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The Medical Journal of Malaysia

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Acknowledgements:
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Example references Journals:
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Rampal L and Liew BS. Coronavirus disease (COVID-19) pandemic. Med J Malaysia 2020; 75(2): 95-7.
Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia 2020; 75(6): 613-25.
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Books and Other Monographs:
Personal Author(s)
Goodman NW, Edwards MB. 2014. Medical Writing: A Prescription for Clarity. 4 th Edition. Cambridge University Press.

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

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

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

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Evaluating healthcare response to COVID-19 across Southeast Asia: A post-Pandemic Reflection and Way Forward

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ABSTRACT

This paper provides a comprehensive analysis of Southeast Asian countries' responses to the COVID-19 pandemic, particularly focusing on Malaysia, Singapore, Thailand, the Philippines, Indonesia, and Myanmar. The primary objective is to explore how the pandemic has evolved in these nations, how the respective healthcare delivery systems responded, and the current COVID-19 status within each country. It presents epidemiological trends and governmental strategies adopted in combating the pandemic. The paper also outlines lessons learned and future challenges, highlighting key areas like global health diplomacy, the need for collaboration, clear government agency communication, and a stance against social discrimination. It culminates in an assessment of the post-pandemic landscape, discussing the transformation of public health policies and the socio-economic implications of pandemic management.

KEYWORDS:
COVID-19, Malaysia, Singapore, Thailand, Philippines, Indonesia, Myanmar, Southeast-Asian Nations, healthcare

INTRODUCTION

The COVID-19 pandemic, a global crisis of unprecedented scale, indelibly marked the early 21st century. Across Southeast Asia, countries with disparate economic, socio-cultural, and political systems navigated the turbulent waters of the pandemic, each charting its course. This paper provides a follow-up on a previous article reported by Rampal et al.,[1] which charted the epidemiological trends and government interventions in these nations during the early uncertainty of the pandemic in 2020. Their prior analysis illuminated each country's unique challenges, reflecting their distinctive socio-economic contexts and health infrastructures. Here, we turn our gaze to the post-pandemic landscape in the six Southeast Asian nations – Malaysia, Singapore, Thailand, Indonesia, the Philippines, and Myanmar.

Most of these countries have moved into an "endemic phase". This paper aims to explore how the pandemic has evolved in these nations, how the respective healthcare delivery systems responded, and the current COVID-19 status within each country.

In doing so, the analysis attempts to derive insights into the nuances of public health governance, the socio-economic implications of pandemic management, and lessons for future crises. By dissecting the successes and shortcomings of each country's response, the objective is to glean lessons that could fortify these nations – and indeed, the broader global community – against future health crises.

Epidemiological trends of the COVID-19 pandemic in the Association of Southeast Asian Nations (ASEAN) countries

The latest available epidemiological data of total COVID-19 cases, deaths, and mortality rates extracted from the World Health Organization's (WHO's) database from January 2020 to 2nd August 2023 for Malaysia, Singapore, Thailand, Philippines, Indonesia, and Myanmar are shown in Table I.[2]

The total number of COVID-19 cases in these six countries accounted for 23,998,461 cases, with a mortality rate of 1.339%. Although the region's mortality rate was slightly higher than that globally, there was considerable diversity in the epidemiological trends among Malaysia, Singapore, Thailand, the Philippines, Indonesia, and Myanmar. Indonesia has reported the highest number of confirmed COVID-19 cases among the six nations, with a total of 6,812,670 cases, followed by Malaysia with 5,081,682 cases. However, Myanmar reported a significantly lower number of cases at 641,074. Looking at the mortality rates, Myanmar stands out with the higher rate (3.04%)followed by Indonesia (2.37%), Philippines (1.59%), Malaysia (0.731%), Thailand (0.723%) and .Singapore which showed a remarkably lower mortality rate at 0.073%.

It is noted that vaccine procurement, distribution, and demand presented varying challenges across the region. The WHO's *Strategy to Achieve Global COVID-19 vaccination by Mid-2022* aimed to cover 70% of the total population by June 2022 and Southeast Asia has notably excelled in this respect.[3] To circumvent COVID-19 Vaccines Global Access (COVAX's) supply constraints, several Southeast Asian countries implemented a multiple-sourcing strategy and benefitted from the supply of vaccines facilitated through Covid-

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diplomacy. Table II summarizes the vaccines authorized by each respective government within the region.[4]

Singapore leads the vaccination trends across the region, with a robust 89.7% of its population having received a complete primary series of vaccinations. Malaysia follows closely with an impressive 85.11% of its population vaccinated. Thailand and the Philippines have also made considerable progress, with vaccination rates of 77.62% and 71.58% respectively, followed by Indonesia and Myanmar with 63.94% and 64.69% of their populations vaccinated. A notable achievement, given the challenges imposed upon health systems in less developed countries globally. Table III summarizes the total number of people and percentage of the population vaccinated with a complete primary series in each country, as well as the percentage of the population.[2]

However, these relatively lower percentages could be ascribed to a combination of an initial lack of vaccine supply and hesitant demand. Vaccine hesitancy was prevalent across Southeast Asia in the early stages of vaccine rollout. Notably, the Philippines, Thailand, and Indonesia reported lower-than-average willingness to get the vaccines, attributed largely to a lack of information about vaccines, misinformation, mistrust, and underestimation of their benefits.[5] In Myanmar, ongoing internal political challenges may have obstructed the country's vaccination rates. However, both the availability and uptake of vaccines have shown a progressive increase over time.

Country-specific situational analysis and trajectories

Malaysia

The COVID-19 pandemic in Malaysia, evolved through a series of waves, each leading to varying governmental responses from strict lockdowns to subsequent easing of restrictions.

Malaysia reported its first cases on 25th January 2020, involving three Chinese tourists.[5] On 17th March 2020, the government initiated a nation-wide Movement Control Order (MCO), lasting until early May. As the situation improved, the government transitioned to the "Conditional Movement Control Order" (CMCO) in May, followed by the "Recovery Movement Control Order" (RMCO) in June 2020.6 During this period, the Malaysian government also established a COVID-19 fund, set up a provisional hospital, and allocated additional funds of 1.6 billion ringgits to the Ministry of Health and 250 billion ringgits to small and medium enterprises.[7]

A state of emergency was declared in January 2021, suspending Parliament and State Legislative assemblies and providing the government with emergency powers to address the pandemic until 1st August 2021. The vaccination program in Malaysia began in February 2021, and was both free and phased.[8] Despite a high initial vaccination rate, hesitancy led to low booster uptake and waste of 8.5 million vaccine doses.[9]

On 1st April 2022, Malaysia transitioned into an endemic phase, relaxing many restrictions including international travel and outdoor mask mandates. In March 2023, the country reported an overall low fatality rate to the virus of 0.7%, and healthcare utilization rates of under 3%.[10] However, the status of Malaysia as an infected area under the Prevention of Infectious Diseases Act has been extended to 31st December 2023.[11]

Beyond healthcare, the pandemic had significant socio-economic impacts, prompting further government stimulus packages. At the first onset of the MCO in March 2020, the Work Bank reported that most Malaysians only had enough savings to live for 1-2 months.[12] There was an increase in the suicide rate reported even during the first year of the COVID-19 pandemic,[13] testament to the profound personal hardship experienced by the Malaysian people during this time.

Nonetheless, in the aftermath of the COVID-19 pandemic, Malaysia is beginning to see signs of regrowth. In the post-pandemic period of 2022, the country achieved an 8.7% GDP growth rate,[14] and has seen unemployment drop to 3.4% as of June 2023.[15] Political stability has also improved after the 15th general election in November 2022. In summary, Malaysia has navigated through the pandemic and into the endemic phase with resilience, despite facing unique challenges and economic hardship.

Singapore

Singapore's journey through the COVID-19 pandemic was marked by early detection, swift responses, and effective control measures. Singapore's prior experience with outbreaks like Severe Acute Respiratory Syndrome (SARS) and avian flu, combined with its relative affluence and significant investment in healthcare infrastructure, laid the groundwork for a robust pandemic response. After confirming its first COVID-19 case on 23rd January 2020, the Singaporean government swiftly escalated the nation's Disease Outbreak Response System Condition (DORSCON) to Orange and later implemented strict Circuit Breaker (CB) lockdown measures from 7th April to 1st June 2020, along with mandates for mask-wearing and social distancing. Parallel to this, the government conducted a robust public health and anti-disinformation campaign informing of up-to-date information surrounding the virus. This overall kept the spread amongst the general population low throughout the early phase of the virus.

However, by late March, COVID-19 clusters were detected at multiple migrant worker dormitories, contributing significantly to the country's total case count. It was estimated that by December 2020, about 47% of the migrant workers living in dormitories tested positive in Polymerase Chain Reaction (PCR) or serology tests for COVID-19. This then led to subsequent waves in which they attempted to isolate, treat, and test dormitory populations while simultaneously and gradually re-opening schools and businesses with safe distancing measures. However, the outbreak in the migrant worker dormitories highlighted a fault-line fault line in Singapore's otherwise pre-pandemic readiness and quick and effective responses.

Singapore was the first Asian country to receive the Pfizer-BioNTech vaccine in December 2020 and has one of the highest vaccination rates in the world. The vaccination

Table I: Latest number of COVID-19 cases, deaths, and mortality rates by countries, as of 2nd August 2023 [2]

Locations	Cases	Deaths	Mortality Rate
Malaysia	5,081,682	37,164	0.731%
Singapore	2,534,940	1,872	0.073%
Thailand	4,755,175	34,425	0.723%
The Philippines	4,172,920	66,592	1.596%
Indonesia	6,812,670	161,895	2.376%
Myanmar	641,074	19,494	3.040%
Worldwide	768,983,095	6,953,743	0.904%

Table II: Vaccinations available in each country in Southeast Asia

Vaccination	Malaysia	Singapore	Thailand	Indonesia	The Philippines	Myanmar
Moderna Spikevax	X	X	X	X	X	
Moderna Spikevax Bivalent Original/ Omicron BA.1		X				
Pfizer/BioNTech Comirnaty	X	X	X	X	X	
CanSino Convidecia	X					
Janssen Jcovden	X		X	X	X	
Oxford/AstraZeneca Vaxzevria	X		X	X	X	
Bharat Biotech Covaxin	X				X	
Sinopharm Covilo	X		X	X	X	X
Sinopharm Inactivated Vero Cells					X	
Sinovac Coronovac	X	X	X	X	X	
Novavax Nuvaxovid		X				
Serum Institute of India COVOVAX (Novavax formulation)			X	X	X	
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Note: The symbol "X" represents a vaccination brand verified by the government.

Table III: Latest number of people vaccinated with a complete primary series, as of 2nd August 2023

Locations	Number	Percentage of population
Malaysia	27,547,903	85.11%
Singapore	5,248,048	89.7%
Thailand	54,181,443	77.62%
The Philippines	78,443,972	71.58%
Indonesia	174,893,201	63.94%
Myanmar	35,196,377	64.69%
Worldwide	5,148,821,611	65.27%

program was free, phased, and widely-adopted, beginning with vaccinations for healthcare workers and vulnerable populations.

As of 13th February 2023, Singapore transitioned into the "Endemic Phase," with the vast majority of COVID-19 restrictions lifted. The transition represents the culmination of extensive efforts by the government and the cooperation of the population in controlling and managing the spread of the virus. The government's multifaceted approach to pandemic management led Singapore to maintain one of the lowest case fatality rates globally. The experiences during the pandemic have fortified Singapore's healthcare system and the country's readiness to manage future public health crises.

Thailand

Thailand's experience with the COVID-19 pandemic was characterized by early surge, firm governmental interventions, and a relatively steady evolution towards endemicity. On the 1st March 2020, the country saw its first confirmed death followed by a surge of cases in the following weeks. To control the spread, the Thai government closed businesses and public venues in Bangkok and other provinces. However, given the centrality of Bangkok within

Table IV: Government Response across Southeast Asia

Locations	Government response	Gaps in response	Current status
Malaysia	1. Movement Control Order (MCO) 2. Economic Stimulus Packages 3. Immunization program 4. Testing and contact tracing via the MySejahtera application 5. Quarantine centres	1. Political crises that hampered early response 2. Inconsistent or confusing messaging from the government 3. Heavy dependence on lockdowns	Declared an "Infectious Endemic Area", as of 30th June 2023
Singapore	1. Early response 2. Lockdowns (Circuit Breaker, phased reopening) 3. Economic measures 4. Isolation and quarantine 5. Testing and contact tracing via the TraceTogether application 6. Vaccination 7. Immunization program 8. Addressing initial vaccine hesitancy	1. Management of the Migrant Worker dormitories	Endemic, as of 13th February 2023
Thailand	1. Lockdown measures 2. Contact tracing 3. Isolation and quarantine 4. Healthcare infrastructure expansion 5. Economic relief measures 6. Vaccination program	1. Vaccine procurement and distribution 2. Support for vulnerable populations 3. Management of outbreaks 4. Impact on tourism	Endemic, as of 1st October 2022
Indonesia	1. Large Scale Social Restrictions (PSBB) 2. Health infrastructure expansion 3. Economic stimulus package 4. (Internal) Travel restrictions 5. Vaccination program 6. Contact tracing and testing	1. Delayed testing and contact tracing 2. Vaccine procurement and distribution 3. Confusion and ineffectiveness of PSBB 4. Concerns about measures for vulnerable groups	Endemic, as of 21st June 2023
The Philippines	1. Community Quarantine Measures 2. Economic stimulus packages (Bayanihan 1 and 2) 3. Vaccination Program 4. Travel restrictions 5. Testing and contact tracing (but expensive and uncoordinated) 6. Healthcare infrastructure expansion	1. Initially delayed lockdown 2. Low healthcare capacity (PPE shortage and low testing) 3. Vaccine procurement and distribution 4. Varied public compliance 5. Data management issues 6. Concerns about measures for vulnerable groups	Endemic, as of 22nd July 2023
Myanmar	1. Travel restrictions 2. Lockdown measures 3. Healthcare infrastructure expansion 4. Economic support 5. Testing and contact tracing (but inefficient)	1. Political instability 2. Low healthcare capacity 3. Limited testing and vaccination 4. Concerns about humanitarian measures 5. Lack of public compliance	Unclear due to the current military coup d'état.

the Thai economy, the sudden closure of businesses within the country's capital led to a mass migration of workers back to their hometowns and the consequent spread of the virus across the country. The government then declared a state of emergency on the 26th March 2020, which was later extended to the 14th January 2021. While the Thai government maintained that this was necessary to prevent imported cases, international rights groups criticized this extended state of emergency as a means to suppress free speech.[16]

By 1st June 2022, the Ministry of Public Health (MOPH) shut down its COVID-19 location tracking application, MorChana, in anticipation of reclassifying the disease to an endemic status. This shift was officially announced on 8th August 2022, when the government declared that COVID-19 would be downgraded to a "communicable disease under surveillance".[17]

The Thai government's handling of the pandemic has seen a mix of strict measures and gradual loosening in line with disease prevalence trends. The government has pledged to boost its currently crippled yet formerly lucrative tourism industry in the face of an endemic recovery, in the form of a stimulus package.[18] The country's journey to managing COVID-19 as an endemic disease shows the importance of balancing public health priorities with social and economic needs.

Indonesia

The COVID-19 pandemic in Indonesia began on 2nd March 2020 and spread to all 34 provinces in the country by 9th April 2020. Indonesia has the second-highest cases in Southeast Asia and the second-highest deaths in Asia and ranks 9th in the world for COVID-19-related deaths.

Instead of a full lockdown, Indonesia implemented "Large Scale Social Restrictions" (PSBB) and later "Community Activities Restrictions Enforcement" (PPKM), which it would later impose and de-escalate depending on new variants and surges in cases.19 These were lifted in all regions by December 2022 as population immunity exceeded expectations, though the pandemic status remained in place.

Vaccinations started on 13th January 2021, with President Joko Widodo receiving the first dose. On 21st June 2023, President Widodo officially announced the revocation of the COVID-19 pandemic status in Indonesia, marking the start of an endemic period.

The Philippines

Once the Philippines reported its first imported case in January 2020, the country was quick to place restrictions on travelers from mainland China, Hong Kong, Macau, and Taiwan. However, the country was slow to impose full lockdowns and travel bans due to the high levels of urbanization in Metro Manila as well as heavy reliance on tourism and overseas foreign workers. Ultimately, this resulted in the virus' hasty spread to all of the country's 81 provinces. Only after the first COVID-19 death was the Philippines put under a state of public health emergency. President Duterte signed the Bayanihan to Heal as One Act, a law granting him additional powers to handle the pandemic, followed by the Bayanihan to Recover as One Act on 11th September 2020.

Due to issues with vaccine procurement, the Philippines only began its phased vaccination program with donated Sinovac vaccines in March 2021. Vaccines were also acquired through the COVAX facility and the Asian Development Bank (ADB) Asia Pacific Vaccine Access Facility (APVAX).

However, the outdoor mask mandate was lifted in September 2022, and the indoor mandate was lifted the following month, except for healthcare facilities, public transport, and medical transport. On 22nd July 2023, President Bongbong Marcos lifted the COVID-19 pandemic state of a public health emergency.

Myanmar

The COVID-19 pandemic situation in Myanmar has seen a dramatic and tumultuous evolution. Although the first case of COVID-19 was only confirmed in Myanmar on 23rd March 2020, the Myanmar President's Office announced the formation of a special committee to tackle COVID-19 on the 30th January 2020. As of February 2020, Myanmar suspended Chinese visas. Myanmar launched community lockdowns promptly as and when they were detected across the country but only culminated in a full lockdown in September 2020.

Despite these early containment measures and public health responses, Myanmar experienced one of the most severe COVID-19 outbreaks in Southeast Asia by late 2020. As a result of six decades of military rule and consistent political precarity, the country had insufficiently invested in healthcare. Myanmar was poorly equipped to handle the growing healthcare needs as well as the economic strain caused by the lockdown.

The situation came to a head when the country faced an unprecedented crisis with the coup d'état that unfolded in February 2021. The political turmoil, accompanied by widespread protests and a civil disobedience movement—some of which were led by healthcare workers—caused severe disruptions to the country's public health response and deepened the economic recession. In the wake of the coup, the testing system and vaccine deployment for COVID-19 reportedly collapsed, further impeding the nation's fight against the pandemic.

The true impact of the pandemic in Myanmar has been difficult to measure due to the lack of adequate testing and limited attention paid to the public health crisis happening alongside the long-drawn-out political unrest. As of now, the COVID-19 situation in Myanmar remains precarious due to political instability and infrastructural constraints, with little available information about the country's plan for endemicity. The country continues to grapple with the challenges of managing the pandemic amid ongoing civil unrest and a crippled healthcare system.

Lessons learned and challenges ahead

Successes

Each Southeast Asian country has distinctly responded to the COVID-19 pandemic, reflecting the specificities of their socio-political context, available resources, and healthcare infrastructure. Strategies have included: imposing lockdowns, activating contact tracing, enforcing social distancing measures, and implementing various forms of travel restrictions. Table IV summarizes the government response, as well as gaps in the response across Southeast Asia.

Southeast Asian countries have demonstrated impressive resilience and adaptability in the face of challenges, engaging in intra-regional healthcare diplomacy, and cooperating to share essential. Several Southeast Asian nations have been beneficiaries of global health diplomacy throughout the pandemic – China donated vaccinations to the Philippines, Malaysia received at least $US 19.93 million in loans and grants from the Asian Development Bank and United States Agency for International Development and the Philippines received $US4.9 billion in loans and grants from a myriad of sources.[20]

Singapore's robust preparedness for a global health crisis positioned it as a significant contributor to global health diplomacy during this period. Singapore was a member of the 'Friends of COVAX' group, a conglomerate of high-income nations committed to ensuring equitable access to COVID-19 vaccine access in low- and middle-income countries.[21] Furthermore, Singapore offered aid to China, Indonesia, and Myanmar, as well as supplying more than 35 countries globally with medical aids such as test kits and hand sanitizers – a diplomatic strategy referred to as "test kit diplomacy".[22] This commendable and effective multilateral altruism offers a template that one hopes will be followed in addressing future healthcare crises.

Lessons

The post-pandemic phase for countries globally has been characterized by intensified endeavors to equip themselves for similar future crises. To fully understand the scope of such

preparations, it is crucial to examine key aspects of the pandemic response that have either been neglected or not sufficiently addressed across Southeast Asia.

The pandemic has laid bare the existing inequalities as well as interdependencies between each country's health infrastructures, necessitating increased collaboration in the face of future pandemics. The high levels of intra-regional migration, both documented and undocumented, have presented significant challenges and underscored the need for collaboration across borders. As such, forging alliances between neighboring countries within Southeast Asia is an imperative public health strategy.

While political instability is someone anticipated within a country's response to a crisis, there is a pressing need for implementing comprehensive measures aimed at deliberate public communication and promotion of public health guidelines. The experiences of the countries considered in this article offer valuable lessons. A study conducted by Hartigan-Go et al.[23] spanning Southeast Asia found that the implementation of public health education programs significantly curtailed vaccine hesitancy.

Furthermore, it is imperative to bolster public communications to counteract misinformation and alleviate pandemic fatigue.[24] Strategies such as the use of official government-endorsed social media platforms in the Philippines, Singapore's Multi-Ministerial Taskforce,[25] and the deployment of apolitical figures like Malaysia's Health Director-General Noor Hisham Abdullah serve as excellent models of effective governmental communication.[26] These strategies sought to provide a trusted source of information and authority on the issue on platforms that would appeal to their target audience, therefore resulting in their success.

Finally, issues such as vaccine shortages and pervasive misinformation related to the virus and vaccinations hindered the fight against the pandemic and ignited social tension, particularly against already marginalized communities.[27] Xenophobia and racism have emerged as unfortunate corollaries of the discrimination and misinformation that circulated globally throughout the pandemic. It is incumbent upon future governments to ardently promote accurate information dissemination and maintain social harmony during already fractious times.

Challenges ahead - Looking forward

Southeast Asian nations face several key challenges. First, managing COVID-19 as an endemic disease will require a shift in strategy. Beyond, its devastating health impact, the virus has inflicted substantial economic, political, and societal damage although with considerable asymmetry across the region. The Asian Development Bank estimates that the pandemic pushed 4.7 million Southeast Asians into extreme poverty and eliminated 9.3 million jobs in the region in 2021 alone.[28] The severe loss in tourism over the past few years, restricted movement across borders, and supply chain disruptions will significantly challenge economic recovery, particularly for low-income countries. As Southeast Asia transitions into the endemic phase, there is an opportunity for ASEAN governments to collectively address their shared situation, prioritizing cooperation, and coordination. Finally, providing comprehensive mental healthcare to address the psychological impact of the pandemic will be crucial in the years ahead. The pandemic has brought about unprecedented stress and anxiety levels, and mental health services need to be strengthened and made widely accessible.

CONCLUSION

The COVID-19 pandemic has indelibly shaped the landscape of Southeast Asia, leaving in its wake a trail of economic, political, and societal disruptions. However, the collective resilience of Southeast Asian nations has also shone through, with each country navigating the crisis with varying strategies that reflect their unique socio-political contexts, resources, and healthcare infrastructures. There have been notable successes, such as efficient vaccine procurement and the initiation of intra-regional healthcare diplomacy. Nevertheless, several challenges remain, including managing endemic COVID-19, driving economic recovery, and enhancing public health infrastructures to ensure preparedness for future pandemics. It has also served as an important learning experience for Southeast Asia Nations. The lessons learned and challenges encountered hopefully guide the region as it embarks on its journey to recovery and resilience, shaping its collective approach to public health, healthcare, and pandemic response.

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ORIGINAL ARTICLE

Prevalence of depression and anxiety among adults with vitiligo in a Malaysian tertiary hospital

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ABSTRACT

Introduction: Vitiligo is a chronic disorder resulting in skin depigmentation with reported global prevalence of 1-2%. This disease is often accompanied by psychosocial distress owing to the cosmetic disfigurement associated with it. The primary objective of this study was to determine the prevalence of depression and anxiety among adults with vitiligo in a local tertiary hospital. In addition, this study also evaluated the association of depression and anxiety with patients' characteristics.

Materials and Methods: This cross-sectional study was conducted among vitiligo patients aged 18 years and older in Hospital Klang, Selangor between October 2021 and June 2022. Assessment instruments used were Vitiligo Area Scoring Index (VASI) and Hospital Anxiety and Depression Scale (HADS). Demographic data and clinical characteristics of vitiligo patients were recorded.

Results: Of the 100 participants, 12 (12%) and 21 (21%) had depression and anxiety, respectively. The mean depression score (HADS-depression component) was 3.4 (SD 3.4) and mean anxiety score (HADS-anxiety component) was 4.7 (SD 3.9). There were significantly higher number of patients with abnormal HADS-D score in the age group of 35-51 years (p=0.029), single status (p=0.001), with employment (p=0.014) and disease duration <2 years (p=0.004). Patients in the divorced/widowed group had a significant association with anxiety (p=0.011).

Conclusion: The prevalence of depression was 12% while anxiety was 21% in our cohort. Vitiligo has a significant psychosocial impact, thus clinicians should actively evaluate the mental health of these patients with the use of screening tools such as HADS and provide appropriate referrals and management.

KEYWORDS:
Depression, anxiety, psychiatric comorbidities, mental health

INTRODUCTION

Vitiligo is an acquired chronic depigmenting skin disorder, which is due to the loss of melanocytes function in the skin, hair or both. This results in depigmentation characterised by whitish macules or patches with typical sharp margin on the skin, and greying of hair.[1-4] The exact pathogenesis of vitiligo has remained unclear, although various factors such as autoimmune, genetic and environmental factors have been thought to place a role in the development of the disease.[1,5] It is estimated that 1-2% of the world population suffered from this condition, with an equal distribution in both genders and across all ethnic groups.[6,7] The disease onset can occur in any age, but those whose disease initiation before the age of 20 is up to 50%.[8,9] Unfortunately, there has not been any curative treatment for this condition although there are various treatments/interventions available to manage vitiligo such as topical corticosteroids, calcineurin inhibitors, phototherapy, and camouflage.[6] The disease is not a life-threatening condition by itself, it nonetheless poses a great cosmetic problem, which would in turn affect a person's emotional and psychological well-being.[10]

Psychological distress is more pronounced in those with darker skin due to the greater contrast between their normal skin colour and their white-coloured skin lesions. Other factors that would affect patients as such are gender; women more than men, age; younger patients more than older patients, marital status; married women more than single women, and site of lesions; exposed area more than area less visible.[11] A meta-analysis of the prevalence and odds of depression in patients with vitiligo found a wide range prevalence between 8 and 33% across 17 studies, depending on the diagnostic tool used.[12]

Anxiety disorder, on the other hand, is characterised by the feeling of worry and uneasiness that are commonly generalised and present an overreaction to a problem that appears to be threatening.[13] Anxiety disorder often precedes depression in response to stressors and warrants higher awareness and greater attention as it can negatively affect adherence to treatment and overall quality of life.[14] As psychological disorders were found to be more common in individuals with vitiligo compared to the general population[15], an assessment of psychological state should be performed during routine clinical evaluation.

There are numerous studies around the world assessing the prevalence of psychological impacts in adult patients with vitiligo. To date, there has been limited data regarding depression and anxiety symptoms in vitiligo patients in the local population. We aim to determine the prevalence of depression and anxiety among adults with vitiligo in a local tertiary hospital and secondarily to evaluate the association of depression and anxiety with patients' characteristics.

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MATERIALS AND METHODS

Study Design

This was a cross-sectional, single-centre, prospective study conducted in the Dermatology Clinic, Hospital Tengku Ampuan Rahimah, Klang, Selangor from 15 October 2021 to 30 June 2022. A total of 100 patients were recruited with the inclusion criteria of age 18 years and above, clinically diagnosed as vitiligo by a dermatologist and consented for the study. Patients with a history of psychiatric and/or physical abnormalities, chronic illness (e.g. malignancy, autoimmune disease, chronic kidney disease, diabetic with multi-organ target damage) and being significantly affected psychologically by the COVID-19 pandemic (those with numerical rating scale score of ≥ 8) were excluded from the study.

Study Procedures

Eligible patients who consented for the study were required to answer a set of questionnaires which included their demographic information (age, gender, ethnicity, marital status, education level, employment status, monthly income, disease duration, Fitzpatrick's skin type). The Hospital Anxiety and Depression Scale (HADS) was then used to evaluate the state of anxiety and depression of all subjects.

Hospital Anxiety and Depression Scale (HADS)

The HADS questionnaire is a validated tool for screening anxiety and depression. The questionnaire comprises seven questions each for anxiety and depression in which the items are scored on a four-point scale from zero (not present) to three (severe). The score for all items are then totalled up to give sub-scale scores on the HADS-A (HADS-anxiety component) and the HADS-D (HADS-depression component) from 0 to 21. Score less than 7 indicates non-cases, 8-10 as mild, 11-14 as moderate, and 15-21 as severe. For a score more than 7, it has a specificity of 0.78 and sensitivity of 0.9 for anxiety; a specificity of 0.79 and sensitivity of 0.83 for depression.16 In this study, patients will be classified as normal (0–7 of 21) and abnormal (8–21 of 21) based on their sub-scale scores in HADS-A and HADS-D.

Disease Severity Assessment

Vitiligo Area Scoring Index (VASI)

The VASI was used to measure the disease severity in vitiligo patients. It is a quantitative scale which estimates the overall area of vitiligo patches and the degree of macular repigmentation within these patches. In VASI, the score for 5 separate regions (hands, upper extremities, trunk, lower extremities, and feet) are summed and provide a severity score ranging from 0 to 100, with the higher score indicating more severe disease and vice versa. The face and neck areas are not included in the overall evaluation in VASI but can be assessed separately.

Body Surface Area (BSA)

The ''rule of 9s'' was used to estimate body surface area (BSA) involved with vitiligo lesions.

Study Analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 22 (SPSS, IBM Corporation, Chicago, IL, USA). Descriptive statistics for continuous variables were expressed as mean ± standard deviation (SD) while categorical variables as frequencies and percentages. Comparisons involving categorical data were performed using the chi-square test and Fisher's exact test. Associations between continuous variables were analysed using Kendall tau-b as normality and linearity assumptions were not met. Particularly, the correlation coefficients between 0.1 and 0.25 were considered low, while the value between 0.26 and 0.5 was considered moderate and those over 0.5 were considered high. A multivariate analysis was carried out using multiple logistic regression to determine the independent associated factors of anxiety and depression. Statistical significance was set at $p<0.05$.

Ethical Approval

This study was approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia (NMRR-21-1666-59815).

RESULTS

Demographic Characteristics

A total of 100 patients with vitiligo were included in this study. The demographic data and patient characteristics are shown in Table I. Out of 100 study subjects, 53 (53%) were females and 47 (47%) were males with a mean age of 47 years (SD 16.8). Majority of the patients were of Malay ethnicity, 44 (44%), followed by Indian, 40 (40%), Chinese, 14 (14%) and others, 2 (2%). 70 (70%) patients were married, 29 (29%) single and 1 (1%) was divorced/widowed. Regarding education background, 54 (54%) patients completed secondary school, 40 (40%) had tertiary education, 4 (4%) only had primary education and 2 (2%) patients never had formal education. 50 (50%) patients were employed and the remaining were unemployed. Our data revealed 62 (62%) patients came from the lower income group, 28 (28%) patients from the middle-income group and 10 (10%) were from the high-income group.

Clinical Characteristics

As shown in Table I, out of 100 patients, most (78 patients, 78%) had vitiligo for more than 2 years duration and the remaining 22 (22%) patients were diagnosed with vitiligo for less than 2 years. With regards to the type of vitiligo, most patients (60, 60%) had the generalised type, followed by 31 (31%) with acrofacial, 6 (6%) with focal and 3 (3%) with segmental vitiligo. Facial involvement was seen in 74 (74%) patients and the remaining had no facial lesions. 20 (20%) patients had genital vitiligo and 80 (80%) patients did not have genital lesions. Only 26 (26%) out of 100 patients used cosmetic camouflage for their vitiligo lesions. As for disease severity, 47 (47%) patients had BSA% involvement of 1%-5%, followed by 33 (33%) patients with BSA involvement more than 5% and 20 (20%) patients with less than 1% BSA involvement. The mean VASI score was 5.49 (SD8.74). Most (66 patients, 66%) received topical treatment alone with the most common skin type being Fitzpatrick's type IV (42 patients, 42%) as all of our patients were of Asian origin.

Depression and Vitiligo

The factors associated with depression in our study

Table I: Demographic and clinical characteristics of study participants

Patient characteristics	Total (n=100), n(%)
Gender	
Male	47 (47)
Female	53 (53)
Age (years), mean (SD)	47 (16.8)
Age group (years)	
18-34	25 (25)
35-51	29 (29)
52-68	36 (36)
69-85	10 (10)
Ethnicity	
Malay	44 (44)
Chinese	14 (14)
Indian	40 (40)
Others	2 (2)
Marital status	
Single	29 (29)
Married	70 (70)
Divorced/widowed	1 (1)
Education	
None	2 (2)
Primary	4 (4)
Secondary	54 (54)
Tertiary	40 (40)
Employment	
Employed	50 (50)
Unemployed	50 (50)
Monthly income (RM)	
No or Low (0-3000)	62 (62)
Middle (3001-5000)	28 (28)
High (>5000)	10 (10)
Disease duration	
<2 years	22 (22)
>2 years	78 (78)
Involvement of face	
Yes	74 (74)
No	26 (26)
Involvement of genital	
Yes	20 (20)
No	80 (80)
Use of camouflage	
Yes	26 (26)
No	74 (74)
Types of vitiligo	
Segmental	3 (3)
Generalised	60 (60)
Acrofacial	31 (31)
Focal	6 (6)
Extent of lesions (BSA, %)	
<1%	20 (20)
1%-5%	47 (47)
>5%	33 (33)
Treatment modalities	
Topical only	66 (66)
Topical + systemic	3 (3)
Topical + phototherapy	27 (27)
Topical + systemic + phototherapy	3 (3)
Others	1 (1)
Fitzpatrick's skin types	
III	9 (9)
IV	42 (42)
V 26 (26)	
VI23 (23)	
VASI score, mean (SD)	5.49 (8.74)

Table II: Factors associated with depression

Demographic characteristics	Depression (HADS-D)		Sig. (p-value)
	Normal	Abnormal	
Age group[b]			
18-34 years	21 (84.0%)	4 (16.0%)	0.029*
35-51 years	22 (75.9%)	7 (24.1%)	
52-68 years	35 (97.2%)	1 (2.8%)	
69-85 years	10 (100.0%)	0 (0.0%)	
Ethnic[b]			
Malay	39 (88.6)	5 (11.4%)	0.366
Chinese	12 (85.7%)	2 (14.3%)	
Indian	36 (90.0%)	4 (10.0%)	
Others	1 (50.0%)	1 (50.0%)	
Gender[a]			
Male	41 (87.2%)	6 (12.8%)	0.824
Female	47 (88.7%)	6 (11.3%)	
Marital[b]			
Single	20 (69.0%)	9 (31.0%)	0.001**
Married	67 (95.7%)	3 (4.3%)	
Divorced/widowed	1 (100.0%)	0 (0.0%)	
Education[b]			
None	2 (100.0%)	0 (0.0%)	0.795
Primary	4 (100.0%)	0 (0.0%)	
Secondary	46 (85.2%)	8 (14.8%)	
Tertiary	36 (90.0%)	4 (10.0%)	
Employmenta			
Employed	40 (80.0%)	10 (20.0%)	0.014*
Unemployed	48 (96.0%)	2 (4.0%)	
Monthly incomeb			
No income	21 (91.3%)	2 (8.7%)	0.897
<RM1000	5 (100.0%)	0 (0.0%)	
RM1001-RM3000	28 (82.4%)	6 (17.6%)	
RM3001-RM5000	25 (89.3%)	3 (10.7%)	
RM5001-RM10000	8 (88.9%)	1 (11.1%)	
>RM10000	1 (100.0%)	0 (0.0%)	
Disease durationb			
<2 years	15 (68.2%)	7 (31.8%)	0.004*
>2 years	73 (93.6%)	5 (6.4%)	
Clinical characteristics			
Involvement of face[b]			
Yes	63 (85.1%)	11 (14.9%)	0.177
No	25 (96.2%)	1 (3.8%)	
Involvement of genital[b]			
Yes	15 (75.0%)	5 (25.0%)	0.060
No	73 (91.3%)	7 (8.8%)	
Use of camouflage[b]			
Yes	23 (88.5%)	3 (11.5%)	1.000
No	65 (87.8%)	9 (12.2%)	
Types of vitiligo[b]			
Segmental	3 (100.0%)	0 (0.0%)	0.614
Generalized	51 (85.0%)	9 (15.0%)	
Acrofacial	29 (93.5%)	2 (6.5%)	
Focal	5 (83.3%)	1 (16.7%)	
Extent of lesion[b]			
<1%	19 (95.0%)	1(5.0%)	0.612
1%-5%	41 (87.2%)	6 (12.8%)	
>5%	28 (84.8%)	5 (15.2%)	
Treatments[b]			
Topical only	58 (87.9%)	8 (12.1%)	0.004*
Topical + systemic	0 (0.0%)	3 (100.0%)	
Topical + photo-therapy	26 (96.3%)	1 (3.7%)	
Topical + systemic + photo-therapy	3 (100.0%)	0 (0.0%)	
Others	1 (100.0%)	0 (0.0%)	
Fitzpatrick's skin types[b]			
III	7 (77.8%)	2 (22.2%)	0.401
IV	37 (88.1%)	5 (11.9%)	
V	22 (84.6%)	4 (15.4%)	
VI	22 (95.7%)	1 (4.3%)	

*p< 0.05
**p<0.001
[a]Chi Square
[b]Fisher Exact test

Table III: Factors associated with anxiety

Demographic characteristics	Anxiety (HADS-A)		Sig. (p-value)
	Normal	Abnormal	
Age group[b]			
18-34 years	20 (80.0%)	5 (20.0%)	0.204
35-51 years	19 (65.5%)	10 (34.5%)	
52-68 years	31 (86.1%)	5 (13.9%)	
69-85 years	9 (90.0%)	1 (10.0%)	
Ethnic[b]			
Malay	35 (79.5%)	9 (20.5%)	0.723
Chinese	11 (78.6%)	3 (21.4%)	
Indian	32 (80.0%)	8 (20.0%)	
Others	1 (50.0%)	1 (50.0%)	
Gender[a]			
Male	40 (85.1%)	7 (14.9%)	0.158
Female	39 (73.6%)	14 (26.4%)	
Marital[b]			
Single	19 (65.5%)	10 (34.5%)	0.011*
Married	60 (85.7%)	10 (14.3%)	
Divorced/widowed	0 (0.0%)	1 (100.0%)	
Education[b]			
None	2 (100.0%)	0 (0.0%)	0.809
Primary	3 (75.0%)	1 (25.0%)	
Secondary	41 (75.9%)	13 (24.1%)	
Tertiary	33 (82.5%)	7 (17.5%)	
Employment[a]			
Employed	38 (76.0%)	12 (24.0%)	0.461
Unemployed	41 (82.0%)	9 (18.0%)	
Monthly income[b]			
No income	19 (82.6%)	4 (17.4%)	0.542
<RM1000	4 (80.0%)	1 (20.0%)	
RM1001-RM3000	23 (67.6%)	11 (32.4%)	
RM3001-RM5000	24 (85.7%)	4 (14.3%)	
RM5001-RM10000	8 (88.9%)	1 (11.1%)	
>RM10000	1 (100.0%)	0 (0.0%)	
Disease duration[b]			
<2 years	14 (63.6%)	8 (36.4%)	0.072
>2 years	65 (83.3%)	13 (16.7%)	
Clinical Characteristics			
Involvement of face[a]			
Yes	59 (79.7%)	15 (20.3%)	0.762
No	20 (76.9%)	6 (23.1%)	
Involvement of genital[b]			
Yes	15 (75.0%)	5 (25.0%)	0.759
No	64 (80.0%)	16 (20.0%)	
Use of camouflage[a]			
Yes	21 (80.8%)	5 (19.2%)	0.797
No	58 (78.4%)	16 (21.6%)	
Types of vitiligo[b]			
Segmental	1 (33.3%)	2 (66.7%)	0.070
Generalized	45 (75.0%)	15 (25.0%)	
Acrofacial	28 (90.3%)	3 (9.7%)	
Focal	5 (83.3%)	1 (16.7%)	
Extent of lesion[b]			
<1%	15 (75.0%)	5 (25.0%)	0.687
1%-5%	39 (83.0%)	8 (17.0%)	
>5%	25 (75.8%)	8 (24.2%)	
Treatment[b]			
Topical only	50 (75.8%)	16 (24.2%)	0.472
Topical + systemic	2 (66.7%)	1 (33.3%)	
Topical + photo-therapy	24 (88.9%)	3 (11.1%)	
Topical + systemic + photo-therapy	2 (66.7%)	1 (33.3%)	
Others	1 (100.0%)	0 (0.0%)	
Fitzpatrick's Skin Types[b]			
III	6 (66.7%)	3 (33.3%)	0.503
IV	34 (81.0%)	8 (19.0%)	
V	19 (73.1%)	7 (26.9%)	
VI	20 (87.0%)	3 (13.0%0	

*p< 0.05
[a]Chi Square
[b]Fisher Exact test

Table IV: Logistic regression analysis of variables associated with HADS-D

Variables	Adjusted OR [95% CI]	p-value
Employment		
Employed	Reference	0.063
Unemployed	0.203 [0.038,1.087]	
Involvement of face		
Yes	Reference	0.244
No	0.272 [0.031, 2.431]	
Involvement of genital		
Yes	Reference	0.110
No	0.300 [0.069,1.315]	
Disease duration		0.006*
<2 years	Reference	
>2 years	0.140 [0.034,0.575]	

Treatment was excluded as it has wide CI.

Table V: Logistic regression analysis of variables associated with HADS-A

Variables	Adjusted odd ratio [95% CI]	p-value
Gender		
Male	Reference	0.246
Female	1.889 [0.645,5.530]	
Disease duration		
<2years	Reference	0.048*
>2years	0.308 [0.096,0.990]	
Vitiligo		
Segmental	Reference	
Generalised	0.178 [0.013,2.400]	0.193
Acrofacial	0.045 [0.003,0.767]	0.032*
Focal	0.161 [0.006,4.527]	0.283

Type of treatment was excluded due to collinearity issues (wide CI).

participants are summarised in Table II. The overall mean depression score (HADS-D) for all study subjects (n=100) was 3.4 (SD 3.4). 88 (88%) patients scored 'normal' and 12 (12%) scored 'abnormal' in HADS-D. There was a statistically significant higher number of patients with abnormal HADS-D score in the age group of 35-51 years (24.1%, n=7), followed by 18-34 years (16%, n=4) and 52-68 years (2.8%, n=1), with p=0.029. More single patients (31%, n=9) were found to have abnormal HADS-D score as compared to patients who were married (4.3%, n=3), with a significant p-value of 0.001. On the other hand, there were statistically significant relationships between depression and employment status. Abnormal HADS-D score were recorded more frequently in patients with employment (20%, n=10) as compared to unemployed patients (4%, n=2), with p-value 0.014.

As for clinical characteristics (Table II), a significantly higher number of patients with vitiligo for >2 years duration (31.8%, n=7) (p=0.004) were found to have depression. In addition, those who were on topical plus systemic treatment (100%, n=3) also reported significant abnormal HADS-D score (p=0.004).

From our analysis of demographic characteristics (Table II), there were no statistically significant relationships between ethnicity, gender, education level and income level with depression in this cohort. Other clinical characteristics like type of vitiligo, facial and genital involvement, use of camouflage, BSA (%) involvement and Fitzpatrick's skin types were also found to have negative relationships with depression.

Anxiety and Vitiligo

The factors associated with anxiety in our study participants are summarised in Table III. The overall mean anxiety score (HADS-A) for all study subjects (n=100) was 4.7 (SD 3.9). 79 (79%) patients scored 'normal' and 21 (21%) scored 'abnormal' in HADS-A. Only marital status was significantly associated with anxiety (p=0.011) in this cohort, in which a higher number of patients with abnormal HADS-A score were found in the divorced/widowed group (100%, n=1), followed by single patients (34.5%, n=10), and married patients (14.3%, n=10).

From our analysis of demographic characteristics (Table III), there were no statistically significant relationships between age, ethnicity, gender, education level, employment status and income level with anxiety in this cohort. All clinical characteristics analysed in this study, namely the disease duration, type of vitiligo, facial and genital involvement, use of camouflage, BSA (%) involvement, treatment and Fitzpatrick's skin types were found to have no significant association with anxiety.

Anxiety and Depression with VASI score

A correlation study was run to further assess the association between VASI score with depression and anxiety among the

patients. Non-parametric, i.e. Kendall tau-b, was chosen as alternative as the data do not meet normal assumptions and there is no linearity between the variables.

The correlation between the VASI score and the total anxiety score (r=0.092, p=0.200) and the correlation between the VASI score and the total depression score (r=0.094, p=0.204) were very weak and statistically insignificant.

Predictors of Depression in Vitiligo Patients
A multiple logistic regression was employed to check on the significant predictors of depression within the group of vitiligo patients (Table IV). The final variables that were fit to the model were chosen using simple logistic regression (SLR) and out of the five(s) variables, only one predictor came out as significant.

By having longer years of disease duration (>2 years), it lowers the odds of suffering from depression by 0.140 time, while controlling for other parameters (Table IV). This finding is found to be significant.

Those that do not have vitiligo involvement of the face, have 0.272 times odd lower suffering from a depression while controlling for other parameters, but this finding is not a significant predictor (Table IV).

Those that do not have involvement of genital, have 0.300 times odd lower of suffering from a depression while controlling for other parameters, but this is found to be insignificant (Table IV).

Unemployed patients have 0.203 times odd lower suffering from depression compared to employed while controlling for other parameters, nevertheless it was found to be insignificant as well (Table IV).

Predictors of Anxiety in Vitiligo patients
A multiple logistic regression was employed to check on the significant predictors of anxiety within the group of vitiligo patients (Table V). The final variables that were fit to the model were chosen using SLR and out of the four(s) variables, only one predictor came out as significant.

Participants with a disease duration of more than 2 years have a 0.308 lower odds of getting anxiety compared to those with a shorter duration of disease (Table V). This finding was found to be significant.

Females have a 1.889 times higher odds of suffering from anxiety compared to males, while controlling for other parameters (Table V). However, this finding is insignificant.

Vitiligo with acrofacial type have a significant 0.032 lower odds of suffering from anxiety as compared to segmental type, while controlling for other parameters (Table V). The other vitiligo types are not a significant predictor for anxiety.

DISCUSSION

Vitiligo is a chronic disorder causing skin depigmentation which can result in a profound psychosocial impairment even though this disease is substantially asymptomatic. Results from qualitative studies supported that vitiligo can cause huge psychological impact on people.[17] This could be due to the stigma associated with the visibility of vitiligo, in addition to unpredictable prognosis and lack of cure which impact on daily social interactions.[18]

The prevalence of depression in our study was 12%, and for anxiety 21% in our patients with vitiligo. These results were lower than the systematic review done by Osinubi et al. which revealed a pooled prevalence of 29% for depression and 33% for anxiety.[15] However, there was high heterogeneity between the included studies in this systematic review where multiple different screening tools were being used. In contrast, our prevalence of depression and anxiety was comparable to the study done by Alshahwan et al. in Saudi Arabia which reported 14.1% and 26.6% for depression and anxiety, respectively.[19] They used the same screening tools (HADS questionnaire) as with our study. A study conducted in our neighbouring country, Singapore, in 2011 also found 17.2% of their vitiligo patients to be depressed.[20] This finding closely matched our results owing to the fact that we have the same diversity of patients (in terms of race, cultures and skin types) as those in Singapore.

Our study found that vitiligo patients in the age group of 35–51 years (p=0.029) and being employed (p=0.014) were significantly associated with depression. This group are in their productive age, having to work and meet other people in the course of their daily job, would probably be more affected psychologically. The same study done in Singapore also suggested higher risk of depression in their vitiligo patients who were younger than 50 years old.[20] This finding was consistent with other international studies showing that younger patients were more prone to depression after being diagnosed with vitiligo when compared to the older patients.[21,22]

In our study, we found that single patients had a significant association with depression (p=0.001). This could be due to the lack of emotional support from a partner or spouse after being diagnosed with a disease which runs a chronic course and with no promising treatment or cure. This is consistent with the findings of Alharbi et al.[23] On the other hand, marital status was found to have no significant association with depression in vitiligo patients in Singapore.[20]

Undoubtedly, recent disease diagnosis and being on more than one treatment modalities were associated with depression. Results of our study found a significant association with depression when having the disease for less than 2 years duration (p=0.004) and using both topical plus systemic treatment (p=0.004). This could be explained by uncertainties towards the nature of the disease and availability of therapeutic options when one is new to the disease. Being on more than one treatment modalities also implies a more severe or extensive disease. Our finding is consistent with a similar study done in Saudi Arabia.[23]

With regards to the association of anxiety with vitiligo, only marital status showed a significant association in our study. Divorced or widowed patients (p=0.011) had significant anxiety and this was followed by patients with single status. A systematic review done by Ezzedine et al., found

statistically significant higher psychosocial burden among unmarried or single relationship status vitiligo patients.[24]

It was surprising to find that other clinical characteristics such as visible lesion sites, Fitzpatrick's skin types, extent of lesions and VASI scores did not show significant relationships with depression and anxiety. One would expect patients with lesions at exposed sites, darker skin types and extensive vitiligo lesions to suffer from depressive and anxiety symptoms.[25] Our findings could be explained by the fact that this study was conducted during the peak of the COVID-19 pandemic in year 2021 to 2022 whereby our country was put under restricted movement control order to curb the spread of COVID-19. This situation had confined majority of Malaysians to their homes, unless there were dire needs to be out and about. By not having physical interactions with others, these could have much reduced the depression and anxiety in relation to the characteristics of vitiligo mentioned above.

Finally, our multiple logistic regression analyses showed lower odds of having depression and anxiety when patients have a disease duration of more than 2 years. On the other hand, Ajose et al. found that vitiligo patients suffer greater psychomorbidity when the disease duration was more than 2 years, likely due to the subsequent realisation of the ineffectiveness of available treatment options.[26] Interestingly, our multiple logistic regression analyses also revealed lesser odds of developing anxiety in the group with acrofacial vitiligo subtype. Perhaps, the compulsory rules of wearing face masks and being confined to homes during the pandemic could be possible explanations.

Our study has a number of limitations, including its cross-sectional nature and the lack of a control group. Thus, we were only able to evaluate the association between psychosocial burden and vitiligo, but not causation. The sample size was relatively small as well due to lower patient's attendance at the dermatology clinic during the national restricted movement control order at the height of the pandemic. A longer study period with the recruitment of more patients would be more accurate to evaluate the impact of vitiligo on mental health. In addition, having an age and sex-matched control group would help to better assess the effect of vitiligo on the psychosocial comorbidities.

Recommendations

Assessment of psychological state during clinical evaluation of patients with vitiligo is essential, as also suggested by the British Association of Dermatology guidelines.[27] The incorporation of screening tools such as HADS in our daily practice should be considered and those found to have abnormal anxiety or depression scores (HADS-A or HADS-D ≥8) should be referred for psychological assessment and treatment. Multidisciplinary approach in treating vitiligo patients with significant psychosocial burden, especially working closely with counsellor and psychiatrist, is very important to reduce disease-related anxiety and stress and thus enhancing the efficacy of therapy. There is also a need for community-based intervention by allied healthcare professionals that aims at increasing society's awareness and acceptance of vitiligo which in turn could reduce stigmatisation to vitiligo patients. Formation of a vitiligo support group supervised by trained nurses will be helpful in delivering reliable information regarding vitiligo in addition to the provision of mutual support among participants.

CONCLUSION

This study demonstrated that vitiligo has a significant impact on the psychosocial well-being of patients. The prevalence of depression was 12% and anxiety was 21% in our cohort. Factors that significantly affect the mental health of patients with vitiligo include younger age group, single or separated relationship status, employed, shorter disease duration, and being on more than one treatment modalities. It must be emphasised that early recognition and provision of psychological treatment to these patients may lead to better treatment compliance and efficacy.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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The usage of Gellhorn pessary in pelvic organ prolapse and in regards to success, continuity of use and effect on symptoms: a retrospective study of 2 years

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ABSTRACT

Introduction: Pelvic organ prolapse (POP) is a condition involving weakened pelvic floor muscles causing organs to protrude. Conservative POP treatment comprises pelvic floor exercises and vaginal pessaries. Besides conservative care, surgery is offered. However, surgery is invasive, risky and unsuitable for those with serious medical conditions. This study aims to assess the acceptance, success and outcomes of the Gellhorn pessary for POP treatment, especially in advanced cases.

Materials and Methods: The present study is a retrospective cohort study using hospital medical records (patient files) from October 2019 to November 2021 (for 2 years). This study was performed in Malaysian women (n=53) suffering from advanced stages of POP, in which Gellhorn pessaries of diameter (44-76mm) were inserted by trained personnel. Pelvic Floor Distress Inventory-20 (PFDI-20) and Pelvic Floor Impact Questionnaire-7 (PFIQ-7) were used to measure patients' symptoms and quality of life before and after Gellhorn pessary fitting. Patients were reassessed every three months for two years and their satisfaction scores were recorded.

Results: We observed a significant difference in pre-test (pre-fitting) and post-test (three months post-fitting) scores on all three subscales and the PFIQ-7 total score. Twenty-eight (52.83%) patients continued the use of Gellhorn pessary for at least 24 months, whereas 25 (47.20%) patients discontinued during this period. A retrospective analysis of the patients who discontinued Gellhorn pessary showed that 13 (24.52%) patients gave up the use of pessary for definitive surgery. It is noteworthy to mention here that only one out of the 13 patients who were awaiting surgery, chose surgery and the remaining 12 changed their mind after being fitted with the Gellhorn pessary. Seven (13.20%) patients declined reinsertion due to discomfort and voiding difficulties and refused further intervention, whereas three (5.66%) patients requested a ring pessary. Two (3.77%) patients, requested the removal of pessary due to vesicovaginal fistula and rectovaginal fistula (caused by an impacted pessary). The rate of continued use was 79.24% (42 patients) after 1st year and 52.83% (28 patients) at the end of two years.

Conclusion: In the current study, the Gellhorn pessary was used to treat stage 3 and 4 POP with significant symptom reduction post-fitting. More than half of the patients continued to use the pessary after 24 months of fitting. Therefore, the Gellhorn pessary can be used as a treatment strategy for stage 3 and 4 POP with reasonable acceptance in the Malaysian population.

KEYWORDS:
Pelvic organ prolapse (POP), Gellhorn pessary, Pelvic Floor Distress Inventory-20 (PFDI-20), Pelvic Floor Impact Questionnaire-7 (PFIQ-7)

INTRODUCTION

Pelvic organ prolapse (POP) is characterised by pelvic floor muscle dysfunction that causes one or more organs to descend and causes a bulge in the vagina. The respective prolapse of an organ is called cystocele, urethrocele, uterine prolapse, rectocele and enterocele. Physiologically, pelvic floor muscles form a hammock supporting the organs in place. However, numerous factors compromise this support resulting in POP.[1] Globally, the prevalence of POP in women is on the rise due to the ageing population and could reach around 40% within a few years. Up to 54% of women with POP also have stress urinary incontinence.[2]

Conservative management of POP includes pelvic floor exercises and vaginal pessaries.[3] Apart from conservative management, there are surgical treatments available as well. However, surgery is an invasive procedure with many risks involved. Furthermore, relapse is also a factor that is quite high when POP is treated with surgery which can increase a patient's financial and mental health burden.[4] In some situations, patients have severe medical conditions or comorbidities that make them a poor candidate for surgery.[5] In such cases, the healthcare provider should inform the patients regarding alternative treatment options.

