with either curative operation or chemotherapy or targeted therapy (Epidermal Growth Factor Receptor Thyrosine Kinase Inhibitors -EGFR TKI and Anaplastic Lymphoma Kinase - ALK Inhibitor) or immunotherapy or combination of treatment modality, with or without radiotherapy.

Kaplan Meier survival curve used to describe the overall survival and subgroups. Log rank test was used to test the survival differences in each subgroup whereas multivariate analysis using Cox Regression hazard to determine the risk factor mortality and adjusted hazard ratio.

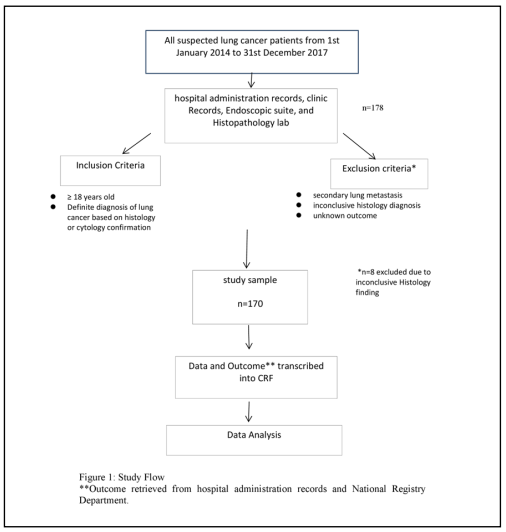

Figure 1 : Study Flow
**Outcome retrieved from hospital administration records and National Registry Department

RESULTS

Patient Characteristics

Data from a total number of 178 patients were included in this study. However, 8 of them were excluded because of inconclusive histology findings. The ages of patients ranged from 33 years to 86 years old with the median age of 63years old (IQR 9.4). Majority of them were males (74%). In all, Malays (69.4%) were most common

patients, followed by Chinese (25.9%), Aborigines (3%) and Indians (1.7%). Among those diagnosed with lung cancer, 64% were smokers (current active and ex-smoker). There were more male smokers (96.5%) than female smokers (3.5%).

Disease Characteristics

Majority of lung cancer patients in Kuantan were diagnosed with non-small cell lung carcinoma (NSCLC) which accounted for 98.2%, whereas small cell lung carcinoma was 1.8%. In subgroup of NSCLC, adenocarcinoma accounted for 74.7%, followed by Squamous cell carcinoma 18.8%, and NSCLC of Non otherwise specified -NOS accounts for 4.7%

There were only 2% of patients presenting with stage 2 and none in stage 1 lung cancer. Majority of patients presented with Stage 3 (18%) and stage 4 (80%). More than half of the numbers of patients presented with good ECOG (ECOG 1: 47.6%, ECOG 2: 16.5%), but only 46.7% (n=81) received definitive treatment; first-line treatment either targeted therapy n=36 (20.2%), or Chemotherapy n=34 (20%), or immunotherapy n=10 (5.9%) or operation n=1 (0.6%). Table I shows the demography and clinical presentation of the patients in the study.

Table I: Demographic and basic characteristics of lung cancer patients in HTAA from year 2014-2017.

Characteristics	n=170
AGE, (in years)	
<60	53 (31%)
≥ 60	117(69%)
range	33yrs-86yrs
median	63yrs (IQR 9.4)
GENDER	n=170
Males	125 (74%)
Females	45 (26%)
RACE	n=170
Malay	118 (69.4%)
Chinese	44 (25.9%)
Others	8 (4.7%)
SMOKING STATUS	n=133
Smoker	85 (64%)
Non-Smoker	48 (36%)
SMOKING AMOUNT (in packs year)	n=91
≤ 15 packs year	56 (61.5%)
> 15 packs year	35 (38.5%)
HISTOLOGY	n=170
Non-Small Cancer Lung cancer	167 (98.2%)
Adenocarcinoma	127 (74.7%)
Squamous cell cancer	32 (18.8%)
Non-Otherwise Specified	8 (4.7%)
Small cell Lung cancer (SCLC)	3 (1.8%)
*ECOG	n=168
1	80 (47.6%)
2	28 (16.7%)
3	26 (15.5%)
4	34 (20.2%)
#CLINICAL STAGING, TNM	n=139
1	0
2	3 (2%)
3	25 (18%)
4	111 (80%)
Treatment	N=170
Definitive Therapy	81 (46.7%)
Targeted Therapy	36 (20.2%)
Immunotherapy	10 (5.9%)
Chemotherapy	34 (20.0%)
Operation	1 (0.6%)
Supportive therapy	89 (52.4%)

* ECOG: Eastern Cooperative Oncology Group - Functional Status
# TNM - 7th lung cancer TNM classification and staging system

Overall Survival

The median overall survival (MOS) for lung cancer patients in HTAA from year 2014 to year 2017 was 28.7 weeks (95% CI 15.7 ,41.7) and 1 year survival was 40.6%.

Patients who were diagnosed with adenocarcinoma had longer MOS 42.7weeks (95% CI 26.3, 59.2) compared to small cell lung cancer 14.4 weeks (95% CI 3.7, 25.2) and squamous cell carcinoma and others 14 weeks (95% CI 3.4, 24.6). Patients with good ECOG function had significant longer survival rate compared to those with poor ECOG function (MOS 62.2weeks vs 9.0 weeks, p <0.001) and patients who received definitive treatment lived longer compared with those received supportive treatment (75.4 weeks vs 10.6weeks, p<0.001). There was no significant difference in MOS for patients with different ages, gender, smoking status, frequency of smoking and the stage of cancer (Table II). Kaplan Meier of overall survival, and different groups are shown in figure 2 and 3.

In multivariate analysis, only 2 factors are independently affecting the survival of lung cancer patients. Those were poor ECOG functional status with adjusted HR: 3.00, (95% CI 2.05 to 4.39, p<0.001) and supportive treatment with adjusted HR:1.4, (95% CI 1.17 to 1.66, p<0.001).

ECOG functional status and survival

Among the patients with good ECOG functional status who received definitive treatment, MOS was 79.1 weeks (95%CI 60.7, 97.6). On the other hand, patients with poor

Table II: Median Overall Survival (MOS) of lung cancer patients for various characteristics

	Med (weeks)	95% CI LL UL	X2 Logrank	df	P
Overall	28.7	15.7 - 41.7			
Age classification					
< 60years	45.6	34.0 - 57.1	1.368	1	0.242
≥60	21.3	10.9 - 31.7			
Sex					
Male	25.6	11.2 - 39.9	2.253	1	0.133
Female	61.3	30.7 - 91.8			
Race					
Malays	36.0	21.0 - 50.9	0.369	1	0.543
Non -Malays	25.6	4.4 - 46.8			
Smoking					
Ever smoked	26.1	10.1 - 42.2	1.034	1	0.309
Never smoked	41.1	22.4 - 59.9			
Smoking					
Non-smoker	41.1	22.9 - 56.7	3.000	2	0.223
≤15pack-years	74.6	-			
>15 pack-years	50.9	0.00- 105.9			
ECOG					
Good	62.3	49.0 - 75.5	61.11	1	<0.001
Poor	9.0	6.6 - 11.4			
Histology type					
SCLC	14.4	3.7 - 25.2	9.688	2	0.008
Adenocarcinoma	42.7	26.3 - 59.2			
Squamous cell and others	14.0	3.4 - 24.6			
Treatment					
Definitive	75.42	59.05 - 91.8	68.948	1	<0.001
Supportive Care	10.57	8.65 - 12.49			
Clinical Staging					
≤Stage 3	19.0	15.2 - 22.8	2.027	1	0.155
Stage 4	16.0	8.2 - 23.8			

ECOG, when treated with definitive treatment showed better MOS then those who were not (42.4 weeks vs 8.7 weeks).

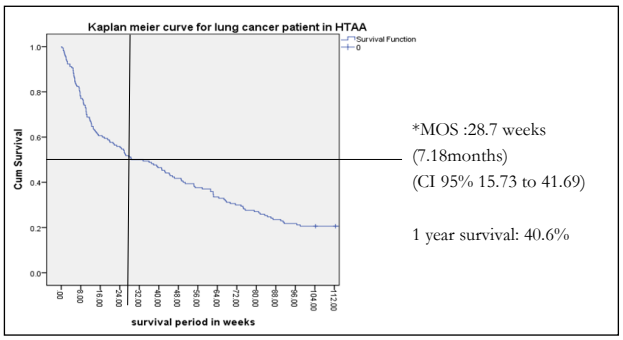

Figure 2: Overall Survival curve for lung cancer patient in HTAA from 2014-2017

Treatment modality and survival

Treatment modality is one of the independent predictors that affect survival of lung cancer patients. Among the patient who received definitive therapy those treated with immunotherapy had a longest MOS 83.4 weeks (95% CI 0.0, 167.1), followed by targeted therapy MOS 75.4 weeks (95% CI 49.4, 101.5), and chemotherapy MOS 64.5 weeks (95% CI 36.4, 92.8); (Table III)

DISCUSSION

The prevalence of lung cancer in Kuantan, Pahang was highest among Malay males, which is similar to the

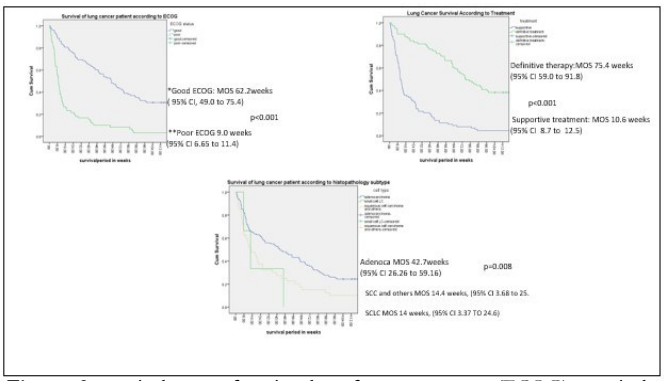

Figure 3: survival curve functional performance status (ECOG), survival curve for treatment type, and Lung cancer survival according to lung cancer histology sub-type

findings from previous national cancer registries.[5] One of the reasons is that the smoking prevalence is highest among Malay males.[11] Among smokers, the ratio of male to female in this study was 27: 1, similar to the data from National Health and Morbidity Survey 2015 (31:1). This can be due to social norm where smoking habit by female is not well accepted in this part of Malaysia.[11.] Majority of the patients (98%) in our study presented at advanced stage of lung cancer at diagnosis. This is similar to the data from a previous study that was conducted in HTAA Kuantan, Pahang a decade ago.[6] In fact, the number of patients presented in early stage of disease in Malaysia including Pahang state is very low in comparison to any other developed countries. For example, data from United States of America between 1996-2003 was 16% of lung cancer patients presented with localized disease and the percentage improved to 20% in year 2015.[27] This is postulated to be due to the lack of free lung cancer screening program and lack of awareness about lung cancer in Malaysia.[12] Despite 65% of patients presented with good ECOG functional status, only 46.7% received definitive therapy.

The characteristics for both studies were similar for age, gender, racial distribution, ECOG on presentation, staging, and smoking status of patients compared to the

Table IV: Survival outcome of lung cancer patient based on treatment modality

Type of treatment	1 year survival (%)	MOS (Weeks)
supportive treatment	10.1	10.5
chemotherapy	67.7	64.5
Targeted therapy	83.3	75.4
Immunotherapy	60	83.4

study that was done 10 years ago. Compared to this previous study by How et al, there was a similar percentage of patient who received the definitive therapy, but the survival had improved by 60%. One of the reasons is that among the patients who were treated with definitive therapy in the current study, 44.4% received targeted therapy and 12.3% received Immunotherapy compared to a decade ago when chemotherapy was the only available first line treatment (table IV).

At the time of the previous study, the price of EGFR inhibitors (Gefitinib) was 50% more expensive than the current price, resulting in only a few patients who could afford this treatment, and the medication was only registered in Malaysia drug formulary (or known as the Blue Book) in year 2014. Furthermore, immunotherapy was not available at that time including the absence of readily available molecular testing to guide optimal treatment.

Compared to results from landmark clinical trials the survival rate of lung cancer patient in our study was slightly low MOS, (IPASS trial MOS 18.8 months vs 17.4 months for TKI whereas KEYNOTE-042 MOS of 20 months vs 19.1 months for immunotherapy) as our cohort included patients who had poor ECOG functional status.[14,15]

The number of patients who underwent curative surgery was extremely low. Only 0.6% underwent surgery and they were all alive at the time of analysis. Patients who underwent curative surgery showed best survival however it is only advocated for early-stage lung cancer. Failure to detect lung cancer in early stage could be the leading cause for this. There is no effective lung cancer screening program nationwide in Malaysia. PEARLS study (Pilot Study for Early Lung Cancer Screening) intended to evaluate the feasibility and outcome of a single low-dose CT thorax as a screening modality was terminated prematurely due to low awareness among the general population, the refusal to be screened, and fear of lung cancer diagnosis.[22]

The limitation of this study is that it is a single-centre retrospective study. Some data was not available i.e. smoking status of patient, number of pack-year, details in subsequent treatment and reason why patients refused treatment.

Thus a multi-centre nationwide prospective study should be conducted to confirm our findings. We recommend that targeted therapy and immune checkpoint inhibitors should be made available in government hospitals as our data confirmed that newer treatment prolonged patients' survival. Education and counselling to patients and their relatives are important to avoid loss in the follow-up. With these measures, we hope the MOS of lung cancer will be further improved in the future.

In conclusion, 98% of lung cancer patients in HTAA Kuantan presented with advance stage. The independent predictor for lung cancer survival in HTAA were ECOG functional status and treatment modality. Good ECOG score and definitive treatment were associated with good overall survival. Patient with poor ECOG score were 3 times more likely to die than those with good functional status and those patients with supportive treatment were also 1.4 times likely to die than those on definitive treatment.

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ORIGINAL ARTICLE

A Cross-Sectional Study on Solid Oral Dosage Form Modifications among Older Patients Admitted to A Malaysian Teaching Hospital

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ABSTRACT

INTRODUCTION: Older adults often require multiple medications, increasing their risk of polypharmacy and drug-related problems (DRPs). Solid oral dosage forms (SODFs) are the most common medication formulation used by patients. However, administering SODFs to older adults can be challenging, especially for those with swallowing difficulties, leading to practices such as crushing, splitting tablets, or opening capsules. These modifications can affect medication efficacy and safety. This study aims to examine the prevalence of SODF modification among hospitalized older adults, the methods used, the reasons for modification, and the appropriateness of these practices. **MATERIALS AND METHOD:** This cross-sectional study included patients aged 60 years and above admitted to the general medical ward of a tertiary teaching hospital. Eligible participants were identified through the hospital's electronic registration system. Sociodemographic and clinical data were collected using a standardized form. Participants were interviewed about their SODF modification practices, and swallowing difficulties were assessed using the PILL-5 questionnaire. **RESULTS:** Of 122 participants, 54.1% were aged 60–69, and 9.8% reported dysphagia. SODF modification was practiced by 55.7%. Swallowing problems and pill dysphagia are significantly associated with SODF modification. Among those modifying SODFs, 47.1% incorrectly believed all medications could be safely altered. Splitting tablets was the most common practice (92.6%). **CONCLUSION:** Both dysphagia and pill dysphagia are significantly associated with SODF modification practices among older patients. Healthcare providers should be vigilant about these practices in older patients with swallowing difficulties. Proper education and assistance in medication handling are essential for this population.

Keywords
Solid oral dosage form, modification, older people

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Received: 23rd September 2024; Accepted: 27th December 2024

Doi: https://doi.org/10.31436/imjm.v24i02.2707

INTRODUCTION

Global advancements in healthcare, early diagnosis, and effective treatments have increased life expectancy, leading to a growing population of older adults.[1] This aging population is associated with a higher prevalence of multi-morbidity, [2] which often necessitates the use of multiple medications.[3,4] Solid oral dosage forms (SODFs), such as tablets and capsules, constitute approximately 65% to 70% of the available dosage forms in the market,[5,6] and are commonly used by older patients.[7,8]

However, administering SODFs to older people presents challenges that sometimes necessitates modifications, such as crushing or splitting tablets and opening capsules.[9] These medication modification practices are often adopted by older adults to overcome difficulties associated with administration, which are influenced by various factors. These factors include the physical characteristics of the medication, such as size and shape, as well as medical conditions like stroke or age-related swallowing difficulties[10] Research indicates that a significant proportion of older people modified medications, highlighting the need to address this issue.[10-13]

SODF modifications can lead to several potential issues, including drug instability, unpalatable taste, and improper administration of doses, potentially resulting in underdosing or overdosing.[11,14] Alarmingly, fatal outcomes from SODF modifications have been reported.[15] Additionally, modifying SODFs adds extra steps for older adults before administering drugs, thus can increase the complexity of their medication regimen, and potentially decreasing medication adherence.[16]

Certain medications in modified-release formulations must be ingested intact to ensure proper drug absorption. Modifying these SODFs can significantly impact their efficacy.[17,18] Furthermore, improper handling of modified SODFs, especially those containing allergenic, teratogenic, or carcinogenic substances, can pose serious health risks.[11] Additionally, off-label use of modified SODFs not explicitly indicated in product labelling can result in legal complications and adverse drug events.[19]

Despite these risks, SODF modification practices remain prevalent among older adults, particularly in care settings where medications administration often relies on caregivers. Studies conducted in Australia and Norway have explored these practices in nursing homes for the elderly. For instance, 18% of SODF modifications were reported in Australian residential aged care facilities, while 20.5% were conducted by nurses in Norwegian nursing homes. Notably, the prevalence of inappropriate SODF modifications was reported to be 32% in the Australian study and 10.7% in the Norwegian study.[7,8] Furthermore, Forough et al. (2020) highlighted that 12.5% of SODF modifications in Australian aged care facilities were classified as inappropriate, with 88.5% of these cases occurring despite the availability of suitable alternative formulations.[20]

Hospitals play a pivotal role in the care of older adults with complex medical conditions and polypharmacy. Unlike nursing homes, where medication management is primarily overseen by caregivers, many hospitalized older adults manage their own medications prior to admission and after discharge. The hospital setting also differs significantly in terms of the acuity of medical conditions and the complexity of care. This population may face unique challenges in medication management, including difficulties in administering SODFs due to acute illnesses, polypharmacy, or dysphagia, which require immediate intervention. A thorough understanding of SODF modification practices in the hospital setting is crucial to improving medication safety for older patients.

Despite the clinical relevance of this issue, no published studies have yet explored the prevalence or practices of SODF modifications among older adults in Malaysia. The objectives of this research are to investigate the prevalence of SODF modifications among a group of inpatient older adults, determine the practices of SODF modification within the group, identify the reasons for the modifications, and assess the appropriateness of the modifications.

MATERIALS AND METHODS

Study design

This cross-sectional study was conducted at Al-Sultan Abdullah Hospital (HASA), a 400-bed teaching hospital affiliated with *Universiti Teknologi* MARA (UiTM) and located in Puncak Alam, Selangor, Malaysia. The study was carried out over a six-week period from June to July 2023. Ethics approval was granted by the Research Ethics Committee of UiTM (600-FF[RES.5/4]), and permission to conduct the research at HASA was obtained from the hospital research committee (500-PJI [18/4/50]). Written informed consent was obtained from all study participants prior to their inclusion in the study.

Study participants

The Inclusion criteria for the study encompassed older patients aged 60 and above who were admitted to the general medical ward at HASA, were currently using at least one long-term SODF medication (defined as medications used for one month or longer), were proficient in either Malay or English, and willing to participate in the study. Exclusion criteria included patients with cognitive impairment or those with inaccessible chronic medication records. The number of participants recruited was determined using the Raosoft sample size calculator, with a 95% confidence level and a 5% margin of error, based on an estimated 170 older

patients in the medical ward over six weeks. The minimum number of participants required for the study was calculated to be 119.

Study tool

The study employed a specially developed data collection form that incorporated a validated questionnaire to assess pill dysphagia. The form was structured into four main sections. Section 1 gathered sociodemographic information, including age, gender, race, and other relevant details. Section 2 covered medical and medication history. Section 3 featured the PILL-5 assessment tool, a validated questionnaire designed to evaluate pill-swallowing difficulty and quantify the severity of pill (capsule and tablet) dysphagia.[21] Finally, Section 4 investigated patients' practices regarding the modification of solid oral dosage forms (SODFs).

The data collection form underwent a review process involving six pharmacists with over five years of clinical experience, ensuring its content relevance and appropriateness. A pilot test was conducted in April 2023 on ten older patients to assess the form's usability and practicality. Both the pharmacist review and the pilot test confirmed the suitability and practicality of the data collection form for the study.

Study procedure

Participants were recruited using a convenience sampling method. Initially, potential participants were identified using an electronic patient registration system. They were then approached face-to-face in the medical ward, where they were screened against the inclusion and exclusion criteria. If eligible, they were asked to provide consent to participate. The primary researcher collected sociodemographic information and clinical details using a standardized data collection form. Various methods were employed to gather this information, including the Hospital Information System (UniMeds), which contains electronic medical records and medication charts, as well as patient interviews.

Comorbidities were assessed using the Age-adjusted Charlson Comorbidity Index (ACCI). This index assigns scores based on comorbid conditions as defined by the Charlson Comorbidity Index (CCI),[22] with additional points assigned based on age above 40 years.[23] Participants were categorized into three ACCI groups: low (0–1), intermediate (2–3), and high (≥ 4).

The Anticholinergic Cognitive Burden (ACB) score for each regular medication was determined using a validated calculator.[24] Medications were scored from 0 (no anticholinergic effects) to 3 (severe anticholinergic effects). The total ACB score for each participant was calculated by summing the scores of all regular medications.

Additionally, the participants completed the PILL-5 questionnaire to assess pill dysphagia using the interviewer-administered questionnaire. The questionnaire comprises five items scored on a scale of 0 to 4. A total score of less than 6 indicates normal pill swallowing, while a score of 6 or higher indicates abnormal swallowing. The internal consistency reliability of the tool was acceptable with a Cronbach's alpha value of 0.895.

Patients were also interviewed about their practices regarding the modification of SODFs. Those who had modified their SODFs were further questioned about specific medications, methods, devices used, administration practices, challenges encountered, and reasons for modification. For each modified SODF, the primary researcher assessed the appropriateness of the modification by reviewing the product inserts and existing guidelines.[25,26]

Statistical analysis

Statistical analysis was performed using IBM SPSS version 28 (IBM, Armonk, NY, USA). Categorical data were presented as frequency and percentage. The chi-square or Fisher's exact tests were used to compare categorical variables. Statistical significance was determined at a *p*-value <0.05.

RESULTS

A total of 156 older patients were hospitalized in the general medical ward during the 6-week data collection period, and all of them were screened for inclusion and exclusion criteria. Twenty-six patients did not meet the inclusion criteria and were excluded from the study. Additionally, of the 130 eligible patients, 8 refused to participate, giving a final total sample of 122 older patients.

Sociodemographic characteristics

The majority of the participants are in the 60–69 age group (66/122, 54.1%) and females (63/122, 51.6%) (Table 1). Most patients show an ACCI score of ≥4 (93/122, 76.2%). Additionally, the presence of dysphagia is noted in 9.8% (12/122) of participants.

Of the 122 participants, 68 (55.7%) practiced SODF modifications, while 54 (44.3%) did not. The analysis of participants' sociodemographic characteristics revealed no significant association with the practice of modifying SODFs. Similarly, no significant association is observed between the clinical characteristics, including ACCI categories and the number of medications, with the practice of modifying SODFs, except for the presence of dysphagia, which is significantly associated with SODF modification.

Table 1. Sociodemographic characteristics of study participants and their association with SODF modification practices (n=122)

Characteristics		All (n=122)	Practice SODF modification, n (%)		*p*-value [a]
			Yes (n=68)	No (n= 54)	
Age Group	60 – 69	66 (54.1)	32 (47)	34 (63)	0.154
	70 – 79	41 (33.6)	25 (36.8)	16 (29.6)	
	≥80	15 (12.3)	11 (16.2)	4 (7.4)	
Gender	Male	59 (48.4)	30 (44.1)	29 (53.7)	0.293
	Female	63 (51.6)	38 (55.9)	25 (46.3)	
Race	Malay	106 (86.9)	58 (85.3)	48 (88.9)	0.559
	Non-Malay	16 (13.1)	10 (14.7)	6 (11.1)	
Marital Status	Single	1 (0.8)	0 (0)	1 (1.8)	0.152 [b]
	Married	88 (72.1)	46 (67.6)	42 (77.8)	
	Widowed/ divorced	33 (27)	22 (32.4)	11 (20.4)	
Living arrangement	Living alone	4 (3.3)	1 (1.5)	3 (5.6)	0.472 [b]
	Living with a non-family caretaker(s)	6 (4.9)	4 (5.9)	2 (3.7)	
	Living with a family member (s)	112 (91.8)	63 (92.6)	49 (90.7)	
Highest education	Primary school	17 (13.9)	10 (14.7)	7 (13)	0.938
	Secondary school	53 (43.4)	30 (44.1)	23 (42.6)	
	Tertiary education	35 (28.7)	18 (26.5)	17 (31.5)	
	No education	17 (13.9)	10 (14.7)	7 (13)	
Employment	Employed	6 (4.9)	3 (4.4)	3 (5.6)	1.000 [b]
	Unemployed / Retired	116 (95.1)	65 (95.6)	51 (94.4)	
Age-adjusted Charlson comorbidity index	Low (0–1)	2 (1.6)	2 (2.9)	0 (0)	0.219 [b]
	Intermediate (2–3)	27 (22.1)	12 (17.6)	15 (27.8)	
	High (≥4)	93 (76.2)	54 (79.4)	39 (72.2)	
Presence of dysphagia[c]	Yes	12 (9.8)	11 (16.1)	1 (1.9)	***0.013*** [b]
	No	110 (90.2)	57 (83.8)	53 (98.1)	
Number of medications taken	<5	31 (25.4)	14 (20.6)	17 (31.5)	0.170
	≥5	91 (74.6)	54 (79.4)	37 (68.5)	
Anticho linergic burden (ACB) risk [d]	Low risk (<3)	113 (92.6)	62 (91.2)	51 (94.4)	0.493
	High risk (≥3)	9 (7.4)	6 (8.8)	3 (5.6)	

[a] Chi-square test used unless specified otherwise.
[b] Fisher's exact test used.
[c] Based on diagnosis documented in patient medical records.
[d] Based on total ACB score of all regular medications taken by patients.

Pill dysphagia and its association with SODF modifications

Table 2 presents patients' responses to the PILL-5 questionnaire items. Overall, 19.1% (13/68) of those practicing SODF modification reported experiencing pills sticking in their throat "almost always" and "always" compared to none among those not practicing SODF modification (*p*-value = 0.002).

Additionally, 10.3% (7/68) of those modifying SODF experienced interference with medication intake due to swallowing problems "almost always" and "always" in contrast to none among those not modifying SODF (*p*-value <0.001). Similarly, the need to crush pills or use other forms of assistance is notably higher among those modifying SODF. Specifically, 11.8% (8/68) of those modifying SODF required assistance "almost always" and "always" compared to none among those not modifying SODF (*p*-value <0.001).

Regarding the PILL-5 score classification, 86.9% (106/122) of participants exhibit a normal pill swallowing score (<6). However, a significantly higher percentage (23.5%) of individuals who practiced SODF modification exhibited dysphagia, as indicated by an abnormal score (≥6), compared to none among those who did not modify SODF (*p*-value <0.001).

Table 2. Pill dysphagia and its association with SODF modifications (n=122)

PILL-5 item	All (n=122)	Practice SODF modification, n (%)		*p*-value [a]
		Yes (n =68)	No (n=54)	
Pills stick in my throat				
Never or almost never	76 (62.3)	36 (52.9)	40 (74.1)	***0.002***
Sometimes	33 (27)	19 (27.9)	14 (25.9)	
Almost always and always	13 (10.7)	13 (19.1)	0 (0)	
Pills stick in my chest				
Never or almost never	115 (94.3)	62 (91.2)	53 (98.1)	0.327 [b]
Sometimes	5 (4.1)	4 (5.9)	1 (1.9)	
Almost always and always	2 (1.6)	2 (2.9)	0 (0)	
I have fear swallowing pills				
Never or almost never	112 (91.8)	59 (86.8)	53 (98.1)	0.059 [b]
Sometimes	8 (6.6)	7 (10.3)	1 (1.9)	
Almost always and always	2 (1.6)	2 (2.9)	0 (0)	
My problem swallowing pills interferes with my ability to take my medicine				
Never or almost never	108 (88.5)	54 (79.4)	54 (100)	***<0.001*** [b]
Sometimes	7 (5.7)	7 (10.3)	0 (0)	
Almost always and always	7 (5.7)	7 (10.3)	0 (0)	
I can't take my pills without crushing, coating, or using other forms of assistance				
Never or almost never	105 (86.1)	51 (75)	54 (100)	***<0.001*** [b]
Sometimes	9 (7.4)	9 (13.2)	0 (0)	
Almost always and always	8 (6.6)	8 (11.8)	0 (0)	
PILL-5 score classification				
• Pill swallowing is normal (score <6)	106 (86.9)	52 (76.5)	54 (100)	***<0.001***
• Pill swallowing is abnormal (score ≥6)	16 (13.1)	16 (23.5)	0 (0)	

[a] Chi-squared test used unless specified otherwise.
[b] Fisher's exact test used.

Medication modification practice among participants

Table 3 presents an overview of the medication modification practices among participants who were engaged in SODF modifications. A considerable portion of participants (32/68, 47.1%) believe that all medications could be safely modified, while 26.5% (18/68) are unsure, and another 26.5% (18/68) consider that not all medications are suitable for modification. Sources of information on SODF modifications vary, with 23.5% (16/68) relying on pharmacists, 22.1% (15/68) on doctors, and only 2.9% (2/68) referring to product leaflets. Overall, the 68 participants who practiced SODF modifications modified a total of 102 medications, averaging 1.5 modified SODFs per person. Among these participants, 63 split medications (92.6%), 5 crushed medications (7.4%), and 2 opened the capsules of medications (2.9%). One participant admitted to splitting and crushing the medications, while another participant practiced opening capsules and crushing the medications.

Table 3. Medication modification practice and experience among participants (n=68)

Medication modification practice and experience		n (%)
Perceived that all medications are safe to be modified	Yes	32 (47.1)
	No	18 (26.5)
	Not Sure	18 (26.5)
Source of information about SODF modification	Pharmacists	16 (23.5)
	Doctors	15 (22.1)
	Product leaflets	2 (2.9)
	Not specified	35 (51.5)
Method of SODF modification [a]	Splitting	63 (92.4)
	Crushing	5 (7.4)
	Opening (capsules)	2 (2.9)
	Splitting and crushing	1 (1.5)
	Opening (capsules) and crushing [b]	1 (1.5)

[a] Participants can provide more than one response and therefore responses do not add up to 100%.
[b] Capsules were opened and the pellets contained inside were crushed.

Specific methods, reasons, administration methods, and types of medications for SODF modifications

Table 4 specifically reports the methods of SODF modification, reasons for modification, administration methods after modification, and the types of medications that were modified before administration. For splitting (n=63), the main methods used are using hands (29/63, 46%), tablet splitters (27%), cutting with a knife (10/63, 15.9%), using scissors (8/63, 12.7%), using teeth (4/63, 6.3%), and using a paper cutter (1/63, 1.6%). The primary reasons for splitting are following the doctor's instructions (74.6%) besides having swallowing difficulty (9/63, 14.3%). Most participants (61/63, 96.8%) swallowed the split medication whole. The most common medications that were split include simvastatin tablet (10/63, 15.9%), atorvastatin tablet (9/63, 14.3%), and bisoprolol tablet (8/63, 12.7%).

In the case of crushing (n=5), the methods used include tablet crushers (2/5, 40%), mortar and pestle (2/5, 40%), and the back of a spoon (1/5, 20%). The main reason for crushing is due to swallowing difficulty (4/5, 80%). After crushing, the medications are either dissolved in water (3/5, 60%) or other liquids (2/5, 40%). The medications usually crushed include metformin (3/5, 60%), amlodipine (2/5, 40%) and atorvastatin (2/5, 40%) tablets.

Meanwhile, the reason for opening capsules (n=2) is primarily due to swallowing difficulty (2/2, 100%). The content of the capsules is either dissolved in water (1/2, 50%) or other liquids (1/2, 50%). The medication capsules commonly opened before administration are omeprazole.

Table 4. Specific methods, reasons, administration methods, and types of medications for SODF modifications

SODF Modification		n (%)
Splitting (n = 63)		
Splitting method used[a]	Using hands	29 (46)
	Using tablet splitter	17 (27)
	Cutting with knife	10 (15.9)
	Using scissors	8 (12.7)
	Using teeth	4 (6.3)
	Using paper cutter	1 (1.6)
Reason for splitting[a]	Follow doctor's instruction	47 (74.6)
	Having swallowing difficulty	9 (14.3)
	Tablet size too big	9 (14.3)
	To save cost	1 (1.6)
Administration method after splitting	Swallow whole	61 (96.8)
	Incorporate in food	2 (3.2)
Medications that were split before administration[b]	Simvastatin tablet	10 (15.9)
	Atorvastatin tablet	9 (14.3)
	Bisoprolol tablet	8 (12.7)
	Metformin tablet	7 (11.1)
	Perindopril tablet	5 (7.9)
	Sitagliptin and metformin film coated tablet	4 (6.3)
	Spironolactone tablet	4 (6.3)
	Atenolol tablet	3 (4.7)
	Empagliflozin tablet	3 (4.7)
	Frusemide tablet	3 (4.7)
	Metoprolol tablet	3 (4.7)
	Prazosin tablet	3 (4.7)
	Levothyroxine tablet	2 (3.2)
	Telmisartan tablet	2 (3.2)
	Valsartan tablet	2 (3.2)
Crushing (n = 5)		
Crushing method used	Using tablet crusher	2 (40)
	Using mortar and pestle	2 (40)
	Using the back of spoon	1 (20)
Reason for crushing	Having swallowing difficulty	4 (80)
	Not specified	1 (20)
Administration method after crushing	Dissolve in water	3 (60)
	Dissolve in other liquid	2 (40)
Medications that were crushed before administration	Metformin tablet	3 (60)
	Amlodipine tablet	2 (40)
	Atorvastatin tablet	2 (40)
	Simvastatin tablet	1 (20)
	Aspirin/glycine tablet	1 (20)
	Clopidogrel tablet	1 (20)
	Ezetimibe tablet	1 (20)
	Ferrous fumarate tablet	1 (20)
	Levetiracetam tablet	1 (20)
	Memantine tablet	1 (20)
	Vitamin B_1, B_6 and B_{12} tablet	1 (20)
	Omeprazole capsule [c]	1 (20)
	Sodium valproate tablet	1 (20)
Opening of capsule (n=2)		
Reason for opening of capsule	Having swallowing difficulty	2 (100)
Administration method after opening of capsule	Dissolve in water	1 (50)
	Dissolve in other liquid	1 (50)
Medication capsule that was opened before administration	Omeprazole capsule	2 (100)

[a] Participants can provide more than one response and therefore responses do not add up to 100%.
[b] Only the top 15 medications are presented.
[c] Capsules were opened and the pellets contained inside were crushed.

Difficulties and problems faced with SODF modification

Among those who practiced SODF modification, the most frequently reported difficulty was the tablet's high hardness (15/68, 22.1%), followed by small tablet size (10/68, 14.7%). Other difficulties included time-consuming modification (2/68, 2.9%), absence of a scoreline on the tablet (2/68, 2.9%), tablet coating starting to dissolve in humid conditions leading to a sticky or slippery surface (2/68, 2.9%), trembling hands (2/68, 2.9%), and the tedious nature of SODF modification (2/68, 2.9%). One participant (1/68, 1.5%) reported requiring assistance from others to modify the SODF. In terms of problems encountered during SODF modification, the most common issue was unequal splitting (30/68, 44.1%), followed by medication spilling out or the tablet cracking into pieces (12/68, 17.6%), and unpalatable taste (7/68, 10.3%).

Inappropriate SODF modifications among study participants

Of all patients who modified SODFs, 13 (19%) practiced modifications deemed inappropriate based on the product leaflet or existing guidelines. The most common inappropriate modifications involve splitting sitagliptin/ metformin film-coated tablets (n=4). Inappropriate splitting was also observed in one case each for erythromycin 250 mg enteric-coated tablets, metformin hydrochloride 500 mg extended-release tablets, perampanel film-coated tablets, sacubitril/ valsartan 50 mg tablets, sodium valproate 200 mg enteric-coated tablets, tenofovir disoproxil fumarate 300 mg tablets, and propranolol hydrochloride 10 mg tablets. Additionally, one case involved opening an omeprazole 20 mg enteric-coated capsule and crushing its pellets. Another case involved crushing a sodium valproate 200 mg enteric-coated tablet, while one patient crushed an aspirin 100 mg and glycine 45 mg combination tablet.

DISCUSSION

This study is the first in Malaysia to investigate SODF modifications among older patients. Our results show that over half of the participants engaged in such

modifications. Nearly 50% of those who modified SODFs believed that all medications were safe to be modified. Many used inappropriate methods, such as using their hands or teeth, and 19% of all patients who modified SODFs practiced inappropriate SODF modifications. These findings underscore the need for healthcare providers to monitor SODF modifications closely and offer appropriate guidance to ensure safe medication use.[29]

In this study, 9.8% of the participants were diagnosed with dysphagia, a prevalence notably lower than the 31% to 64% reported in previous research.[30,31] The discrepancy in prevalence rates is likely due to variations in assessment methods. Previous studies employed tools such as the 10-item Eating Assessment Tool (M-EAT-10), the multiple consistency test, and the water swallow test,[32] whereas this study relied on the physician's notes for a dysphagia diagnosis. Despite the lower observed prevalence, the findings of this study indicate that individuals who modified SODFs are significantly more likely to have a dysphagia diagnosis than those who did not engage in SODF modifications.

Research suggests that healthcare providers are often less proactive in addressing swallowing difficulties,[33] resulting in inadequate attention to issues related to dysphagia. As a result, patients with dysphagia may resort to unsupervised modifications of SODFs, which could be inappropriate. In this study, a significantly higher proportion of older patients who modified their SODFs had abnormal pill swallowing difficulties (PILL-5 scores of ≥6) compared to those who did not engage in such modifications. This finding proposes that the PILL-5 questionnaire holds potential as a tool for screening pill dysphagia and could aid in identifying patients who may require additional interventions in medication administration.[21]

In this study, inappropriate modifications were observed in 19% of participants who modify SODFs. This prevalence is consistent with previous studies, which report rates of inappropriate SODF modifications ranging from 10.7% to 32%.[7,8,13,20] Identified inappropriate modifications include splitting extended-release or film-coated formulations and crushing enteric-coated tablets. These modifications can disrupt the delivery systems of the formulations, increasing risks of toxicity, and causing poor taste and potential skin irritation.[25,34] Additionally, crushing enteric-coated tablets compromises their protective coatings, leading to reduced efficacy and potential gastric irritation.[18]

These inappropriate modifications may arise from a lack of awareness that certain SODFs cannot be safely modified. This is supported by the prevalent belief among study participants that all medications are safe to modify, reflecting a misunderstanding of the safety of SODF modifications.[35,36] Furthermore, only a small proportion of patients received information on SODF modifications from pharmacists or physicians, suggesting that many patients undertake these modifications without adequate professional oversight.

The lack of adequate guidance is further highlighted by the observation that, although most patients who split medications do so according to their physician's instructions, many used inappropriate methods, such as splitting tablets with their hands or teeth. Additionally, although most modified medications were not deemed inappropriate according to product leaflets or existing guidelines, many patients who split or crushed their medications reported issues such as uneven splits and medications spilling or cracking. These findings suggest that while medication modifications may be safe for many patients, the process can lead to suboptimal dosing, potentially impacting clinical outcomes.[36-38] Notably, patients who split, crush, or open capsules often mix them with food or non-water liquids, risking food-drug interactions that could compromise medication efficacy and safety.[39]

Our study highlights the need for healthcare providers to be more proactive in offering guidance on SODF modifications and emphasizes the critical role of vigilant patient care for older patients, especially those with dysphagia or pill dysphagia. Educating patients and caregivers about the risks of inappropriate SODF modifications is essential for ensuring optimal medication management and patient safety.

LIMITATION

Despite the valuable insights gained from this study, several limitations must be acknowledged. The study was conducted in a single center and involved only the general medical wards, which limits the generalizability of the findings to other healthcare settings and wards. Furthermore, the skewness in the distribution of participants based on sociodemographic characteristics, such as ethnicity, limited the representativeness of the general older population in Malaysia. Additionally, the study was conducted over a short data collection period of six weeks, resulting in a small sample size. The reliance on self-reported data may introduce recall bias, and potential social desirability bias might have affected participants' responses, leading to an overestimation or underestimation of their practices. The study also did not measure the impact of SODF modifications on clinical outcomes.

Future studies could replicate this research with a larger sample across multiple centers to provide a broader perspective on SODF modification practices. Longitudinal studies could further enhance our understanding by offering evidence of the long-term impact of SODF modifications on patient outcomes. Additionally, developing strategies to support patients in safely modifying their medications when necessary is warranted.

CONCLUSION

This study examines the prevalence and practices of SODF modifications among older patients at a Malaysian teaching hospital. Over half of the participants engaged in SODF modification practices, primarily through pill splitting. There was a significant association between dysphagia and pill dysphagia, with SODF modifications. Some modifications were found to be inappropriate, potentially compromising patient safety and therapeutic effectiveness. Future longitudinal and multi-center research is needed to further explore SODF modification practices among older patients. Additionally, developing standardized guidelines and training for healthcare providers is essential to ensure safe SODF modifications. The study underscores the importance of addressing inappropriate SODF modifications to improve medication management and safety for older patients, highlighting the need for proper education and support for both patients and caregivers in medication administration.

ACKNOWLEDMENT

The authors would like to express their sincere gratitude to Universiti Teknologi MARA (UiTM), particularly the Faculty of Pharmacy, for their continuous support. We are especially thankful for the provision of research facilities, technical resources, and academic guidance that significantly contributed to the successful completion of this study.

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ORIGINAL ARTICLE

Occurrence of aac(6')-Ib-cr and Qnr Genes among Quinolone-Resistance Enterobacteriaceae Isolated from Patients with Urinary Tract Infection in Najaf, Iraq

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ABSTRACT

INTRODUCTION: The *aac(6')-Ib-cr* gene is one of the most common genes among plasmids and has dual activity against both aminoglycoside and quinolone antibiotics, making it among the most important plasmid-mediated quinolone resistance genes. This research aimed to confirm the frequency of *aac(6')-Ib-cr* and *qnr* genes in quinolone-resistant *Enterobacteriaceae* isolates obtained from patients with urinary tract infection in Najaf, Iraq. **MATERIALS AND METHODS:** Quinolone resistance was examined in 318 urine samples taken from individuals who had suspected urinary tract infections (135 *Klebsiella pneumonia* cases, 75 *Proteus mirabilis* cases, and 108 *Escherichia coli* cases). Using PCR, antibiotic susceptibility patterns were assessed for quinolone resistance isolates and the presence of the *aac(6')-Ib-cr, qnrA*, *qnrB*, and *qnrS* were looked into. **RESULTS:** Quinolone-resistant isolates totaling 176 were identified. *aac(6')-Ib-cr* was detected in 93 (52.8%) cases, 50 of which were *E. coli*, 39 were *K. pneumoniae*, and 4 were *P. mirabilis*, according to PCR analysis data. *qnrA* 6 (3.4%), *qnrB* 22 (12.5%), and *qnrS* 5 (2.8%) isolates were identified to have the following *qnr* genes. *P. mirabilis* did not have the *qnrS* gene, which was absent from all analyzed genes detected in bacterial isolates. **CONCLUSION:** It was shown that of the plasmid-mediated quinolone resistance genes, the *aac(6')-Ib-cr* gene was the most common. Every gene analyzed was present in both *K. pneumoniae* and *E. coli*.

Keywords
Plasmid-mediated quinolone resistance, *qnr* genes, PMQR, *qnrA*, *aac(6')-Ib-cr*

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Received: 23th May 2024; Accepted: 12th November 2025

Doi: https://doi.org10.31436/imjm.v24i02/2618

INTRODUCTION

Many resistance mechanisms against quinolones have been established by *Enterobacteriaceae*. The mechanisms mostly entail a mutation in the chromosomal genes (DNA gyrase then topoisomerase IV), which encode quinolone targets, and/or decreased drug permeability.[1,2] Genes on plasmids, such as *Qnr, QepA* and *Oqx*AB (plasmid-mediated efflux pump), and an aminoglycoside acetyltransferase *aac(6')-Ib-cr* gene variation, can also cause quinolone resistance.[3]

It becomes more difficult to treat quinolone-resistance *Enterobacteriaceae* infections when plasmid-mediated quinolone resistance (PMQR) is prevalent, because it promotes the spread of resistance.[4] The presence of *qnr* genes in *Enterobacteriaceae* species that are less sensitive to fluoroquinolones.[5]

Aminoglycosides have been a mainstay in treating infections produced by *Enterobacteriaceae*. In contrast, aminoglycoside-resistant strains of these bacteria have emerged in recent years.[6] Nosocomial infections produced by *Enterobacteriaceae* are particularly difficult to treat because of three processes that reduce the efficiency of aminoglycosides. These consist of altered ribosome binding sites, the emergence of enzymes that modify aminoglycosides, and decreased cell permeability or absorption.[7]

Aminoglycoside-modifying enzymes are the chief machine of aminoglycoside resistance in *Enterobacteriaceae*.[8] The structural disintegration of aminoglycosides by acetyltransferases and other enzymes is a possibility, as phosphotransferases, and adenyltransferases.[9] The aminoglycoside acetyltransferase *aac(6')-Ib* mainly encodes resistance to specific aminoglycoside antibiotics

(kanamycin, tobramycin, and amikacin).[10] This gene may have another function in a variation of the 6'-N-aminoglycoside acetyltransferase (*aac(6')-Ib*-cr) gene, to acetylate quinolones with piperazinyl subunit (for example ciprofloxacin and norfloxacin) only.[1] This gene may present in a multidrug-resistant plasmid within the cassette of the class one integron, which can carry many other quinolone resistance genes.[1,10]

Given that there are no clear indications of, the *aac(6')-Ib-cr* gene's existence in Al-Najaf, Iraq. Finding out how common the *aac(6')-Ib-cr* and plasmid-mediated quinolone resistance (PMQR) genes are in clinical isolates of *Enterobacteriaceae* resistant toward quinolones in Al-Najaf, Iraq, is the goal of this study.

MATERIAL AND METHODS

Bacterial isolation

Al-Zahra Education Hospital for Parenthood and Pediatrics, Al-Sader Medical City, and Al-Hakeem Overall Hospital remained the three hospitals in Al-Najaf city midpoint from which 318 midstream urine samples were collected from patient roles who presented with urinary tract infections between January 2020 and December 2022. The VITEK 2 system and VITEK 2 GN ID Card (Biomerieux, France) were used to authenticate each strain of bacteria.

Antimicrobial susceptibility testing and detection of quinolone resistance isolates

The antibiotic sensitivity tests were achieved in compliance with the Clinical Laboratory Standard Institute (CLSI) standard. [11] To identify isolates resistant to quinolones, all isolates were tested against ciprofloxacin (CIP, 5 μg) and nalidixic acid (ND, 5 μg) (Cypress, Belgium). The results were verified using MIC strips (Liofilchem, Italy).

Antibiotic resistance patterns were conducted according CLSI guidelines.[11] Ampicillin (AM, 10 μg), amoxicillin (AX, 25 μg), cefotaxime (CTX, 30 μg), ceftazidime (CAZ, 30 μg), ceftriaxone (CTR, 30 μg), cefoxitin (FOX, 30 μg), aztreonam (ATM, 30 μg), imipenem (IPM, 10 μg), meropenem (MEM, 10μg), levofloxacin (LEV, 5 μg), lomefloxacin (LOM, 10 μg), norfloxacin (NOR, 10 μg), ofloxacin (OFX, 5 μg), amikacin (AK, 30 μg), tobramycin (TOB, 10 μg), gentamycin (CN, 10 μg), netilmicin (NET, 30 μg), sulphamethazole (SMZ, 250 μg), trimethoprim (TMP, 5 μg).

Detection of plasmid-mediated quinolone resistance (PMQR) genes

The cells underwent a previously described analysis to detect the presence of the *aac(6')-Ib* gene. Using previously described primers to amplify every known variant of the target gene, the primers were selected.[12] PCR amplification conditions were 95˚C for 3 minutes, followed by 94˚C for 45 seconds, 55˚C for 45 seconds, 72˚C for 45 seconds for 34 cycles, and 72˚C for 5 minutes as the final extension. The amplification yielded 482 bp. The PCR results were given to a gel documentation system (Biometra, Germany) for visualization, and they were electrophoresed. After restriction, *aac(6')-Ib* showed 272 bp and 210 bp fragments, but *aac(6')-Ib-cr* did not exhibit a restriction site. These PCR-positive isolates were then subjected to additional analysis using the BtsCl enzyme. Using primer sets, monoplex PCR was used to screen for *qnrA*, *qnrB*, and *qnrS*. PCR amplification conditions previously described, the 512 bp, 417 bp, and 469 bp PCR products were obtained accordingly.[13] The agarose was stained with ethidium bromide; the electrophoresis was performed at 70 volts for 90 minutes.

RESULTS

The present study revealed that out of the 318 clinical isolates, *Enterobacteriaceae* strains were found in the midstream urine samples collected where *Escherichia coli*) ,(%34 ,108 *Klebsiella pneumoniae* (135, 42.5%), and *Proteus mirabilis* (75, 23.5%).

In the current investigation, 176 isolates (60 *E. coli*, 74 *K. pneumoniae*, and 42 *P. mirabilis*) were shown to be resistant to quinolones based on CLSI standards. The pattern of antimicrobial resistance against quinolone resistance found in 176 isolates is displayed in Table I. According to An analysis of the design for resistance to antibiotics, the majority of quinolone-resistant bacteria in this study were resistant to penicillin (99.3%) and amoxicillin (98.8%).

There were followed by sulphamethazole (82.9%), trimethoprim (80.1%), cefotaxime (79.5%), ceftazidime (76.1%), ceftriaxone (74.4%), and aztreonam (63.6). We can observe that the fluoroquinolone group had a high level of resistance to lomefloxacin (66.4%), although the other fluoroquinolones, levofloxacin (36.9%), norfloxacin (48.2%), and ofloxacin (50.5%), had intermediate resistance. Amikacin (21.5%), tobramycin (69.3%), gentamycin (58.5%), and netilmicin (26.1%) were also found in this investigation

Table I: Antibiotic susceptibility pattern of 176 quinolone-resistance *Enterobacteriaceae* clinical isolates

Antibiotics	E. coli (60 isolates) n. (%)	K. pneumoniae (74 isolates) n. (%)	Proteus spp (42 isolates) n. (%)	Total (176 isolates) n. (%)
Ampicillin	59 (98.3)	74 (100)	42 (100)	175 (99.3)
Amoxicillin	58 (96.7)	74 (100)	42 (100)	174 (98.8)
Cefotaxime	51 (85)	64 (86.5)	25 (59.5)	140 (79.5)
Ceftazidime	50 (83.3)	63 (85.1)	21 (50)	134 (76.1)
Ceftriaxone	48 (80)	61 (82.4)	22 (52.4)	131 (74.4)
Cefoxitin	11 (18.3)	39 (52.7)	21 (50)	71 (40.3)
Aztreonam	42 (70)	59 (79.7)	11(26.2)	112 (63.6)
Imipenem	6 (10)	23 (31.1)	0 (0)	29 (16.4)
Meropenem	15 (25)	25 (33.8)	0 (0)	40 (22.7)
Levofloxacin	28 (46.7)	24 (32.4)	13 (31)	65 (36.9)
Lomefloxacin	41 (68.3)	56 (75.7)	20 (47.6)	117 (66.4)
Norfloxacin	33 (55)	35 (47.3)	17 (40.5)	85 (48.2)
Ofloxacin	34 (56.7)	36 (48.6)	19 (45.2)	89 (50.5)
Amikacin	2 (3.3)	26 (35.1)	10 (23.8)	38 (21.5)
Tobramycin	40 (66.7)	52 (70.3)	30 (71.4)	122 (69.3)
Gentamycin	37 (61.7)	39 (52.7)	27 (64.3)	103 (58.5)
Netilmicin	4 (6.7)	29 (39.2)	13 (31)	46 (26.1)
Sulphamethazole	54 (90)	62 (83.8)	30 (71.4)	146 (82.9)
Trimethoprim	47 (78.3)	66 (89.2)	28 (66.7)	141 (80.1)

All 176 quinolone resistance isolates investigated through PCR for the existence of *aac(6')-Ib*, *qnrA*, *qnrB*, *qnrS* genes. A total of 131 (74.4%) were demonstrated that harbored *aac(6')-Ib* gene, the most common gene found in *E. coli* 54 (90%) followed by *K. pneumoniae* 57 (77%) and *P. mirabilis* 20 (47.6%) (Figure .(1 In the same manner, the present study confirmed that the *aac(6')-Ib-cr* gene 93 (52.8%) of isolates *E. coli* 50 (83%) followed by *K. pneumoniae* 39 (52.7%) and *P. mirabilis* 4 (9.5%) The *qnrA* was found most frequently in *P. mirabilis* 3 (7.1%), followed by *K. pneumoniae* 2 (2.7%), and *E. coli* 1 (1.6%) (Figure 2). A total of 17 (23%) *K. pneumonia* isolates carried *qnrB* gene (Figure 3), while only 1 (14%) carried *qnrS* (Figure 4). In *E. coli*, both qnrB and qnrS were detected in 4 (6.6%) isolates while in *P. mirabilis* harbor only *qnrB* gene. Table II demonstrated the frequency of the plasmid-mediated quinolone resistance (PMQR) gene among 176 quinolone resistance isolates.

Table II: Frequency of plasmid-mediated quinolone resistance (PMQR) gene among 176 quinolone resistance isolates

Gene	E. coli n=60	K. pneumonia n=74	Proteus spp n=42	Total n=176
aac(6')-Ib	54 (90%)	57 (77%)	20 (47.6%)	131 (74.4%)
aac(6')-Ib-cr	50 (83.3%)	39 (52.7%)	4 (9.5%)	93 (52.8%)
qnrA	1 (1.7%)	2 (2.7%)	3 (7.1%)	6 (3.4%)
qnrB	4 (6.7%)	17 (23%)	0	21 (11.9%)
qnrS	4 (6.7%)	1 (1.4%)	0	5 (2.8%)

DISCUSSION

Quinolone antibiotic was first discovered in the sixties in the last century and used to treat urinary tract infections in adult patients, then it developed to treat other sites of infection over time.[14] However, an expansion in the use of quinolone and fluoroquinolone group classes of antibiotics led to the appearance of resistance against this group.[15] Quinolone resistance mediated by plasmids was initially recognized in the members of the *Enterobacteriaceae* family. Over time, many of the genes that produce quinolone resistance within this category have been identified.[16] The prevalence of PMQR genes in Al-Najaf city was fairly assessed.[17] Therefore, in this study, we investigated the presence of these genes among three members of the *Enterobacteriaceae* family (*E. coli, K. pneumoniae*, and *P. mirabilis*) and understood their antibiotic susceptibility background.

In our study, the results show 52.8% of collected quinolone-resistance *Enterobacteriaceae* clinical isolates harbor at least one PMQR gene. These results were significantly high, several studies accomplished worldwide revealed a lower rate. In Algeria,[18] Europe, Spain,[19] and Mexico,[15] rates are 13.5%, 20%, 31.8%, and 32.1% respectively. The *aac(6')-Ib-cr* gene causes resistance to quinolone as well as aminoglycoside, especially it is responsible for reducing susceptibility to ciprofloxacin in vivo[1]. In this study, the prevalence of *aac(6')-Ib-cr* gene was 52.8%, and this finding may explain the high level of resistance to ciprofloxacin and norfloxacin, especially when combined with chromosomal mutation.[3] The rate

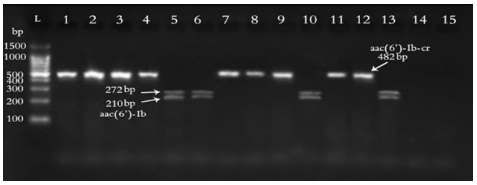

Figure 1: Agarose gel of PCR amplification products of *K. pneumoniae*. isolates amplified with primer targeting the *aac(6')-Ib* genes after digested with BstCI. Lane (L), molecular size marker (100 bp), lane (1,2,3,4,7,8,9,11,12) display positive results with *aac(6')-Ib-cr*, lane (5, 6, 10, 13) display *aac(6')-Ib* wild-type genes.

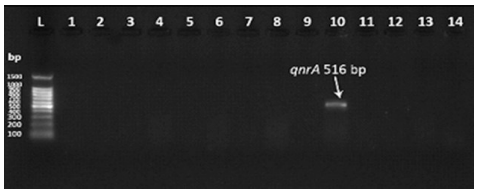

Figure 2: Agarose gel of PCR amplification products of *Proteus spp.* isolates amplified with primer targeting the *qnrA* genes. Lane (L), molecular size marker (100 bp), lane (10) displays positive results with *qnrA*, lane (1,2,3,4,5,6,7,8,9,11,12,13,14) displays negative results with *qnrA* genes.

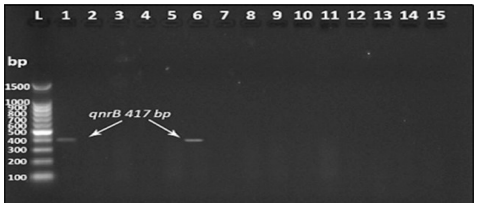

Figure 3: Agarose gel of PCR amplification products of *E. coli.* isolates amplified with primer targeting the *qnrB* genes. Lane (L), molecular size marker (100 bp), lane (1,6) displays positive results with *qnrB*, lane (2,3,4,5,7,8,9,10,11,12,13,14) displays negative results with *qnrB* genes.

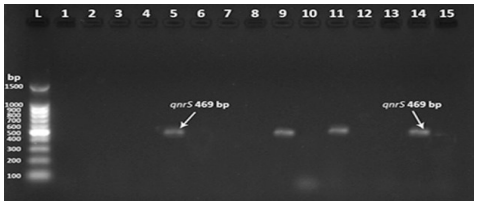

Figure 4: Agarose gel of PCR amplification products of *E. coli* isolates amplified with primer targeting the *qnrS* genes. Lane (L), molecular size marker (100 bp), lane (5,9,11,14) displays positive results with *qnrS*, lane (1,2,3,4,6,7,8,10,12,13) displays negative results with *qnrS* genes.

of *aac(6')-Ib-cr* gene in the present study was similar to the study conducted in Iran 68.6%[25], and higher than a study conducted in Brazil 40.8%26, Mexico 15.1%20. The *aac (6')-Ib-cr* gene was present more frequently in *E. coli* 83% followed by *K. pneumoniae* 52.7%, and less frequently in *P. mirabilis* 9.5%, in agreement with other studies.[18,20] The high frequency of *aac(6')-Ib-cr* gene puts the therapeutic options in the narrow circle where it is expressed as resistant to both quinolone and aminoglycoside drugs in the future.

In this study, the prevalence of Qnr determinants was found in 23.8% of *Enterobacteriaceae* quinolone resistance isolates. The *qnr* gene was strongly associated with various species of *Enterobacteriaceae* worldwide.[21] A previous study has reported that *qnr* genes represent 5.7% in China,[22] 15.1% in Tunisia,[23] and 28.7% in Spain,[18] of quinolone-resistance *Enterobacteriaceae* clinical isolates. Among the 176 quinolone-resistance *Enterobacteriaceae* clinical isolates, the frequency of *qnrA* was 6 (3.4%), three of them found in *P. mirabilis*. This finding was close to results accomplished in India,[23] and Iran,[24] while another study conducted in Europe and Brazil didn't record this gene in *Enterobacteriaceae* isolates.[25,26] The *qnrB* in the present study was found in 21 (11.9%) *Enterobacteriaceae* quinolone resistance isolates, 17 located in *K. pneumonia*. This result was higher than recorded in Qatar,[27] Sweden.[29] The *qnrB* gene was the most prevalent *qnr* resistance gene, not only in this study but also recorded by studies conducted in Morocco,[28] Iran,[24] Austria,[29] and Turkey.[4] Five isolates carried the *qnrS* gene, mostly in *E. coli*, this result was similar to that recorded in Eurpe.[30]

Unfortunately, there is no clear strategy in our country to control the administration and use of antibiotics, as they are given without a prescription in pharmacies, and therefore it is difficult to reduce the spread of antibiotic resistance genes among bacteria, which in turn reduces the effect and treatment options for infected patients, which leads to aggravating the health condition. The limitation of this study is that no equal number of isolates from each bacterium selected from the *Enterobacteriaceae* family. Not all PMQR genes were screened, which gives incomplete information about resistance genes.

CONCLUSIONS

Isolates with elevated quinolone resistance, particularly to cephalosporins and penicillins, were detected. *aac(6')-Ib-cr* was the most common PMQR gene among the isolates, with a widespread frequency of these genes observed. Every gene that was checked turned up in *K. pneumoniae* and *E. coli*. Investigation of quinolone resistance genes in Al-Najaf necessitates more research, in Iraq, since the limitation of data in this area.

FUNDING

Self-funding

CONFLICT OF INTEREST

Researchers don't have any conflicts of interest.

ACKNOWLEDGMENTS

The writers express their thankfulness to the personnel of the Bacteriology Laboratory at Al-Najaf Hospitals for their help in gathering clinical specimens for this investigation.

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ORIGINAL ARTICLE

A Retrospective Cohort Single-Centre Study of Prophylactic Vs. Preemptive Valganciclovir Therapy in Cytomegalovirus-At-Risk Kidney Transplant Recipients in Malaysia

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ABSTRACT

INTRODUCTION: Valganciclovir is commonly used for prophylaxis or preemptive therapy to prevent post-transplant cytomegalovirus (CMV) infection and disease in kidney transplant recipients. However, there are a limited data on the outcome and the association between valganciclovir and clinical characteristics of kidney transplant recipients, particularly those who are CMV seronegative (R-) receiving a transplant from CMV seropositive donors (D+), as well as in populations with high CMV seroprevalence. **MATERIALS AND METHODS:** This retrospective, single-center cohort study collected clinical data from kidney transplantation recipients at a tertiary referral hospital from January 2020 to June 2022. The data on the recipients' demographics, CMV risk categories, clinical characteristics, and types of valganciclovir therapy were obtained. Associations between clinical data, CMV risk categories, and therapies were determined. **RESULTS:** Among 110 kidney recipients, 9 were classified as high-risk and 101 as intermediate-risk. There were no significant differences found in the recipients' demographics and underlying factors between the risk categories. CMV infection occurred significantly less in the prophylaxis group than in the preemptive group (22.2% vs. 59.4%, p=0.04). There were no significant differences in one-year graft outcomes or patient survival observed between prophylaxis and preemptive therapies. Leukopenia incidence was higher in patients receiving prophylaxis. The incidence of co-infection with CMV viremia was similar between high-risk and intermediate-risk recipients. A significant association was found between CMV risk categories and prophylactic therapy in relation to post-transplant complications, CMV viremia clearance duration, and peak titer. **CONCLUSION:** Valganciclovir was the preferred therapy to prevent CMV infection and disease in kidney transplant recipients, with prophylactic therapy showing particular benefit in high-risk groups without increasing complications.

Keywords
Cytomegalovirus, Kidney transplantation, Preemptive, Prophylaxis, Yalganciclovir

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Received: 8th July 2024; Accepted: 13th January 2025

Doi: https://doi.org10.31436/imjm.v24i02/2666

INTRODUCTION

Valganciclovir, a prodrug of ganciclovir, is widely used in prevention and treatment of cytomegalovirus (CMV) infection in solid organ and bone marrow transplant recipients.[1] It is administered orally and is rapidly converted to ganciclovir, the active antiviral agent.[2] The drug acts by inhibiting viral DNA polymerase, thus preventing viral replication.[2]

Studies have demonstrated the effectiveness of valganciclovir in prevention of CMV infection in paediatric kidney transplant recipients[3], renal transplant recipients,[4] and thoracic organ transplant recipients.[5] However, its use is associated with adverse effects, including leukopenia, fever, abdominal pain, and an increased risk of opportunistic infections.[6] Studies also shown that there is a higher occurrence of CMV infection among high risk liver transplant recipients receiving valganciclovir prophylaxis compared to ganciclovir prophylaxis.[7] Additionally, a retrospective analysis by Brown et al. showed that low-dose

valganciclovir is both effective and safe for prevention of CMV disease in renal transplant recipients.[8] In a previous study that emphasized on the impact of CMV disease on solid organ transplant recipients, the adverse effect of vangiclacvir has also been explored.[9]

CMV infections are a major concern following kidney transplantation, as CMV is the most common opportunistic infection in this patient group. CMV infection can be classified into two categories, CMV infection and CMV disease. CMV infection refers to the presence of CMV replication, while CMV disease involves clinical signs and symptoms attributable to the infection. Despite effective antiviral therapy, studies have shown that CMV infections can persist after kidney transplant, leading to adverse outcomes.

The American Society of Transplantation guidelines emphasize on the importance of distinguishing between CMV replication and latency, with clinical signs and symptoms of CMV disease including fever, abdominal pain, and myelosuppression. Identifying factors that influence the development of CMV infection and disease after kidney transplantation is essential for effective prevention, management, and treatment. Wei & Yi (2020) highlight the importance of understanding the risk factors associated with CMV viremia, particularly the donor and recipient CMV serostatus (D+/R-) and recipients who have received anti-lymphocyte antibody therapy. Additionally, demographic and factors such as such as donor and recipient age, pre-transplant hemodialysis duration, estimated post-transplant glomerular filtration rate (eGFR), acute rejection, transplant type, non-white race, diabetes mellitus, and cyclosporine therapy contribute to CMV risk.[10] Post-transplant factors, including the use of thymoglobulin or anti-thymocyte globulin (ATG) for induction and maintenance of immunosuppression, also play a role in increasing the risk of CMV viremia.[11,12] These multifactorial risk factors highlight the complexity of managing and preventing CMV-related complications in kidney transplant recipients.