Vaginal pessaries belong to one of two main categories: supportive (ring pessary, etc.) or space-occupying (Gellhorn pessary, etc.).[6] Ring pessaries are generally easier to remove, lower the risk of erosions and require lesser visits to the clinic.[3] However, up to 56% of ring pessary users could experience complications such as extrusion, haemorrhage, severe vaginal discharge, pain and constipation, leading to a high discontinuation rate within one year.[7] Moreover, ring pessaries get dislodged easily in comparison to space-occupying Gellhorn pessaries, hence they are not suitable for

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advanced prolapse and the Gellhorn pessary could be more effective.[8,9]

The Gellhorn pessary is an effective and long-term treatment for POP because it creates suction against the proximal vagina, which supports the pelvic organs even in advanced-stage POP. The Gellhorn pessary can also be used as a treatment option for POP after other treatments fail.[10] It has a high success rate in patients with posterior compartment and stage 4 prolapse.[11] As per our clinical experience, support pessary is usually used in Malaysia as the mainstay amongst pessary types for the conservative management of POP while Gellhorn pessary is not widely used. Furthermore, as per our literature search (using google scholar and Pubmed databases using keywords Gellhorn pessary & Malaysia) Gellhorn pessary's acceptance and success rate is unknown in Malaysia. Therefore, an analysis of its acceptance, success rates and reasons for discontinuation is required. Our study will enable healthcare providers to make informed decisions regarding the use of the Gellhorn pessary and will contribute to shared decision-making between doctors and patients by facilitating personalised treatment planning. Moreover, our study could serve as the baseline for comparisons with other treatment modalities of POP.

MATERIALS AND METHODS

Study Design

The present study is a retrospective cohort study using hospital medical records (patient files).

Study Population

We conducted a retrospective clinical review of 61 patients of symptomatic POP with stages 3 and 4 from October 2019 to November 2021. Based on the inclusion and exclusion criteria, 53 women were selected. Due to the stage of prolapse in the selected patients, 27 patients were not able to fit a ring pessary, 13 patients had initially failed ring pessary fitting (for successful ring pessary fitting, the internal vaginal calibre must be wider than the vaginal opening to retain a ring pessary, and patients who had a wide introitus and were unable to retain the pessary were placed under the category of 'ring pessary failure') and 13 were awaiting surgery (who had their surgery scheduled for at least after three months). They were given the option of a Gellhorn pessary as an alternative to surgery or till the date of operation (see Table I).

Inclusion Criteria

Records of patients with stage 3 and stage 4 POP were included in this study with complete follow-up data for at least three months after their Gellhorn pessary fitting.

Exclusion Criteria

Patients who were sexually active were not part of the present study as space-occupying pessaries interfere with sexual activity. Any allergy history of the patients was also checked before the pessary fitting to ensure that none of them were allergic to silicone as the Gellhorn pessaries are usually made of silicone. Patients with atrophic vagina and erosion were also not fitted with the Gellhorn pessary because the Gellhorn pessary also has vaginal dryness, itching and erosion as its side effects which could cause further complications. Atrophic vagina and some erosions are often found in women with advanced stage POP, especially those who have used a ring pessary in the past so such patients were thence not routed for Gellhorn pessary fitting. Furthermore, patients with abnormal pap smears were also not fitted with Gellhorn pessary and were referred to the Oncology Department.

Pessary Type

Gellhorn pessaries manufactured by the Cooper Surgical, Inc. were used and the range of pessary diameter varied from 44 mm to 76 mm.

Pessary Fitting Procedure

Trained personnel inserted the Gellhorn pessary in patients with POP. We manually managed prolapse before the pessary fitting. Measurement between both sacrospinous processes and one finger breath of space between the pessary and the vagina determined the size of the pessary. We asked the patients to walk, cough, micturate and execute the Valsalwa manoeuvre to ensure the pessary did not expel during daily activities. After confirmation of in situ pessary placement, we recommended the patients return for a follow-up appointment in 2 weeks to record their symptoms and get a general evaluation of their condition. We changed the pessary size of patients who had discomfort. Retaining the pessary after 2 weeks without any complaints was considered a successful fitting. We collected data on every follow-up regarding symptoms, factors affecting satisfaction and refusal for pessary re-fitting.

Data Collection

We collected data from the medical records of patients who visited our urogynaecology unit for stage 3 and 4 POP. Pelvic Floor Distress Inventory-20 (PFDI-20) and Pelvic Floor Impact Questionnaire-7 (PFIQ-7) were used to measure patients' symptoms and quality of life before and after (at 3 months follow-up visit) Gellhorn pessary fitting. Patients came for a follow-up every three months for condition re-evaluation.

Numerous factors were reported (verbally) by patients that, according to them, were behind their doing away with Gellhorn pessary. These factors were then noted in their hospital record files. In a similar manner, we also asked the patients who continued the use of Gellhorn pessary for at least two years to verbally rate their satisfaction on a scale of 1 to 10 where 1 meant least satisfied and 10 meant extremely satisfied with the pessary. Their rating was again noted in their files.

Ethical Considerations

All the procedures used during this study adhered fully to the Malaysian Medical Association's (MMA) Code of Medical Ethics. Furthermore, Gellhorn pessary is a non-invasive management for third and fourth degree prolapses so patients were not exposed to higher levels of risk of harm. Informed consent question was part of the forms that patients filled before the procedure, so, only those patients' data were chosen who voluntarily allowed us. Therefore, institutional review board's exemption or waiver or consent was not needed in this retrospective study.

Table I:Patient characteristics, indications, main side effect and reasons for removal of Gellhorn pessary

		Primary Indication (n=27)	Postring pessary failure (n=13)	Awaiting Surgery (n=13)	Total (n=53)
Patient characteristics	Age (mean±SD)	63.33 (6.67)	64.62 (7.96)	61.77 (6.31)	63.26 (6.86)
	Parity (mean±SD)	3.88 (1.31)	3.54 (1.26)	3.31 (1.37)	3.66 (1.31)
	Prior surgery history	2 (7.40%)	2 (15.38%)	2 (15.38%)	6 (11.32%)
Duration	Completed 1 year	21 (77.77%)	9 (69.23%)	12 (92.30%)	42 (79.24%)
	Completed 2 year	13 (48.14%)	6 (46.15%)	9 (69.23%)	28 (52.83%)
Side Effects	Pain/discomfort	22 (81.48%)	10 (76.92%)	10 (76.92%)	Exp:42 (79.24%) Rmvd:5 (9.43%)
	Discharge	21 (77.77%)	13 (100%)	11 (84.61%)	Exp: 45 (84.90%) Rmvd:0 (0.00%)
	Bleeding	7 (25.92%)	1 (7.69%)	2 (15.38%)	Exp:10 (18.87%) Rmvd:3 (5.66%)
	Voiding Difficulty	3 (11.11%)	2 (15.38%)	0 (0.00%)	Exp:5 (9.43%) Rmvd:5 (9.43%)
	Defaecation difficulty	1 (3.70%)	1 (7.69%)	1 (7.69%)	Exp: 3 (5.66%) Rmvd:0 (0.00%)
	Impacted pessary/fistula	0 (0.00%)	1 (7.69%)	1 (7.69%)	Exp:2 (3.77%) Rmvd:2 (3.77%)
	Difficult removal and insertion	5 (18.51%)	2 (15.38%)	1 (7.69%)	Exp:8 (15.09%) Rmvd:8 (15.09%)
	Unexplained	1 (3.70%)	0 (0.00%)	1 (7.69%)	Exp:2(3.77%) Rmvd:2(3.77%)

Table II: Results of repeated measures t-test of PFIQ-7

	Pre-test		Post-test				
Measure	Mean	S.D.	Mean	S.D.	T	df	p
UIQ7	58.31	5.97	55.62	6.52	5.022	52	<0.01
CRAIQ7	56.43	6.50	53.58	6.41	4.227	52	<0.01
POPIQ7	93.08	2.93	54.66	22.07	12.873	52	<0.01
PFIQ7	207.82	10.12	163.86	22.73	14.115	52	<0.01

Analysis

All data were collected and measured. We estimated percentages of symptoms affecting satisfaction and of each factor influencing pessary discontinuation. The difference in symptoms before and after pessary fitting was assessed on PFIQ-7 using a repeated measures t-test. The statistical significance level used was $p<0.001$.

RESULTS

Gellhorn pessary fitting showed an initial success rate of 100%; retaining the pessary after two weeks without any complaints was considered a successful fitting. Information of the patient characteristics is shown in Table I. Furthermore, Figure 1 shows the outcome of our study. Twenty-eight patients (52.83%) preferred to continue the pessary after 24 months. A total of 25 patients (47.16%) discontinued the use of Gellhorn pessary. Out of these, 13 (24.53%) patients gave up the use of pessary for definitive surgery based on personal preference (reason not explicitly disclosed by patients), and seven patients (13.21%) refused reinsertion, whereas 3 (5.67%) patients requested a ring pessary due to discomfort and voiding difficulties. Two patients (3.77%) developed a fistula due to impacted pessary and discontinued the use of Gellhorn pessary. The number and percentage of patients who discontinued the use of Gellhorn pessary during the first and second year is shown in Figure 2. During the first year, 11 patients (20.75%) relinquished the use of the Gellhorn pessary, while 14 patients (26.42%) in the second year (a total of 25 patients or 47.17% in two years).

Many side effects of using Gellhorn pessary were reported (verbally) by the patients. These side effects (with percentage of patients who experienced them) were: discomfort (79.25%), abnormal vaginal bleeding (18.87%), voiding difficulties (9.43%), defaecation difficulties (5.66%), difficulties in re-fitting (15%), and fistula (3.77%). We tried to resolve these symptoms through conservative management, but still, a few of them got their pessaries removed owing to these side effects (for details see Table I).

It is noteworthy to mention here that initially 13 patients were fitted with Gellhorn pessary owing to the long waiting time for their scheduled surgery; only one (1.88%) patient (out of those initial 13) ultimately chose surgery. And the remaining 12 cancelled their surgeries after getting fitted with a Gellhorn pessary. This underscores the importance of Gellhorn pessary use as a viable alternative to surgery in the management of advanced POP. On the other hand, some (12 or 22.64%) patients got their pessaries removed and they opted for surgery although they were initially not awaiting surgery for their treatment.

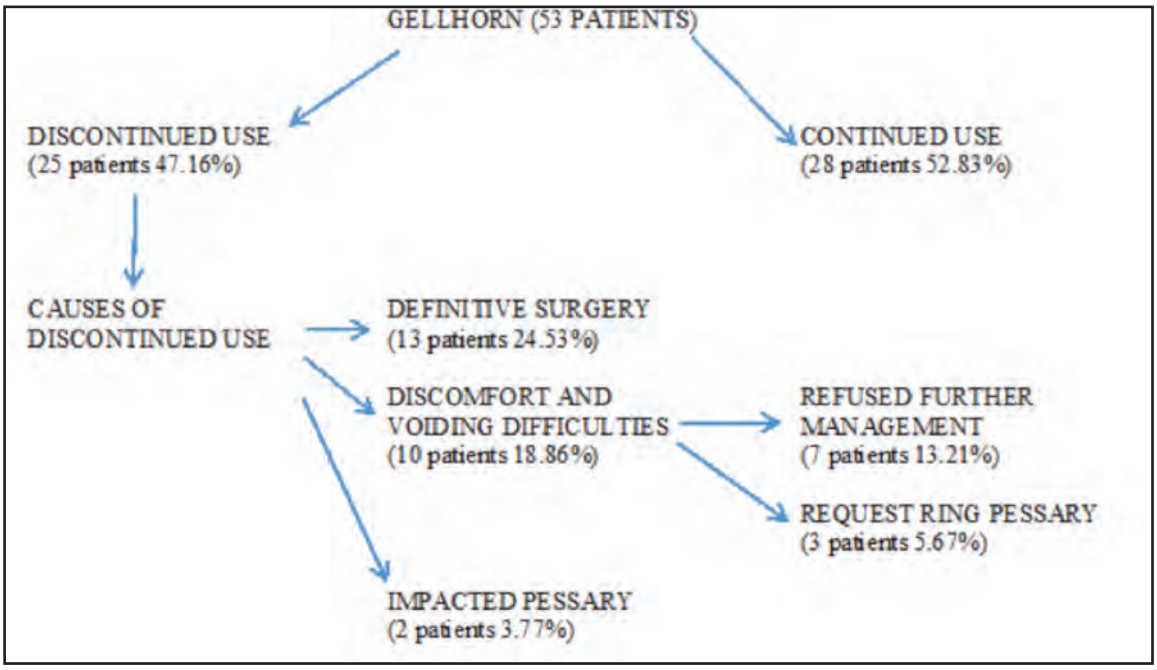

Fig. 1: Outline of the study.

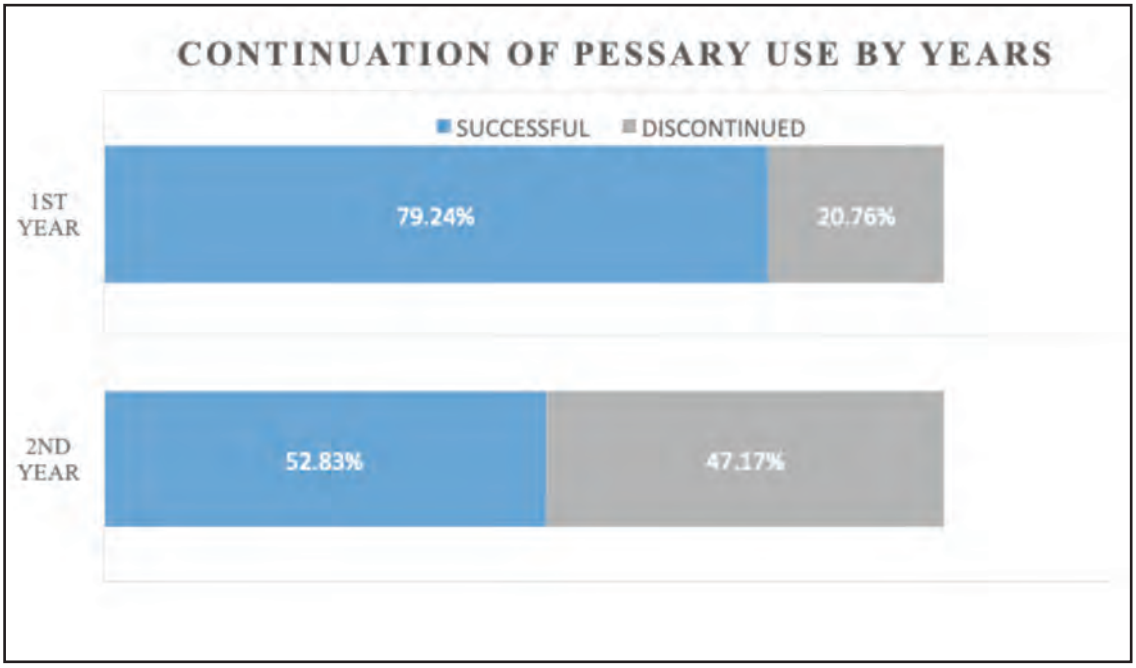

Fig. 2: The continuous use of pessary for the first and second year.

The patients who completed two years with Gellhorn pessary were asked to verbally rate their satisfaction with the pessary; a rating of 1 meant least satisfied and 10 meant highly satisfied.

Their answers showed that 68% of the patients chose 7, while 25% of patients described their satisfaction as 6 and only 7% described their satisfaction as 5.

No cut-off values were chosen to indicate the level of satisfaction, as lower rating meant less satisfaction and higher ratings meant higher satisfaction. The most frequent Gellhorn pessary sizes used were 57mm (46%), followed by 51mm (29%) and 64mm (15%).

Repeated measures t-test results of PFIQ-7 showed a significant improvement in the quality of life after the Gellhorn pessary fitting. Pre-test scores on all three scales

decreased significantly, i.e., on UIQ7 from 58.31(5.97) to 55.62(6.52), CRAIQ7 from 56.43(6.50) to 53.58(6.41), POPIQ7 from 93.08 (2.93) to 54.66 (22.07) and on the combined PFIQ-7 from 207.82 (10.12) to 163.86 (22.73) (see Table II).

Before Gellhorn's pessary fitting, the PFDI-20 showed a severity of distress score in 85% (45/53) of patients for Pelvic Organ Prolapse Distress Inventory 6 in patients suffering from POP while 15 % of patients experienced a moderate degree of distress for Pelvic Organ Prolapse Distress Inventory 6. We could not include the post-fitting results of PFDI-20 in this study because that data were incomplete to the extent that we were unable to calculate any meaningful results from it.

DISCUSSION

First-line treatment for POP comprises pelvic floor exercises and vaginal pessaries, regardless of age or type of prolapse.[12-14] In a recent Cochrane meta-analysis, women who used pessaries in conjunction with pelvic floor muscle training reported fewer symptoms of POP and improved quality of life.[3] Pessaries have been proven to effectively manage the symptoms of prolapse (PFDI-20 and PFIQ-7 scores) and improve self-perception of body image in a way similar to surgery.[15-17]

In the present study, 79.24% of women continued to use the Gellhorn pessary after the initial fitting during the first year, while the success rate of continuation was 52.83% in second year. Mao et al.[10] reported that difficulties associated with placement and removal influence the use of pessaries. More than 70% of discontinuity occurred within the first month of fitting due to the associated symptoms.[18] A long-term study indicated a decrease in the likelihood of sustained use over time.[19] The present study showed a discontinuity rate of 47.14% during second year. The symptoms affecting patient satisfaction were discomfort, abnormal vaginal bleeding, voiding difficulties, defecation difficulties, difficulties in re-fitting and fistula. Impacted pessary led to complications of vesicovaginal fistula and rectovaginal fistula in two patients (3.77%) and resulted in discontinuation of use. Management of vesicovaginal fistula involved the insertion of a silicon catheter and broad-spectrum antibiotics for 10 days. As for the rectovaginal fistula, the patient was given stool softener for one month and covered with broad-spectrum antibiotics for 2 weeks. These two patients refused any further intervention.

Patient-reported outcome measures, known as PROMs, are frequently used to evaluate and quantify the degree and severity of symptoms. The Pelvic Floor Distress Inventory (PFDI-20) and the Pelvic Floor Impact Questionnaire (PFIQ-7) are reliable tools for assessing the quality of life in women with POP. The PFIQ-7 is used to assess the effect of POP on quality of life, and PFDI-20 is used to check the extent of POP symptoms and related complaints.[20] All patients reported a significant improvement in their quality of life after the Gellhorn pessary fitting.

The current study shows that Gellhorn pessary is an effective alternative treatment option in the management of symptomatic third and fourth-degree prolapse. Discussion with patients regarding the pros and cons of pessary before fitting could improve the success rates as the adverse effects were manageable. Our findings suggest that Gellhorn pessary is a viable option for patients who are unwilling or unfit for surgery and have a third or fourth degree of POP. A strength of this study was our focus on the Gellhorn pessary with a long-term follow-up duration (up to 2 years).

LIMITATIONS OF THE STUDY AND FUTURE DIRECTIONS

The present study provides valuable insights into a novel phenomenon of Gellhorn pessary use in Malaysian population. However, there are certain limitations of the present study as well which should be addressed by future researchers. Firstly, the present study was a retrospective study with limited available data; therefore, it is recommended that future researchers should conduct prospective studies on this topic to further understand the factors affecting Gellhorn pessary use in Malaysia. Secondly, our study included a relatively small sample size of the continuation group, so future researchers should aim for a larger sample size. Thirdly and finally, we mainly utilised quantitative data in our study which has a built-in limitation of being restrictive. Future researchers should try and investigate the challenges and benefits of Gellhorn pessary use through qualitative research, i.e., interviews etc.

CONCLUSION

We conclude that Gellhorn pessary has a reasonable success rate and patience acceptance after two years of use. Most patients who continued the use of pessary showed good satisfaction and improved quality of life. This pessary can be used as a reasonable treatment option in conservative patient management of advanced prolapse before moving towards surgical management, increasing the available conservative treatment options in Malaysia. Our study paved a way towards non-surgical management of prolapse, exploiting space-filling pessaries in older women who are no longer sexually active and wish to manage their condition without surgery. All main side effects of Gellhorn pessary; pain, discharge, bleeding and fistula were conservatively managed.

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COMPETING INTEREST DECLARATION

The authors declare that there are no conflicts of interest.

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Validation study of AR Gynae endotrainer - a new mobile laparoscopic simulator

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ABSTRACT

Introduction: In gynaecology, laparoscopy is the choice of treatment for a lot of procedures as it is considered safe and effective. However, laparoscopic surgery requires skills that are different from those required for open surgery. In order to acquire the skills, a surgeon needs specific training. The aim of this study was to validate the AR Gynae endotrainer, a new mobile laparoscopic simulator, as a comparable box trainer for gynaecology laparoscopic training, comparing it with the well-established Karl Storz SZABO-BERCI-SACKIER laparoscopic trainer.

Materials and Methods: A randomised prospective crossover study was designed to compare the AR Gynae endotrainer versus Karl Storz SZABO-BERCI-SACKIER laparoscopic trainer as a tool for training gynaecology laparoscopic skills. Participants were assigned to perform two specially designed tasks used for laparoscopic training using both endotrainers. All subjects evaluated both simulators concerning their performance by the use of a questionnaire comparing: design, ports placement, visibility, ergonomics, triangulation of movement, fulcrum effect, depth perception, ambidexterity, resources for training, and resources for teaching. The overall score was defined as the median value obtained. The ability and time taken for participants to complete the tasks using both endotrainers were also compared. A total of 26 participants were enrolled in this study, including 13 Masters's students from the Department of Obstetrics & Gynaecology and 13 Masters's students from the Department of Surgery, Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia.

Results: A better performance was observed with AR Gynae as compared to Karl Storz endotrainer in five out of ten items evaluated in the questionnaire. Additionally, the overall score of AR Gynae endotrainer (median of 3.98) was comparable to that of Karl Storz endotrainer (median of 3.91) with p=0.519. For the items design and resources for teaching, the evaluation for AR Gynae endotrainer was significantly higher with p-values of 0.003 and 0.032, respectively. All participants were able to complete both tasks using both endotrainers. The time taken to complete both tasks was comparable on both endotrainers. Also, the AR Gynae endotrainer was cheaper.

Conclusions: The AR Gynae endotrainer was found to be a convenient and cost-effective laparoscopic simulator for gynaecology laparoscopic training and was comparable to the established Karl Storz SZABO-BERCI-SACKIER laparoscopic trainer.

KEYWORDS:
Laparoscopy, AR Gynae endotrainer, simulator, endotrainer, minimally invasive surgery

INTRODUCTION

Minimally invasive surgery, and laparoscopy, in particular, have been the 'gold standard' for several surgical procedures in the last decade. In gynaecology, laparoscopy is the choice of treatment for several procedures, for example, dye test to assess the tubal patency, tubal ligation as one of the sterilisation methods, salpingostomy or salphingectomy in ectopic pregnancy, cystectomy, myomectomy as well as hysterectomy in benign cases.

Laparoscopic procedures are considered safe and effective. The implementation of operative laparoscopy has reduced the duration of hospital stay and the convalescence period, which has helped to improve patient outcomes and enhance recovery after surgery.[1,2]

Laparoscopic skills, however, are very different from those used in open surgery and require specific training. The surgeon has to become proficient in handling the new instruments with a limited range of movement, the considerable loss of depth perception and haptic feedback, dealing with the counter-intuitive manipulation of the instruments (fulcrum effect), and the two-dimensional (2-D) representation of the three-dimensional (3-D) operating field.[3,4]

It is difficult to teach these skills to the surgeons in training by apprenticeship method because it requires a longer time to practice and more learning opportunities in clinical practice. Thus, simulation training was developed. Training can be done on either traditional box trainers or virtual reality simulators (VRS), which have been shown to be effective methods for providing laparoscopic skills training.[5]

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Unfortunately, barriers to simulation training, including the unaffordability of conventional endotrainers due to the high prices and low accessibility have been a constraint. This can be improved by using mobile box trainer, as it is more affordable, accessible, and mobile and therefore allow trainees to train according to their own schedule.[6,7]

In Malaysia, to date, there is no proper training centre for minimal invasive surgery, specifically in gynaecology. As an initiative, five lecturers from the Department of Obstetrics and Gynaecology (O&G), School of Medical Sciences, Universiti Sains Malaysia (USM), Kelantan, Malaysia, have collaborated to produce the AR Gynae endotrainer.

AR Gynae endotrainer is a mobile box trainer that was invented specifically for the practice of laparoscopy surgery in gynaecology. It is the first of its kind invented locally in Malaysia with the intention of making it available to gynaecologists at an affordable price. A patent application has been deposited at the Intellectual Property Corporation of Malaysia under the number CRLY00017323.

The purpose of this study was to validate the AR Gynae endotrainer, a new mobile laparoscopic simulator, as a comparable BT for gynaecology laparoscopic training, comparing it with the well-established Karl Storz SZABO-BERCI-SACKIER laparoscopic trainer.

MATERIALS AND METHODS

AR Gynae Endotrainer

AR Gynae endotrainer is made from fiberglass. Its shape is very special, it mimics a real patient's abdomen in laparoscopy surgery which is inflated and distended. It is a one-piece product, relatively small and very light, thus portable and can easily be carried anywhere. The size is about 49×35×24cm, and it weighs only two kilograms. The ports are placed as in actual laparoscopy gynaecology surgery. There are two ipsilateral ports on each side (right and left) and one suprapubic port placed 12cm from the pubic bone area. Each port's hole is covered with a round rubber clip. The distance between the ports is 8 to 1 cm. It has a fixed camera and LED light inside positioned at the umbilical site. It needs to be connected to a laptop with a front camera and ready to be used. No electrical power supply is needed (Figure 1). AR Gynae endotrainer comes with a specially designed board with different exercises used for practice. The board is inserted inside the 'abdomen' through a door placed at the lower part of the endotrainer. Two exercises used in AR Gynae endotrainer – 'Beans Transfer' and 'Bands Transfer' are inspired by one of the tasks used in the Fundamental of Laparoscopic Surgery (FLS) simulator, which is Peg Transfer. Peg Transfer is used to develop eye-hand coordination, depth perception as well as visual-spatial perception in a monocular viewing system. It also develops coordinated use of dominant and non-dominant hands (ambidexterity), a skill proven to translate into better intracorporeal suturing skills.8 AR Gynae endotrainer is very cheap and affordable. It costs about MYR2,000.

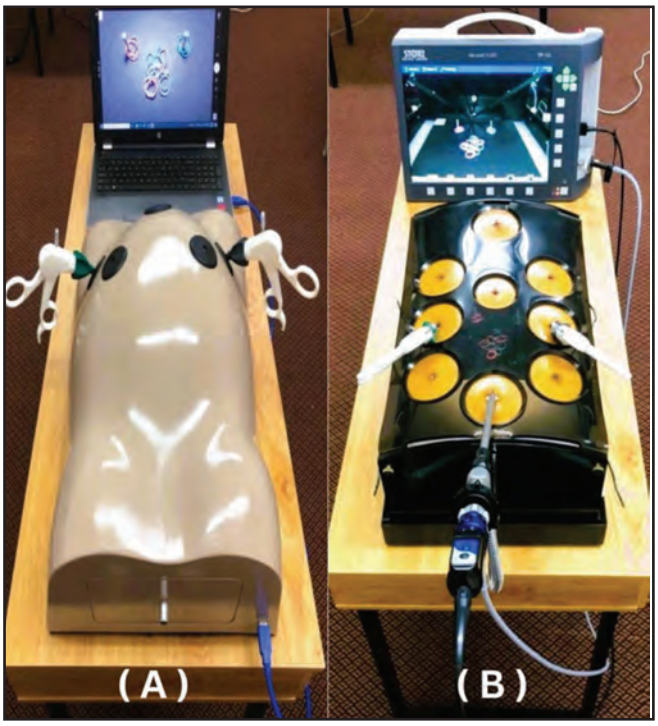

Fig. 1: AR Gynae endotrainer (A) and SZABO-BERCI-SACKIER laparoscopic trainer (B).

KARL STORZ SZABO-BERCI-SACKIER LAPAROSCOPIC TRAINER

Karl Storz is the leading endoscope manufacturer based in Germany. It is an established brand and very well known for its advanced technology and quality. Karl Storz had produced endotrainers for different types of surgery, and one of them is SZABO-BERCI-SACKIER laparoscopic trainer, which is used for training laparoscopy in surgery, gynaecology and urology. It was designed to simulate various laparoscopic procedures, especially the different suturing techniques. It contains diaphragms at the typical puncture sites and a flexible endoscope holder that provides the surgeon with the ability to manipulate instruments with both hands. The endoscope is connected to a compact and portable all-in-one system called TELE PACK X LED that has a high-resolution display and powerful LED light source just like the real one used in the operating room (Figure 1). The exercise board can just be placed inside the endotrainer. The SZABO-BERCI-SACKIER laparoscopic trainer costs about MYR12,000. Together with the endoscope and the system, it costs more than MYR100,000, according to the local supplier.

STUDY DESIGN

This study was a randomised prospective crossover study that was designed to validate AR Gynae endotrainer as a comparable box trainer for gynaecology laparoscopic training, comparing it with Karl Storz SZABO-BERCI-SACKIER laparoscopic trainer. It was conducted at the Department of Obstetrics & Gynaecology, Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia. It has been approved by the Ethics Committee of the School of Medical Sciences, USM (USM/JEPeM/20120642).

Table I: Socio-demographic characteristics of participants

Variables	Mean (SD)	n(%)
Age (Years)	33.92(1.41)	
Years of service as a medical officer	7.27(1.51)	
Year of masters training	3.50(0.65)	
Gender		
Male		16(61.5)
Female		10(38.5)
Ethnic		
Malay		15(57.7)
Chinese		4(15.4)
Indian		5(19.2)
Others		2(7.7)
Dominant hand		
Right		24(92.4)
Left		2(7.7)
HKCOG level (O&G)		
2		7(53.8)
3		6(46.2)

Table II: Comparison of quality between AR Gynae and Karl Storz endotrainers

Variables	Tools		Mean difference (95%CI)	t-statistics (df)	p-value*
	AR Gynae Endotrainer Mean (SD)	Karl Storz Endotrainer Mean (SD)			
Q1 (Design)	4.19(0.63)	3.54(0.76)	0.65(0.24,1.07)	3.28(25)	0.003
Q2(Ports placement)	4.00(0.57)	3.92(0.63)	0.08(-0.18,0.33)	0.63(25)	0.538
Q3 (Visibility)	3.69(0.93)	3.88(0.71)	-0.19(-0.62,0.24)	-0.93(25)	0.363
Q4 (Ergonomics)	3.81(0.75)	3.81(0.75)	0.00(-0.58,0.27)	0.00(25)	>0.950
Q5 (Triangulation of movement)	3.77(0.77)	3.92(0.69)	-0.15(-0.58,0.27)	-0.75(25)	0.461
Q6 (Fulcrum effect)	3.85(0.61)	4.04(0.66)	-0.19(-0.54,0.15)	-1.15(25)	0.259
Q7 (Depth perception)	3.88(0.82)	3.85(0.68)	0.04(-0.33,0.41)	0.21(25)	0.832
Q8 (Ambidexterity)	4.00(0.75)	4.08(0.56)	-0.08(-0.36,0.20)	-0.57(25)	0.574
Q9 (Resources for training)	4.31(0.68)	4.00(0.63)	0.31(-0.03,0.65)	1.87(25)	0.073
Q10 (Resources for teaching)	4.35(0.69)	4.08(0.56)	0.27(0.03,0.51)	2.27(25)	0.032
Total score	3.98(0.54)	3.91(0.46)	0.07(–0.16,0.30)	0.65(25)	0.519

*Paired t-test was applied.

Table III: Comparison of ability to complete both tasks using both endotrainers

Variables	Tools		p-value*
	AR Gynae endotrainer n(%)	Karl Storz endotrainer n(%)	
Task 1 (Beans transfer)			
Complete	26(100.0)	26(100.0)	-
Not complete	0(0.0)	0(0.0)	
Task 2 (Bands transfer)			
Complete	26(100.0)	26(100.0)	-
Not complete	0(0.0)	0(0.0)	

*Pearson Chi-square test was applied.

Table IV: Comparison of time taken to complete both tasks using both endotrainers

Variables	Method		Mean difference (95%CI)	t-statistics (df)	p-value*
	AR Gynae Endotrainer Mean (SD)	Karl Storz Endotrainer Mean (SD)			
Task 1 (Beans transfer)	2.48(0.54)	2.41(0.49)	0.07(–0.10,0.24)	0.84(25)	0.410
Task 2 (Bands transfer)	3.04(0.55)	2.72(0.77)	0.32(0.02,0.62)	2.19(25)	0.038

[a]Paired t-test was applied.

A total of 26 participants were recruited among Masters's students of O&G HUSM who are of level two and above according to Hong Kong College of Obstetricians and Gynaecologists (HKCOG) criteria of levels of gynaecological laparoscopic surgery and also Masters's students of Surgery HUSM who may perform basic laparoscopic procedures, i.e., appendicectomy and cholecystectomy.

Written informed consent was taken after an explanation of the study design was given. Before performing the tasks on the simulators, participants received a general introduction to the AR Gynae and Karl Storz endotrainers. They were given a standardised and thorough explanation of the tasks, including a video demonstration.

There are two tasks that were performed by all participants, which are 'beans transfer' and 'bands transfer'. In the first task, which is 'beans transfer', two types of beans, ten of each type, were mixed together and placed in a container in the middle of the training board. Participants transferred the beans into two containers on the board according to the type of beans using atraumatic graspers. Both hands were used alternately in this task.

While in the second task, which is 'bands transfer', two different colour bands, ten of each colour, were mixed together and placed in the middle of the training board. Participants transferred the bands into two polls on the board according to the colour of the bands using atraumatic graspers. Both hands were used alternately in this task. The time taken to transfer all those beans and bands was recorded. Time started when graspers entered the endotrainer and stopped once all beans or bands were in place. The ability of participants in completing the tasks was also recorded.

Participants performed both tasks using both AR Gynae endotrainer and Karl Storz endotrainer consecutively. The starting order of simulators was randomised for each participant based on a random draw (13 participants started with AR Gynae endotrainer first, and another 13 participants started with Karl Storz endotrainer first). The estimated time taken to complete both tasks on both endotrainers was about 30 minutes.

Before performing the tasks, a 10-minute warm-up period was given to each participant. After completing the tasks, participants responded to a questionnaire containing ten items based on a five-point Likert scale, with scores from 1 to 5: 1. Insufficient; 2. Regular; 3. Good; 4. Very good; 5. Excellent. The following items will be analysed: 1. Design; 2. Ports placement; 3. Visibility; 4. Ergonomics; 5. Triangulation of movement; 6. Fulcrum Effect; 7. Depth perception; 8. Ambidexterity; 9. Resources for training; 10. Resources for teaching. The overall score was defined as the median of the ten items.

Data entry and analysis were done using Statistical Package for the Social Sciences (SPSS) version 24.0. Descriptive statistics included the calculation of the mean and standard deviation (SD) for numerical and frequency (n) and percent (%) for categorical variables. Comparison between the two endotrainers regarding the scores of each item of the questionnaire and also the time taken to complete the tasks was carried out using Paired t-test while comparison regarding the ability to complete the tasks was carried out using Pearson's Chi-square test. In all analyses, the significance level was set at 0.05 ($p<0.05$).

RESULTS

A total of 26 participants were recruited for this study. The mean years of masters training was 3.50 years (0.65). The socio-demographic data of all participants were presented in Table I.

Table II described the comparison of quality between AR Gynae and Karl Storz endotrainers. There was no significant mean between both endotrainers except for Q1 and Q10, where participants rated higher scores for AR Gynae endotrainer. However, the differences were quite small. For the total score, the mean between both groups shows no significant differences.

A comparison of the ability to complete both tasks using both endotrainers was presented in Table III.

Table IV presented the comparison time of completion of tasks in both endotrainers. There were no significant mean differences in the time taken to complete task 1 (beans transfer) using both endotrainers. However, there were significant mean differences for task 2 (bands transfer; $p=0.038$). The time taken to complete the bands transfer task by AR Gynae endotrainer was longer by 0.32 minutes.

DISCUSSION

The advent of laparoscopy marked a fundamental change in the evolution of surgery. It advanced rapidly and influenced gynaecology as well. Nowadays, it has become a routine approach due to its safety and effectiveness. Troncoso-Bacelis et al.,[9] advocate that laparoscopic skills gained from training using simulators promote the transfer of learning to the operating room, which was proven by the reduction of the operating time of surgery.

There are various models of simulators for training in the acquisition of basic and advanced laparoscopic skills available in the current market. Generally, they can be subdivided into two categories: box trainer and virtual reality simulators, according to Loukas et al.[10] Box trainer is a traditional method used for laparoscopic training. It is a system of physical reality, where trainees can use the actual surgical instruments and interact with physical models such as inanimate models (rubber bands, beans, silicone, sponges) and animal organs, thus allowing the real feel of force feedback. Virtual reality simulators (VRS) are a new concept for laparoscopic training. In VRS, only virtual instruments are used, and the control mechanisms are integrated through appropriate sensors. They came with simulation software that reproduces scenarios and platforms with various procedures of different difficulty levels (e.g., salphingectomy and cystectomy). Training on both types of simulators results in a significant overall improvement in laparoscopic surgical skills with no significant differences between both methods, as proven in many studies.[11-13] However, VRS has

disadvantages for its high cost and inability to reproduce important tasks like suturing, although they are better models to simulate advanced laparoscopic procedures.

In recent years, laparoscopic training outside the operating room has been strongly encouraged due to patient safety concerns, resident work-hour restrictions, and an increasingly litigious medico-legal environment. It is significant to have a proper laparoscopic training program to validate the teaching through systematic simulation of technical skills as the next step to integrate the simulation training within the curricular breadth. However, as of now, there is no standardised laparoscopic training program available for gynaecology residents. Training can be time-based, repetition-based, or proficiency-based.[14] General surgery literature has shown that structured proficiency-based training in simulation-enhanced curricula is superior to conventional residency training with regard to knowledge and technical skills acquisition.[15,16] Eliane et al.[17] have described a laparoscopic training program for residents in gynaecology at a tertiary academic centre in Canada through a comprehensive laparoscopy curriculum consisting of cognitive didactic and interactive sessions, low-fidelity box trainer and high-fidelity virtual reality simulator technical skills, and high-fidelity team simulation. The outcome of the study indicated that participation in a comprehensive simulation-based training curriculum for gynaecology laparoscopy leads to a superior improvement in knowledge and technical performance in the operating room compared with conventional residency training. A standardised structured laparoscopic training program for gynaecology residents should be developed to acquire proficiency in laparoscopic techniques.

Palter et al.[18] have developed a structured training system and a comprehensive assessment curriculum in surgical instrumental laparoscopy, demonstrating effectiveness with significant improvement in performance on surgical skills with laparoscopic box training. In the present study, the AR Gynae endotrainer is a box trainer that was specially invented for the practice of laparoscopy surgery in gynaecology. It has a unique design that mimics real patients' abdomen with the placement of the ports like in actual laparoscopy gynaecology surgery. It comes with specially designed training boards with two different exercises inspired by one of the tasks used in the FLS simulator, Peg Transfer. Another four tasks used in the FLS simulator are Pattern Cutting, Endoloop Placement, Extracorporeal Suturing, and Intracorporeal Suturing in which all of them have been extensively tested to ensure that they reflect those technical skills that are fundamental to the performance of laparoscopic surgery.[19-21] Henao et al.[22] in their study, observed a progressive effect in the surgical skills after the implementation of laparoscopic simulator training according to the FLS. In the future, AR Gynae endotrainer probably should have produced more training boards with various kinds of exercises implementing other tasks in FLS as they reflect different technical skills needed for laparoscopic surgery.

In addition, the AR Gynae endotrainer is very light and portable. It does not require an electrical power supply and just needs to be connected to a laptop with a front camera, thus making it readily used for training everywhere, even at home. Most importantly, it is also cheap and much more affordable. In this study, the novel AR Gynae endotrainer was compared to a commercially available model, SZABO-BERCI-SACKIER laparoscopic trainer by Karl Storz, regarding technical, training, and teaching aspects with the purpose of demonstrating its utility as a tool for gynaecology laparoscopic training. Generally, the study demonstrated that all parameters that evaluated the devices showed good performance for both studied simulators. It was found that AR Gynae endotrainer performance was better than the reference simulator in several technical aspects, such as the simulator's design, port placement, and depth perception. Moreover, the AR Gynae endotrainer was also rated better concerning its ability as a resource for training and teaching laparoscopic surgical skills, as well as the global performance, evaluated by the overall score. However, there were no significant mean differences between both endotrainers except for design and resources for teaching aspects ($p<0.05$), in which AR Gynae endotrainer was rated higher. However, the time taken by the participants to complete both tasks by using AR Gynae endotrainer was a bit longer. This is possibly because Karl Storz endotrainer is a transparent box, and the training board inside it can be seen through directly by the participants while handling the tasks. Vice versa, AR Gynae endotrainer is opaque, and in fact, it is more real. Another possible contributing factor was that the Karl Storz endotrainer is connected to the TELE PACK X LED system that has a high-resolution display and powerful LED light source, thus having a better clarity effect. However, the duration differences were quite small, and furthermore, all participants were able to complete both tasks using both simulators. These findings demonstrated that AR Gynae endotrainer is a comparable box trainer for gynaecology laparoscopic training.

In a nutshell, more laparoscopic simulators developments must be pursued. This initial study appears to be promising, but more randomised controlled studies are required to confirm the present results. This study had limitations as it did not evaluate objective parameters. Also, the number of participants involved was small to draw definitive conclusions.

CONCLUSION

Hundreds of studies done over the years throughout the world have proved that laparoscopic surgical skills can be acquired by simulation training. Although simulation training cannot substitute the operating room practice in total, it does increase patient safety and reduce the operating time of surgery. The low accessibility of conventional simulators can be improved by using a mobile, low-cost box trainer. The present study intended to validate AR Gynae endotrainer as a comparable box trainer for gynaecology laparoscopic training, which may help gynaecologists to practise laparoscopic skills at an affordable price. The AR Gynae endotrainer appears to be a useful, convenient, and cost-effective simulator for gynaecology laparoscopic training.

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The association between COVID-19 and atopy in Baghdad, Iraq, 2022

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) has high morbidity and mortality especially in preexisting risk groups. In atopic diseases the IgE and eosinophils are commonly elevated. This study aims to determine the potential association between COVID-19 and atopic diseases in Iraqi patients.

Materials and Methods: A cross-sectional study done in Baghdad on 112 patients who attended Al-Zahraa Allergic Center. Their demographic characteristics, total IgE, eosinophil counts and PCR result for COVID-19 were determined.

Results: The means for IgE and eosinophils were 245.7±260.1IU/ml and 444.5±117.1cells/microliter sequentially. Around 32.1% had high IgE level (i.e., atopic) and 11.6% had COVID-19. Among the atopic patients, 33.3%, 30.5% and 36.2% had atopic dermatitis, allergic rhinitis and asthma respectively. More than half (58.3%) of them were male, 55.5% aged <45 years, 36.2% were retired or had no job, 69.5% were graduated from secondary school or more and 88.8% lived in urban areas. There is no significant association in IgE level between those with and without COVID-19, which means that exposure to SARS Cov2 virus could not be a trigger or exacerbation for atopic diseases. Also, there was no association between atopic patients with COVID-19 and those without it regarding type of atopy, age, sex, occupation, education, type of living area.

Conclusions: Atopy is not a risk factor for COVID-19.

KEYWORDS:
COVID-19, atopy, allergy, atopic diseases

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection is a new, rapidly spreading infectious disease.[1] Recently, there was a rapid increase in cases worldwide due to the omicron (B.1.1.529) variant of the virus, even in vaccinated populations.[2] COVID-19 affects all the age groups, with high morbidity and mortality especially in pre-existing risk groups.[3] It demonstrates a clinically different manifestations ranging from asymptomatic presentation to critically illness with severe pneumonia, acute respiratory distress syndrome, respiratory failure or multiple organ failure. Accumulating evidences demonstrated that COVID-19 has also an extrapulmonary involvement, including neurological, smelling sensation, cardiovascular, digestive, hepatobiliary, renal, endocrinologic, dermatologic system and others.[4] Atopy is defined as a personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce Immunoglobulin E (IgE) antibodies in response to ordinary exposure to allergens.[5,6] It is a genetically determined deposition to develop allergic rhinitis, asthma and atopic dermatitis as a result of type I hypersensitivity reactions.[7-9] Atopic diseases are characterised by high level of total serum IgE.[10] Those atopic diseases are common, and they have a great burden on the communities as well as on the individuals, especially in developing countries.[11] Elevation in the measurements of total serum IgE and eosinophil cells are common in those diseases.[12,13] Atopic diseases especially asthma and rhinitis are of concern during COVID-19 pandemic, since their symptoms overlap during the early stages. There are controversial findings in publications on COVID-19 and type I hypersensitivity. Therefore, this study was carried out to report on the association between them.

MATERIALS AND METHODS

It is a cross – sectional study carried out in Al-Zahraa Consulting Center for Allergy and Asthma in Baghdad which deals with patients who had allergy, asthma or any type of atopic diseases. Iraqi people who had atopy were considered as a study population in this work. A total of 112 adult atopic patients who attended that centre were included in the study for the period April to July 2022, through four working days per week. The cases were selected according to the following inclusion criteria: (1) Their age was 18 years and more. (2) They were diagnosed to have atopic hypersensitivity (asthma, allergic rhinitis or atopic dermatitis). The exclusion criteria of cases were: (1) Those who refused to participate. (2) Those who attended the mentioned centre for conditions other than atopy. (3) Those who were not sure about their status of infection with COVID-19. The requested data from the enrolled patients were demographic characteristics, total IgE level, eosinophil counts and polymerase chain reaction (PCR) result for checking the COVID-19 infection (whether acute or not) at the interview or within the last two weeks, regardless the onset of their symptoms.

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Table I: Frequency, percent and association between some variables and COVID-19 among the atopic participants with high total IgE

Variable		Total No.	+ve COVID-19 No.	Chi- square	p-value
Type of atopy	Allergic rhinitis	11	1	1.87	0.39
	Asthma	13	4		
	Atopic dermatitis	12	2		
Age classification	˂40 years	20	3	0.56	0.67
	≥40years	16	4		
Sex	Male	21	3	0.85	0.41
	Female	15	4		
Occupation	Governmental work	12	4	3.91	0.27
	Private company	3	1		
	Self-employed	8	0		
	Retired or no job	13	2		
Education	˂ Secondary graduation	11	2	0.01	1.00
	≥ Secondary graduation	25	5		
Living place	Urban	32	5	2.68	0.16
	Rural	4	2		
Total IgE (Ln) ± SD		**-ve COVID-19**	**+ve COVID-19**	**t-test**	**p-value**
		2.66 ± 0.24	2.63 ± 0.29	-0.23	0.81

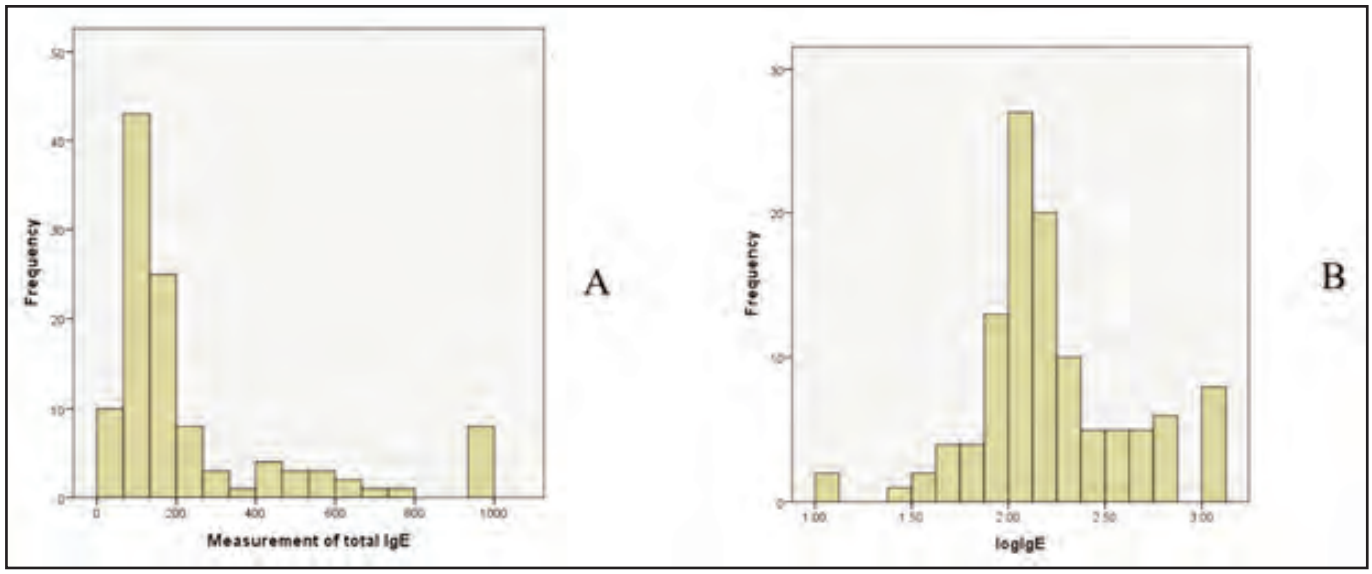

Fig. 1: Histogram charts of the frequency distribution of arithmetic values (A) and natural logarithm values (B) of serum total IgE for all participated patients.

RESULTS

The serum total IgE mean was 245.7±260.1IU/ml. The eosinophil count measurements mean was 444.5±117.1cells/microliter. The distribution of total IgE was skewed to the left Figure 1(A), then data were transformed to natural logarithm (ln) to get a normal distribution Figure 1(B).

Out of the total participants, thirty-six patients (32.1%) had a high level of total IgE (more than 200IU/ml) i.e atopic patients.[14,15] Thirteen patients (11.6%) were infected with COVID-19. The characteristics of COVID-19 patients are shown in Table I.

DISCUSSION

The distribution of total IgE was skewed to the left, which is similar to that reported in some literatures.[14,16] A transformation to ln was carried to get the normal distribution. An atopy state was found in 32.1%. It might be due to the type of patients who are attending the study setting which is a specialised centre for allergy and asthma i.e., most of patients complain of allergy. Allergies other than atopy (serum sickness, arthus reaction, etc.) were out of the scope of that centre, due to limited resources of diagnosis. The rate of COVID-19 was 11.6%. This relatively low rate might be explained by the fact that the data collection period (April to July 2022) was a time of regressed epidemic of COVID-19 in Iraq. PCR was limited to those patients with respiratory symptoms. Uncleared information in case detection of

COVID-19 could be behind this low figure of the disease, because Iraqi ministry of health officially consider only the PCR results in its diagnosis, regardless the CT-scan findings (if present). Globally, asthma and other atopic diseases 'allergic rhinitis and atopic dermatitis' have profoundly increased in frequency within the last decades. Notably, all combined, they now affect approximately 20% of the global population. Allergic rhinitis and atopic dermatitis are more prevalent than asthma around the world,[17] but the current study shows that the percent of those three manifestations of atopy is approximately equal. More than half of patients (58.3%) were males. Another Sweden study showed the female percent was 50.5%.[18] Slightly more than half of the studied atopic patients (55.5%) were below 40 years of age, this might reflect the relatively ordinary age groups of patients who attend the mentioned centre. Slightly more than one-third (36.2%) of the studied patients were retired or had no job. Another study done in Poland revealed that 42% of attended allergic patients were also retired.[19] The largest proportion of the studied patients (69.5%) completed their secondary school or university; as mentioned in the Polish study, which revealed that the largest group (36%) of allergic patients were also graduated from high school.[19] The majority of participants (88.8%) lived in urban areas, this might be due to the place of the study setting that is located inside Baghdad centre which is an urban area. There is no significant association in IgE level between those with and without COVID-19, which means that exposure to SARS Cov2 virus could not be a trigger or exacerbation for atopic diseases. Also, there was no statistical difference between atopic patients with COVID-19 and those without it regarding the following variables: type of atopy (whether it was asthma, allergic rhinitis, or atopic dermatitis), age of patients, sex of them, their occupation, their educational status and their type of living area. Multiple studies published recently do not prove that SARS Cov2 virus could cause a serious illness in individuals with atopy.20 There are controversy findings in literation about atopy and COVID-19.[21] Many studies indicated that atopic diseases do not represent a risk factor for COVID-19 susceptibility or its severity.[22,23] Moreover, there are studies revealed that asthma and atopic diseases are associated generally with a lower risk of infection and severity of COVID-19.[22] Some studies proposed that the inhaled steroids might give some degree of protection against COVID-19 infection and severity. In contrast, chronic or recurrent use of systemic corticosteroids before getting COVID-19 could be a risk factor for poor outcomes and worse survival in patients with asthma and atopy. Some studies showed that treatment for severe asthma 'especially the biological therapy' does not increase the risk of getting COVID-19 or increasing its severity.[24] In addition, an Iranian study showed that allergic rhinitis was reversely associated with the severity of COVID-19.[25] Spectacularly, a Swedish study has found that the genetic factors underlying predisposition to atopic diseases are protective against COVID-19.[26]

LIMITATIONS OF THE STUDY

Since the cycle threshold values of COVID-19 PCR (or their cut off point) could not be traced in the current study for the patients with positive results of SARS CoV2 in order to estimate the viral load or the duration of infection, the recently infected cases could not be identified from the oldest ones, and thus the probable effect of this confounding issue on the measurements of serum total IgE could not be assessed.

CONCLUSION

Among the atopic patients, there is no significant association between COVID-19 and total serum IgE, type of atopy, age, sex, occupation, education, and living area, so atopy is not a risk factor for COVID-19.

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CKD-CHECK toolkit to improve doctors' practice in managing chronic kidney disease rapid progressors: a pilot study in primary care setting

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ABSTRACT

Introduction: Chronic kidney disease (CKD) rapid progression is associated with higher risk of end-stage kidney disease and higher mortality rate. Monitoring and recognition of CKD rapid progression is still lacking, however interventions have been shown to improve this. Thus, this study aimed to evaluate the acceptability and feasibility of CKD-CHECK toolkit and preliminary measure the outcome of the CKD-CHECK toolkit in assisting primary care doctor to order further tests for CKD rapid progressors and trigger appropriate nephrology referral.

Materials and Methods: The CKD-CHECK (CKD-CHECK EGFR Chart in Kidney disease) is a toolkit that was developed to auto-generate patients' eGFR trend using a line graph, displaying the trend visually over a year. It identifies patients with rapid CKD progression, triggers the doctors to order appropriate tests (proteinuria quantification or renal imaging) and helps in decision making (continued monitoring at primary care level or referral to nephrologist). The toolkit was piloted among medical officers practising in a hospital-based primary care clinic treating patients with eGFR<60ml/min/1.73m^2 using an interventional before-after study design from February to May 2022. In the pre-intervention period, the CKD patients were managed based on standard practice. The doctors then used the CKD-CHECK toolkit on the same group of CKD patients during the intervention period. The feasibility and acceptability of the toolkit was assessed at the end of the study period using the Acceptability of Intervention Measure (AIM) and Feasibility of Intervention Measure (FIM) questionnaires. All patients' clinical data and referral rate were collected retrospectively through medical files and electronic data systems. Comparison between the pre- and post-intervention group were analysed using paired t-test and McNemar test, with statistical significance p value of <0.05.