Immunosuppression following transplantation significantly increases the risk of cytomegalovirus (CMV) infection, leading to severe morbidity and mortality in solid organ transplant (SOT) recipients.[13] CMV infection in SOT recipients is associated with acute and chronic graft rejection, allograft dysfunction, heightened susceptibility to opportunistic infections, reduced patient survival, and increased healthcare costs.[13] The prevalence of CMV viremia among kidney transplant recipients further underscores the critical concern regarding the interplay between immunosuppression with CMV infection, and their implications on the health outcomes of transplant recipients.[14]

Prophylaxis and preemptive therapy are the primary strategies for prevention of cytomegalovirus (CMV) infection or disease in SOT recipients. Prophylaxis strategy by administration of antiviral agents in prevention of CMV infection, is particularly crucial in high-risk recipients with a CMV-positive (D+) donor and CMV-negative (R−) recipient.[15] In contrast, preemptive therapy by initiating antiviral treatment upon detecting the early signs of CMV replication has been shown to result in significantly lower rates of CMV disease compared to prophylaxis in certain specific transplant recipient groups.[15]

This approach allows for early intervention when viral replication is detected, effectively reducing the incidence and severity of CMV disease in SOT recipients. Additionally, preemptive therapy has proven effective in reducing the risk of prophylaxis failure

A key advantage of preemptive therapy is its ability to tailor treatment to individual patients through real-time PCR monitoring of CMV viral load. This approach allows for early intervention when viral replication is detected, effectively reducing the incidence and outcomes of CMV disease in SOT recipients.[15] Additionally, preemptive therapy has proven effective in reducing the risk of primary prophylaxis failure in preventing CMV infection and disease, positioning it as a targeted and efficient management strategy for CMV.[15]

This study aimed to compare the effectiveness of valganciclovir as prophylaxis or preemptive therapy in high-risk and intermediate-risk groups. It also sought

to examine the relationship between recipients' risk categories and their demographic and clinical characteristics.

MATERIALS AND METHODS

Data collection

This was a retrospective cohort study, conducted at a single centre by employing convenience sampling over a period of two and a half years, from January 2020 to June 2022, for collection of comprehensive data. Clinical data were gathered from recipients aged 13 to 70 years old who underwent kidney transplantation at the Nephrology Department of Kuala Lumpur Hospital. Recipients managed with valganciclovir as part of either prophylactic or pre-emptive therapies, following established guidelines to prevent CMV disease were included in the study, and recipients with a post-transplant follow-up period of fewer than 6 months were excluded.

Clinical outcomes including CMV infection and disease were monitored for 12 months post-transplantation. CMV infection was defined as the presence of CMV replication in blood without symptoms, detected by real-time PCR (>200 IU/ml), whilst CMV disease was defined as CMV infection with attributable symptoms including fever, malaise, leucopenia, thrombocytopenia, or evidence of tissue-invasive disease (e.g., colitis, pneumonitis, hepatitis). All recipients were followed up for a minimum of 12 months post-transplantation to assess both CMV-related outcomes and graft survival.

Graft outcomes were monitored over a period of one year, focusing on several key parameters such as acute kidney injury (defined as an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or ≥1.5 times baseline within 7 days), acute allograft dysfunction (characterized by sustained decline in eGFR more than 25% from baseline, not attributable to acute rejection), and graft rejection (defined as biopsy-proven rejection according to the Banff 2013 criteria). Graft loss was described as a return to renal replacement therapy such as dialysis, graft removal, retransplantation, or the death of the recipients.

In terms of risk categorization, the recipients were divided into intermediate-risk and high-risk groups according to the their CMV donor/recipient serostatus as determined by the pretransplant CMV serology. The intermediate-risk group included recipients with a positive or negative CMV donor serostatus and a positive recipients serostatus, (D+/R+ or D-/R+). The high-risk group, included recipients with a positive CMV donor serostatus and a negative CMV recipient serostatus (D+/R-), or those within the intermediate-risk group (D+/R+ or D-/R+) who received anti-lymphocyte preparations as part of their treatment regimen.

Clinical data were meticulously collected and included several key variables. The recipients' demographic information, such as age at transplantation, race, gender, and the donor/recipient relationship, were recorded. Clinical characteristics that might influence CMV infection and disease were also examined, including the primary cause of end-stage renal disease (ESRD), pre-transplant CMV serostatus, duration of pre-transplant hemodialysis, baseline eGFR, and the use of antiviral therapy (prophylaxis or pre-emptive therapy with valganciclovir). For prophylaxis, recipients were administered 450 mg of oral valganciclovir daily for six months. In contrast, recipients on pre-emptive therapy received 900 mg of valganciclovir daily for the first 14 days, followed by secondary prophylaxis with 450 mg daily for three months, and the dosage of valganciclovir was adjusted based on renal function to ensure appropriate dosing.

Additional clinical data included the use of immunosuppressive induction therapy such as thymoglobulin or anti-thymocyte globulin [ATG], basiliximab; as well as the type of immunosuppressive drugs for maintenance such as mycophenolate; type of transplantation; presence of leucopenia, defined as white blood cell count less than 4.0x10^9^/L; co-morbidities including diabetes mellitus and hypertension; clinical outcomes such as co-infections with other microorganisms, graft rejection or graft loss and mortality rate) and post-transplant complications including oedema, anaemia, diarrhoea, dyslipidaemia, and relevant conditions.

The dependent variables for this study included the risk categories of the recipients, categorized as either high-risk or intermediate-risk, and the types of CMV viraemia, classified as either CMV infection or CMV disease. The independent variables examined in this study encompassed a wide range of factors, including the recipients' demographic characteristics and underlying factors, co-morbidities, clinical outcomes and complications, types of therapy administered, length of CMV therapy, and type of immunosuppressive drugs for maintenance, co-infections by other infectious agents, graft outcomes and patients' survival.

This study received ethical approval from the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia with approval number: NMRR-20-993-53201. In compliance with ethical standards, the confidentiality of all participants was maintained through data anonymization, and secure methods of data storage were employed. Additionally, all procedures followed the relevant institutional guidelines for research involving human subjects, ensuring the protection of participant rights throughout the study.

Statistical analysis

The percentage of independent variables was evaluated using frequency analysis. Unless otherwise specified, both dependent and independent variables are expressed as the median and interquartile range (IQR). To determine the associations between risk categories and demographics, the clinical characteristics and outcomes were assessed. P-values were determined by Mann–Whitney U-test and Student t-test for continuous variables, according to their distribution, and Fisher's exact test for categorical variables. All p-values were two-sided, with the p-values of <0.05 were considered statistical significance. Statistical analyses were conducted using SPSS software (Version 23.0, IBM Corp, Armonk, NY, United States).

RESULTS

Recipients' demography and underlying factors

Out of 115 kidney transplant recipients selected for the study, five were excluded due to an inadequate post-transplant follow-up duration (<6 months; range 2-4 months). Of the remaining 110 recipients included in the analysis, 9 (8.1%) were categorized as high-risk for CMV infection or disease [(D+/R-) and (D+/R+ or D-/R+) receiving anti-lymphocyte preparations] and 101 (91.8%) were categorized as intermediate-risk (D+/R+) (Figure 1).

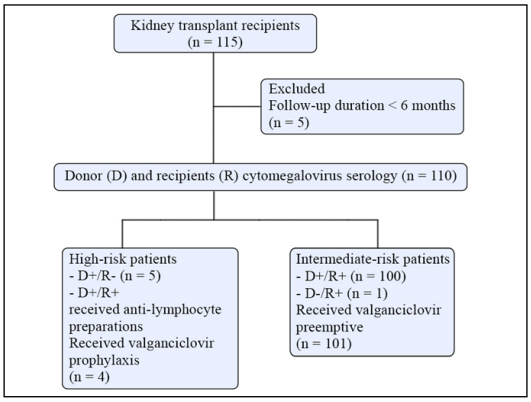

Figure 1 Distribution of the kidney recipients' risk categories

The baseline characteristics of the recipients are summarized in Table 1. Majority of the recipients were male, older than 35 years old, underwent ABO-incompatible (ABOi) transplantation, received a graft from a living donor, and treated with basiliximab as the immunosuppressant induction agent.

Regarding immunosuppressive induction therapy, all (100%) intermediate-risk recipients received basiliximab, while 55.6% of high-risk recipients did so (p=1.00). Additionally, 44.4% of high-risk recipients received thymoglobulin (p=1.00), whereas none of the intermediate-risk recipients were administered this therapy.

There was no significant difference between the high-risk and intermediate-risk recipients in terms of the age, sex, presence of diabetes mellitus, type of kidney transplantation, ABO-incompatible (ABOi) transplantation, pre-transplant donor-specific antibodies, or the donation from blood relatives. Regarding the immunosuppressive induction therapy, 100% of intermediate-risk recipients received basiliximab, while only 55.6% of high-risk recipients did so (p=1.00). Additionally, 44.4% of high-risk recipients received thymoglobulin (p=1.00), whereas none of the intermediate-risk recipients were administered with this therapy.

Regarding maintenance immunosuppressive therapy, nearly all recipients were treated with tacrolimus, mycophenolate mofetil, and methylprednisolone, with a slightly higher proportion of high-risk recipients receiving these therapies. The median duration of post-transplant follow-up was similar between the high-risk recipients and intermediate-risk recipients, 29 months (IQR 26.0-35.5 months) and 28 months (IQR 27.0-31.5 months), respectively (p=0.45)

Table 1 : Recipients' Demographics and Clinical Characteristics by Risk Category

Characteristics	High-risk recipients[a] (n=9)	Intermediate-risk recipients[b] (n=101)	p-value[c]
Demographics			
Age, years, mean+ SD	42.7+12	37.8+10	0.18[d]
Male sex, n (%)	7 (77.8)	65 (64.4)	0.72
Clinical Parameters			
Baseline eGFR, ml/ min/1.73m² (mean ± SD)	42.5 ± 10.2	43.2 ± 11.4	0.68
Diabetes mellitus, n (%)	3 (33.3)	11 (10.9)	0.09
Transplantation Details			
ABO-incompatible, n (%)	6 (66.7)	73 (72.3)	0.71
Related donor, n (%)	6 (66.7)	81 (80.2)	0.39
Immunosuppression Induction therapy			
Basiliximab, n (%)	5 (55.6)	100 (100.0)	0.00
Thymoglobulin n (%) Maintenance therapy	4 (44.4.)	0 (0.0)	1.00
TAC + MMF + MP, n (%)	9 (100.0)	99 (98.0)	1.00
TAC + EVR + MP, n (%)	0 (0.0)	2 (2.0)	1.00
Follow-up Duration, months, median (IQR)	29 (26.0-35.5)	28 (27.0-31.5)	0.45

D+. Donor CMV seropositive; R-, recipient CMV seronegative; D-, donor seronegative; R+, recipient seropositive; eGFR: Estimated glomerular filtration rate; SD, standard deviation; IQR, interquartile range; DSA, donor-specific antibody; TAC, tacrolimus; MMF, mycophenolate mofetil; EVR, everolimus; MP, methylprednisolone.

[a] High-risk: D+/R- and (D+/R+ or D-/R+) receiving anti-lymphocyte preparations
[b] Intermediate-risk: D+/R+ or D-/R+
[c] P-values based on Mann-Whitney U-test unless otherwise specified
[d] By Student t-test

Clinical outcomes and complications

The incidence of cytomegalovirus (CMV) infection was significantly higher in high-risk recipients (5/9, 55.6%) compared to intermediate-risk recipients (22/101, 22.0%) (p=0.04). Although the incidence of CMV disease was also higher in high-risk recipients (1/9, 11.1%) than in intermediate-risk recipients (6/101, 5.9%), this difference was not statistically significant (p=0.46). One intermediate -risk patient experienced a series of CMV infections, beginning as early as one month post-transplant, which progressed to multiple CMV-related diseases, including colitis, acute hepatitis, diarrhea, acute gastritis, and esophagitis.

Valganciclovir was used as prophylactic therapy in high-risk recipients and preemptive therapy in intermediate-risk. The clinical outcomes are shown in Table 2. The incidence of CMV infection was significantly higher in high-risk recipients 5/9 (55.6%) than the intermediate-risk recipients 22/101 (22.0%) (p=0.04). Although CMV disease incidence was also higher in high-risk recipients, 1/9 (11.1%) than in the intermediate-risk recipients 6/101 (5.9%), this difference was not statistically significant (p=0.46). One intermediate-risk recipients experienced a series of CMV infections, beginning as early as one month psot transplantation which progressed into multiple CMV-related diseases, including colitis, acute hepatitis, diarrhoea, acute gastritis, and esophagitis.

There was no significant difference in the incidence of co-infectious pathogens other than CMV between the two-group; 2/9 (22.2%) in high-risk recipients and 23/101 (22.8%) in intermediate-risk recipients (p=1.00). Other pathogens that were isolated or detected included *Escherichia coli, Acinetobacter spp., Staphylococcus aureus, Klebsiella pneumonia, Pseudomonas spp., Enterobacter cloacae* and *Burkholderia pseudomallei, Candida albicans, Tinea pedis* and BK polyomavirus (BKV).

The median estimated glomerular filtration rate (eGFR) at 12 months post transplantation was similar between the two groups: 46.4 (IQR 41.0–64.0)ml/min/1.73m² in high-risk recipients (n=9) and 46.5 (IQR 41.3–52.5)ml/ min/1.73m² in intermediate-risk recipients (n=101). There was no significant difference in leukopenia findings among both groups; high-risk recipients (n=1/9, 11.1%) and intermediate-risk recipients (n=4/101, 4.0%, p= 0.35).

Post-transplant complications were significantly higher in intermediate-risk recipients (50/101, 49.5%) than the high-risk recipients (1/9, 11.1%) with p value <0.05. The complications observed complications included delayed graft function, acute allograft dysfunction, dehydration, hypophosphatemia, dyslipidemia, hyponatremia, hypoalbuminemia, persistent proteinuria, acute tubular necrosis, pancytopenia, fever, cardiomyopathy, acute antibody-mediated rejection (ABMR), acute. T-cell–mediated rejection (TCMR), renal artery thrombosis,

Table 2: Clinical Outcomes with Valganciclovir Therapies at 12 Months Post-Transplant

Outcomes	Prophylaxis Valganciclovir High-risk Recipients[a] (n=9)	Preemptive Valganciclovir Intermediate-risk Recipients[b] (n=101)	P-value[c]
CMV Events			
CMV infection[d], n (%)	2 (22.2)	60 (59.4)	0.04
- Mean time to first infection, days (range)	185 (170-200)	85 (30-140)	0.02
CMV disease[e], n (%)	1 (11.1)	46 (45.5)	0.08
- Mean time to first disease, days (range)	250 (-)	120 (45-270)	0.03
Clinical Parameters			
Co-infection with other microorganisms[f], n (%)	2 (22.2)	23 (22.8)	1.00
eGFR at 12 months, ml/ min/1.73 m^2, median (IQR)	46.5 (41.3–52.5)	46.4 (41.0–64.0)	0.22
Leukopenia[g], n (%)	3 (33.3)	18 (17.8)	0.37
Co-infection with other microorganisms[7], n (%)	2 (22.2)	23 (22.8)	1.00
Post-transplant complication[h], n (%)	1 (11.1)	50 (49.5)	0.04
CMV Viremia Characteristics			
Duration of CMV viremia clearance, days, median (IQR)	14 (7-25)	26 (17-54)	0.02
Peak titer, 10^9/mL, median (IQR)	18 (7.0-43.0)	105 (18.0-213.0)	<0.01

D+. Donor CMV seropositive; R-, recipient CMV seronegative; D-, donor seronegative; R+, recipient seropositive; CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; IQR, interquartile range.
[a] High-risk: D+/R- and (D+/R+ or D-/R+) receiving anti-lymphocyte preparations
[b] Intermediate-risk: D+/R+ or D-/R+
[c] P-values: Mann-Whitney U-test for continuous variables; Fisher's exact test for categorical variables
[d] CMV infection defined as CMV replication in blood (>200 IU/ml) without symptoms
[e] CMV disease defined as CMV infection with attributable symptoms (fever, organ involvement)
[f] Including bacterial infections, BK virus, and fungal infections
[g] Leucopenia defined as white blood cell count $<4.0 \times 10^9$/L
[h] Including delayed graft function, acute allograft dysfunction, dehydration, etc.

macrocytic anaemia, perinephric hematoma, gout, chronic diarrhoea, pedal oedema, recurrent focal segmental glomerulosclerosis (FSGS) and ischemic heart disease. The duration of CMV viremia clearance was significantly faster in high-risk recipients receiving prophylaxis than in intermediate-risk receiving preemptive therapy, 14 (7-25) vs 26 (17-54) days, respectively. The CMV viremia peak titers were significantly lower in high- than intermediate-risk recipients, 18 (7.0-43.0) vs 105 (18.0-213.0) CMV peak titres, respectively.

Valganciclovir as prophylaxis and preemptive therapy

The prophylaxis dose was 450 mg oral valganciclovir/day for 6 months. Pre-emptive therapy recipients received initial treatment with valganciclovir 900 mg/day for 14 days, followed by secondary prophylaxis consisting of valganciclovir 450 mg/day for 3 months. All valganciclovir dosages were adjusted according to renal function. At a median follow-up duration of 24 months, CMV infection developed significantly less in the prophylaxis therapy than in the pre-emptive group (22.2%, 2/9 vs 59.4%, 60/101, respectively; p=0.04). Lower percentages of CMV disease were also seen in the prophylaxis therapy than in the pre-emptive therapy, but the difference was not significant (11.1%, 1/9 vs 45.5%, 46/101 respectively, p=0.08). In intermediate-risk recipients with pre-emptive valganciclovir, CMV infection was developed within the first three months after transplantation and CMV disease within the first nine months after transplantation, while in the high-risk recipients with valganciclovir prophylaxis, CMV infection was developed after six months of transplantation and CMV disease within the first 12 months after transplantation.

Graft outcomes and patients' survival

Graft and recipient survival and graft rejection data are shown in Table 3 and. Acute kidney injury (AKI) was seen in 1/9 (11.1%) and 14/101 (13.9%) in high-risk and intermediate-risk recipients, respectively. Acute allograft dysfunction was observed in 1/9 (11.1%) and 11/101 (11.9%) in high-risk and intermediate-risk recipients, respectively. These graft dysfunction cases were predominantly due to causes other than rejection, including medication-related effects, infections, and haemodynamic factors. There were 0/9 (00.0%) cases and 2/101 (2.0%) cases of acute antibody-mediated rejection (ABMR) in high-risk and intermediate-risk recipients, respectively, and 1 case of acute T-cell–mediated rejection (TCMR) in the intermediate group. No incidence of death occurred in the current study group.

Table 3: Graft outcomes and patients' survival with valganciclovir therapies.

	Prophylaxis valganciclovir High-risk recipients (D+/ R-) and (D+/ R+, D-/R+) receiving anti-lymphocyte preparations (n = 9)	Preemptive valganciclovir Intermediate-risk recipients (D+/R+, D-/ R+) n = 101	P-value[a]
Acute kidney injury (AKI), n (%)	1 (11.1)	14 (13.9)	1.00
Acute allograft dysfunction, n (%)	1 (11.1)	11 (11.9)	1.00
Acute antibody-mediated rejection (ABMR), n (%)	0 (0.0)	2 (2.0)	1.00
Acute T-cell–mediated rejection (TCMR), n (%)	0 (0.0)	1 (1.0)	1.00
Death, n (%)	0 (0.0)	0 (0.0)	1.00

[a] P-values: Fisher's exact test for categorical variables.

DISCUSSION

Cytomegalovirus (CMV) viraemia significantly affects clinical outcomes post-solid organ transplantation, exacerbated by immunosuppression, leading to symptomatic CMV disease with severe morbidity and occasional mortality.[16] In this study, 115 kidney transplant recipients were initially included, with 5 excluded due to insufficient post-transplant follow-up (<6 months). The remaining 110 recipients showed an 8.1% high-risk (D+/R- and D+/R+ or D-/R+ with anti-lymphocyte preparations) and 91.8% intermediate-risk (D+/R+) distribution.

Immunosuppression modulates the risk of CMV infection, underscoring the need to comprehend the interplay between immunosuppression and CMV infection.[17] The prevalence of CMV disease in transplant recipients, without pre-emptive or prophylaxis therapy, remains a critical concern despite advancements, posing a substantial threat to solid-organ transplant recipients.[18] The selection between prophylaxis and pre-emptive therapy for preventing CMV in transplant recipients is a subject of continuous research and debate. Reports of high rates of delayed-onset post prophylaxis CMV disease emphasize the necessity for targeted and effective preventive strategies tailored to the specific transplant population.[19]

The baseline characteristics, including age, sex, and transplantation factors, were comparable between high-risk and intermediate-risk recipients, indicating a well-balanced study population. However, a significant disparity in immunosuppression induction strategies was observed, with 100.0% of intermediate-risk recipients receiving basiliximab compared to 55.6% in the high-risk group. Furthermore, thymoglobulin was administered to 44.4% of high-risk recipients, while none among the intermediate-risk recipients received this treatment.

In this study, valganciclovir played a crucial role in managing cytomegalovirus (CMV) in kidney transplant recipients through prophylactic and preemptive strategies. High-risk recipients, constituting 8.1% of the cohort, had a significantly higher incidence of CMV infection (22.0%) than intermediate-risk recipients. Although CMV disease rates were elevated in high-risk recipients (11.1%) compared to the intermediate-risk group (5.9%), statistical significance was not reached. Remarkably, an intermediate -risk case experienced early-onset CMV infections leading to multiple diseases. Co-infection rates with other pathogens were similar between high-risk and intermediate-risk recipients. Renal function, assessed by estimated glomerular filtration rate, was comparable at the 12-month post-transplant mark. However, intermediate-risk recipients had a significantly higher post-transplant complication rate (49.5%) than high-risk recipients (11.1%). Additionally, high-risk recipients showed faster CMV viremia clearance and lower peak titers, suggesting potential prophylaxis benefits.

The usage of prophylaxis therapy in this study showed a lower incidence of CMV infection and CMV disease (delayed-onset disease) by 6 months after transplant in high-risk recipients. Studies have shown that universal prophylaxis can reduce the initial risk of CMV infection and disease (20)(21). However, there is concern about the high risk of late-onset CMV disease, which usually begins with D+/R- recipients after discontinuing prophylaxis.[22] This may increase mortality and/or death.[22,23,24]

However, some studies show the benefits of universal prophylaxis[25] compared preemptive therapy and universal prophylaxis in high-risk kidney and liver transplant recipients (D+/R-). In their group, consistent with previous studies by[26], late-onset CMV disease was not severe or life-threatening. They also showed that CMV reactivation in the first two years post-transplant, regardless of the preventive measures used, was a risk factor for transplant failure 5 years post-transplant.[25]

No statistically significant differences between the two therapy strategies were observed for leukopenia. The cause of leukopenia is usually multifactorial. Besides, CMV infection or the disease itself is often caused by the side effects of CMV antivirals such as valganciclovir and immunosuppressive agents.[27] The CMV infection has marked myelosuppression effects in renal transplant recipients and has been reported to have leukopenia or neutropenia as a manifestation.[28] Age at transplantation was not associated with the development of leukopenia;

however, older recipients had a higher incidence of leukopenia[28], as observed in this study group.

The high-risk recipients demonstrated a significantly faster median clearance of CMV viremia compared to their intermediate-risk counterparts, aligning with the findings of a previous study[29] that reported a swifter clearance of CMV DNAemia in the prophylaxis group beyond the 12-month post-transplant period. Additionally, the median peak titer of CMV viremia was notably lower in high-risk recipients under prophylaxis compared to intermediate-risk recipients. However, it is worth noting that contrary findings have been reported;[30] observed a significantly higher median CMV antigenemia peak titer in high-risk patients compared to intermediate-risk patients, while[29] found no difference in the median peak titer between recipients undergoing prophylaxis and preemptive approaches. These variations in results may be attributed to factors such as differences in antiviral selection, immunosuppressive status, the presence, or absence of CMV-specific T-cell immunity, suboptimal antiviral drug levels, or resistance to antiviral medications.[31]

In this study, occurrences of acute kidney injury (AKI), acute allograft dysfunction, acute antibody-mediated rejection (ABMR), and acute T-cell–mediated rejection (TCMR) were observed at higher rates in intermediate-risk recipients compared to high-risk recipients, although these differences did not reach statistical significance. Numerous studies have established a connection between AKI and unfavorable long-term graft outcomes.[32] The delayed graft function observed in this study may signify post-transplant AKI. In solid organ transplant (SOT) recipients, CMV infection often manifests through indirect effects, contributing to outcomes like acute rejection, graft failure, and mortality, collectively termed the 'indirect effects of CMV infection.[33] Additional factors leading to AKI in transplant recipients, such as obstruction of a single-functioning kidney, vascular thrombosis, drug toxicity, and drug-induced thrombotic microangiopathy [34], were not specifically identified in this study.

Initiating preemptive therapy in intermediate-risk cases during the early post-transplant period may permit mild CMV replication, resulting in CMV infection.[35] Such infections could potentially contribute to graft rejection. In alignment with findings from other investigations, our study lends support to the universal prophylaxis approach, emphasizing its advantage in suppressing early CMV replication, as opposed to preemptive therapy, thereby reducing the risk of graft rejection, particularly within the initial 3 months following transplantation in high-risk (D+/R-) kidney transplant recipients.[25,35]

This study has several limitations, such as its retrospective design, leading to incomplete clinical and laboratory data. Additionally, the convenience sampling employed may introduce bias into the results. It is crucial to note that this study contributes new data specific to the Malaysian setting.

CONCLUSION

The use of valganciclovir as antiviral prophylaxis in high-risk kidney transplant recipients, compared to preemptive therapy in intermediate-risk kidney transplant recipients, demonstrated superior efficacy in prevention of CMV infection and slowing the progression of CMV disease in these groups. This strategy did not pose an increased risk of opportunistic infections, allograft rejection, graft loss, drug resistance development, or mortality.

FUNDING

This study was funded by UPM GP-IPS research grant GPIPS/2020/9690500.

ACKNOWLEDGMENT

We would like to express our sincere gratitude to the staff and experts in the Nephrology Department and Microbiology (Virology) Unit Department, Kuala Lumpur Hospital, for their invaluable clinical and technical support.

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ORIGINAL ARTICLE

The Modification and Validation of the Medication Compliance Questionnaire (MCQ) for the Assessment of Adherence to Antiretroviral Therapy (ART)

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ABSTRACT

INTRODUCTION: Anti-retroviral therapy (ART) significantly improves the prognosis of human immunodeficiency virus (HIV) infection. Yet long-term and complex regimens often lead to non-adherence. Maintaining at least 95% adherence is crucial for effective ART and thus preventing drug resistance. The Medication Compliance Questionnaire (MCQ) has been used for adherence assessment in antihypertensive treatment, with an 80% cut-off level. This study aimed to modify and validate the MCQ for assessing adherence to ART. **MATERIALS AND METHODS:** The MCQ underwent modification with the incorporation of a new rating scale and scoring method. A pilot study was conducted at the Infectious Disease Clinic, Hospital Raja Perempuan Zainab II, Kelantan. Inclusion criteria were adults living with HIV (PLHIV), on ART for at least two months and who can communicate in Malay. Fisher's Exact test was used to determine validity, sensitivity, and specificity. Cronbach's alpha and intra-class correlation coefficients were used to evaluate reliability, with significance set at $p < 0.05$. **RESULTS:** A total of 60 PLHIV adults participated in this pilot study. Viral load served as the validity criterion for the modified MCQ, showing a significant association with adherence ($p=0.018$). Sensitivity and specificity values were 100.0% and 79.5%, respectively. Cronbach's alpha coefficients for drug-taking and drug-stopping behaviour domains were 0.65 and 0.90, respectively. **CONCLUSION:** The modified MCQ is a valid and reliable tool for assessing adherence to ART, demonstrating high sensitivity and adequate specificity. It is suitable for use in clinical practice to improve medication therapy management for PLHIV.

Keywords
Medication Compliance Questionnaire, adherence assessment, questionnaire validation, anti-retroviral therapy

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Received: 23th May 2024; Accepted: 4th December 2024

Doi: https://doi.org10.31436/imjm.v24i02/2623

INTRODUCTION

Anti-retroviral therapy (ART) significantly improves the prognosis of human immunodeficiency virus (HIV) infection; however, long-term treatment and maintenance of strict adherence to treatment is required.[1] The key factor for the success of treatment is good medication adherence, defined as the degree to which a patient follows the treatment plan agreed upon with their healthcare provider.[2] Adherence is often quantified as a percentage, reflecting the proportion of doses taken as prescribed.[3] In contrast to other chronic diseases, HIV infection necessitates a high adherence rate of approximately 95% to ensure effective viral suppression, owing to the rapid replication and high mutation rate of the virus.[4] Maintaining a minimum adherence rate of at least 95% is crucial for suppressing HIV viral load to below 400 copies/mL in most individuals.[5] Suboptimal adherences can lead to sub-therapeutic drug levels, compromising treatment efficacy and potentially resulting in increased viral load, decreased CD4 count, a higher risk of HIV transmission, and an elevated risk of developing resistance to ART drugs.[6] Unfortunately, only one-third of people living with HIV (PLHIV) adhere to their medication as prescribed.[7] In Nigeria, the non-adherence rate to ART was reported to be as high as 40%.[8] Even when patients fully understand the consequences of non-adherence, adherence rates remain suboptimal.[2,4]

Non-adherence to ART regimens can stem from the complexities of the treatment, which often requires taking more than two dozen pills, tablets, or capsules daily. Additionally, the necessity for complete adherence and the long-term nature of the treatment contribute to this challenge.[5] Therefore, there is a need to develop a convenient tool for monitoring ART adherence. Assessing adherence behaviour accurately in PLHIV is essential in ensuring treatment planning is effective and efficient. A review of the literature reported many methods used to measure adherence.[9] Direct measurements of adherence include drug assays of blood or urine,[10] surrogate laboratory markers,[11] and directly observing patients receiving the medications.[12] Indirect adherence measurements include the self-report adherence questionnaire,[13] pill count,[14] electronic monitoring devices,[15] and review of prescription records or secondary database analysis.[16]

Currently, there is no standard reference method that can be advocated to evaluate adherence because each method has its own advantages and limitations.[12] One of the most accurate methods of measuring adherence is by direct measures. However, these are costly.[17] Indirect measures, such as self-report adherence questionnaire, provides a practical and flexible method for adherence assessment and provides a unique chance to identify patient concerns. The self-report method is used widely due to its simplicity, relatively inexpensive and implementation ease in a patient's follow-up.[18] However, it is often linked with adherence overestimation and its outcomes vary compared to direct measures such as therapeutic drug monitoring.[19] Several self-reported adherence questionnaires exist, although they were not tailored specifically for HIV infection. Examples of these questionnaires are Morisky Medication Adherence Scale,[20] Patient Medication Adherence Questionnaire,[21], Brief Medication Questionnaire[22], Malaysia Medication Adherence Assessment Tool (MyMAAT)[23] and Medication Compliance Questionnaire (MCQ).[24]

Most of the Questionnaires mentioned required license for usage and not available in languages commonly used in Malaysia. The MCQ is available in Malay, English, Chinese and Tamil languages and can be completed within 10 minutes. Therefore, it was chosen as a tool in assessing adherence in this study.

The MCQ serves as a tool to assess adherence from the viewpoint of the patients. MCQ was originally developed and validated with hypertensive patients at the Family Medicine Clinic, Hospital Universiti Sains Malaysia, Kelantan. This questionnaire employs a five-level Likert scale comprising ten items focusing on drug-taking and drug-stopping behaviours.[24] Additionally, the MCQ has been utilized to evaluate adherence among patients with ischaemic heart disease[25] and cancer[26] in Malaysia.

In 2003, the World Health Organization (WHO) outlined adherence to long-term therapies as a behaviour influenced by five dimensions of obstacles. These dimensions include barriers associated with the healthcare team or system, the therapy itself, the patient's condition, the patient themselves, and socioeconomic factors.[2] Instances of therapy-related barriers encompass side effects and the complexity of drug regimens.[27] Condition-related barriers often involve the severity of symptoms, levels of disability (physical, psychological, social, and vocational), disease progression rate, severity, and access to effective treatments.[2] Patient-related barriers notably include forgetfulness, low self-efficacy, and misconceptions about diseases and medications.[27]

Many of these barriers fall within the assessment domains of drug-taking behaviour and drug-stopping behaviour in the MCQ. Barriers to adherence in ART are similarly multi-dimensional.[28] If healthcare providers restrict adherence assessments to only one or two barrier types, they risk overlooking other patient concerns that, while reported less frequently, can significantly impact adherence. Hence, the MCQ was selected as the tool for assessing adherence in this study. MCQ is an instrument with good validity and reliability.[24] However, the results may differ in other diseases and populations.[29] Therefore, the objective of this study is to modify and revalidate the MCQ to be used in adherence assessment of PLHIV.