Results: A total of 25 medical officers used the toolkit on 60 CKD patients. The medical officers found the CKD-CHECK toolkit to be highly acceptable and feasible in primary care setting. The baseline characteristics of the patients were a mean age of 72 years old, predominantly females and Chinese ethnicity. Majority of the CKD patients had diabetes mellitus, hypertension and dyslipidemia. The numbers of CKD rapid progressors was similar (26.7% in the pre-intervention group vs 33.3% in the post-intervention group). There were no significant differences in terms of proteinuria assessment and ultrasound kidney for CKD rapid progressors before and after the intervention. However, a significant number of CKD rapid progressors were referred to nephrologists after the use of CKD-CHECK toolkit (p=0.016).

Conclusions: CKD-CHECK toolkit is acceptable and feasible to be used in primary care. Preliminary findings show that the CKD-CHECK toolkit improved the primary care doctor's referral of rapid CKD progressors to nephrologists.

KEYWORDS:
CKD rapid progressor, CKD toolkit, nephrology, primary care, feasibility, acceptability

INTRODUCTION

Chronic kidney disease (CKD) is defined as evidence of kidney damage with or without estimated Glomerular Filtration Rate (eGFR) less than 60ml/min/1.73m^2 that is present more than three months.[1] It is associated with increased risks for all-cause mortality and caused impairment in quality of life.[2] Globally, the prevalence of CKD in 2017 is 9.1% and has resulted in 1.2 million deaths.[3] In Malaysia, its prevalence has increased from 9.07% in the year 2011 to 15.48% in the year 2018.[4] There were almost 40,000 patients in Malaysia who required dialysis in 2016.[5] It is estimated that this figure will reach up to 106,249 cases in year 2040.[6] In term of economic burden, the total annual expenditure of end stage renal disease (ESRD) by the public sector in Malaysia has increased 94% from Malaysian Ringgit (MYR) 572 million purchasing power parity in 2010 to MYR1.12 billion in 2016.[7]

Numerous studies have reported that CKD patients did not follow the same decline rate in their eGFR.[8,9] A prospective study conducted at primary care looking into the five-year outcomes of CKD has reported that change in eGFR at year 1 significantly influenced CKD progression.[10] CKD patients who experience loss of eGFR of more than 5 ml/min/1.73 m^2 per

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year are referred as CKD rapid progressors.[1] The prevalence of CKD rapid progressors in primary care ranged from 25 - 40%.[11,12] These individuals faced higher risk to progress to end stage renal disease, requiring dialysis and had a greater mortality rate compared to those with a slower decline in their eGFR.[9,10] Given this scenario, some guidelines have highlighted the rapid decline in eGFR rate as a criterion for nephrology referral.[1,13] However, up to 40% of CKD rapid progressors were not referred to nephrologists by primary care doctors.[12] These late referrals to nephrologist have been linked to higher risk of unplanned dialysis, hospitalisation rate and increased treatment cost.[14] Conversely, those rapid progressors who were referred early to nephrologists exhibited a slower decline in their GFR rate and experienced better health outcomes.[15]

Based on a previous study, primary care doctors in Malaysia had an average of 40 consultations per day, with each consultation lasting less than 15 minutes.[16] However, the patients managed by primary care doctors in public clinics were more chronic and complex compared to those who visited private sectors.[17] Other than time factors, up to 51% of primary care doctors were found lacking in knowledge and familiarity with the CKD guideline.[18] This limits their ability to integrate CKD care into practice. All these led to therapeutic inertia in which the doctors failed to identify CKD rapid progressors and refer them to nephrologist earlier.[19]

Interventions such as automated reporting of eGFR with creatinine have been introduced more than a decade ago in assisting the doctors for recognising CKD. The eGFR value would be included in the test report whenever creatinine test was ordered. However, not all laboratories in Malaysia provide automated eGFR report, especially in government primary care clinics.[20] eGFR value needs to be manually calculated by the primary care doctors and documented in the patient's medical record.[21]

Furthermore, the findings on the improvement of CKD detection and appropriate nephrology referrals using automated reporting of eGFR were inconsistent. A study done by Akbari et al., reported that the number of appropriate referrals to nephrologist increased by 43.2% after the introduction of automatic reporting of the eGFR.[22] However, the appropriateness of nephrology referrals in Australia has fallen significantly from 74.3% before the eGFR reporting to 65.2% thereafter.[23] Similar findings were shown in a Canadian study which reported that up to 62.7% of nephrology referrals were considered as inappropriate and has contributed to longer clinic appointment waiting time.[24] In the United Kingdom, the ASSIST-CKD program used software to create a five-year graph of all the eGFR results for patients with eGFR less than 50ml/min/1.73m^2.[25] The graphs were reviewed by laboratory staff, renal pharmacist or renal nurse to determine if the patient sustained a rapid decline in their eGFR. For patients who met the criteria, the printed report was sent to the respective general practitioners (GP). This report included the patient's graph, ways to contact nephrologists and how to make the nephrology referral. A total of 90% of GPs found that the eGFR graphs were helpful and up to 48% of GP had referred a patient on receipt of a graph to a nephrologist. Similarly, intervention that use trigger tool to notify the doctors of a falling eGFR trend have received positive feedback from doctors.[26]

In view of the potential benefit of tools in assisting CKD rapid progression identification and management, this study's aims were twofold. Firstly, we aim to assess the acceptability and feasibility of the newly developed CKD-CHECK toolkit, a tool that auto-generates a graph showing visual representation of the patient's eGFR trend. Second, we aim to preliminary measure the outcome of the CKD-CHECK toolkit to improve the management of CKD rapid progressors in a primary care clinic, in terms of improving further test for these patients and subsequently aid in appropriate referral of rapid progressors to nephrologists.

MATERIALS AND METHODS

This pilot study was a single arm, pre- and post-intervention study that was conducted at a university-based primary care clinic in Kuala Lumpur, Malaysia between the period of February to August 2022. The pre-intervention period started from February to March 2022. The intervention was subsequently introduced in April 2022. This was a clinic-wide intervention study where all medical officers practising during the study period received training to use the toolkit. The medical officers used the toolkit on patients until August 2022.

Eligibility Criteria

The inclusion criteria of this study include medical officers who were practising at the university-based primary care clinic during study period and clinically managed CKD patients. The medical officers would use the CKD-CHECK toolkit on patients with the following characteristics: patients aged 18 years old and above, eGFR<60ml/min/1.73m^2, have been followed up at least a year at the clinic, had at least two recorded serum creatinine results, minimum three months apart throughout a year and had not been referred to a nephrologist. Patients who were pregnant and had acute kidney injury for the past 3 months were excluded from this study. Acute kidney injury was defined as an increase an increase in serum creatinine of at least 26.5µmol/L within 48 hours or by a 50% increase in serum creatinine from baseline within 7 days, or a urine volume of less than 0.5ml/kg/h for at least six hours.[1] For this initial pilot study we focused the toolkit to be used on only patients diagnosed with CKD stage 3 and below.

Sample Size Calculation and Justification

In this study, we aimed to assess the acceptability and feasibility of CKD-CHECK toolkit among medical officers and preliminary measure the outcome of the CKD-CHECK toolkit in assisting medical officers to manage CKD rapid progressors. Considering the limited availability of medical officers within the study setting, all medical officers (n=25) were recruited to answer the questionnaire on acceptability and feasibility of CKD-CHECK toolkit.

The secondary objective of this study was to preliminary measure the outcome of CKD-CHECK toolkit in assisting medical officers to manage CKD rapid progressors. In order to establish the required sample size for statistical analysis,

based on recommendations for pilot studies by Whitehead et al.[27], and considering a drop-out rate of 20%, a total of 60 patients were assessed by the medical officers using convenience sampling method.

Standard Practice

All CKD patients were managed according to Malaysian Clinical Practice Guideline (CPG) on CKD 2018.[13] The medical officers traced the patient's blood and urine test results through online laboratory system. eGFR values of each patient were calculated manually by entering the patient's gender, age and creatinine level using online eGFR calculators. These values were documented in patient's case note. Renal profile and albuminuria were monitored at least annually in CKD patients. Urine test for proteinuria would be repeated 3 to 6 months later if the initial result was abnormal. Subsequently, patient's GFR and albuminuria categories were documented in the case note, based on KDIGO guideline.[1] The frequency of follow up of each patient was determined by their risk of CKD progression. For CKD patient who experienced rapid loss of eGFR more than 5ml/min/1.73m^2, renal imaging would be ordered by the medical officer. The renal imaging would be carried out at tertiary centre, located 2km distance from the clinic. For those CKD patients who met the criteria of nephrology referrals, such as rapidly declining eGFR more than 5ml/min/1.73m^2 and eGFR <30ml/min/1.73m^2, the medical officers would arrange for nephrology clinic referral at the tertiary hospital.

Intervention

A review of the literature was done to look at current tools available to assist doctors in identifying CKD and monitor eGFR progression.[22-26,28] Our toolkit was developed based on the favourable outcome of the ASSIST CKD study[25] which generates eGFR trend over time. Other factors that were associated with CKD rapid progression and may influence decision making were also derived from literature including age, gender, co-morbidities, medications, HbA1C value, proteinuria and renal imaging.[13,29] In order to develop the content of the CKD-CHECK toolkit, expert input was sought from a Family Medicine Specialist and nephrologist. To reach the aim of easier identification of CKD rapid progressors, we deemed having a visual representation of the eGFR trend using a line graph was ideal as it is simple to interpret, shows a trend over time, produces trends and patterns and will aid in decision making.[25,26] The content of the CKD-CHECK toolkit consist of three sections.

Section A of CKD-CHECK gathered information on the background of the patient and their medical history. This includes the patient's registration number, race, comorbidity and their medications. The comorbidities listed were diabetes mellitus (DM), hypertension (HPT), dyslipidaemia, cardiovascular disease and stroke. If the patient had another medical illness other than what had been listed, the doctors elaborated further at the provided empty column. The medication history of the patient was gathered by ticking at the relevant checkbox if the patient was on angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs), statin or aspirin. If the patient was not on any of the listed medications, the checkboxes remain unticked.

Section B consists of a table which included date, the patient's age, gender, serum creatinine level, calculated eGFR value, lowest eGFR level and difference between highest and lowest eGFR value. This section required the doctor to input the patient's age (in year) and creatinine level (µmol/l) according to date. A warning message would pop out if the doctors keyed in the value outside the normal range. The normal range of age was set between 19-90 years old while the creatinine level was between 50-900 µmol/l. The eGFR values were calculated automatically using the 2021 CKD-EPI creatinine equation,[30] which equals to 142 × min (Standardised Scr/K, 1) α × max (Standardised Scr/K, 1) -1.200 × 0.9938 age × 1.012 (if female), where Scr is serum creatinine (mg/dl), κ is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. The lowest eGFR level and the differences between the highest and lowest eGFR were calculated and shown in the table. A line graph with the time length (in month) at the x-axis and eGFR value (ml/min/1.73m^2) at the y-axis was plotted automatically next to the table. This section aims to aid the doctors to take note if the patient had rapid decline of eGFR level based on the graph.

Section C of CKD-CHECK listed two referral criteria to nephrologists based on CKD-CHECK: 'eGFR≤30ml/min/1.73m^2' and 'loss of eGFR ≥5ml/min/1.73m^2 in a year'. The patient met the criteria of 'eGFR≤30 ml/min/1.73m^2' if the column of lowest eGFR value shown in the table was ≤30ml/min/1.73m^2. A column written 'CAUTION' would appear next to it, together with the following message 'please order urinalysis, proteinuria quantification, USG KUB to look for reversible causes, please refer nephrologist if no evidence of obstruction on USG KUB'. If the differences between the highest and lowest eGFR of patient was ≥5, a column written 'CAUTION' would appear next to the criteria of 'loss of eGFR≥5ml/min/1.73m^2 in a year'. A message would appear as 'if the eGFR trend is dropping, please order urinalysis, proteinuria quantification, USG KUB to look for reversible causes, please refer to a nephrologist if no evidence of obstruction on USG KUB'. Some patients could have experienced acute kidney injury in the past but already recovered from it, their line graph would dip before returning to baseline kidney function. Since the toolkit was unable to exclude those eGFR values, the medical officers were reminded to review the line graph and manage accordingly. If the patient did not meet either criterion, a column of 'CONTINUE MONITORING' would appear. The doctor can print out this CKD-CHECK and attach it with the written referral letter to the nephrologist. The toolkit has 2 versions depending on the gender of the patient. The example of CKD-CHECK for male and female CKD patients are shown in Figures 1 and 2.

This CKD-CHECK toolkit was made available on the Google Sheet® platform. For testing this initial concept of the CKD-CHECK toolkit, Google Sheet® was used as it was easily accessible by the doctors from each consultation rooms' computer, was relatively easy to use and was free. The CKD-CHECK toolkit may later be integrated in the electronic medical record or lab system if found to be beneficial. After the toolkit was developed, it underwent evaluation of its

content by two experts consisting of another Family Medicine Specialist familiar with the clinic's set-up and managing CKD and by a nephrologist practicing in a university-based tertiary hospital. No major changes were made to the toolkit.

Outcome Measures

The primary outcome measures of this study were to evaluate the acceptability and feasibility of our CKD-CHECK toolkit among medical officers. Acceptability was defined as the perception among medical officers that the intervention is satisfactory while feasibility was defined as the extent to which CKD-CHECK toolkit can be successfully used in primary care setting.[31]

We measured the acceptability of the CKD-CHECK toolkit using the Acceptability of Intervention Measure (AIM) questionnaire. This questionnaire has been validated and has shown good reliability with a Cronbach alpha of 0.85.[31] Medical officers were asked to what extent they agreed with the following statements using a 5-point Likert scale (1=completely disagree to 5=completely agree): (1) CKD-CHECK toolkit meets my approval, (2) CKD-CHECK toolkit is appealing to me, (3) I like CKD-CHECK toolkit, (4) I welcome CKD-CHECK toolkit. The total score for each construct fell within the range of 4-20, with higher scores indicating a greater perception of acceptability of the CKD-CHECK toolkit.

The feasibility of the CKD-CHECK toolkit was assessed using the Feasibility of Intervention Measure (FIM) questionnaire. This questionnaire has been validated and has shown good reliability with a Cronbach's alpha of 0.89.[31] Medical officers were requested to indicate their level of agreement with the following statements, utilising a 5-point Likert scale ranging from 1 (completely disagree) to 5 (completely agree): (1) CKD-CHECK seems implementable, (2) CKD-CHECK toolkit seems possible, (3) CKD-CHECK toolkit seems doable, (4) CKD-CHECK toolkit seems easy to use. Each construct's total score ranged from 4-20, with higher scores indicating a better perception of the CKD-CHECK toolkit's feasibility. In addition, a section was included for the medical officers to give their feedback and suggestions on how to improve the toolkit.

For the secondary objective of this study which is the preliminary measure the outcome of the CKD-CHECK toolkit, the outcome measures included the following:

Appropriate proteinuria assessment requested by medical officers for CKD rapid progressors. It is recommended that albuminuria is monitored at least annually in CKD patients according to guideline.[1] An abnormal urine test for proteinuria should be repeated after 3 to 6 months.[13] The appropriateness of ordering urine test for proteinuria was determined when the medical officers requested the urine test for patients who had not done it in the previous one year or repeated the urine test for patients who had proteinuria. The urine tests include urine full examination microscopy examination (UFEME), urine albumin: creatinine ratio (UACR) or urine protein: creatinine index (UPCI).

Appropriate renal imaging orders for CKD rapid progressors: Renal imaging is indicated for CKD patients who experienced rapid loss of eGFR more than 5ml/min/1.73m^2.[13] The appropriateness of ordering renal imaging for CKD rapid progressor was determined if patients who met the above criteria were or were not ordered for renal imaging and if there was any documentation of such request in the medical records.

Appropriate nephrology referral of CKD rapid progressors by medical officers: The criteria of nephrology referrals include rapidly declining eGFR>5ml/min/1.73m^2 and eGFR<30 ml/min/1.73m^2.[13] The referral of CKD patients to nephrologist was considered appropriate if such criteria were met.

Study Flow

All the medical officers were given a talk on CKD management based on the latest local guideline before the study initiation. During the pre-intervention period, the CKD patients were managed according to the standard practices by medical officers. The medical officers were instructed to mark the patient's name on the attendance list if they met the study's inclusion criteria. The study site investigator then recorded all the highlighted names on a weekly basis for data collection at a later stage. The data collection period for the pre intervention period was set at two months. A total of 77 patients were identified, however four patients who had nephrology follow up were excluded. A yellow sticker was placed on the continuation sheet inside the medical record as identification of the pre-intervention group. Subsequently, a briefing and demonstration on how to use the CKD-CHECK toolkit was given to the same group of medical officers. A soft copy of the user guide manual on how to use the toolkit was also distributed to each medical officer. The toolkit needed to be used during their consultation with the same group of CKD patients. The medical officers accessed the toolkit by logging in Google drive with the provided username and password. They were required to make a copy the toolkit and rename the file using patient's registration number. Once the new toolkit was opened, the medical officers entered the patient's relevant information such as patient's registered number, age, co-morbidities, and medications. They were required to enter the patient's available serum creatinine level within the past one year, with retrospective input from the day of encounter. All the serum creatinine values were traced from the online laboratory system. The toolkit would then generate the patient's eGFR trend via a line graph and be used by the medical officers to aid their decision making. The data collection period for the post intervention period was set at 6 months. Throughout follow-up, five CKD patients defaulted their clinic appointment and eight patients were not accessed by using CKD-CHECK toolkit. At the end of the study period, questionnaires were collected from medical officers. Figure 3 summarises the flow of this study.

Data Collection

Secondary data of the patients assessed using the CKD-CHECK toolkit by the medical officers were extracted retrospectively from the medical records, online laboratory system and drug prescription system at the end of study period. Information such as the patient's socio-demographic characteristics and medical comorbidities were obtained from their medical records. Medication recorded includes antihypertensive medication (ACE inhibitors, ARBs, beta

Table I: The baseline sociodemographic and clinical characteristics of patients evaluated using the CKD-CHECK toolkit (N = 60)

Variables	Category	n (%)	Mean (SD)
Age (years)			72.58 (SD±8.62)
Gender	Male	28 (46.7)	
	Female	32 (53.3)	
Ethnicity	Malay	22 (36.7)	
	Chinese	34 (56.7)	
	Indian	4 (6.7)	
Comorbidities	Diabetes mellitus	52 (86.7)	
	Hypertension	60 (100.0)	
	Dyslipidaemia	57 (95.0)	
	Ischemic heart disease	9 (15.0)	
	Stroke	1 (1.7)	
	Benign prostatic hyperplasia	2 (3.3)	
	Congestive heart failure	3 (5.0)	
	Gout	6 (10.0)	

SD – Standard Deviation

Table II: The baseline medication, laboratory data and ultrasound of patients evaluated using the CKD-CHECK toolkit (N = 60)

Variables	n (%)
Angiotensin-converting enzyme (ACE) inhibitors	37 (61.7)
Angiotensin receptor blockers (ARBs)	14 (23.3)
Beta blockers	27 (45.0)
Calcium channel blockers	32 (53.3)
Loop diuretics	14 (23.3)
Thiazide diuretics	14 (23.3)
Alpha blocker	4 (6.7)
Metformin	28 (46.7)
Sulphonylurea	19 (31.7)
Dipeptidyl peptidase IV (DPP IV) inhibitors	8 (13.3)
Sodium-glucose cotransporter-2 (SGLT2) inhibitors	6 (10.0)
Insulin	25 (41.7)
Statin	56 (93.3)
Aspirin	26 (43.3)
Baseline proteinuria	40 (66.7)
Baseline renal imaging	29 (48.3)

Table III: Clinical and laboratory data of patients evaluated using the CKD-CHECK toolkit (n=60)

Variables	Category	Group		*p* value
		Pre-intervention (n=60) n (%)	Post-intervention (n=60) n (%)	
Systolic BP (mmHg)		136.42 (SD±14.60)	134.45 (SD±13.32)	0.390[a]
Diastolic BP (mmHg)		74.25 (SD±9.27)	73.35 (SD±9.81)	0.498[a]
HbA1c (%) (n=52)		7.71 (SD±1.47)	7.81 (SD±1.56)	0.624[a]
eGFR (ml/min/1.73m2)		45.47 (SD±8.09)	40.72 (SD±7.96)	<0.001[a]*
CKD rapid progressors	Yes	16 (26.7)	20 (33.3)	0.125[b]
	No	44 (73.3)	40 (66.7)	

[a] Paired t-test, [b] McNemar test, *significant as p<0.05; SD – Standard Deviation.

Table IV: Comparison of outcome measures pre and post intervention among CKD rapid progressors (n=16)

Variables	Category	Group		*p* value
		Pre-intervention (n=16) n (%)	Post-intervention (n=16) n (%)	
Appropriate proteinuria assessment for CKD rapid progressor	Yes	9 (56.3)	10 (62.5)	>0.999[a]
	No	7 (43.7)	6 (37.5)	
Appropriate order renal imaging for CKD rapid progressor	Yes	4 (25.0)	5 (31.3)	>0.999[a]
	No	12 (75.0)	11 (68.8)	
Appropriate nephrology referral for CKD rapid progressor	Yes	3 (18.8)	10 (62.5)	0.016[a]*
	No	13 (81.3)	6 (37.5)	

[a]McNemar test, *significant as p<0.05

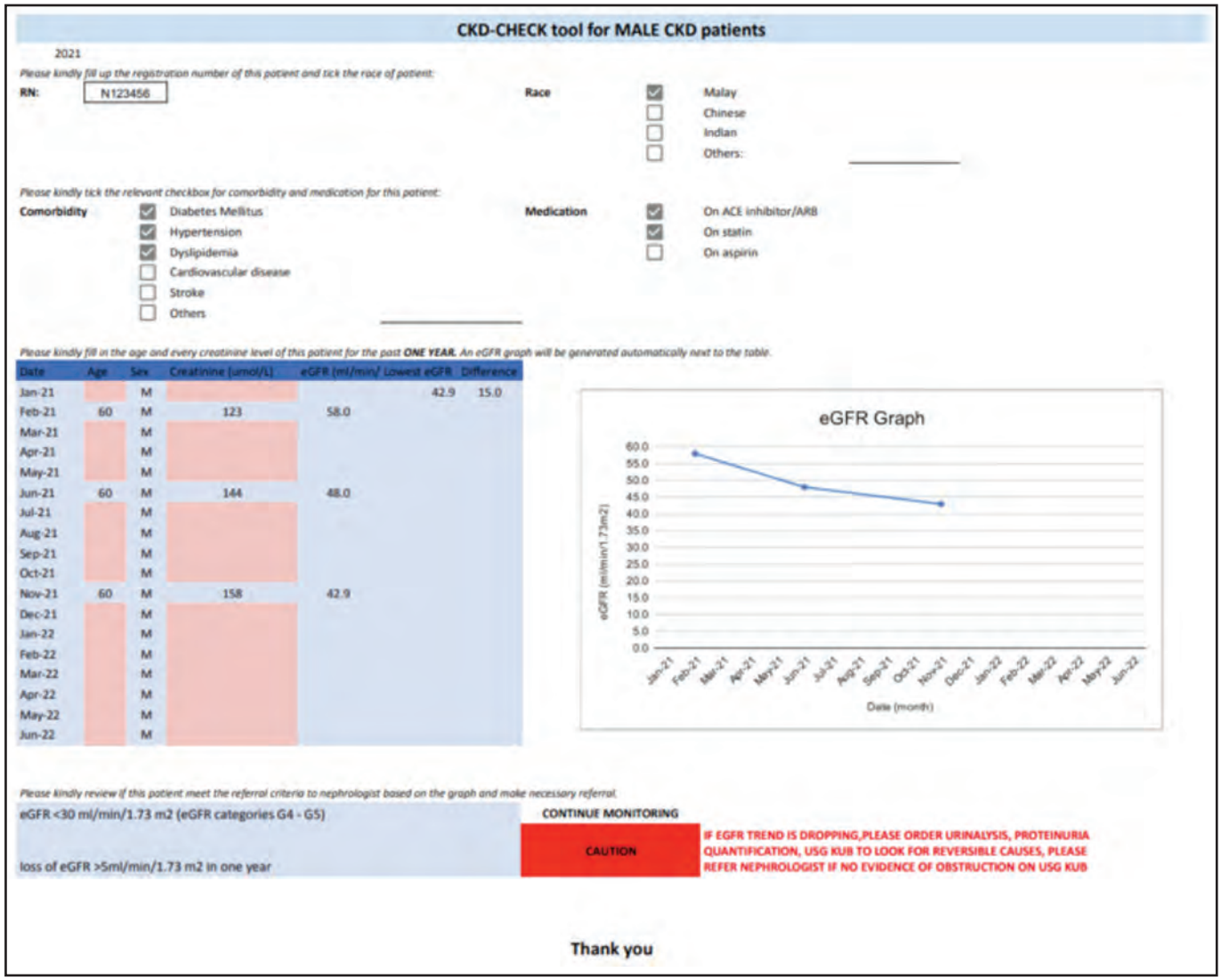

Fig. 1: Example of CKD-CHECK toolkit for male CKD patient.

blockers, calcium channel blockers, loop diuretics, thiazide diuretics and alpha blocker), oral hypoglycaemic agents (metformin, sulphonylurea, dipeptidyl peptidase IV [DPP IV] inhibitors, sodium-glucose cotransporter-2 [SGLT2] inhibitors), insulin, statin and aspirin. The patient's creatinine level for the past 1 year, most recent HbA1c level and urine test for proteinuria were obtained through the online laboratory system. eGFR values were calculated based on the most recent serum creatinine level available during clinic visit. Baseline urine test for proteinuria is defined as a test that was carried out within a year from the current visit was recorded. Baseline ultrasound kidney, bladder and ureter (KUB) refer to any renal imaging that was performed at any time before the current follow-up visit. Any subsequent management of the patient's post intervention including ordering of urine test for proteinuria, renal imaging and

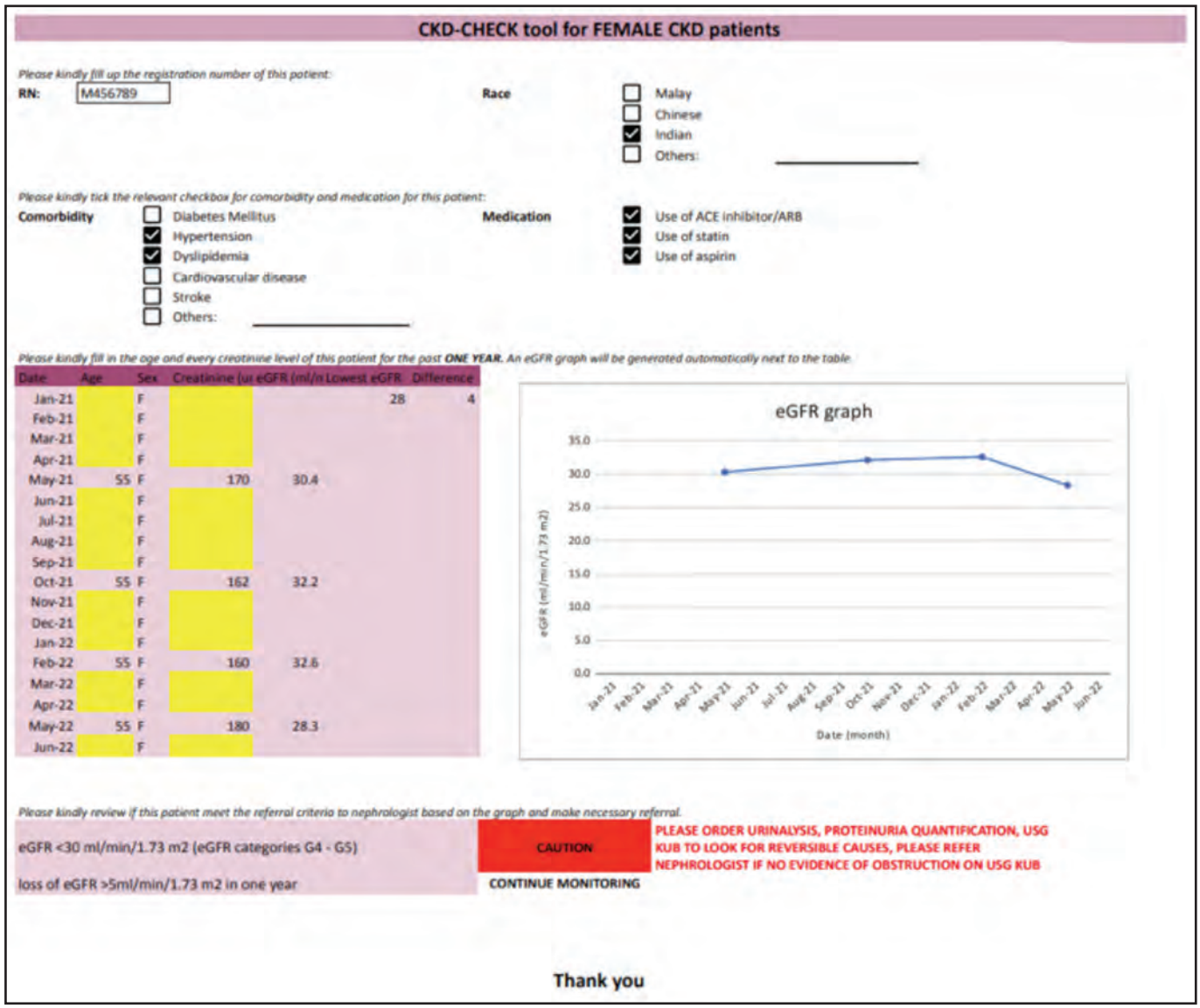

Fig. 2: Example of CKD-CHECK toolkit for female CKD patient.

referral to the nephrologist by medical officers were collected from medical records and online laboratory systems. At the end of the study period, the medical officers were required to complete a post-intervention questionnaire consisting of the AIM and FIM that was given via Google Form. They were required to provide feedback on improvement of CKD-CHECK toolkit.

Data Analysis

Descriptive statistics were used to describe the implementation outcome measures: the acceptability (AIM) and feasibility (FIM) of using the tool, and socio-demographic and clinical characteristics of the patients assessed. Categorical data were described in absolute numbers (n) and percentages (%). Continuous variables were presented using mean and standard deviation (SD). Paired t-test was used to compare the mean of pre- and post-intervention groups. We compared secondary outcome measures of investigations ordered and nephrology referrals before and after the intervention using the McNemar test for matched pairs. All data analysis was done using the Statistical Package for Social Sciences (SPSS) version 27. (SPSS Inc., Chicago, IL, USA). All probability values are two-sided, and a level of significance of less than 0.05 (p-value<0.05) were considered as statistically significant.

Ethical Consideration

Any CKD patients who met the criteria for nephrology referral but missed during follow-up were recorded in the medical records, for the doctors to refer them accordingly.

RESULTS

A total of 25 medical officers were involved in this study. More than two-thirds were females (76%) and the mean age of the medical officers were 36.68 years. Up to 80% of them had been practising in primary care clinics for more than 6 years, with the minimum years of practice being 3 years and maximum being 11 years. The responses of medical officers on acceptability and feasibility of CKD-CHECK toolkit

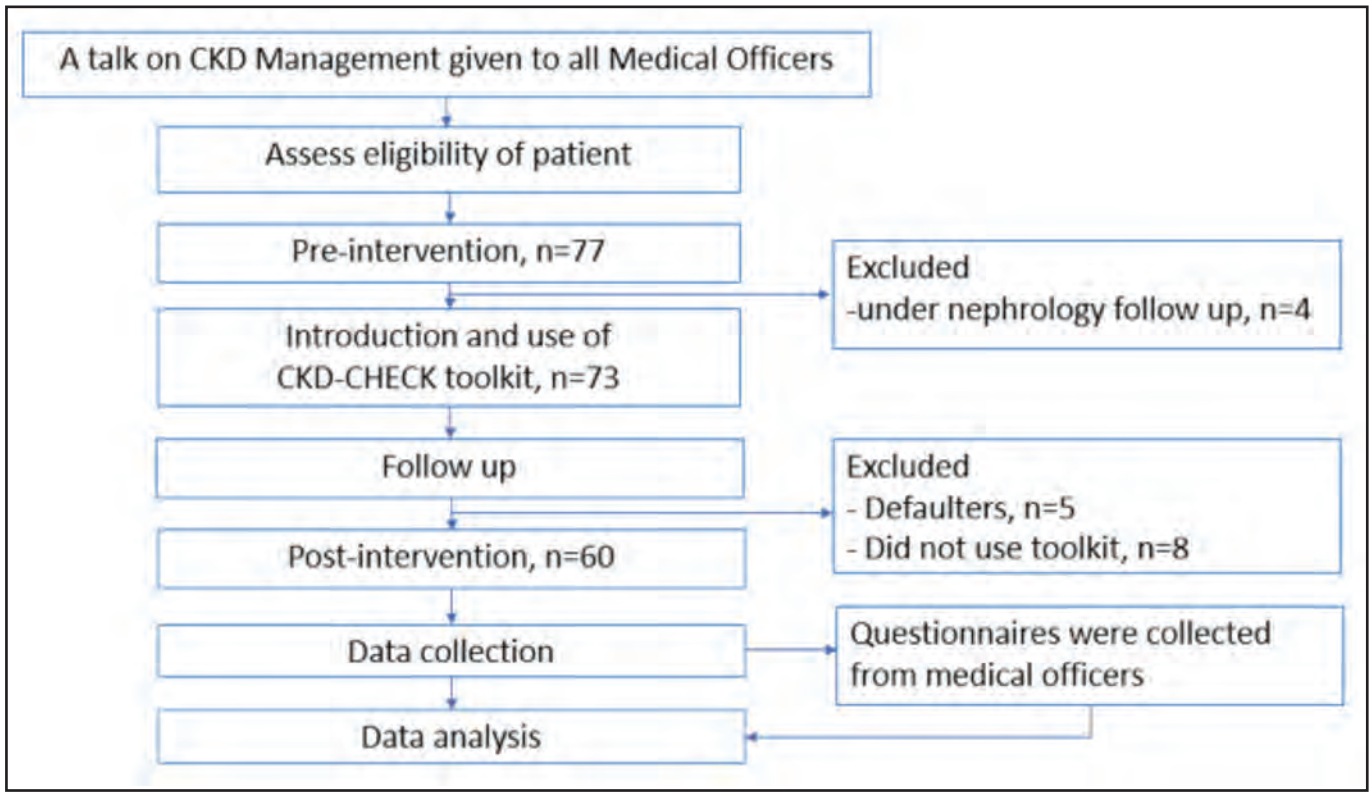

Fig. 3: Study flow chart.

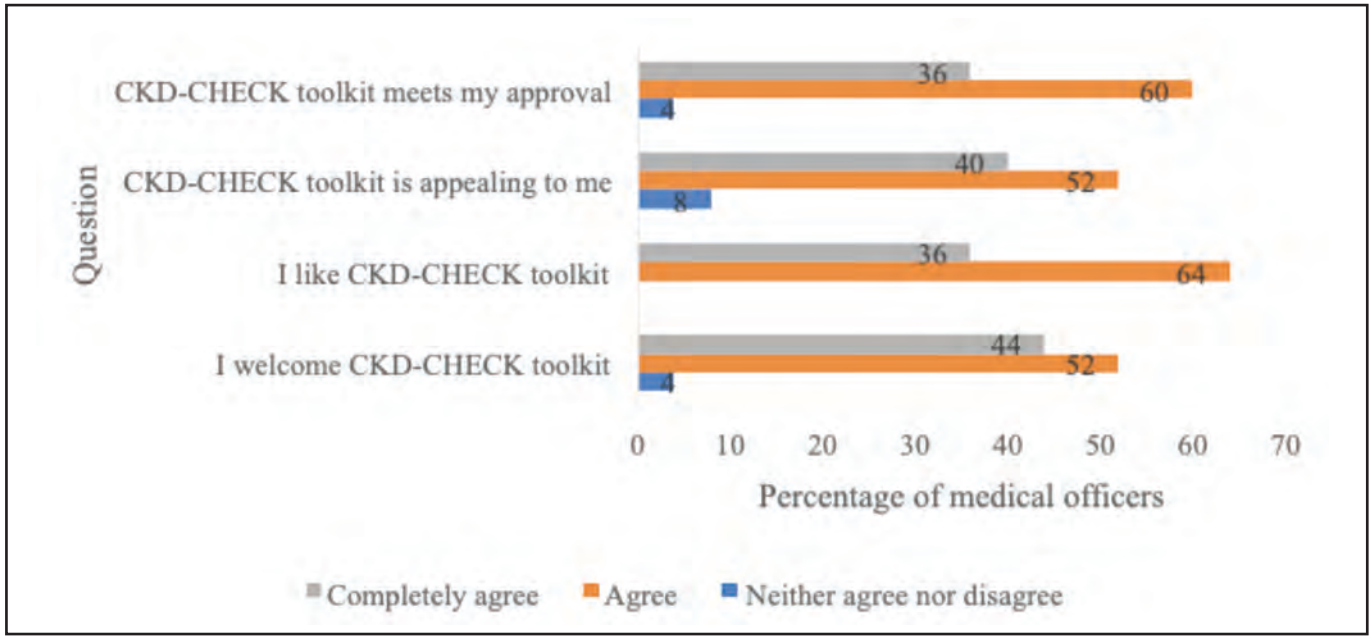

Fig. 4: Acceptability of CKD-CHECK TOOLKIT among medical officers using the AIM.

questionnaire are shown in Figures 4 and 5 respectively. In terms of acceptability of CKD-CHECK toolkit, more than 90% of medical officers found the toolkit to be appealing, met their approval and they welcomed CKD-CHECK toolkit. All of them like this toolkit. For feasibility of CKD-CHECK toolkit, all medical officers agreed that CKD-CHECK toolkit seems possible and easy to use. 96% of them agreed that the CKD-CHECK toolkit seems implementable. Only 8% of medical officers neither agree nor disagree that CKD-CHECK toolkit was doable. The mean score for both FIM and AIM were 17.4 out of 20, indicating a high-level perception of acceptability and feasibility of the CKD-CHECK toolkit among medical officers in this university-based primary care clinic. Regarding the feedback from medical officers, most of them

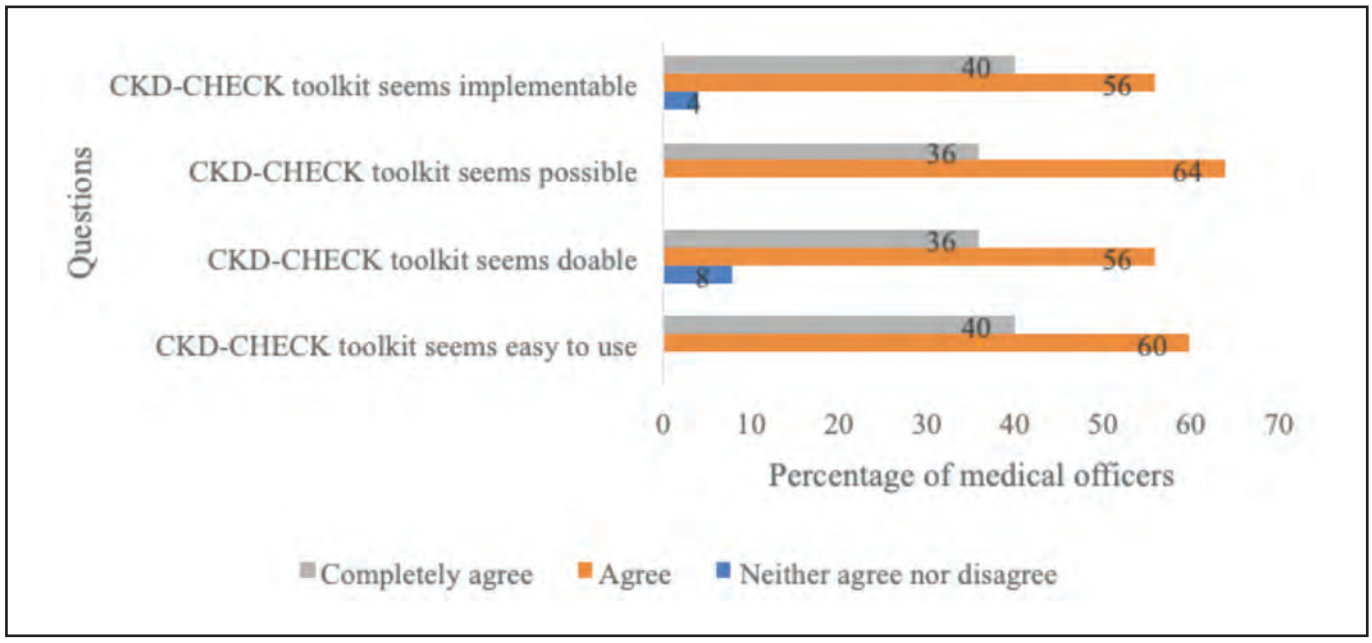

Fig. 5: Feasibility of the CKD-CHECK toolkit among medical officers using the FIM.

thought that CKD-CHECK toolkit helped them in monitoring eGFR progression and it was user friendly. However, a few medical officers preferred less data to be entered by them.

The medical officers used the CKD-CHECK toolkit on the same 60 patients seen during the pre-intervention period. No data was missed during the post-intervention period. The baseline sociodemographic and clinical characteristics of patients are shown in Tables I to III. Most of the patients were female, of Chinese ethnicity and had comorbid of DM, HPT and dyslipidaemia. The most commonly used medications among CKD patients were ACE inhibitors, CCB and statins.

For clinical and investigation data, the blood pressure and HbA1c of the patients before and after intervention showed no significant difference (Table III). The mean eGFR values of the patients have declined, where it was significantly lower during post-intervention period (40.72ml/min/1.72m^2- stage 3b) as compared to pre-intervention period (45.47ml/min/1.72m^2- stage 3a), with p<0.001. The proportion of CKD rapid progressors is similar pre-intervention (26.7%) and post-intervention (33.2%), and the difference was not significant.

Table IV shows the comparison between the pre- and post-intervention period for the secondary outcome measures among CKD rapid progressors. There were no significant differences in terms of proteinuria assessment and requests of renal imaging for CKD rapid progressors before and after the intervention. In terms of nephrology referral, a significant number of CKD rapid progressors were referred appropriately. However, despite the use of the CKD-CHECK toolkit, 37.5% of patients were still not referred. Based on the review of the medical files, the most common reasons for not referring in ranking order were doctors choosing to continue to monitor CKD trend (n=2), awaiting patients to perform renal imaging (n=2) and patients refusing to be seen by nephrologists (n=2).

DISCUSSION

The aims of this study were to assess the acceptability and feasibility of the newly developed CKD-CHECK toolkit and also to preliminarily explore the outcome of the toolkit to aid primary care doctors in their clinical decision making on whether to order further tests and make appropriate referrals of CKD rapid progressors to the nephrology clinic. The CKD-CHECK toolkit utilised a simple Google sheet to auto-generate a line graph showing the patient's eGFR trend once their serum creatinine levels were inserted. The visual depiction of the eGFR trend, along with the tool indicating when the eGFR trend meets the criteria for rapid progression, serves as a prompt for primary care doctors to take appropriate management actions. It is important to recognise the eGFR trend as several studies[8,9] have found that not all the CKD patients progress in a similar pattern. Due to the high morbidity and mortality rates among CKD rapid progressors, early identification of this group of patients has become important.

Although there are several toolkits on monitoring of CKD progression available, our toolkit is different as eGFR trend of CKD patient is represented in a line graph, generated automatically in Google sheet and interpreted directly by the respective doctor. A reminder would pop out if the doctors entered the value outside the normal range that was preset in the toolkit. This has reduced the chances that the graph could have been plotted wrongly by the doctors.[32] Despite this additional measure, we acknowledge that transcriptional errors may still occur and not be detected if the incorrect values lie within the normal ranges. Our toolkit's feature of direct interpretations of eGFR graph by the treating doctor is crucial in deciding the subsequent management of CKD patients. In a previous study, the graph was interpreted by the other health personnel before it was sent to the treating doctor.[25] This might prolong the patient's waiting time for subsequent appropriate management and nephrology referral. Besides notifying the doctors on patient's falling

eGFR trend,[26] our toolkit also has a trigger tool that provides guidance to doctors on subsequent management before nephrology referral was made. At the time of writing, a web-based app for use by healthcare workers and supported by the Malaysian Society of Nephrology (myCKDCPG) had been recently released which provides easy reference to the Malaysian CKD clinical practice guideline. It also uses a similar eGFR slope calculator and decision aid tool and utilises the Kidney Failure Risk Equation (KFRE), a widely used tool to predict risk of patients developing ESRD. Another app, The Care for Kidney app, supported by the National Kidney Foundation, has also been made available, although this app focuses on patients as the utiliser. It has a section where the patient can input their own eGFR value and a graph can be generated. These new developments support the benefits of utilising eGFR trend monitoring through a graph similar to the CKD-CHECK toolkit.

Our toolkit was highly accepted and deemed feasible by medical officers in this university-based primary care clinic. This is consistent with study findings that majority of primary healthcare providers prefer supportive technology to assist them in managing CKD patients.[33] The possible reasons may be because our tool has the potential to provide good quality nephrology referral by including sequential eGFR results and the indication for referrals,[34] facilitating collaboration between primary care doctors and nephrologists in managing CKD rapid progressors. Furthermore, the implementation of our tool did not require any additional cost, allows repetitive use and only require an easy access to the network.

In our study, the mean eGFR value of our CKD patients declined significantly during the pre-intervention to post-intervention period. This was consistent with study findings that nearly half of their CKD patients experienced decline in their eGFR, but with different rates of eGFR decline.[8] Our data was comparable with a study done by Go et al that 23% of diabetic patients and 15.3% of non-diabetic patients experienced rapid decline in their eGFR.[11] Since the majority of our CKD patients were having diabetes, they were more likely to experience rapid progression of CKD. In contrast to a study conducted in Hong Kong, only 10% of their CKD patients progress rapidly.[8]

Looking at the practice of the doctors with regards to CKD management, the testing rate of proteinuria among our CKD rapid progressors did not defer after the use of CKD-CHECK toolkit. A study in the United States that used automated electronic medical record alerts for healthcare providers has also reported similar findings.[35] In contrast to another study, the implementation of a CKD checklist in a primary care clinic has reported that patients in the intervention group had higher testing rates of albuminuria.[36] The possible explanation of low testing of proteinuria in our study could be due to our healthcare providers prioritise monitoring other parameters such as eGFR. In addition, our CKD patients might feel a financial burden with the total cost for blood and urine test and opted not to proceed with urine test for proteinuria.

In our study, a third of our patients met the criteria to proceed with renal imaging. An evaluation of new referrals to the nephrology outpatient department for renal ultrasounds also indicated that only 40% of the ultrasound requests meet the guidelines' requirements.[37] However, there was no significant improvement in ordering renal imaging for CKD rapid progressors after the use of CKD-CHECK toolkit. We hypothesised that logistics and scheduling issues could be the one of the reasons why the renal imaging was not requested for CKD rapid progressors. In our clinic setting, the ultrasound would be done in a different centre and required additional appointments for the patient. This is challenging particularly for patients who require multiple appointments or who have mobility issues. Thus, may result in delays or difficulties in accessing the necessary imaging services.

The preliminary finding from this pilot study shows improvement in nephrology referral from 18.8-62.5% when comparing the primary care doctors' practice before and after using the CKD-CHECK toolkit. This significant improvement of detection of CKD rapid progressors and subsequent referral is promising as previously there may have been gaps in practice of doctors to recognise the rapid CKD progressor as one of the important criteria for nephrology referral. A study conducted in Canada by Akbari has shown that the total number of nephrology referrals increased by 43% after automatic reporting of the eGFR.[22] In our study, unfortunately there were still 37.5% of rapid progressors not being referred to nephrologists despite the use of our toolkit. This was relatively lower compared to a study finding which reported that 54.6% of patients who met criteria were not referred to nephrologists.[38] The reasons for missed referral from our study were the decision by doctors to continue monitoring eGFR trend, awaiting results of renal imaging prior to referral and refusal of some patients to be referred to the nephrologists. A systematic review looking at delayed referral of CKD patients to nephrology revealed that they were more likely to be in the older age group and having multiple comorbidities.[39] Fear and denial from the CKD patients themselves were some of the factors that led to late referral to nephrologist.[40] Missing the diagnosis of rapid CKD progression despite the use of this toolkit could still be a possible reason for missed referral, although this was not specifically looked at in our study. An additional factor that may contribute to the non-referral of CKD rapid progressors, despite being identified by our toolkit, could be the higher threshold among doctors in a university-based primary care clinic for referring patients to nephrologists. This could be attributed to the ease of communication with the nephrology team for any consultation, which enhances the doctors' confidence in delaying referrals to nephrologists.

The limitation of our study includes the utilisation of an external system (Google sheet) for graph creation and data entry, which may introduce additional complexity to the current workflow. All the data needs to be entered manually by the doctors and typo errors could possibly occur. While Google sheet allows free access initially, subscription may be required in the future to accommodate large data storage. The initial concept of the CKD-CHECK toolkit on Google sheet may later be utilised in the electronic medical records system or lab system. The passive use of this toolkit by medical officers which they need to key in the data manually by themselves could be another limitation. As this was a single-arm study design, there was also presence of possible

unidentified confounders in this study. The awareness of medical officers on nephrology referral could have increased with the use of CKD-CHECK, contributing to a higher number of nephrology referrals. Ideally, a proper assessment should be carried out to ensure all doctors have a homogenous understanding about CKD management. Regarding our toolkit, since this toolkit focuses only on eGFR trend of CKD patients, a revised version should include albuminuria or proteinuria results. To further help the decision making by doctors, a scoring system that predicts the need for renal replacement therapy in the future- Kidney Failure Risk Estimate (KFRE) could potentially be incorporated in the toolkit based on the already entered data in the toolkit. Since this study was conducted at a single-centre university based primary care clinic, the findings may not be generalisable to other settings. For future research purposes, a qualitative study should be carried out to get the feedback from medical doctors on the feasibility of the toolkit in other clinic settings. A two-arms, multicentre study with cross-over design using CKD-CHECK toolkit then should be conducted to fully determine its effectiveness.

CONCLUSION

This pilot study has demonstrated that the CKD-CHECK toolkit was deemed feasible and acceptable to be used by our primary care doctors. Initial preliminary findings of the effectiveness of the toolkit seems promising but further larger scale studies would need to be conducted before this tool can be used in clinical practice. Once fully tested, the CKD-CHECK toolkit has the potential to be incorporated into the electronic health data system, making it accessible by all healthcare clinics and tertiary hospitals.

ACKNOWLEDGEMENTS

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FUNDING AND CONFLICT OF INTEREST

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

ETHICAL APPROVAL

This study was approved by the Universiti Kebangsaan Malaysia (UKM) Research Ethics Committee and Institute of Medical Research Ethics Committee (FF-2022-010).

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A prospective study of incidence and outcome of acute kidney injury among hospitalised patients in Malaysia (My-AKI)

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ABSTRACT

Introduction: The incidence of acute kidney injury (AKI) among hospitalised patients has not been well studied in Malaysia.

Materials and Methods: We conducted a prospective, multicentre study in seven hospitals in West Malaysia. All the adults admitted in March 2017 fulfilling Kidney Disease Improving Global Outcomes (KDIGO) criteria for AKI were included.

Results: Of the 34,204 patients screened, 2,457 developed AKI (7.18%), 13.1% of which occurred in intensive care unit (ICU). There were 60.2% males with a mean age of 57.8 (±17.5) years. The most common comorbidities were hypertension (55.0%), diabetes (46.6%), ischaemic heart disease (15.1%) and chronic kidney disease (12.0%). The commonest causes of AKI were sepsis (41.7%), pre-renal (24.2%) and cardiorenal syndrome (10.8%). Nephrotoxin exposure was reported in 31%. At diagnosis, the proportion of AKI stages 1, 2 and 3 were 79.1%, 9.7%, 11.2%, respectively. Referral to nephrologists was reported in 16.5%. Dialysis was required in 176 (7.2%) patients and 55.6% were performed in the ICU. Acidosis (46.2%), uraemia (31.6%) and electrolyte disturbance (11.1%) were the commonest indications. Continuous renal replacement therapy (CRRT) was required in 14%. The average length of hospital stay was 9.5 days. In-hospital mortality was 16.4%. Among survivors, full and partial renal recovery was seen in 74.7% and 16.4% respectively while 8.9% failed to recover. After a mean follow-up of 13.7 months, 593 (30.2%) of survivors died and 38 (1.9%) initiated chronic dialysis. Mortality was highest among those with malignancies (Hazard Ratio, HR 2.14), chronic liver disease (HR 2.13), neurological disease (HR 1.56) and cardiovascular disease (HR 1.17).

Conclusion: AKI is common in hospitalised patients and is with associated high mortality during and after hospitalisation.

KEYWORDS:
Acute kidney injury, prospective study, Malaysia

INTRODUCTION

Acute kidney injury (AKI) is a condition with rapid reduction in renal function. It is independently associated with morbidity, mortality, increased length of hospital stays, progression of chronic kidney disease (CKD), increased need for renal replacement therapy (RRT) and increased healthcare costs. The incidence varies from 5 to 20% of hospitalised patients in developed countries.

In Malaysia, the incidence of AKI among hospitalised patients has not been well studied. Single centre studies over the past few decades have shown increasing incidence of AKI among hospitalised patients.[1-3] The Malaysian Registry of Intensive Care in 2016 reported that 15.7% of the patients in intensive care unit (ICU) developed AKI within the first 24 hours of their admission.[4]

In the past there has been a lack of standardisation in defining AKI. Recently, consensus has been reached on the universal definition and staging of AKI after harmonising the previous definitions and staging systems to allow early detection and management of AKI.[5,6] This will also enable future research on the incidence, aetiologies, risk factors, outcomes and efficacy of therapeutic interventions for AKI globally.

All hospitalised patients are at risk of AKI either through their presenting illness, complications or iatrogenic causes. The rising incidence of AKI in developed countries is largely driven by sepsis, dehydration or volume depletion, trauma and exposure to nephrotoxic drugs. It may also be related to aggressive medical and surgical therapies on an ageing population with multiple comorbidities. These patients are mostly admitted under the care of non-nephrology healthcare professionals, who may not be familiar with the early detection of AKI. Prevention and optimum care of AKI

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in these patients may not be provided in a timely manner.[7] In 2009, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) in the United Kingdom described systemic deficiencies in the care of patients who died from AKI and only 50% of them had received "good" care. Deficiencies included failure in AKI prevention, recognition, therapy and timely access to specialist services.[8] Published series on AKI suggested that up to 30% of cases may be preventable, with a further significant percentage potentially remediable through simple interventions such as volume repletion, discontinuing and/or avoiding certain potentially nephrotoxic agents and earlier recognition of conditions causing rapid progression of AKI.[9-11] It is therefore, important to raise awareness of AKI and its prevention among healthcare professionals.

AKI in developing countries is commonly due to gastroenteritis or infections-related diseases such as malaria, leptospirosis and dengue. These are largely preventable and occur in young and healthy individuals.[12] Patients with AKI have a poorer prognosis with mortality ranging from 10 to 80% depending on the patient population.[13-15] A total of 5 to11% of ICU patients will require renal replacement therapy (RRT) and long-term survival is poor.[16-19] AKI is a risk factor for the development of chronic kidney disease (CKD), worsening of pre-existing CKD and may lead to end stage kidney disease (ESKD).[20-22]

The purpose of this study is to determine the incidence and evaluate the causes, risk factors and outcomes of AKI among hospitalised adult patients in Malaysia.

MATERIALS AND METHODS

This is a prospective, observational study designed to determine the incidence and outcomes of AKI in hospitalised patients (18 years and above) in seven hospitals in western states of Peninsular Malaysia.

Approval and waiver of informed consent was obtained from the Ethics Committee as no intervention was planned and confidentiality of patient information was maintained (NMRR-16-2033-32927). This study was supported by a research grant from the Ministry of Health Malaysia.

Patients were identified in March 2017. Daily laboratory data of serum creatinine of patients admitted from 12:01 am 1st March 2017 until 12:00 midnight 31st March 2017 was obtained from the pathology department of each hospital. A screening list was generated using STATA programme version 10 to identify potential patients fulfilling the criteria for AKI.[23] All the new admissions during this study period were screened for AKI using the Kidney Disease Improving Global Outcomes (KDIGO) 2012 definition of AKI.[5] Urine output was excluded as a criterion for recruitment because it was not possible to obtain accurate records of urine output for patients in the general wards. Patients with AKI who were readmitted during the study period were excluded.

Nephrologists were not involved in the management of the patients unless a referral was made. Patients alerted by the screening process were reviewed within 48 hours. Clinical and laboratory data from the patients' medical notes were reviewed and possible causes of AKI were identified.

Inclusion criteria for the study included hospitalised adults (18 years and older) who fulfilled the criteria for AKI during the study period. Patients with ESKD on dialysis and renal transplant patients or patients with increasing creatinine due to advancing CKD (as determined by the investigators) were excluded.

AKI was defined as an increase in serum creatinine of 0.3mg/dl (26.5µmol/l) within 48 hours or an increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.[5]

Baseline creatinine was defined as creatinine level at or within 7 days before the hospital admission, or the lowest creatinine (excluding the post dialysis creatinine if dialysis was initiated) during the index hospitalisation for those whose baseline creatinine were unknown.[24-26]

Serum creatinine concentration was measured by Jaffe method at six sites and kinetic enzymatic method at one site. The creatinine assay calibration was traceable to isotope dilution mass spectroscopy method.

Renal recovery was determined at hospital discharge. Full renal recovery was defined as return of serum creatinine to or below baseline or within 20% of baseline creatinine. Partial renal recovery was defined as serum creatinine which remained 20% above the baseline, but below 50% and not dialysis dependent or if previously required dialysis and is now dialysis independent. Failure to recover renal function was defined as serum creatinine remaining 50% above the baseline or dialysis dependence.[27] The total number of hospital admissions of adults (18 years and older) was compiled from the admissions office of each hospital.

The electronic records of the National Registration Department (NRD) were searched for deaths up till 31st December 2018. A search of the National Renal Registry (NRR) was also made to identify those who started on chronic dialysis up till 31st December 2018. Both NRD and NRR datasets included only Malaysian citizens.

Statistical analyses were performed using STATA version 10. Normally distributed continuous variables were described using mean and standard deviation, or median with interquartile range (IQR) for variables that were not normally distributed. Categorical data were described using proportions and percentages. Normally distributed data were analysed with t-test and one-way ANOVA. Categorical data were compared using a Pearson Chi-squared test. Data that were not normally distributed were analysed using Mann-Whitney U-test, Wilcoxon signed rank test, and Kruskal-Wallis test.

Univariate and multivariate survival analysis were performed using the likelihood ratio test of the stratified Cox proportional hazard model to determine the significance of covariates for the Malaysian cohort. Covariates included in the univariate analysis were age, gender, race, comorbid

conditions (hypertension, diabetes mellitus, chronic lung disease, endocrine disease, malignancy, chronic liver disease, arthropathy, gastrointestinal disease, psychiatric disease, haematological disease, connective tissue disease, HIV infection), CKD, cardiovascular disease, neurological disease, primary aetiology (sepsis, prerenal, cardiorenal syndrome, obstructive uropathy, drug induced, hypertensive emergency, ischaemic acute tubular necrosis, hepatorenal syndrome, intratubular obstruction, glomerulonephritis, dengue, malaria, leptospirosis, contrast induced), history of exposure to nephrotoxic drugs, referral to nephrology, admission to ICU and dialysis dependence. Factors which were found to be significant were included in the multivariate analysis. P-value of <0.05 was considered statistically significant.

RESULTS

A total of 34,204 adult admissions were screened from seven hospitals, of which 2,457 developed AKI (incidence rate 7.18%) (Figure 1).

There were 1,480 (60.2%) males and the mean age on admission was 57.8 (±17.5) years. The ethnic distribution reflects the general population but there were 109 foreigners (4.4%). The most common comorbidities were hypertension (55.0%), diabetes mellitus (46.6%), ischaemic heart disease (15.1%), chronic lung disease (12.2%) and CKD (12.0%) (Table I).

A sole aetiology was found in 1 902 (77.4%) while 22.5% had multiple causes for AKI. The common causes of AKI were sepsis (41.7%), prerenal (24.2%) and cardiorenal syndrome (10.8%).

The common causes of sepsis included pneumonia, diabetic foot ulcers, cellulitis, intra-abdominal sepsis and pyelonephritis/urinary tract infection. Prerenal causes included haemorrhage, acute gastroenteritis and dehydration. Cardiorenal syndrome was caused by cardiogenic shock, congestive heart failure, valvular heart disease and other cardiac diseases.

There were 175 cases of dengue fever, 20 with leptospirosis, one snake bite and malaria each, 72 with gastroenteritis and 17 pregnancy-related. Dengue contributed to 7.1% of AKI. The causes of pregnancy related AKI included preeclampsia, abruptio placenta, septic abortion, ruptured ectopic pregnancy and hyperemesis gravidarum.

At the diagnosis, 79.1% were at KDIGO stage 1, 9.7% were at stage 2 and 11.2% were at stage 3.

Exposure to nephrotoxins was reported in 760 (31%) of 2,457 patients and this included angiotensin converting enzyme inhibitors and angiotensin receptor blockers (432), diuretics (323), non-steroidal anti-inflammatory drugs (78), traditional medications (58), contrast media (51), aminoglycosides (9), other antibiotics (9), illicit drugs (10), antivirals (8) and antifungals (2). However, only 46 (1.9%) cases were deemed drug-associated AKI and 16 (0.7%) were related to contrast media.

The nephrology departments received 405 (16.5%) referrals for further clinical management. Of these referrals, 176 (43.4%) patients were started on RRT (Table II). A total of 404 (16.4%) AKI patients were admitted to ICU during their hospitalisation. Of these, 322 (13.1%) developed AKI while in ICU.

Patients needing dialysis made up 7.2% of the total AKI population and the majority (55.6%) were performed in the ICU. Acidosis (46.2%), uraemia (31.6%) and electrolyte disturbance (11.1%) were the commonest indications for RRT (Table III).

At the start of dialysis, the mean blood urea was 28.1 (±12.1)mmol/l, serum creatinine was 548.5 (±368.3) µmol/l and potassium were 4.63 (±1.0)mmol/l. Of the 171 with full data 24 (14.0%) required continuous renal replacement therapy (CRRT) and 147 (86.0%) haemodialysis (HD) or slow low efficiency dialysis (SLED). A total of 20 patients on CRRT were on inotropic support and another two had intracranial bleed. Of the 24 patients on CRRT, 20 were on continuous veno-venous hemofiltration (CVVH) and two each were on continuous veno-venous haemodialysis (CVVHD) and hemodiafiltration (CVVHDF). The patients on CRRT made up 25.3% of those dialysed in ICU.

In-hospital mortality was 16.4% (404 deaths). At discharge, 74.7% of survivors had full renal recovery, 16.4% partial and 8.9% failed to recover. The mean serum creatinine on discharge was 119.5 (±89.8) µmol/l. The average length of stay was 9.49 (±11.4) days. Five patients still required haemodialysis on discharge (0.2% of all patients).

The outcome of 1,964 Malaysians from this cohort was traced from the NRD and NRR as of 31st December 2018 (89 foreigners were excluded and considered lost to follow-up at discharge). Mean follow-up of the total cohort was 13.74 (±9.8) months, ranging from one day to 22 months and the median follow-up was 21.5 months. A total of 593 patients died after discharge from hospital (30.2%). Mortality was highest in the first 3 months of admission. Survival of the cohort at three months and one year was 71% and 63% respectively. A total of 38 patients (1.9% of those on follow-up) subsequently initiated chronic dialysis (34 HD, 4 peritoneal dialysis) (Table IV, Figure 2).

In the multivariate analysis, advanced age and having certain comorbidities increased the mortality risk. Mortality was higher in those with chronic liver disease (Hazard Ratio, HR 2.13, 95% Confidence Interval, 95%CI 1.63, 2.76), malignancy (HR 2.14, 95%CI 1.79, 2.55), neurological disease (HR 1.56, 95%CI 1.33, 1.84) and cardiovascular disease (HR 1.17, 95%CI 1.02, 1.35). In contrast, diabetes mellitus and CKD had no significant effect on mortality.

The risk was higher among foreigners (HR 3.02, 95%CI 1.91, 4.79). Hepatorenal syndrome (HR 1.94, 95%CI 1.24, 3.04), cardiorenal syndrome (HR 1.35, 95%CI 1.11, 1.65) and sepsis-associated AKI (HR 1.25, 95%CI 1.10, 1.43) were poor predictors for survival. Dengue fever (HR 0.13, 95%CI 0.05, 0.32) and ischaemic acute tubular necrosis (HR 0.35, 95%CI 0.17, 0.70) were associated with better outcomes.

Table I: Demography of patients with Acute Kidney Injury (AKI) (N=2 457)

Parameters	No. (%)
Age (Mean±SD)	57.8 (±17.5)
Gender	
Male	1480 (60.2)
Female	977 (39.8)
Race	
Malay	1283 (52.2)
Chinese	579 (23.6)
Indian	469 (19.1)
Foreigner	109 (4.4)
Others	16 (0.7)
Comorbidity	
Yes	2002 (81.5)
No	455 (18.5)
General comorbidities	
Hypertension	1352 (55.0)
Diabetes mellitus	1144 (46.6)
Chronic lung disease	299 (12.2)
Endocrine disease	244 (9.9)
Malignancy	194 (7.9)
Chronic liver disease	90 (3.7)
Arthropathy	59 (2.4)
Gastrointestinal disease	51 (2.1)
Psychiatric disease	32 (1.3)
Haematological disease	24 (1.0)
Connective tissue disease	22 (0.9)
HIV infection	18 (0.7)
Renal comorbidities	
Chronic kidney disease	294 (12.0)
Prostate disease	74 (3.0)
Urolithiasis	48 (2.0)
Urological malignancy	8 (0.3)
Obstructive uropathy	6 (0.2)
Pyelonephritis	1 (0.0)
Neurogenic bladder	1 (0.0)
Others	2 (0.1)
Cardiovascular comorbidities	
Ischemic heart disease	371 (15.1)
Congestive heart failure	133 (5.4)
Cardiac arrhythmias	62 (2.5)
Congenital heart disease	22 (0.9)
Peripheral vascular disease	20 (0.8)
Valvular heart disease	13 (0.5)
Aortic aneurysm	2 (0.1)
Others	7 (0.3)
Neurological comorbidities	
Stroke/Transient ischaemic attack	197 (8.0)
Chronic neurological diseases	54 (2.2)
Others	3 (0.1)
Miscellaneous comorbidities	41 (1.7)
Primary aetiology of AKI	
Sepsis associated AKI	1023 (41.7)
Prerenal	595 (24.2)
Cardiorenal syndrome	266 (10.8)
Dengue	175 (7.1)
Obstructive uropathy	96 (3.9)
Drug associated AKI	46 (1.9)
Hypertensive emergency	45 (1.8)
Ischaemic acute tubular necrosis	42 (1.7)
Hepatorenal syndrome	31 (1.3)
Leptospirosis	20 (0.8)
Intratubular obstruction	19 (0.8)
Glomerulonephritis	19 (0.8)
Contrast induced AKI	16 (0.7)
Malaria	1 (0.1)
Others	60 (2.4)
KDIGO stage AT AKI diagnosis	
1	1944 (79.1)
2	237 (9.7)
3	276 (11.2)
Mean baseline serum creatinine (µmol/l)	104.2 (±70.8)

KDIGO- Kidney Disease Improving Global Outcomes

Table II: In-patient course of acute kidney injury

Parameters	Number (%)
Referred to nephrology	
Yes	405 (16.5)
No	2,052 (83.5)
History of ICU admission	
Yes	404 (16.4)
No	2,053 (83.6)
AKI diagnosed in ICU	
Yes	322 (13.1)
No	2,135 (86.9)
Started on dialysis	
Yes	176 (7.2)
No	2,281 (92.8)

ICU-Intensive Care Unit

Table III: Renal replacement therapy results, N = 171, 5 missing

Parameters	No (%)
Where was RRT first started	
ICU	95 (55.6)
Non-ICU	76 (44.4)
Indication for first RRT	
Acidosis	79 (46.2)
Uraemia	54 (31.6)
Electrolyte disturbance	19 (11.1)
Overload	9 (5.3)
Oliguria	9 (5.3)
Paraquat poisoning	1 (0.5)
First RRT mode	
IHD/SLED	147 (86)
CRRT	24 (14)
PD	0 (0)
Mean±SD	
Blood urea at initiation of RRT (mmol/l)	28.1 (±12.1)
Serum creatinine (µmol/l)	548.5 (±368.3)
Bicarbonate (N = 166)	15.4 (±5.0)
Potassium (mmol/l) (N = 170)	4.63 (±1.0)
Lactate mmol/l (N = 69)	4.4 (±4.0)

ICU-Intensive Care Unit; CRRT - Continuous renal replacement therapy; IHD - Intermittent haemodialysis; SLED - Slow low efficiency dialysis; PD - Peritoneal dialysis

Table IV: Matching with National Renal Registry for Malaysians who developed end stage kidney disease (N=1 964) excluding 89 foreigners

Parameter	Number	%
Matched	38	1.9
Not matched	1 926	98.1
Modality		
Haemodialysis	34	89.5
Peritoneal dialysis	4	10.5
Outcome		
Alive	32	84.2
Dead	6	15.8

Date of study: March 2017
Date of matching: 31 December 2018

Table V: Univariate and multivariate analysis of risk factors associated with mortality for patients with Acute Kidney Injury from admission till 31st Dec 2018 (N = 2 457)

Parameters	5	Univariate			Multivariate		
	Number	HR	95% CI	*p* value	HR	95% CI	*p* value
Risk factors							
Age		1.03	1.02-1.03	<0.001	1.02	1.02-1.03	<0.001
Ethnicity							
Malay	1 283	1			1		
Chinese	579	1.36	1.19-1.56	<0.001	1.07	0.93-1.23	0.355
Indian	469	0.87	0.74-1.03	0.097	0.88	0.74-1.03	0.114
Foreigner	109	1.84	1.17-2.89	0.008	3.02	1.91-4.79	<0.001
Others	16	1.04	0.56-1.95	0.890	0.88	0.47-1.65	0.696
Diabetes mellitus							
No		1			1		
Yes	1144	1.22	1.09-1.36	0.001	1.09	0.96-1.25	0.181
Hypertension							
No		1			1		
Yes	1 352	1.22	1.09-1.37	0.001	0.84	0.74-0.97	0.018
Chronic liver disease							
No		1			1		
Yes	90	2.00	1.57-2.54	<0.001	2.13	1.63-2.76	<0.001
Malignancy							
No		1			1		
Yes	194	2.18	1.84-2.58	<0.001	2.14	1.79-2.55	<0.001
Chronic kidney disease							
No		1			1		
Yes	434	1.34	1.15-1.57	<0.001	1.02	0.86-1.20	0.818
Cardiovascular disease							
No		1			1		
Yes	630	1.38	1.21-1.57	<0.001	1.17	1.02-1.35	0.028
Neurological disease							
No		1			1		
Yes	254	1.73	1.48-2.04	<0.001	1.56	1.33-1.84	<0.001
Aetiology: Ischaemic ATN							
No		1			1		
Yes	42	0.36	0.18-0.72	0.004	0.35	0.17-0.70	0.003
Aetiology: Cardio-renal syndrome							
No		1			1		
Yes	266	1.28	1.08-1.52	0.004	1.35	1.11-1.65	0.003
Aetiology: Sepsis associated AKI							
No		1			1		
Yes	1023	1.34	1.19-1.50	<0.001	1.25	1.10-1.43	0.001
Aetiology: Hepatorenal syndrome							
No		1			1		
Yes	31	2.08	1.40-3.09	0.001	1.94	1.24-3.04	0.004
Aetiology: Dengue							
No		1			1		
Yes	175	0.05	0.02-0.13	<0.001	0.13	0.05-0.32	<0.001
Management risk profiling							
History of ICU admission							
No		1			1		
Yes	404	1.65	1.433-1.89	<0.001	1.67	1.43-1.95	<0.001
Nephrology referral							
No		1			1		
Yes	405	2.03	1.78-2.32	<0.001	1.48	1.23-1.79	<0.001
Requirement for RRT							
No		1			1		
Yes	176	2.67	2.25-3.16	<0.001	1.45	1.14-1.85	0.003

HR-Hazard Ratio; 95%CI-95% Confidence Intervals; ATN-Acute tubular necrosis, Hazard ratio (HR) for death among hospitalised patients with AKI.

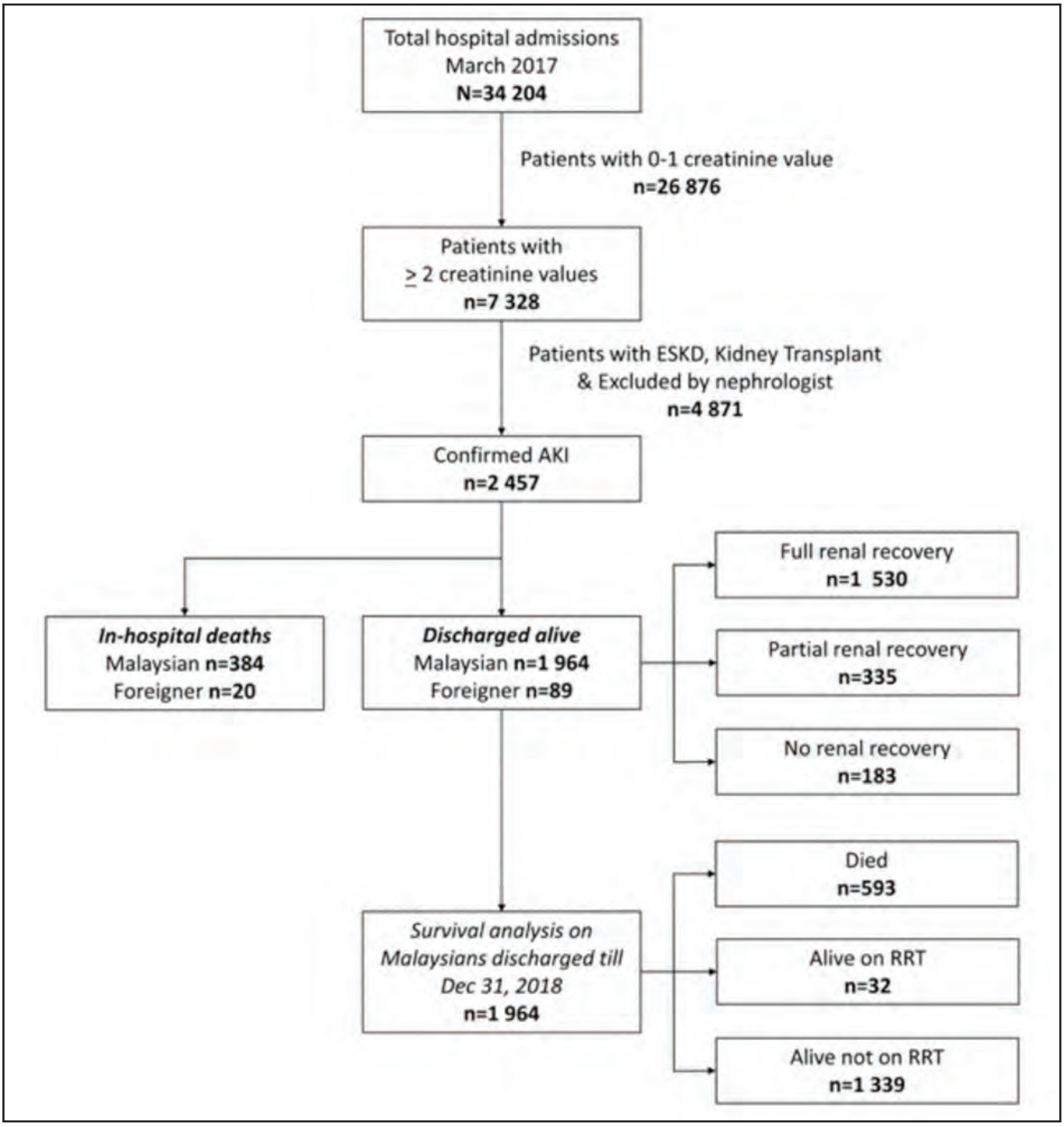


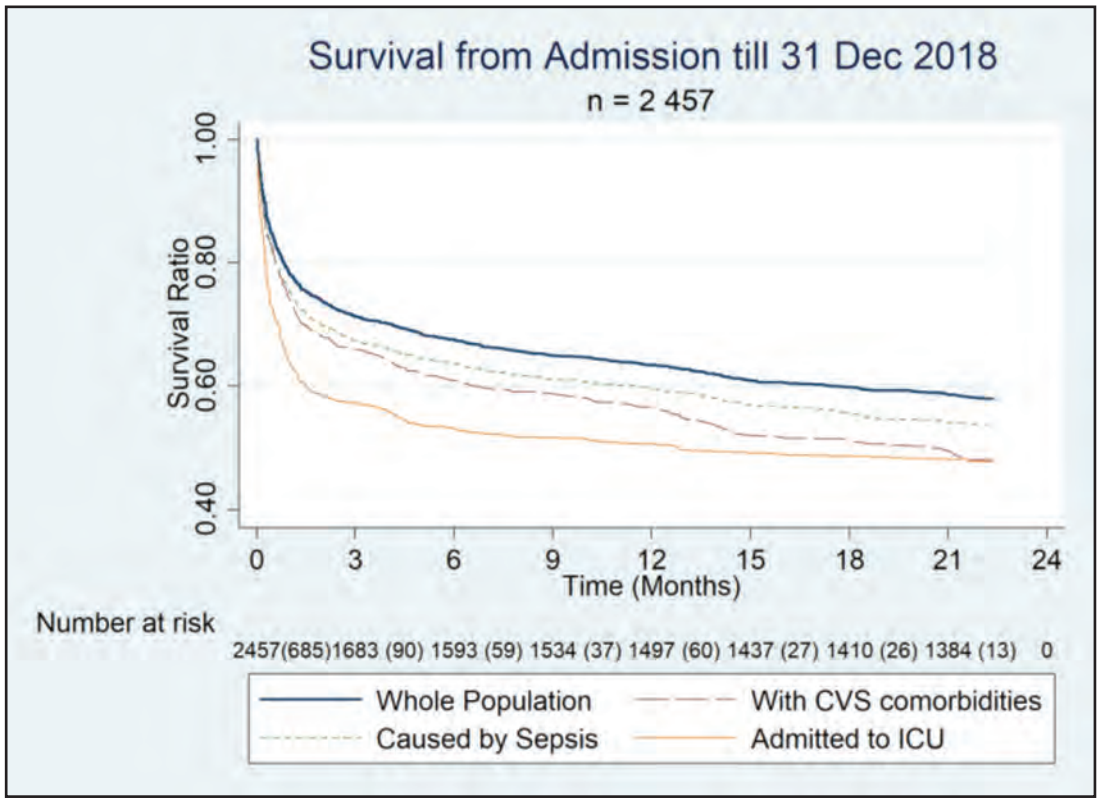
Fig. 1: Flow diagram.

Nephrology referral (HR 1.48, 95%CI 1.23, 1.79), ICU admission (HR 1.67, 95%CI 1.43, 1.95) and dialysis requirement (HR 1.45, 95%CI 1.14, 1.85]) also predicted death (Table V, Figure 2).

DISCUSSION

This is the first prospective, multicentre study in Malaysia using the KDIGO AKI 2012 criteria to define the incidence, aetiologies and outcomes of AKI among hospitalised patients. We included an extended follow-up duration up to 22 months.

The baseline creatinine was determined as the lowest creatinine during the hospitalisation as serum creatinine within seven days before hospitalisation was commonly not available. This methodology was adopted from the KDIGO AKI and various other groups.[26,28,29]



Hospital mortality: 404 out of 2 457 = 16.4%

Population	Number of subjects	Number of deaths (Rate)	In-hospital mortality (Rate)	Survival				
				30 days	60 days	90 days	1 year	1.5 year
Whole population	2 457	997 (40.6%)	404 (16.4%)	0.78	0.74	0.71	0.63	0.60
With CVS Comorbidities	535	277 (51.8%)	100 (36.1%)	0.74	0.68	0.66	0.55	0.52
Caused by sepsis	1 023	461 (45.1%)	209 (45.3%)	0.75	0.70	0.67	0.59	0.56
Admitted to ICU	404	204 (50.5%)	136 (66.7%)	0.64	0.59	0.57	0.50	0.49

CVS-cardiovascular, ICU-intensive care unit

Fig. 2: Survival curve for all AKI patients from admission till 31st December 2018 (N = 2 457).

All of the participating centres are public hospitals funded by the Ministry of Health Malaysia and are equipped with intensive care units. Four centres are tertiary referral hospitals, and the remaining three centres are district hospitals.

The incidence of hospitalised AKI (7.2%) was comparable to Yang L et al.,28 but lower than other studies in China (11.6%), Japan (11.6%) and United States of America (18.3%).[29-31] The discrepancies might be due to differences in methodology and population case-mix. The mean age of our cohort (57.8 years) was similar to study by Yang L et al., but relatively younger compared to other reports.

Four out of five patients (81.5%) who developed AKI had at least one comorbidity. There was a high prevalence of diabetes in our study cohort, consistent with the rising prevalence of 17.5% among the general Malaysian population.[32]

Malaysia is categorised among upper middle-income countries by the World Bank.[33] The rate of AKI incidence attributed to gastroenteritis was 3%. Gastroenteritis caused 19% of AKI in a series from Malawi[34] and 23% of AKI with febrile illness from a recent study in India.[35] Only a small proportion of AKI was associated with tropical diseases and pregnancy. Leptospirosis, malaria and snake bite causing AKI was also rare. The initiative from the International Society of Nephrology aspires to eliminate preventable deaths from AKI by 2025.[36] All the patients who required dialysis were referred to nephrologists to facilitate transition between different modalities of dialysis such as CRRT, SLED and intermittent HD. Peritoneal dialysis was not utilised to treat AKI patients in any of the participating centres.

The patients who were admitted to the ICU and acquired AKI were usually more ill hence they have higher mortality. Most of those who received CRRT were on inotropic support.

The overall in-hospital mortality was 16.4%, mostly in relation to the cause of AKI and severity of illness. There was also an increased death rate after being discharged home (30.2%) and 1.9% progressed to end-stage kidney failure during an average follow-up of 13.7 months. A single centre study from Singapore reported a mortality rate of 9.4% among AKI patients within six months of post-discharge from hospital for AKI.[37] Another study from Canada showed a mortality of 28.0% at one year.[38] Therefore, it is important that patients with a history of AKI are followed up long term. Foreigners (n=89, 3.6%) were excluded from follow-up analysis as they were not registered with NRD and NRR.

Besides this, dengue fever is a cause for concern as it is endemic in Malaysia. Dengue as a cause of AKI is unique to the region. Our study showed that dengue patients who developed AKI had five times higher mortality (1.1%) compared to the national reported dengue mortality of 0.21%.[39] However, from multivariate analysis, dengue had better outcome compared to other causes of AKI. Factors that contribute to better prognosis of dengue include nationwide active surveillance, adherence to standard protocol and clinical practice guidelines as well as dengue outcome being a key performance indicator for administrators in the Ministry of Health.[40]

The main treatment is assessment of fluid status and timely fluid resuscitation. The condition tends to improve when the proper amount of fluid has been replaced, although in a small percentage, complications can arise, with deterioration to shock syndrome and the patient goes into ICU.

This multicentre study revealed the common causes, population at risk of developing AKI and the predictors of mortality. The incidence of AKI in hospitals and mortality may be reduced by early detection and prompt management of risk factors. Renal replacement therapy escalates the costs and mortality.

The strength of the study includes the large population studied, inclusion of multiple sites and the use of the KDIGO 2012 criteria for AKI.

However, there are limitations to the study. The statistical power of this study might improve with longer duration of follow-up and involvement of more sites especially from East Malaysia. Case-mix from this region might differ from West Malaysia. Apart from this, urine output criteria for diagnosis of AKI were not included, and hospitalised patients who only had a single or no serum creatinine test were excluded. This might underestimate the actual number of AKI.

CONCLUSION

Acute Kidney Injury (AKI) is common in hospitalised patients. It is associated with high in-patient mortality and increased mortality even after discharge. There is a risk of end stage kidney disease (ESKD), and patients need continued surveillance. It is recommended to have a guideline for AKI in Malaysia and to raise awareness so that there is earlier diagnosis and treatment of this serious condition.

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DISCLOSURES

None

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Factors associated with in-hospital mortality among infective endocarditis patients

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ABSTRACT

Introduction: Despite recent advancements in the diagnosis and management of infective endocarditis (IE), it is associated with substantial morbidity and mortality. Our study objective is to determine the factors associated with in-hospital mortality in IE patients among the local population.

Materials and Methods: All IE patients who were diagnosed with definite or possible IE and were treated at Sarawak Heart Centre from 1st January 2020 to 31st December 2022 were recruited. We examined the demographic features of the subjects and the factors that contributed to in-hospital mortality. Multivariate logistic regression was used to analyse the associated factors and in-hospital mortality.

Results: Our study population comprised a total of 37 patients with a mean age of 46.4 years and male predominance. The in-hospital mortality rate of IE in this study was 44.4%. Haemodynamic instability and anaemia were found to be strong predictors of IE survival outcome, with an odds ratio of 51.5 and 35.7 respectively. Patients with vascular phenomenon and heart failure were at 10.5- and 6.0-times higher odds of dying, however, these two associations were found to be not statistically significant.

Conclusion: The in-hospital mortality due to IE in our study was among the highest in developing countries. Factors of hypotension and optimal response to individual hemodynamic parameters may confer lower mortality. While anaemia is demonstrable as a risk factor for inpatient mortality, a target has yet to be reasonably established.

KEYWORDS:
Associated factors, infective endocarditis, in-hospital mortality

INTRODUCTION

There has been significant progress and improvements in the diagnosis as well as medical and surgical management of infective endocarditis (IE) in the last decade. Yet, it could result in fatal outcomes and is also characterised by substantial morbidity and mortality.[1,2] A systematic review involving 19 studies in developing countries showed mortality rates ranging from 7-46%.[3] Another study in Malaysia conducted by Sunil et al., reported a high in-hospital mortality rate of 35.7% and a complication rate as high as 85.7%.[4] Nevertheless, there is a dearth of research on IE in low- and middle-income (LMIC) countries.[3]

In developing countries, IE is a disease of male predominance.[5,6] Predisposing factors of IE and factors associated with mortality among IE patients are important in the management and prevention of IE. Many factors were found to increase predisposition to IE, which includes rheumatic heart disease, congenital heart disease, valvulopathy or previous valve replacement, and immunosuppressive state.[3,7-9] In addition, predictors of mortality in IE have been explored in previous research. A study done by Collonnaz et al., showed that prognostic factors of 3-month mortality include age ≥70 years, Charlson comorbidity index ≥2, Staphylococcal IE, septic shock, cerebral embolism, and serum creatinine level ≥18µmol/l; while prognostic factors of 1-year mortality include age ≥70 years, Charlson comorbidity index ≥2*time, high blood pressure*time, Staphylococcal IE, septic shock, cerebral embolism, and serum creatinine level ≥180µmol/l.[10] Among intravenous drug users who presented with a first episode of IE, surgery and referral to addiction treatment were associated with lower mortality while left-sided infection and bilateral involvement were associated with higher mortality.[11]

The primary objective of our study is to determine the factors associated with in-hospital mortality in IE patients among the local population. Hopefully, this will allow more focus on the delivery of care for these at-risk groups to improve the treatment outcome.

MATERIALS AND METHODS

Study Design and Setting

A descriptive study was conducted at the Department of Cardiology in the Sarawak Heart Centre (SHC), which is a tertiary cardiac centre located in an urban setting. This study design was selected to describe the factors that were associated with in-hospital mortality.

Participants

Participants consisted of patients who were diagnosed with IE and were treated at the Department of Cardiology, SHC from 1st January 2020 to 31st December 2022. Included were patients who were diagnosed with definite or possible IE using the Modified Duke's Criteria.[7] Excluded were patients

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who were initially diagnosed and treated as IE but were later confirmed to be other diagnoses.

Outcomes Measured
The primary outcome of this study was in-hospital mortality. In-hospital mortality was determined from patients' documented status upon discharge from the medical record.

Instruments Used
A baseline demographic form was used to collect the participants' baseline demographic data and other relevant information.

Data Collection
Demographic data such as patients' age, gender, ethnicity, and IE risk factors were collected in a retrospective manner. In addition, we also collected data on drug allergy, recent antibiotic use, presenting symptoms, vascular phenomenon, immunologic phenomenon, creatinine clearance, type of microorganisms cultured and complications that arose during the treatment. Information related to treatment adherence to the Malaysia Clinical Practice Guidelines (CPG) for the Prevention, Diagnosis and Management of Infective Endocarditis' such as blood culture collection process, echocardiographic features, and appropriateness of antibiotics and surgery, were gathered.

Data Analysis
Data were analysed using the Statistical Package for Social Science (SPSS) version 27.0 software (Chicago, Illinois, USA). Normality was assessed using the Kolmogorov-Smirnov test. Descriptive statistics were used to describe the demographic data of participants. Categorical variables were presented using percentages and frequencies, whilst continuous variables were presented using the mean and standard deviation or median and interquartile ranges, depending on the normality. Parametric tests were used for data which were normally distributed whereas non-parametric tests were used for data which were not normally distributed. Multivariate logistic regression was then used to analyse the associated factors and in-hospital mortality. Statistical significance was set at p-value <0.05.

Ethics
Approval from the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia was obtained before the commencement of the study (Approval number: NMRR ID-23-01673-6JT). Written informed consent was waived by the MREC.

RESULTS

Participant Recruitment
A total of 37 patients were recruited in the study. Initially, a total of 46 patients were selected using convenience sampling but nine patients were excluded, four were due to revision of diagnosis and the remaining five were due to the non-retrievable medical records.

Participant Profile
Table I showed the socio-demographic and clinical characteristics of the 37 patients in the study.

Primary Outcome
Seven out of the 42 factors in our study were shown to be associated with in-hospital mortality using Pearson's Chi-square test (Table II). These include anaemia (p=0.024), vascular phenomenon (p=0.020), classification of IE (p=0.023), complications (p=0.016), haemodynamic instability (p=0.001), heart failure (p=0.023), and embolic stroke (p=0.049). Those factors that were found to be statistically significant were further examined using multivariate logistic regression (Table III). As hemodynamic instability, heart failure and embolic stroke were complications of IE, only these variables were included in the multivariate analysis.

In the multivariate analysis, hemodynamic instability, anaemia, vascular phenomenon and heart failure were associated with in-hospital mortality, with odds ratios (95% confidence intervals, 95%CI) of 51.5 (95%CI 3.1, 853.3), 35.7 (95%CI 1.1, 1203.1), 10.5 (95%CI 0.7, 168.5) and 6.0 (95%CI 0.2, 147.6) respectively. However, vascular phenomenon and heart failure were not statistically significant.

DISCUSSION

Key Findings and Comparison to the Existing Literature
The mean age of the patients in our study was comparable to that of a Malaysian study performed from 2005 to 2017 (46.4 years vs. 50.0 years, respectively),[4] with male predominance. Among our study population, 13.5% had chronic rheumatic heart disease. This percentage is in tandem with the prevalence of rheumatic heart disease in our country of 14 per 1000 population.[12,13] Hence, appropriate prevention measures and management of rheumatic heart disease might play a role in the reduction of IE incidence.

About half of our study population had culture-negative IE, which was remarkably high as compared to only 22% in one Malaysian study.[4] This resulted in a lower proportion of definite IE among our study population. Negative cultures might be caused by a number of factors, including inappropriate blood culture-taking process, administration of antibiotics before blood culture collection, and recent antibiotic use. However, neither the negative culture nor the type of organisms cultured was significantly associated with in-hospital mortality in our study population.

Antibiotic therapy was considered appropriate if the correct antibiotic was used, using the correct route and for the correct duration.[14] Both the appropriateness of the empirical and culture-guided antibiotic therapy was remarkably low at 5.9% and 52.4% respectively, although both were not significantly associated with in-hospital mortality. Ceftriaxone was the most commonly prescribed antibiotic for empirical treatment among our patients, although it was not the recommended antibiotic according to our national guidelines.[7] It was a common antibiotic used due to its once-daily administration and avoidance of having to insert a central venous catheter. However, the usage of broad-spectrum antibiotics such as ceftriaxone for an extended duration may give rise to collateral damage, especially antibiotic resistance.[16,17]

Table I: Socio-demographic and clinical characteristics of the study population (n=37)

Characteristics	n (%)
Age (years)[a]	46.4 (17.0)
Gender	
Male	28 (75.7)
Female	9 (24.3)
Ethnicity	
Malay	9 (23.7)
Chinese	12 (31.6)
Indigenous	16 (42.1)
Presenting hospitals	
SHC	10 (27.0)
Others	27 (73.0)
Risk factors	
Pre-existing cardiopathy	3 (8.1)
Diabetes mellitus	6 (16.2)
Cancer	0 (0.0)
Chronic kidney disease	9 (24.3)
CRHD	5 (13.5)
non-CRHD valvulopathy	3 (8.1)
Valve prosthesis	5 (13.5)
CIED	1 (2.7)
Past history of IE	2 (5.4)
Intravenous drug user	2 (10.0)
Alcohol	4 (19.0)
Invasive procedure	2 (5.4)
Drug allergy	2 (5.7)
Recent antibiotic use	4 (10.5)
Signs and symptoms	
Fever	19 (52.8)
Weight loss	5 (13.9)
Appetite loss	8 (22.2)
Fatigue	11 (30.6)
Dyspnoea	15 (41.7)
Arthralgia	1 (2.8)
Vascular phenomenon	10 (27.0)
Immunologic phenomenon	1 (2.7)
Investigations	
Anaemia	23 (63.9)
ESR[a]	73 (25)
More than 20 mm/hour	33 (89.2)
CRP[b]	48 (222)
Creatinine clearance[b]	50.7 (32.0)
Had three sets of blood cultures obtained	26 (70.3)
Had echocardiogram performed	37 (100.0)
Culture-positive	21 (56.8)
Methicillin-sensitive *Staphylococcus aureus*	7 (33.3)
α-Streptococci	7 (33.3)
Enterococcus faecalis	2 (9.5)
Haemophilus *sp.*	1 (4.8)
Others	4 (19.0)
Echocardiogram	
Transthoracic	26 (70.3)
Transoesophageal	2 (5.4)
Both	9 (24.3)
Topography	
Aortic valve	10 (27.0)
Mitral valve	16 (43.2)
Aortic and mitral valves	4 (10.8)
Other valves	6 (16.2)
CIED	1 (2.7)
Vegetation size	
Longest diameterb	1.3 (1.2)
Less than 1 cm	8 (22.9)
1 cm or more	27 (77.1)

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Table I: Socio-demographic and clinical characteristics of the study population (n=37)

Characteristics	n (%)
Type of IE	
Native	32 (86.5)
Prosthetic, early	1 (2.7)
Prosthetic, late	2 (5.4)
CIED, early	1 (2.7)
CIED, late	0 (0.0)
Native and prosthetic	1 (2.7)
Classification of IE	
Definite	12 (32.4)
Possible	25 (67.6)
Empirical antibiotic	
Benzyl penicillin or ampicillin plus gentamicin	8 (21.6)
Ceftriaxone	25 (67.6)
Others	4 (10.8)
Appropriateness of antibiotic	
Empirical	2 (5.9)
Culture-guided	11 (52.4)
Surgery	
Indicated for surgery	35 (94.6)
Referral to cardiothoracic team for surgery	20 (60.6)
Surgery performed	0 (0.0)
Referral to infectious disease physician	10 (27.0)
Complications	31 (83.8)
Haemodynamic instability (Requiring ICU admission and/or intubation)	18 (48.6)
Severe valvular incompetence	20 (58.8)
Heart failure	15 (40.5)
Embolic stroke	9 (24.3)
Non-cerebral embolic localisation	6 (16.2)
Acute kidney injury	17 (45.9)
Transaminitis	8 (21.6)
Adverse drug reaction	2 (5.4)
In-hospital mortality outcome	
Alive	20 (55.6)
Dead	16 (44.4)
Alive	
With complication(s)	6 (30.0)
Without complication	14 (70.0)

CIED: Cardiac implantable electronic device, CRHD: Chronic rheumatic heart disease, CRP: C-Reactive protein, ESR: Erythrocyte sedimentation rate, ICU: Intensive care unit, IE: Infective endocarditis, SHC: Sarawak Heart Centre
[a]Presented in mean and standard deviation
[b]Presented in median and interquartile range

None of the patients in our cohort proceeded to cardiac surgery, with most having clinical indications for this.

The development of complications had a strong association with in-patient mortality, with haemodynamic instability being the most significant risk factor. The percentage of patients who developed complications in our study was comparable to the reported percentage in another study performed in Malaysia (83.8% vs.85.7% respectively).[4]

In our study, individuals who had anaemia at presentation were 35.7 times more likely to succumb to IE (p=0.046). This is an important finding as anaemia might reflect the severity of IE which is also an important prognostic indicator.[18]

The in-hospital mortality of our study population was greater than many of the developing countries (44.4% vs. 739% respectively), except for Brazil which has an IE in-hospital mortality rate of 46%.[3] This highlighted the dire need for greater efforts to improve IE management in order to reduce the seemingly higher mortality in our local setting. A significant portion of severely ill patients may be responsible for care escalation to a tertiary care facility in our cohort while relatively stable patients are typically retained in their respective peripheral hospitals, pooled statistical quantification of which remains challenging in heterogenous, resource-limited regions.

Strengths and Limitations

The limitations of this study were its single-centre design and small sample size. On the other hand, the strength of this study was that it represented the local population in Sarawak which has its unique geographical coverage and limitations, and little published data on this subject.

Recommendations

The primary determinants of oxygen supply are cardiac output, haemoglobin concentration and arterial blood oxygen saturation whereas blood pressure is the product of cardiac output and systemic vascular resistance.[19,20] Metric-based management of hypotension comprises four general steps: monitor perfusion, manage cause, maintain blood

Table II: Factors associated with in-hospital mortality (n=37)

Factors	Outcomesa		P-value
	Alive n (%)	Dead n (%)	
Age			
Age <50 years old	10 (55.6)	8 (44.4)	1.000
Age ≥50 years old	10 (55.6)	8 (44.4)	
Gender			
Male	14 (51.9)	13 (48.1)	0.439
Female	6 (66.7)	3 (33.3)	
Ethnics			
Malay	4 (50.0)	4 (50.0)	0.638
Chinese	8 (66.7)	4 (33.3)	
Indigenous	8 (50.0)	8 (50.0)	
Presenting hospital			
SHC	5 (50.0)	5 (50.0)	0.677
Others	15 (57.7)	11 (42.3)	
Cardiopathy			
Yes	2 (66.7)	1 (33.3)	0.686
No	18 (54.5)	15 (45.5)	
Diabetes mellitus			
Yes	3 (50.0)	3 (50.0)	0.764
No	17 (56.7)	13 (43.3)	
CKD			
Yes	3 (33.3)	6 (66.7)	0.121
No	17 (63.0)	10 (37.0)	
CRHD			
Yes	2 (40.0)	3 (60.0)	0.451
No	18 (58.1)	13 (41.9)	
non-CRHD valvulopathy			
Yes	2 (66.7)	1 (33.3)	0.686
No	18 (54.5)	15 (45.5)	
Valve prosthesis			
Yes	2 (40.0)	3 (60.0)	0.451
No	18 (58.1)	13 (41.9)	
CIED			
Yes	1 (100.0)	0 (0.0)	0.364
No	19 (54.3)	16 (45.7)	
Past history of IE			
Yes	0 (0.0)	2 (100.0)	0.340
No	20 (58.8)	14 (41.2)	
IVDU			
Yes	0 (0.0)	2 (100.0)	0.080
No	11 (64.7)	6 (35.3)	
Alcohol			
Yes	2 (50.0)	2 (50.0)	0.648
No	10 (62.5)	6 (37.5)	
Invasive procedure			
Yes	1 (50.0)	1 (50.0)	0.871
No	19 (55.9)	15 (44.1)	
Drug allergy			
Yes	2 (100.0)	0 (0.0)	0.169
No	16 (50.0)	16 (50.0)	
Fever			
Yes	13 (72.2)	5 (27.8)	0.064
No	7 (41.2)	10 (58.8)	
Weight loss			
Yes	3 (60.0)	2 (40.0)	0.889
No	17 (56.7)	13 (43.3)	
Appetite loss			
Yes	4 (57.1)	3 (42.9)	1.000
No	16 (57.1)	12 (42.9)	
Fatigue			
Yes	5 (45.5)	6 (54.5)	0.344
No	15 (62.5)	9 (37.5)	
Dyspnoea			
Yes	6 (40.0)	9 (60.0)	0.076
No	14 (70.0)	6 (30.0)	
Arthralgia			
Yes	0 (0.0)	1 (100.0)	0.241
No	20 (58.8)	14 (41.2)	

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Table II: Factors associated with in-hospital mortality (n=37)

Factors	Outcomesa		P-value
	Alive n (%)	Dead n (%)Anaemia	
Anaemia			
Yes	10 (43.5)	13 (56.5)	0.024
No	10 (83.3)	2 (16.7)	
ESR			
20 mm/hour or less	4 (100.0)	0 (0.0)	0.058
More than 20 mm/hour	16 (50.0)	16 (50.0)	
Vascular phenomenon			
Yes	2 (22.2)	7 (77.8)	0.020
No	18 (66.7)	9 (33.3)	
Immunologic phenomenon			
Yes	1 (100.0)	0 (0.0)	0.364
No	19 (54.3)	16 (45.7)	
Classification of IE			
Definite	3 (27.3)	8 (72.7)	0.028
Possible	17 (68.0)	8 (32.0)	
Vegetation size			
Less than 1cm	3 (37.5)	5 (62.5)	0.317
1 cm or more	15 (57.7)	11 (42.3)	
Culture-positive			
Yes	9 (45.0)	11 (55.0)	0.154
No	11 (68.8)	5 (31.3)	
Organism cultured			
Methicillin-sensitive Staphylococcus aureus	3 (42.9)	4 (57.1)	0.904
Streptococci	3 (42.9)	4 (57.1)	
Enterococci	1 (50.0)	1 (50.0)	
Others	2 (66.7)	1 (33.3)	
Choice of empirical antibiotic			
Benzyl penicillin or ampicillin plus gentamicin	4 (50.0)	4 (50.0)	0.353
Ceftriaxone	15 (62.5)	9 (37.5)	
Others	1 (25.0)	3 (75.0)	
Appropriateness of empirical antibiotic			
Yes	0 (0.0)	2 (100.0)	0.133
No	17 (54.8)	14 (45.2)	
Appropriateness of culture-guided antibiotic			
Yes	4 (40.0)	6 (60.0)	0.653
No	5 (50.0)	5 (50.0)	
Referral to cardiothoracic surgeon			
Yes	8 (42.1)	11 (57.9)	0.280
No	8 (61.5)	5 (38.5)	
Referral to infectious disease physician			
Yes	6 (60.0)	4 (40.0)	0.739
No	14 (53.8)	12 (46.2)	
Complications			
Yes	14 (46.7)	16 (53.3)	0.016
No	8 (100.0)	0 (0.0)	
Haemodynamic instability (Requiring ICU admission and/ or intubation)			
Yes	3 (17.6)	14 (82.4)	< 0.001
No	17 (89.5)	2 (10.5)	
Severe valvular incompetence			
Yes	8 (42.1)	11 (57.9)	0.208
No	9 (64.3)	5 (35.7)	
Heart failure			
Yes	5 (33.3)	10 (66.7)	0.023
No	15 (71.4)	6 (28.6)	
Stroke secondary to vegetation embolism			
Yes	2 (25.0)	6 (75.0)	0.049
No	18 (64.3)	10 (35.7)	
Non-cerebral embolic localisation			
Yes	2 (33.3)	4 (66.7)	0.230
No	18 (60.0)	12 (40.0)	
Acute kidney injury			
Yes	6 (37.5)	10 (62.5)	0.051
No	14 (70.0)	6 (30.0)	
Transaminitis			
Yes	3 (37.5)	5 (62.5)	0.244
No	17 (60.7)	11 (39.3)	

CIED: Cardiac implantable electronic device, CRHD: Chronic rheumatic heart disease, ICU: Intensive care unit, IE: Infective endocarditis, SHC: Sarawak Heart Centre

Table III: Multivariate analysis of in-hospital mortality among IE patients. (n=37)

Variables	Odds Ratio	95% CI	P-value
Anaemia			
Yes	35.7	1.1, 1203.1	0.046
No	Reference group		
Vascular phenomenon			
Yes	6.0	0.2, 147.6	0.274
No	Reference group		
Haemodynamic instability			
Yes	51.5	3.1, 853.3	0.006
No	Reference group		
Heart failure			
Yes	10.5	0.7, 168.5	0.097
No	Reference group		

IE: Infective endocarditis; 95%CI - 95% Confidence Intervals.

pressure and match supply to demand,[19] which may result in better mortality outcomes.

Restrictive transfusion has been proposed in non-bleeding anaemic, critically ill patients though a target has yet to be established and it does not necessarily confer a better outcome.[21-24] Consideration for transfusion on an ad hoc basis should be exercised with caution. Although utilising prospective trials may be considered an optimal approach, the presence of cohort heterogeneity and ethical considerations regarding possible adverse outcomes could pose challenges in terms of designing such studies.

With regard to national efforts in curbing the disease, an IE registry could be initiated for the consolidation of data on the disease nationwide and to identify key areas that could potentially improve the management of IE in our country. This plays an important part in the learning of the disease characteristics among our local population and to tailor the management according to the clinical requirement. The distribution of resources could also focus on key areas that have the most potential to improve IE mortality outcomes.

At the hospital level, interval clinical audits are imperial to ensure quality control and improvements, especially on the method of blood culture collection and the appropriateness of antibiotic treatments in accordance with our national guidelines. Clinical audits also enable healthcare personnel to keep constantly updated with the latest knowledge in IE management in order to deliver the best treatment to patients through regular continuing medical education (CME) at every hospital level as part of the audit cycle.

Human capital development, specifically those involved in the management of IE, should be accelerated, as are facilities required to manage IE, especially when there is multisystem involvement.

CONCLUSION

The in-hospital mortality due to IE in our study was among the highest in developing countries. Factors of hypotension and optimal response to individual hemodynamic parameters may confer lower mortality. While anaemia is demonstrable as a risk factor for inpatient mortality, a target has yet to be reasonably established.

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Pulmonologist-led ultrasound guided lung biopsy safety and efficacy: a 4-year experience from a tertiary centre in Northern Malaysia

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ABSTRACT

Introduction: Ultrasound guided lung biopsy (USLB) is a minimally invasive diagnostic tool with short examination time and real-time monitoring conducted bedside for accurate diagnosis in order to provide the best treatment. However, it is not widely performed by pulmonologists. We aim to explicate the efficacy and safety of USLB led by pulmonologists. The objective of this study is to assess safety and efficacy of USLB performed by pulmonologists in an outpatient setting.

Materials and Methods: We retrospectively enrolled patients who underwent the procedure from January 2018 to April 2022. Under real time ultrasound (Hitachi Medical ProSound F37), thoracic lesions adjacent to the chest wall were sampled with a full-core biopsy needle (CT Core Single Action Biopsy Device, 18G × 15 cm, Vigeo, Italy). Chest x-ray was performed 30 minutes post procedure ruling out pneumothorax. Patients were discharged home 1-2 hours post biopsy. Data was analysed using Microsoft Excel 2010 and Statistical Package for Social Science (SPSS) Version 26.

Results: A total of 18 patients (14 males, 4 females) underwent USLB for lung tumours. Biopsies were histologically deemed adequate with an overall diagnostic yield of 77.8% (14/18). A total of 57% were positive for thoracic malignancy (21% squamous cell carcinoma, 21% adenocarcinoma, 15% small cell carcinoma) and another 43% were positive for extra thoracic malignancy (1 hepatocellular carcinoma, 2 DLBCL, 1 Hodgkin's lymphoma, 1 seminoma, 1 thymoma). Four patients had inconclusive results but managed to get positive results from surgical or lymph node biopsy (thymoma and adenocarcinoma). Statistical analysis showed more than two passes are needed to achieve a positive HPE yield (*p* value<0.05). There were nil complications to all the cases done.

Conclusions: USLB can safely and effectively be performed by trained pulmonologists with excellent accuracy and low complication rate in outpatients.

KEYWORDS:
Ultrasound, lung biopsy, pulmonologist

INTRODUCTION

Lung cancer is the second most common cancer and the leading cause of cancer death worldwide in both males and females.[1] In Malaysia, lung cancer is the third most common cancer nationwide (1st most common in men and 4th most common in women) for the year 2020 accounting for 10% of all malignancies. Lung cancer is also the most common cancer-related death with 5-year observed survival rate of 9% and 5-year relative survival rate of 11% which is the lowest compared to other malignancies. However, 90% of patients were diagnosed at stage III, IV.[2,3] Hence it is crucial to evaluate each patient with any form of thoracic lesions in order to obtain an accurate diagnosis and manage accordingly. In recent years, there have been new advancements in lung cancer management, especially in molecular targeted therapy which has improved survival and quality of life.[4] However, to determine if a patient is suitable for the targeted therapy, better quality and quantity of samples are required for histological analysis.

There are various methods of lung biopsy such as surgical biopsy, bronchoscopy transbronchial lung biopsy (TBLB), endobronchial ultrasound (Linear or Radial EBUS)-guided biopsy, CT-guided biopsy, and ultrasound-guided biopsy.[5,6] Each of these methods has its own advantages and disadvantages. Ultrasound has been proven to be valuable as it is relatively inexpensive, mobile and widely available in most hospitals, including some district hospitals.

Ultrasound guided lung biopsy (USLB) is a minimally invasive diagnostic tool, requires short examination time and low complication rate with real-time monitoring at the bedside as compared to surgical biopsy.[6,7] USLB and CT-guided lung biopsy are preferable when diagnosing peripheral lung lesions as compared to bronchoscopy which is preferred for central lung lesions. USLB has an added advantage of no radiation exposure and is more economical with a similar success rate as CT-guided lung biopsy.

However, it is not widely performed by pulmonologists worldwide. Hence, we aim to explicate the efficacy and safety of USLB lead by pulmonologists in outpatient settings in Northern Malaysia. We hope to encourage pulmonologists to use this procedure in the future for accurate diagnosis in patients with lung mass.

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MATERIALS AND METHODS

Patients

We retrospectively enrolled and reviewed all the patients who underwent USLB as an outpatient in the Respiratory department, Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia from January 2018 to April 2022. Patients' demographic data, previous medical and surgical illness history was taken from electronic medical records (eHis), clinic files and procedure book. All patients provided a written consent prior to the procedure.