MATERIALS AND METHODS

The Instrument

The MCQ is available in both Malay and English. It consists of ten items concerning drug-taking behaviour (Questions 1 to 7) and drug-stopping behaviour (Questions 8 to 10). A five-level Likert scale from 1 (never) to 5 (very frequent) is used. Internal consistency reliabilities (Cronbach's alpha) were 0.67 and 0.84, and test-retest single measure intraclass correlation coefficients were 0.78 and 0.93, respectively, for each domain.[30] Unfortunately, the content validity index was not included in the study. The MCQ can be completed in 10 minutes.

Modification of MCQ

To assess the adherence levels among participants, we established a common cut-off point of 80% using a five-level Likert scale, which was deemed appropriate for capturing varying degrees of adherence. The scale was defined as follows: 1 (never) corresponding to 20%, 2 (seldom) to 40%, 3 (sometimes) to 60%, 4 (frequent) to 80%, and 5 (very frequent) to 100%. This structure allows for a straightforward categorization of adherence levels.

To measure a more stringent cut-off point of 95%, we recognized the need for modifications to the instrument. Specifically, we employed a continuous measurement scale, which allows for finer distinction of adherence scoring. This involved converting the Likert scale responses into a 0–100-point scale, enabling a precise assessment of adherence percentages. For example, rather than being limited to discrete categories, participants' responses could now reflect a continuum of adherence levels. This approach facilitates a more accurate identification of adherence rates, particularly for those achieving close to the 95% threshold, thereby enhancing the instrument's sensitivity and specificity in evaluating adherence to HIV therapy. Through these modifications, we aimed to capture the full range of adherence behaviour, allowing for a comprehensive analysis of the relationship between adherence and treatment outcomes.

Pilot Study to Evaluate Validity and Reliability of MCQ Participants and Study Setting

The cross-sectional investigation took place at the Infectious Disease Clinic within Hospital Raja Perempuan Zainab II, a publicly funded tertiary hospital situated in the state of Kelantan, East Malaysia. To ensure adequate representation, an estimated target sample size of 60 People Living with HIV (PLHIV) was determined, factoring in a 20% anticipated drop-out rate, based on an item-to-subject ratio of 1:5.[31] Inclusion criteria comprised individuals diagnosed with HIV infection, receiving antiretroviral therapy for a minimum of two months, aged 18 years or older, and proficient in communicating in the Malay language.

Patients were contacted by the investigator during their routine follow-up appointments at the Infectious Disease Clinic using convenience sampling. They were briefed about the aim of the study, procedures and invited to sign a written informed consent form upon agreeing to participate. To maintain privacy and focus, participants completed the modified MCQ in a counselling room. The investigator gathered demographic and clinical information of the participants. The medical records were reviewed for viral load and CD4 counts, and demographic and clinical information were collected on the same day by the investigators (Figure 1).

The modified MCQ (as shown in Figure 2) was given twice to assess the test-retest reliability, with a two-week interval between the initial and subsequent sessions to minimize recall bias. This duration was considered adequate to prevent alterations that might influence responses, yet not too brief as to facilitate recollection of previous answers.[32]

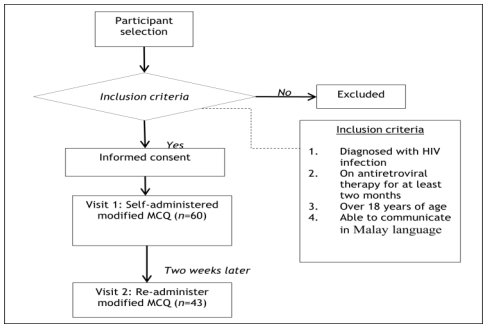


Figure 1: Flow chart of the modified MCQ validation study

Statistical Analysis

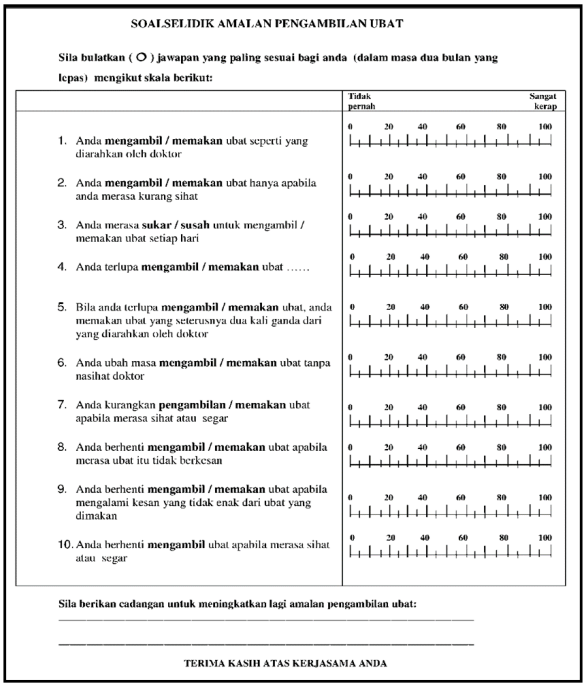
Descriptive statistics were utilized to depict the demographic and disease characteristics of the participants alongside their medication adherence scores. For continuous variables, means and standard deviations (SD) were computed, while categorical variables were expressed as frequencies (n) and percentages. Validity was assessed by examining the association between compliance and subjects' viral load using Fisher's Exact test, with a significance level set at $p<0.05$. Sensitivity (true positive) and specificity (true negative) values of the adjusted MCQ were also determined. Sensitivity gauged the test's accuracy in identifying poor virologic control among non-adherent patients, while specificity assessed its accuracy in identifying good virologic control among adherent patients.[33]

Internal consistency was assessed by Cronbach's alpha to evaluate correlations between the items in the factor. A Cronbach's alpha of above 0.9 was considered excellent, while values above 0.7 and 0.6 were noted as good and acceptable, respectively.[34] Single measure ICC was used to assess test–retest reliability. The ICC measured the stability of the items or agreement between modified scores, with 0 to 0.2 being considered poor agreement, 0.3 to 0.4 as fair agreement, 0.5 to 0.6 as moderate agreement, 0.7 to 0.8 as strong agreement, and above 0.8 as almost perfect agreement.[35]

RESULTS

Descriptive statistics were employed to describe the demographic and disease characteristics of the subjects. Means and standard deviations (SD) were calculated for continuous variables, while frequencies (n) and percentages were used for categorical variables.

The association between compliance and subjects' viral load was determined using Fisher's Exact test. A significant *p*-value of 0.018 was obtained, indicating a meaningful relationship.



SOALSELIDIK AMALAN PENGAMBILAN UBAT

Sila bulatkan (○) jawapan yang paling sesuai bagi anda (dalam masa dua bulan yang lepas) mengikut skala berikut:

	Tidak pernah — Sangat kerap
1. Anda **mengambil / memakan** ubat seperti yang diarahkan oleh doktor	0 20 40 60 80 100
2. Anda **mengambil / memakan** ubat hanya apabila anda merasa kurang sihat	0 20 40 60 80 100
3. Anda merasa **sukar / susah** untuk mengambil / memakan ubat setiap hari	0 20 40 60 80 100
4. Anda terlupa **mengambil / memakan** ubat ……	0 20 40 60 80 100
5. Bila anda terlupa **mengambil / memakan** ubat, anda memakan ubat yang seterusnya dua kali ganda dari yang diarahkan oleh doktor	0 20 40 60 80 100
6. Anda ubah masa **mengambil / memakan** ubat tanpa nasihat doktor	0 20 40 60 80 100
7. Anda kurangkan **pengambilan / memakan** ubat apabila merasa sihat atau segar	0 20 40 60 80 100
8. Anda berhenti **mengambil / memakan** ubat apabila merasa ubat itu tidak berkesan	0 20 40 60 80 100
9. Anda berhenti **mengambil / memakan** ubat apabila mengalami kesan yang tidak enak dari ubat yang dimakan	0 20 40 60 80 100
10. Anda berhenti **mengambil** ubat apabila merasa sihat atau segar	0 20 40 60 80 100

Sila berikan cadangan untuk meningkatkan lagi amalan pengambilan ubat:

TERIMA KASIH ATAS KERJASAMA ANDA

Figure 2: The modified MCQ

The sensitivity and specificity values of the modified MCQ were generated. The sensitivity was found to be 100.0%, indicating the instrument's ability to predict poor virologic control correctly in non-adherent patients. The specificity was determined to be 79.5%, reflecting the instrument's ability to correctly predict good virologic control in adherent patients. Internal consistency was assessed using Cronbach's alpha. Coefficients of 0.65 for the drug-taking behaviour domain and 0.90 for the drug-stopping behaviour domain were obtained. Correlations of corrected item-total ranged from 0.46 to 0.85 for the drug-taking behaviour domain and from 0.70 to 0.89 for the drug-stopping behaviour domain.

Test-retest reliability was assessed using single measure intra-class correlation coefficients (ICCs). Values of 0.87 for the drug-taking behaviour domain and 0.95 for the drug-stopping behaviour domain were observed, indicating strong to almost perfect agreement.

Overall, the modified MCQ was shown to be a valid and reliable instrument for assessing adherence to ART, with high sensitivity and adequate specificity. Therefore, it is deemed suitable for use in clinical practice to enhance medication therapy management for PLHIV.

Demographic and clinical characteristic of the participants in the pilot study

A total of 60 PLHIV participants took part in the pilot study. Majority were Malays with the mean age of 37.0 years and almost equal numbers of males and females. Majority of the patients (n=56, 93.0%) were adherent to highly active antiretroviral therapy (HAART) with a mean score of 99.3. The mean CD4 count was 278.0 cell/mm^3 with a range of 2 to 796 cell/mm^3. The mean viral load was 18,007.7 copies/ml and 28.3% (n=17) participants had an undetectable viral load (Table I).

Table I: The demographic and clinical characteristic of the participants in the pilot study (n=60)

Characteristics	n	%	Mean	SD
Age (years)			37.0	6.7
Gender				
Male	31	51.7		
Female	29	48.3		
Ethnicity				
Malay	59	98.3		
Chinese	1	1.7		
Modified MCQ score			99.3	1.9
Adherent	56	93.0		
Non-adherent	4	7.0		
Liver function				
ALP (IU/L)			122.9	80.4
AST (IU/L)			39.8	31.5
ALT (IU/L)			37.5	37.5
Renal function				
Creatinine clearance (ml/min)			78.3	21.8
CD4 count (cell/mm^3)			278.0	174.2
Viral load (copies/ml)			18,007.7	61,741.7
0* to 50	27	62.8		
51 to 400	4	9.3		
401 to 2,000	2	4.7		
More than 2,000	10	23.26		

*0 means undetectable with limit of detection of 20 copies/ml
(17 participants had undetectable viral)

Validity testing of the modified instrument

Virological outcome or viral load was used as the criterion for validity analysis. In this investigation, a participant was categorized as non-adherent if their most recent viral load (obtained during the pilot study's three-month timeframe) exceeded 400 copies/mL.[36] Out of the 60 patients, only 43 (71.7%) underwent viral load testing within this timeframe. Using Fisher's exact test, there was a significant association between the adherence and viral load (p=0.018) (Table II).

Table II: Association between adherence measured by the modified MCQ and virological outcome (viral load) (n=60)

Adherence	Viral load (copies/mL) n (%)		Total (n)	p-value
	400 or less	More than 400		
Adherent	31 (100.0)	8 (66.7)	4	**0.018**
Non-adherent	0 (0.0)	4 (33.3)	39	
Total (n)	31	12	43	

Fisher's exact test
Viral load of 400 or less indicated good control
Viral load of more than 400 indicated poor control

Sensitivity and specificity analysis of the modified Instrument

From the analysis, the findings indicated sensitivity (true positive) and specificity (true negative) values of 100.0% and 79.5%, respectively, for the modified MCQ (Table III).

Table III: The sensitivity and specificity of the modified MCQ

Viral load (copies/mL)	Adherent (%)	Non-adherent (%)
400 or less	79.5	0
More than 400	20.5	100
Sensitivity & specificity	Sensitivity 100%	Specificity 79.5%

Reliability analysis of the modified instrument

Internal consistency

The modified MCQ demonstrated varying levels of internal consistency across its domains. The Cronbach's alpha for the Drug Taking Behaviour domain (Questions 1 to 7) was 0.65, while the Drug Stopping Behaviour domain (Questions 8 to 10) showed a high Cronbach's alpha of 0.90. Notably, if Question 3 were removed, the Cronbach's alpha for the Drug Taking Behaviour domain would increase to 0.82. However, Question 3 was retained in the final version of the MCQ due to its significant contribution to the construct.

The corrected item-total correlations ranged from 0.46 to 0.85 for the Drug Taking Behaviour domain and from 0.70 to 0.89 for the Drug Stopping Behaviour domain (see Table IV). These correlations indicate how well each question aligns with the overall domain score, with higher values (generally above 0.3) suggesting meaningful contributions to the construct being measured.

For the Drug Taking Behaviour domain, Questions 1 and 2 both exhibited high mean scores (99.7) and low standard deviations (1.81), along with strong corrected item-total correlations of 0.85. Removing these questions would decrease the overall alpha to 0.59, highlighting their positive contribution to the reliability of the instrument. Question 3 had the highest corrected item-total correlation at 0.91, and its removal would lower the alpha to 0.82, underscoring its importance. Questions 4 and 5 demonstrated moderate correlations and would not significantly impact overall reliability if deleted, while Questions 6 and 7 showed strong correlations (0.80 and 0.81), positively contributing to the domain's reliability.

In the Drug Stopping Behaviour domain, Question 8 had a high mean score (99.7) and low variability (SD=1.81) but a lower corrected item-total correlation of 0.70. Removing it would result in a Cronbach's alpha of 1.00, suggesting it may not fit well with the other items. Conversely, Questions 9 and 10 exhibited high mean scores and strong corrected item-total correlations (0.89), indicating their critical role in maintaining the reliability of the scale; their removal would decrease the alpha to 0.80.

Overall, this analysis illustrates the reliability of each question within the domains related to drug adherence. It highlights which questions contribute positively to the overall construct and identifies items that may require further consideration for refinement or removal to enhance the overall reliability of the questionnaire.

Table IV: Cronbach's alpha value of each question in each domain

Domain	Mean	SD	Corrected item-total correlation	Cronbach's alpha if item deleted
Drug taking behaviour				
Question 1	99.7	1.81	0.85	0.59
Question 2	99.7	1.81	0.85	0.59
Question 3	96.3	12.94	0.91	0.82
Question 4	98.9	3.07	0.46	0.61
Question 5	99.7	1.81	0.72	0.60
Question 6	99.8	1.29	0.80	0.62
Question 7	99.9	0.65	0.81	0.64
Drug stopping behaviour				
Question 8	99.7	1.81	0.70	1.00
Question 9	99.8	1.30	0.89	0.80
Question 10	99.8	1.30	0.89	0.80

Test-retest reliability

Although all participants agreed for a two-week test-retest reliability analysis, only 43 of them turned-out to complete the MCQ questionnaire. The ICC value for drug taking behaviour domain was 0.87 (0.78, 0.93) with *p*-value <0.001. The ICC value for drug stopping behaviour was 0.95 (0.95, 0.99) with *p*-value <0.001. The ICC of 0.87 for drug taking behaviour indicates a strong reliability, meaning that the modified MCQ consistently measures the drug-taking behaviour of PLHIV over time. The narrow confidence interval (0.78, 0.93) supports the precision of this reliability estimate.

The ICC of 0.95 for drug stopping behaviour indicates an excellent reliability, suggesting that the modified MCQ is very consistent in measuring the drug-stopping behaviour of PLHIV. The extremely narrow confidence interval (0.95, 0.99) further confirms the precision and robustness of this estimate. Overall, the high ICC values and their statistical significance demonstrate that the modified MCQ is a reliable instrument for assessing medication adherence behaviours in both domains.

DISCUSSION AND CONCLUSION

Modification of the Instrument

The initial MCQ employed a Likert scale to evaluate adherence among hypertensive patients. A Likert scale consists of a sequence of discrete terms or statements, allowing patients to select the response that best matches their state or experience. The original MCQ utilized a five-level Likert scale, spanning from 1 to 5, with 'never' at one end and 'very frequent' at the other. Scores formulated with negative wording were reversed, and all scores were transformed to a 0 to 100% scale with intervals of 20%. This standardized scale effectively gauged adherence in hypertensive patients, where achieving a minimum total score of 80% signified consistent compliance with 'frequent' and 'very frequent' adherence across all questionnaire items.[30]

However, in the context of HIV infection, a 95% adherence rate is widely cited as essential to keep HIV load inhibition below 400 copies/mL.[19] Therefore, the original MCQ's five-level Likert scale was modified to assess a 95% adherence score in HIV patients. Negatively worded scores were reversed, and all scores were converted to a 0 to 100% scale.

In this study, the scale was modified to a continuous rating scale ranging from 0 (very unlikely) to 100 (very likely). This continuous numerical scale allowed patients to choose the value that best described their state or experience. The ends of the scale were anchored with descriptive words, such as 'very unlikely' or 'very likely'.[37] For content validation, the modified scale was reviewed and deemed appropriate by the original MCQ author. The new rating scale allowed PLHIV to place a mark at the appropriate position on a line that runs from 0 to 100, offering more options and potentially more accurate responses.[38] Since the modification only involved

the scale and scoring method, the validation was also applicable to the English version.

In this study, a high adherence rate (93%) to HAART was observed using the modified MCQ. The result was comparable to the reported adherence rates among PLHIV in Uganda (88-93%).[39] However, recent studies in Ethiopia revealed high rates of poor adherence, such as 71.8% in North-Eastern Ethiopia[40] and 66.3% in Eastern Ethiopia.[41] The adherence rate in this study was slightly higher than those in Thailand (82-85%)[42] but higher than the 68% reported in Asia by the TREAT Asia Studies to Evaluate Resistance Monitoring.[43]

According to the Malaysian guidelines for managing adult HIV infection with antiretroviral therapy,[44] patients start with vitamins to evaluate adherence behaviour before initiating HAART. Medication counselling and education were provided by trained pharmacists in the Medication Therapy Adherence Clinic for Retroviral Disease program, which consists of pre-HAART, initiating HAART, and follow-up HAART counselling.[45] Regular educational sessions and on-site counselling at clinics probably contributed to the remarkable adherence rate observed in this study.

Validation Testing and Reliability Analysis of the Modified Instrument

The link between adherence and HAART effectiveness was determined for criterion validity of the modified MCQ. The criterion used for this analysis was the virological outcome, which has been previously established in other adherence studies. [46,47] Adherence was defined as achieving a score of at least 95% on the modified MCQ, while effectiveness was defined as a viral load of fewer than 400 copies/ml within a three-month assessment period.

Criterion validity was assessed in a sample of 43 participants (71.7%) who had available viral load reports. Our findings demonstrated a positive association between adherence, as measured by the modified MCQ, and virological outcomes. Specifically, 100% of adherent patients achieved good virological outcomes, while none of the non-adherent patients did. This significant correlation reinforces the validity of the modified MCQ and aligns with previous research.[13,47]

Sensitivity and specificity of the modified MCQ were evaluated. Sensitivity was defined as the ability to accurately predict poor virological outcomes in non-adherent patients, and specificity as the ability to accurately predict good virological outcomes in adherent patients.[33] The sensitivity of the modified MCQ was 100%, and the specificity was 79.5%, indicating it was a sensitive and specific instrument for assessing adherence to ART.[48]

Reliability was assessed by internal consistency and test-retest analysis. Internal consistency, measured using Cronbach's alpha, showed coefficients of 0.65 for drug-taking behaviour and 0.90 for drug-stopping behaviour domains, consistent with the original MCQ.[30] High Cronbach's alpha values indicate good internal consistency, although values above 0.9 may suggest item redundancy.[50]

Test-retest reliability was assessed using single measure ICC, which was 0.87 and 0.95 for each domain, indicating excellent stability and reliability of the modified MCQ. These results were better than those reported by[30], demonstrating the modified MCQ's stability in the PLHIV population.

STUDY LIMITATIONS

This study had a few limitations. Firstly, most respondents were Malays, not representing the heterogeneous communities of Malaysia. Secondly, recall bias might have occurred during test-retest reliability assessment. If the time interval between test administrations was short, respondents might remember their previous responses, leading to artificially inflated correlations.

The modified MCQ was demonstrated to be a valid and reliable instrument for assessing adherence to ART in PLHIV. With its high sensitivity and adequate specificity, it proves to be an effective tool for clinical practice. Its implementation can significantly enhance medication

therapy management for PLHIV, contributing to better virological outcomes and overall health management.

We recommend further refining of the MCQ and conducting factor analysis could provide insights into the underlying structure of the instrument. This analysis may help identify any redundant items and enhance the overall validity and reliability of the questionnaire.

CONFLICT OF INTEREST

The authors declare that no conflict of interest may arise from the research publication.

ETHICS APPROVAL

Registration for this study was completed through the National Medical Research Register (NMRR)and ethically approved by the Malaysia Ministry of Health Research Ethical Committee (MREC) with the NMRR identification number NMRR-12-335-11995. Signed, written informed consent was acquired from all patients before the study.

ACKNOWLEDGMENT

The authors would like to thank the Director General of Health Malaysia for his permission to publish this paper. This work was financially supported by Universiti Sains Malaysia RU Grant (grant no. 1001/PSK/8620015).

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CASE REPORT

Navigating the Diagnostic Maze of Psoriatic Arthritis sine Psoriasis in Primary Care.

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Keywords
back pain, Spondyloarthritis, Psoriatic, Arthritis

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Received: 8th August 2024; Accepted: 26th December 2024

Doi: https://doi.org/10.31436/imjm.v24i02/2693

ABSTRACT

Psoriatic arthritis, a seronegative spondyloarthropathy is an autoimmune inflammatory joint disease. However, the diagnosis is often delayed due to the absence of specific biomarkers and a lack of awareness among primary care providers, who may be unable to recognize the key features of the condition. We present a case of a 30-year-old woman with a 9-month history of lower back pain and multiple joint pain. Despite elevated inflammatory markers like C-reactive protein and erythrocyte sedimentation rate, other initial tests including rheumatoid factor and antinuclear antibody tests were all negative. The appearance of new skin lesions in the 10th month prompted further evaluation and resulted in a diagnosis of psoriatic arthritis. Treatment with Celecoxib and Methotrexate led to significant improvement in her condition. This case underscores the crucial role of primary care providers in the early detection and management of spondyloarthropathy, helping to prevent joint damage and enhance patient outcomes.

INTRODUCTION

Seronegative spondyloarthropathies (SpA) are a group of autoimmune, inflammatory arthritis conditions that include psoriatic arthritis (PsA), ankylosing spondylitis (AS), juvenile-onset SpA, enteropathic arthritis, and reactive arthritis. Common clinical features in SpA include asymmetrical peripheral arthritis, inflammatory back pain, dactylitis, enthesitis, and extra-articular manifestations. These conditions are characterized by a negative rheumatoid factor (RF) and pose significant challenges in early diagnosis. A delay in diagnosis of SpA with an average delay of 5 to 7 years, or even longer in women, can lead to structural joint damage.[1] Even a 6-month delay in diagnosis can increase the risk of joint erosion and negatively impact patient outcomes.[2] Early recognition and detection by primary care providers is crucial to mitigate the risk of joint erosion and improve long-term outcomes.

CASE REPORT

A 30-year-old woman presented with a 9-month history of intermittent lower back and joint pain. The lower back pain was characterized by an achy, stiff sensation, typically lasting for 30 minutes to an hour. The pain worsened with rest and improved with movement, frequently disrupting her sleep with severe pain, rated 8/10, which caused her to wake up in agony during the night. Despite multiple medical consultations, her symptoms persisted. Initial investigations, including anti-nuclear antibody (ANA), rheumatoid factor (RF) and radiographic yielded normal results. She was initially diagnosed with musculoskeletal pain and prescribed analgesics for symptom management.

As her symptoms worsened, the patient developed pain in both her heels, her right wrist, and the small joints in her right hand, which significantly impacted her daily activities and work performances, resulting in frequent medical leaves. Despite attempting various supplements and over-the-counter analgesics, her symptoms persisted. Throughout her illness, she denied experiencing any depressive episodes. After nine months of unresolved pain, she sought a second opinion at a tertiary hospital's primary care clinic.

On examination, onycholysis was noted on her right thumb (Figure 1), but there were no signs of nail pitting, transverse ridging, or tenderness and swelling in her hands. There was mild tenderness and fusiform swelling over the right fourth toe, consistent with dactylitis (Figure 2), along with mild swelling of the right heel, suggesting enthesitis. Otherwise, there were no visible skin lesions, unremarkable neurological and motor examinations and her spine examination revealed a full range of motion without deformity; Schober's test was negative and the sacroiliac joint was non-tender.

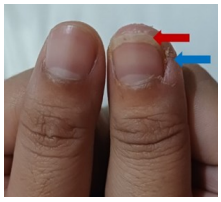

Figure 1: Onycholysis (red arrow) of right thumbnail with periungual involvement (blue arrow).

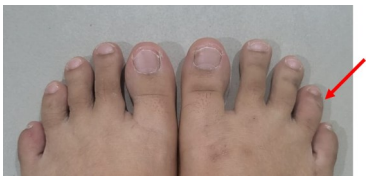

Figure 2: The presence of tender and fusiform swelling over the right 4th toe (dactylitis) with post-inflammatory hyperpigmentation.

Re-evaluation revealed elevated inflammatory markers, with CRP level of 36 mg/L and an ESR of 38 mm/hour, alongside negative RF, ANA and anti-cyclic citrullinated peptide (anti-CCP) tests. A pelvic x-ray showed irregularities and sclerosis in both iliac bones with a normal sacroiliac joint (Figure 3). Based on these findings, she was diagnosed with inflammatory back pain (IBP) with suspected diagnosis of seronegative rheumatoid arthritis, and referred to rheumatology for further evaluation.

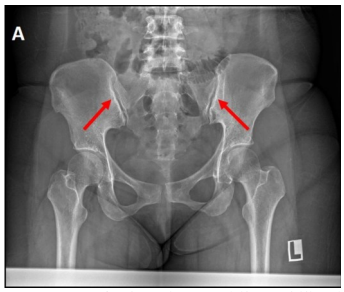

Figure 3: Presence of sclerosis over bilateral iliac bone and irregularities with normal sacroiliac joints

One month later, during the rheumatology assessment, new scaly skin lesions appeared on her scalp, elbow, knee and foot. She had no prior history of such lesions or family history of psoriasis. A dermatology referral confirmed the presence of plaque psoriasis affecting 1-2% of her body surface area, including the previously mentioned areas as well as the intergluteal cleft and bilateral postauricular regions (Figure 4). She was treated with topical corticosteroids and coal tar shampoo. Her human leukocyte antigen B27 (HLA-B27) testing was negative and magnetic resonance imaging (MRI) of the sacroiliac joints revealed bilateral iliac bone fat metaplasia, indicative of post-inflammatory changes consistent with axial spondyloarthritis (SpA).

The patient met the Classification Criteria for Psoriatic Arthritis (CASPAR) and was diagnosed with Psoriatic Arthritis (PsA). Due to persistent disease activity, she was initiated on a treatment regimen consisting of Celecoxib 200 mg twice daily, Methotrexate 15 mg once a week, and Folate 5 mg daily (excluding the day of methotrexate administration). Follow-up assessments revealed normalized ESR and CRP levels, significant pain relief, and clinical remission achievement which enable her to resume normal daily activities.

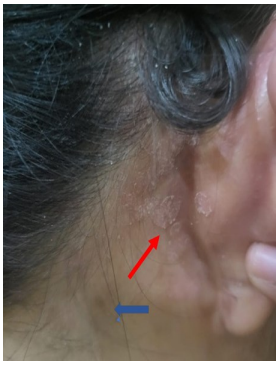

Figure 4: Post-inflammatory hyperpigmentation (blue arrow) with thin, mild psoriatic plaque with scaling (red arrow) were detected on her scalp and right posterior auricular.

DISCUSSION

Differentiating between inflammatory and mechanical low back pain is crucial as their treatments differ significantly. This patient's primary presentation was inflammatory back pain (IBP), a hallmark feature of axial SpA, which typically manifests before the age of 40. She met all five Assessment of Spondyloarthritis International Society (ASAS) criteria of IBP: age of onset less than 40 years old, insidious onset, nocturnal pain, lack of improvement with rest and improvement occurs with movement.

In this case, psoriasis developed 10 months after the onset of arthritis, illustrating the phenomenon of PsA sine psoriasis, which affects 13.5-24.6% of PsA cases globally.[3]

The prevalence of PsA sine psoriasis in Malaysia remains underreported. Typically, psoriasis appears 7–12 years prior to arthritis.[4] Thus, the delayed skin manifestation in this patient poses significant diagnostic and treatment challenges to the primary care. However, PsA can still be diagnosed in the absence of visible psoriasis using the CASPAR criteria, which offer high specificity (98.7%) and sensitivity (91.4%).[3]

PsA comprises of six key domains which include enthesitis, dactylitis, axial, nail, skin, and peripheral arthritis. Nail psoriasis, dactylitis, enthesitis, and distal interphalangeal (DIP) involvement are the key features that differentiate the diagnosis of PsA sine psoriasis from rheumatoid arthritis (RA) and other forms of SpA. While PsA typically begins asymmetrically and oligoarticularly, it may progress to a symmetric pattern resembling RA. Notably, PsA often affects the DIP joints, whereas RA predominantly involves the wrists and small hand joints symmetrically, sparing the DIP joints.[5]

Early detection of skin or nail lesions is crucial for diagnosing PsA. While psoriasis on the trunk or limbs is easily noticeable, lesions in areas such as the scalp, intergluteal region, umbilicus, elbows, knees and nails are often overlooked, as illustrated in this case.[6] Nail involvement is present in 40% of psoriasis patients but affects up to 80% of those with PsA, with fingernails being more commonly being affected than toenails.[7] Key signs of nail involvement include pitting, onycholysis and transverse ridging.

Enthesitis and dactylitis are common in PsA, affecting 30-50% and 40-50% of patients, respectively. Enthesitis typically involves the plantar fascia and Achilles' tendon, while dactylitis, is often typically seen in the feet, is associated with more severe disease.[5,6,8] Therefore, a comprehensive lower limb examination is essential to identify these key features in PsA.

Axial involvement occurs in 25-70% of PsA, predominantly affecting the spine and sacroiliac joints. Compared to AS, axial PsA generally presents with milder symptoms and radiographic findings. HLA-B27, a genetic marker for AS, has a low association with axial PsA, with positivity rate of 14-40% in PsA versus over 80% in AS.[9] While HLA-B27 testing is helpful, a positive result does not confirm axial SpA and a negative test does not exclude it.[1] Elevated ESR and CRP levels are common but not always present. For suspected axial involvement, an anterior-posterior pelvic x-ray should be performed and evaluated using the modified New York criteria. However, relying on plain x-ray alone may delay diagnosis by up to 10 years due to the late radiographic changes.[1] Therefore, MRI is preferred for early detection of active inflammatory changes such as subchondral bone edema, synovitis and capsulitis, as well as chronic lesions like fat metaplasia, sclerosis, erosions, joint space narrowing, syndesmophytes and ankylosis.[1,10]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment for axial PsA. In this case, the patient also had other PsA manifestations, including dactylitis, enthesitis, peripheral arthritis, and skin and nail involvement. Thus, she was started on methotrexate, a conventional Disease Modifying Anti-Rheumatic Drug (DMARD), which led to clinical improvement and remission. Although biologic DMARDs are recommended for treating axial PsA, they were not used in this case due to the absence of active sacroiliitis and the patient's positive response to methotrexate and NSAIDs.[9]

Primary care providers should be more vigilant in recognizing IBP and clinical features of PsA. This case highlights the diagnostic complexity of PsA and the importance of thorough history-taking, clinical examination, laboratory test and MRI to distinguish PsA from other forms of SpA.

CONCLUSION

Early detection of PsA in the absence of skin lesions is challenging and often leads to misdiagnosis. The ASAS IBP and CASPAR criteria can help primary care providers in identifying inflammatory back pain and diagnosis of PsA earlier. An early referral to rheumatologist and timely treatment can prevent joint damage and improve quality of life. Therefore, it is essential for primary care providers to be familiar with the clinical features of PsA to ensure early recognition and intervention.

CONFLICT OF INTEREST

The authors have no conflict of interest.