Procedure

Patients were positioned in lateral decubitus, dorsal decubitus or sitting position based on the puncture point. By using an ultrasound machine (Hitachi Medical ProSound F37), the location and size of the lesions are determined via a curvilinear or liner probe (example shown in Image 1A). Also based on these images and doppler scan, we were able to decide on the most suitable site for biopsy with the shortest and safest approach. Under real time ultrasound, thoracic lesions adjacent to the chest wall were sampled with a full-core biopsy needle (CT Core Single Action Biopsy Device, 18G × 15 cm, Vigeo, Italy) under local anaesthesia as shown in Image 1B. Chest x-ray was performed 30 minutes post procedure ruling out pneumothorax. Patients were discharged home 1-2 hours post biopsy. Each pulmonologist that performed this procedure has a minimum of t years of training in ultrasound thorax imaging and credentialed in performing USLB.

Statistical Analysis

Data was collected using Microsoft Excel 2010 and analysed using SPSS Version 26 via Wilcoxon signed rank test. P value of <0.05 was taken as significant.

RESULTS

A total of 18 patients (14 males, 4 females) with age ranging from 29 to 80 years old underwent USLB for lung tumours. Mean age group is 56.3±18.4 years old. Majority of the patients are male (78%) and mostly are Malay ethnicity (89%) while the rest are Chinese. Average duration of procedure is 20 minutes.

Location of lung lesions varies from right lung (45% in upper lobe, 5% in middle lobe, 5% in lower lobe), left lung (12% in upper lobe, 5% in lower lobe) to mediastinal area (28%). Only 12 out of 18 patients managed to get a CT Thorax done prior to procedure while another six patients did not undergo CT thorax prior to procedure in view of the availability and waiting time for CT thorax which included the period of COVID-19 pandemic from 2020 to 2022 where there is a lot of restriction in the access of CT scan. The biopsy was done prior to CT to reduce the waiting time to diagnosis as ultrasound is readily available in the procedure room and easily done prior to procedure after reviewing patients' latest chest x-ray.

The size of the lesion also varies but about 83% have lesions more than 7cm and 12% did not have proper documentation on lesion size. The mean size of lesion of those documented is about 11.3±4.1mm. Mean size of the sample taken for the biopsy is 1.92cm^2 which is adequate for histopathology and molecular testing. Summary of patients' characteristics as shown in Table I.

Biopsies were histologically deemed adequate with an overall diagnostic yield of 77.8% (14/18). Results as shown in Table II are as follows: 57% were positive for thoracic malignancy (21% squamous cell carcinoma, 21% adenocarcinoma, 15% small cell carcinoma) and another 43% were positive for extrathoracic malignancy (1 hepatocellular carcinoma, 2 DLBCL, 1 Hodgkin's lymphoma, 1 seminoma, 1 thymoma). Four patients had inconclusive results, however, were able to yield positive results from surgical or lymph node biopsy (thymoma and adenocarcinoma). Despite inconclusive results, there were no delays in obtaining the diagnosis as patients were promptly referred for surgical biopsy. These were not related to learning curve pattern as these results were across time from 2020 to 2022. These lung lesions were at a more difficult location and difficult to obtain via a trucut biopsy.

Mean number of passes done to obtain an adequate sample is 3.5±1.1. Statistical analysis showed >2 passes are needed to achieve a positive HPE yield (p value <0.05).

There were no complications for all the cases done either during or post procedure. All patients were discharged 2 hours post procedure once confirmed no complications via chest x-ray.

DISCUSSION

Imaging guided lung biopsy (Ultrasound or Computer Tomograph, CT) is traditionally performed by interventional radiologists. However, in recent years, USLB has gained traction among pulmonologists worldwide. USLB can be performed under local anaesthesia with real time monitoring which makes it a safe procedure to be performed in an outpatient setting in a general procedure room. Compared to traditional CT-guided lung biopsy, USLB demonstrates similar precision but added benefits of safety as there is no added radiation.[5] Hence, it can be performed at the bedside with less effort, time, and cost.

Literature search using PubMed and Google Scholar revealed no study from Malaysia has been previously published on pulmonologist led USLB.

Based on our study, it is eminent that the number of passes plays a significant role in acquiring a satisfactory diagnosis. More passes can safely be made, yielding more accurate results. There were four cases that did not obtain any yield by which one showed necrotic tissue, two showed normal cells and one resulted in a non-representative sample. Based on our analysis of these four cases, some only had two passes when retrieving the sample which may explain the negative results.

According to a study by Lee MH et al., USLB requires less passes as compared to CT guided biopsy in order to achieve adequate yield (mean, 3.1±1.8 vs. 4.4±1.9, respectively, p<0.001).[8]

Table I: Characteristics of patients who underwent ultrasound-guided lung biopsy

Subject characteristics	Number of patients (%)
Sex	
Male	14 (78%)
Female	4 (22%)
Age	
21-40	4 (22%)
41-60	5 (28%)
61-80	8 (44%)
>80	1 (6%)
Ethnicity	
Malay	16 (89%)
Chinese	2 (11%)
Indian	0
Others	0
Duration of procedure	
10-20min	3 (17%)
>20 min	15 (83%)
Location	
Right	
Upper lobe	8 (44%)
Middle lobe	1 (6%)
Lower lobe	1 (6%)
Left	
Upper lobe	2 (11%)
Lower lobe	1 (6%)
Mediastinal	5 (27%)
Size of lesion	
4-5cm	1 (6%)
>7cm	15 (83%)
Not documented	2 (11%)
No of passes	
2	4 (22%)
3	5 (28%)
4	7 (39%)
5	2 (11%)
Complications	
Yes	0
No	18 (100%)

Table II: Results of sample from ultrasound-guided lung biopsy

Pathological type	Number of cases
Thoracic malignancy	
Adenocarcinoma	3 (17%)
Squamous cell carcinoma	3 (17%)
Small cell carcinoma	2 (10%)
Extrathoracic malignancy	
Hepatocellular carcinoma	1 (6%)
Diffuse large B-cell lymphoma	2 (10%)
Hodgkin's lymphoma	1 (6%)
Germ cell tumour (seminoma)	1 (6%)
Thymoma	1 (6%)
Inconclusive	
Thymoma (surgical biopsy)	1 (6%)
Adenocarcinoma (surgical and lymph node biopsy)	2 (10%)
Non-representative	1 (6%)

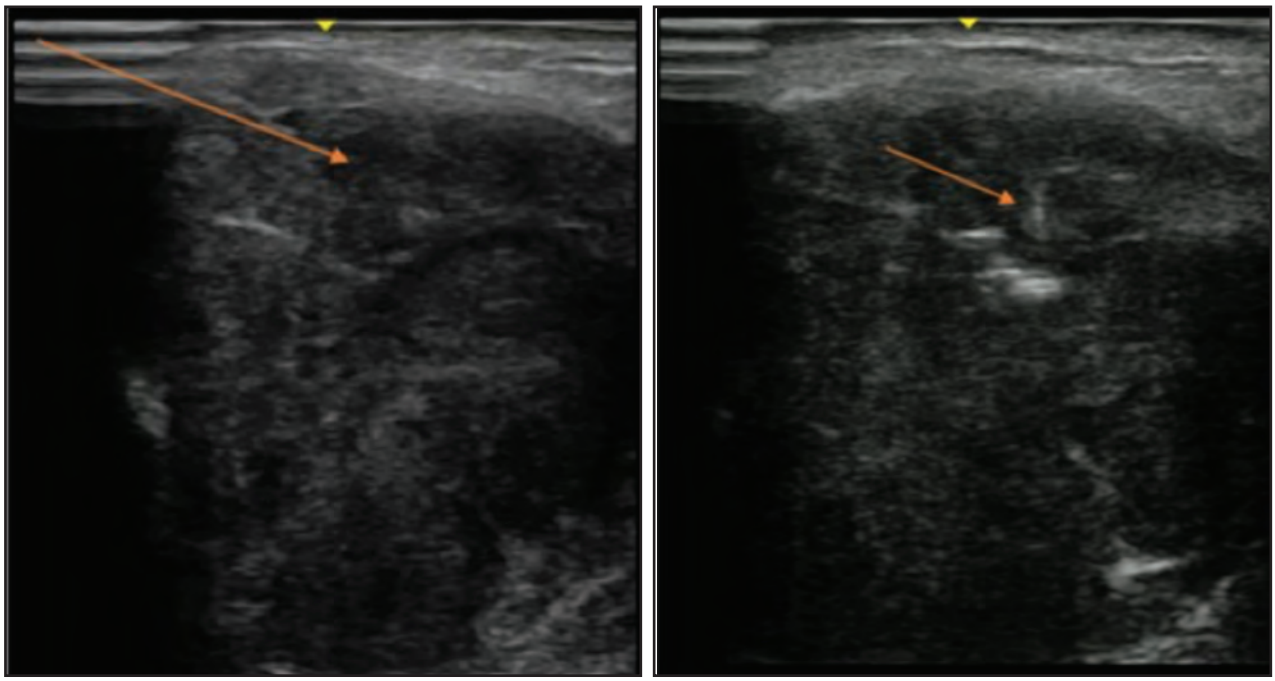

Image 1A Image 1B

Image 1A shows a lung mass (as shown by orange arrow) while image 1B showing full-core biopsy needle within the lesion (orange arrow).

USLB has shown a low rate of complications where none of the patients, involved in this study, developed any complications during or post procedure and were safely discharged within 2 hours after the procedure. Main complications that have been documented are pneumothorax and haemorrhage but at a negligible percentage in comparison to other methods.[9,10]

The risk of developing pneumothorax post USLB is higher in certain patients. The factors being older patients, patients with severe respiratory disease, smaller, deeper lung lesions and also technical factors such as the type and size of biopsy needle, longer procedure duration, biopsies in the middle or lower lobe, transgression of a fissure and multiple needle repositioning or pleural passes.[11]

The next most common complication of USLB is haemorrhage which is usually mild. But there is a higher risk of high-grade haemorrhage in the older age group, female sex, patients with emphysema, pulmonary hypertension, usage of coaxial technique, subsolid lesions, non-subpleural location and smaller lesions.[11] Lastly, the rarest complication of USLB is air embolism which is quoted to be 0.001-0.003% as quoted in a meta-analysis by Tomiyama et al.[12]

Nevertheless, these complications can be monitored in real time using the ultrasound post procedure and can be addressed in a timely manner.[5] The technical success rate of USLB based on our retrospective study is 100% as there were no documented complications during or post procedure. Multiple studies have also shown that USLB has fewer complications in comparison to CT-guided lung biopsy with a shorter duration of procedure.[8-11]

These findings are consistent with the findings in a study published by Diacon et al.,[13] that USLB can safely be done by pulmonologist for lesions 20 mm or more with high yield for malignant diseases including mesothelioma.[13]

On top of that, USLB has high efficacy of diagnosing malignancy which in our study only three cases of malignancy were missed. The histopathology results were divided into thoracic malignancy, extra thoracic malignancy and inconclusive results. Thoracic malignancy that was obtained were adenocarcinoma (17%), squamous cell carcinoma (17%) and small cell carcinoma (10%). On the other hand, extra thoracic malignancy includes diffuse large B-cell lymphoma (10%), hepatocellular carcinoma (6%), Hodgkin lymphoma (6%), germ cell tumour (6%) and thymoma (6%).

Another benefit of USLB by pulmonologist is a shorter waiting time (within 1 week) compared procedure done by interventional radiologist (within 2-4 weeks) which in turn leads to faster diagnosis and initiation of treatment. This procedure can be done under daycare setting by pulmonologist and thus avoiding unnecessary admission as compared to being done by interventional radiologist which requires admission about 2-3 days. There is no difference between procedure done by pulmonologist or interventional radiologist as both are trained in the procedure and use the same method.

Our study has certain limitations including small sample size of only 18 patients and it is a retrospective study for which it is prone to selection bias. A prospective study with larger sample size is needed to compare the efficiency of USLB with that of other methods.

Looking to the foreseeable future, there are now new technologies in ultrasound where contrast agents can be used to visualise microcirculation in lesions to differentiate the pathology of the lesion prior to the biopsy whether its benign or malignant.[14]

CONCLUSIONS

In conclusion, Ultrasound guided lung biopsy (USLB) can safely and effectively be performed by trained pulmonologists mainly for peripheral thoracic lesions with excellent accuracy and exceptionally low complication rate in outpatients. Mastering this technique also enables a pulmonologist to expedite the diagnosis of patients with lung mass.

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ORIGINAL ARTICLE

Peripartum hysterectomy clinical characteristics and outcomes- a hospital based retrospective audit study

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ABSTRACT

Introduction: The study aims to evaluate and report on the clinical characteristics, incidence, risk factors and associated complications of emergency and planned peripartum hysterectomy in a single training and research tertiary health care centre in Malaysia.

Materials and Methods: We conducted a 6-year retrospective cross-sectional study from the 1st January 2016 until 31st December 2021. Clinical, demographic characteristics, perioperative parameters, operative indications, blood loss, maternal/neonatal outcomes and complications were analysed. Patients were subdivided, analysed and studied in two subgroups- emergency hysterectomy (EH) and planned hysterectomy (PH).

RESULTS: There were 65 cases of peripartum hysterectomy out of total 100,567 deliveries, with a prevalence rate of 0.06%. Overall, the majority of patients were multiparous (96.9%), having previous caesarean scar (73.8%) or diagnosed with placenta praevia (75.4%). More than half of the total patients (61.5%) have both previous caesarean scar and concomitant placenta praevia. EH was carried out in 39(60%) patients while 26(40%) patients underwent PH. The only indication for surgery in the PH group (100%) was abnormal placentation while the most common indication for surgery in the EH group (53.8%) was postpartum haemorrhage related to abnormal placentation. Patients who underwent EH were more likely to have massive blood loss (p=0.001), require ICU admissions (p=0.001), have DIVC cycles transfused (mean [SD] regime: 1.35 [0.95] vs 0.54 [0.99]; p=0.002), have lower postoperative haemoglobin level (mean [standard deviation, SD] haemoglobin: 9.23g/l [SD1.8] vs. 10.8 g/l [SD1.86]; p=0.001) and have higher difference between pre/post operative haemoglobin level (mean [SD] haemoglobin difference: 1.78g/l [SD6.34] vs 0.32g/l [SD1.7]; p=0.008) compared to patients with PH. Red blood cell transfusion, operating time, length of stay, weight of babies and Apgar score between two groups showed no significant differences. A significant reduction of blood loss between the first and the second half duration of the study (mean [SD] blood loss: 6978 ml [SD 4999.45] vs. 4100ml [SD2569.48]; p=0.004) was also observed. In the emergency group, 'non-placental cause' EH required significantly more red blood cell transfusion than 'placental cause' (p<0.05) while in the PH group, no significant difference was observed between the occlusive internal iliac artery 'balloon' and 'no balloon' subgroup in terms of operating time, total blood loss or blood transfusion. Overall complications showed more cases of post operative fever and re-laparotomy in the EH group (18.4% vs. 7.6%) while urinary tract injuries including injuries to bladder and ureter occurred only in the PH group (9.4% vs. 0%).

Conclusion: The majority of peripartum hysterectomy cases are due to placenta accreta spectrum disorders. Planned peripartum hysterectomies have a lower morbidity rate compared to emergency hysterectomies. Therefore, early identification of placenta accreta spectrum disorders and timely planning for elective procedures are crucial to minimise the need for emergency surgery.

KEYWORDS:
Elective peripartum hysterectomy, emergency peripartum hysterectomy, placenta accrete spectrum

INTRODUCTION

Peripartum hysterectomy is regarded as the most dramatic life-saving surgical venture in obstetrics. It is accompanied by substantial morbidity and mortality risk has been quoted to be more than 25 times compared to non-obstetric hysterectomy.[1] When this procedure is performed an emergency setting, it is usually done as a final resort to manage acute life-threatening haemorrhage. Emergency hysterectomy (EH) represents the most challenging complication that any obstetrician will ever face and even in the hands of the most experienced, EH could still be a formidable procedure to perform. This is largely due to the technical and operative difficulties resulting from pregnancy changes such as enlarged uterine and ovarian vessels, friable pelvic tissue, distortion of the anatomy, intrusion of the placenta into other organs in placenta percreta cases and scarring from previous caesarean sections.[2] In an emergency situation, the patient is also likely to be seriously ill.[2]

On the other hand, planned hysterectomy (PH) allows surgeons to prepare for the operation well ahead of time and

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allows optimisation of patients pre-operatively. Planned peripartum hysterectomy was mostly performed in the past for uterine fibroids, malignancy and for sterilisation purpose. However, in recent years most cases consist of placenta accreta spectrum (PAS) and uterine atony.[3-5] Although many studies show a reduction in blood loss, PH may still present a high complication rate due to the complex nature and surgical demands specific to the indications in this group.[6] Briery et al., in his study concluded that PH allows surgeons to prepare for safe surgical procedures and to prevent morbidities with no increase in intra-/postoperative complications.[7] A study by Oge et al. in 2022 asserted that peripartum hysterectomies, when planned and conducted by an experienced team, demonstrated a lower need for transfusions and yielded improved neonatal outcomes in comparison to their emergency counterparts.[3] However, some of these findings were contradictory.

Data comparing these outcomes in Malaysia are lacking. Therefore, the objective of this study was to evaluate the incidence, risk factors, outcomes, complications of peripartum hysterectomy cases and compare outcomes among emergency and PH in one of the main public tertiary hospitals in Malaysia. The study is anticipated to suggest timely interventions to improve the quality of care in women at risk of peripartum hysterectomy.[8]

MATERIALS AND METHODS

This was a retrospective cross-sectional study on all patients who underwent either emergency or planned peripartum hysterectomy in our centre over a 6-year period. Hospital Sultanah Nur Zahirah is the only tertiary hospital in the state of Terengganu. It has the highest number of hospital births in Malaysia, handling close to 18,000 deliveries annually. Peripartum hysterectomy is defined as hysterectomy performed after 22 weeks of pregnancy, within 24 hours of the delivery of the baby. From the 1st January 2016 until 31st December 2021, medical records of all the patients who underwent peripartum hysterectomy were retrieved from the computerised hospital information system and patients who fulfilled the criteria were recruited into the study.

PH patients consisted of patients who were antenatally diagnosed with PAS by ultrasound and/or magnetic resonance imaging (MRI) during the study period. These patients were screened based on at least two risk factors including concomitant placenta praevia and previous caesarean scar. A single dedicated team managed all the PH cases while EH cases were managed by the on-call team of the day. All hysterectomy specimens were sent for histopathological examination.

Demographic parameters, preoperative variables, operative indications, operating time, blood loss/transfusion, maternal and neonatal outcomes and complications were reviewed. The patients were further divided into the emergency and planned hysterectomy group and the outcomes were compared according to this categorisation. The definition of massive blood loss is bleeding that exceeds 2500 ml.9 Patients in the EH group were further divided into subgroups 'placental' or 'non-placental' cause based on final histopathological diagnosis. The patients in the PH group were categorised into 'balloon' and 'no balloon' subgroups depending on preoperative placement of occlusive balloon in the internal iliac artery.

Data analysis was performed using IBM SPSS (Statistical Package for Social Science) Version 27.0. Numerical variables were presented as means and standard deviations (SD) whereas categorical data were presented as frequencies and percentages. Statistical tests were done according to the aims of the study. Depending on the type of dependent variables, independent t test or chi square test were selected accordingly.

This study was approved by the Ministry of Health Medical Research Ethics Committee and the National Medical Research Registry (NMRR ID-23-01171-PUD).

RESULTS

A total of 100,567 deliveries were recorded during the study period with a caesarean section rate of 21.78% comprising 21,905 cases. A total of 65 patients were identified to have undergone peripartum hysterectomy with a prevalence rate of 0.06%. EH contributed to 60% (39 cases) of the cases while 26 cases (40%) were planned cases (PH).

Overall, the majority of patients were multiparous (96.9%), having previous caesarean scar (73.8%) or diagnosed with placenta praevia (75.4%). More than half of the total patients (61.5%) have both previous caesarean scar and concomitant placenta praevia. In the PH group, 16 (65%) patients had preoperative internal iliac artery balloon occlusion (IIABO) performed by visiting interventional radiologists while another 10 patients underwent elective operation without IIABO.

From the perspective of diagnosis, out of the total of 47 PAS patients, 39 patients fulfilled the screening criteria and were screened for PAS during the pregnancy while eight patients were not screened. Correct diagnosis was made in 84.6% (33/39) patients. The remaining 15.4% (6/39) patients proved to have placenta accreta (4/6) and placenta increta (2/6) on the final histological diagnosis. In the EH group, one fifth of patients (7/33) who were already diagnosed with PAS and planned for PH, developed bleeding or contraction before the elective date necessitating emergency operation.

We subsequently conducted a sub analysis to review the cases in the emergency and planned peripartum hysterectomy groups. The most common indication for hysterectomy in both EH and PH was abnormal placentation with 53.8% and 100% cases respectively (Table I). Histologically, placenta accreta is the most common abnormal placentation in EH (47.6%) while placenta percreta is the most common abnormal placentation in PH (57.7%) leading to hysterectomy. The next common indication for EH was uterine atony (20.5%) and ruptured uterus (10.3%) (Table I).

There was no significant difference in age, parity, gestational age and baseline haemoglobin level between two groups (Table II). In the EH group, only eight patients underwent

Table I: Indications for peripartum hysterectomy

	Emergency hysterectomy (EH) n=39 [n (%)]	Planned hysterectomy (PH) n=26 [n (%)]	Overall n=65 [n (%)]
Placenta accreta spectrum (PAS):			
Accreta	10(25.6)	2(7.7)	12(18.5)
Increta	8(20.5)	9(34.6)	17(26.2)
Percreta	3(7.7)	15(57.7)	18(27.7)
Total PAS*	**21(53.8)**	**26(100)**	**47(72.3)**
Uterine atony	**8(20.5)**	**0(0)**	**8(12.3)**
Uterine rupture	**4(10.3)**	**0(0)**	**4(6.2)**
Others:			
Extensive cervical tear	1(2.6)	0(0)	1(1.5)
Cervical tear and atonic uterus	1(2.6)	0(0)	1(1.5)
Extended tear	1(2.6)	0(0)	1(1.5)
Broad ligament haematoma	1(2.6)	0(0)	1(1.5)
Bleeding post emergency myomectomy	1(2.6)	0(0)	1(1.5)
Placenta praevia	1(2.6)	0(0)	1(1.5)
Total others:	**6(15.4)**	**0(0)**	**6(9.2)**

*PAS, Placenta accreta spectrum

Table II: Demographic data, mode of delivery, perioperative parameters and outcomes

	Emergency hysterectomy (EH) n=39 [mean (SD)]	Planned hysterectomy (PH) n=26 [mean (SD)]	p-value
Demographic data			
Age (years)	35.52(5.19)	36.12(4.75)	0.637
Parity	3.78(1.45)	3.77(1.44)	0.890
Mean gestation (weeks)	36.23(3.17)	35.19(1.96)	0.141
Mode of delivery			
Vaginal	8(20.5)	0(0)	0.014*
Caesarean	31(79.5)	26(100)	
Neonatal outcome			
Birth weight (grams)	2652.71(58.07)	2500.90(453.3)	0.308
Apgar score @ 1 min	7.76(1.95)	8.04(1.91)	0.59
Apgar score @ 5 mins	8.58(1.60)	8.48(1.75)	0.83
Perioperative parameters			
Pre-operative haemoglobin(g/dl)	10.99(1.76)	11.09(1.29)	0.794
Red blood cell transfusion (pints)	5.82(3.49)	3.96(5.52)	0.101
Postoperative haemoglobin (g/dl)	9.23(1.81)	10.8(1.86)	0.001*
Difference pre/postoperative Hb (g/dl)	1.78(2.27)	0.32(1.70)	0.008*
Duration of hospital stay (days)	7.84(6.34)	7.84(5.87)	1.00
Temperature (°Celcius)	37.42(0.47)	37.27(0.19)	0.148
Transfusion of DIVC cycles*	1.35(0.95)	0.54(0.99)	0.002*
Blood loss n (%)			
≥2.5 litres	37(94.9)	15(57.7)	
<2.5 litres	2(5.1)	11(42.3)	
N	39	26	
Chi square	13.48		
P			**0.001***
Prevalence ratio (95%CI)	1.64(1.17-2.31)		
ICU n (%)			
ICU admission	29(74.4)	6(23.1)	
No ICU admission	10(25.6)	20(76.9)	
N	39	26	
Chi square	16.51		
P			**0.001***
Prevalence ratio (95%CI)	3.22(1.56, 6.66)		

*DIVC defined as transfusion of six units cryoprecipitate, four units fresh frozen plasma and four units platelets)

Table III: Comparing planned hysterectomy (PH); with or without balloon tamponade and emergency hysterectomy (EH); placental or non-placental cause

	Planned Hysterectomy (PH)						
	Balloon		No balloon		T	df	p
	n	Mean SD	N	Mean SD			
Operating time (minutes)	17	150.12(47.53)	9	186.22(91.45)	-1.33	24	0.194
Blood loss (ml)	17	3000(3200)	9	2500(12500)	-0.83	-	0.403
Blood transfusion (pints)	17	2.53(2.74)	9	6.67(8.22)	-1.47	8.95	0.176
	Emergency Hysterectomy (EH)						
	Placental cause		Non placental		T	df	p
	n	Mean SD	N	Mean SD			
Operating time (minutes)	23	247.00(243.16)	16	318.7(275.06)	-0.85	37	0.396
Blood loss (ml)	23	6500(4000)	16	5250(4625)	-	-	0.877
Blood transfusion (pints)	23	5.00(2.58)	16	7.19(4.12)	-2.03	37	0.049*

Table IV: Pattern of estimated blood loss in 1st half and 2nd half of the 6 years study duration

Year	N	Estimated blood loss [mean (SD)]	T	*p*-value
2016-2018	37	6978.38(4999.45) ml	3.015	0.004*
2019-2021	28	4100.00(2569.48) ml		

Table V: Intraoperative and postoperative complication

No	Complications	Planned Hysterectomy (PH) (n=26)	Emergency Hysterectomy (EH) n=39)	% of total cases
1	Post operative fever	3	8	16.9
2	Re-laparotomy	2	4	9.2
3	Bladder injury	4	0	6.1
4	Ureteric injury	2	0	3.1
5	Vascular injury	1	1	3.1
6	Intra-abdominal sepsis	0	1	1.5
7	Deep vein thrombosis	1	0	1.5
8	Splenic injury	0	1	1.5
9	Pulmonary embolism	0	1	1.5
10	Transfusion related acute lung injury (TRALI)	0	1	1.5

vaginal deliveries while the majority of patients (79.5%) had caesarean deliveries which culminated into hysterectomies due to intractable haemorrhage (Table II).

Patients in the emergency group EH had significantly lower postoperative haemoglobin level, higher difference between pre/post operative haemoglobin level and higher DIVC cycles transfusion rate compared to the patients in the planned group PH (p value <0.05) (Table II). However, there was no significant difference in duration of hospital stay, red blood cell transfusion and postoperative fever. There were no cases of maternal mortality found in both the groups during the study period.

There were no differences in the neonatal outcomes between the two groups with the mean birth weight of 2652.71gm (SD58.07) in the EH group and 2500gm (SD453.3) in the PH group (Table II). There was also no significant difference between the APGAR score of these babies at 1 minute and 5 minutes of life. There were no cases of perinatal mortality during the study period in both groups.

Significantly more patients in the EH group suffered from massive blood loss as compared to patients in the PH group (p=0.001) and majority of them also required postoperative intensive care unit (ICU) admissions (p=0.001) (Table II).

When operating time, blood loss and blood transfusion were compared between subgroups of patients in EH and PH, non-placental cause EH required more blood transfusion (p<0.05) and cases of PH with balloon (IIABO) on average showed more blood loss but did not reach statistically significant difference (Table III).

We also looked into comparing the estimated intraoperative blood loss for patients who underwent peripartum hysterectomy between the years 2016-2018 and the years 2019-2021 and found a significant reduction of blood loss between two groups (Table IV). The mean blood loss in the first 3 years was 6978.38 ml (SD 4999.45) while the mean blood loss for the last 3 years was 4100 ml (SD2569.48).

Regarding overall complications, there were more cases of postoperative fever and re-laparotomy in the EH group (18.4% vs. 7.6%) while urinary tract injuries including

injuries to bladder and ureter occurred only in the PH group (9.4% vs. 0%) (Table V).

DISCUSSION

The overall prevalence rate of peripartum hysterectomy in our study was 0.6 for every 1000 deliveries. The rate for EH was lower at 0.38 for every 1000 deliveries. In the developed countries, the rate is generally less than 1 per 1000 deliveries while in the developing countries the rate between 1.5 to 6.9 per 1000 deliveries has been quoted.[10-16] A comprehensive meta-analysis involving almost 8000 women with peripartum hysterectomy worldwide has demonstrated an inverse correlation between the prevalence of peripartum hysterectomy and income setting whereby higher prevalence was associated with decreasing income setting and vice versa.[4]

We believe that the results of our study are reflective of other public hospitals in Malaysia. Our study demonstrated that the most common indication for peripartum hysterectomy were cases of abnormal placentation or PAS. This contrasts with a local study by Rachagan & Sivanesaratnam conducted a few decades ago, which identified uterine rupture and uterine atony as the most common indications for obstetric hysterectomy, a finding that was corroborated by international studies from the same period.[17-20] The decline in hysterectomy for these cases may be due to the advent of pharmacological and non-pharmacological therapeutics in producing efficient oxytocic drugs, balloon and suture tamponades, and also advanced radiological intervention. However, consistent with the global increase of caesarean section rate, the incidence of PAS disorders resulting in peripartum hysterectomy had increased accordingly. Other recent studies demonstrated similar findings.[3,13,21]

Our study demonstrated that fewer morbidities associated with planned as compared to emergency surgeries, consistent with other studies.[3,7] Massive blood is less likely to occur in planned cases. Mendoza et al. studied elective versus emergency peripartum hysterectomy exclusively in PAS cases and his team found lower blood loss in elective cases compared to emergency cases.[22] Echoing this, a study by Briery et al. conducted over 15 years ago, found that patients who underwent emergent caesarean hysterectomy were more likely to experience higher blood loss and require red cell transfusion.[7] However, in his study, most planned cases comprised of uterine fibroids and most emergency cases comprised of uterine atony.[7] Recent study by Oge et al. showed a similar cohort of patients like ours in the elective group but majority of his emergency cases were cases of atonic uterus (57.1%).[3] On the contrary, most of our emergency cases (53.8%) were PAS cases.

Ideally, all the PAS cases should be identified during pregnancy to allow for planned elective operations. In our study, our screening protocol successfully detected 84.6% of PAS cases, but it's crucial to note that six undiagnosed cases led to severe complications. These included total blood loss exceeding 5 l, high morbidity, two instances requiring relaparotomy, one bladder injury, and ICU admissions for all the affected cases. In each of these situations, the attempted removal of the placenta increased morbidity, as evidenced in the study by Ellar et al.[23] Adherent placenta can be diagnosed with the use of ultrasound with a sensitivity of 89.5%, as reported by Esakoff et al.[24] Similarly, a large systematic review in 2013 involving 3,707 pregnancies noted an average sensitivity of 90.72% (95%CI 87.2, 93.6).[25] Interestingly in one study where the investigators were blinded to the clinical risk factors of PAS, the diagnostic sensitivity of ultrasound was reduced to 53.5%.[26] The cases which were misdiagnosed were mainly of the least invasive form of PAS. It is not surprising therefore to observe that most of our elective cases were cases of placenta percreta and most of our emergency cases were cases of placenta accreta.

Our current screening protocol mandates detail sonographic assessment by a senior maternal foetal medicine (MFM) consultant to exclude PAS in patients with both previous caesarean scar and concomitant placenta praevia.[27] A total of eight patients in our study were not screened for PAS as they had only a single risk factor. While it's not feasible to screen all patients, one should look for evidence of PAS even during a routine ultrasound examination. MRI on the other hand has an excellent diagnostic accuracy in identifying the depth and the topography of placental invasion.[28] The threshold to request for MRI examination should be low in cases with doubtful ultrasound findings.

The current guideline from RCOG is to deliver patient with PAS at 35+0 to 36+6 weeks in the absence of preterm delivery risk while ACOG recommends delivery between 34+0 to 35+6 weeks.[29,30] Pettit et al., in 2019 found that one third of the cases of placenta accreta diagnosed prenatally in his study were still delivered in an unplanned manner.[31] Our experience showed that despite already being diagnosed, one fifth (7/33) of the cases underwent emergency operation before the elective date. Most cases (5/7) had bleeding or went into labour after 34 weeks. The overall neonatal outcome at 34 weeks in most major centres throughout the country is excellent.[32] Among the proposed strategies to reduce emergency cases is the consideration of earlier delivery of PAS cases at 34 weeks, yet this decision should be individualised, considering factors such as previous antepartum haemorrhage, shortened cervical length, preterm premature rupture of membranes (PPROM), and the presence of uterine contractions.

Subgroup analysis in our study showed that non placental cause EH required more blood transfusion than placental cause EH ($p<0.05$) despite lesser blood loss. Non placental cause EH include cases of ruptured uterus and cervical tear amongst other causes which could cause torrential bleeding in a short time interval. Anticipating such complication could have resulted in overzealous resuscitation. Conversely, cases of PH with occlusive balloon showed more blood loss on average although the difference did not reach statistical significance. This could be due to the fact that majority of cases selected for pre-operative IIABO were the more severe degree of placentation invasion e.g., placenta percreta.

One interesting observation in this study is a significant reduction in massive blood loss as observed in the last three years. This trend is related to an emphasis on

multidisciplinary management planning, availability of better and more advanced resuscitative equipment, initiation of massive transfusion protocol (MTP), and practice of early administration of antifibrinolytics during haemorrhage.

The strengths of this study include having the same dedicated team who managed all planned hysterectomies, and all cases were managed in only one tertiary centre. Despite analysing 6 years of data, the study has several limitations. These include a small sample size, the retrospective design of the study, and crucially, the diverse indications for surgery and varying severity of PAS cases in both planned and emergency situations. These differences, particularly in the clinical context of the cases, may have influenced the outcomes and should be considered when interpreting the results.

CONCLUSION

In conclusion, planned peripartum hysterectomies markedly reduce morbidity compared to emergency procedures. Early detection of placenta accreta spectrum disorders coordinated care involving an experienced team, multi-disciplinary approach and the adoption of massive transfusion protocols are all crucial to minimising morbidity and enhancing patient outcomes in peripartum hysterectomies.

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CONFLICT OF INTEREST

This study received no external funding and has no declared conflicts of interest.

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Parent's perception of digital device use among their preschool children and its associated factors in Kota Setar, Kedah

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ABSTRACT

Introduction: Digital devices are an integral part of children's lives, and its use is associated with both risks and benefits. The aim of this study was to determine parent's perception of digital device use among their preschool children.

Materials And Methods: A cross-sectional study was conducted among parents of 145 children in the year 2020. Participants were selected using multistage randomisation technique from 10 of the 75 registered government kindergartens in Kota Setar District, Kedah. Data were collected using a self-administered questionnaire. Analysis was done using descriptive statistics and the association between parent's demographic characteristics and the overall perception of digital media use by their preschool children was tested using Chi-square test.

Results: A total of 150 questionnaires were distributed, and 145 were returned (96.7% response rate) out of which 139 were complete. We found that parent's overall perception of their preschool children using digital devices was mixed, where about one-third of them perceived that digital device use was a risk, one-third perceived it as beneficial while one-third were unsure. The common perception of risk was that digital devices impaired children's physical (71.9-90.6%) and intellectual domains (71.9-86.3%) especially causing damage to eyesight (90.6%), causing addiction (86.3%) and exposed to radiation (81.3%). The perceived benefits of using digital device were mainly in the social domain, promoting technology awareness (64.8%), easily accessible and portable (63.3%) and entertaining (64.0%). They also perceived that digital devices promoted creative and interactive learning (62.6%). Parent's overall perception of digital media use was associated with their employment status (p=0.028).

Conclusion: Parent's overall perception regarding digital device use among their preschool children was mixed. They perceived that digital devices commonly cause risk to the physical and intellectual aspects of their children while there are some benefits to the social aspects. There is an association between parent's overall perception and employment status.

KEYWORDS:
Child, digital device, parents, perception, preschool

INTRODUCTION

Digital devices have a major impact on our day-to-day activities. It has now extended into the children's world mainly in education, social relationship and communication aspects, through devices such as smartphones, laptops and tablets.[1] The impact of using these devices on children has both, benefits as well as potential risks. A systemic review showed that the interconnection between children and digital technology has dual effects with some positive implications in educational aspects and some negative implications such as delayed development in social and language skills.[2]

In the academic perspective, digital devices contribute to a positive attitude towards children's learning by increasing alphabet recognition, boost reading skills and mathematical knowledge. Cognitively, it enhances visual intelligence skills and helps to develop their psychomotor skills. On the hind side, digital devices negatively affect preschool children in physical, psychological and social aspects of development as they tend to become less physically active and are at risk of musculoskeletal problems and obesity. Psychologically, there is a risk of developing addictive disorders, depression, aggression or violent behaviour, which stems from the inability to discriminate fantasy from reality. In the social context, digital device usage showed a high incidence of decreased family time, communication between family members, increased social isolation and impeded the development of their interpersonal skills.[3]

In Malaysia, about 95.9% of preschool children use digital devices, which mostly (95%) belong to their parents and start early in life with a mean age of exposure at 3.9 years (SD1.25).[4] Hence, parents have an important role in mediating digital device use and are responsible for the appropriate use of these devices among their preschool children. However, many of them are unsure regarding the effects of these devices and technology use by their young children and have numerous concerns regarding this issue.[5] Hence the aim of this study is to assess parent's perception of digital device use among their young children for better understanding of their perspectives on this matter.

MATERIALS AND METHODS

This is a cross-sectional study done in Kota Setar district, Kedah, in February 2020. Data were collected using

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multistage randomisation technique. Epicalculator was used to calculate the sample size for this study using the expected frequency of 50% with an acceptable margin of error 5%. An additional 20% was included for the possibility of incomplete or unreturned questionnaires giving the final sample size of 145. To achieve this sample size, 10 government kindergartens were selected randomly from the 75 which were registered in the district, using the fish bowl technique. After obtaining permission for the study from the principals of each kindergarten, 15 students (all between ages 4 and 6 years) were selected randomly by computer from each school using the student's registry. The selected students were then given an envelope containing the information sheet regarding the study, consent form and the questionnaire to be filled by their parents. They were instructed to return these forms to their respective class teacher within a week. The researcher then collected these forms from the class teachers. Parents who could not understand the national language, Bahasa Melayu or refused to participate, were excluded.

Digital devices were defined as all smartphones, touch screen tablets (e.g., ipad), laptops or desktop computers with an exception to television to avoid duplication of information as TV programs can be viewed through digital devices. A self-administered questionnaire was used to assess parent's perception of digital device use among their children. This questionnaire was developed in the English language from the literature search.[6,7] It was then translated (forwards and backwards) to the local language (Bahasa Melayu) by two linguists. Parent's perception of risk and benefits of their preschool children using digital devices was assessed using 12 statements in four domains (physical, intellectual, emotional and social). Each of these statements was followed by a 5-point Likert scale response option (strongly agree, agree, neutral, disagree, strongly disagree) from which the parents were instructed to select one. Content validation for the questionnaire was done by two family medicine specialists and piloted among 30 parents from another kindergarten for face validity. Selections of options 'agree' and 'strongly agree' were analysed together as an agreement to the statement, and selections of 'disagree' and 'strongly disagree' were analysed together as a disagreement to the statement while the option 'neutral' was analysed separately. The overall perception of parents with regards to digital media use among their preschool child was assessed by a single question 'Do you think that your preschool child's digital device use causes more benefit than harm?' This question was followed by three answer options of 'yes', 'no' or 'unsure'. The internal consistency for perceived risks and benefits questionnaire was 0.974 and 0.713, respectively. Data were analysed using IBM SPSS version 26. Parent's perceived risk and benefits of digital device use by their preschool children was described using descriptive statistics while Chi-square test was used to determine the association between parent's demographic characteristics and the overall perception of digital media use by their preschool children. This study was approved by University Kebangsaan Malaysia (UKM) research ethics committee (FF-2019-381) and Kota Setar district Department of Education.

RESULTS

A total of 150 questionnaires were sent out to parents of preschool children, and 145 responses were received (96.7% response rate). Out of this, 139 responses were complete and were subjected to analysis. For the perception of risk, most parents perceived that digital device use among their preschool children would cause risk to their physical (71.9-90.6%) and intellectual domains (71.9-86.3%). A large majority of them (90.6%, n=126) perceived that digital device causes damage to eyesight, results in device addiction (86.3%, n=120) and exposes their children to radiation (81.3%, n=113). They also commonly perceive that digital devices affect their child's emotion and social domains, making them impatient and socially isolated (Table I).

As for the benefits of digital device use, more than half of them (n=87, 62.6%) indicated that it promotes creative and interactive learning. They also perceive that digital device was favourable in the social domain promoting technology awareness (n=90, 64.8%), is entertaining (n=89, 64.0%), and is easily accessible and portable (n=88, 63.3%) (Table II).

However, the overall parent's perception regarding digital device use among their preschool children was mixed, where about one-third of them (30.2%, n=42) perceived more benefit, one-third (34.5%, n=48) perceived more harm, while the remaining one-third (35.3%, n=49) were unsure of its effects. Parent's overall perception of digital device use was associated with employment status (p=0.028). Table III shows an association between the overall perception and parent's demographic characteristics.

DISCUSSION

Digital devices are fast gaining popularity among young children, and it is important to assess parent's perception on its use. Studies have found that exposure to digital technology among preschool children can cause both adverse effects and benefits. The risks of prolonged exposure affect behavioural aspects such as conduct disorders, sleep disorders, attention deficit, higher prevalence of obesity and depression. They also tend to experience physical problems such as headaches, neck, shoulder pain and poor posture.[8,9] On the other hand, some benefits have been observed in the cognitive, psychosocial and social aspects of development. Since parents are the main mediators of device use among young children, assessing their perception sheds light on their views on this matter.

Our study found that the overall perception of parents regarding their preschool children using digital devices was mixed with one-third of them perceived as more benefit, while one-third perceived as more risk and one-third were unsure. Among parents who perceived that digital device use was a risk, they were mainly concerned about the negative impact on the physical (71.9-90.6%) and intellectual (71.9-86.3%) aspects of their children. They were particularly concerned about possible eye damage, addiction and radiation effects related to digital device use. However, only a small percentage of parents perceived risk of using digital devices to the social and emotional aspects of their children. Parents in Singapore and Italy also had similar concerns

Table I: Parent's perceived risk of digital device use among preschool children

Perception of risks in domains	Agree n (%)	Neutral n (%)	Disagree n (%)
Physical			
Damages eyesight	126 (90.6)	12 (8.6)	1 (0.8)
Exposed to radiation	113 (81.3)	21(15.1)	5 (3.6)
Inactive lifestyle	100 (71.9)	25 (18.0)	14 (10.1)
Intellectual			
Causes device addiction	120 (86.3)	15 (10.8)	4 (2.9)
Has undesirable contents	103 (74.0)	25 (18.0)	11 (8.0)
Causes over-dependence	100 (71.9)	31 (22.3)	8 (5.8)
Emotional			
Causes poor social–emotional development	81 (58.3)	38(27.3)	20 (14.4)
Causes impatience	85 (61.2)	31 (22.3)	23 (16.5)
Encourages tantrums	79 (56.8)	37 (26.7)	23(16.5)
Social			
Causes social isolation	85 (61.2)	26 (18.7)	28 (20.1)
Causes poor social skills	78 (56.1)	31 (22.3)	30 (21.6)
Causes poor communication skills	74 (53.3)	32 (23.0)	33 (23.7)

Table II: Parent's perceived benefits of digital device use among preschool children

Perception of benefits	Agree n (%)	Neutral n (%)	Disagree n (%)
Physical			
Improves movements and coordination of hands and fingers	59 (42.5)	54 (38.8)	26 (18.7)
Improves sensation of vision, hearing and touch	43 (30.9)	64 (46.0)	32 (23.1)
Improves reflexes	49 (35.3)	62 (44.6)	28 (20.1)
Intellectual			
Improves academic achievement	55 (39.6)	75 (53.9)	9 (6.5)
Promotes creative and interactive learning	87 (62.6)	46 (33.1)	6 (4.3)
Enhances learning process	81 (58.3)	54 (38.8)	4 (2.9)
Emotional			
Appreciates music	70 (50.4)	58 (41.7)	11 (7.9)
Encourages independence	43 (30.9)	61 (43.9)	35 (25.2)
Reduces tantrums	28 (20.1)	72 (51.8)	39 (28.1)
Social			
Promotes technology awareness	90 (64.8)	43 (30.9)	6 (4.3)
Easily accessible and portable	88 (63.3)	46 (33.1)	5 (3.6)
Entertaining	89 (64.0)	41 (29.5)	9 (6.5)

Table III: Association between overall perception of digital device use and parent's demographic characteristics

		Benefit n (%)	Harm n (%)	Unsure n (%)
Overall perception of digital device use		42 (30.2)	48 (34.5)	49 (35.3)
Parent's characteristics	**Benefit n (%)**	**Harm n (%)**	**Unsure n (%)**	**p-value**
Ethnicity				
Malay	35 (30.2)	43 (37.1)	38 (32.7)	0.280[a]
Others	7 (30.4)	5 (21.8)	11 (47.8)	
Relationship				
Father	17 (39.5)	14 (32.6)	12 (27.9)	0.502[b]
Mother	24 (26.1)	32 (34.8)	36 (39.1)	
Others	1 (25.0)	2 (50.0)	1 (25.0)	
Occupation status				
Employed	27 (31.8)	35 (41.2)	23 (27.0)	0.028[a]
Unemployed	15 (27.8)	13 (24.1)	26 (48.1)	
Total income				
< RM 2500 (Low)	18 (32.7)	19 (34.6)	18 (32.7)	0.190[a]
RM 2500-5000 (Middle)	16 (28.6)	15 (26.8)	25 (44.6)	
> RM 5000 (High)	8 (28.6)	14 (50.0)	6 (21.4)	
Education level of parent				
School	16 (32.0)	14 (28.0)	20 (40.0)	0.424[a]
Tertiary education	26 (29.5)	34 (38.7)	29 (31.8)	

[a]Pearson's chi-square test. bFisher's exact test.

where they were mainly concerned regarding the risk of digital device towards their children's physical and intellectual development especially visual deterioration, eye irritation, addiction, sleep disorders and their overall health.[7,10] This suggests that parents were either more concern about physical and academic aspects rather than social and emotional aspects of their child or they were unaware that digital device use could affect the emotional and social development of young children. This finding is in contrast to parents in the United States of America (USA) where only a small percentage (11%) of them believed that the use of digital device can cause long-term physical, emotional and intellectual damage.[6] Parents in different parts of the world have different perception towards the impact of digital devices on their children, probably due to differences in the socio-cultural aspects of each country.

Parents in our study perceived that digital device use by their preschool children was beneficial, especially in the social (63.3-64.8 %) and intellectual domains (39.6-62.6%). They perceived that digital device promoted technology awareness, was entertaining, easily accessible, portable and promoted creative and interactive learning. An earlier study showed positive psychosocial and cognitive outcomes when digital media was used for less than 30 minutes a day among children between ages 3–5 years.[11] Playing games is important for children's learning process, and the use of smartphones and other digital devices provides an excellent gaming environment for the digitally minded child. Technology-assisted play is different from the traditional play where it can stimulate imagination and guide children to follow certain rules. Children who are familiar with the technology are able to make changes to the game which influences the outcome of their play and eventually creates a link to real life.[1] Parents in Singapore also perceived the benefits of digital device on their children's intellectual development especially in improving academic performance, promoting creativity and interactive learning.[7] This may be because there are a large number of applications (apps) for touchscreen devices which are marketed as 'educational' products to promote sales. However, more than half of these apps are of low-quality design hence, parents need to be aware of this and match it with their children's learning needs and goals.[12]

Although parents were mostly able to identify their specific perceptions of risk and benefits of their child using digital device, their overall perception of risks and benefits was mixed. This is not surprising as recent information also suggests there are both advantages and disadvantages of using digital device among young children. According to American Academy of Paediatrics (AAP), there are evidence-based benefits, such as promoting early learning, increased social contact, exposure to information and enhancing knowledge. On the other hand, there are risks such as impact on sleep, attention, learning, obesity, depression and exposure to unsafe content.[13] The American Academy of Child and Adolescent Psychiatry (AACAP) announced new guidelines which now state that parents need to be involve, know the content of appropriate games and apps as not all of these apps promote learning and encourage them to monitor their children's time in the virtual world.[14]

Our study found an association between parent's overall perception of preschool children using digital devices with employment status (p=0.028). We postulate the possibility that parents who are employed are more familiar with digital device use and hence are aware of the pro and cons of young children using these devices. However, an earlier study showed that parent's own skills using digital devices and technology did not influence their perception regarding concerns in mediating their preschool children in using these devices, suggesting that perception is affected by interplay between multiple factors.[15] An earlier study in USA found that parents with higher education were against their children spending excessive time on digital devices as they perceived that there are other better methods for child play.[6] In contrast, our study did not show any association between parent's education level with their overall perception (p=0.424). Education may not be the only factor influencing perception as multiple internal (e.g., personality, expectation, experiences, attitude, emotion, behaviour, motivation, culture) and external factors (e.g., changes in the intensity or magnitude of stimuli and repeated exposure) influence people's perception. Malaysian parent's personality, culture and experiences may differ from those of American parents, attributing to the difference in perception towards young children's digital device use, irrespective of parent's education level.

Digital devices are here to stay and will remain an integral part of everyone's daily lives, including young children. It will be a major challenge to prevent children from using these devices as more and more of their peers join the digital race. Parents have the responsibility to show good role modelling and guide these young children towards a healthy experience with digital devices. Physicians also can contribute by assisting and motivating parents in providing evidence-based recommendations such as co-viewing, monitoring content and limiting exposure time, which are all beneficial actions in mediating digital device use among children.[16]

One of the limitations of this study is that data were collected from kindergartens in one state; hence, the results may not be applicable to the entire population. We could not exclude, recall and socially desirable bias which may have caused under or over-reporting of information. Another difficulty which the researchers faced was that the age for preschool children in Malaysia is between 4 and 6 years while in other countries, the age group for preschool had a wide variation; hence, comparing our findings with other studies was challenging.

CONCLUSION

Parent's overall perception regarding the risks and benefits of digital device use among their preschool children was mixed where one-third of them perceived it as beneficial, one-third perceived it as harmful and another one-third were unsure. Most parents' perception of risks for using digital device was regarding the effect on physical and intellectual aspects of their children such as damage to eyesight, device addiction and radiation exposure. However, they also perceived some benefits of digital device use on the social and intellectual

aspects of their child. They perceive that digital devices raised technology awareness, are easily accessible, portable, entertaining and promoted creative and interactive learning. Parent's overall perception of digital media use was associated with their employment status. Their mixed perception and main concerns regarding the use of digital device by their preschool children highlights the importance of parental mediation in terms of control and supervision related its use.

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ORIGINAL ARTICLE

Awareness of pelvic organ prolapse and attitude towards its treatment among Malaysian women

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ABSTRACT

Introduction: The aim of this study is to determine the level of awareness of pelvic organ prolapse (POP) and factors that influence the attitude towards the treatment of POP among Malaysian women.

Materials and Methods: This was a cross-sectional study of 400 women from registered non-government organisations (NGOs) in Malaysia who voluntarily answered questionnaires distributed through Google form via emails. Data were analysed using descriptive statistics, independent t-test and one-way ANOVA test.

Results: Four hundred respondents participated in this study. The mean age was 40.42 years old (SD=12.566). The mean score for the studied population was 4.96 (SEM 0.124). Only 58 (14.5%) respondents obtained a score of eight or more, and 235 (58.8%) respondents scored between 4 and 7. The rest of 107 (26.7%) respondents scored 3 and less. There were statistically significant differences in the mean score for level of awareness between marital statuses, menopausal status, number of children and occupation. There were only 273 (68%) respondents who will seek treatment if they experience symptoms of POP. The most frequent reasons for not seeking treatment were unawareness of the availability of medical treatment for POP (69 %).

Conclusion: Majority of the respondents have an inadequate level of awareness on POP. Although more than half of the respondents will seek treatment if they experience symptoms of POP, concerns raised by those who chose not to seek treatment should be addressed by a more effective public awareness programme. This includes the unawareness of the availability of medical treatment and the embarrassment to see medical practitioners.

KEYWORDS:
Knowledge, treatment-seeking behaviour, uterine prolapse

INTRODUCTION

Pelvic organ prolapse (POP) refers to a falling, slipping or downward displacement of different vaginal compartments and their neighbouring organs such as bladder, rectum or bowel.[1] It is a common disorder with the global prevalence of uterine prolapse reported to be between 2 and 20%.[2] Symptomatic prolapse was demonstrated by 118 (6%) of the women in a population-based study of 2,001 women.[3] Vaginal prolapse affects quality of life negatively and is associated with urinary, bowel and sexual symptoms.[4] The main obstacles described by the participants were lack of information and feeling of shame, thus leading to a deficiency of knowledge about POP and delay in seeking health care services.[4]

Despite the prevalence of POP, many women are unaware of available treatment modalities. In a study by Shrestha et al.,[5] women with POP symptoms did not use health care facilities provided despite exhibiting a high level of knowledge on POP and having access to nearby hospitals. A community-based study in north India self-reported POP shows 57% of women received no treatment. Reasons for not accessing health care include uncooperative family members, lack of time and lack of money.[6] Another study showed reasons for not accessing health care include fear of disclosure due to social stigma, lack of funds and poor support.[7,8]

Healthcare providers may be able to enhance service quality and access, as well as resolve the obstacles that discourage women from pursuing POP treatment by examining their attitudes towards POP treatment. Several studies have specifically addressed the issue of POP awareness and knowledge in Nepal, Vienna and Moscow, the United States and the US/Mexico border, which demonstrated a gap in knowledge and awareness about POP, risk factors and treatment options.[2,9-11] Hence, the aim of this study was to assess the awareness regarding POP and attitudes towards treatment among Malaysian women.

MATERIALS AND METHODS

This was a cross-sectional study involving women working in registered non-government organisations (NGOs) in Malaysia.

The list of registered NGOs was obtained from Malaysia Central portal (http://www.mycen.com.my/malaysia/ngo_02.html) which listed all the registered NGOs in Malaysia. Every NGO was assigned a specific number, and NGOs were selected using a simple random sampling with Microsoft Excel. The inclusion criteria for the respondents were Malaysian women aged above 20 years old, and the exclusion criteria were pregnant women and those who were unable to understand the English language.

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In view of no local data on the prevalence of POP, the sample size estimation for this study was calculated based on the published data by Samuelsson et al.,[12] who reported that the prevalence of any degree of POP was 30.8% in a Swedish population of women aged 20–59 years old. Using OpenEpi software with a confidence limit of 5% and a confidence interval of 95%, the sample size obtained was 328. Considering 20% of possible non-responders, the minimum sample size was 394.

The questionnaire used in this study consisted of three parts. The first part was on the sociodemographic background of the respondents. The second part was ten items for the assessment of the level of awareness on POP. Eight items were adapted from Prolapse and Incontinence Knowledge Questionnaire (PIKQ) by Aparna et al.[13] PIKQ comprised two distinct, 12-item scales: a Urinary Incontinence scale to assess patient knowledge about urinary incontinence and a POP scale to evaluate patient knowledge about POP. However, a 10-item questionnaire was created to suit the studied population by using eight adapted items taken from the PIKQ and additional two other items to achieve the objective of this study. There is a mixture of correct and incorrect statements within the 10-item. The respondents will need to answer whether they 'agree', 'disagree' or 'not sure' with the statement given for each item. One mark was awarded to each correctly answered item. The total number of correctly answered items for each participant was recorded. A higher score meant a higher level of awareness on POP.

The third part was on the assessment of their treatment-seeking behaviour for POP. This part had three main questions: whether they have any of the symptoms of POP listed, whether they think it is normal to have any of the symptoms, and whether they will seek treatment if they have any symptoms. If they answered 'no' to question Number 3, they will need to answer another question to justify why they would not seek treatment.

Content validity was performed by five Obstetrics and Gynaecology Specialists, and face validity assessment was performed by five women attending the outpatient clinic before its use in this study. It was then tested in 20 healthy women without any symptoms of POP to determine whether the questions were understandable.

The first 50 NGOs from the randomised generated list were selected and invited to participate in this study, but only 27 NGOs responded and agreed to participate. The questionnaire was distributed through emails, which they subsequently shared with women working in their organisation. Participation was voluntary (convenience sampling). A patient information leaflet, including the inclusion and exclusion criteria, was provided on the front page of the questionnaire, and those who were suitable and agreeable to participate in this study proceeded to answer the questionnaire.

The data were analysed using Statistical Package for Social Science (SPSS) version 20.0 (SPSS Inc, Chicago, IL). All the independent variables were classified into categorical and was presented in the form of absolute number and their corresponding percentages values. Analysis using independent t-test and one-way ANOVA with post hoc test Bonferroni's procedure was used to determine the association between mean score and studied variables. The significant level is preset at α=0.05.

Ethics approval was obtained from the Universiti Teknologi MARA Research Ethics Committee (Reference number: 600-IRM(5/1/16)).

RESULTS

A total of 400 respondents participated in this study. The mean age was 40.42 (SD 12.57) years old. Table I shows the demographic details of the respondents.

There were 10 items to assess respondents' awareness of POP. The number of respondents who answered correctly for each statement is shown in Table II. There is no cut-off point to interpret the score; however, the higher score they get indicates the higher level of awareness. The mean score for the studied population was 4.96 (SEM 0.124). Only 58 (14.5 %) respondents obtained a score of 8 or more, and 235 (58.8%) respondents got a score between 4 and 7. The rest of 107 (26.7%) respondents scored ≤3.

From this study, there was a low incidence of self-perceived symptoms of POP. There were 111 (27.8%) respondents who reported having at least one of the symptoms enquired. The commonest symptom was incomplete voiding (65, 16.3%), followed by feeling something was coming down per vagina (58, 14.5%) and sense of heaviness in the vagina (51, 12.8%). The majority of the respondents (365 respondents, 91%) agreed that it is not normal to have POP symptoms. However, only 273 (68%) respondents will seek treatment if they experience POP symptoms. It was also found that the commonest reason for women not seeking treatment was unaware of the existence of medical treatment (69, 43%) and embarrassment to see a doctor (46, 28%).

Table 3 compares the mean score of the level of awareness for each of the demographic factors. There were statistically significant differences in the mean score for level of awareness between marital statuses, menopausal status, number of children and occupation. The mean score for single women is significantly lower than for married women (mean difference, MD: -0.985, 95%CI: -1.75, -0.22; p=0.004). Menopausal women had significantly higher mean score than non-menopausal women (MD: 0.79, 95%CI: 0.22, 1.35; p=0.007). It also showed that the mean score of nulliparous women is significantly lower than multiparous women (MD: -1.302, 95% CI: -2.06, -0.54; p<0.001), the mean score for nulliparous women is significantly lower than the grand multiparous women (MD: -1.520, 95%CI: -2.47, -0.57; p≤0.001). The mean score of women with a professional career is significantly higher than women with a non-professional career (MD: 1.094, 95%CI: 0.3, 1.89; p=0.002). No significant differences in the mean score between different groups of educational status and monthly income.

Table I: Demographic detail of the respondents

	Number, n (%)
Marital status	
Single	95 (24)
Married	292 (73)
Divorcee	7 (2)
Widowed	6(1)
Number of children	
Nulliparous	115 (28.7)
Para 1	29 (36.0)
Para 2-4	182 (81.5)
Para 5 or more	74 (18.5)
Attained menopause	95 (24)
Educational status	
Secondary school	50 (13)
College/university	350 (87)
Household income	
Less than RM3000[a]	117 (29)
Between RM3000 and RM5000	151 (38)
More than RM7000	132 (33)
Occupation	
Professional[b]	114 (28)
Non-professional[b]	159 (40)
Housewife/unemployed	38 (10)
Student	48 (12)
Retired	41 (10)

[a]Professional is defined as job that requires specialised knowledge and advanced skills in an area, requiring certification such as a college degree. Non-professional is defined as jobs that often manual or repetitive in nature, do not require any college degree and rely on on-job training. [b]RM is Ringgit Malaysia, which is the Malaysian's currency

Table II: Frequencies of correct answers to 10-item assessment on awareness on pelvic organ prolapse

Statement	Number, n (%)
Pelvic organ prolapse is more common in younger woman than in older women. (FALSE)	119 (29.8)
Increased number of giving birth increases the risk of pelvic organ prolapse. (TRUE)	212 (53.0)
Pelvic organ prolapse can happen at any age. (TRUE)	270 (67.5)
Certain exercise can help reduce the risk of pelvic organ prolapse. (TRUE)	315 (78.8)
Symptoms of pelvic organ prolapse may include vaginal heaviness. (TRUE)	209 (52.3)
Frequent heavy lifting can lead to pelvic organ prolapse. (TRUE)	321(80.3)
Obese women are more likely to get pelvic organ prolapse. (TRUE)	111(27.8)
Infections of the private part can cause pelvic organ prolapse. (FALSE)	82(20.5)
Pelvic organ prolapse is the descent of the uterus, bladder or rectum through the vagina. (TRUE)	211 (52.8)
Surgical removal of the uterus is the only treatment for pelvic organ prolapse. (FALSE)	133 (33.3)

DISCUSSION

This study found that the overall awareness on POP among the studied population was still inadequate, with the mean score for level of awareness was only 4.96, together with the observation of the unsatisfactory pattern of score that only about a quarter of the respondents scored a reasonably good mark of ≥8. This finding was similar to other studies that also demonstrated a similar pattern of low knowledge and awareness on POP. Just 9.1% of 331 married women in Suklagandaki municipality, Tanahun, had a clear understanding of uterine prolapse and its risk factors, according to a survey.[2] In other studies, the percentage of women who had adequate knowledge of POP range from 20% to 65%.[14-17] Although the questionnaire used to evaluate the knowledge and awareness is not standardised in all these similar studies, the similar findings still emphasise that there is a lack of awareness on POP among women, and Malaysian women are included.

Based on the assessment, the items on risk factors and treatment for POP had the lowest percentage of correct answers. Only a quarter of the respondents were aware that POP is more common among older women than younger women, it is not caused by infection, and obesity increases the risk of POP. Also, only a third of the respondents were aware that surgery is not the only treatment option for POP. These findings are consistent with a systematic review that included nineteen studies. It reported that most women have a gap in the knowledge of pelvic floor muscle dysfunctions, cannot identify risk factors for these disorders and do not understand their treatment options.[18]

Therefore, it is crucial to include information on risk factors and causes of POP during the health education programme to empower them with adequate knowledge that hopefully will translate to a healthier lifestyle to reduce their risk of developing POP. Another aspect that should be integrated into any health education programme or patient education

Table III: Comparison of mean score of the level of awareness for each of the demographic factors

	n	Mean score (SE)	t or F (df)	Mean difference (95% CI)	p-value
Marital status					
Single	95	4.21 (0.244)	3.995[a] (3)		0.008*
Divorcee	7	4.71 (1.063)			
Widow	6	5.50 (1.057)			
Married	292	5.20 (0.144)			
Menopausal status					
Yes	95	5.56 (0.241)	2.732[a] (398)	0.79 (0.22,1.35)	0.007*
No	305	4.77 (0.142)			
Educational status					
Secondary school	50	4.82 (0.301)	-0.420[b] (398)	-0.16 (-0.89,0.58)	0.675
College/University	350	4.98 (0.135)			
Income					
Less than RM3000[c]	117	4.78 (0.207)	1.040[d] (2)		0.354
RM3000–RM7000	151	4.88 (0.207)			
More than RM7000	132	5.20 (0.226)			
Number of children					
Nulliparous	115	4.06 (0.224)	9.311[e] (3)		<0.001*
Para 1	29	4.38 (0.492)			
Para 2–4	182	5.36 (0.175)			
Para 5 or more	74	5.58 (0.277)			
Occupation					
Professional	114	5.46 (0.238)	5.453[f] (3)		0.001*
Non-professional	159	4.37 (0.187)			
Housewife/unemployed	79	5.35 (0.267)			
Student	48	5.04 (0.362)			

[a]One-way ANOVA test; mean score "single" and "married" (p = 0.004) was significantly different by post hoc test Bonferroni's procedure. [b]Independent t-test. [c]RM is Ringgit Malaysia, which is the Malaysian's currency. [d]One-way ANOVA test. [e]One-way ANOVA test; mean score "nulliparous" and "Para2-4" (p<0.001) and "nulliparous" and "Para 5 or more" (p=0.001) were significantly different by post hoc test Bonferroni's procedure. [f]One-way ANOVA test; mean score "professional" and "non-professional" (p=0.002) was significantly different by post hoc test Bonferroni's procedure.

pamphlet is the treatment options for POP. Conservative management by regular supervised pelvic floor exercise sessions with a pelvic physiotherapist, biofeedback programmes and vaginal pessaries should be made known to women, apart from surgery.

This studied population had a low incidence of self-perceived symptoms of POP. However, unfortunately, there was no further question asked on whether those with symptoms have sought any treatment or not. On the other hand, most respondents agreed that it is not normal to have symptoms of POP. However, only 273 (68%) respondents will seek treatment if they experience any symptoms of pelvic organ prolapse. It is important to note that this is an assumption question because respondents do not have symptoms. This may or may not be their actual action when they really have the symptoms. However, this assessment is crucial to understand the women better in order to identify the potential barrier towards the treatment of POP.

Unawareness of the existence of medical treatment for POP (43% of women) was the most prevalent reason for not seeking treatment in this study. This is also demonstrated in a study by Hammad et al.,[19] where the unawareness of medical treatment, lack of adequate knowledge about the condition and belief that the disease is part of normal ageing are essential determinants of the treatment-seeking behaviour for POP. It reflects a lack in health promotional activities in educating women on POP and its treatment option available. The next most common reasons for not seeking treatment were an embarrassment to see a doctor. The embarrassment to discuss POP symptoms with healthcare providers was identified as one of the strongest determinants of treatment-seeking behaviour[19] and contributed to the delay in seeking medical services.[4]

The apprehension that women have to come forward and report if they have POP symptoms is understandable, given POP involves their private genital area. Discussing health problems affecting the private genital area is often a social taboo in certain communities including Malaysia. It can be overcome by creating more awareness, particularly among the family practitioner. The bonding that they have with the women can potentially provide a more trusted environment for them to seek further advice. Another significant determinant of treatment-seeking behaviour was when symptoms had interfered with their physical activities.[19] It is unfortunate as delaying treatment-seeking will only prolong their suffering with the symptoms caused by the POP. Worst, some women only present when decubitus ulcer had already formed with bleeding and infection.

A study by Jackson et al.,[11] found three common themes that mainly influence women's understanding of POP: culture, presence of barriers, and misconception. Another qualitative study among 14 women with POP awaiting surgical intervention demonstrated six factors that behave as barriers for women with POP from seeking health care. It includes the absence of information, blaming oneself, feeling ignored by the doctor, having a covert condition, adapting to successive impairment, trivialising the symptoms and de-prioritising own health.[4] It is crucial to use this information to plan any health education programme or educational materials on the POP to increase the effectiveness of the interventions.

This study also found that level of awareness is statistically significantly associated with marital status, educational status, occupation and number of children they have. Women who are married, menopausal, multiparous, and working as professionals had a higher mean score, indicating a higher level of awareness on POP than their comparative groups. No significant difference in the level of awareness in different levels of education and income groups was demonstrated. Similarly, Subedi et al.,[14] showed no significant association between the level of knowledge on POP and the level of education and type of education. However, they found a significant association between the level of awareness and the age of having the first child, which was not studied in this survey. On the contrary, a study by Singh et al.,[16] reported a significant association between the level of knowledge on risk factors of POP and the womens' education level, and also, age at first childbirth.

It is an interesting observation that the mean score is increasingly higher with the increasing number of parity. It is vital to address this by incorporating information about POP during antenatal class and emphasise that pelvic floor exercise is an excellent preventative measure that women should start practice since their first pregnancy.

This study had few limitations. It was challenging to obtain an ideal representative sample of Malaysian women. Hence, this study involved women from various NGOs in Malaysia that may represent women from the general population in Malaysia to a certain extent. The method of electronic delivery of the questionnaire limits the possibility for the researchers to track how many women received the invitation for this study; hence, the response rate could not be reported. The participation was voluntary; therefore, the risk of selection bias is unavoidable. Another limitation is that, as the women were invited to answer the questionnaires via Google Form through emails, the possibility of the participants discussing or looking up the answers cannot be excluded. The questionnaire used in this study did not undergo a rigorous validation process. However, content validation and face validation were performed, followed by a pilot study among 20 women, that at least provide some basis that the questionnaire was a reliable tool for this study.

This study provides an insight into women's understanding of POP and their attitudes towards its treatment. A multi-prong approach is crucial where active participation from Primary Care and Public Health practitioners is essential in educating women on POP. Health promotion activities and materials should include important information on POP, including its risk factors, symptoms, prevention and treatment options. These interventions should be made accessible to women, both urban and rural. Ensuring the programme and materials are culturally appropriate is essential to facilitate engagement with women and increase acceptance.

It is known that discussing pelvic floor problems, including POP, may still be taboo for certain groups of women. Hence, raising awareness and normalising discussion on this topic may hopefully open the doors to women who wish to inquire more on POP or seek treatment. A dedicated walk-in clinic for women to attend for various women's health issues, including POP, can be a good platform to encourage women to come forward for consultation or assessment. Approachable healthcare practitioners may reduce the anxiety or fear among women to seek help.

CONCLUSION

In conclusion, most of the respondents have an inadequate level of awareness of pelvic organ prolapse. Though more than half of the respondents will seek treatment if they experience pelvic organ prolapse, the remaining who will not seek treatment should not be ignored. Among the common reasons for not seeking pelvic organ prolapse treatment include unawareness of the availability of medical treatment followed by embarrassment to see medical practitioners.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Comparison of pineapple juice and mannitol as oral contrast agents for magnetic resonance enterography

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ABSTRACT

Introduction: We aimed to compare the degree of bowel distension and image quality between pineapple juice and different mannitol concentrations, as well as patients' acceptance and side effects of these different magnetic resonant enterography (MRE) oral contrast agents.

Materials and Methods: Seventy-five participants underwent MRE as an initial investigation or follow-up for inflammatory bowel disease. A systematic sampling method was used to divide the participants into three different groups: group 1 received 6.7% mannitol concentration, group 2 received 3.3% mannitol concentration and group 3 received pineapple juice as an oral contrast agent during their MRE examination. The degree of bowel distension on MRE images was assessed by a radiologist by measuring the bowel diameter from inner wall to inner wall at specified levels, while qualitative analysis was evaluated based on the presence of artefacts. All patients were asked to score their acceptance of the oral contrast and were asked about side effects such as diarrhoea, abdominal discomfort and vomiting.

Results: All patients were able to completely ingest 1.5L of oral contrast. The mean diameter of bowel distension was 2.1cm in patients who received 6.7% mannitol concentration, 2.0cm in patients who received 3.3% mannitol concentration and 1.6 cm in patients who received pineapple juice. Two-thirds of patients who received 6.7% mannitol and 3.3% mannitol solutions had good-quality MRE images, but 68% of patients who received pineapple juice had poor-quality MRE images. Twenty-four patients (96%) who received pineapple juice rated it as slightly acceptable and acceptable but only 12 patients (48%) who received 6.7% mannitol solution rated it as slightly acceptable and acceptable. Eighty-eight percent of patients who received 6.7% mannitol solution experienced at least one form of side effect as compared to 44% of patients who received 3.3% mannitol solution and 18% of patients who received pineapple juice.

Conclusion: Optimum small bowel distension and good image quality can be achieved using 3.3% mannitol concentration as an oral contrast agent. Increase in mannitol concentration does not result in significant improvement of small bowel distension or image quality but is instead related to poorer patient acceptance and increased side effects. Pineapple juice is more palatable than mannitol and produces satisfactory small bowel distension. However, the small bowel distension is less uniform when using pineapple juice with a considerable presence of artefacts. Mannitol, 3.3% concentration, is therefore recommended as an endoluminal contrast agent for bowel in MRE.

KEYWORDS:
Oral contrast, magnetic resonance enterography, mannitol, pineapple juice

INTRODUCTION

The small bowel represents the largest section of the human digestive tract. Due to its length, small diameter and the variety of pathologic changes, this region often presents a diagnostic challenge. The most frequently encountered disorders include acute and chronic inflammatory processes along with their complications. Some diseases, such as Crohn's disease can cause mucosal changes like wall thickening, ulcerations, wall nodularity or areas of stricture. Others, such as lymphoma, may cause abnormal dilatation. Tumours of the small bowel are usually single but may be multiple, particularly in certain syndromes such as familial polyposis. Most small bowel diseases have similar signs and symptoms which are non-specific, for example, abdominal pain, diarrhoea, anorexia, and loss of weight, which make it difficult to diagnose by clinical examination alone.

A large variety of invasive and non-invasive diagnostic methods are available to assess the small bowel. However, despite the development of modern endoscopic techniques[1], radiological imaging remains central for diagnosis and therapeutic monitoring. Magnetic resonance enterography (MRE) is a specialised magnetic resonance imaging (MRI) technique which uses a biphasic oral non-absorbable contrast agent to assess the small bowel. MRE has been proven to be equivalent to computed tomography enterography (CTE) in evaluating the small bowel but has the added advantage of being non-ionising.[2]

An adequate degree of bowel distension is important for optimal imaging of the small bowel. Collapsed bowel segments may result in false negative or false positive results where small areas of abnormalities may be missed. Volumen® (E-Z-EM Canada), a mannitol-based solution, is currently the most frequently used oral contrast agent for

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MRE, but there has been a shortage of supply in our local setting due to logistic factors. Therefore, there has been a demand for an alternative oral contrast agent.

Several studies have described experiences using various types of oral contrast agents for MRE, from mannitol-based solution, barium-based solution to a natural solution such as pineapple juice.[3-10] There are only a few studies comparing the different filling methods, and to the best of our knowledge, there is no study which draws a comparison between different mannitol concentrations and pineapple juice. The main objective of this study was to compare the effectiveness and patient acceptability of pineapple juice, a proven natural oral contrast agent for MRE,[5] with different mannitol solution concentrations, that are both easily available in our setting, in patients undergoing MRE. Specifically, the study aimed to compare the degree of bowel distension and image quality between pineapple juice and different mannitol concentrations, as well as patients' acceptance and side effects of these different oral contrast agents.

MATERIALS AND METHODS

The local Institutional Research and Ethics Committee approved this case–control study which was carried out for a 1-year duration at a tertiary teaching hospital. Informed consent was obtained from the patients who agreed to participate in this study. A total of 75 participants were enrolled (38 women and 37 men; age range 14-71 years). All participants underwent MRE as an initial investigation or follow-up for inflammatory bowel disease (IBD).

a) Sampling

The systematic sampling method was then used to divide the participants into three different groups (groups 1, 2 and 3), which would determine the type of oral contrast agent that they would receive during their MRE examination. Each patient consumed only one type of oral contrast. The oral contrast agents that were given were as follows:

(1) 6.7% mannitol concentration was given to patients in group 1 (500ml 20% W/V mannitol mixed with 1000ml of water),
(2) 3.3% mannitol concentration was given to patients in group 2 (250ml 20% W/V mannitol mixed with 1250ml of water), and
(3) pineapple juice was given to patients in group 3 (500ml of pure ready-made pineapple juice mixed with 1000ml of water).

Patient Preparation

All MREs were performed on a 3T Verio and a 1.5T Verio MRI scanner (Siemens). Patients fasted for at least 6 hours before the procedure and were required to ingest a total of 1.5 litres of oral contrast in 1 hour, taken in three separate doses. The first 600 ml was taken 1 hour before the scan, the second 600 ml was taken 30 minutes before the scan and the final 300ml was taken just prior to scan.

Procedure

Three sets of scans were performed, and IV hyoscine 10mg or IV glucagon 0.25mg was given in between the sets to reduce bowel movement. IV gadolinium was given after the second set of the scan. Images were acquired in the axial and coronal planes. Multiple MRI sequences were used, namely T2 steady-state coherent, T1 spoiled 3D GRE variant and T2 echo-planar fast spin echo sequences. The summary of the scanning protocol is shown in Figure 1.

At the end of the procedure, patients were asked to score their acceptance of the oral contrast ranging from 1 (unacceptable) to 5 (acceptable). Within a week, the patients were contacted by phone and were asked about any side effects of the oral contrast given. Three main symptoms were asked: diarrhoea, abdominal discomfort and vomiting after they received the oral contrast agent.

Image Analysis

The degree of bowel distension on the MRE images was assessed by a senior radiologist, who was blinded to the type of oral contrast agents, by using T2 steady-state coherent coronal images. Quantitative analysis of small bowel distension was performed by measuring the bowel diameter from inner wall to inner wall at the following specified levels:

(1) at the second part of duodenum (D2) for assessment of duodenum,
(2) at the level of superior mesenteric artery for assessment of jejunum,
(3) at the level of S1 vertebra for assessment of ileum, and
(4) at the right iliac fossa for assessment of terminal ileum.

The bowel loops with the largest diameter were selected for measurement at each level, with a total of four measurements for each patient.

Meanwhile, qualitative analysis of bowel distension was carried out by the same radiologist based on the presence of artefacts, particularly chemical shift artefacts, or the amount of bowel collapse. Scored of a three-point scoring system were given as follows: 1=Poor (presence of artefacts/collapsed bowel in >70% of the small bowel); 2=Fair (presence of artefacts/collapsed bowel in 30-70% of the small bowel); and 3=Good (presence of artefacts/collapsed bowel in <30% of the small bowel). Examples of images with their respective scores are shown in Figure 2.

Statistical analysis was performed using SPSS version 26.0. A comparison between all three solutions in terms of bowel dilatation, image quality, patient acceptance and side effects were made using two-way ANOVA, and a comparison between two solutions was made using t-test. P value of <0.05 was considered to be significant.

RESULTS

Bowel Distension

All patients were able to completely ingest 1.5 L of oral contrast before the scan. Quantitative analysis of the bowel distension showed the highest and most uniform bowel distension in patients who received 6.7% mannitol concentration (mean diameter of 2.1cm), followed by patients who received 3.3% mannitol concentration (mean diameter of 2.0cm). Patients who received pineapple juice as oral contrast showed the poorest degree of bowel distension, most noticeably involving the distal small bowel (mean

Table I: Mean diameter of different segments of the small bowel.

Oral contrast agent	Mean diameter of small bowel (cm)				
	Duodenum	Jejunum	Ileum	Terminal ileum	Overall
6.7% mannitol concentration	2.1	2.1	2.1	2.1	2.1
3.3% mannitol concentration	2.0	2.0	2.1	1.9	2.0
Pineapple juice	1.7	1.8	1.5	1.5	1.6

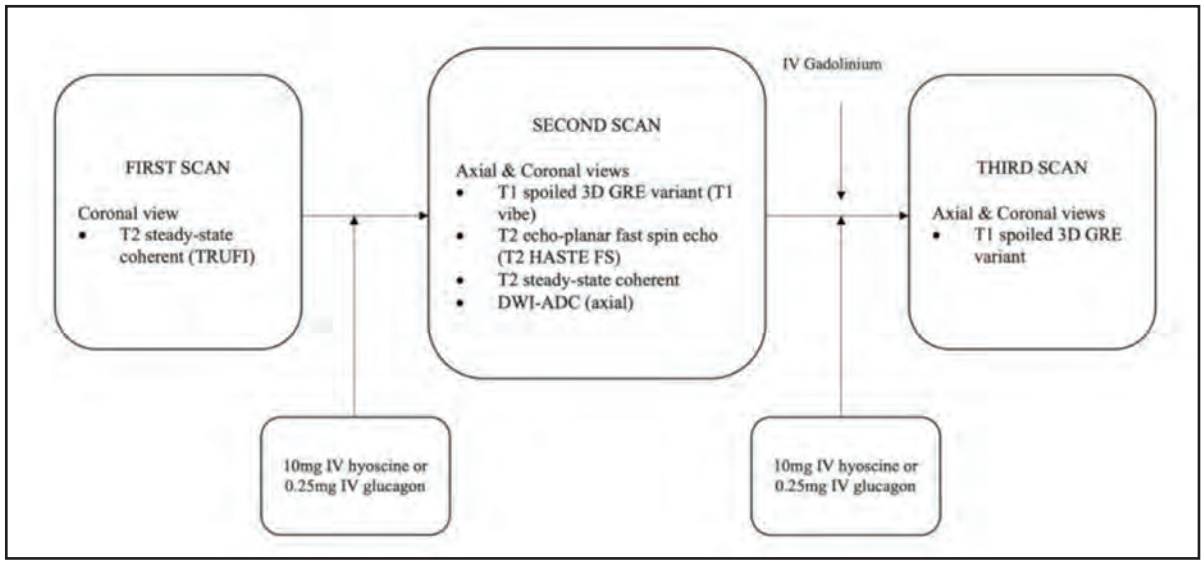

Fig. 1: Summary of the MRE scanning protocol.

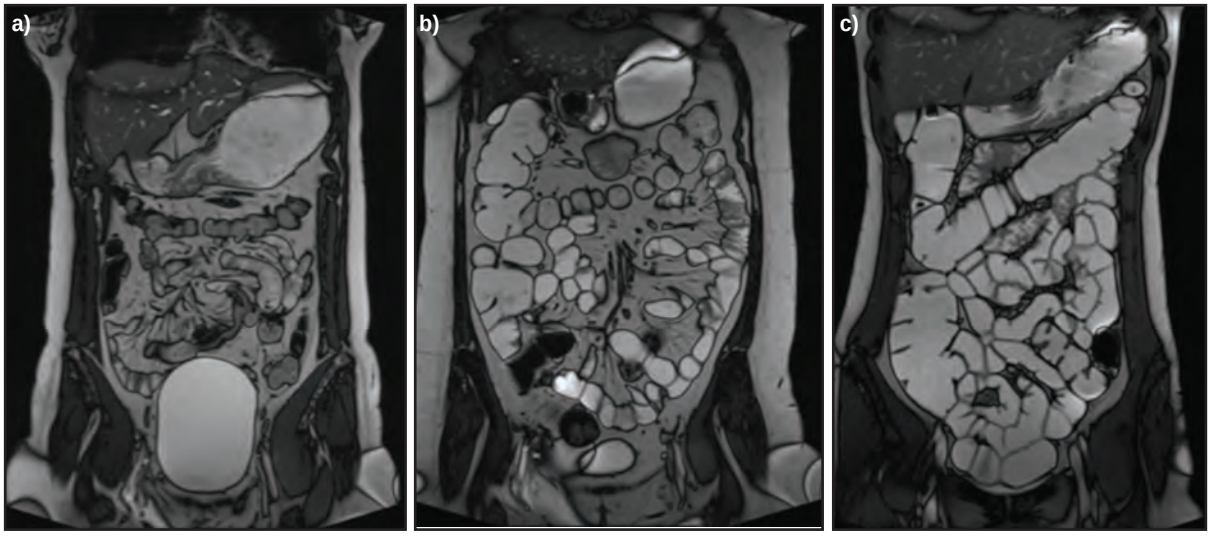

Fig. 2: (a-c) Example of images on coronal T2 steady-state coherent with (a) score 1, (b) score 2 and (c) score 3.

diameter of 1.6cm). The mean diameter of the different segments of the small bowel is shown in Table I.

There was a significant difference in the degree of small bowel distension between the three oral contrast agents in all segments of the small bowel ($p \leq 0.01$) (Figure 3). Specifically, there was a significant difference between 6.7% mannitol and pineapple juice, and between 3.3% mannitol and pineapple juice in all small bowel segments ($p \leq 0.04$). However, there was no significant difference in the degree of bowel distension in patients who received 6.7% mannitol and 3.3% mannitol for all segments of the small bowel (p=0.11-0.88).

Image Quality

The quality of MRE images in patients who were given 6.7% mannitol and 3.3% mannitol solutions was superior to pineapple juice. The MRE images were scored as 3 (i.e. good) in 64% of patients who received 6.7% mannitol and 3.3% mannitol solutions, respectively. Only less than 10% of MRE

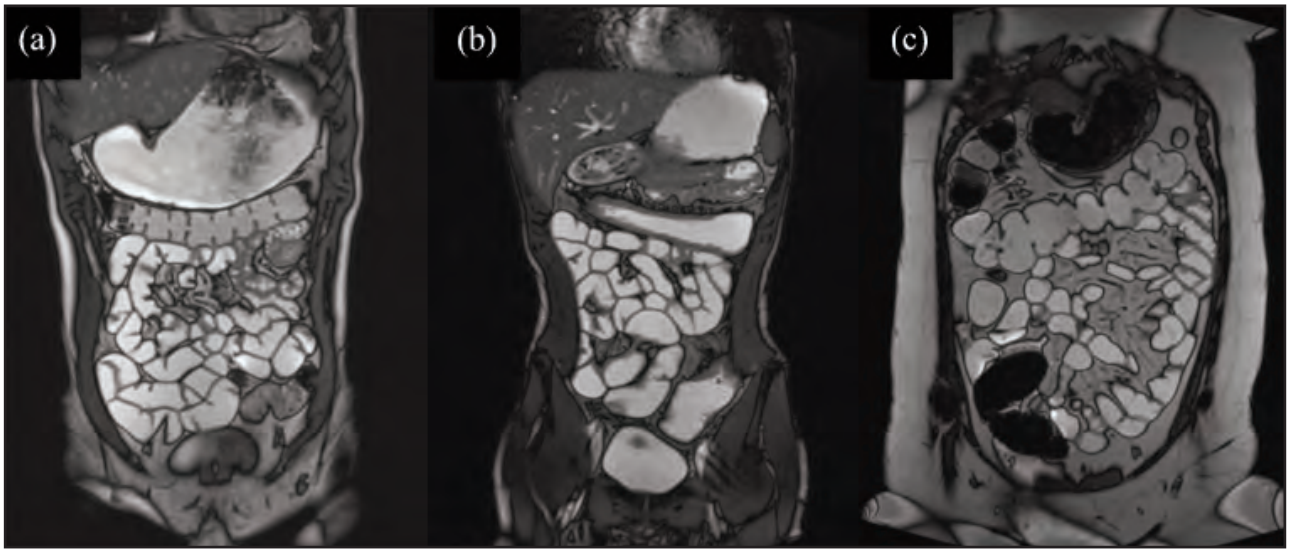

Fig. 3: (a-c) T2 steady-state coherent coronal images demonstrating different bowel distension between (a) 6.7% mannitol, (b) 3.3% mannitol, and (c) pineapple juice.

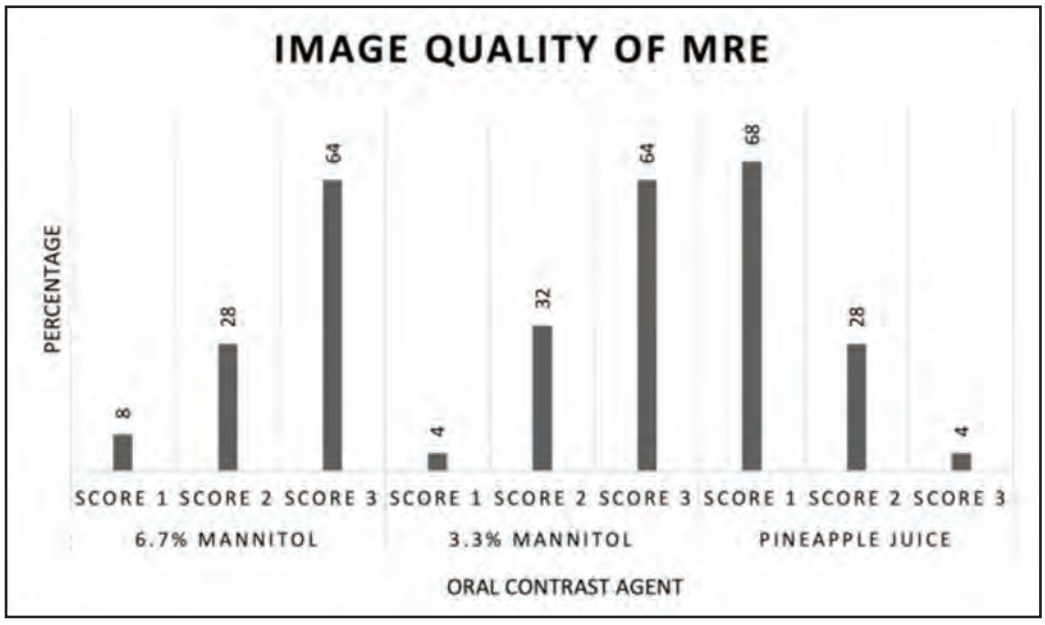

Fig. 4: Distribution of image quality scores of different oral contrast agents.

images in these two groups were scored as 1 (i.e., poor). On the contrary, 68% of patients who received pineapple juice had MRE images which were scored as 1 (i.e., poor) with only 4% had MRE images which were scored as 3 (i.e., good). The distribution of image quality scores of each oral contrast agent is shown in Figure 4.

All three solutions showed a significant difference in image quality ($p \leq 0.01$), where there is a significant difference in the image quality between the two mannitol solutions and pineapple juice ($p<0.01$, respectively). However, no significant difference was found in the image quality between 6.7% mannitol and 3.3% mannitol ($p=0.82$).

Patients' acceptance

Patients who received pineapple juice as oral contrast gave higher acceptance scores as compared to those who received mannitol. Twenty-four patients (96%) who received pineapple juice rated it as 4 (slightly acceptable) and 5 (acceptable). Among patients who received 6.7% mannitol solution, only 12 patients (48%) rated it as 4 (slightly acceptable) and 5 (acceptable). Three patients (12%) rated it as 2 (slightly unacceptable) and 1 (unacceptable) while 10 patients (40%) rated it as 3 (neutral). Most patients who received 3.3% mannitol found it to be slightly acceptable, with 20 patients (80%) rating it as 4, while five patients (20%) rated it as 3 (neutral) and 2 (slightly unacceptable).

Side Effects

Side effects such as vomiting, diarrhoea and abdominal discomfort were more common in patients who received 6.7% mannitol solution as oral contrast; 88% of them experienced at least one form of side effect as compared to 44% of patients who received 3.3% mannitol solution and 18% of patients who received pineapple juice. Diarrhoea was the commonest side effect among patients who received 6.7% mannitol solution (17 patients), while vomiting was the commonest side effect among patients who received 3.3% mannitol solution (5 patients). None of the patients who received pineapple juice experienced vomiting; the commonest side effect in this group was abdominal discomfort (3 patients).

DISCUSSION

MRE is one of the excellent methods to investigate small bowel pathology such as IBD, but it needs to be done using the correct type of oral contrast, suitable oral contrast volume, proper timing of oral contrast administration and correct image acquisition.[11] Advantages of MRE include superior soft tissue characteristics and nonionizing, which is very beneficial in young patients with Crohn's disease who will require multiple repeated examinations.[3] Many oral contrast agents have been studied, including the different mannitol concentrations, milk, water and even pineapple juice.[3,5] The ideal oral contrast for assessing endoluminal pathology must produce good bowel distension and image quality by demonstrating good contrast between bowel wall and bowel content.[12,13]

Mannitol solution is generally accepted as an oral contrast agent for MRE due to its non-absorbable and non-metabolized properties.[14] Small bowel distension was most optimal in our patients who received 6.7% and 3.3% mannitol concentrations as compared to those who received pineapple juice. The mean distension for both mannitol concentrations was 2.1cm and 2.0cm, respectively, which is comparable to published literature which used 3% mannitol concentration.[14] There is no significant increase in the degree of bowel distension despite an increase in mannitol concentration. The small bowel distension achieved using mannitol in this study is superior to published literature, which used water, juice and milk as oral contrast agents.[5]

Pineapple juice is a natural manganese-containing agent that has been shown to produce satisfactory results when used as an oral contrast agent in abdominal MRI.[5,15,16] The mean small bowel dilatation in patients who received pineapple juice in our study was 1.6cm, similar to the published literature done by Elsayed NM et al., in 2015.[5] Distension of ileum and terminal ileum was poorer in this group of patients, with significantly inferior image quality compared to those in the mannitol group, which was not observed in other studies.[15,16] A possible explanation for this is that the manganese concentration of the pineapple juice that was given to our patients was not quantified, and this is one of the limitations of our study. Our study used commercially available pineapple juice which was diluted in 1000 ml water to make it more palatable, which could affect the manganese concentration. Reported manganese concentration levels of 2.76mg/dl and 12.7mg/dl have been shown to produce good image quality.[15,16]

To our knowledge, there is no specific diameter to determine acceptable bowel distension. In order to get an adequate bowel distension for diagnosis, the absorption of water molecules needs to be delayed by adding some additives such as sorbitol or mannitol.[3] However, this will lead to water retention in the bowel, thus causing adverse effects such as vomiting, diarrhoea and abdominal discomfort as observed in our subjects who received mannitol as the oral contrast agent.

In our study, the subjects involved were either suspected to have IBD or follow-up patients. Based on a systematic review by Dominik et al., the degree of bowel distension is depending on a few factors such as the presence of bowel wall thickening, fibrosis, and strictures as a result of chronic inflammation in IBD.[17] Although these conditions may affect the result of our study, the measurement of bowel distension is made at the widest and non-affected bowel segment.

We noticed that poor image quality is mainly due to poor bowel distension and the presence of chemical shift artefact. Chemical shift artefacts occur due to spatial misregistration of fat and water molecule, which can frequently present in abdominal MRI, particularly involving the water in the bowel lumen and the surrounding mesenteric fat. Poor bowel distension causes clumping of the bowel, and with the presence of air within the collapsed bowel lumen, the diagnostic quality of the image will be degraded.

Overall, our patients rated pineapple juice as the most palatable oral contrast agent with the least side effects. Patients who received 6.7% mannitol experienced the most side effects, particularly diarrhoea which was experienced by 68% of them, followed by abdominal discomfort and vomiting which were experienced by 56% and 28% of patients, respectively. These adverse effects are significantly lesser (p=0.02) for the lower mannitol concentration (3.3%), which shows only 40% of the patients had mild symptoms of either vomiting, diarrhoea and abdominal discomfort. To reduce the possibility of overlapping symptoms from the underlying IBD, close monitoring within a 1-week duration is made, where we assume the symptoms within this period are likely attributed to the oral contrast given.

Based on our observation, most of the patients who received mannitol as oral contrast showed distended stomach which can lead to vomiting. Therefore, a proper measurement of bowel capacity should be considered to reduce vomiting as a side effect. Mannitol is a type of sugar alcohol used as a sweetener and medication,[18] thus it produces a sweet taste and was well-tolerated by subjects. However, because of its high incidence of side effects, most of the subjects gave a lower score for acceptance, especially for 6.7% mannitol solution.

Another limitation of this study is that we only use one radiologist to evaluate our MRE images in a limited time as we have a limited experts on reading MRE images in our local setting.

CONCLUSION

Small bowel distension and image quality are better with mannitol than with pineapple juice. Optimum small bowel distension and good image quality can be achieved using 3.3% mannitol concentration as an oral contrast agent. Increase in mannitol concentration does not result in significant improvement of small bowel distension or image quality but is instead related to poorer patient acceptance and increased side effects. Pineapple juice is more palatable compared to mannitol and produces satisfactory small bowel distension. However, the small bowel distension is less uniform when using pineapple juice with a considerable presence of artefacts. Therefore, a 3.3% mannitol concentration, which is widely available, should be the preferred endoluminal contrast agent for MRE.

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FINANCIAL DISCLOSURE

This research has not received specific aid from agencies of the public sector, commercial sector or non-profit entities.

CONFLICT OF INTEREST DISCLOSURE

The authors declared no conflict of interest.

MAIN POINTS:

- MRE is a specialised MRI technique which uses a biphasic oral non-absorbable contrast agent to assess the small bowel and has been proven to be equivalent to CTE in evaluating the small bowel but has the added advantage of being non-ionising.
- The ideal MRE oral contrast for assessing endoluminal pathology must produce good bowel distension and image quality by demonstrating good contrast between bowel wall and bowel content.
- 3.3% mannitol concentration solution is the preferred MRE oral contrast agent as it is widely available, produces optimal bowel distension and good image quality with fairly good patient acceptance and moderate side effects.

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ORIGINAL ARTICLE

Prevalence of Prolonged Grief Disorder (PGD) among bereaved relatives in a Malaysia Palliative Care Unit (PCU)

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ABSTRACT

Introduction: Prolonged grief disorder (PGD) is a diagnosis characterised by severe, persistent and disabling grief beyond 6 months post-death of a loved one. The new text revision of DSM-5 (DSM-5-TR) approved a new diagnosis PGD on March 2022. In Malaysia, PGD is not routinely screened in healthcare settings and hence goes untreated. The aim of this study is to identify prevalence and factors related to PGD among bereaved relatives whose loved ones had access to PCU services.

Materials And Methods: A cross-sectional study involving bereaved individuals in Palliative Care Unit Hospital Selayang. Participants (n=175) were recruited through telephone, and a validated tool Prolonged Grief Disorder Scale (PG-13) was asked to identify PGD. Further data collected were concomitant stressors in life and support system in the bereaved individual.

Results: Prevalence of PGD was 2.9% (n=5), and subthreshold PGD was 4% (n=7). A model of multiple logistic regression calculated most of the traditional risk factors were not significant except having an increased responsibility as a single parent after passing of a spouse or loved one, had 10 times increased odds of PGD (Odds Ratios: 10.93; 95% Confidence Interval: 2.937, 40.661). Otherwise, immediate family support (80%), religion (60%) and community (40%) support were the top three coping mechanisms of our PGD cohort, although they were not significant in a multiple logistic regression model.

Conclusion: Our PGD percentage may not be as high as those of other countries, but nonetheless they exist and their needs are just as important. The authors hope that this paper may create an awareness among the healthcare clinicians about PGD in our society, for a greater access of service to understand them and better public awareness.

KEYWORDS:
Prolonged grief disorder; complicated grief; grief and bereavement; palliative care; prevalence

INTRODUCTION

Grief is described as a central experience in response to the loss of something loved and valued.[1] It is deemed a normal reaction when referring to distress of an individual resulting from bereavement[2] and consequences of bereavement will vary for each individual.[3] A bereaved individual experience a sense of losing control, and an intense distress, anxiety, yearning, sadness, fear, loneliness and preoccupation.[4,5]

Despite the fact that bereavement can be highly distressing, most individuals are resilient and have sufficient internal resources and external support to adequately cope with their grief. Even though it is associated with a period of acute suffering, over time most people slowly readjust. They adapt to a life without the deceased without adverse health-related effects.[6]

Adapting from Tonkin's model growing around grief; making new friends, having new experiences and beginning to look forward are examples of 'growing around grief'.[7] There will be times when the bereaved would experience grief with such intensity like it has just happened, while trying to get on with life- is a normal concept. But through time, they will find ways to keep the memory of the person who has died, while at the same time moving forward with their lives.

The dual process model or Stroebe's dual process model of coping describes grief as a process of moving between two modes of functioning- the 'loss orientation', where people focus on the emotions (usually sad and difficulty) associated with their loss. And on the other hand, the 'restoration orientation', where people focus on the demands of reorganising their lives and returning to everyday tasks and issues. It is only when the bereaved gets trapped in either one mode, that a problem may arise.[8]

For some, they experience notable dysfunction for atypically long periods of time following a significant loss, which is known as prolonged grief disorder (PGD).[9] World Health Organization (WHO) described its core symptoms as a pervasive yearning for the deceased or persistent preoccupation with the deceased accompanied by intense emotional pain (e.g., sadness, guilt, anger, denial, blame, difficulty accepting the death, feeling one has lost a part of one's self, an inability to experience positive mood, emotional numbness, difficulty in engaging with social or other activities).[10] Individuals suffering from PGD find it difficult to engage in social or enjoyable activities, a reduced ability to experience positive mood and difficulties accepting the death of their loved. These disturbances cause significant debilitating lifestyle in personal, family, social, educational,

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occupational or other important areas of functioning.[10] A time frame of at least six months is proposed to allow natural grief reactions in the setting following death of a significant someone and clearly exceeds expected social, cultural or religious norms for the individual's culture, may be assigned a diagnosis of PGD.[9]

PGD can lead to medical complications associated with severe mental and physical health problems and even suicide.[11] Neimeyer et al.,[12] observed bereaved individualsin in the PGD cohort reported higher utilisation of medical services.

PGD was formally included in the 11th revision of the International Classification of Disease (ICD-11) in 2018. In 2020, the American Psychiatric Association approved a new diagnosis of PGD, and release the new text revision of DSM-5 (DSM-5-TR), on March 2022.[13] It has a more specific criteria and required the occurrence of a persistent and pervasive grief response characterised by persistent longing or yearning and/or preoccupation with the deceased accompanied by at least 3 of 8 additional symptoms that include disbelief, intense emotional pain, feeling of identity confusion, avoidance of reminders of the loss, feelings of numbness, intense loneliness, meaninglessness or difficulty engaging in ongoing life. The difference with the diagnosis by DSM-5-TR is the duration of death of the loved one at least 12 months and not 6 months.

Researchers have found symptoms of PGD to be similar symptoms as found in other mental disorders. Thus, the inclusion of the diagnostic criteria for PGD in DSM-5-TR helps clinicians use a common standard to differentiate between normal grief and a persistent and disabling grief.

The prevalence of PGD is estimated between 7% and 10% of bereaved adults who will experience the persistent symptoms of PGD.[14-18]

In Malaysia, most healthcare facility does not have bereavement services, even less so with screening of PGD. This would be one of the first research into prevalence of PGD in Malaysia. Our differences in ethnicity and cultural background compared to the Western World or First world countries would give us a different insight as to the prevalence of PGD and identify the factors related to PGD in our population.

MATERIALS AND METHODS

The present study is a cross-sectional study involving bereaved individuals in Palliative Care Unit (PCU) Hospital Selayang. It has inpatient, outpatient and day-care services. Bereaved individuals from this centre were reached via telephone after their loved ones had passed more than 6 months for purposive sampling method.

The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) has provided ethical approval for this study on the 13th April 2021 with reference number NMRR-20-2937-55902 (IIR). Data collection from participants took a total of 9 months to complete from December 2020 up to September 2021.

Selection Criteria

The study included bereaved individuals more than 18 years old, that has lost a loved one who has been registered under PCU Hospital Selayang. Duration post-death was a minimum of 6 months who had died in the PCU ward of hospital Selayang or those that passed away at home after being terminally discharged from the same hospital.

The exclusion criteria were bereaved caregivers who experienced loss less than 6 months. Also, those that were unable to understand the study protocol and consent process.

Statistical Methods

The study is a prospective cross-sectional data collection.

Statistical data analysed using IBM SPSS Statistics Version 24. Data were entered following SPSS format and analysed using descriptive statistics for frequencies and multiple logistic regression for variable selections. The p-value of two variables were determined by Pearson correlation.

Sample Size

Sample size estimation was calculated using the local population proportion formulae.[19]

Sample size (n) without Finite Population Correction:

$$= \frac{\left(Z_{1-\frac{\alpha}{2}}\right)^2 p(1-p)}{d^2}$$

where n = sample size, Z = level of confidence, α = alpha, p = expected prevalence or proportion, and d = precision.

Prior data indicated that the prevalence of PGD was 0.1.[14] If the Type I error probability and precision are 0.05 and 0.05, respectively, a sample size of 139 is needed. However, considering an additional 20% dropout rate, the sample size is 174 participants with 80% confidence level.

Procedure

All bereaved individuals who fulfilled the inclusion criteria were recruited via telephone by 2 doctors trained for this study. The telephone calls were done independently to allow privacy. Those who gave verbal consent, proceeded to undergo series of self-reported questionnaires done through the telephone call. All participants were contacted once to complete the questionnaire.

Measures

Relevant sociodemographic data were collected from the bereaved carers as listed in Table I. A validated tool to identify PGD using the PG-13 questionnaire were administered in English or Malay language. The reliability scale for both languages using Cronbach's alpha value was 0.836 (which indicates good reliability). The validity value using Kaiser-Meyer-Olkin and Bartlett's test measure $p<0.05$ for English and Malay language.

After the questionnaire, participants were identified as PGD, subthreshold PGD and PGD not present (Table II). Furthermore, concomitant stressors present in the bereaved individuals' life that may have complicated the bereavement process are shown in Table III. Lastly, the questionnaire also looked for coping mechanisms, strengths and support systems of the participant (Table IV).

Prolonged Grief Disorder (PGD) Scale
PGD was measured using a validated and diagnostic tool; the Prolonged Grief Disorder Scale (PG-13).[9,20] It is a 13-item self-report questionnaire including PGD symptoms of separation distress; cognitively, emotionally and behavioural change at least 6 months post-loss and must be associated with significant functional impairment.

The PG-13 included eleven Likert-type questions and two "yes/no" questions, which evaluated symptoms of separation distress and other cognitive-emotional behaviours specific to PGD. The nine symptoms of PGD consist of feeling stunned, intense emotional pain, bitterness, numbness, a loss of self, trouble accepting the reality of the loss, a mistrust of others, difficultly moving on and that life is meaningless since their loss.

The eleven 5-point Likert scale from 1 (not at all) to 5 (very much). A PGD diagnoses must meet the following four criteria: (1) at least daily separation distress (score of 4+ on item 1 or 2); (2) at least five cognitive, emotional, or behavioural symptoms (score of 4+ on at least five of nine items from 4 through 12); (3) symptoms of separation distress at least 6 months after the loss (item 3) and (4) significantly impaired social, occupational, or other important areas of functioning (score of 4+ on item 13).

Furthermore, PGD subthreshold cases met three of the four PGD criteria, and on the other hand, anything below that was not inclined towards PGD.[2] The PG-13 questionnaire can be summed and used as an assessment tool to measure the severity of PGD symptoms; higher scores reflect greater symptoms of PGD.

Concomitant Life Stressors
There were some concomitant life stressors of the bereaved individual that were included in the questionnaire. These were: (1) increased responsibility as a single parent after their spouse passed on, (2) pressures from the workplace, (3) role as a caregiver for another person, (4) serious financial challenges, (5) unemployment, and (6) relationship struggles/ divorce.[21,22] Participants were asked whether they had ever experienced each of these factors during or after the death of their loved ones; to respond in a "yes/no". The survey also explored on the health of the caregivers and if they suffered from any medical illnesses which would contribute to additional stress (eg. burden of the disease, medications, doctors' appointments etc). The medical illnesses that were included were those under a follow up from a healthcare practitioner. Participants were also asked if they encountered cumulative losses that could contribute to their own grieving process. The response was a "yes/no" format and free text.

Support System/Coping Mechanisms
Participants were enquired on their existing support system or coping strategies; whether it be from their: (1) immediate family, (2) relatives, (3) community, (4) religion or (5) others. They answered in a yes/ no format and free text.

Follow-Up
Further assistance is offered in terms of a counsellor for those who needed it.

RESULTS

A total of 175 participants fulfilled the inclusion criteria and completed the questionnaire via phone call. Participants' demographics available in Table I. Participant's column was divided into overall participants that took part in this study, participants that did not have PGD, Subthreshold PGD and identified to have PGD
PGD and subthreshold PGD.

The prevalence of PGD and subthreshold PGD post-bereavement were determined using PG-13 criteria as a binary measure and presented in Table II. The results showed the prevalence of PGD was 5 out of 175 (2.9%) and subthreshold PGD was 7 of 175 (4%) bereaved individual.

Stressors in life of all the participants and its subgroups are shown in Table III anf IV. Overall, most of our participants had stressors unrelated to those mentioned or none at all. Among the risk factors asked, participants had cumulative losses (29.1%), own medical illness (24.6%) and financial issues (21.1%). Breaking down the subcategories showed cumulative losses to be more predominant in the PGD category of 40% compared to the others. Based on results presented in Table III, subthreshold PGD group had no medical illness to cope with (100%), whereas only a quarter in the no PGD group. Those with PGD carried most (80%) of the risk factor for insufficient financial resources.

Risk factors that fall less than 10% for all participants were work-related stress (9.7%), parenting-related stress (8.6%), unemployment (5.7%) and being a caregiver to another ill person (3.4%). Participants in PGD and subthreshold PGD group had higher rates of work-related stress; 40% and 14.3%, respectively. Overall parenting-related stress overall was only 8.6%, but majority of the participants with those risk factors fall in the PGD group (60%) and subthreshold PGD group (28.6%).

The results showed that being a caregiver to an ill person and unemployment was not one of the risk factors in PGD group.

In a multiple logistic regression model for PGD and subthreshold PGD with conventional risk factors (pressures from work, unemployment, financial hardships, caregiver for another person, personal relationship problems, e.g., divorce, cumulative losses, or own medical illnesses) were not found to be significant in a simple regression model. On the other hand, the estimated 10 times higher odds (Odds Ratios, OR: 10.93, 95% CI 2.937, 40.661) of developing PGD and subthreshold PGD when there is an increased responsibility as a single parent after the passing of their spouse or loved ones.

The support system of the overall bereaved participants and its subgroups (PGD not present, subthreshold PGD and PGD present) are shown in Table V. Across all groups, immediate family support is at a high ≥80% throughout, and those without PGD had the most support at 86.5%. This was followed by religion, contributing to 41.7% of our bereaved participants. Most of them were Muslim (25.7%), followed by Buddhist (16.6%), then Hindu (7.4%), Christian (4%) and others (0.6%). It is apparent that our PGD participants had religion as a second major component in their manner of coping at 60%.