ACKNOWLEDGEMENT

The authors appreciate the cooperation of the patient in providing her consent for the case to be used for learning and publication purposes. Thanks to Hospital Raja Perempuan Zainab II (HRPZ II) for their contribution to the management of this patient

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CASE REPORT

From Weight Loss to Bedroom Gains: A Case Report on Bariatric Surgery Resolving Erectile Dysfunction

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Keywords
Erectile Dysfunction (ED), Obesity, marital satisfaction , Anxiety

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Received: 20th June 2024; Accepted: 19th February 2025

Doi: https://doi.org/10.31436/imjm.v24i02/2647

ABSTRACT

This case involves a 59-year-old Malay man who struggled with erectile dysfunction (ED) due to his poorly controlled underlying health conditions for about two years. Despite long-term management for diabetes, hypertension, and dyslipidemia, his weight gain and worsening sugar control affected his ability to maintain an erection during sexual activity. He tried various medications and treatments, including traditional remedies and oral drugs like Kamagra, with little success. Eventually, he underwent bariatric surgery, which led to improvements in his ED, along with better control of other health issues. Psychological factors, like stress and desperation, also played a significant role in his journey, highlighting the importance of holistic care and proper management of both physical and mental health in addressing er ED ectile dysfunction. This case underscores the potential benefits of bariatric surgery in obese patients with ED and emphasizes the need for comprehensive healthcare approaches to manage these complex issues effectively.

INTRODUCTION

Erectile dysfunction (ED) is a condition that extends beyond its impact on the physical health of men, influencing various aspects of their lives and relationships. Beyond its physiological effects, ED can cause emotional distress, erode self-esteem, and strain intimate relationships. ED often serves as a barometer for overall health, reflecting underlying conditions such as cardiovascular disease, obesity, or psychological factors like stress and anxiety. Consequently, addressing ED requires a holistic approach, encompassing medical intervention, lifestyle changes, and open communication between partners. By acknowledging the broader implications of ED, we can foster a more supportive and understanding environment.

In Malaysia, ED is a very common, though frequently taboo, problem among men. The most recent National Health and Morbidity Survey (NHMS) in Malaysia showed that there is a prevalence of moderate to ED in up to 31.6% of the population.[1] Despite its widespread occurrence, cultural taboos and stigma surrounding discussions of sexual health can hinder individuals from seeking help or openly addressing their concerns. However, recognizing ED as a medical condition rather than a personal failure is crucial in promoting awareness and encouraging men to seek professional assistance.

Malaysia is also grappling with the growing issue of obesity. In the World Health Organization (WHO) report of 2019, Malaysia ranked highest among Asian nations, with over 64% of the male population being overweight or obese.[2] Based on the NHMS 2015, the rate of obesity in individuals aged 18 and above was over 17.7% (equivalent to 3.3 million people), while the rate of overweight patients was 30% (equivalent to 5.6 million people). [3] Currently, bariatric surgery is the only effective option for attaining sustained weight loss in persons with obesity. Over the past decade, there has been a notable increase in the number of individuals choosing bariatric surgery and reaping numerous benefits.[4]

Male sexual dysfunction refers to a range of health issues, specifically including a decrease in sexual desire (libido), difficulty achieving or maintaining an erection, or problems with ejaculation. ED is the most prevailing problem associated with obesity in male patients. In contrast, hypertension, dyslipidemia,

obesity, and diabetes mellitus, which are components of the metabolic syndrome, are reversible risk factors for ED. After bariatric surgery, a complicated mechanism reduces the metabolic risk factors, which lead to a more marked resolution of erectile function. However, given the complexity of ED's origins, treating the problem will require a multidisciplinary approach.

A study involving male obese patients showed that erectile ED was common before bariatric surgery[5], with significant improvement post-surgery. Another study found that bariatric surgery is more effective than non-surgical weight loss in improving erectile performance and hormone levels in morbidly obese men.[6] However, this case discussed here represents the delicate management of a patient who faced difficulties in encountering an ED during the initial treatment.

CASE REPORT

This is a case of a 59-year-old Malay gentleman who has had a longstanding ED since his underlying comorbidities became uncontrolled in the past two years. He is a non-smoker and does not take any alcohol. He has been under primary care follow-up for diabetes mellitus, hypertension, and dyslipidemia for almost 10 years, but noticed his problem with erection when his weight increased above 85 kg and worsening of blood sugar control. He struggled to gain an erection and penetration during attempted sexual intercourse with his wife. His libido was normal, and he claimed to have a normal morning erection. His International Index of Erectile Function (IIEF-5) was 5. Psychologically, he was less satisfied, leading to less motivation and anxiousness upon attempting intercourse. He was married to a 47-year-old lady for 20 years. His wife's libido is normal, and her sexual satisfaction was not up to expectations. Thus, the pressure and tension led to high expenditure in various clinics and private hospitals for medication and treatment for the erectile problem.

His visits to the general practitioner started around two years ago. He was initially using traditional supplements such as *Tongkat Ali*, with no positive results. He was then prescribed oral Kamagra but stopped the usage after two pills. He claimed to have an erection but was unable to achieve ejaculation even after 30 minutes and started to feel mild chest discomfort after the intake of the traditional drug. He attempted a few more medications such as oral Sildenafil and Tadalafil subsequently, but his ED did not improve. He also took a course of platelet-rich plasma intra-cavernosal injection without success. One of the GPs eventually referred him to a private center in Kuala Lumpur for bariatric surgery. He underwent bariatric surgery in January 2023. He was then referred to a teaching hospital men's health clinic for further ED management. He had spent up to RM 30,000 of his earnings.

Clinically, the patient looked well without exhibiting distress or low mood upon encounter. He was well-hydrated, well-kept, and able to express his worry clearly. He was of a good build, is not obese, and had no pallor or jaundice. His hair distribution is appropriate. Upon examination his genital organ was grossly normal, and his testicular size was average at 20 ml bilaterally. He exhibited no sign of hypogonadism.

After the bariatric surgery, the IIEF-5 score improved from 5 to 8 (Table I). The laboratory blood parameters showed improvement in the underlying comorbidities (Table II). The blood sugar control improved with an HbA1c of 5.7% and a low-density lipoprotein level of 2.7 mmol/L. Throughout the men's health clinic follow-up his renal and liver functions were normal. His serum testosterone level was normal at 18.72 mmol/L.

He was re-started on oral Sildenafil 100 mg on a per-needed basis upon the encounter, with counseling on the correct way to take the medication. With mild improvement in erectile function, he was keen to change to oral Tadalafil due to previous experience, and it was easier to consume. He tolerated Tadalafil, and his IIEF-5 score improved to 15 (Table I). His Erection Hardness Score improved from 2 to 3. He gradually tapered down his medication and eventually maintained his erection for up to 20 minutes without the help of any PDE-5 inhibitor.

Table I: IIEF-5 score for the patient through the follow-up

Over the past four weeks,						
1	How do you rate your confidence that you could get and keep an erection?	Very low 1[1]	Low 2[2]	Moderate 3[3]	High 4	Very high 5
2	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/ never 1[1]	A few times 2[2]	Sometimes 3[3]	Most of the times 4	Almost always/ always 5
3	During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?	Almost never/ never 1[1]	A few times 2[2]	Sometimes 3[3]	Most of the times 4	Almost always/ always 5
4	During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult 1[1,2]	Very difficult 2	Difficult 3[3]	Slightly difficult 4	Not diffficult
5	When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/ never 1[1,2]	A few times 2	Sometimes 3[3]	Most of the times 4	Almost always/ always 5

[1] Score during pre-bariatric surgery encounter
[2] Score during post-bariatric surgery encounter, before PDE-5 inhibitor treatment
[3] Score during post-bariatric surgery encounter, after PDE-5 inhibitor treatment

Table II: IIEF-5 score for the patient through the follow-up

	Pre bariatric surgery (January 2023)	**Post bariatric surgery (May 2023)**
Weight (kg)	90.7	70.1
BMI (kg/m^2)	31.0	23.9
HbA1c (%)	7.0	5.7
LDL (mmol/L)	3.2	2.7
Triglycerides (mmol/L)	1.51	1.2
Serum Testosterone (ng/dL)	-	18.73

DISCUSSION

Erectile dysfunction and obesity are two prevalent health concerns affecting millions worldwide. ED refers to the consistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance.[7] It is persistently an underreported issue despite its high prevalence and negative impact psychologically and financially, as well as the availability of numerous successful treatments. The stigma of discussing ED as a problem remains a central issue, and the appropriate way to tackle this is to prepare healthcare providers with ample knowledge and communication skills to approach them. Effective screening of men's health problems during regular non-communicable disease follow-ups or outpatient clinic visits is vital in tackling these issues.

In our case, the patient did not reveal his concern about his sexual problem during his regular follow-up. Instead, he went to alternative clinics to seek opinions and treatment.

Obesity is characterized by excess body fat accumulation, often leading to various metabolic complications. There is significant association between obesity and ED, with obese men found to experience a 50% higher incidence of ED.[8] Obesity also contributes to the development of cardiovascular diseases and type 2 diabetes, which are known risk factors for ED. Currently, the only mainstay of treatment for obesity with complications is bariatric surgery.

Understanding the interplay between obesity and ED is crucial for healthcare professionals in managing these conditions effectively. Addressing obesity through lifestyle modifications or surgical interventions like bariatric surgery may improve overall health and alleviate ED, ultimately enhancing the quality of life for affected individuals. Systematic reviews have mentioned that despite the significant benefit of bariatric surgery on ED, multifactorial causes need to be considered and managed altogether.[9]

Psychological factors play a significant role in both ED and obesity. Factors such as stress, anxiety, sadness, and low feelings of self-worth might contribute to the development or worsening of the condition.[10] They may interfere with sexual arousal, performance, and satisfaction, resulting in challenges in attaining or sustaining an erection. In our patient, the pressure and desperation led to an unhealthy search for a proper treatment. Over-spending and trials of the possibly harmful, yet-to-be-approved methods may bring more damage to patients.

It is essential to review the general health condition of each ED patient, despite reviews and case reports supporting the importance of weight loss through bariatric surgery in improving the outcome. A healthy lifestyle, keeping the co-existing comorbidities under control, healthy aging, and proper sexual health education are crucial to ensure ED is managed accordingly.[1] Our patient

was followed up thoroughly for his diabetes problem, hypertension, and dyslipidemia. He managed to maintain his weight, and he was assisted with a PDE-5 inhibitor initially to assist in his ED problem. With support from his spouse and maintenance of healthy lifestyle, he was eventually able to regain satisfaction in his sexual life.

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CASE REPORT

Peptoniphilus asaccharolyticus Septic Abortion Precipitating Cerebral Venous Thrombosis

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ABSTRACT

Peptoniphilus, a Gram-positive anaerobic coccus, is an opportunistic bacterium in the human microbiota. Obstetrics-associated *Peptoniphilus asaccharolyticus* infections are rarely reported, with only four reported cases, all patients recovered without complications. We describe a *P. asaccharolyticus* septic abortion at 8 weeks of gestation, complicated with cerebral venous thrombosis (CVT) and septic ileus. A 33 year-old Indonesian lady who is 8 weeks pregnant presented with sudden right-sided body weakness, with heavy vaginal bleeding and fever. She had attempted a self-induced abortion using over-the-counter medication prior to symptom onset. She was pale and septic. Besides evacuation of conception products, the patient was hospitalized for parenteral antibiotics therapy. Brain CT angiography revealed CVT. Anaerobic blood culture grew *P. asaccharolyticus,* identified via MALDI-TOF mass spectrometry. Her admission was complicated with septic ileus. Following eight days of antibiotics treatment, she requested a transfer to her hometown hospital for care continuation. *P. asaccharolyticus* is a disastrous organism to complicate septic abortions. Early clinical suspicion and prompt initiation of effective antibiotics are critical.

Keywords
Septic abortion, Peptoniphilus, cerebral venous thrombosis, MALDI-TOF

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Received: 24th March 2024; Accepted: 27th February 2025

Doi: https://doi.org/10.31436/imjm.v24i02/2571

INTRODUCTION

The Peptoniphilus genus is a Gram-positive obligate anaerobic coccus belonging to the family *Peptoniphilaceae.* Formerly classified under the genus Peptostreptococcus, it is now a separate genus consisting of 17 species. They are known as members of human gastrointestinal, genitourinary and skin microbiota. Increasing number of human infections caused by this opportunistic pathogen have been reported. Individuals with prosthetic joints or other foreign body introduction, the immunosuppressed and the elderly are at higher risk for infection. However, obstetric cases of Peptoniphilus spp. infections have been rarely reported, with only four cases documented globally. Notably, none of these cases involved septic abortion complicated by CVT. We present a case of *Peptoniphilus asaccharolyticus* septic abortion, complicated with cerebral venous thrombosis (CVT) and septic ileus.

CASE HISTORY

A 33 year old Indonesian lady was referred by a private hospital for symptomatic anaemia. Initially, she presented to the hospital complaining of sudden onset of right-sided body weakness and numbness. She had been having heavy vaginal bleeding for a week, worsening during the last two days. Additionally, she reported vomiting and abdominal pain for four days and two days of fever, chills and rigors. Upon discovering she was 8 weeks pregnant, she resorted to terminating pregnancy using over-the-counter unnamed medication, which she inserted intra-vaginally, one day prior to symptom onset. She denies facial asymmetry or drooling of saliva.

On examination, she appeared pale, lethargic, febrile with a temperature of 38°C and tachycardic of 110 beats per minute. She was normotensive with normal oxygen saturation under room air. Abdominal and cardiorespiratory examinations were unremarkable. Neurological examination revealed right-side facial palsy, and hypotonia, with a low muscle power scale of 0/5 over the right upper and lower limbs, compared to 5/5 on the contralateral side. A bedside abdominal ultrasound scan

revealed a thickened endometrial lining of 4.3cm, with neither adnexal mass nor pelvic free fluid.

Urgent full blood count revealed leucocytosis with a total white cell count of 20.67 x 10^3/μL and moderate anaemia with haemoglobin of 7.2 g/dL. The urine dipstick for the pregnancy test was positive. Platelet count, coagulation profile, and renal and liver function tests were unremarkable. Serum β-human chorionic gonadotropin (β-hCG) was elevated (4,999 mIU/mL).

Per vaginal examination revealed approximately 50 cc of the retained product of conception, which the attending doctor evacuated with sponge forceps. A post-evacuation transvaginal ultrasound showed a reduction in endometrial thickness to 2 cm. The patient was given intramuscular oxytoxin/ergometrin 500 μg/5 IU, a peripheral blood sample was aseptically collected and cultured, and the patient's antibiotic therapy was then commenced with intravenous (IV) ceftriaxone 2 gm daily and IV metronidazole 500 mg thrice daily. She was then admitted to the ward for a blood transfusion.

A computed tomography angiogram of the brain and carotids was performed and demonstrated cerebral venous thrombosis of the superior sagittal sinus and right sigmoid sinus, with acute venous infarct at the left frontal lobe (Figure 1). There was no evidence of aneurysm or arterio-venous malformation. She was started on subcutaneous enoxaparin 60 mg twice daily.

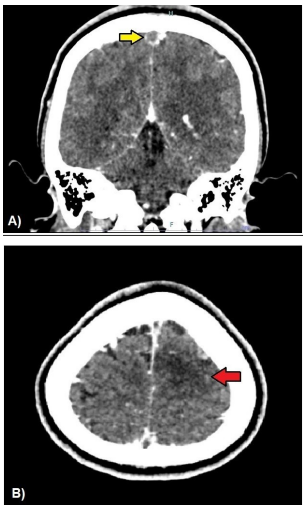

Figure 1 (A) and (B): Computed tomography angiogram of patient's brain. Note the filling defect over the superior sagittal sinus (yellow arrow), suggestive of cerebral venous sinus thrombosis, with acute venous infarct at the left frontal lobe (red arrow).

After 25 hours of incubation in BD BACTEC™, blood culture was flagged positive. A Gram stain was performed and showed Gram-positive cocci in clusters. Aerobic cultures on blood agar, chocolate agar, and MacConkey agar did not yield any growth. After 48 hours of anaerobic incubation, the anaerobic blood agar culture demonstrated pure growth of small, mucoid, grey colonies (Figure 2). The growth was identified via matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF) MS (Bruker Daltonics, Bremen, Germany), yielding *Peptoniphilus asaccharolyticus* with log[score] value of 2.17, using a direct transfer method. Antimicrobial susceptibility testing was performed via gradient minimum inhibitory concentration (MIC) strip (LiofilchemÒ, Roseto degli Abruzzi, Italy), using a 0.5 McFarland colony inoculum suspension and incubated anaerobically in an anaerobe chamber for 48 hours. The isolate demonstrated susceptibility to both penicillin and metronidazole, with MIC levels of 0.016 μg/mL and 0.75 μg/mL, respectively, as interpreted according to the Clinical and Laboratory Standards Institute (CLSI) M100, 34th Edition guidelines.

Figure 2: *Peptoniphilus asaccharolyticus* colonies on blood agar medium, following 48 hours of anaerobic incubation. Note the opaque greyish non-haemolytic colony with raised center.

The aerobic blood culture remained sterile during the five days of incubation. High vaginal swab culture grew *Candida albicans*. Products of conception tissue were not sent for culture; instead, only a tissue swab was sent, which also grew *Candida albicans*.

On her fifth day of admission, her condition was complicated by septic ileus, which resolved after one day of nasogastric tube insertion and hydration. After the eighth day of hospitalization, she was discharged upon her request to be transferred to a district hospital in Indonesia for continuation of care, nearer to her relatives.

DISCUSSION

Up to 30% of human anaerobic infections are caused by Gram-positive anaerobic cocci, commonly encountered in the female genital tract, soft tissue, and orthopaedic infections. Peptoniphilus species is reported to be isolated from blood, bone, joint, skin, and soft tissue infections, vaginosis, and various organ abscesses such as kidneys, peritonsillar, and spine. Most Peptoniphilus infections, similar to other anaerobic infections are part of polymicrobial infections, with few monomicrobial infections reported among the elderly, immunosuppressed, and post-operative patients.[1] For this patient, *P. asaccharolyticus* was not isolated in the products of conception because only a swab was sent. According to our local laboratory flow, only aerobic culture will be performed for swab cultures. A proper tissue culture, instead of the swab, would guarantee a better organism yield, including anaerobic bacteria. This highlights the importance of proper communication between clinicians and laboratory staff in alerting both to the possibility of anaerobic infections in cases of septic abortion and the correct way to obtain and transport relevant clinical specimens for better organism yield.

Anaerobic bacterial infections have been a diagnostic challenge for both clinicians and microbiologists alike. With severe, invasive infections abruptly manifesting in patients, clinicians usually treat the infections empirically with antibiotic agents targeting Gram-negative bacteria, some of which do not have coverage against anaerobic microorganisms.

From the microbiology laboratory staff's perspective, anaerobic organisms are not only fastidious and require special culture media and prolonged incubation conditions, but conventional bacterial identification testing often fails to differentiate beyond the genus level. For instance, biochemical testing fails to differentiate between *P. harei* and *P. asaccharolyticus*. Fortunately, MALDI -TOF MS has proved reliable in identifying clinically significant anaerobic bacteria. Although inferior to its newer competitors, VITEK MS and MALDI Biotyper system, the identification accuracy of *Peptoniphilus spp* using MALDI-TOF MS was found to be as high as 86%, with a 95% CI of 81 to 91%.[2]

Cerebral venous thrombosis is a rare venous thrombotic event predominant in females. It is triggered by the imbalance between haemostasis, rendering sluggish venous blood flow and disturbance in cerebral perfusion. For this patient, her known prothrombotic risk factors include pregnancy and sepsis, although there may be additional undiagnosed thrombophilia or comorbidity predisposing to the phenomenon. Fortunately, CVT carries a good prognosis, and most patients survive with almost no permanent neurological deficit. Our patient was lost in follow-up due to her transfer to her hometown hospital, thus her recovery was not confirmed. The chronological association between foetal outcome and obstetric CVT remains uncertain. Bertani described a severe case of CVT in early trimester pregnancy, leading to significant long-term neurological damage and spontaneous abortion.[3] In our case, septic abortion occurred prior to the neurological event.

Brown and colleagues have compiled 15 cases of peptoniphilus bacteraemia and their outcomes. Among these cases, all three pregnancy-related peptoniphilus bloodstream infections involved young mothers. The prognosis for the conceptus was grimmer than that of adults. Specifically, the overall mortality rate of adult patients was 20%, involving elderly patients above 80 years old with significant comorbidities. However, despite the survival of all peptoniphilus-infected pregnant mothers, only one was able to return home with her surviving newborn.[4] This may be due to the differences in the gestational age between the patients at the time of infection, as the mother of the only surviving baby was in the third trimester at the onset of infection. This theory is supported by Althaqafi and colleagues, who reported second-trimester loss.[1] Based on the previously discussed case reports, our case represents the fifth documented instance of *P. asaccharolyticus* septic abortion worldwide.

The Malaysian National Antimicrobial Guideline recommends a 14-day regime of the combination therapy of ampicillin, gentamicin, and metronidazole for septic abortions. Alternative combinations include ampicillin/ sulbactam plus oral doxycycline or clindamycin with gentamicin. Although the clinician empirically treated this patient with ceftriaxone and metronidazole instead of

the recommended antibiotics, the isolate was tested susceptible to both antibiotics.

CONCLUSION

Septic abortion can aggravate the rare pregnancy-induced cerebral venous sinus thrombosis. The anaerobic peptoniphilus is an organism capable of complicating septic abortions. Upon clinical suspicion of septic abortion, immediate commencement of effective antibiotics is vital for achieving a favourable prognosis for patients. MALDI-TOF MS serves as a reliable diagnostic tool for rapid identification of anaerobic organisms.

ACKNOWLEDGEMENT

Special thanks are extended to the Director General of Health for his permission to publish this article.

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ORIGINAL ARTICLE

Occurrence of aac(6')-Ib-cr and Qnr Genes among Quinolone-Resistance Enterobacteriaceae Isolated from Patients with Urinary Tract Infection in Najaf, Iraq

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ABSTRACT

INTRODUCTION: The *aac(6')-Ib-cr* gene is one of the most common genes among plasmids and has dual activity against both aminoglycoside and quinolone antibiotics, making it among the most important plasmid-mediated quinolone resistance genes. This research aimed to confirm the frequency of *aac(6')-Ib-cr* and *qnr* genes in quinolone-resistant *Enterobacteriaceae* isolates obtained from patients with urinary tract infection in Najaf, Iraq. **MATERIALS AND METHODS:** Quinolone resistance was examined in 318 urine samples taken from individuals who had suspected urinary tract infections (135 *Klebsiella pneumonia* cases, 75 *Proteus mirabilis* cases, and 108 *Escherichia coli* cases). Using PCR, antibiotic susceptibility patterns were assessed for quinolone resistance isolates and the presence of the *aac(6')-Ib-cr, qnrA*, *qnrB*, and *qnrS* were looked into. **RESULTS:** Quinolone-resistant isolates totaling 176 were identified. *aac(6')-Ib-cr* was detected in 93 (52.8%) cases, 50 of which were *E. coli*, 39 were *K. pneumoniae*, and 4 were *P. mirabilis*, according to PCR analysis data. *qnrA* 6 (3.4%), *qnrB* 22 (12.5%), and *qnrS* 5 (2.8%) isolates were identified to have the following *qnr* genes. *P. mirabilis* did not have the *qnrS* gene, which was absent from all analyzed genes detected in bacterial isolates. **CONCLUSION:** It was shown that of the plasmid-mediated quinolone resistance genes, the *aac(6')-Ib-cr* gene was the most common. Every gene analyzed was present in both *K. pneumoniae* and *E. coli*.

Keywords
Plasmid-mediated quinolone resistance, *qnr* genes, PMQR, *qnrA*, *aac(6')-Ib-cr*

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Received: 23th May 2024; Accepted: 12th November 2025

Doi: https://doi.org10.31436/imjm.v24i02/2618

INTRODUCTION

Many resistance mechanisms against quinolones have been established by *Enterobacteriaceae*. The mechanisms mostly entail a mutation in the chromosomal genes (DNA gyrase then topoisomerase IV), which encode quinolone targets, and/or decreased drug permeability.[1,2] Genes on plasmids, such as *Qnr, QepA* and *Oqx*AB (plasmid-mediated efflux pump), and an aminoglycoside acetyltransferase *aac(6')-Ib-cr* gene variation, can also cause quinolone resistance.[3]

It becomes more difficult to treat quinolone-resistance *Enterobacteriaceae* infections when plasmid-mediated quinolone resistance (PMQR) is prevalent, because it promotes the spread of resistance.[4] The presence of *qnr* genes in *Enterobacteriaceae* species that are less sensitive to fluoroquinolones.[5]

Aminoglycosides have been a mainstay in treating infections produced by *Enterobacteriaceae*. In contrast, aminoglycoside-resistant strains of these bacteria have emerged in recent years.[6] Nosocomial infections produced by *Enterobacteriaceae* are particularly difficult to treat because of three processes that reduce the efficiency of aminoglycosides. These consist of altered ribosome binding sites, the emergence of enzymes that modify aminoglycosides, and decreased cell permeability or absorption.[7]

Aminoglycoside-modifying enzymes are the chief machine of aminoglycoside resistance in *Enterobacteriaceae*.[8] The structural disintegration of aminoglycosides by acetyltransferases and other enzymes is a possibility, as phosphotransferases, and adenyltransferases.[9] The aminoglycoside acetyltransferase *aac(6')-Ib* mainly encodes resistance to specific aminoglycoside antibiotics

(kanamycin, tobramycin, and amikacin).[10] This gene may have another function in a variation of the 6'-N-aminoglycoside acetyltransferase (*aac(6')-Ib*-cr) gene, to acetylate quinolones with piperazinyl subunit (for example ciprofloxacin and norfloxacin) only.[1] This gene may present in a multidrug-resistant plasmid within the cassette of the class one integron, which can carry many other quinolone resistance genes.[1,10]

Given that there are no clear indications of, the *aac(6')-Ib-cr* gene's existence in Al-Najaf, Iraq. Finding out how common the *aac(6')-Ib-cr* and plasmid-mediated quinolone resistance (PMQR) genes are in clinical isolates of *Enterobacteriaceae* resistant toward quinolones in Al-Najaf, Iraq, is the goal of this study.

MATERIAL AND METHODS

Bacterial isolation

Al-Zahra Education Hospital for Parenthood and Pediatrics, Al-Sader Medical City, and Al-Hakeem Overall Hospital remained the three hospitals in Al-Najaf city midpoint from which 318 midstream urine samples were collected from patient roles who presented with urinary tract infections between January 2020 and December 2022. The VITEK 2 system and VITEK 2 GN ID Card (Biomerieux, France) were used to authenticate each strain of bacteria.

Antimicrobial susceptibility testing and detection of quinolone resistance isolates

The antibiotic sensitivity tests were achieved in compliance with the Clinical Laboratory Standard Institute (CLSI) standard. [11] To identify isolates resistant to quinolones, all isolates were tested against ciprofloxacin (CIP, 5 μg) and nalidixic acid (ND, 5 μg) (Cypress, Belgium). The results were verified using MIC strips (Liofilchem, Italy).

Antibiotic resistance patterns were conducted according CLSI guidelines.[11] Ampicillin (AM, 10 μg), amoxicillin (AX, 25 μg), cefotaxime (CTX, 30 μg), ceftazidime (CAZ, 30 μg), ceftriaxone (CTR, 30 μg), cefoxitin (FOX, 30 μg), aztreonam (ATM, 30 μg), imipenem (IPM, 10 μg), meropenem (MEM, 10μg), levofloxacin (LEV, 5 μg), lomefloxacin (LOM, 10 μg), norfloxacin (NOR, 10 μg), ofloxacin (OFX, 5 μg), amikacin (AK, 30 μg), tobramycin (TOB, 10 μg), gentamycin (CN, 10 μg), netilmicin (NET, 30 μg), sulphamethazole (SMZ, 250 μg), trimethoprim (TMP, 5 μg).

Detection of plasmid-mediated quinolone resistance (PMQR) genes

The cells underwent a previously described analysis to detect the presence of the *aac(6')-Ib* gene. Using previously described primers to amplify every known variant of the target gene, the primers were selected.[12] PCR amplification conditions were 95˚C for 3 minutes, followed by 94˚C for 45 seconds, 55˚C for 45 seconds, 72˚C for 45 seconds for 34 cycles, and 72˚C for 5 minutes as the final extension. The amplification yielded 482 bp. The PCR results were given to a gel documentation system (Biometra, Germany) for visualization, and they were electrophoresed. After restriction, *aac(6')-Ib* showed 272 bp and 210 bp fragments, but *aac(6')-Ib-cr* did not exhibit a restriction site. These PCR-positive isolates were then subjected to additional analysis using the BtsCl enzyme. Using primer sets, monoplex PCR was used to screen for *qnrA*, *qnrB*, and *qnrS*. PCR amplification conditions previously described, the 512 bp, 417 bp, and 469 bp PCR products were obtained accordingly.[13] The agarose was stained with ethidium bromide; the electrophoresis was performed at 70 volts for 90 minutes.

RESULTS

The present study revealed that out of the 318 clinical isolates, *Enterobacteriaceae* strains were found in the midstream urine samples collected where *Escherichia coli*) ,(%34 ,108 *Klebsiella pneumoniae* (135, 42.5%), and *Proteus mirabilis* (75, 23.5%).

In the current investigation, 176 isolates (60 *E. coli*, 74 *K. pneumoniae*, and 42 *P. mirabilis*) were shown to be resistant to quinolones based on CLSI standards. The pattern of antimicrobial resistance against quinolone resistance found in 176 isolates is displayed in Table I. According to An analysis of the design for resistance to antibiotics, the majority of quinolone-resistant bacteria in this study were resistant to penicillin (99.3%) and amoxicillin (98.8%).

There were followed by sulphamethazole (82.9%), trimethoprim (80.1%), cefotaxime (79.5%), ceftazidime (76.1%), ceftriaxone (74.4%), and aztreonam (63.6). We can observe that the fluoroquinolone group had a high level of resistance to lomefloxacin (66.4%), although the other fluoroquinolones, levofloxacin (36.9%), norfloxacin (48.2%), and ofloxacin (50.5%), had intermediate resistance. Amikacin (21.5%), tobramycin (69.3%), gentamycin (58.5%), and netilmicin (26.1%) were also found in this investigation

Table I: Antibiotic susceptibility pattern of 176 quinolone-resistance *Enterobacteriaceae* clinical isolates

Antibiotics	E. coli (60 isolates) n. (%)	K. pneumoniae (74 isolates) n. (%)	Proteus spp (42 isolates) n. (%)	Total (176 isolates) n. (%)
Ampicillin	59 (98.3)	74 (100)	42 (100)	175 (99.3)
Amoxicillin	58 (96.7)	74 (100)	42 (100)	174 (98.8)
Cefotaxime	51 (85)	64 (86.5)	25 (59.5)	140 (79.5)
Ceftazidime	50 (83.3)	63 (85.1)	21 (50)	134 (76.1)
Ceftriaxone	48 (80)	61 (82.4)	22 (52.4)	131 (74.4)
Cefoxitin	11 (18.3)	39 (52.7)	21 (50)	71 (40.3)
Aztreonam	42 (70)	59 (79.7)	11(26.2)	112 (63.6)
Imipenem	6 (10)	23 (31.1)	0 (0)	29 (16.4)
Meropenem	15 (25)	25 (33.8)	0 (0)	40 (22.7)
Levofloxacin	28 (46.7)	24 (32.4)	13 (31)	65 (36.9)
Lomefloxacin	41 (68.3)	56 (75.7)	20 (47.6)	117 (66.4)
Norfloxacin	33 (55)	35 (47.3)	17 (40.5)	85 (48.2)
Ofloxacin	34 (56.7)	36 (48.6)	19 (45.2)	89 (50.5)
Amikacin	2 (3.3)	26 (35.1)	10 (23.8)	38 (21.5)
Tobramycin	40 (66.7)	52 (70.3)	30 (71.4)	122 (69.3)
Gentamycin	37 (61.7)	39 (52.7)	27 (64.3)	103 (58.5)
Netilmicin	4 (6.7)	29 (39.2)	13 (31)	46 (26.1)
Sulphamethazole	54 (90)	62 (83.8)	30 (71.4)	146 (82.9)
Trimethoprim	47 (78.3)	66 (89.2)	28 (66.7)	141 (80.1)

All 176 quinolone resistance isolates investigated through PCR for the existence of *aac(6')-Ib*, *qnrA*, *qnrB*, *qnrS* genes. A total of 131 (74.4%) were demonstrated that harbored *aac(6')-Ib* gene, the most common gene found in *E. coli* 54 (90%) followed by *K. pneumoniae* 57 (77%) and *P. mirabilis* 20 (47.6%) (Figure .(1 In the same manner, the present study confirmed that the *aac(6')-Ib-cr* gene 93 (52.8%) of isolates *E. coli* 50 (83%) followed by *K. pneumoniae* 39 (52.7%) and *P. mirabilis* 4 (9.5%) The *qnrA* was found most frequently in *P. mirabilis* 3 (7.1%), followed by *K. pneumoniae* 2 (2.7%), and *E. coli* 1 (1.6%) (Figure 2). A total of 17 (23%) *K. pneumonia* isolates carried *qnrB* gene (Figure 3), while only 1 (14%) carried *qnrS* (Figure 4). In *E. coli*, both qnrB and qnrS were detected in 4 (6.6%) isolates while in *P. mirabilis* harbor only *qnrB* gene. Table II demonstrated the frequency of the plasmid-mediated quinolone resistance (PMQR) gene among 176 quinolone resistance isolates.