Table I: Demographics of participants

Demographic	Overall (n=175)	PGD not present (n=163)	Subthreshold PGD (n=7)	PGD present (n=5)
Bereavement period (in months); Mean (SD)	9.16 (2.4)	9.16 (2.5)	9.14 (1.5)	9.2 (2.3)
Relationship with deceased; n (%)				
Father	49 (28.0)	48 (29.4)	1 (14.3)	0 (0.0)
Mother	45 (25.7)	44 (27.0)	1 (14.3)	0 (0.0)
Husband	36 (20.6)	28 (17.2)	4 (57.1)	4 (80)
Others	20 (11.4)	19 (11.7)	1 (14.3)	0 (0.0)
Siblings	12 (6.9)	12 (7.4)	0 (0.0)	0 (0.0)
Wife	6 (3.4)	5 (3.1)	0 (0.0)	1 (20)
Grandmother	4 (2.3)	4 (2.5)	0 (0.0)	0 (0.0)
Grandfather	3 (1.7)	3 (1.8)	0 (0.0)	0 (0.0)
Main caregiver; n (%)				
Yes	135 (77.1)	123 (75.5)	7 (100)	5 (100)
No	40(22.9)	40(24.5)	0 (0.0)	0 (0.0)
Very close relationship; n (%)				
Yes	159 (90.0)	147 (90.2)	7 (100.0)	5 (100.0)
Somewhat	13(7.4)	13(8.0)	0 (0.0)	0 (0.0)
No	3(1.7)	3(1.8)	0 (0.0)	0 (0.0)
Duration post-death of loved one; n (%)				
6 months	35 (20.0)	35 (20.0)	0 (0.0)	0 (0.0)
7-11 months	102 (58.3)	91 (55.8)	7 (100.0)	4 (80.0)
12 months	21 (12.0)	21 (12.9)	0 (0.0)	0 (0.0)
12-15 months	17 (9.7)	16 (9.8)	0 (0.0)	1 (20.0)

Table II: Subcategory PGD not present, subthreshold PGD, PGD

PG13 Subcriteria	Overall (n=175)	PGD not present (n=163)	Subthreshold PGD (n=7)	PGD present (n=5)
Separation distress; n (%)	73 (41.7)	61 (37.4)	7 (100.0)	5 (100.0)
Cognitive, emotional and behavioral symptoms; n (%)				
≥5/9 items from question #4-12	8 (4.6)	0 (0.0)	3 (42.9)	5 (100.0)
<5 items from question #4-12	167 (95.4)	163 (100.0)	4 (57.1)	0 (0.0)
Symptoms of separation distress ≥6months after the loss; n (%)	73(41.7)	61(37.4)	7 (100)	5(100)
Functional impairment; n (%)				
Yes	12(6.9)	3(1.8)	3(42.9)	7(100.0)
No	163(93.1)	160(98.2)	4(57.1)	0 (0.0)

Table III: Stress factors with PGD and no PGD underwent regression analyses

Stress Factors	PGD and subthreshold PGD (n=12)	No PGD (n=163)	Simple Logistic Regression		Multiple Logistic
			Crude OR (95% CI)	P Value	Adj. OR (95% CI)
Pressure from parenting-related stress; n(%)					
Yes	5 (33.3)	10 (66.7)	10.93 (2.94, 40.66)	<0.001	10.93 (2.94, 40.66)
No	7 (4.4)	153 (95.6)	1.00		1.00
Pressure from work; n(%)					
Yes	3 (17.6)	14 (82.4)	3.55 (0.86, 14.63)	0.080	
No	9 (5.7)	149 (94.3)	1.00		
Financial challenges; n(%)					
Yes	6(16.2)	31(83.8)	1.436 (1.065, 1.938)	0.018	
No	6(4.3)	132(95.7)	1.00		
Other factors; n (%)					
Yes	6(5.3)	108(94.7)	0.908 (0.768, 1.074)	0.261	
No	6(9.8)	55(90.2)	1.00		

NS: Not significant
NA: Not applicable

Table IV: Stress factors with PGD and no PGD unable to proceed with regression analyses

Stress Factors	PGD and subthreshold PGD (n=12)	No PGD (n=163)	P Value
Being a caregiver to another ill person; n(%)			
Yes	1 (16.7)	5 (83.8)	0.351
No	11 (6.5)	158 (93.5)	
Unemployment; n (%)			
Yes	0 (0.0)	10 (100.0)	>0.995
No	12 (7.3)	153 (92.7)	

Table V: Support system with PGD and non PGD

Support system	PGD and subthreshold PGD (n=12)	No PGD (n=163)	Simple Logistic Regression	
			Crude OR (95% CI)	P value
Immediate family; n(%)				
Yes	10(6.6)	141(93.4)	0.780 (0.160, 3.800)	0.759
No	2(8.3)	22(91.7)	1.00	
Relatives; n(%)				
Yes	3(4.5)	64(95.5)	0.516 (0.134, 1.977)	0.334
No	9(8.3)	99(91.7)	1.00	
Community; n(%)				
Yes	7(9.6)	66(90.4)	0.681 (0.143, 3.247)	0.630
No	5(4.9)	97(95.1)	1.00	
Religion; n (%)				
Yes	7(9.6)	66(90.4)	2.058 (0.626, 6.760)	0.234
No	5(4.9)	97(95.1)	1.00	

PGD: Prolonged grief disorder

The support from relatives is more than one-third in overall participants, with none of them being a pillar of support for those in the PGD group. On the other hand, 40% of the PGD group had community support.

The second logistic regression model included the support system (from family, relatives, community and/ or religion), which did not show any significant difference for those without PGD and those with PGD and subthreshold PGD.

DISCUSSION

The timing of this study was conducted during the height of Malaysian's movement control order (MCO) due to the global pandemic of COVID-19; as the data collection ran from December 2020 till September 2021. A cross-sectional online survey done in China in 2020, showed prevalence of PGD at a high of 37.8% among people bereaved due to COVID-19.[10] Conversely, outside of the pandemic era, the prevalence of PGD was estimated 10% in bereaved adults from a systematic review and meta-analysis.[14]

Surprisingly, despite the pandemic, our data collection showed the prevalence of PGD to be 2.9% and subthreshold PGD was only 4%. Both values were unusually low when compared to studies that were previously conducted before and during the pandemic. There are possible reasons for this, patients under PCU care have distinctive prognosis and death of a loved one is anticipated, unlike a healthy person dying from COVID-19. Being under PCU, an explanation about the prognosis and end of life would have been addressed adequately.

Another explanation would be the Asian culture in Malaysia with three major ethnicities; the Malays, Chinese and Indians. While the Chinese strategies had a strong pragmatic emphasis, the Malay and Indian strategies evolved around a religious/spiritual axis.[23] These findings add knowledge about cross-cultural perceptions regarding death. In our study, support from religion aspect was the second-highest coping mechanism for our bereaved participants.

For the Malays, who were all Muslims, the fate of the person was decided by the Will of Allah whose wishes were decreed in the Quran. The afterlife, as described in the Quran, was keenly anticipated because they believe that their life on Earth is temporary, but their life after death is permanent.23 The Islamic teaching, increased actions of making supplication (doa) for the dead; getting closer to God as they remember the deceased; being patient and accepting (redha)[24] may have alleviated their grieving process. The ethnic specific responses unique to the bereaved Malays were: frequent visits to the graves; the recitation of tahlil or 'Surah Yasseen and kenduri arwah' (i.e. Yasin and feast of spirits in English).[24]

The Chinese view death as a gate, which consciousness departs from one life and begins the journey to a new life called the *Gate of Death*. According to popular belief, the gate between the world of the living and that of the ghosts opens

on the first of the lunar July, and it remains open for the whole lunar month. Buddha taught that on this day, wondrous food offering to Buddha and Sangha, and the merits accrued may save one's parents and a remembrance of them. Furthermore, Buddhist teaching, a way to help ease the grief of separation, is to concentrate one's energies on performing Buddhist practices and acts of merits, and then dedicate the merits to all sentient beings, including our dear ones.[25]

For the Christians, death is the separation of the immortal soul and the mortal body. In other words, when a person dies, their spirit goes back to God, the body returns to dust and the soul of that person no longer exist.

On the other hand, Hindus and Sikhs among the Indians, practices the concepts of *ATMAN* (self or soul), *KARMA* (law of cause and effect), and Reincarnation. They believe that the *ATMAN* is immortal; perceiving death as a passenger to another life, not the end.[23]

What racial and religion of diverse groups teaches, are the impermanence of the physical body and there is life after death. Losing a loved one may seem more bearable knowing that they are not completely gone.

Being part of Asia, Malaysians place a strong emphasis on family connection as the major source of identity and protection against the hardships of life. The family model is an extended on including the immediate family and relatives, and loyalty to the family is expected.[26] The family model is reflected in our study, with most of our bereaved participants (86.3%) having an immediate family supporting them.

PGD has its own known risk factors which are used in complicated bereavement risk assessment tool (CBRAT), bereavement risk index (BRI) and modified bereavement risk index. In a study by Zordan et al. showed that traditional risk factors (serious financial problems, drug or alcohol dependency, cumulative losses, multiple stressful situations, seen mental health professional, medication for mental health problem, family history of mental illness, experienced the death of a parent in childhood, overly controlling parents, experienced childhood abuse or neglect) were not significant in increasing the risk of PGD.[2] Our results were not much different than theirs. To add further, during the COVID-19 pandemic, all economic losses combined across industries, Malaysia suffered a total loss of RM~1-2.4 billion per day during MCO1.0, 2.0 and 3.0.[27] The nosediving economy was the result of more than 100,000 Malaysians having loss of employment.[28] Despite this glaring fact, work-related problems, unemployment and financial issues were not significant risk factors predisposing our participants to PGD.

Increased responsibility as a parent after a spouse passes on was a significant risk factor in PGD in our bereaved participants in Malaysia ($p<0.001$; 95% Confidence Intervals: 2.937, 40.661). Even though immediate family ties and support may be present, it does not relieve the burden of being a single parent. This finding brings awareness and recognition that single parenting is challenging and as a society, we need to find measures to support single parenting families during their bereavement phase.

LIMITATIONS

There are a number of strengths and limitations pertaining to this study. A thorough demographic background of the bereaved individual; their race, gender, age, occupation and financial background could help us narrow down on how each demographic difference plays a role in bereavement within our society.

The other limiting factor would be the dialogue in which the interview was done. Our local language is the Malay language, and hence, some of the sessions were conducted in our native tongue. The validation of PG-13 questionnaire was in English and not in the Malay language, whether there be any meaning loss behind the translation cannot be excluded.

This study was done in a single centre, hence data interpretation may not represent the whole of Malaysia. Moreover, there is a large difference in number of participants between those with subthreshold PGD (n=7) and PGD (n=5) compared to those without PGD (n=163). Consequently, due to the large disproportion, it may cause false insignificance during statistical calculations.

Strength

Moving on to the strength of this study, it was able to capture PGD and subthreshold PGD in a cohort of bereaved individuals in PCU Hospital Selayang. Although reaching out to bereaved individuals may be done unofficially in hospices and palliative care unit throughout Malaysia, screening for PGD is not done. This study not only identified PGD and subthreshold PGD, but also narrowed down single parenting after a passing of a spouse to be a significant risk factor for PGD.

In addition to that, the study demonstrates a low prevalence for PGD maybe due to the support from family connection and religious beliefs of our people carrying them through grief. Another strength of this study, was the recruitment process. Compared to other studies where they encountered challenges in recruiting participants, most of our PCU bereaved individuals gave consent to participate in this study. Perhaps telephone calls made the research process more convenient for the participants. Besides, during the pandemic with MCO, most participants were at home and had spare time to answer the questionnaire. This also shows the character of Malaysians being more obliging to government officials.

Future Research

Future research should aim to develop a screening process and its risk factors predisposing them to PGD specifically for PC in our setting and to focus/fine tune on types management for better support of our local people. Being able to understand the aetiology of PGD may bring us closer to preventing PGD.

CONCLUSION

Our PGD percentage may not be as high as those of other countries, but nonetheless they exist and their needs are just as important. PGD is a debilitating disease where the person is stuck at intense levels of grief up to the rest of their life. If we are able to identify those with PGD, appropriate, timely referral and management could lead them to a more purposeful life and contribution to society. They require professional assistance and support in integrating life without their loved ones. However, due to a lack of resources, there are no support groups or dedicated counsellors for our bereaved individuals. Perhaps a different approach to our resource scarcity may be done through online counselling/therapy to support our bereaved individuals in suburban and urban areas.

The authors hope that this paper may create an awareness among healthcare clinicians about PGD in our society, for greater access of service to understand them and better public awareness.

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Self-reported bone fracture among Malaysian adults: Baseline findings of PURE Malaysia cohort study

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ABSTRACT

Introduction: In Malaysia, studies on self-reported bone fractures are scarce. Due to the fact that bone fractures may serve as an indicator of osteoporosis in the community, this study aimed to identify the factors associated with their occurrence among adults in Malaysia.

Materials and Methods: Epidemiological data for self-reported bone fractures were obtained through direct interviews using a validated questionnaire from the Prospective Urban and Rural Epidemiology (PURE) study.

Results: Of 15,378 respondents, 6.63% (n=1019) reported bone fractures, with a higher proportion of men (65.8%, n=671) than women (34.2%, n=348). Higher odds of self-reporting bone fractures were seen in males (aOR, 2.12; 95%CI: 1.69, 2.65), those with a history of injury (aOR 5.01; 95%CI: 3.10, 6.32) and those who were obese (aOR: 1.46; 95% CI: 1.13, 1.89), highly active (aOR 1.25; 95%CI: 1.02, 1.53), smokers (aOR 1.35; 95%CI: 1.11, 1.65) and alcohol consumers (aOR 1.67; 95%CI: 1.20,2.32).

Conclusion: Adopting a healthier lifestyle that includes a balanced diet and moderate physical activity is critical for weight loss, increased muscle and bone mass and better stability, which reduces the likelihood of fractures following a fall.

KEYWORDS:
Bone health, fractures, fragility, incidence, self-reported, osteoporosis

INTRODUCTION

A fracture occurs when bones cannot withstand the pressure applied to them, resulting in a crack or break. Studies have shown that fractures cause substantial functional deficits and are a significant cause of disability and disease load across all world regions.[1,2] In Malaysia, the most comprehensive study on bone fractures to date was conducted to identify the incidence of hip fractures between 1996 and 1997.[3] This study reported an incidence of hip fractures of 88 per 100,000 and 218 per 100,000 in males and females, respectively. These numbers were predicted to escalate by 3.55 times by 2050, constituting the largest increase in the Asian region. The report also projected an increase in reported fracture cases from 6,000 to 21,000 per year, costing nearly USD125 million (MYR540 million) in healthcare expenditures.[4]

The occurrence of bone fractures has been commonly associated with gender and age, as well as modifiable risk factors such as BMI, history of previous fractures, smoking and insufficient dietary calcium and vitamin D intake.[5-9] Although Malaysia is predicted to be an ageing nation by 2030 when 15% of its population is aged 60 and above,[10] little is known regarding the factors associated with self-reported bone fractures. As bone fractures may act as an indicator for the severity of osteoporosis, this study aimed to determine the prevalence of self-reported bone fractures and identify its associated factors in Malaysia's adult population.

MATERIALS AND METHODS

The Prospective Urban Rural Epidemiology (PURE) study is an ongoing investigator-led study involving 27 countries, including Malaysia, which aims to determine the impact of societal influences on the prevalence of select non-communicable diseases. Data were collected using established and validated questionnaires designated by the local researchers involved in the PURE study. The comprehensive methodology of the overall study has been detailed in previous studies.[11,12]

A total of 15,378 Malaysian adults between 35 and 70 years of age were recruited from select urban and rural areas. The potential respondents were purposively sampled through the community leaders of the sampling regions. Health screening and health promotion booths were set up in the communities' assembly halls, and attendees who were interested in participating were briefed on the study. Prior to a basic physical examination, eligible respondents were asked to sign a consent form and provide information on their medical history. Only respondents who intend to continue living in their current home for a further 4 years were selected to join this study to ensure the feasibility of long-term follow-up. All data were gathered through face-to-face interviews conducted by well-trained research assistants.

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Table I: Socio-demographic, lifestyle characteristics and events reported among Malaysian adults' population with and without bone fracture (N = 15,378)

Variables	Categories	Fractured bone/s		p-value
		Yes n (%)	No n (%)	
Age	<50	495 (7.2)	6379 (92.8)	0.010*
	≥50	524 (6.2)	7980 (93.8)	
Gender	αFemale	348 (4.03)	8277 (96.0)	<0.001**
	Male	671 (9.94)	6082 (90.1)	
Education level (n=15,367)	Low	353 (5.47)	6099 (94.5)	<0.001**
	High	666 (7.47)	8249 (92.5)	
Employment status (n=13,080)	No	315 (5.2)	5742 (94.8)	<0.001**
	Yes	624 (8.9)	6399 (91.1)	
Socioeconomic status (n=15,378)	Low	394 (6.24)	5918 (93.8)	0.009*
	Middle	521 (6.63)	7341 (93.4)	
	High	104 (8.64)	1100 (91.4)	
Marital status (n=15,329)	Currently unmarried	92 (6.01)	1440 (94)	0.292
	Currently married	926 (6.71)	12871 (93.3)	
BMI (n=15,378)	Normal	300 (6.1)	4596 (93.9)	0.115
	Overweight	521 (6.7)	7269 (93.3)	
	Obese	198 (7.4)	2494 (92.6)	
IPAQ (n=14,142)	Inactive	311 (6.0)	4859 (94.0)	0.003*
	Minimally active	281 (6.1)	4307 (93.9)	
	Highly active	333 (7.6)	4051 (92.4)	
Smoking status (n=15,213)	No	606 (5.18)	11091 (94.8)	<0.001**
	Yes	404 (11.5)	3112 (88.5)	
Alcohol consumption (n=15,334)	No	934 (6.36)	13745 (93.6)	<0.001**
	Yes	81 (12.4)	574 (87.6)	
Asthma (n=15,349)	No	952 (6.5)	13745 (93.5)	<0.001**
	Yes	67 (10.3)	585 (89.7)	
COPD (n=15,345)				
	No	1015 (6.6)	14286 (93.4)	0.513
	Yes	4 (9.1)	40 (90.9)	
Diabetes (n=15,353)	No	867 (6.5)	12404 (93.5)	0.191
	Yes	152 (7.3)	1930 (92.7)	
Hypertension (n=15,359)	No	767 (6.7)	10682 (93.3)	0.544
	Yes	251 (6.4)	3659 (93.6)	
Injuries	No	85 (7.5)	1052 (92.5)	<0.001**
	Yes	180 (30.9)	403 (69.1)	
Injury (machinery)	No	258 (15.3)	1423 (84.7)	0.032*
	Yes	4 (40.0)	6 (60.0)	
Injury (crash)	No	259 (15.4)	1426 (84.6)	0.019*
	Yes	3 (50)	3 (50)	
Injury (fall)	No	195 (13.6)	1242 (86.4)	<0.001**
	Yes	66 (25.7)	191 (74.3)	
Injury (motor vehicle accident)	No	161 (11.4)	1253 (88.6)	<0.001**
	Yes	104 (34.3)	199 (65.7)	
Injury (struck by object)	No	226 (14)	1383 (86)	<0.001**
	Yes	36 (39.6)	55 (60.4)	
Calcium intake (n=11,064)	<RNI	588 (6.6)	8307 (93.4)	0.133
	≥RNI	163 (7.5)	2006 (92.5)	

*significant at p-value <0.05, **significant at p-value <0.001, IPAQ = International Physical Activity Questionnaire, RNI = Recommended Nutrient Intake

Study Instruments

Questionnaires

The questionnaire consisted of three sections, a) Adult Questionnaire, b) International Physical Activity Questionnaire (IPAQ) and c) Food Frequency Questionnaire (FFQ). Information on socio-demographic characteristics, medical history and injuries was gathered using the Adult Questionnaire, while the IPAQ collected data on the respondents' metabolic rates (METs) in min/week. Based on MET, participants' physical activity level was categorised as inactive, minimally active or highly active. Daily calcium intake data were obtained through the semi-quantitative FFQ and were then categorised according to the recommended daily calcium intake of 1000 mg/day per the recommended nutrient intakes (RNI) for Malaysia.[13] Each questionnaire was validated and pretested as part of the study protocol prior to the start of the study. Data on bone fractures were derived from respondents' self-reporting of bone fracture incidents. They were asked if they have had a bone fracture in their lifetime and to specify the body parts that were involved.

Physical Examination

A basic physical examination was conducted to obtain each respondent's height, weight, blood pressure and blood glucose level. Height and weight were measured using the calibrated SECA 213 stadiometer (Hammer Steindamm,

Table II: Associated factors for self-reported bone fracture among Malaysian adults' population (N=8,555)

Variables	Categories	B	S.E.	OR (95% CI)	p-value
Age (years old)	<50	0.154	0.098	1.166 (0.962,1.413)	0.117
	≥50			1.0	
Gender	Female			1.0	
	Male	0.750	0.114	2.117 (1.693,2.647)	<0.001**
Education level	Low			1.0	
	High	0.164	0.106	1.179 (0.957,1.452)	0.122
Employment status	No			1.0	
	Yes	0.142	0.101	1.152 (0.946,1.405)	0.160
Socioeconomic status	Low			1.0	0.124
	Middle	-0.029	0.101	0.971 (0.797,1.184)	0.774
	High	0.316	0.181	1.371 (0.963,1.954)	0.080
BMI	Normal			1.0	0.013
	Overweight	0.178	0.103	1.194 (0.975,1.463)	0.086
	Obese	0.380	0.130	1.462 (1.133,1.885)	0.003*
IPAQ	Inactive			1.0	0.089
	Minimally active	0.056	0.109	1.058 (0.854,1.31)	0.606
	Highly active	0.221	0.104	1.247 (1.018,1.529)	0.033*
Smoking status	No			1.0	
	Yes	0.303	0.101	1.354 (1.111,1.651)	0.003*
Alcohol consumption	No			1.0	
	Yes	0.510	0.169	1.666 (1.195,2.321)	0.003*
Asthma	No			1.0	
	Yes	0.227	0.191	1.254 (0.862,1.825)	0.237
Self-reported injuries	No			1.0	
	Yes	1.612	0.118	5.013 (3.975,6.322)	<0.001**
Calcium Intake (mg/day)	<RNI	0.038	0.108	1.039 (0.84,1.284)	0.726
	≥RNI			1.0	

*significant at p-value <0.05, **significant at p-value <0.001, classification table (overall correctly classified percentage – 92.8%), Hosmer Lemeshow test = 0.066 and model fitness, R^2 = 9.6%, IPAQ = International Physical Activity Questionnaire, RNI = Recommended Nutrient Intake

Hamburg, Germany) and TANITA BC-558 IRONMAN Segmental Body Composition Analyzer (Arlington Heights, Illinois, United States), respectively. Blood pressure was taken twice after 5 minutes of rest in a seated position using the OMRON automatic blood pressure monitor (HEM-7111; OMRON Healthcare, Tokyo, Japan). The measurements were taken two times, and the average were recorded. Blood glucose readings were taken using the GlucoSure Auto Code glucometer (GlucoSure S70009; Medical Taiwan, Hsinchu, Taiwan).

Statistical Analysis

Descriptive analysis was performed for the socio-demographic characteristics of all the 15,378 adults who participated in the study. Factors associated with self-reported bone fractures were determined using multiple regression analysis. This was conducted for 8,555 respondents with the most complete data for all independent variables investigated in this study.

Ethical Approval

The protocol of this study was approved by the Hamilton Health Sciences Research Ethics Board (grant no. 101414). Local ethics approval was obtained from the Research and Ethics Committee of Universiti Kebangsaan Malaysia (UKM) Medical Center and the Research Ethics Committee of Universiti Teknologi Mara (UiTM) (project code: PHUM-2012-01).

RESULTS

Of the 15,387 respondents who participated in the study, 1,019 respondents (6.63%) self-reported a bone fracture. As presented in Table I, they were predominantly male, were less than 50 years old, had a high level of education, were currently employed and had a high socioeconomic status. Self-reported bone fractures were also more prevalent among those who were highly physically active, were smokers, consumed alcohol, had asthma and had previous injuries.

Table II displays the factors associated with self-reported bone fractures. Male respondents (adjusted odds ratio (aOR), 2.12; 95% confidence interval (95%CI): 1.69, 2.65) had two times higher odds of self-reporting a bone fracture than female respondents. Respondents who had previously sustained an injury (aOR: 5.01; 95%CI: 3.10, 6.32) had five times higher odds of self-reporting bone fractures than those who had not previously sustained an injury. Obese individuals (aOR: 1.46; 95%CI: 1.13, 1.89), smokers (aOR: 1.35; 95%CI: 1.11, 1.65) and alcohol drinkers (aOR: 1.67; 95%CI: 1.20, 2.32) were 1.5, 1.4 and 1.7 times higher odds to self-report bone fractures, respectively. In addition, respondents who reported being highly active (aOR, 1.25; 95% CI, 1.02, 1.53) were 1.2 times higher odds to have self-reported bone fractures than those who reported being inactive.

DISCUSSION

This study reveals several important findings pertaining to the factors associated with self-reported bone fractures in Malaysian adults. Male respondents and those who reported

previous injuries were more likely to self-report bone fractures. Further descriptive analysis of the respondents' previous injuries revealed that motor vehicle accidents (48.8%), falls (31.0%) and being struck by objects (16.9%) were the three most common causes of injuries resulting in self-reported fractures. This can be explained by the modes of transport used in Malaysia to commute to and from work. Men often prefer to ride motorcycles, particularly in urban areas, in order to avoid heavy traffic, whereas women typically opt to drive cars or take public transportation. [14,15] In rural areas, motorcycles are preferred due to their mobility and narrower road conditions. Studies have shown that more than 50% of road accident fatalities in Malaysia involved motorcyclists and the risk of motorcyclists suffering bone fractures is higher compared to occupants of other vehicles.[15,16]

Compared to individuals with normal BMI, this study found that obese individuals were more likely to experience self-reported bone fractures. In general, obesity has been reported to increase the risk of fractures at certain body sites while being protective against fractures at others.[17,18] Individuals with obesity have been found to be more likely to sustain fractures in the ankle, upper and lower leg regions while having a decreased risk of hip and pelvis fractures. The hip and pelvic region may be protected by the fat surrounding it, which absorbs the impact of the fall and thus reduces the risk of fracture. On the other hand, excessive stresses associated with introversion or extroversion of the ankle, as well as bending or torsion of the legs, may increase the risk of fracture following a fall in obese individuals.

Individuals who were highly active and engaged in higher frequencies of physical activity had higher odds of self-reporting bone fractures. Physical activities, which generally require intense mobility and movement that includes challenging the body's centre of gravity and balance, may increase the risk of falls and cause bone fractures.[19,20] One study found that 5-10% of all falls result in fractures, with more than 90% of hip fractures occurring as a result of a fall.[21] Additionally, it is essential to consider that highly active individuals, already acclimated to rigorous exercise routines, often allocate extended periods in their training regimens to higher-intensity activities. This prolonged engagement in high-intensity exercises can exert excessive strain on specific muscle groups, potentially leading to symptoms such as muscle fatigue, cramping, or an increased susceptibility to falls that may ultimately culminate in fractures.[22,23] Simultaneously, participating in high-impact activities and exercises, characterised by their demanding physical nature and frequent contact, further elevates the risk of fractures.

This study also revealed that smokers were more likely to self-report bone fractures compared to non-smokers. Several experimental studies on rats found that both the structure and strength of rats' femurs were lower in the group exposed to tobacco smoke.[24,25] These studies suggest that the content of tobacco smoke, particularly nicotine and polycyclic aromatic hydrocarbons, may significantly lower bone mass density, thus increasing the risk of bone fragility and fracture. These chemicals may cause changes in bone's collagen fibre composition and cross-linking, thereby altering its structure and apparent material strength properties. Any interference with the cross-linking process of bone causes poor mineralisation, leading to compromised bone-strength properties.[26,27] Thus, any injuries or falls are more likely to cause a fracture.

Alcohol consumption among this study's respondents was found to increase the odds of self-reported bone fractures. Alcohol affects bone metabolism, as it displaces the intake of other critical nutrients, particularly in long-term heavy drinkers, resulting in reduced bone mineral density. In this scenario, thinning of the bones occurs, increasing the risk of fractures due to a fall.[28,29] Another possible explanation is that drinking is often associated with altered gait and balance and the sensation known as the 'spins', which is likely caused by either alcohol's effect on inner ear function[30] or the presence of ethyl alcohol in the central nervous system, which may impair the transmission of nerve impulses at the synapse, causing deleterious effects on both the sensory and motor systems.[31] These side effects of alcohol consumption may contribute to an increased risk of fractures following a fall among those who consume alcohol.

Although inadequate calcium intake is a well-known risk factor for bone fractures, this study did not share this result, as a majority (80.4%) of the studied population reported consuming less than the 1000mg of calcium per day recommended by the RNI from the Ministry of Health (MOH).[32] The findings of this study are consistent with the reported mean daily calcium intake among the Malaysian population of 357mg/day, which is only 35.7% of the RNI.[33] Aside from the typical Asian diet, which includes the diet of Malaysia, containing fewer calcium-rich foods such as milk and cheese, these types of food are quite expensive, particularly for those with lower household incomes. According to a nutrition-based study involving 187 countries conducted by Singh and colleagues, across the 21 world regions, people living in East Asia and Oceania countries had the lowest daily milk intake, less than a quarter of a serving per day.[34] Calcium deficiency may also be attributed to the high sodium and carbohydrate content of the majority of local delicacies that are preferred and familiar to local palates, which may cause Malaysians to be less likely to choose naturally calcium-rich foods such as milk and cheese.

The main limitation in this study was the analysis based on self-reported fractures provided by study participants. Access to medical records or radiographic imaging for independent verification of the anatomical location of these fractures is not available. While self-reporting represents a useful approach for data collection in large-scale epidemiological studies, it does introduce a potential source of variability in research. The accuracy of self-reported fractures may vary, and there may be instances where fractures are either over-reported or unreported. In the study conducted by Baleanu et al.,[35] it was observed that only 14.4% of all self-reported fractures turned out to be false positives. Furthermore, despite annual follow-up, 21.3% of fractures were not reported.[36] It is worth noting that such false reporting of fractures by individuals is relatively uncommon. Another limitation that should be noted is the nature of cross-sectional study, which

limits the understanding of causal relationships between bone fractures and risk factors, especially dietary intake of calcium. Thus, future research should consider follow-up study with the utilisation of radiological methods, such as bone mineral density measurement, to ascertain the risk factors related to bone fractures.

CONCLUSION

The prevalence of self-reported bone fractures among this study's respondents was 6.63%. Among other factors, males, those who reported previous injuries and those who were obese were more likely to suffer self-reported bone fractures. Thus, based on the findings of this study, a healthier lifestyle that includes weight loss, a balanced diet, moderate physical activity, smoking cessation and reduced alcohol consumption is recommended to reduce the risk of fracture. Healthy weight loss accompanied by increased muscle and bone mass may aid in lowering the risk of fractures caused by falls.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Characterisation of admissions and readmissions after 20 days of illness among COVID-19 patients

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ABSTRACT

Introduction: There has been an observed number of readmissions after an index COVID-19 admission, including admissions after an initial home quarantine. The purpose of this study was to identify the clinical characteristics and outcomes of COVID-19 patients who were readmitted or admitted after an initial home quarantine between 21 and 90 days of illness.

Materials and Methods: This was a single-centre retrospective cohort study comprising patients admitted to a state hospital in Selangor, Malaysia, between August and October 2021. The demographic data, clinical characteristics, presenting complaints, laboratory tests, organ dysfunction, use of invasive ventilation, intensive care unit (ICU) admissions, length of hospitalisation and mortality were collected and analysed.

Results: The analysis involved a total of 195 cases. More than a quarter of the cases (52 [26.7%]) were related to the initial COVID-19 infection. Nine cases (4.6%) required mechanical ventilation, while eight cases (4.1%) were admitted to the ICU. The overall mortality was 17 cases (8.7%). Surviving patients were younger (49.5 vs. 58.4 years), less likely to have diabetes mellitus (48.3% vs. 82.4%), or chronic kidney disease (12.9% vs. 41.2%); had higher levels of admission haemoglobin (12.6 vs. 9.1g/dL) and albumin (33.0 vs. 21.0g/L); lower white blood cells (10.2 vs. 13.0 × 10^9/L), creatinine (81.2 vs. 151.9μmol/L) and C-reactive protein (18.2 vs. 135.0mg/L) at admission; less likely to have MI (6.7% vs. 23.5%), sepsis (3.4% vs. 47.1%), or acute kidney injury (3.4% vs. 17.6%) and organ dysfunction (25.3% vs. 94.1%).

Conclusion: Approximately a quarter of patients were admitted or readmitted due to direct COVID-19 complications between 21 and 90 days of illness. The baseline oxygen requirements at admission were independently associated with mortality, invasive mechanical ventilation and ICU admissions. Further research is needed to establish a risk model for patients returning to a hospital to predict their risk of post-COVID complications.

KEYWORDS:
COVID-19, SARS-CoV-2, readmission, mortality, ventilation

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in late December 2019 in Wuhan City, China.[1] Successively on 25 January 2020, Malaysia reported its first case of COVID-19.[2] On 11 March 2020, the World Health Organisation (WHO) declared COVID-19 a pandemic after more than 118,000 cases were detected in 114 countries and 4,291 people lost their lives.[3] COVID-19 is broken down into five clinical stages in Malaysia. The disease is mild in some people; however, in some, it may progress to pneumonia, acute respiratory distress syndrome and multiorgan dysfunction.[4] It also poses a wide spectrum of devastating complications like organising pneumonia (OP), venous thrombotic events especially pulmonary embolism (PE), myocardial infarction (MI), ischaemic stroke, reduction of estimated glomerular filtration rate (eGFR) and a new term coined as 'Long COVID Syndrome'.[5-11] The emergence of COVID-19 has led to a dramatic loss of human life worldwide, placing huge pressure on the healthcare systems across the world. The COVID-19 Intensive Care Unit (ICU) utilisation rate in Malaysia averaged 49.2% per day in 2021.[12] The Ministry of Health (MOH) Malaysia reported a record of 17,045 new coronavirus cases on 25 July 2021, bringing the total number of infections in the country past one million. The Delta variant was partly responsible for the surge, being more infectious and able to be transmitted more quickly compared with previous strains.[13]

There was an increasing number of readmissions after an index admission for COVID-19, including the admissions after an initial home quarantine, which posed a tremendous challenge to hospitals that were already strained and overwhelmed. The readmission rate ranged from 8% to 24% within the first six months.[14] In a study in New York, the United States of America (USA), 7.9% of patients returned to the emergency department (ED) and 4.5% of patients were readmitted within 30 days of discharge, mainly due to morbidities from COVID-19. The most common primary diagnosis of readmission was hypoxic respiratory failure (68.8%), followed by thromboembolism (12.5%) and sepsis (6.3%), with one in five (22.9%) of readmitted COVID-19 survivors died.[15] Another study from Pennsylvania, USA showed that 21% of readmissions were due to cardiac causes and 9% mortality among the readmissions.[14] A multicentre observational study in Spain reported that 11.7% of patients died during readmission.[16] The distribution of hospital resources may not be optimal due to a lack of understanding regarding the characterisation of readmitted patients. Day 20

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was the cut-off point of interest as any admission within the first 20 days would be managed differently due to the concern of infectious virus shedding and isolation, in accordance with the interim guidance from the Centre for Disease Control and Prevention (CDC).[17] This study aimed to identify the demographic and clinical characteristics of COVID-19 patients who were admitted (or readmitted) between 21 and 90 days of illness, the causes of admission (i.e., the presenting complaints and the diagnoses), the outcomes (i.e., use of invasive ventilation, ICU admission and mortality), and further description of the factors associated with the outcomes.

MATERIALS AND METHODS

Research Design

This study involved a single-centre retrospective cohort design based on the medical records of a cohort comprising patients admitted between 1 August and 31 October 2021 in Tengku Ampuan Rahimah Hospital (HTAR), Klang, Selangor, Malaysia, between day-21 and day-90 after the initial confirmed COVID-19 diagnosis. The aim of this study was to analyse the clinical characteristics of patients with COVID-19 who were admitted and those readmitted to the hospital between day-21 and day-90 after being released from home quarantine or discharged from index admission. Readmission referred to patients who were (re-)admitted after being discharged from the index hospital or low-risk quarantine centre admission for COVID-19, while admission referred to patients who were admitted for the first time after initial home quarantine for COVID-19. Only the very first encounter data that fulfilled the inclusion criteria were collected for patients with multiple admissions between days 21 and 90 of illness within the study period.

Study Population

The cohort comprised patients over 18 years old who were admitted into the HTAR medical ward between day-21 and day-90 after initial confirmed COVID-19 diagnosis. Patients who were initially under home quarantine or initially admitted to different healthcare centres and discharged were also included in this study.

Data Collection

The data were collected manually from health records and entered into the database by retrospective review of medical records. An online electronic data capture system was developed using Google Forms to collect and evaluate the patients' demographic data (age, sex, and race), clinical characteristics (comorbidity and initial COVID-19 category), presenting complaints at admission, laboratory tests, final diagnosis, organ dysfunction, use of invasive ventilation, ICU admissions, length of hospitalisation and mortality. Additionally, the patients' identifiable data were pseudonymised for anonymity purposes.

The following are several definitions pertaining to this study:

i. COVID-19 vaccination was complete if the patient had taken a second dose before the admission or readmission and had lapsed more than 14 days. Those who had never taken, only taken one dose, or taken a second dose of COVID-19 vaccine less than 14 days before the admission or readmission were grouped in the incomplete vaccination status.
ii. Initial COVID-19 category was based on the patient's worst COVID-19 clinical stage during the first 20 days.
iii. The PE and OP were diagnosed based on the computed tomography (CT) scan of thorax reported by the radiologist.
iv. Diabetes emergency and hyperglycaemia related to glucocorticosteroids were defined as DKA or hyperosmolar hyperglycaemia state or random blood glucose of more than 11 mmol/l in patients on glucocorticosteroid treatment.
v. Bacterial pneumonia was diagnosed by a physician based on the clinical presentation compatible with acute respiratory infection and consistent radiological findings, with or without a positive microbiological test.
vi. Post-COVID condition: Clinical diagnosis by the attending physician based on the symptoms that developed after acute COVID-19 infection following microbiological recovery, with the exclusion of other diagnoses that could account for the symptoms.
vii. Sepsis was defined as the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).
viii. AKI was defined as a 50% increase in the baseline creatinine level or a creatinine level greater than 177 umol/L (2 mg/dl) if the previous value was unknown.
ix. The term 'admission related to COVID-19' referred to any admission or readmission with a diagnosis that was either directly (e.g., OP, PE or post-COVID condition) or indirectly (e.g., hyperglycaemia, diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic syndrome (HHS) due to steroids administered, or any bleeding due to anticoagulant received as part of COVID-19 treatment) caused by COVID-19. A diagnosis such as MI that could not be entirely attributed to COVID-19 was not considered linked.
x. Organ dysfunction was identified using the score equal to or more than 2 scores in the individual system in the Sequential Organ Failure Assessment (SOFA) score:
    a. Respiratory: PaO2/FiO2 <300 or SaO2/FiO2 ≤220
    b. Coagulation: Platelet $<100 \times 10^3/mm^3$
    c. Liver: Bilirubin is >34 umol/L (2.0mg/dL)
    d. Cardiovascular: use of any inotrope
    e. Central nervous system (CNS): Glasgow Coma Score (GCS) is ≤12
    f. Renal: Creatinine ≥177 umol/L (2.0mg/dL)

Data Analysis

In this study, quantitative variables were expressed as median [interquartile range] or mean [SD] while categorical variables were expressed as absolute frequencies and percentages. The chi-square test and Fisher's exact test were used to compare the categorical variables while Student's t-test and the Mann–Whitney U Test were used to compare the continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were also used where $p<0.05$ was considered statistically significant. All analyses were performed using IBM's SPSS Statistics for Windows version 26.0.

Ethical Aspects

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and the

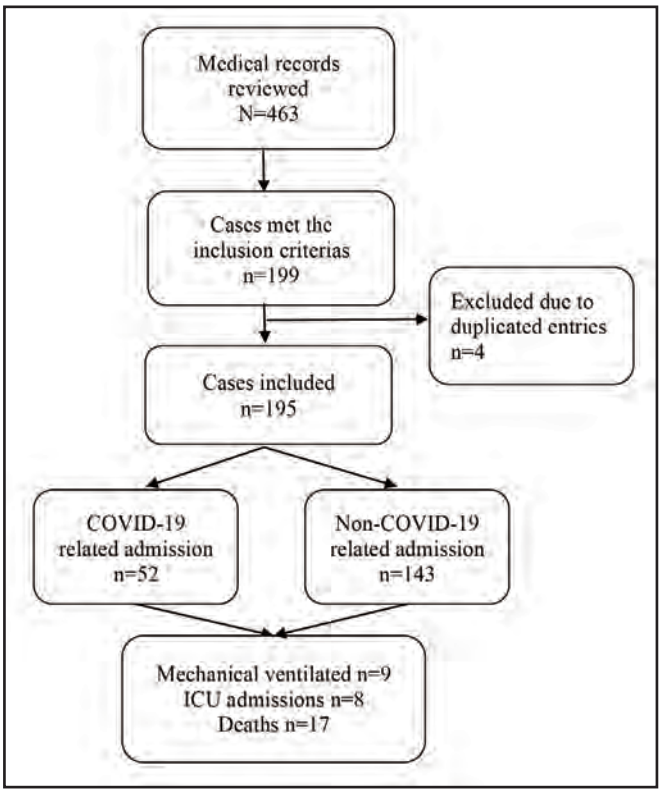

Fig. 1: Study cohort.

Malaysian Good Clinical Practice Guideline. The study had been approved by the Malaysia Medical Research and Ethics Committee (MREC).

RESULTS

From the 463 medical records reviewed, 199 cases met the inclusion criteria. After excluding four cases because of duplicated entries, a total of 195 cases were included in the analysis (Figure 1).

Baseline Characteristics

Table I shows the clinical characteristics of patients who were discharged alive compared to those who did not. The univariate analysis revealed that the surviving patients were younger (49.5 vs. 58.4 years, p=0.004). The majority of patients (153 [78.5%]) had at least one comorbidity, with a mean (SD) of 1.9 (1.4) comorbidities. Diabetes mellitus (DM) (48.3% vs. 82.4%, p=0.007) and chronic kidney disease (12.9% vs. 41.2%, p=0.007) were less prevalent among the survivors. The common symptoms at presentation were shortness of breath (91 [46.7%]), followed by chest pain (38 [19.5%]), fever (37 [19%]), and cough (36 [18.5%]). The symptoms that surviving cases were less likely to present were loss of appetite (29.4% vs. 5.1%, p=0.003) and dizziness (17.6% vs. 3.9%, p=0.045).

The surviving patients required lower baseline oxygen supplementation at admission (p=0.001); those not requiring any oxygen supplementation (65.7% vs. 29.4%), nasal prong (18.0% vs. 23.5%), face mask till high flow nasal cannulation (HFNC) (15.7% vs 35.3%), and mechanical ventilation (0.6% vs. 11.8%). They also had higher levels of admission haemoglobin (median 12.6g/dL [IQR, 10.7-14.3g/dL] vs 9.1 g/dL [IQR, 6.8-12.1g/dL]) and albumin (median 33.0g/L, [IQR, 28.0-37.0g/L] vs 21.0 g/L [IQR, 18.5-24.0g/L]), and lower levels of admission white blood cells (median 10.2 × 10^9/L [IQR, 8.3-13.4 × 10^9/L] vs 13.0 × 10^9/L [IQR, 9.6-17.8 × 10^9/L]), creatinine (median 81.2 µmol/L [IQR, 62.9-119.3µmol/L] vs 151.9 [IQR, 82.3-502.0µmol/L]), and C-reactive protein (CRP) (median 18.2 mg/L (IQR, 4.1-61.2mg/L) vs 135.0 mg/L [IQR, 52.1-202.7mg/L]). Moreover, those who survived were less likely to have MI, sepsis or acute kidney injury (AKI) as the diagnosis. Organ dysfunction was significantly lower (45 [25.3%] vs 16 [94.1%]) among the surviving patients compared to the deceased patients. Respiratory, haematology, cardiovascular (CVS), renal, and central nervous system (CNS) dysfunction was less common in survivors. Furthermore, the surviving cases were less likely to undergo invasive mechanical ventilation at admission (2.8% vs. 23.5%, p=0.004) than mortality cases.

The results further showed that approximately a quarter (52 [26.7%]) of readmission cases were related to previous COVID-19 infection but not associated with mortality. Out of 54 patients discharged with steroids during the initial COVID-19 admission, 19 (35.2%) were readmitted for bacterial pneumonia, thus showing a significant association between steroid use (19 [35.2%] vs. 18 [12.8%]; OR, 3.71; 95% CI, 1.76-7.82; p<0.001) with a diagnosis of bacterial pneumonia.

Outcome

Nine cases (4.6%) required mechanical ventilation during the admission, and eight cases (4.1%) were admitted into the ICU. The median LOS was 6 days (IQR 4-10 days) with a range of 0–64 days. Most cases (134 [68.7%]) did not have any organ dysfunction. As the primary endpoint, the majority of the patients (178 [91.3%]) were discharged alive, while the overall mortality was 17 (8.7%).

DM (8 [88.9%] vs. 92 [49.5%]) and higher initial COVID-19 category severity (categories 4 & 5) (8 [88.9%] vs. 88 [47.3%]) were more likely to have invasive mechanical ventilation (Table II). Higher oxygen requirements at admission were associated with invasive mechanical ventilation. Patients needing invasive mechanical ventilation were also associated with higher creatinine levels (median 169.0µmol/L [IQR, 82.1-367.6µmol/L] vs. 82.4µmol/L [IQR, 62.6-122.9µmol/L]), lower albumin (median 24.0g/L [IQR, 18.5-27.0g/L] vs. 33.0g/L [IQR, 26.0-37.0g/L]), and higher CRP (median 142.0 mg/L [IQR, 38.0-187.1mg/L] vs. 19.5mg/L [IQR, 4.2-67.7mg/L]). Sepsis was found to be significantly related to the need for invasive ventilation (3 [33.3%] vs. 11 [5.9%]). In terms of organ dysfunction, dysfunction in the respiratory (7 [77.8%] vs. 21 [11.3%]), cardiovascular (4 [44.4%] vs. 11 [5.9%]), renal (3 [33.3%] vs. 12 [6.5%]), and central nervous system (3 [33.3%] vs. 9 [4.8%]) required invasive ventilation more frequently.

ICU admission was noted to have an association with higher baseline oxygen requirements (Table III); no need for oxygen (0 vs. 65.2%]), nasal prong (0 vs. 19.3%), facemask till HFNC (100% vs. 13.9%) and mechanical ventilation (0 vs. 1.6%).

Table I: Baseline characteristics of patients admitted after 20 days of COVID-19 stratified by mortality

Characteristics	Patients, No. (%)			p-value
	Overall	Alive	Death	
Demographic characteristics				
Age, mean (SD), years	50.3 (15.5)	49.5 (15.7)	58.4 (10.2)	0.004**
Age >60 years	59 (20.3)	51 (28.7)	8 (47.1)	0.164
Male gender	114 (58.5)	104 (58.4)	10 (58.8)	0.975
Race				0.213
Malay	117 (60.0)	110 (61.8)	7 (41.2)	
Indian	44 (22.6)	39 (21.9)	5 (29.4)	
Chinese	26 (13.3)	21 (11.8)	5 (29.4)	
Others	2 (1.0)	2 (1.1)	0	
Foreigners	6 (3.1)	6 (3.4)	0	
Comorbidities				
Hypertension	111 (56.9)	99 (55.6)	12 (70.6)	0.234
DM	100 (51.3)	86 (48.3)	14 (82.4)	0.007**
Hyperlipidaemia	28 (14.4)	27 (15.2)	1 (5.9)	0.475
Ischaemic heart disease	33 (16.9)	30 (16.9)	3 (17.6)	1.000
CKD	30 (15.4)	23 (12.9)	7 (41.2)	0.007**
Heart failure	10 (5.1)	9 (5.1)	1 (5.9)	1.000
Cerebrovascular accident	10 (5.1)	9 (5.1)	1 (5.9)	1.000
Asthma	8 (4.1)	8 (4.5)	0	1.000
COPD	8 (4.1)	8 (4.5)	0	1.000
Cancer	5 (2.6)	4 (2.2)	1 (5.9)	1.000
Number of comorbidity				0.336
0	42 (21.5)	41 (23.0)	1 (5.9)	
1	39 (20.0)	35 (19.7)	4 (23.5)	
2	45 (23.1)	42 (23.6)	3 (17.6)	
3	44 (22.6)	38 (21.3)	6 (35.3)	
4 or more	25 (12.8)	22 (12.4)	3 (17.6)	
Smoking	46 (23.6)	45 (25.3)	1 (5.9)	0.080
Vaccination status				0.155
Incomplete	135 (69.2)	121 (68.0)	14 (82.4)	
Complete	59 (30.3)	57 (32.0)	2 (11.8)	
Initial COVID-19 category				0.182
Mild (Categories 1–3)	99 (50.8)	93 (52.2)	6 (35.3)	
Severe (Categories 4–5)	96 (49.2)	85 (47.8)	11 (64.7)	
Symptoms				
Shortness of breath	91 (46.7)	81 (45.5)	10 (58.8)	0.293
Chest pain	38 (19.5)	37 (20.8)	1 (5.9)	0.203
Fever	37 (19.0)	35 (19.7)	2 (11.8)	0.745
Cough	36 (18.5)	33 (18.5)	3 (17.6)	1.000
Reduced appetite	14 (7.2)	9 (5.1)	5 (29.4)	0.003**
Dizziness	10 (5.1)	7 (3.9)	3 (17.6)	0.045**
Day of illness at admission, mean (SD), d	42.7 (16.9)	42.8 (17.3)	41.2 (12.2)	0.612
Day 21-42	111 (56.9)	102 (57.3)	9 (52.9)	0.729
Day 43-90	84 (43.1)	76 (42.7)	8 (47.1)	
Baseline oxygen requirement				0.001**
Nil	122 (62.6)	117 (65.7)	5 (29.4)	
Nasal prong	36 (18.5)	32 (18.0)	4 (23.5)	
Face mask till HFNC	34 (17.4)	28 (15.7)	6 (35.3)	
Mechanical ventilation	3 (1.5)	1 (0.6)	2 (11.8)	
Baseline laboratory values, median (IQR)				
Haemoglobin, g/dL	12.4 (10.4-14.2)	12.6 (10.7-14.3)	9.1 (6.8-12.1)	0.001**
White blood cells, 10^9/L	10.4 (8.3-13.7)	10.2 (8.3-13.4)	13.0 (9.6-17.8)	0.032**
Platelet, 10^9/L	297 (224-370)	297 (230-374)	224 (182-317)	0.057
Creatinine, µmol/L	83.4 (63.3-127.0)	81.2 (62.9-119.3)	151.9 (82.3-502.0)	0.011**
Albumin, g/L	32.0 (26.0-37.0)	33.0 (28.0-37.0)	21.0 (18.5-24.0)	<0.001**
C-reactive protein, mg/L	21.3 (4.4-72.3)	18.2 (4.1-61.2)	135.0 (52.1-202.7)	<0.001**

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Table I: Baseline characteristics of patients admitted after 20 days of COVID-19 stratified by mortality

Characteristics	Patients, No. (%)			p-value
	Overall	Alive	Death	
Final diagnosis				
Bacterial pneumonia	45 (23.1)	40 (22.5)	5 (29.4)	0.549
OP	27 (13.8)	24 (13.5)	3 (17.6)	0.711
PE	32 (16.4)	27 (15.2)	5 (29.4)	0.164
MI	16 (8.2)	12 (6.7)	4 (23.5)	0.038**
Sepsis	14 (7.2)	6 (3.4)	8 (47.1)	<0.001**
Unstable angina	12 (6.2)	12 (6.7)	0	0.605
Heart failure	11 (5.6)	9 (5.1)	2 (11.8)	0.247
AKI	9 (4.6)	6 (3.4)	3 (17.6)	0.033**
COVID-19 relationship				0.399
Yes	52 (26.7)	46 (25.8)	6 (35.3)	
No	143 (73.3)	132 (74.2)	11 (64.7)	
Organ Dysfunction	61 (31.3)	45 (25.3)	16 (94.1)	<0.001**
Respiratory	28 (14.4)	21 (11.8)	7 (41.2)	0.004**
Haematology	16 (8.2)	10 (5.6)	6 (35.3)	0.001**
CVS	15 (7.7)	8 (4.5)	7 (41.2)	<0.001**
Renal	15 (7.7)	8 (4.5)	7 (41.2)	<0.001**
Liver	15 (7.7)	13 (7.3)	2 (11.8)	0.625
CNS	12 (6.2)	2 (1.1)	10 (58.8)	<0.001**
Gastrointestinal	3 (1.5)	2 (1.1)	1 (5.9)	0.241
Length of stay, median (IQR), d	6 (4-10)	6 (4-10)	8 (3-12)	0.877
Mechanical ventilation	9 (4.6)	5 (2.8)	4 (23.5)	0.004**
ICU admission	8 (4.1)	8 (4.5)	0	1.000

Abbreviations: SD, standard deviation; y, years; DM, diabetes mellitus; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; d, day; HFNC, high flow nasal cannulation; IQR, interquartile range; OP, organising pneumonia; PE, pulmonary embolism; MI, myocardial infarction; AKI, acute kidney injury; CVS, cardiovascular system; CNS, central nervous system; ICU, intensive care unit.

Table II: Univariable comparison of patients admitted into the hospital after 20 days of COVID-19 by need for invasive mechanical ventilation

Characteristics	Patients, n (%)		p-value
	No ventilation (n=186)	Ventilation (n=9)	
Demographic characteristics			
Age, mean (SD), years	50.3 (15.7)	50.6 (10.6)	0.957
Age >60 years	57 (30.6)	2 (22.2)	0.726
Male gender	108 (58.1)	6 (66.7)	0.738
Race			0.855
Malay	110 (59.1)	7 (77.8)	
Indian	43 (23.1)	1 (11.1)	
Chinese	25 (13.4)	1 (11.1)	
Others	2 (1.1)	0	
Foreigners	6 (3.2)	0	
Comorbidities			
Hypertension	105 (56.5)	6 (66.7)	0.735
DM	92 (49.5)	8 (88.9)	0.035**
Hyperlipidaemia	26 (14.0)	2 (22.2)	0.620
Ischaemic heart disease	31 (16.7)	2 (22.2)	0.650
CKD	27 (14.5)	3 (33.3)	0.145
Number of comorbidities			0.170
0	42 (22.6)	0	
1	38 (20.4)	1 (11.1)	
2	43 (23.1)	2 (22.2)	
3	41 (22.0)	3 (33.3)	
4 or more	22 (11.8)	3 (33.3)	
Smoking	45 (24.2)	1 (11.1)	0.688
Vaccination status			0.281
Incomplete	127 (68.6)	8 (88.9)	
Complete	58 (31.4)	1 (11.1)	
Initial COVID-19 category			0.017**
Mild (Categories 1-3)	98 (52.7)	1 (11.1)	
Severe (Category 4-5)	88 (47.3)	8 (88.9)	
Symptoms			
Shortness of breath	86 (46.2)	5 (55.6)	0.736
Chest pain	38 (20.4)	0	0.210
Fever	36 (19.4)	1 (11.1)	1.000
Cough	34 (18.3)	2 (22.2)	0.673
Reduced appetite	13 (7.0)	1 (11.1)	0.496
Dizziness	9 (4.8)	1 (11.1)	0.384

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Table II: Univariable comparison of patients admitted into the hospital after 20 days of COVID-19 by need for invasive mechanical ventilation

Characteristics	Patients, n (%)		p-value
	No ventilation (n=186)	Ventilation (n=9)	
Day of illness at admission, median (IQR), d	39.5 (28.0-56.0)	35.0 (25.0-40.5)	0.198
Baseline oxygen requirement			<0.001**
Nil	122 (65.6)	0	
Nasal prong	35 (18.8)	1 (11.1)	
Face mask till HFNC	29 (15.6)	5 (55.6)	
Mechanical ventilation	0	3 (33.3)	
Baseline laboratory values, median (IQR)			
Haemoglobin, g/dL	12.4 (10.5-14.2)	10.9 (8.2-13.5)	0.168
White Blood cell, 10^9/L	10.4 (8.3-13.9)	12.7 (8.6-13.8)	0.471
Platelet, 10^9/L	297 (224-371)	293 (200-367)	0.695
Creatinine, µmol/L	82.4 (62.6-122.9)	169.0 (82.1-367.6)	0.031**
Albumin, g/L	33.0 (26.0-37.0)	24.0 (18.5-27.0)	0.006**
C-reactive protein, mg/L	19.5 (4.2-67.7)	142.0 (38.0-187.1)	0.013**
Final diagnosis			
Bacterial pneumonia	43 (23.1)	2 (22.2)	1.000
OP	25 (13.4)	2 (22.2)	0.361
PE	29 (15.6)	3 (33.3)	0.168
MI	16 (8.6)	0	1.000
Sepsis	11 (5.9)	3 (33.3)	0.019**
Unstable angina	12 (6.5)	0	1.000
Heart failure	11 (5.9)	0	1.000
AKI	7 (3.8)	2 (22.2)	0.058
Organ dysfunction	52 (28.0)	9 (100.0)	<0.001**
Respiratory	21 (11.3)	7 (77.8)	<0.001**
Haematology	15 (8.1)	1 (11.1)	0.545
CVS	11 (5.9)	4 (44.4)	0.002**
Renal	12 (6.5)	3 (33.3)	0.024**
Liver	13 (7.0)	2 (22.2)	0.145
CNS	9 (4.8)	3 (33.3)	0.012**
Gastrointestinal	2 (1.1)	1 (11.1)	0.133
Length of stay, median (IQR), d	6 (4-10)	10 (6-23)	0.091

Abbreviations: SD, standard deviation; y, years; DM, diabetes mellitus; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; d, day; HFNC, high flow nasal cannulation; OP, organising pneumonia; PE, pulmonary embolism; MI, myocardial infarction; AKI, acute kidney injury; CVS, cardiovascualr system; CNS, central nervous system.