Table II: Frequency of plasmid-mediated quinolone resistance (PMQR) gene among 176 quinolone resistance isolates

Gene	E. coli n=60	K. pneumonia n=74	Proteus spp n=42	Total n=176
aac(6')-Ib	54 (90%)	57 (77%)	20 (47.6%)	131 (74.4%)
aac(6')-Ib-cr	50 (83.3%)	39 (52.7%)	4 (9.5%)	93 (52.8%)
qnrA	1 (1.7%)	2 (2.7%)	3 (7.1%)	6 (3.4%)
qnrB	4 (6.7%)	17 (23%)	0	21 (11.9%)
qnrS	4 (6.7%)	1 (1.4%)	0	5 (2.8%)

DISCUSSION

Quinolone antibiotic was first discovered in the sixties in the last century and used to treat urinary tract infections in adult patients, then it developed to treat other sites of infection over time.[14] However, an expansion in the use of quinolone and fluoroquinolone group classes of antibiotics led to the appearance of resistance against this group.[15] Quinolone resistance mediated by plasmids was initially recognized in the members of the *Enterobacteriaceae* family. Over time, many of the genes that produce quinolone resistance within this category have been identified.[16] The prevalence of PMQR genes in Al-Najaf city was fairly assessed.[17] Therefore, in this study, we investigated the presence of these genes among three members of the *Enterobacteriaceae* family (*E. coli, K. pneumoniae*, and *P. mirabilis*) and understood their antibiotic susceptibility background.

In our study, the results show 52.8% of collected quinolone-resistance *Enterobacteriaceae* clinical isolates harbor at least one PMQR gene. These results were significantly high, several studies accomplished worldwide revealed a lower rate. In Algeria,[18] Europe, Spain,[19] and Mexico,[15] rates are 13.5%, 20%, 31.8%, and 32.1% respectively. The *aac(6')-Ib-cr* gene causes resistance to quinolone as well as aminoglycoside, especially it is responsible for reducing susceptibility to ciprofloxacin in vivo[1]. In this study, the prevalence of *aac(6')-Ib-cr* gene was 52.8%, and this finding may explain the high level of resistance to ciprofloxacin and norfloxacin, especially when combined with chromosomal mutation.[3] The rate

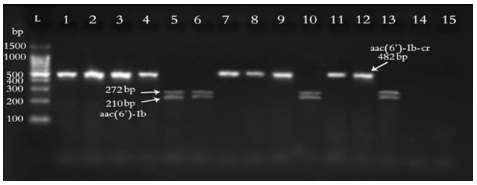

Figure 1: Agarose gel of PCR amplification products of *K. pneumoniae*. isolates amplified with primer targeting the *aac(6')-Ib* genes after digested with BstCI. Lane (L), molecular size marker (100 bp), lane (1,2,3,4,7,8,9,11,12) display positive results with *aac(6')-Ib-cr*, lane (5, 6, 10, 13) display *aac(6')-Ib* wild-type genes.

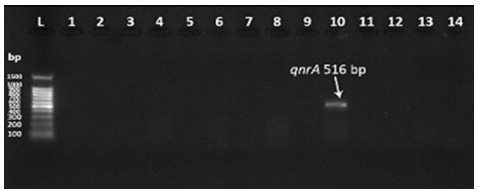

Figure 2: Agarose gel of PCR amplification products of *Proteus spp.* isolates amplified with primer targeting the *qnrA* genes. Lane (L), molecular size marker (100 bp), lane (10) displays positive results with *qnrA*, lane (1,2,3,4,5,6,7,8,9,11,12,13,14) displays negative results with *qnrA* genes.

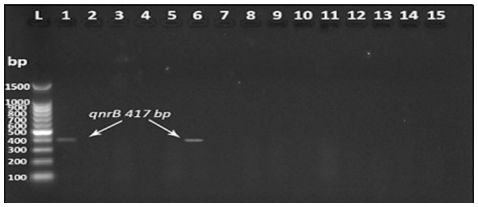

Figure 3: Agarose gel of PCR amplification products of *E. coli.* isolates amplified with primer targeting the *qnrB* genes. Lane (L), molecular size marker (100 bp), lane (1,6) displays positive results with *qnrB*, lane (2,3,4,5,7,8,9,10,11,12,13,14) displays negative results with *qnrB* genes.

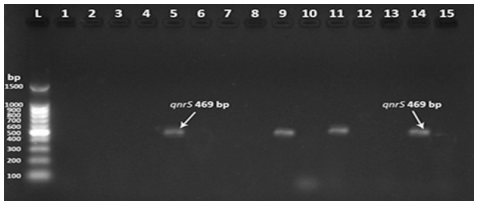

Figure 4: Agarose gel of PCR amplification products of *E. coli* isolates amplified with primer targeting the *qnrS* genes. Lane (L), molecular size marker (100 bp), lane (5,9,11,14) displays positive results with *qnrS*, lane (1,2,3,4,6,7,8,10,12,13) displays negative results with *qnrS* genes.

of *aac(6')-Ib-cr* gene in the present study was similar to the study conducted in Iran 68.6%[25], and higher than a study conducted in Brazil 40.8%26, Mexico 15.1%20. The *aac (6')-Ib-cr* gene was present more frequently in *E. coli* 83% followed by *K. pneumoniae* 52.7%, and less frequently in *P. mirabilis* 9.5%, in agreement with other studies.[18,20] The high frequency of *aac(6')-Ib-cr* gene puts the therapeutic options in the narrow circle where it is expressed as resistant to both quinolone and aminoglycoside drugs in the future.

In this study, the prevalence of Qnr determinants was found in 23.8% of *Enterobacteriaceae* quinolone resistance isolates. The *qnr* gene was strongly associated with various species of *Enterobacteriaceae* worldwide.[21] A previous study has reported that *qnr* genes represent 5.7% in China,[22] 15.1% in Tunisia,[23] and 28.7% in Spain,[18] of quinolone-resistance *Enterobacteriaceae* clinical isolates. Among the 176 quinolone-resistance *Enterobacteriaceae* clinical isolates, the frequency of *qnrA* was 6 (3.4%), three of them found in *P. mirabilis*. This finding was close to results accomplished in India,[23] and Iran,[24] while another study conducted in Europe and Brazil didn't record this gene in *Enterobacteriaceae* isolates.[25,26] The *qnrB* in the present study was found in 21 (11.9%) *Enterobacteriaceae* quinolone resistance isolates, 17 located in *K. pneumonia*. This result was higher than recorded in Qatar,[27] Sweden.[29] The *qnrB* gene was the most prevalent *qnr* resistance gene, not only in this study but also recorded by studies conducted in Morocco,[28] Iran,[24] Austria,[29] and Turkey.[4] Five isolates carried the *qnrS* gene, mostly in *E. coli*, this result was similar to that recorded in Eurpe.[30]

Unfortunately, there is no clear strategy in our country to control the administration and use of antibiotics, as they are given without a prescription in pharmacies, and therefore it is difficult to reduce the spread of antibiotic resistance genes among bacteria, which in turn reduces the effect and treatment options for infected patients, which leads to aggravating the health condition. The limitation of this study is that no equal number of isolates from each bacterium selected from the *Enterobacteriaceae* family. Not all PMQR genes were screened, which gives incomplete information about resistance genes.

CONCLUSIONS

Isolates with elevated quinolone resistance, particularly to cephalosporins and penicillins, were detected. *aac(6')-Ib-cr* was the most common PMQR gene among the isolates, with a widespread frequency of these genes observed. Every gene that was checked turned up in *K. pneumoniae* and *E. coli*. Investigation of quinolone resistance genes in Al-Najaf necessitates more research, in Iraq, since the limitation of data in this area.

FUNDING

Self-funding

CONFLICT OF INTEREST

Researchers don't have any conflicts of interest.

ACKNOWLEDGMENTS

The writers express their thankfulness to the personnel of the Bacteriology Laboratory at Al-Najaf Hospitals for their help in gathering clinical specimens for this investigation.

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ORIGINAL ARTICLE

A Retrospective Cohort Single-Centre Study of Prophylactic Vs. Preemptive Valganciclovir Therapy in Cytomegalovirus-At-Risk Kidney Transplant Recipients in Malaysia

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ABSTRACT

INTRODUCTION: Valganciclovir is commonly used for prophylaxis or preemptive therapy to prevent post-transplant cytomegalovirus (CMV) infection and disease in kidney transplant recipients. However, there are a limited data on the outcome and the association between valganciclovir and clinical characteristics of kidney transplant recipients, particularly those who are CMV seronegative (R-) receiving a transplant from CMV seropositive donors (D+), as well as in populations with high CMV seroprevalence. **MATERIALS AND METHODS:** This retrospective, single-center cohort study collected clinical data from kidney transplantation recipients at a tertiary referral hospital from January 2020 to June 2022. The data on the recipients' demographics, CMV risk categories, clinical characteristics, and types of valganciclovir therapy were obtained. Associations between clinical data, CMV risk categories, and therapies were determined. **RESULTS:** Among 110 kidney recipients, 9 were classified as high-risk and 101 as intermediate-risk. There were no significant differences found in the recipients' demographics and underlying factors between the risk categories. CMV infection occurred significantly less in the prophylaxis group than in the preemptive group (22.2% vs. 59.4%, p=0.04). There were no significant differences in one-year graft outcomes or patient survival observed between prophylaxis and preemptive therapies. Leukopenia incidence was higher in patients receiving prophylaxis. The incidence of co-infection with CMV viremia was similar between high-risk and intermediate-risk recipients. A significant association was found between CMV risk categories and prophylactic therapy in relation to post-transplant complications, CMV viremia clearance duration, and peak titer. **CONCLUSION:** Valganciclovir was the preferred therapy to prevent CMV infection and disease in kidney transplant recipients, with prophylactic therapy showing particular benefit in high-risk groups without increasing complications.

Keywords
Cytomegalovirus, Kidney transplantation, Preemptive, Prophylaxis, Yalganciclovir

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Received: 8th July 2024; Accepted: 13th January 2025

Doi: https://doi.org10.31436/imjm.v24i02/2666

INTRODUCTION

Valganciclovir, a prodrug of ganciclovir, is widely used in prevention and treatment of cytomegalovirus (CMV) infection in solid organ and bone marrow transplant recipients.[1] It is administered orally and is rapidly converted to ganciclovir, the active antiviral agent.[2] The drug acts by inhibiting viral DNA polymerase, thus preventing viral replication.[2]

Studies have demonstrated the effectiveness of valganciclovir in prevention of CMV infection in paediatric kidney transplant recipients[3], renal transplant recipients,[4] and thoracic organ transplant recipients.[5] However, its use is associated with adverse effects, including leukopenia, fever, abdominal pain, and an increased risk of opportunistic infections.[6] Studies also shown that there is a higher occurrence of CMV infection among high risk liver transplant recipients receiving valganciclovir prophylaxis compared to ganciclovir prophylaxis.[7] Additionally, a retrospective analysis by Brown et al. showed that low-dose

valganciclovir is both effective and safe for prevention of CMV disease in renal transplant recipients.[8] In a previous study that emphasized on the impact of CMV disease on solid organ transplant recipients, the adverse effect of vangiclacvir has also been explored.[9]

CMV infections are a major concern following kidney transplantation, as CMV is the most common opportunistic infection in this patient group. CMV infection can be classified into two categories, CMV infection and CMV disease. CMV infection refers to the presence of CMV replication, while CMV disease involves clinical signs and symptoms attributable to the infection. Despite effective antiviral therapy, studies have shown that CMV infections can persist after kidney transplant, leading to adverse outcomes.

The American Society of Transplantation guidelines emphasize on the importance of distinguishing between CMV replication and latency, with clinical signs and symptoms of CMV disease including fever, abdominal pain, and myelosuppression. Identifying factors that influence the development of CMV infection and disease after kidney transplantation is essential for effective prevention, management, and treatment. Wei & Yi (2020) highlight the importance of understanding the risk factors associated with CMV viremia, particularly the donor and recipient CMV serostatus (D+/R-) and recipients who have received anti-lymphocyte antibody therapy. Additionally, demographic and factors such as such as donor and recipient age, pre-transplant hemodialysis duration, estimated post-transplant glomerular filtration rate (eGFR), acute rejection, transplant type, non-white race, diabetes mellitus, and cyclosporine therapy contribute to CMV risk.[10] Post-transplant factors, including the use of thymoglobulin or anti-thymocyte globulin (ATG) for induction and maintenance of immunosuppression, also play a role in increasing the risk of CMV viremia.[11,12] These multifactorial risk factors highlight the complexity of managing and preventing CMV-related complications in kidney transplant recipients.

Immunosuppression following transplantation significantly increases the risk of cytomegalovirus (CMV) infection, leading to severe morbidity and mortality in solid organ transplant (SOT) recipients.[13] CMV infection in SOT recipients is associated with acute and chronic graft rejection, allograft dysfunction, heightened susceptibility to opportunistic infections, reduced patient survival, and increased healthcare costs.[13] The prevalence of CMV viremia among kidney transplant recipients further underscores the critical concern regarding the interplay between immunosuppression with CMV infection, and their implications on the health outcomes of transplant recipients.[14]

Prophylaxis and preemptive therapy are the primary strategies for prevention of cytomegalovirus (CMV) infection or disease in SOT recipients. Prophylaxis strategy by administration of antiviral agents in prevention of CMV infection, is particularly crucial in high-risk recipients with a CMV-positive (D+) donor and CMV-negative (R−) recipient.[15] In contrast, preemptive therapy by initiating antiviral treatment upon detecting the early signs of CMV replication has been shown to result in significantly lower rates of CMV disease compared to prophylaxis in certain specific transplant recipient groups.[15]

This approach allows for early intervention when viral replication is detected, effectively reducing the incidence and severity of CMV disease in SOT recipients. Additionally, preemptive therapy has proven effective in reducing the risk of prophylaxis failure

A key advantage of preemptive therapy is its ability to tailor treatment to individual patients through real-time PCR monitoring of CMV viral load. This approach allows for early intervention when viral replication is detected, effectively reducing the incidence and outcomes of CMV disease in SOT recipients.[15] Additionally, preemptive therapy has proven effective in reducing the risk of primary prophylaxis failure in preventing CMV infection and disease, positioning it as a targeted and efficient management strategy for CMV.[15]

This study aimed to compare the effectiveness of valganciclovir as prophylaxis or preemptive therapy in high-risk and intermediate-risk groups. It also sought

to examine the relationship between recipients' risk categories and their demographic and clinical characteristics.

MATERIALS AND METHODS

Data collection

This was a retrospective cohort study, conducted at a single centre by employing convenience sampling over a period of two and a half years, from January 2020 to June 2022, for collection of comprehensive data. Clinical data were gathered from recipients aged 13 to 70 years old who underwent kidney transplantation at the Nephrology Department of Kuala Lumpur Hospital. Recipients managed with valganciclovir as part of either prophylactic or pre-emptive therapies, following established guidelines to prevent CMV disease were included in the study, and recipients with a post-transplant follow-up period of fewer than 6 months were excluded.

Clinical outcomes including CMV infection and disease were monitored for 12 months post-transplantation. CMV infection was defined as the presence of CMV replication in blood without symptoms, detected by real-time PCR (>200 IU/ml), whilst CMV disease was defined as CMV infection with attributable symptoms including fever, malaise, leucopenia, thrombocytopenia, or evidence of tissue-invasive disease (e.g., colitis, pneumonitis, hepatitis). All recipients were followed up for a minimum of 12 months post-transplantation to assess both CMV-related outcomes and graft survival.

Graft outcomes were monitored over a period of one year, focusing on several key parameters such as acute kidney injury (defined as an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or ≥1.5 times baseline within 7 days), acute allograft dysfunction (characterized by sustained decline in eGFR more than 25% from baseline, not attributable to acute rejection), and graft rejection (defined as biopsy-proven rejection according to the Banff 2013 criteria). Graft loss was described as a return to renal replacement therapy such as dialysis, graft removal, retransplantation, or the death of the recipients.

In terms of risk categorization, the recipients were divided into intermediate-risk and high-risk groups according to the their CMV donor/recipient serostatus as determined by the pretransplant CMV serology. The intermediate-risk group included recipients with a positive or negative CMV donor serostatus and a positive recipients serostatus, (D+/R+ or D-/R+). The high-risk group, included recipients with a positive CMV donor serostatus and a negative CMV recipient serostatus (D+/R-), or those within the intermediate-risk group (D+/R+ or D-/R+) who received anti-lymphocyte preparations as part of their treatment regimen.

Clinical data were meticulously collected and included several key variables. The recipients' demographic information, such as age at transplantation, race, gender, and the donor/recipient relationship, were recorded. Clinical characteristics that might influence CMV infection and disease were also examined, including the primary cause of end-stage renal disease (ESRD), pre-transplant CMV serostatus, duration of pre-transplant hemodialysis, baseline eGFR, and the use of antiviral therapy (prophylaxis or pre-emptive therapy with valganciclovir). For prophylaxis, recipients were administered 450 mg of oral valganciclovir daily for six months. In contrast, recipients on pre-emptive therapy received 900 mg of valganciclovir daily for the first 14 days, followed by secondary prophylaxis with 450 mg daily for three months, and the dosage of valganciclovir was adjusted based on renal function to ensure appropriate dosing.

Additional clinical data included the use of immunosuppressive induction therapy such as thymoglobulin or anti-thymocyte globulin [ATG], basiliximab; as well as the type of immunosuppressive drugs for maintenance such as mycophenolate; type of transplantation; presence of leucopenia, defined as white blood cell count less than 4.0x10^9^/L; co-morbidities including diabetes mellitus and hypertension; clinical outcomes such as co-infections with other microorganisms, graft rejection or graft loss and mortality rate) and post-transplant complications including oedema, anaemia, diarrhoea, dyslipidaemia, and relevant conditions.

The dependent variables for this study included the risk categories of the recipients, categorized as either high-risk or intermediate-risk, and the types of CMV viraemia, classified as either CMV infection or CMV disease. The independent variables examined in this study encompassed a wide range of factors, including the recipients' demographic characteristics and underlying factors, co-morbidities, clinical outcomes and complications, types of therapy administered, length of CMV therapy, and type of immunosuppressive drugs for maintenance, co-infections by other infectious agents, graft outcomes and patients' survival.

This study received ethical approval from the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia with approval number: NMRR-20-993-53201. In compliance with ethical standards, the confidentiality of all participants was maintained through data anonymization, and secure methods of data storage were employed. Additionally, all procedures followed the relevant institutional guidelines for research involving human subjects, ensuring the protection of participant rights throughout the study.

Statistical analysis

The percentage of independent variables was evaluated using frequency analysis. Unless otherwise specified, both dependent and independent variables are expressed as the median and interquartile range (IQR). To determine the associations between risk categories and demographics, the clinical characteristics and outcomes were assessed. P-values were determined by Mann–Whitney U-test and Student t-test for continuous variables, according to their distribution, and Fisher's exact test for categorical variables. All p-values were two-sided, with the p-values of <0.05 were considered statistical significance. Statistical analyses were conducted using SPSS software (Version 23.0, IBM Corp, Armonk, NY, United States).

RESULTS

Recipients' demography and underlying factors

Out of 115 kidney transplant recipients selected for the study, five were excluded due to an inadequate post-transplant follow-up duration (<6 months; range 2-4 months). Of the remaining 110 recipients included in the analysis, 9 (8.1%) were categorized as high-risk for CMV infection or disease [(D+/R-) and (D+/R+ or D-/R+) receiving anti-lymphocyte preparations] and 101 (91.8%) were categorized as intermediate-risk (D+/R+) (Figure 1).

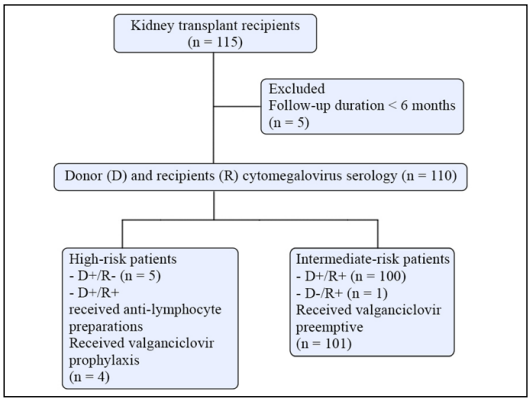

Figure 1 Distribution of the kidney recipients' risk categories

The baseline characteristics of the recipients are summarized in Table 1. Majority of the recipients were male, older than 35 years old, underwent ABO-incompatible (ABOi) transplantation, received a graft from a living donor, and treated with basiliximab as the immunosuppressant induction agent.

Regarding immunosuppressive induction therapy, all (100%) intermediate-risk recipients received basiliximab, while 55.6% of high-risk recipients did so (p=1.00). Additionally, 44.4% of high-risk recipients received thymoglobulin (p=1.00), whereas none of the intermediate-risk recipients were administered this therapy.

There was no significant difference between the high-risk and intermediate-risk recipients in terms of the age, sex, presence of diabetes mellitus, type of kidney transplantation, ABO-incompatible (ABOi) transplantation, pre-transplant donor-specific antibodies, or the donation from blood relatives. Regarding the immunosuppressive induction therapy, 100% of intermediate-risk recipients received basiliximab, while only 55.6% of high-risk recipients did so (p=1.00). Additionally, 44.4% of high-risk recipients received thymoglobulin (p=1.00), whereas none of the intermediate-risk recipients were administered with this therapy.

Regarding maintenance immunosuppressive therapy, nearly all recipients were treated with tacrolimus, mycophenolate mofetil, and methylprednisolone, with a slightly higher proportion of high-risk recipients receiving these therapies. The median duration of post-transplant follow-up was similar between the high-risk recipients and intermediate-risk recipients, 29 months (IQR 26.0-35.5 months) and 28 months (IQR 27.0-31.5 months), respectively (p=0.45)

Table 1 : Recipients' Demographics and Clinical Characteristics by Risk Category

Characteristics	High-risk recipients[a] (n=9)	Intermediate-risk recipients[b] (n=101)	p-value[c]
Demographics			
Age, years, mean+ SD	42.7+12	37.8+10	0.18[d]
Male sex, n (%)	7 (77.8)	65 (64.4)	0.72
Clinical Parameters			
Baseline eGFR, ml/ min/1.73m² (mean ± SD)	42.5 ± 10.2	43.2 ± 11.4	0.68
Diabetes mellitus, n (%)	3 (33.3)	11 (10.9)	0.09
Transplantation Details			
ABO-incompatible, n (%)	6 (66.7)	73 (72.3)	0.71
Related donor, n (%)	6 (66.7)	81 (80.2)	0.39
Immunosuppression Induction therapy			
Basiliximab, n (%)	5 (55.6)	100 (100.0)	0.00
Thymoglobulin n (%) Maintenance therapy	4 (44.4.)	0 (0.0)	1.00
TAC + MMF + MP, n (%)	9 (100.0)	99 (98.0)	1.00
TAC + EVR + MP, n (%)	0 (0.0)	2 (2.0)	1.00
Follow-up Duration, months, median (IQR)	29 (26.0-35.5)	28 (27.0-31.5)	0.45

D+. Donor CMV seropositive; R-, recipient CMV seronegative; D-, donor seronegative; R+, recipient seropositive; eGFR: Estimated glomerular filtration rate; SD, standard deviation; IQR, interquartile range; DSA, donor-specific antibody; TAC, tacrolimus; MMF, mycophenolate mofetil; EVR, everolimus; MP, methylprednisolone.

[a] High-risk: D+/R- and (D+/R+ or D-/R+) receiving anti-lymphocyte preparations
[b] Intermediate-risk: D+/R+ or D-/R+
[c] P-values based on Mann-Whitney U-test unless otherwise specified
[d] By Student t-test

Clinical outcomes and complications

The incidence of cytomegalovirus (CMV) infection was significantly higher in high-risk recipients (5/9, 55.6%) compared to intermediate-risk recipients (22/101, 22.0%) (p=0.04). Although the incidence of CMV disease was also higher in high-risk recipients (1/9, 11.1%) than in intermediate-risk recipients (6/101, 5.9%), this difference was not statistically significant (p=0.46). One intermediate -risk patient experienced a series of CMV infections, beginning as early as one month post-transplant, which progressed to multiple CMV-related diseases, including colitis, acute hepatitis, diarrhea, acute gastritis, and esophagitis.

Valganciclovir was used as prophylactic therapy in high-risk recipients and preemptive therapy in intermediate-risk. The clinical outcomes are shown in Table 2. The incidence of CMV infection was significantly higher in high-risk recipients 5/9 (55.6%) than the intermediate-risk recipients 22/101 (22.0%) (p=0.04). Although CMV disease incidence was also higher in high-risk recipients, 1/9 (11.1%) than in the intermediate-risk recipients 6/101 (5.9%), this difference was not statistically significant (p=0.46). One intermediate-risk recipients experienced a series of CMV infections, beginning as early as one month psot transplantation which progressed into multiple CMV-related diseases, including colitis, acute hepatitis, diarrhoea, acute gastritis, and esophagitis.

There was no significant difference in the incidence of co-infectious pathogens other than CMV between the two-group; 2/9 (22.2%) in high-risk recipients and 23/101 (22.8%) in intermediate-risk recipients (p=1.00). Other pathogens that were isolated or detected included *Escherichia coli, Acinetobacter spp., Staphylococcus aureus, Klebsiella pneumonia, Pseudomonas spp., Enterobacter cloacae* and *Burkholderia pseudomallei, Candida albicans, Tinea pedis* and BK polyomavirus (BKV).

The median estimated glomerular filtration rate (eGFR) at 12 months post transplantation was similar between the two groups: 46.4 (IQR 41.0–64.0)ml/min/1.73m² in high-risk recipients (n=9) and 46.5 (IQR 41.3–52.5)ml/ min/1.73m² in intermediate-risk recipients (n=101). There was no significant difference in leukopenia findings among both groups; high-risk recipients (n=1/9, 11.1%) and intermediate-risk recipients (n=4/101, 4.0%, p= 0.35).

Post-transplant complications were significantly higher in intermediate-risk recipients (50/101, 49.5%) than the high-risk recipients (1/9, 11.1%) with p value <0.05. The complications observed complications included delayed graft function, acute allograft dysfunction, dehydration, hypophosphatemia, dyslipidemia, hyponatremia, hypoalbuminemia, persistent proteinuria, acute tubular necrosis, pancytopenia, fever, cardiomyopathy, acute antibody-mediated rejection (ABMR), acute. T-cell–mediated rejection (TCMR), renal artery thrombosis,

Table 2: Clinical Outcomes with Valganciclovir Therapies at 12 Months Post-Transplant

Outcomes	Prophylaxis Valganciclovir High-risk Recipients[a] (n=9)	Preemptive Valganciclovir Intermediate-risk Recipients[b] (n=101)	P-value[c]
CMV Events			
CMV infection[d], n (%)	2 (22.2)	60 (59.4)	0.04
- Mean time to first infection, days (range)	185 (170-200)	85 (30-140)	0.02
CMV disease[e], n (%)	1 (11.1)	46 (45.5)	0.08
- Mean time to first disease, days (range)	250 (-)	120 (45-270)	0.03
Clinical Parameters			
Co-infection with other microorganisms[f], n (%)	2 (22.2)	23 (22.8)	1.00
eGFR at 12 months, ml/ min/1.73 m^2, median (IQR)	46.5 (41.3–52.5)	46.4 (41.0–64.0)	0.22
Leukopenia[g], n (%)	3 (33.3)	18 (17.8)	0.37
Co-infection with other microorganisms[7], n (%)	2 (22.2)	23 (22.8)	1.00
Post-transplant complication[h], n (%)	1 (11.1)	50 (49.5)	0.04
CMV Viremia Characteristics			
Duration of CMV viremia clearance, days, median (IQR)	14 (7-25)	26 (17-54)	0.02
Peak titer, 10^9/mL, median (IQR)	18 (7.0-43.0)	105 (18.0-213.0)	<0.01

D+. Donor CMV seropositive; R-, recipient CMV seronegative; D-, donor seronegative; R+, recipient seropositive; CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; IQR, interquartile range.
[a] High-risk: D+/R- and (D+/R+ or D-/R+) receiving anti-lymphocyte preparations
[b] Intermediate-risk: D+/R+ or D-/R+
[c] P-values: Mann-Whitney U-test for continuous variables; Fisher's exact test for categorical variables
[d] CMV infection defined as CMV replication in blood (>200 IU/ml) without symptoms
[e] CMV disease defined as CMV infection with attributable symptoms (fever, organ involvement)
[f] Including bacterial infections, BK virus, and fungal infections
[g] Leucopenia defined as white blood cell count $<4.0 \times 10^9$/L
[h] Including delayed graft function, acute allograft dysfunction, dehydration, etc.

macrocytic anaemia, perinephric hematoma, gout, chronic diarrhoea, pedal oedema, recurrent focal segmental glomerulosclerosis (FSGS) and ischemic heart disease. The duration of CMV viremia clearance was significantly faster in high-risk recipients receiving prophylaxis than in intermediate-risk receiving preemptive therapy, 14 (7-25) vs 26 (17-54) days, respectively. The CMV viremia peak titers were significantly lower in high- than intermediate-risk recipients, 18 (7.0-43.0) vs 105 (18.0-213.0) CMV peak titres, respectively.

Valganciclovir as prophylaxis and preemptive therapy

The prophylaxis dose was 450 mg oral valganciclovir/day for 6 months. Pre-emptive therapy recipients received initial treatment with valganciclovir 900 mg/day for 14 days, followed by secondary prophylaxis consisting of valganciclovir 450 mg/day for 3 months. All valganciclovir dosages were adjusted according to renal function. At a median follow-up duration of 24 months, CMV infection developed significantly less in the prophylaxis therapy than in the pre-emptive group (22.2%, 2/9 vs 59.4%, 60/101, respectively; p=0.04). Lower percentages of CMV disease were also seen in the prophylaxis therapy than in the pre-emptive therapy, but the difference was not significant (11.1%, 1/9 vs 45.5%, 46/101 respectively, p=0.08). In intermediate-risk recipients with pre-emptive valganciclovir, CMV infection was developed within the first three months after transplantation and CMV disease within the first nine months after transplantation, while in the high-risk recipients with valganciclovir prophylaxis, CMV infection was developed after six months of transplantation and CMV disease within the first 12 months after transplantation.

Graft outcomes and patients' survival

Graft and recipient survival and graft rejection data are shown in Table 3 and. Acute kidney injury (AKI) was seen in 1/9 (11.1%) and 14/101 (13.9%) in high-risk and intermediate-risk recipients, respectively. Acute allograft dysfunction was observed in 1/9 (11.1%) and 11/101 (11.9%) in high-risk and intermediate-risk recipients, respectively. These graft dysfunction cases were predominantly due to causes other than rejection, including medication-related effects, infections, and haemodynamic factors. There were 0/9 (00.0%) cases and 2/101 (2.0%) cases of acute antibody-mediated rejection (ABMR) in high-risk and intermediate-risk recipients, respectively, and 1 case of acute T-cell–mediated rejection (TCMR) in the intermediate group. No incidence of death occurred in the current study group.

Table 3: Graft outcomes and patients' survival with valganciclovir therapies.

	Prophylaxis valganciclovir High-risk recipients (D+/ R-) and (D+/ R+, D-/R+) receiving anti-lymphocyte preparations (n = 9)	Preemptive valganciclovir Intermediate-risk recipients (D+/R+, D-/ R+) n = 101	P-value[a]
Acute kidney injury (AKI), n (%)	1 (11.1)	14 (13.9)	1.00
Acute allograft dysfunction, n (%)	1 (11.1)	11 (11.9)	1.00
Acute antibody-mediated rejection (ABMR), n (%)	0 (0.0)	2 (2.0)	1.00
Acute T-cell–mediated rejection (TCMR), n (%)	0 (0.0)	1 (1.0)	1.00
Death, n (%)	0 (0.0)	0 (0.0)	1.00

[a] P-values: Fisher's exact test for categorical variables.

DISCUSSION

Cytomegalovirus (CMV) viraemia significantly affects clinical outcomes post-solid organ transplantation, exacerbated by immunosuppression, leading to symptomatic CMV disease with severe morbidity and occasional mortality.[16] In this study, 115 kidney transplant recipients were initially included, with 5 excluded due to insufficient post-transplant follow-up (<6 months). The remaining 110 recipients showed an 8.1% high-risk (D+/R- and D+/R+ or D-/R+ with anti-lymphocyte preparations) and 91.8% intermediate-risk (D+/R+) distribution.

Immunosuppression modulates the risk of CMV infection, underscoring the need to comprehend the interplay between immunosuppression and CMV infection.[17] The prevalence of CMV disease in transplant recipients, without pre-emptive or prophylaxis therapy, remains a critical concern despite advancements, posing a substantial threat to solid-organ transplant recipients.[18] The selection between prophylaxis and pre-emptive therapy for preventing CMV in transplant recipients is a subject of continuous research and debate. Reports of high rates of delayed-onset post prophylaxis CMV disease emphasize the necessity for targeted and effective preventive strategies tailored to the specific transplant population.[19]

The baseline characteristics, including age, sex, and transplantation factors, were comparable between high-risk and intermediate-risk recipients, indicating a well-balanced study population. However, a significant disparity in immunosuppression induction strategies was observed, with 100.0% of intermediate-risk recipients receiving basiliximab compared to 55.6% in the high-risk group. Furthermore, thymoglobulin was administered to 44.4% of high-risk recipients, while none among the intermediate-risk recipients received this treatment.

In this study, valganciclovir played a crucial role in managing cytomegalovirus (CMV) in kidney transplant recipients through prophylactic and preemptive strategies. High-risk recipients, constituting 8.1% of the cohort, had a significantly higher incidence of CMV infection (22.0%) than intermediate-risk recipients. Although CMV disease rates were elevated in high-risk recipients (11.1%) compared to the intermediate-risk group (5.9%), statistical significance was not reached. Remarkably, an intermediate -risk case experienced early-onset CMV infections leading to multiple diseases. Co-infection rates with other pathogens were similar between high-risk and intermediate-risk recipients. Renal function, assessed by estimated glomerular filtration rate, was comparable at the 12-month post-transplant mark. However, intermediate-risk recipients had a significantly higher post-transplant complication rate (49.5%) than high-risk recipients (11.1%). Additionally, high-risk recipients showed faster CMV viremia clearance and lower peak titers, suggesting potential prophylaxis benefits.

The usage of prophylaxis therapy in this study showed a lower incidence of CMV infection and CMV disease (delayed-onset disease) by 6 months after transplant in high-risk recipients. Studies have shown that universal prophylaxis can reduce the initial risk of CMV infection and disease (20)(21). However, there is concern about the high risk of late-onset CMV disease, which usually begins with D+/R- recipients after discontinuing prophylaxis.[22] This may increase mortality and/or death.[22,23,24]

However, some studies show the benefits of universal prophylaxis[25] compared preemptive therapy and universal prophylaxis in high-risk kidney and liver transplant recipients (D+/R-). In their group, consistent with previous studies by[26], late-onset CMV disease was not severe or life-threatening. They also showed that CMV reactivation in the first two years post-transplant, regardless of the preventive measures used, was a risk factor for transplant failure 5 years post-transplant.[25]

No statistically significant differences between the two therapy strategies were observed for leukopenia. The cause of leukopenia is usually multifactorial. Besides, CMV infection or the disease itself is often caused by the side effects of CMV antivirals such as valganciclovir and immunosuppressive agents.[27] The CMV infection has marked myelosuppression effects in renal transplant recipients and has been reported to have leukopenia or neutropenia as a manifestation.[28] Age at transplantation was not associated with the development of leukopenia;

however, older recipients had a higher incidence of leukopenia[28], as observed in this study group.

The high-risk recipients demonstrated a significantly faster median clearance of CMV viremia compared to their intermediate-risk counterparts, aligning with the findings of a previous study[29] that reported a swifter clearance of CMV DNAemia in the prophylaxis group beyond the 12-month post-transplant period. Additionally, the median peak titer of CMV viremia was notably lower in high-risk recipients under prophylaxis compared to intermediate-risk recipients. However, it is worth noting that contrary findings have been reported;[30] observed a significantly higher median CMV antigenemia peak titer in high-risk patients compared to intermediate-risk patients, while[29] found no difference in the median peak titer between recipients undergoing prophylaxis and preemptive approaches. These variations in results may be attributed to factors such as differences in antiviral selection, immunosuppressive status, the presence, or absence of CMV-specific T-cell immunity, suboptimal antiviral drug levels, or resistance to antiviral medications.[31]

In this study, occurrences of acute kidney injury (AKI), acute allograft dysfunction, acute antibody-mediated rejection (ABMR), and acute T-cell–mediated rejection (TCMR) were observed at higher rates in intermediate-risk recipients compared to high-risk recipients, although these differences did not reach statistical significance. Numerous studies have established a connection between AKI and unfavorable long-term graft outcomes.[32] The delayed graft function observed in this study may signify post-transplant AKI. In solid organ transplant (SOT) recipients, CMV infection often manifests through indirect effects, contributing to outcomes like acute rejection, graft failure, and mortality, collectively termed the 'indirect effects of CMV infection.[33] Additional factors leading to AKI in transplant recipients, such as obstruction of a single-functioning kidney, vascular thrombosis, drug toxicity, and drug-induced thrombotic microangiopathy [34], were not specifically identified in this study.

Initiating preemptive therapy in intermediate-risk cases during the early post-transplant period may permit mild CMV replication, resulting in CMV infection.[35] Such infections could potentially contribute to graft rejection. In alignment with findings from other investigations, our study lends support to the universal prophylaxis approach, emphasizing its advantage in suppressing early CMV replication, as opposed to preemptive therapy, thereby reducing the risk of graft rejection, particularly within the initial 3 months following transplantation in high-risk (D+/R-) kidney transplant recipients.[25,35]

This study has several limitations, such as its retrospective design, leading to incomplete clinical and laboratory data. Additionally, the convenience sampling employed may introduce bias into the results. It is crucial to note that this study contributes new data specific to the Malaysian setting.

CONCLUSION

The use of valganciclovir as antiviral prophylaxis in high-risk kidney transplant recipients, compared to preemptive therapy in intermediate-risk kidney transplant recipients, demonstrated superior efficacy in prevention of CMV infection and slowing the progression of CMV disease in these groups. This strategy did not pose an increased risk of opportunistic infections, allograft rejection, graft loss, drug resistance development, or mortality.

FUNDING

This study was funded by UPM GP-IPS research grant GPIPS/2020/9690500.

ACKNOWLEDGMENT

We would like to express our sincere gratitude to the staff and experts in the Nephrology Department and Microbiology (Virology) Unit Department, Kuala Lumpur Hospital, for their invaluable clinical and technical support.

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ORIGINAL ARTICLE

The Modification and Validation of the Medication Compliance Questionnaire (MCQ) for the Assessment of Adherence to Antiretroviral Therapy (ART)

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ABSTRACT

INTRODUCTION: Anti-retroviral therapy (ART) significantly improves the prognosis of human immunodeficiency virus (HIV) infection. Yet long-term and complex regimens often lead to non-adherence. Maintaining at least 95% adherence is crucial for effective ART and thus preventing drug resistance. The Medication Compliance Questionnaire (MCQ) has been used for adherence assessment in antihypertensive treatment, with an 80% cut-off level. This study aimed to modify and validate the MCQ for assessing adherence to ART. **MATERIALS AND METHODS:** The MCQ underwent modification with the incorporation of a new rating scale and scoring method. A pilot study was conducted at the Infectious Disease Clinic, Hospital Raja Perempuan Zainab II, Kelantan. Inclusion criteria were adults living with HIV (PLHIV), on ART for at least two months and who can communicate in Malay. Fisher's Exact test was used to determine validity, sensitivity, and specificity. Cronbach's alpha and intra-class correlation coefficients were used to evaluate reliability, with significance set at $p < 0.05$. **RESULTS:** A total of 60 PLHIV adults participated in this pilot study. Viral load served as the validity criterion for the modified MCQ, showing a significant association with adherence ($p=0.018$). Sensitivity and specificity values were 100.0% and 79.5%, respectively. Cronbach's alpha coefficients for drug-taking and drug-stopping behaviour domains were 0.65 and 0.90, respectively. **CONCLUSION:** The modified MCQ is a valid and reliable tool for assessing adherence to ART, demonstrating high sensitivity and adequate specificity. It is suitable for use in clinical practice to improve medication therapy management for PLHIV.

Keywords
Medication Compliance Questionnaire, adherence assessment, questionnaire validation, anti-retroviral therapy

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Received: 23th May 2024; Accepted: 4th December 2024

Doi: https://doi.org10.31436/imjm.v24i02/2623

INTRODUCTION

Anti-retroviral therapy (ART) significantly improves the prognosis of human immunodeficiency virus (HIV) infection; however, long-term treatment and maintenance of strict adherence to treatment is required.[1] The key factor for the success of treatment is good medication adherence, defined as the degree to which a patient follows the treatment plan agreed upon with their healthcare provider.[2] Adherence is often quantified as a percentage, reflecting the proportion of doses taken as prescribed.[3] In contrast to other chronic diseases, HIV infection necessitates a high adherence rate of approximately 95% to ensure effective viral suppression, owing to the rapid replication and high mutation rate of the virus.[4] Maintaining a minimum adherence rate of at least 95% is crucial for suppressing HIV viral load to below 400 copies/mL in most individuals.[5] Suboptimal adherences can lead to sub-therapeutic drug levels, compromising treatment efficacy and potentially resulting in increased viral load, decreased CD4 count, a higher risk of HIV transmission, and an elevated risk of developing resistance to ART drugs.[6] Unfortunately, only one-third of people living with HIV (PLHIV) adhere to their medication as prescribed.[7] In Nigeria, the non-adherence rate to ART was reported to be as high as 40%.[8] Even when patients fully understand the consequences of non-adherence, adherence rates remain suboptimal.[2,4]

Non-adherence to ART regimens can stem from the complexities of the treatment, which often requires taking more than two dozen pills, tablets, or capsules daily. Additionally, the necessity for complete adherence and the long-term nature of the treatment contribute to this challenge.[5] Therefore, there is a need to develop a convenient tool for monitoring ART adherence. Assessing adherence behaviour accurately in PLHIV is essential in ensuring treatment planning is effective and efficient. A review of the literature reported many methods used to measure adherence.[9] Direct measurements of adherence include drug assays of blood or urine,[10] surrogate laboratory markers,[11] and directly observing patients receiving the medications.[12] Indirect adherence measurements include the self-report adherence questionnaire,[13] pill count,[14] electronic monitoring devices,[15] and review of prescription records or secondary database analysis.[16]

Currently, there is no standard reference method that can be advocated to evaluate adherence because each method has its own advantages and limitations.[12] One of the most accurate methods of measuring adherence is by direct measures. However, these are costly.[17] Indirect measures, such as self-report adherence questionnaire, provides a practical and flexible method for adherence assessment and provides a unique chance to identify patient concerns. The self-report method is used widely due to its simplicity, relatively inexpensive and implementation ease in a patient's follow-up.[18] However, it is often linked with adherence overestimation and its outcomes vary compared to direct measures such as therapeutic drug monitoring.[19] Several self-reported adherence questionnaires exist, although they were not tailored specifically for HIV infection. Examples of these questionnaires are Morisky Medication Adherence Scale,[20] Patient Medication Adherence Questionnaire,[21], Brief Medication Questionnaire[22], Malaysia Medication Adherence Assessment Tool (MyMAAT)[23] and Medication Compliance Questionnaire (MCQ).[24]

Most of the Questionnaires mentioned required license for usage and not available in languages commonly used in Malaysia. The MCQ is available in Malay, English, Chinese and Tamil languages and can be completed within 10 minutes. Therefore, it was chosen as a tool in assessing adherence in this study.

The MCQ serves as a tool to assess adherence from the viewpoint of the patients. MCQ was originally developed and validated with hypertensive patients at the Family Medicine Clinic, Hospital Universiti Sains Malaysia, Kelantan. This questionnaire employs a five-level Likert scale comprising ten items focusing on drug-taking and drug-stopping behaviours.[24] Additionally, the MCQ has been utilized to evaluate adherence among patients with ischaemic heart disease[25] and cancer[26] in Malaysia.

In 2003, the World Health Organization (WHO) outlined adherence to long-term therapies as a behaviour influenced by five dimensions of obstacles. These dimensions include barriers associated with the healthcare team or system, the therapy itself, the patient's condition, the patient themselves, and socioeconomic factors.[2] Instances of therapy-related barriers encompass side effects and the complexity of drug regimens.[27] Condition-related barriers often involve the severity of symptoms, levels of disability (physical, psychological, social, and vocational), disease progression rate, severity, and access to effective treatments.[2] Patient-related barriers notably include forgetfulness, low self-efficacy, and misconceptions about diseases and medications.[27]

Many of these barriers fall within the assessment domains of drug-taking behaviour and drug-stopping behaviour in the MCQ. Barriers to adherence in ART are similarly multi-dimensional.[28] If healthcare providers restrict adherence assessments to only one or two barrier types, they risk overlooking other patient concerns that, while reported less frequently, can significantly impact adherence. Hence, the MCQ was selected as the tool for assessing adherence in this study. MCQ is an instrument with good validity and reliability.[24] However, the results may differ in other diseases and populations.[29] Therefore, the objective of this study is to modify and revalidate the MCQ to be used in adherence assessment of PLHIV.

MATERIALS AND METHODS

The Instrument

The MCQ is available in both Malay and English. It consists of ten items concerning drug-taking behaviour (Questions 1 to 7) and drug-stopping behaviour (Questions 8 to 10). A five-level Likert scale from 1 (never) to 5 (very frequent) is used. Internal consistency reliabilities (Cronbach's alpha) were 0.67 and 0.84, and test-retest single measure intraclass correlation coefficients were 0.78 and 0.93, respectively, for each domain.[30] Unfortunately, the content validity index was not included in the study. The MCQ can be completed in 10 minutes.

Modification of MCQ

To assess the adherence levels among participants, we established a common cut-off point of 80% using a five-level Likert scale, which was deemed appropriate for capturing varying degrees of adherence. The scale was defined as follows: 1 (never) corresponding to 20%, 2 (seldom) to 40%, 3 (sometimes) to 60%, 4 (frequent) to 80%, and 5 (very frequent) to 100%. This structure allows for a straightforward categorization of adherence levels.

To measure a more stringent cut-off point of 95%, we recognized the need for modifications to the instrument. Specifically, we employed a continuous measurement scale, which allows for finer distinction of adherence scoring. This involved converting the Likert scale responses into a 0–100-point scale, enabling a precise assessment of adherence percentages. For example, rather than being limited to discrete categories, participants' responses could now reflect a continuum of adherence levels. This approach facilitates a more accurate identification of adherence rates, particularly for those achieving close to the 95% threshold, thereby enhancing the instrument's sensitivity and specificity in evaluating adherence to HIV therapy. Through these modifications, we aimed to capture the full range of adherence behaviour, allowing for a comprehensive analysis of the relationship between adherence and treatment outcomes.

Pilot Study to Evaluate Validity and Reliability of MCQ Participants and Study Setting

The cross-sectional investigation took place at the Infectious Disease Clinic within Hospital Raja Perempuan Zainab II, a publicly funded tertiary hospital situated in the state of Kelantan, East Malaysia. To ensure adequate representation, an estimated target sample size of 60 People Living with HIV (PLHIV) was determined, factoring in a 20% anticipated drop-out rate, based on an item-to-subject ratio of 1:5.[31] Inclusion criteria comprised individuals diagnosed with HIV infection, receiving antiretroviral therapy for a minimum of two months, aged 18 years or older, and proficient in communicating in the Malay language.

Patients were contacted by the investigator during their routine follow-up appointments at the Infectious Disease Clinic using convenience sampling. They were briefed about the aim of the study, procedures and invited to sign a written informed consent form upon agreeing to participate. To maintain privacy and focus, participants completed the modified MCQ in a counselling room. The investigator gathered demographic and clinical information of the participants. The medical records were reviewed for viral load and CD4 counts, and demographic and clinical information were collected on the same day by the investigators (Figure 1).

The modified MCQ (as shown in Figure 2) was given twice to assess the test-retest reliability, with a two-week interval between the initial and subsequent sessions to minimize recall bias. This duration was considered adequate to prevent alterations that might influence responses, yet not too brief as to facilitate recollection of previous answers.[32]

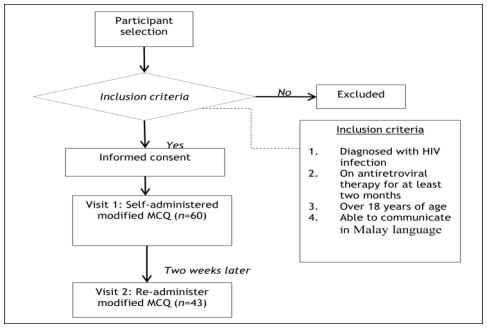


Figure 1: Flow chart of the modified MCQ validation study

Statistical Analysis

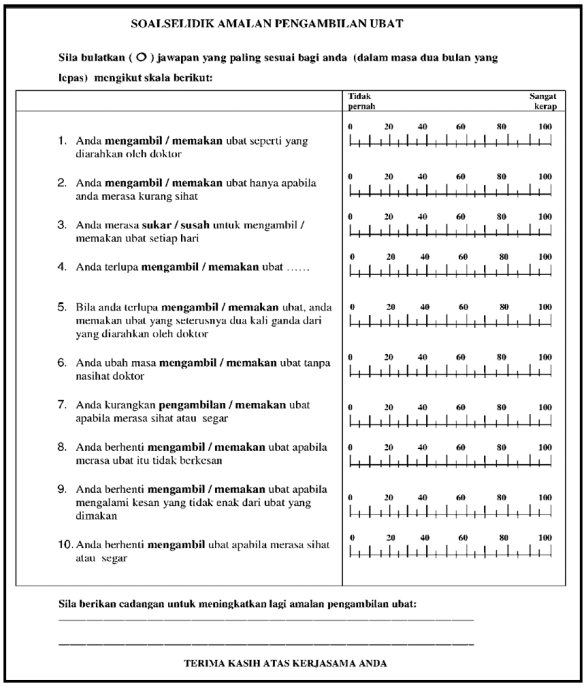
Descriptive statistics were utilized to depict the demographic and disease characteristics of the participants alongside their medication adherence scores. For continuous variables, means and standard deviations (SD) were computed, while categorical variables were expressed as frequencies (n) and percentages. Validity was assessed by examining the association between compliance and subjects' viral load using Fisher's Exact test, with a significance level set at $p<0.05$. Sensitivity (true positive) and specificity (true negative) values of the adjusted MCQ were also determined. Sensitivity gauged the test's accuracy in identifying poor virologic control among non-adherent patients, while specificity assessed its accuracy in identifying good virologic control among adherent patients.[33]

Internal consistency was assessed by Cronbach's alpha to evaluate correlations between the items in the factor. A Cronbach's alpha of above 0.9 was considered excellent, while values above 0.7 and 0.6 were noted as good and acceptable, respectively.[34] Single measure ICC was used to assess test–retest reliability. The ICC measured the stability of the items or agreement between modified scores, with 0 to 0.2 being considered poor agreement, 0.3 to 0.4 as fair agreement, 0.5 to 0.6 as moderate agreement, 0.7 to 0.8 as strong agreement, and above 0.8 as almost perfect agreement.[35]

RESULTS

Descriptive statistics were employed to describe the demographic and disease characteristics of the subjects. Means and standard deviations (SD) were calculated for continuous variables, while frequencies (n) and percentages were used for categorical variables.

The association between compliance and subjects' viral load was determined using Fisher's Exact test. A significant *p*-value of 0.018 was obtained, indicating a meaningful relationship.



SOALSELIDIK AMALAN PENGAMBILAN UBAT

Sila bulatkan (○) jawapan yang paling sesuai bagi anda (dalam masa dua bulan yang lepas) mengikut skala berikut:

	Tidak pernah — Sangat kerap
1. Anda **mengambil / memakan** ubat seperti yang diarahkan oleh doktor	0 20 40 60 80 100
2. Anda **mengambil / memakan** ubat hanya apabila anda merasa kurang sihat	0 20 40 60 80 100
3. Anda merasa **sukar / susah** untuk mengambil / memakan ubat setiap hari	0 20 40 60 80 100
4. Anda terlupa **mengambil / memakan** ubat ……	0 20 40 60 80 100
5. Bila anda terlupa **mengambil / memakan** ubat, anda memakan ubat yang seterusnya dua kali ganda dari yang diarahkan oleh doktor	0 20 40 60 80 100
6. Anda ubah masa **mengambil / memakan** ubat tanpa nasihat doktor	0 20 40 60 80 100
7. Anda kurangkan **pengambilan / memakan** ubat apabila merasa sihat atau segar	0 20 40 60 80 100
8. Anda berhenti **mengambil / memakan** ubat apabila merasa ubat itu tidak berkesan	0 20 40 60 80 100
9. Anda berhenti **mengambil / memakan** ubat apabila mengalami kesan yang tidak enak dari ubat yang dimakan	0 20 40 60 80 100
10. Anda berhenti **mengambil** ubat apabila merasa sihat atau segar	0 20 40 60 80 100

Sila berikan cadangan untuk meningkatkan lagi amalan pengambilan ubat:

TERIMA KASIH ATAS KERJASAMA ANDA

Figure 2: The modified MCQ

The sensitivity and specificity values of the modified MCQ were generated. The sensitivity was found to be 100.0%, indicating the instrument's ability to predict poor virologic control correctly in non-adherent patients. The specificity was determined to be 79.5%, reflecting the instrument's ability to correctly predict good virologic control in adherent patients. Internal consistency was assessed using Cronbach's alpha. Coefficients of 0.65 for the drug-taking behaviour domain and 0.90 for the drug-stopping behaviour domain were obtained. Correlations of corrected item-total ranged from 0.46 to 0.85 for the drug-taking behaviour domain and from 0.70 to 0.89 for the drug-stopping behaviour domain.

Test-retest reliability was assessed using single measure intra-class correlation coefficients (ICCs). Values of 0.87 for the drug-taking behaviour domain and 0.95 for the drug-stopping behaviour domain were observed, indicating strong to almost perfect agreement.

Overall, the modified MCQ was shown to be a valid and reliable instrument for assessing adherence to ART, with high sensitivity and adequate specificity. Therefore, it is deemed suitable for use in clinical practice to enhance medication therapy management for PLHIV.

Demographic and clinical characteristic of the participants in the pilot study

A total of 60 PLHIV participants took part in the pilot study. Majority were Malays with the mean age of 37.0 years and almost equal numbers of males and females. Majority of the patients (n=56, 93.0%) were adherent to highly active antiretroviral therapy (HAART) with a mean score of 99.3. The mean CD4 count was 278.0 cell/mm^3 with a range of 2 to 796 cell/mm^3. The mean viral load was 18,007.7 copies/ml and 28.3% (n=17) participants had an undetectable viral load (Table I).

Table I: The demographic and clinical characteristic of the participants in the pilot study (n=60)

Characteristics	n	%	Mean	SD
Age (years)			37.0	6.7
Gender				
Male	31	51.7		
Female	29	48.3		
Ethnicity				
Malay	59	98.3		
Chinese	1	1.7		
Modified MCQ score			99.3	1.9
Adherent	56	93.0		
Non-adherent	4	7.0		
Liver function				
ALP (IU/L)			122.9	80.4
AST (IU/L)			39.8	31.5
ALT (IU/L)			37.5	37.5
Renal function				
Creatinine clearance (ml/min)			78.3	21.8
CD4 count (cell/mm^3)			278.0	174.2
Viral load (copies/ml)			18,007.7	61,741.7
0* to 50	27	62.8		
51 to 400	4	9.3		
401 to 2,000	2	4.7		
More than 2,000	10	23.26		

*0 means undetectable with limit of detection of 20 copies/ml
(17 participants had undetectable viral)

Validity testing of the modified instrument

Virological outcome or viral load was used as the criterion for validity analysis. In this investigation, a participant was categorized as non-adherent if their most recent viral load (obtained during the pilot study's three-month timeframe) exceeded 400 copies/mL.[36] Out of the 60 patients, only 43 (71.7%) underwent viral load testing within this timeframe. Using Fisher's exact test, there was a significant association between the adherence and viral load (p=0.018) (Table II).

Table II: Association between adherence measured by the modified MCQ and virological outcome (viral load) (n=60)

Adherence	Viral load (copies/mL) n (%)		Total (n)	p-value
	400 or less	More than 400		
Adherent	31 (100.0)	8 (66.7)	4	**0.018**
Non-adherent	0 (0.0)	4 (33.3)	39	
Total (n)	31	12	43	

Fisher's exact test
Viral load of 400 or less indicated good control
Viral load of more than 400 indicated poor control

Sensitivity and specificity analysis of the modified Instrument

From the analysis, the findings indicated sensitivity (true positive) and specificity (true negative) values of 100.0% and 79.5%, respectively, for the modified MCQ (Table III).

Table III: The sensitivity and specificity of the modified MCQ

Viral load (copies/mL)	Adherent (%)	Non-adherent (%)
400 or less	79.5	0
More than 400	20.5	100
Sensitivity & specificity	Sensitivity 100%	Specificity 79.5%

Reliability analysis of the modified instrument

Internal consistency

The modified MCQ demonstrated varying levels of internal consistency across its domains. The Cronbach's alpha for the Drug Taking Behaviour domain (Questions 1 to 7) was 0.65, while the Drug Stopping Behaviour domain (Questions 8 to 10) showed a high Cronbach's alpha of 0.90. Notably, if Question 3 were removed, the Cronbach's alpha for the Drug Taking Behaviour domain would increase to 0.82. However, Question 3 was retained in the final version of the MCQ due to its significant contribution to the construct.

The corrected item-total correlations ranged from 0.46 to 0.85 for the Drug Taking Behaviour domain and from 0.70 to 0.89 for the Drug Stopping Behaviour domain (see Table IV). These correlations indicate how well each question aligns with the overall domain score, with higher values (generally above 0.3) suggesting meaningful contributions to the construct being measured.

For the Drug Taking Behaviour domain, Questions 1 and 2 both exhibited high mean scores (99.7) and low standard deviations (1.81), along with strong corrected item-total correlations of 0.85. Removing these questions would decrease the overall alpha to 0.59, highlighting their positive contribution to the reliability of the instrument. Question 3 had the highest corrected item-total correlation at 0.91, and its removal would lower the alpha to 0.82, underscoring its importance. Questions 4 and 5 demonstrated moderate correlations and would not significantly impact overall reliability if deleted, while Questions 6 and 7 showed strong correlations (0.80 and 0.81), positively contributing to the domain's reliability.

In the Drug Stopping Behaviour domain, Question 8 had a high mean score (99.7) and low variability (SD=1.81) but a lower corrected item-total correlation of 0.70. Removing it would result in a Cronbach's alpha of 1.00, suggesting it may not fit well with the other items. Conversely, Questions 9 and 10 exhibited high mean scores and strong corrected item-total correlations (0.89), indicating their critical role in maintaining the reliability of the scale; their removal would decrease the alpha to 0.80.

Overall, this analysis illustrates the reliability of each question within the domains related to drug adherence. It highlights which questions contribute positively to the overall construct and identifies items that may require further consideration for refinement or removal to enhance the overall reliability of the questionnaire.

Table IV: Cronbach's alpha value of each question in each domain

Domain	Mean	SD	Corrected item-total correlation	Cronbach's alpha if item deleted
Drug taking behaviour				
Question 1	99.7	1.81	0.85	0.59
Question 2	99.7	1.81	0.85	0.59
Question 3	96.3	12.94	0.91	0.82
Question 4	98.9	3.07	0.46	0.61
Question 5	99.7	1.81	0.72	0.60
Question 6	99.8	1.29	0.80	0.62
Question 7	99.9	0.65	0.81	0.64
Drug stopping behaviour				
Question 8	99.7	1.81	0.70	1.00
Question 9	99.8	1.30	0.89	0.80
Question 10	99.8	1.30	0.89	0.80

Test-retest reliability

Although all participants agreed for a two-week test-retest reliability analysis, only 43 of them turned-out to complete the MCQ questionnaire. The ICC value for drug taking behaviour domain was 0.87 (0.78, 0.93) with *p*-value <0.001. The ICC value for drug stopping behaviour was 0.95 (0.95, 0.99) with *p*-value <0.001. The ICC of 0.87 for drug taking behaviour indicates a strong reliability, meaning that the modified MCQ consistently measures the drug-taking behaviour of PLHIV over time. The narrow confidence interval (0.78, 0.93) supports the precision of this reliability estimate.

The ICC of 0.95 for drug stopping behaviour indicates an excellent reliability, suggesting that the modified MCQ is very consistent in measuring the drug-stopping behaviour of PLHIV. The extremely narrow confidence interval (0.95, 0.99) further confirms the precision and robustness of this estimate. Overall, the high ICC values and their statistical significance demonstrate that the modified MCQ is a reliable instrument for assessing medication adherence behaviours in both domains.

DISCUSSION AND CONCLUSION

Modification of the Instrument

The initial MCQ employed a Likert scale to evaluate adherence among hypertensive patients. A Likert scale consists of a sequence of discrete terms or statements, allowing patients to select the response that best matches their state or experience. The original MCQ utilized a five-level Likert scale, spanning from 1 to 5, with 'never' at one end and 'very frequent' at the other. Scores formulated with negative wording were reversed, and all scores were transformed to a 0 to 100% scale with intervals of 20%. This standardized scale effectively gauged adherence in hypertensive patients, where achieving a minimum total score of 80% signified consistent compliance with 'frequent' and 'very frequent' adherence across all questionnaire items.[30]

However, in the context of HIV infection, a 95% adherence rate is widely cited as essential to keep HIV load inhibition below 400 copies/mL.[19] Therefore, the original MCQ's five-level Likert scale was modified to assess a 95% adherence score in HIV patients. Negatively worded scores were reversed, and all scores were converted to a 0 to 100% scale.

In this study, the scale was modified to a continuous rating scale ranging from 0 (very unlikely) to 100 (very likely). This continuous numerical scale allowed patients to choose the value that best described their state or experience. The ends of the scale were anchored with descriptive words, such as 'very unlikely' or 'very likely'.[37] For content validation, the modified scale was reviewed and deemed appropriate by the original MCQ author. The new rating scale allowed PLHIV to place a mark at the appropriate position on a line that runs from 0 to 100, offering more options and potentially more accurate responses.[38] Since the modification only involved

the scale and scoring method, the validation was also applicable to the English version.

In this study, a high adherence rate (93%) to HAART was observed using the modified MCQ. The result was comparable to the reported adherence rates among PLHIV in Uganda (88-93%).[39] However, recent studies in Ethiopia revealed high rates of poor adherence, such as 71.8% in North-Eastern Ethiopia[40] and 66.3% in Eastern Ethiopia.[41] The adherence rate in this study was slightly higher than those in Thailand (82-85%)[42] but higher than the 68% reported in Asia by the TREAT Asia Studies to Evaluate Resistance Monitoring.[43]

According to the Malaysian guidelines for managing adult HIV infection with antiretroviral therapy,[44] patients start with vitamins to evaluate adherence behaviour before initiating HAART. Medication counselling and education were provided by trained pharmacists in the Medication Therapy Adherence Clinic for Retroviral Disease program, which consists of pre-HAART, initiating HAART, and follow-up HAART counselling.[45] Regular educational sessions and on-site counselling at clinics probably contributed to the remarkable adherence rate observed in this study.

Validation Testing and Reliability Analysis of the Modified Instrument

The link between adherence and HAART effectiveness was determined for criterion validity of the modified MCQ. The criterion used for this analysis was the virological outcome, which has been previously established in other adherence studies. [46,47] Adherence was defined as achieving a score of at least 95% on the modified MCQ, while effectiveness was defined as a viral load of fewer than 400 copies/ml within a three-month assessment period.

Criterion validity was assessed in a sample of 43 participants (71.7%) who had available viral load reports. Our findings demonstrated a positive association between adherence, as measured by the modified MCQ, and virological outcomes. Specifically, 100% of adherent patients achieved good virological outcomes, while none of the non-adherent patients did. This significant correlation reinforces the validity of the modified MCQ and aligns with previous research.[13,47]

Sensitivity and specificity of the modified MCQ were evaluated. Sensitivity was defined as the ability to accurately predict poor virological outcomes in non-adherent patients, and specificity as the ability to accurately predict good virological outcomes in adherent patients.[33] The sensitivity of the modified MCQ was 100%, and the specificity was 79.5%, indicating it was a sensitive and specific instrument for assessing adherence to ART.[48]

Reliability was assessed by internal consistency and test-retest analysis. Internal consistency, measured using Cronbach's alpha, showed coefficients of 0.65 for drug-taking behaviour and 0.90 for drug-stopping behaviour domains, consistent with the original MCQ.[30] High Cronbach's alpha values indicate good internal consistency, although values above 0.9 may suggest item redundancy.[50]

Test-retest reliability was assessed using single measure ICC, which was 0.87 and 0.95 for each domain, indicating excellent stability and reliability of the modified MCQ. These results were better than those reported by[30], demonstrating the modified MCQ's stability in the PLHIV population.

STUDY LIMITATIONS

This study had a few limitations. Firstly, most respondents were Malays, not representing the heterogeneous communities of Malaysia. Secondly, recall bias might have occurred during test-retest reliability assessment. If the time interval between test administrations was short, respondents might remember their previous responses, leading to artificially inflated correlations.

The modified MCQ was demonstrated to be a valid and reliable instrument for assessing adherence to ART in PLHIV. With its high sensitivity and adequate specificity, it proves to be an effective tool for clinical practice. Its implementation can significantly enhance medication

therapy management for PLHIV, contributing to better virological outcomes and overall health management.

We recommend further refining of the MCQ and conducting factor analysis could provide insights into the underlying structure of the instrument. This analysis may help identify any redundant items and enhance the overall validity and reliability of the questionnaire.

CONFLICT OF INTEREST

The authors declare that no conflict of interest may arise from the research publication.

ETHICS APPROVAL

Registration for this study was completed through the National Medical Research Register (NMRR)and ethically approved by the Malaysia Ministry of Health Research Ethical Committee (MREC) with the NMRR identification number NMRR-12-335-11995. Signed, written informed consent was acquired from all patients before the study.

ACKNOWLEDGMENT

The authors would like to thank the Director General of Health Malaysia for his permission to publish this paper. This work was financially supported by Universiti Sains Malaysia RU Grant (grant no. 1001/PSK/8620015).

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CASE REPORT

Navigating the Diagnostic Maze of Psoriatic Arthritis sine Psoriasis in Primary Care.

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Keywords
back pain, Spondyloarthritis, Psoriatic, Arthritis

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Received: 8th August 2024; Accepted: 26th December 2024

Doi: https://doi.org/10.31436/imjm.v24i02/2693

ABSTRACT

Psoriatic arthritis, a seronegative spondyloarthropathy is an autoimmune inflammatory joint disease. However, the diagnosis is often delayed due to the absence of specific biomarkers and a lack of awareness among primary care providers, who may be unable to recognize the key features of the condition. We present a case of a 30-year-old woman with a 9-month history of lower back pain and multiple joint pain. Despite elevated inflammatory markers like C-reactive protein and erythrocyte sedimentation rate, other initial tests including rheumatoid factor and antinuclear antibody tests were all negative. The appearance of new skin lesions in the 10th month prompted further evaluation and resulted in a diagnosis of psoriatic arthritis. Treatment with Celecoxib and Methotrexate led to significant improvement in her condition. This case underscores the crucial role of primary care providers in the early detection and management of spondyloarthropathy, helping to prevent joint damage and enhance patient outcomes.

INTRODUCTION

Seronegative spondyloarthropathies (SpA) are a group of autoimmune, inflammatory arthritis conditions that include psoriatic arthritis (PsA), ankylosing spondylitis (AS), juvenile-onset SpA, enteropathic arthritis, and reactive arthritis. Common clinical features in SpA include asymmetrical peripheral arthritis, inflammatory back pain, dactylitis, enthesitis, and extra-articular manifestations. These conditions are characterized by a negative rheumatoid factor (RF) and pose significant challenges in early diagnosis. A delay in diagnosis of SpA with an average delay of 5 to 7 years, or even longer in women, can lead to structural joint damage.[1] Even a 6-month delay in diagnosis can increase the risk of joint erosion and negatively impact patient outcomes.[2] Early recognition and detection by primary care providers is crucial to mitigate the risk of joint erosion and improve long-term outcomes.

CASE REPORT

A 30-year-old woman presented with a 9-month history of intermittent lower back and joint pain. The lower back pain was characterized by an achy, stiff sensation, typically lasting for 30 minutes to an hour. The pain worsened with rest and improved with movement, frequently disrupting her sleep with severe pain, rated 8/10, which caused her to wake up in agony during the night. Despite multiple medical consultations, her symptoms persisted. Initial investigations, including anti-nuclear antibody (ANA), rheumatoid factor (RF) and radiographic yielded normal results. She was initially diagnosed with musculoskeletal pain and prescribed analgesics for symptom management.

As her symptoms worsened, the patient developed pain in both her heels, her right wrist, and the small joints in her right hand, which significantly impacted her daily activities and work performances, resulting in frequent medical leaves. Despite attempting various supplements and over-the-counter analgesics, her symptoms persisted. Throughout her illness, she denied experiencing any depressive episodes. After nine months of unresolved pain, she sought a second opinion at a tertiary hospital's primary care clinic.

On examination, onycholysis was noted on her right thumb (Figure 1), but there were no signs of nail pitting, transverse ridging, or tenderness and swelling in her hands. There was mild tenderness and fusiform swelling over the right fourth toe, consistent with dactylitis (Figure 2), along with mild swelling of the right heel, suggesting enthesitis. Otherwise, there were no visible skin lesions, unremarkable neurological and motor examinations and her spine examination revealed a full range of motion without deformity; Schober's test was negative and the sacroiliac joint was non-tender.

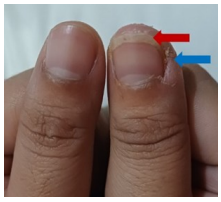

Figure 1: Onycholysis (red arrow) of right thumbnail with periungual involvement (blue arrow).

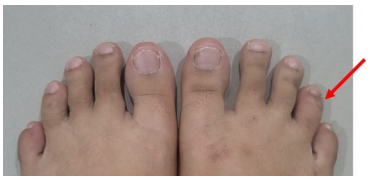

Figure 2: The presence of tender and fusiform swelling over the right 4th toe (dactylitis) with post-inflammatory hyperpigmentation.

Re-evaluation revealed elevated inflammatory markers, with CRP level of 36 mg/L and an ESR of 38 mm/hour, alongside negative RF, ANA and anti-cyclic citrullinated peptide (anti-CCP) tests. A pelvic x-ray showed irregularities and sclerosis in both iliac bones with a normal sacroiliac joint (Figure 3). Based on these findings, she was diagnosed with inflammatory back pain (IBP) with suspected diagnosis of seronegative rheumatoid arthritis, and referred to rheumatology for further evaluation.

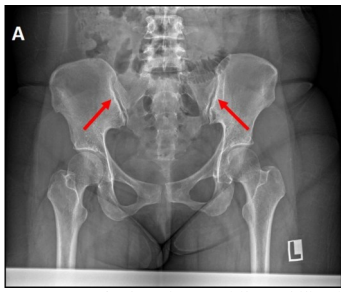

Figure 3: Presence of sclerosis over bilateral iliac bone and irregularities with normal sacroiliac joints

One month later, during the rheumatology assessment, new scaly skin lesions appeared on her scalp, elbow, knee and foot. She had no prior history of such lesions or family history of psoriasis. A dermatology referral confirmed the presence of plaque psoriasis affecting 1-2% of her body surface area, including the previously mentioned areas as well as the intergluteal cleft and bilateral postauricular regions (Figure 4). She was treated with topical corticosteroids and coal tar shampoo. Her human leukocyte antigen B27 (HLA-B27) testing was negative and magnetic resonance imaging (MRI) of the sacroiliac joints revealed bilateral iliac bone fat metaplasia, indicative of post-inflammatory changes consistent with axial spondyloarthritis (SpA).

The patient met the Classification Criteria for Psoriatic Arthritis (CASPAR) and was diagnosed with Psoriatic Arthritis (PsA). Due to persistent disease activity, she was initiated on a treatment regimen consisting of Celecoxib 200 mg twice daily, Methotrexate 15 mg once a week, and Folate 5 mg daily (excluding the day of methotrexate administration). Follow-up assessments revealed normalized ESR and CRP levels, significant pain relief, and clinical remission achievement which enable her to resume normal daily activities.

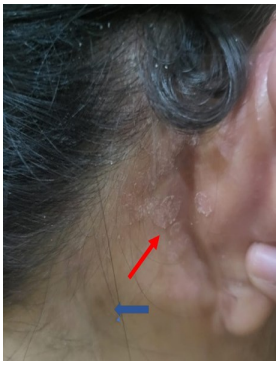

Figure 4: Post-inflammatory hyperpigmentation (blue arrow) with thin, mild psoriatic plaque with scaling (red arrow) were detected on her scalp and right posterior auricular.

DISCUSSION

Differentiating between inflammatory and mechanical low back pain is crucial as their treatments differ significantly. This patient's primary presentation was inflammatory back pain (IBP), a hallmark feature of axial SpA, which typically manifests before the age of 40. She met all five Assessment of Spondyloarthritis International Society (ASAS) criteria of IBP: age of onset less than 40 years old, insidious onset, nocturnal pain, lack of improvement with rest and improvement occurs with movement.

In this case, psoriasis developed 10 months after the onset of arthritis, illustrating the phenomenon of PsA sine psoriasis, which affects 13.5-24.6% of PsA cases globally.[3]

The prevalence of PsA sine psoriasis in Malaysia remains underreported. Typically, psoriasis appears 7–12 years prior to arthritis.[4] Thus, the delayed skin manifestation in this patient poses significant diagnostic and treatment challenges to the primary care. However, PsA can still be diagnosed in the absence of visible psoriasis using the CASPAR criteria, which offer high specificity (98.7%) and sensitivity (91.4%).[3]

PsA comprises of six key domains which include enthesitis, dactylitis, axial, nail, skin, and peripheral arthritis. Nail psoriasis, dactylitis, enthesitis, and distal interphalangeal (DIP) involvement are the key features that differentiate the diagnosis of PsA sine psoriasis from rheumatoid arthritis (RA) and other forms of SpA. While PsA typically begins asymmetrically and oligoarticularly, it may progress to a symmetric pattern resembling RA. Notably, PsA often affects the DIP joints, whereas RA predominantly involves the wrists and small hand joints symmetrically, sparing the DIP joints.[5]

Early detection of skin or nail lesions is crucial for diagnosing PsA. While psoriasis on the trunk or limbs is easily noticeable, lesions in areas such as the scalp, intergluteal region, umbilicus, elbows, knees and nails are often overlooked, as illustrated in this case.[6] Nail involvement is present in 40% of psoriasis patients but affects up to 80% of those with PsA, with fingernails being more commonly being affected than toenails.[7] Key signs of nail involvement include pitting, onycholysis and transverse ridging.

Enthesitis and dactylitis are common in PsA, affecting 30-50% and 40-50% of patients, respectively. Enthesitis typically involves the plantar fascia and Achilles' tendon, while dactylitis, is often typically seen in the feet, is associated with more severe disease.[5,6,8] Therefore, a comprehensive lower limb examination is essential to identify these key features in PsA.

Axial involvement occurs in 25-70% of PsA, predominantly affecting the spine and sacroiliac joints. Compared to AS, axial PsA generally presents with milder symptoms and radiographic findings. HLA-B27, a genetic marker for AS, has a low association with axial PsA, with positivity rate of 14-40% in PsA versus over 80% in AS.[9] While HLA-B27 testing is helpful, a positive result does not confirm axial SpA and a negative test does not exclude it.[1] Elevated ESR and CRP levels are common but not always present. For suspected axial involvement, an anterior-posterior pelvic x-ray should be performed and evaluated using the modified New York criteria. However, relying on plain x-ray alone may delay diagnosis by up to 10 years due to the late radiographic changes.[1] Therefore, MRI is preferred for early detection of active inflammatory changes such as subchondral bone edema, synovitis and capsulitis, as well as chronic lesions like fat metaplasia, sclerosis, erosions, joint space narrowing, syndesmophytes and ankylosis.[1,10]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment for axial PsA. In this case, the patient also had other PsA manifestations, including dactylitis, enthesitis, peripheral arthritis, and skin and nail involvement. Thus, she was started on methotrexate, a conventional Disease Modifying Anti-Rheumatic Drug (DMARD), which led to clinical improvement and remission. Although biologic DMARDs are recommended for treating axial PsA, they were not used in this case due to the absence of active sacroiliitis and the patient's positive response to methotrexate and NSAIDs.[9]

Primary care providers should be more vigilant in recognizing IBP and clinical features of PsA. This case highlights the diagnostic complexity of PsA and the importance of thorough history-taking, clinical examination, laboratory test and MRI to distinguish PsA from other forms of SpA.

CONCLUSION

Early detection of PsA in the absence of skin lesions is challenging and often leads to misdiagnosis. The ASAS IBP and CASPAR criteria can help primary care providers in identifying inflammatory back pain and diagnosis of PsA earlier. An early referral to rheumatologist and timely treatment can prevent joint damage and improve quality of life. Therefore, it is essential for primary care providers to be familiar with the clinical features of PsA to ensure early recognition and intervention.

CONFLICT OF INTEREST

The authors have no conflict of interest.

ACKNOWLEDGEMENT

The authors appreciate the cooperation of the patient in providing her consent for the case to be used for learning and publication purposes. Thanks to Hospital Raja Perempuan Zainab II (HRPZ II) for their contribution to the management of this patient

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CASE REPORT

From Weight Loss to Bedroom Gains: A Case Report on Bariatric Surgery Resolving Erectile Dysfunction

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Keywords
Erectile Dysfunction (ED), Obesity, marital satisfaction , Anxiety

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Received: 20th June 2024; Accepted: 19th February 2025

Doi: https://doi.org/10.31436/imjm.v24i02/2647

ABSTRACT

This case involves a 59-year-old Malay man who struggled with erectile dysfunction (ED) due to his poorly controlled underlying health conditions for about two years. Despite long-term management for diabetes, hypertension, and dyslipidemia, his weight gain and worsening sugar control affected his ability to maintain an erection during sexual activity. He tried various medications and treatments, including traditional remedies and oral drugs like Kamagra, with little success. Eventually, he underwent bariatric surgery, which led to improvements in his ED, along with better control of other health issues. Psychological factors, like stress and desperation, also played a significant role in his journey, highlighting the importance of holistic care and proper management of both physical and mental health in addressing er ED ectile dysfunction. This case underscores the potential benefits of bariatric surgery in obese patients with ED and emphasizes the need for comprehensive healthcare approaches to manage these complex issues effectively.

INTRODUCTION

Erectile dysfunction (ED) is a condition that extends beyond its impact on the physical health of men, influencing various aspects of their lives and relationships. Beyond its physiological effects, ED can cause emotional distress, erode self-esteem, and strain intimate relationships. ED often serves as a barometer for overall health, reflecting underlying conditions such as cardiovascular disease, obesity, or psychological factors like stress and anxiety. Consequently, addressing ED requires a holistic approach, encompassing medical intervention, lifestyle changes, and open communication between partners. By acknowledging the broader implications of ED, we can foster a more supportive and understanding environment.

In Malaysia, ED is a very common, though frequently taboo, problem among men. The most recent National Health and Morbidity Survey (NHMS) in Malaysia showed that there is a prevalence of moderate to ED in up to 31.6% of the population.[1] Despite its widespread occurrence, cultural taboos and stigma surrounding discussions of sexual health can hinder individuals from seeking help or openly addressing their concerns. However, recognizing ED as a medical condition rather than a personal failure is crucial in promoting awareness and encouraging men to seek professional assistance.

Malaysia is also grappling with the growing issue of obesity. In the World Health Organization (WHO) report of 2019, Malaysia ranked highest among Asian nations, with over 64% of the male population being overweight or obese.[2] Based on the NHMS 2015, the rate of obesity in individuals aged 18 and above was over 17.7% (equivalent to 3.3 million people), while the rate of overweight patients was 30% (equivalent to 5.6 million people). [3] Currently, bariatric surgery is the only effective option for attaining sustained weight loss in persons with obesity. Over the past decade, there has been a notable increase in the number of individuals choosing bariatric surgery and reaping numerous benefits.[4]

Male sexual dysfunction refers to a range of health issues, specifically including a decrease in sexual desire (libido), difficulty achieving or maintaining an erection, or problems with ejaculation. ED is the most prevailing problem associated with obesity in male patients. In contrast, hypertension, dyslipidemia,

obesity, and diabetes mellitus, which are components of the metabolic syndrome, are reversible risk factors for ED. After bariatric surgery, a complicated mechanism reduces the metabolic risk factors, which lead to a more marked resolution of erectile function. However, given the complexity of ED's origins, treating the problem will require a multidisciplinary approach.

A study involving male obese patients showed that erectile ED was common before bariatric surgery[5], with significant improvement post-surgery. Another study found that bariatric surgery is more effective than non-surgical weight loss in improving erectile performance and hormone levels in morbidly obese men.[6] However, this case discussed here represents the delicate management of a patient who faced difficulties in encountering an ED during the initial treatment.

CASE REPORT

This is a case of a 59-year-old Malay gentleman who has had a longstanding ED since his underlying comorbidities became uncontrolled in the past two years. He is a non-smoker and does not take any alcohol. He has been under primary care follow-up for diabetes mellitus, hypertension, and dyslipidemia for almost 10 years, but noticed his problem with erection when his weight increased above 85 kg and worsening of blood sugar control. He struggled to gain an erection and penetration during attempted sexual intercourse with his wife. His libido was normal, and he claimed to have a normal morning erection. His International Index of Erectile Function (IIEF-5) was 5. Psychologically, he was less satisfied, leading to less motivation and anxiousness upon attempting intercourse. He was married to a 47-year-old lady for 20 years. His wife's libido is normal, and her sexual satisfaction was not up to expectations. Thus, the pressure and tension led to high expenditure in various clinics and private hospitals for medication and treatment for the erectile problem.

His visits to the general practitioner started around two years ago. He was initially using traditional supplements such as *Tongkat Ali*, with no positive results. He was then prescribed oral Kamagra but stopped the usage after two pills. He claimed to have an erection but was unable to achieve ejaculation even after 30 minutes and started to feel mild chest discomfort after the intake of the traditional drug. He attempted a few more medications such as oral Sildenafil and Tadalafil subsequently, but his ED did not improve. He also took a course of platelet-rich plasma intra-cavernosal injection without success. One of the GPs eventually referred him to a private center in Kuala Lumpur for bariatric surgery. He underwent bariatric surgery in January 2023. He was then referred to a teaching hospital men's health clinic for further ED management. He had spent up to RM 30,000 of his earnings.

Clinically, the patient looked well without exhibiting distress or low mood upon encounter. He was well-hydrated, well-kept, and able to express his worry clearly. He was of a good build, is not obese, and had no pallor or jaundice. His hair distribution is appropriate. Upon examination his genital organ was grossly normal, and his testicular size was average at 20 ml bilaterally. He exhibited no sign of hypogonadism.

After the bariatric surgery, the IIEF-5 score improved from 5 to 8 (Table I). The laboratory blood parameters showed improvement in the underlying comorbidities (Table II). The blood sugar control improved with an HbA1c of 5.7% and a low-density lipoprotein level of 2.7 mmol/L. Throughout the men's health clinic follow-up his renal and liver functions were normal. His serum testosterone level was normal at 18.72 mmol/L.

He was re-started on oral Sildenafil 100 mg on a per-needed basis upon the encounter, with counseling on the correct way to take the medication. With mild improvement in erectile function, he was keen to change to oral Tadalafil due to previous experience, and it was easier to consume. He tolerated Tadalafil, and his IIEF-5 score improved to 15 (Table I). His Erection Hardness Score improved from 2 to 3. He gradually tapered down his medication and eventually maintained his erection for up to 20 minutes without the help of any PDE-5 inhibitor.

Table I: IIEF-5 score for the patient through the follow-up

Over the past four weeks,						
1	How do you rate your confidence that you could get and keep an erection?	Very low 1[1]	Low 2[2]	Moderate 3[3]	High 4	Very high 5
2	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/ never 1[1]	A few times 2[2]	Sometimes 3[3]	Most of the times 4	Almost always/ always 5
3	During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?	Almost never/ never 1[1]	A few times 2[2]	Sometimes 3[3]	Most of the times 4	Almost always/ always 5
4	During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult 1[1,2]	Very difficult 2	Difficult 3[3]	Slightly difficult 4	Not diffficult
5	When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/ never 1[1,2]	A few times 2	Sometimes 3[3]	Most of the times 4	Almost always/ always 5

[1] Score during pre-bariatric surgery encounter
[2] Score during post-bariatric surgery encounter, before PDE-5 inhibitor treatment
[3] Score during post-bariatric surgery encounter, after PDE-5 inhibitor treatment

Table II: IIEF-5 score for the patient through the follow-up

	Pre bariatric surgery (January 2023)	**Post bariatric surgery (May 2023)**
Weight (kg)	90.7	70.1
BMI (kg/m^2)	31.0	23.9
HbA1c (%)	7.0	5.7
LDL (mmol/L)	3.2	2.7
Triglycerides (mmol/L)	1.51	1.2
Serum Testosterone (ng/dL)	-	18.73

DISCUSSION

Erectile dysfunction and obesity are two prevalent health concerns affecting millions worldwide. ED refers to the consistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance.[7] It is persistently an underreported issue despite its high prevalence and negative impact psychologically and financially, as well as the availability of numerous successful treatments. The stigma of discussing ED as a problem remains a central issue, and the appropriate way to tackle this is to prepare healthcare providers with ample knowledge and communication skills to approach them. Effective screening of men's health problems during regular non-communicable disease follow-ups or outpatient clinic visits is vital in tackling these issues.

In our case, the patient did not reveal his concern about his sexual problem during his regular follow-up. Instead, he went to alternative clinics to seek opinions and treatment.

Obesity is characterized by excess body fat accumulation, often leading to various metabolic complications. There is significant association between obesity and ED, with obese men found to experience a 50% higher incidence of ED.[8] Obesity also contributes to the development of cardiovascular diseases and type 2 diabetes, which are known risk factors for ED. Currently, the only mainstay of treatment for obesity with complications is bariatric surgery.

Understanding the interplay between obesity and ED is crucial for healthcare professionals in managing these conditions effectively. Addressing obesity through lifestyle modifications or surgical interventions like bariatric surgery may improve overall health and alleviate ED, ultimately enhancing the quality of life for affected individuals. Systematic reviews have mentioned that despite the significant benefit of bariatric surgery on ED, multifactorial causes need to be considered and managed altogether.[9]

Psychological factors play a significant role in both ED and obesity. Factors such as stress, anxiety, sadness, and low feelings of self-worth might contribute to the development or worsening of the condition.[10] They may interfere with sexual arousal, performance, and satisfaction, resulting in challenges in attaining or sustaining an erection. In our patient, the pressure and desperation led to an unhealthy search for a proper treatment. Over-spending and trials of the possibly harmful, yet-to-be-approved methods may bring more damage to patients.

It is essential to review the general health condition of each ED patient, despite reviews and case reports supporting the importance of weight loss through bariatric surgery in improving the outcome. A healthy lifestyle, keeping the co-existing comorbidities under control, healthy aging, and proper sexual health education are crucial to ensure ED is managed accordingly.[1] Our patient

was followed up thoroughly for his diabetes problem, hypertension, and dyslipidemia. He managed to maintain his weight, and he was assisted with a PDE-5 inhibitor initially to assist in his ED problem. With support from his spouse and maintenance of healthy lifestyle, he was eventually able to regain satisfaction in his sexual life.

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CASE REPORT

Peptoniphilus asaccharolyticus Septic Abortion Precipitating Cerebral Venous Thrombosis

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ABSTRACT

Peptoniphilus, a Gram-positive anaerobic coccus, is an opportunistic bacterium in the human microbiota. Obstetrics-associated *Peptoniphilus asaccharolyticus* infections are rarely reported, with only four reported cases, all patients recovered without complications. We describe a *P. asaccharolyticus* septic abortion at 8 weeks of gestation, complicated with cerebral venous thrombosis (CVT) and septic ileus. A 33 year-old Indonesian lady who is 8 weeks pregnant presented with sudden right-sided body weakness, with heavy vaginal bleeding and fever. She had attempted a self-induced abortion using over-the-counter medication prior to symptom onset. She was pale and septic. Besides evacuation of conception products, the patient was hospitalized for parenteral antibiotics therapy. Brain CT angiography revealed CVT. Anaerobic blood culture grew *P. asaccharolyticus,* identified via MALDI-TOF mass spectrometry. Her admission was complicated with septic ileus. Following eight days of antibiotics treatment, she requested a transfer to her hometown hospital for care continuation. *P. asaccharolyticus* is a disastrous organism to complicate septic abortions. Early clinical suspicion and prompt initiation of effective antibiotics are critical.

Keywords
Septic abortion, Peptoniphilus, cerebral venous thrombosis, MALDI-TOF

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Received: 24th March 2024; Accepted: 27th February 2025

Doi: https://doi.org/10.31436/imjm.v24i02/2571

INTRODUCTION

The Peptoniphilus genus is a Gram-positive obligate anaerobic coccus belonging to the family *Peptoniphilaceae.* Formerly classified under the genus Peptostreptococcus, it is now a separate genus consisting of 17 species. They are known as members of human gastrointestinal, genitourinary and skin microbiota. Increasing number of human infections caused by this opportunistic pathogen have been reported. Individuals with prosthetic joints or other foreign body introduction, the immunosuppressed and the elderly are at higher risk for infection. However, obstetric cases of Peptoniphilus spp. infections have been rarely reported, with only four cases documented globally. Notably, none of these cases involved septic abortion complicated by CVT. We present a case of *Peptoniphilus asaccharolyticus* septic abortion, complicated with cerebral venous thrombosis (CVT) and septic ileus.

CASE HISTORY

A 33 year old Indonesian lady was referred by a private hospital for symptomatic anaemia. Initially, she presented to the hospital complaining of sudden onset of right-sided body weakness and numbness. She had been having heavy vaginal bleeding for a week, worsening during the last two days. Additionally, she reported vomiting and abdominal pain for four days and two days of fever, chills and rigors. Upon discovering she was 8 weeks pregnant, she resorted to terminating pregnancy using over-the-counter unnamed medication, which she inserted intra-vaginally, one day prior to symptom onset. She denies facial asymmetry or drooling of saliva.

On examination, she appeared pale, lethargic, febrile with a temperature of 38°C and tachycardic of 110 beats per minute. She was normotensive with normal oxygen saturation under room air. Abdominal and cardiorespiratory examinations were unremarkable. Neurological examination revealed right-side facial palsy, and hypotonia, with a low muscle power scale of 0/5 over the right upper and lower limbs, compared to 5/5 on the contralateral side. A bedside abdominal ultrasound scan

revealed a thickened endometrial lining of 4.3cm, with neither adnexal mass nor pelvic free fluid.

Urgent full blood count revealed leucocytosis with a total white cell count of 20.67 x 10^3/μL and moderate anaemia with haemoglobin of 7.2 g/dL. The urine dipstick for the pregnancy test was positive. Platelet count, coagulation profile, and renal and liver function tests were unremarkable. Serum β-human chorionic gonadotropin (β-hCG) was elevated (4,999 mIU/mL).

Per vaginal examination revealed approximately 50 cc of the retained product of conception, which the attending doctor evacuated with sponge forceps. A post-evacuation transvaginal ultrasound showed a reduction in endometrial thickness to 2 cm. The patient was given intramuscular oxytoxin/ergometrin 500 μg/5 IU, a peripheral blood sample was aseptically collected and cultured, and the patient's antibiotic therapy was then commenced with intravenous (IV) ceftriaxone 2 gm daily and IV metronidazole 500 mg thrice daily. She was then admitted to the ward for a blood transfusion.

A computed tomography angiogram of the brain and carotids was performed and demonstrated cerebral venous thrombosis of the superior sagittal sinus and right sigmoid sinus, with acute venous infarct at the left frontal lobe (Figure 1). There was no evidence of aneurysm or arterio-venous malformation. She was started on subcutaneous enoxaparin 60 mg twice daily.

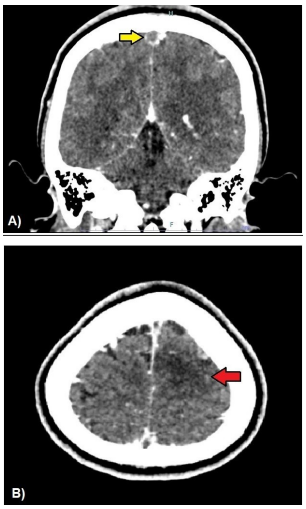

Figure 1 (A) and (B): Computed tomography angiogram of patient's brain. Note the filling defect over the superior sagittal sinus (yellow arrow), suggestive of cerebral venous sinus thrombosis, with acute venous infarct at the left frontal lobe (red arrow).

After 25 hours of incubation in BD BACTEC™, blood culture was flagged positive. A Gram stain was performed and showed Gram-positive cocci in clusters. Aerobic cultures on blood agar, chocolate agar, and MacConkey agar did not yield any growth. After 48 hours of anaerobic incubation, the anaerobic blood agar culture demonstrated pure growth of small, mucoid, grey colonies (Figure 2). The growth was identified via matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF) MS (Bruker Daltonics, Bremen, Germany), yielding *Peptoniphilus asaccharolyticus* with log[score] value of 2.17, using a direct transfer method. Antimicrobial susceptibility testing was performed via gradient minimum inhibitory concentration (MIC) strip (LiofilchemÒ, Roseto degli Abruzzi, Italy), using a 0.5 McFarland colony inoculum suspension and incubated anaerobically in an anaerobe chamber for 48 hours. The isolate demonstrated susceptibility to both penicillin and metronidazole, with MIC levels of 0.016 μg/mL and 0.75 μg/mL, respectively, as interpreted according to the Clinical and Laboratory Standards Institute (CLSI) M100, 34th Edition guidelines.

Figure 2: *Peptoniphilus asaccharolyticus* colonies on blood agar medium, following 48 hours of anaerobic incubation. Note the opaque greyish non-haemolytic colony with raised center.

The aerobic blood culture remained sterile during the five days of incubation. High vaginal swab culture grew *Candida albicans*. Products of conception tissue were not sent for culture; instead, only a tissue swab was sent, which also grew *Candida albicans*.

On her fifth day of admission, her condition was complicated by septic ileus, which resolved after one day of nasogastric tube insertion and hydration. After the eighth day of hospitalization, she was discharged upon her request to be transferred to a district hospital in Indonesia for continuation of care, nearer to her relatives.

DISCUSSION

Up to 30% of human anaerobic infections are caused by Gram-positive anaerobic cocci, commonly encountered in the female genital tract, soft tissue, and orthopaedic infections. Peptoniphilus species is reported to be isolated from blood, bone, joint, skin, and soft tissue infections, vaginosis, and various organ abscesses such as kidneys, peritonsillar, and spine. Most Peptoniphilus infections, similar to other anaerobic infections are part of polymicrobial infections, with few monomicrobial infections reported among the elderly, immunosuppressed, and post-operative patients.[1] For this patient, *P. asaccharolyticus* was not isolated in the products of conception because only a swab was sent. According to our local laboratory flow, only aerobic culture will be performed for swab cultures. A proper tissue culture, instead of the swab, would guarantee a better organism yield, including anaerobic bacteria. This highlights the importance of proper communication between clinicians and laboratory staff in alerting both to the possibility of anaerobic infections in cases of septic abortion and the correct way to obtain and transport relevant clinical specimens for better organism yield.

Anaerobic bacterial infections have been a diagnostic challenge for both clinicians and microbiologists alike. With severe, invasive infections abruptly manifesting in patients, clinicians usually treat the infections empirically with antibiotic agents targeting Gram-negative bacteria, some of which do not have coverage against anaerobic microorganisms.

From the microbiology laboratory staff's perspective, anaerobic organisms are not only fastidious and require special culture media and prolonged incubation conditions, but conventional bacterial identification testing often fails to differentiate beyond the genus level. For instance, biochemical testing fails to differentiate between *P. harei* and *P. asaccharolyticus*. Fortunately, MALDI -TOF MS has proved reliable in identifying clinically significant anaerobic bacteria. Although inferior to its newer competitors, VITEK MS and MALDI Biotyper system, the identification accuracy of *Peptoniphilus spp* using MALDI-TOF MS was found to be as high as 86%, with a 95% CI of 81 to 91%.[2]

Cerebral venous thrombosis is a rare venous thrombotic event predominant in females. It is triggered by the imbalance between haemostasis, rendering sluggish venous blood flow and disturbance in cerebral perfusion. For this patient, her known prothrombotic risk factors include pregnancy and sepsis, although there may be additional undiagnosed thrombophilia or comorbidity predisposing to the phenomenon. Fortunately, CVT carries a good prognosis, and most patients survive with almost no permanent neurological deficit. Our patient was lost in follow-up due to her transfer to her hometown hospital, thus her recovery was not confirmed. The chronological association between foetal outcome and obstetric CVT remains uncertain. Bertani described a severe case of CVT in early trimester pregnancy, leading to significant long-term neurological damage and spontaneous abortion.[3] In our case, septic abortion occurred prior to the neurological event.

Brown and colleagues have compiled 15 cases of peptoniphilus bacteraemia and their outcomes. Among these cases, all three pregnancy-related peptoniphilus bloodstream infections involved young mothers. The prognosis for the conceptus was grimmer than that of adults. Specifically, the overall mortality rate of adult patients was 20%, involving elderly patients above 80 years old with significant comorbidities. However, despite the survival of all peptoniphilus-infected pregnant mothers, only one was able to return home with her surviving newborn.[4] This may be due to the differences in the gestational age between the patients at the time of infection, as the mother of the only surviving baby was in the third trimester at the onset of infection. This theory is supported by Althaqafi and colleagues, who reported second-trimester loss.[1] Based on the previously discussed case reports, our case represents the fifth documented instance of *P. asaccharolyticus* septic abortion worldwide.

The Malaysian National Antimicrobial Guideline recommends a 14-day regime of the combination therapy of ampicillin, gentamicin, and metronidazole for septic abortions. Alternative combinations include ampicillin/ sulbactam plus oral doxycycline or clindamycin with gentamicin. Although the clinician empirically treated this patient with ceftriaxone and metronidazole instead of

the recommended antibiotics, the isolate was tested susceptible to both antibiotics.

CONCLUSION

Septic abortion can aggravate the rare pregnancy-induced cerebral venous sinus thrombosis. The anaerobic peptoniphilus is an organism capable of complicating septic abortions. Upon clinical suspicion of septic abortion, immediate commencement of effective antibiotics is vital for achieving a favourable prognosis for patients. MALDI-TOF MS serves as a reliable diagnostic tool for rapid identification of anaerobic organisms.

ACKNOWLEDGEMENT

Special thanks are extended to the Director General of Health for his permission to publish this article.

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