Respiratory dysfunction was associated with a higher incidence of ICU admission (87.5% vs. 11.2%). There was a difference in the length of stay between patients admitted into the ICU and those who did not (median, 15 days [IQR, 10-29 days] vs 6 days [IQR, 4-10 days]).

Multivariate analysis was not performed as there were under 20 cases on one side of the event for all outcomes of the study.

DISCUSSION

COVID-19 survivors are still at risk of further complications after the initial acute infectious period. This study provides insight into the clinical presentation and outcomes of COVID-19 survivors when they were admitted on day-21 to day-90 of their illness at a tertiary centre in Malaysia.

As expected, younger age is associated with better survival as older age predisposes patients to complications. Almost 80% of the cohort studied had a burden of at least one comorbidity; notably, a similar picture was seen in multicentre retrospective research done in the United States by Verna et al.[18] Our study found that diabetes is an independent risk factor for both mortality and the need for invasive mechanical ventilation in the univariate analysis, which is in line with other studies.[19-26] Diabetes is commonly associated with a pro-inflammatory state and may contribute to the risk of a more severe course of COVID-19, which may eventually lead to one's demise. However, in our study, DM was not associated with ICU admission as demonstrated in most studies. CKD also showed proportionately higher mortality in COVID-19 survivors.[27] Furthermore, the increased production but decreased clearance of pro-inflammatory cytokines contribute to high mortality in these patients. This suggests that patients with DM or CKD who were hospitalised for COVID-19 might need extra monitoring post-discharge. Initial COVID-19 severity was independently associated with the need for invasive mechanical ventilation. As the initial COVID-19 severity category was based on oxygen requirement and lung involvement, it was not surprising that it was associated with invasive mechanical ventilation for readmitted COVID-19 survivors. Therefore, more severe COVID-19 survivors may need longer inpatient pulmonary rehabilitation or a shorter interval for outpatient review post-discharge. Vaccination against COVID-19 did not confer extra protection on COVID-19 survivors that were readmitted. It was worth noting that at the time of commencement and during the length of the study, the recommended vaccination doses to be considered complete vaccination were two doses, each being 6 months apart.

Table III: Univariable comparison of patients admitted into the hospital after 20 days of COVID-19 by need for ICU admission

Characteristics	Patients, n (%)		p-value
	No ICU admission (n=187)	ICU admission (n=8)	
Demographic characteristics			
Age, mean (SD), y	50.6 (15.4)	44.0 (18.2)	0.243
Age>60y	57 (30.5)	2 (25.0)	1.000
Male gender	107 (57.2)	7 (87.5)	0.143
Race			0.762
Malay	113 (60.4)	4 (50.0)	
Indian	41 (21.9)	3 (37.5)	
Chinese	25 (13.4)	1 (12.5)	
Others	2 (1.1)	0	
Foreigners	6 (3.2)	0	
Comorbidities			
Hypertension	106 (56.7)	5 (62.5)	1.000
DM	94 (50.3)	6 (75.0)	0.280
Hyperlipidaemia	26 (13.9)	2 (25.0)	0.322
Ischaemic heart disease	31 (16.6)	2 (25.0)	0.625
CKD	29 (15.5)	1 (12.5)	1.000
Number of comorbidities			0.344
0	41 (21.9)	1 (12.5)	
1	39 (20.9)	0	
2	43 (23.0)	2 (25.0)	
3	40 (21.4)	4 (50.0)	
4 or more	24 (12.8)	1 (12.5)	
Smoking	43 (23.0)	3 (37.5)	0.395
Vaccination status			1.000
Incomplete	129 (69.4)	6 (75.0)	
Complete	57 (30.6)	2 (25.0)	
Initial COVID-19 category			0.493
Mild (Categories 1-3)	96 (51.3)	3 (37.5)	
Severe (Categories 4-5)	91 (48.7)	5 (62.5)	
Symptoms			
Shortness of breath	85 (45.5)	6 (75.0)	0.149
Chest pain	37 (19.8)	1 (12.5)	1.000
Fever	36 (19.3)	1 (12.5)	1.000
Cough	35 (18.7)	1 (12.5)	1.000
Reduced appetite	14 (7.5)	0	1.000
Dizziness	10 (5.3)	0	1.000
Day of illness at admission, median (IQR), d	39.0 (28.0-55.0)	38.5 (25.3-69.5)	0.774
Baseline oxygen requirement			<0.001**
Nil	122 (65.2)	0	
Nasal prong	36 (19.3)	0	
Face mask till HFNC	26 (13.9)	8 (100.0)	
Mechanical ventilation	3 (1.6)	0	
Baseline laboratory values, median (IQR)			
Haemoglobin, g/dL	12.4 (10.3-14.1)	13.5 (10.8-15.4)	0.489
White Blood cell, 10^9/L	10.4 (8.3-13.4)	13.8 (8.9-17.0)	0.234
Platelet, 10^9/L	298 (226-371)	236 (202-284)	0.121
Creatinine, µmol/L	81.9 (62.7-124.5)	115.8 (89.0-432.5)	0.071
Albumin, g/L	33.0 (26.0-37.0)	30.5 (19.0-41.3)	0.780
C-reactive protein, mg/L	20.3 (4.4-68.4)	87.5 (12.6-137.0)	0.206
Final diagnosis			
Bacterial pneumonia	44 (23.5)	1 (12.5)	0.684
OP	25 (13.4)	2 (25.0)	0.306
PE	30 (16.0)	2 (25.0)	0.620
MI	16 (8.6)	0	1.000
Sepsis	14 (7.5)	0	1.000
Unstable angina	12 (6.4)	0	1.000
Heart failure	11 (5.9)	0	1.000
AKI	8 (4.3)	1 (12.5)	0.320
Organ dysfunction	53 (28.3)	8 (100.0)	<0.001**
Respiratory	21 (11.2)	7 (87.5)	<0.001**
Haematology	15 (8.0)	1 (12.5)	0.502
CVS	13 (7.0)	2 (25.0)	0.118
Renal	15 (8.0)	0	1.000
Liver	14 (7.5)	1 (12.5)	0.479
CNS	12 (6.4)	0	1.000
Gastrointestinal	3 (1.6)	0	1.000
Length of stay, median (IQR), d	6.0 (4.0-10.0)	15 (10-29)	0.001**

Abbreviations: SD, standard deviation; y, years; DM, diabetes mellitus; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; d, day; HFNC, high flow nasal cannulation; OP, organising pneumonia; PE, pulmonary embolism; MI, myocardial infarction; AKI, acute kidney injury; CVS, cardiovascular; CNS, central nervous system.

Complete vaccination was shown to confer protection in the multivariate analyses in Taib et al.,[28] however, the multivariate analysis was unable to proceed in our study due to low numbers on one side of the event, i.e., mortality.

Shortness of breath was the highest reported symptom at presentation (46.7%) in our study, which was comparable to previous literature that showed 50% of patients reported respiratory distress as a presenting complaint.[29] This study demonstrated that the presenting complaint of loss of appetite was one of the main symptoms associated with mortality; further analysis showed that this was especially significant in the elderly cohort, which was consistent as they were generally presented with atypical symptoms rather than typical infectious or respiratory symptoms. Dizziness was another significant symptom among non-survivors in our study, although the number was small yet still statistically significant. However, further analysis showed that the symptom was not associated with the elderly population or hypotension. Those readmitted early (between days 21 and 42 of illness) were not shown to be associated with mortality. Nonetheless, this group of early readmitted patients was more likely to have a final diagnosis related to COVID-19 illness compared to those who were readmitted later (between days 43 and 90 of illness). This is in line with past research, which reported that COVID-19 survivors who were readmitted within 30 days of discharge mostly had the condition directly associated with COVID-19.[15]

Composite endpoints of mortality, use of invasive ventilation, and mortality were associated with those with higher baseline oxygen requirements. Baseline oxygen requirement and respiratory dysfunction were the only factors associated with ICU admission, subsequently explaining the fact that the primary criterion for ICU admission was respiratory dysfunction in that overwhelming period. Past studies showed that there is a high proportion of COVID-19 survivors with diffusing capacity for carbon monoxide (DLCO) impairment and lung injury 3 months after discharge [30] and these symptoms remain highly prevalent even 1 year after discharge.[31] The laboratory findings of higher creatinine, higher CRP, and lower albumin were found to be related to both mortality and the use of invasive mechanical ventilation. Furthermore, elevated CRP and creatinine levels as well as higher IL-6, tumour necrosis factor-α (TNF-α) and ferritin levels were found in non-survivors as compared to the survivors of COVID-19 infection.[32] Increased production and decreased clearance of pro-inflammatory cytokines by the kidney also contribute to high mortality in these patients. Hypoalbuminaemia had long been associated with poor outcomes in clinical settings.[16] As an 'inverse acute phase reactant', albumin may serve as a protective factor against cytokine storms as a result of COVID-19 pathologic sequelae. This study found that the end point of mortality was associated with the final diagnosis of sepsis, MI, or AKI. COVID-19 may cause sepsis similar to bacterial infections[33], may potentially be associated with myocardial injury leading to a type II MI,[16] linked to coronary thrombosis,[7-8] and cause eGFR reduction;[27] however, we cannot conclude a direct causal relationship. Furthermore, the cardiovascular background risks were high in our cohort, i.e., hypertension (56.9%), DM (51.3%) and ischaemic heart disease (16.9%). There was an increased risk of secondary bacterial infection in patients treated with steroids for the initial COVID-19 phase. The finding is consistent with Obata et al. who reported a higher rate of bacterial and fungal infections associated with steroid use among patients with COVID-19 infection.[34] More than a quarter of the readmitted cases were discharged with steroids, while more than one-third of these cases had bacterial pneumonia – both recorded a statistically significant association. Nonetheless, the diagnosis of bacterial pneumonia captured in our study was based on suggestive clinical and imaging features that did not necessarily yield a positive culture.

Our findings further indicated that respiratory, CVS, renal, and CNS dysfunctions were associated with mortality and the need for invasive mechanical ventilation. Haematology dysfunction was also associated with mortality. The association between respiratory, CVS, and renal dysfunction with invasive mechanical ventilation can happen in either direction. Sepsis was most likely to establish the link between haematological dysfunction and mortality. The effects of COVID-19 effects on the respiratory and renal systems had been discussed earlier, with previous research suggesting cardiovascular reactivity as a post-acute sequela of COVID-19 infection with a pronounced incidence of postural hypotension,[35] which could be the mechanism of the CVS dysfunction. Although COVID-19 also causes neurological complications, including depressed levels of consciousness, the neurological symptoms of post-acute COVID-19 are usually mild. Furthermore, the CNS dysfunction observed in our cohort could likely be influenced by numerous other factors not related to COVID-19; however, this was not further examined due to its complexity. The overall mortality rate from this study stood at 8.7%, which was comparatively lower than other studies.[15-16,18] This could owe to the possibility that the most fragile patients did not survive during the index admission.

STRENGTHS AND LIMITATIONS

This study was based on a local population and hence the characteristics compiled may stand as the predictors for local Malaysian populations. The identification of predictors and patterns of readmission will allow for the development of targeted interventions for hospitalised COVID-19 patients in their index admission as well as readmission.

There were several limitations in this study. First, we did not have the benefit of readmission rate data as the number of admission upon initial diagnosis of COVID-19 illness is unavailable. The lack of patient registry in a well-developed computerised system further made this data very difficult to compute. Second, this was a single-centre study; thus, extrapolation of the results should be done with caution. Third, the small sample size prevented multivariable analysis.

CONCLUSION

This study showed that approximately a quarter of patients were readmitted into the hospital due to direct COVID-19 complications. Age, DM and CKD were the baseline characteristics independently associated with mortality for patients who were readmitted between 20 and 90 days after

the initial COVID illness. Whereas, DM and the initial highest COVID-19 category were independently associated with invasive mechanical ventilation for this cohort of patients. Baseline oxygen requirements at admission were independently associated with all three outcomes: mortality, invasive mechanical ventilation and ICU admission. Furthermore, the laboratory findings of low haemoglobin, low albumin, high white blood cells, high creatinine, and high CRP; final diagnosis of MI, sepsis and AKI; as well as organ dysfunction of respiratory, haematology, CVS, renal and CNS were associated with poorer outcomes.

Currently, there is no established guideline on the guidance and prioritisation of care for patients with morbidity after recovering from initial discharge or home quarantine of COVID-19. Further research is needed to analyse the effect of COVID-19 on morbidity and mortality within the first 90 days of illness and beyond in local settings and to establish a risk model for patients returning to a hospital to predict their risk of post-COVID-19 complications.

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DECLARATION

This study has no conflict of interest and is not funded by any organisation.

ETHICAL APPROVAL

This study was registered with the National Medical Research Register (NMRR) and approved by the Medical Research and Ethics Committee (MREC) and the Ministry of Health (MOH). MREC Approval Letter 21-02279-AUO (1) dated 15 December 2021. NMRR ID 21-02279-AUO (IIR)

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COVID-19 vaccine safety and side effects in children aged 5-11 years: a cross-sectional study

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ABSTRACT

Introduction: The COVID-19 pandemic has prompted a global drive for vaccination, including children. Despite the urgency, understanding the safety and side effects remains crucial. Our study aimed to evaluate the safety of the Pfizer-BioNTech (BNT162b2) vaccine in children by determining the proportion of vaccinated children who experienced side effects and identifying factors associated with post-vaccination side effects.

Materials and Methods: A cross-sectional study was conducted among children who received the COVID-19 vaccine between 3 February and 8 May 2022. Data were collected using a self-administered questionnaire filled out by the parent or legal guardian.

Results: The mean age of the study participants was 9 years old and 43.1% were males. Out of the 195 participants in the study, 62 (31.8%) reported side effects after vaccination. The most frequently reported side effects were pain at the injection site (29.7%, n=58), fever (15.9%, n=31), localised inflammation (10.8%, n=21) and arthralgia/myalgia (9.2%, n=18). There were no reported severe adverse events such as anaphylaxis or myocarditis. Most side effects occurred within the first two days post-vaccination. There was a higher proportion of side effects among children with underlying co-morbidities. No significant differences were observed based on age, weight, ethnicity and the presence of allergies, or the use of premedication.

Conclusion: The BNT162b2 vaccine was generally well-tolerated in children, with most side effects being mild and self-limiting. These findings support the safety of the COVID-19 vaccine and would guide healthcare professionals, parents and policy-makers in making informed decisions about COVID-19 vaccination, especially among high-risk groups.

KEYWORDS:
COVID-19, SARS-CoV-2, vaccine, adverse effects, children

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic has significantly impacted global health, prompting the rapid development and distribution of effective vaccines. The initial vaccination efforts targeted the adult population due to their higher risk for severe disease. However, the importance of including the paediatric population in these efforts quickly became evident as part of the broader strategy to emerge from the pandemic.

Despite their general resilience, children remain susceptible to infection, often through household contacts or school settings.[1,2] Although children often experience milder forms of COVID-19,[3,4] there are instances where it can lead to severe outcomes, including the need for hospitalisation, admission to the intensive care unit and mechanical ventilation.[5-7] Additionally, they are at risk for serious post-infectious complications, such as multi-system inflammatory syndrome (MIS-C) or long COVID.[8-10] The impact of COVID-19 extends beyond health, causing disruptions to children's social interactions, school attendance and potentially affecting long-term cognitive and social development.[11] Therefore, COVID-19 vaccination plays an important role in safeguarding children against infection.

Healthcare stakeholders across the world have implemented extensive safety monitoring efforts to ensure a favourable risk-to-benefit ratio for COVID-19 vaccines. The Pfizer-BioNTech BNT162b2 vaccine, in particular, has demonstrated promising safety and efficacy in phase 2/3 clinical trials involving adolescent and younger children.[12] The safety and efficacy of the vaccine have been further demonstrated by real-world data and its broad use worldwide.[13] Malaysia initiated the National COVID-19 Immunisation Program for children aged 5-11 years (PICKids) on February 3, 2022. In this program, eligible children received two doses of Pfizer-BioNTech's Comirnaty, spaced 8 weeks apart.[14] During the period of the study, the Pfizer-BioNTech BNT162b2 was the sole vaccine approved and available for administration in the eligible paediatric population.

A detailed understanding of vaccine adverse effects is vital, as it provides healthcare professionals, parents and policymakers with the necessary information to make informed decisions about paediatric COVID-19 vaccination. There is a need to publish local data on the safety of the COVID-19 vaccine in children, where differences in ethnicity, genetic composition and environmental factors could influence the occurrences and manifestations of side effects. Therefore, we aim to evaluate the safety of the COVID-19 vaccine in children by determining the proportion of vaccinated children who experienced side effects and identify factors associated with these post-vaccination side effects.

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Table I: Baseline characteristics of the study population

Baseline characteristics	Total, N=195
Age in years, mean (SD)	9 (2.0)
Weight in kilograms, mean (SD)	28.9 (10.5)
Gender	
Male	84 (43.1%)
Female	111(56.9%)
Ethnicity	
• Malay	156 (80.0%)
• Chinese	29 (14.9%)
• Indian	10 (5.1%)
Comorbidities[a]	
• None	148 (75.9)
• Respiratory	26 (13.3)
• Prematurity	11 (5.6)
• Cardiovascular	6 (3.1)
• Neurological	3 (1.5)
• Genetic	3 (1.5)
• Others	12 (6.2)
Allergy historya	
• None	155 (79.5)
• Dust	23 (11.8)
• Seafood	16 (8.2)
• Pet	11 (5.6)
• Egg	9 (4.6)
• Dairy	8 (4.1)
• Medication	7 (3.6)
• Nuts	6 (3.1)
• Others	11 (5.6)

[a]A subject may have more than one of the following subcategories

Table II: Comparison of side effects after the first or second dose of Pfizer-BioNTech (Comirnaty) vaccine

Side effect	Either dose, n (%)	First dose, n (%)	Second dose, n (%)	p-value
Any side effect	62 (31.8)	41 (21.0)	56 (28.7)	0.079[a]
Pain at injection site	58 (29.7)	40 (20.5)	51 (26.2)	0.396[b]
Fever	31 (15.9)	15 (7.7)	26 (13.3)	0.332[a]
Inflammation/redness	21 (10.8)	13 (6.7)	19 (9.7)	0.818[a]
Arthralgia/myalgia	18 (9.2)	11 (5.6)	16 (8.2)	0.850[a]
Malaise	13 (6.7)	9 (4.6)	12 (6.2)	0.951[a]
Headache	13 (6.7)	7 (3.6)	12 (6.2)	0.593[a]
Pruritus	5 (2.6)	0	5 (2.6)	-
Chills	4 (2.1)	3 (1.5)	3 (1.5)	0.695[b]
Nausea/vomiting	3 (1.5)	2 (1.0)	1 (0.5)	0.572[b]
Rash	3 (1.5)	0	3 (1.5)	-
Dyspnea	2 (1.0)	1 (0.5)	1 (0.5)	1.0[b]
Chest pain	1 (0.5)	0	1 (0.5)	-
Insomnia	1 (0.5)	0	1 (0.5)	-
Diarrhea	1 (0.5)	0	1 (0.5)	-
Lymphadenopathy	1 (0.5)	0	1 (0.5)	-
Inconsolable crying	0	0	0	-
Anaphylaxis	0	0	0	-
Myocarditis	0	0	0	-

[a]Chi-squared tests, [b]Fisher-exact tests.

MATERIALS AND METHODS

We invited a total of 516 children of hospital staff members from Hospital Tuanku Ja'afar Seremban to participate in this cross-sectional study. This group was selected because the hospital's designated vaccination centre specifically catered to these children. The children received two doses of the Pfizer Comirnaty® vaccine (BNT162b2) between 3 February and 8 May 2022 at the facility.

The parent or guardian were invited to participate in a self-administered survey via a Google form link 2 weeks after the children received their second vaccine dose. The survey was conducted in Bahasa Malaysia and consisted of the following domains: demographic details, underlying comorbidities, allergy history and description of side effects after vaccination. Participation for consent was obtained through an "I agree" checkbox in the Google form survey, signifying informed consent. Participants who selected "I disagree" would be allowed to withdraw from the study.

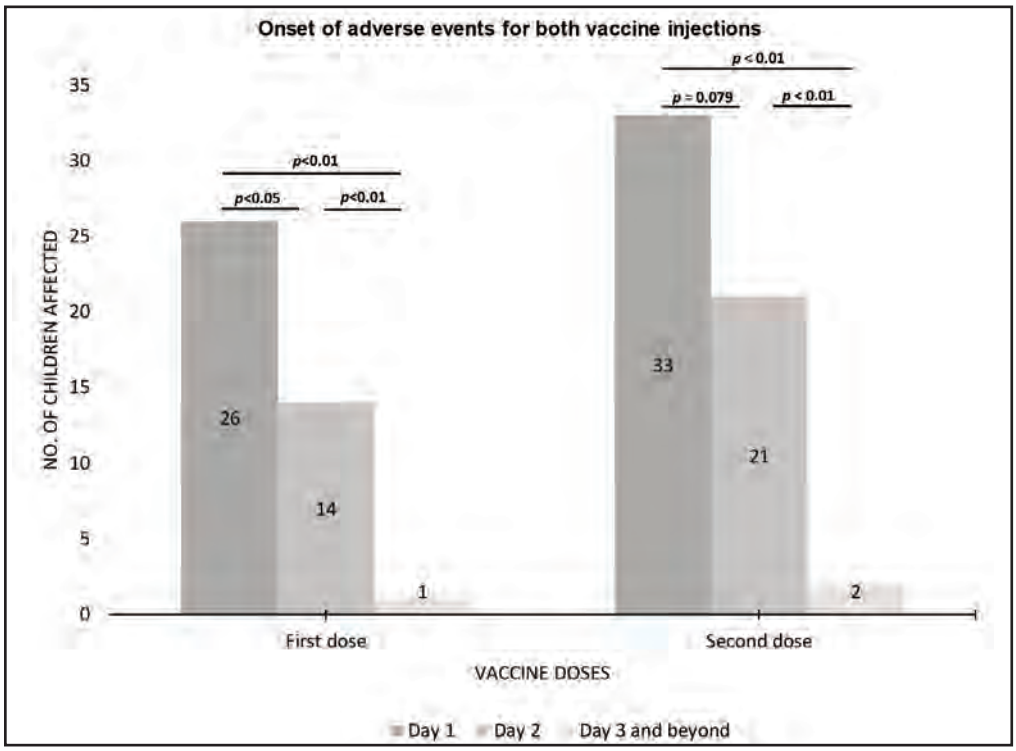

Fig. 1: Comparison of onset of side effects for both vaccine doses. *(p-values were computed via Chi-squared tests).*

The primary outcome measures were the proportion of children experiencing side effects from either vaccine dose. These side effects were reported directly by the parents or guardians, providing first-hand accounts of their child's reactions to the vaccine. Additionally, we described the vaccine's side effects and analysed sociodemographic differences between children who developed side effects from those who did not.

Data analysis was performed using descriptive statistics. Categorical variables were presented as frequencies and percentages, and continuous variables as means with standard deviations (SD). Categorical variables were compared using Chi-squared tests and Fisher exact tests, depending on whether the assumptions for the Chi-square test were met. The independent t-test was used for comparing means of continuous variables. Statistical significance was set based on a p-value of <0.05.

Ethical Approval for the Study

This study was approved by the Medical Research and Ethics Committee (MREC), and was granted the approval ID: NMRR ID-22-00987-QOQ (IIR). The survey was anonymous and ensured the confidentiality of the participant's information. No personal or identifiable data were collected during the course of the study.

RESULTS

The study included 195 participants who completed the survey. Detailed baseline characteristics of the study population are provided in Table I. The mean age of the study participants was 9 years old (SD 2.0), and 43.1% were males. The predominant ethnic group was Malays (80.0%), a representation of the hospital's workforce demographics. Nearly a quarter of the participants (24.1%, n=47) had underlying comorbidities, with respiratory disorders being the most prevalent (13.3%). A history of allergy was present in 20.5% of the participants, with dust and seafood allergies being the most common.

Our data revealed approximately one-third of the participants (31.8%, n=62) experienced side effects following immunisation with the COVID-19 vaccine (Table II). Pain at the injection site (29.7%, n=58), fever (15.9%, n=31), localised inflammation/redness (15.9%, n=21) and arthralgia/myalgia (9.2%, n=18) were the most frequently reported side effects. Although a larger proportion of participants reported these side effects after the second dose than the first, these differences were not statistically significant. Two (1.0%) of the 195 participants were hospitalised after receiving the second vaccine dose; one due to chest pain but tested positive for COVID-19, and another a child with pre-existing eczema who developed generalised rash one day after receiving the second dose of vaccine. Both cases had uneventful hospital stays. Otherwise, there were no reported severe side effects such as anaphylaxis, myocarditis or deaths.

We further investigated the onset of post-vaccination side effects. Among the subjects who developed side effects after the initial dose, 97.6% (n= 40) reported experiencing them within the first two days post-vaccination (Figure 1). The frequency of participants experiencing side effects was significantly higher on the day following vaccination

compared to the second and third days. A similar pattern was observed with the second dose, with 96.4% (n=54) developing side effects within two days.

Subsequent analysis compared the characteristics of individuals who did and did not experience side effects (Table III). We observed that the proportion of participants who experienced side effects was higher among those with underlying comorbidities compared to those without (33.9% vs. 19.5%, p=0.029). A sub-analysis of the various comorbidities showed no specific comorbidity was associated with a higher proportion of side effects. Otherwise, no significant differences were observed based on age, weight, sex, ethnicity and the presence of allergies between both groups. We also examined the potential effect of premedication on post-vaccination side effects. Premedication regimens included common drugs such as paracetamol, antihistamines, non-steroidal anti-inflammatory drugs (NSAIDs) and steroids. There were no significant differences in the proportion of participants developing side effects between the premedicated and non-premedicated groups.

In our study, 17.4% (n=34) were diagnosed with COVID-19 following the first dose of vaccination, prior to the administration of the second dose. Following the second dose, this proportion decreased significantly to 4.6% (n=9), a change which was statistically significant (p<0.001). Notably, none of the participants who developed COVID-19 following vaccination required hospitalisation.

DISCUSSION

In Malaysia, a remarkable 3,312,886 doses of COVID-19 vaccines have been administered to children aged 5 to 11 years as of 31 December 2022, according to the National Pharmaceutical Regulatory Agency (NPRA).[15] National data revealed 523 adverse events following immunisation (AEFI) reports in this age group, translating to a rate of 158 AEFI per 1,000,000 doses administered. The AEFI rates in children were lower than the overall AEFI reporting rate (369 per 1,000,000 doses), with the vast majority (94%) being non-serious effects. This data highlights the vaccine's favourable safety profile.

In line with this national data, our study found that approximately one-third of the participants reported mild, self-limiting side effects post vaccination. These findings are consistent with data from other international vaccine safety reporting platforms and the NPRA, as well as our previous publication among the adult population.[15-17] Myocarditis was notably absent in our cohort, a risk often associated with COVID-19 vaccination in adult and adolescent populations.[18,19] The disparity may be due to differences in vaccine dosage and scheduling. The children vaccine contains lower doses and are spaced eight weeks apart, as opposed to the three-week interval used in adults during the pandemic. This regimen likely contributed to a lower incidence of severe adverse events in children.

Our findings reveal that most side effects appeared soon after vaccination and predominantly within the first 2 days. This pattern remained consistent across both doses of the vaccine, and tally with the findings from other studies.[17,20] Notably, some children did contract COVID-19 following vaccination. However, none of them required hospitalisation, suggesting the vaccine mitigated the disease severity. We also observed a decrease in the number of reported COVID-19 following the second dose of the vaccine. However, drawing definitive conclusions about the vaccine role in prevention of COVID-19 is challenging, due to the coincidental decline in COVID-19 incidence during this period.

In our analysis, a higher proportion of participants with pre-existing comorbidities experienced side effects when compared to their healthy counterparts. This observation could be due to the more attentive health monitoring by their parents, leading to them being more likely to report any perceived side effects following vaccination. However, it is important to clarify that this observation does not imply the vaccine poses increased risk for children with pre-existing conditions. The presence of comorbidities are recognised risk factor for severe outcomes in paediatric COVID-19.[21] The WHO's Strategic Advisory Group of Experts on Immunisation (SAGE) recommended that these children should be given a medium to high priority in receiving COVID-19 vaccines.[22] This recommendation highlights the significant benefits of vaccination, which outweigh the potential risks of side effects. Prior studies have identified a history of allergy as a risk factor for side effects following vaccination, potentially due to the heightened immune system responses to certain substances.[23,24] The COVID-19 vaccine adverse reactions have been thought to be related to an ingredient called polyethylene glycol (PEG), a component of lipid nanoparticle used to encase and stabilise the mRNA, aiding its delivery into the cells.[25] However, our data did not show any significant differences in the occurrence of side effects between children with pre-existing allergies and those without. Additionally, the proportion of participants who experienced side effects was comparable between those who received premedication and those who did not, suggesting that premedication may not be necessary for COVID-19 vaccination.

This study has several limitations. First, the single-centre nature of this study limits the ability to generalise our findings to the general population. However, focusing on our local community allowed for a detailed exploration of vaccine side effects, capturing specific details which are potentially overlooked in broader national data. Our study's results on the onset of adverse effects and the analysis of factors such as age, weight, comorbidities, allergy history and premedication usage add valuable information, complementing the broader data reported by the NPRA. Second, participation in the study was voluntary and dependent on the willingness of the vaccine recipient's parents to respond to our invitation. This may have introduced a degree of selection bias, as parents of children who experienced side effects may have been more inclined to participate in the study. Third, our study had a lower-than-expected response rate. While the low response rate can impact the representativeness of our findings, it does not undermine the valuable insights gathered from those who chose to participate. Lastly, as the Pfizer-BioNTech (Comirnaty) vaccine was the only one administered to the target population, a comparison with other vaccine types was not possible.

CONCLUSION

In conclusion, our findings demonstrate the generally mild and manageable side effects experienced by children following COVID-19 vaccination. This study adds to the body of evidence supporting the safety of COVID-19 vaccines in the paediatric population and serves as a historical record of the vaccine safety during this unprecedented pandemic that deeply impacted our nation. Additionally, our study offers crucial insights into the patterns of these side effects and their influencing variables. This data would aid in informed decision-making and parenteral counselling processes. Future research involving a larger and more diverse sample size and comparison across different types of COVID-19 vaccines would be beneficial for a more comprehensive understanding of paediatric COVID-19 vaccination.

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ORIGINAL ARTICLE

Comparison of the effect of scalp block analgesia bupivacaine 0.25% and clonidine 2 µg/kg with bupivacaine 0.25% and dexamethasone 8 mg on cortisol levels and Numeric Rating Scale in craniotomy tumour

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ABSTRACT

Introduction: Craniotomy tumour is brain surgery that can induce a stress response. The stress response can be measured using haemodynamic parameters and plasma cortisol concentration. The stress response that occurs can affect an increase in sympathetic response, such as blood pressure and heart rate, which can lead to an increase in intracranial pressure. Scalp block can reduce the stress response to surgery and post-operative craniotomy tumour pain. The local anaesthetic drug bupivacaine 0.25% is effective in reducing post-operative pain and stress in the form of reducing plasma cortisol levels. The adjuvant addition of clonidine 2 µg/kg or dexamethasone may be beneficial.

Materials and Methods: A randomised control clinical trial was conducted at the Central Surgery Installation and Hasan Sadikin General Hospital Bandung and Dr. Mohammad Husein Hospital Palembang from December 2022 to June 2023. A total of 40 participants were divided into two groups using block randomisation. Group I receives bupivacaine 0.25% and clonidine 2 µg/kg, and group II receives bupivacaine 0.25% and dexamethasone 8 mg. The plasma cortisol levels of the patient will be assessed at (T0, T1 and T2). All the patient were intubated under general anesthaesia and received the drug for scalp block based on the group being randomised. Haemodynamic monitoring was carried out.

Results: There was a significant difference in administering bupivacaine 0.25% and clonidine 2µg/kg compared to administering bupivacaine 0.25% and dexamethasone 8 mg/kg as analgesia for scalp block in tumour craniotomy patients on cortisol levels at 12 hours post-operatively (T1) (p=0.048) and 24 hours post-surgery (T2) (p=0.027), while post-intubation cortisol levels (T0) found no significant difference (p=0.756). There is a significant difference in Numeric Rating Scale (NRS) at post-intubation (T0) (p=0.003), 12 hours post-operatively (T1) (p=0.002) and 24 hours post-surgery (T2) (p=0.004), There were no post-procedure scalp block side effects in both groups.

Conclusion: The study found that scalp block with 0.25% bupivacaine and 2µg/kg clonidine is more effective in reducing NRS scores and cortisol levels compared bupivacaine 0.25% and dexamethasone 8mg in tumour craniotomy patients.

KEYWORDS:
Bupivacaine, clonidine, cortisol, dexamethasone, scalp block

INTRODUCTION

Craniotomy surgery for tumour is a brain surgery that can induce stress response, especially during laryngoscopy, cranial pin placement and skin incisions. During these procedures, it is important to adhere to the principles of neuroanesthesia to prevent increased intracranial pressure and ensure optimal cerebral perfusion and oxygenation. Tissue trauma that occurs during surgery not only has an impact on peripheral sensitisation but also has an impact on the endocrine system.[1,2]

Anaesthesia management in neuroanaesthesia patients is based on the effects of drugs on the physiology of the central nervous system, including cerebral blood flow, cerebral blood volume, intracranial pressure, autoregulation, response to carbon dioxide, and the production and absorption of cerebrospinal fluid. Anaesthesia drugs can affect cerebral haemodynamics, cerebral metabolism and intracranial pressure to improve outcomes in patient with brain tumour. The qualifications of anaesthetic drugs includes must be easy to control, the drug must have a stable intracranial haemodynamic and homeostatic effect, must not affect neurophysiological monitoring, have an antinociceptive effect and must protect the brain against pain due to tissue trauma during surgery.[3,4]

The pain of craniotomy surgery for brain tumour can activate the hypothalamic–pituitary–adrenal (HPA) axis and trigger the release of releasing factor. The releasing factor then triggers the anterior pituitary to secrete adrenocorticotropic hormone and release cortisol. The increase in cortisol levels due to surgery varies depending on the degree of surgery. The stress response functions to secrete hormones are needed by the body for pain regulatory functions, including tissue protection and regeneration, immunological activity and metabolic regulation. Studies

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show that high cortisol levels correlate with severe post-operative pain intensity. Excessively elevated cortisol levels can contribute to post-operative changes in the immune system, and the patient's outcome may be worse. Increased cortisol levels have an immunosuppressive effect, reducing the ability of natural killer (NK) cells and T cell responses and can cause cognitive impairment in patients.[5,6]

Peripheral nerve block is effective in reducing stress and pain response and can be used as an analgesic in craniotomy surgery. Scalp block combined with general anaesthesia can reduce the response to pinning and incision, as well as maintain haemodynamic stability and perioperative analgesia. A study showed that scalp block using 0.5% bupivacaine succeeded in reducing the neuroendocrinal stress response which was characterised by decreased plasma cortisol levels. This peripheral nerve block can be given as an adjuvant and combined with general anaesthesia to provide good pain control during and post-operative period. Several studies have investigated the potentiation and prolongation of the sensory effects of peripheral nerve blocks with the use of clonidine or dexamethasone. The addition of an adjuvant to the scalp block resulted in an earlier onset of the block with better perioperative hemodynamic stability.[3,7,8] Aim of this study is for alternative analgesia to reduce intracranial pressure.

MATERIALS AND METHODS

This study is a randomised control clinical trial. Patients were predetermined by a double-blind (patients and researcher) randomised process for group selection by block randomisation. Participants were recruited with inclusion and exclusion criteria. Inclusion criteria include patients aged 18–65 years, and brain tumour sufferers diagnosed with supratentorial tumour who will undergo craniotomy surgery, tumour size <10 cm and Glasgow Coma Scale 15. Exclusion criteria with patients suffering from pituitary and pheochromocytoma tumours, a patient has an extracranial tumour.

Researchers determined that each block consisted of two subjects, and each block consisted of group I, namely bupivacaine 0.25% and clonidine 2µg/kg. and group II, namely bupivacaine 0.25% and dexamethasone 8 mg. For example, blocks are given odd number codes for blocks I-II and even numbers for blocks II-I. Next, randomisation of the numbers is carried out and then replaced with related blocks. Participants were patients at the Central Surgery Installation who is planned for elective craniotomy surgery for tumour from December 2022 until sample size is reached. The patients were treated post-operatively in the ICU Hasan Sadikin Hospital (RSHS) Bandung and Dr. Mohammad Husein Hospital (RSMH) Palembang. The sample size was 40 patients divided into two treatment groups of 20 patients in each group. The data collected includes primary data derived from the patients' medical records.

Group 1 received scalp block bupivacaine 0.25% and clonidine 2 µg/kg. Group 2 received bupivacaine 0.25% and dexamethasone 8 mg. Group 1 will be administered clonidine 2µg/kg, (according to the patient's ideal body weight). In 3cc syringe which was mixed into the bupivacaine 25cc (70mg) syringe that had been prepared earlier. Group 2, dexamethasone 8mg was given, put into a 3cc syringe and then mixed into the bupivacaine 25cc (70mg) syringe that had been prepared earlier.

Blood samples from the participants were taken T0-before surgery, T1-12 hours after T0, and T2-24 hours after T0 check plasma cortisol levels and hemodynamics. A 5 ml of blood sample was taken and stored is put into the EDTA tube. The cortisol levels were examined using the ELISA technique.

After taking the blood at T0, the patients were intubated under general anaesthesia with neuroanesthesia principles. The patients were given the following induction drug doses of propofol 2mg/kg, fentanyl 2µg/kg and rocuronium 1.2mg/kg. Patients were given sevoflurane maintenance not more than 1 MAC, intravenous propofol 1-2 mg/kg/hour and intermittent rocuronium 10 mg every hour. Each drug for scalp block was prepared according to randomisation.

The scalp block was given on seven nerves, the supraorbital nerve, supratrochelear nerve, auriculotemporal and zygomaticotemporal nerve, Greater occipital nerve (GON) and occipital nerve (TON). On each nerve, 2cc is needed at each point. Haemodynamic monitoring was conducted for each patient, if there is an intraoperative pain response characterised by an increase in heart rate (HR) and blood pressure (BP) of more than 20%, fentanyl rescue may be given mg/kg body weight with an interval of 30 minutes which can be repeated up to three times. Blood pressure, heart rate, respiratory rate and peripheral oxygen saturation were measured and recorded. The scalp suturing operation on the craniotomy was completed; the patient was extubated and monitored in the intensive care unit and was given post-operative analgesic paracetamol 1 gram per 8 hours for 5 days.

Univariate analysis was performed to determine the frequency distribution of the variables studied. Univariate analysis presents the frequency of events in the form of numbers and percentages. Bivariate analysis was conducted to determine the average difference between the dependent and independent variables.

Analysis using the unpaired T-test statistic to compare mean cortisol at T0, T1, T2, between Group 1 and Group 2 participants. Analysis of data categories with Chi-square test. If the chi-square test requirements are not met, then the Fisher Exact test will be carried out. All analysis has a degree of confidence of 95% and an α value of 0.05. Primary data is entered into SPSS 24.0.

RESULTS

In the calculation of the difference in cortisol levels 12 hours post-operation (T1) compared to the initial cortisol levels (T0), there is a slight increase in the mean cortisol levels, namely 1.66+15.74 in the group receiving 0.25% bupivacaine and 2 µg/kg (Group 1) clonidine, while in the group receiving 0.25% bupivacaine and 8 mg dexamethasone (Group 2) , there is an increase in the mean

Tabel I: Sociodemographics characteristics of respondent

Variables	Bupivakain 0.5% + Klonidin 0.2 µg/ kg		Bupivakain 0.5% + Dexametason 8mg/kg	
	n	%	n	%
Age				
17-40 years	3	15.0	5	21.6
41-64 years	17	85.0	12	78.4
Gender				
Male	4	20.0	7	35.0
Female	16	80.0	13	65.0
Body mass index (kg/m2)				
Low (<18.5)	0	0	0	0
Normal (18.5-24.9)	20	100.0	19	95.0
Overweight (>25)	0	0	1	5.0
Duration (O'clock)				
<4 O'clock	19	95.0	17	85.0
>4 O'clock	1	5.0	3	15.0

Group 1: Bupivacain 0.5% + Clodine 0.2 µg/ kg
Group 2 : 0,5% +Dexamethasone 8mg/kg

Table II: Differences in plasma cortisol levels between test groups

Variables	Bupivacain 0.5% + Dexamethasone 0.2 µg/ kg (Group 1) Mean + SD	Bupivacain 0.5% + Dexamethasone 8 mg/kg (Group 1) Mean + SD	p*
Cortisol T0	9.87 + 8.06	8.02 + 5.05	0.756*
Cortisol T1	11.53 + 17.59	17.13 + 12.35	0.048*
Cortisol T2	12.22 + 24.13	25.85 + 27.71	0.027*
Cortisol ΔT0-T1	1.66 + 15.74	9.10 + 11.50	0.030*
Cortisol ΔT0-T2	2.34 + 22.60	17.83 + 27.84	0.009*

*Uji Mann–Whitney.

Table III: Differences in Numeric Rating Scale (NRS) between test groups

Variable	Bupivacain 0.5% + Clonidine 0.2 µg/ kg Mean + SD	Bupivacaine 0.5% + Dexamethasone 8 mg/kg Mean + SD	p*
NRS T0	3.6+1.84	2.10+0.71	0.003*
NRS T1	2.15+1.13	3.30+1.08	0.002*
NRS T2	2.10+1.02	3.45+1.57	0.004*

*Uji Mann-Whitney ($p < 0.05$).

cortisol levels of 9.10±11.50. According to Mann–Whitney test, a significant difference was found in the difference in cortisol levels 12 hours post-operation compared to the initial cortisol levels (ΔT0–T1) between these two groups ($p<0.001$).

In the calculation of the difference in cortisol levels 24 hours post-operation (T2) compared to the initial cortisol levels (T0), there is a slight increase in the mean cortisol levels, namely 2.34±22.60 in the group receiving 70 mg bupivacaine and 2 µg/kg clonidine, while in the group receiving 0.25% bupivacaine and 8 mg dexamethasone, there is an increase in the mean cortisol levels of 17.83±27.84. According to Mann–Whitney test, a significant difference was found in the difference in cortisol levels 24 hours post-operation compared to the initial cortisol levels (ΔT0-T2) between these two groups ($p<0.05$). The complete result is shown in Table II.

In 0.25% bupivacaine and 2 µg/kg clonidine group, the mean Numeric Rating Scale (NRS) at baseline (T0) was 3.6+1.84, which was higher compared 0.25% bupivacaine and 8 mg dexamethasone group, with a mean NRS of 2.10+0.71. Based on the Mann-Whitney test, there was a significant difference in the initial Numeric Rating Scale (NRS) between these two groups ($p<0.01$).

In the 0.25% bupivacaine and 2 µg/kg clonidine group, the mean Numeric Rating Scale (NRS) 12 hours post-operation (T1) was 2.15+1.13, which was lower compared to the 0.25% bupivacaine and 8 mg dexamethasone group, with a mean NRS of 3.30+1.08. Based on Mann–Whitney test, there was a significant difference in the Numeric Rating Scale (NRS) 12 hours post-operation (T1) between these two groups ($p<0.05$).

In the 0.25% bupivacaine and 2 µg/kg clonidine group, the mean Numeric Rating Scale (NRS) 24 hours post-operation (T2) was 2.10+1.02, which was lower compared to the 0.25% bupivacaine and 8 mg dexamethasone group, with a mean NRS of 3.45+1.57. Based on the Mann-Whitney test, there was a significant difference in the Numeric Rating Scale (NRS) 24 hours post-operation (T2) between these two groups. More details are presented in Table II.

All research subjects in both the group receiving 0.25% bupivacaine and 2 µg/kg clonidine, as well as the group receiving 0.25% bupivacaine and 8 mg dexamethasone, did

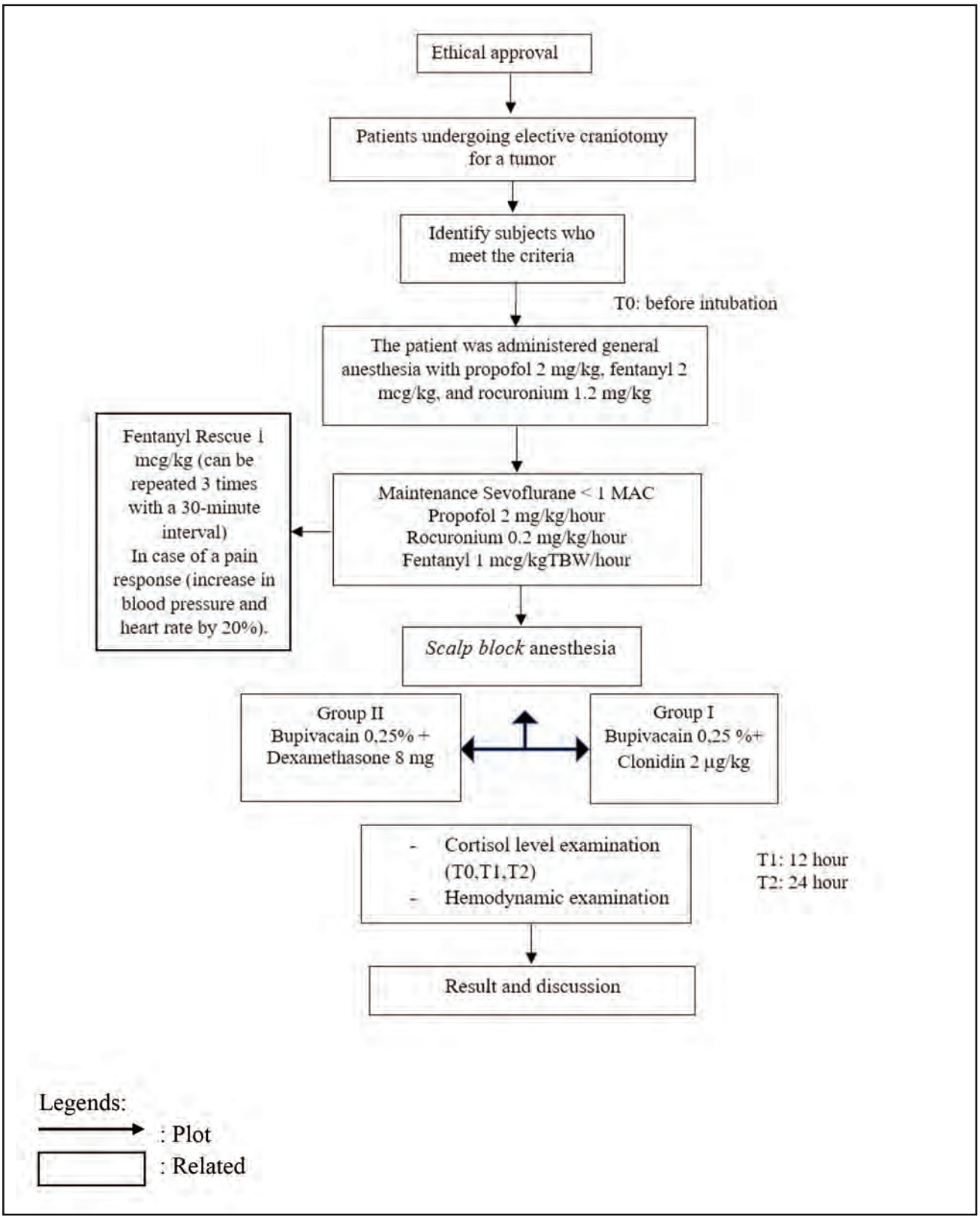

Fig. 1: Study procedural

not experience any side effects such as bradycardia, hypotension or post-procedure allergies following scalp block.

All research subjects, in the group given bupivacaine 0.25% and clonidine 2 µg/kg, or in the group given bupivacaine 0.25% and dexamethasone 8 mg, had no side effects after the scalp block procedure. These results are supported by scalp block studies with 0.25% bupivacaine in the addition of clonidine 2µg/kg (group III), in the group addition clonidine 1 µg/kg (group II), compared with group I (control) at each time of hemodynamic calculation, both during pin placement, skin incision and dura incision. In the group with the addition of clonidine 1µg/kg (group II), there was a significant difference compared to the control group at the time of pin placement, while in the skin incision and dura incision, there was no significant difference compared to the control group. It appears that there is an effect of accelerating onset. Treatment side effects were also observed during the study. Observed side effects such as bradycardia, hypotension and desaturation were not found in any study subjects. Giving a scalp block with clonidine up to 2µg/kg is safe for craniotomy patients.

In the assessment of pain using the Numeric Rating Scale (NRS), patients are asked to evaluate the pain they are experiencing using a scale of 0-10. The higher the number chosen, the more intense the pain experienced. A score of 0 means no pain, 1-3 means mild pain, 4-6 means moderate pain and 7-10 means severe pain. Post-operative pain management for craniotomy is typically performed routinely, especially 24 hours post-operation, due to the risk of post-operative edoema and bleeding.

In the assessment of the first 24 hours post-craniotomy using the NRS, 87% of patients experienced pain (NRS 1-3: 32%, NRS 4-7: 44%, NRS 8-10: 11%). During the first 24 hours after craniotomy, 87% of patients experienced pain. Despite post-operative pain management with strong analgesics, more than 44% of patients suffered from moderate pain, and 10% of patients experienced severe pain during the first 24 hours after craniotomy. The high incidence of moderate to severe pain after craniotomy makes standard pain evaluation using the NRS important for routine assessment.

The findings of this study are supported by research that compared groups receiving 0.25% levobupivacaine with the addition of 2 µg/kgBB clonidine and those receiving single 0.25% levobupivacaine in craniotomy patients. Their findings indicated a decrease in NRS and a significant difference in NRS ($p<0.05$) in the group receiving 0.25% levobupivacaine with the addition of 2µg/kg BB clonidine, especially at 12 and 24 hours post-craniotomy. The use of clonidine as an adjunct to peripheral nerve blocks has a local anaesthetic effect and can inhibit the potential working component of C fibres, which is greater than that of A-α fibres. In scalp blocks, the addition of clonidine primarily facilitates peripheral nerve block through the hyperpolarization of cationic current activation. In sodium currents in dorsal root ganglia, clonidine reduces the amplitude of sodium currents that are sensitive to tetrodotoxin and resistant to tetrodotoxin.

Dexamethasone has been used as an adjuvant to local anesthaesia in peripheral and neuraxial nerve blocks. Dexamethasone acts on K+ channels in nociceptive C fibres via glucocorticoid receptors thereby influencing fibre activity. Reduces local anaesthetic absorption by inducing vasoconstriction levels and decreasing C fibre activity by inhibiting potassium channels. The combination of regional and general anaesthesia for surgery has proven to be beneficial for patients with the aim of reducing the perioperative stress response in the form of pain, thereby reducing the activation of the HPA axis stress response.

DISCUSSION

In craniotomy surgery, tissue damage occurs and the release of inflammatory mediators, resulting in peripheral sensitisation and causing a stress response. The stress response is thought to be due to stimulation during scalp incision, periosteal release, dural opening and brain retraction, which activates the HPA system which functions to secrete hormones needed by the body for pain-regulating functions, including tissue protection and regeneration. immunological activity and metabolic regulator. Studies show that high cortisol levels correlate with severe pain intensity after surgery. Elevated cortisol levels have an immunosuppressive effect, namely reducing the ability of NK and T cells responses and can cause cognitive impairment in patients. Therefore, it is important to reduce cortisol levels.[9-12]

Scalp block technique used in craniotomy surgery with 0.25% bupivacaine as an adjuvant to general anaesthesia can provide an option to improve intraoperative analgesia with more stable haemodynamics, as well as the need for less intravenous anaesthesia or volatile anaesthetics. However, this scalp block technique can only last for a few hours. This situation demands prolongation of analgesia which can be achieved by improving the quality of local anaesthesia. To overcome this problem, several drugs have been clinically tested and proven useful as additional agents for local anaesthesia which are called adjuvants.[13-15]

The scalp consists of five layers, which are called SCALP, namely skin, connective tissue or subcutaneous tissue, aponeurosis galea, loose areolar tissue or loose connective tissue, and pericranium (pericranium). The five layers are shortened to scalp. Scalp block is a regional anaesthetic for the peripheral nerves that innervate the scalp and provides an analgesic effect over a long period of time and relieves post-operative pain.[8,16,17]

Preemptive analgesia by scalp block prevents the initiation of physiological and neurological responses to stimulation, thus reducing patient morbidity, leading to faster recovery, better surgical outcomes, decreased endocrine stress response to surgery, reduced hyperglycaemic response, improved respiratory function, early mobilisation, early discharge and reduced healthcare costs. This peripheral nerve block can be supplemented with adjuvants and combined with general anaesthesia to provide effective pain control during and after surgery.[5]

The results of this study are in line with other studies of patients undergoing elective supratentorial craniotomy. A study of 80 patients, 43 male and 37 female who underwent elective supratentorial craniotomy. These were randomly divided into two equal groups. Group A patients received under general anaesthesia with fentanyl. Group B patients received scalp blocks using bupivacaine (0.5%) and epinephrine (1:400.000) and patients received fentanyl 2µg/kg (during maintenance of general anaesthesia). The fentanyl group had higher plasma cortisol levels than Group B. Group B had a faster recovery period.

Cortisol was considered to have significantly decreased in the group that underwent scalp block with bupivacaine. This occurred because during the craniotomy surgery there was damage to the tissue and the release of inflammatory mediators, resulting in peripheral sensitisation and causing a stress response[12,18,19]

The decrease in cortisol levels when using a scalp block occurs because clonidine potentiates the action of the local anaesthetic bupivacaine, improving the quality of anaesthesia and extending the duration of sensory block. Sensory block reduces activation of the HPA axis, then reducing cortisol production. A meta analysis study compared the cortisol levels of patients undergoing minimally invasive surgery (grade 1) against patients undergoing moderate and highly invasive surgery (degrees 2 and 3), it was found that cortisol levels increased 2 times in grade I, 4 times in grade II and 3.5 times in grade III when compared with healthy control individuals at 24 hours post-operatively. Plasma cortisol levels then decreased after 24 hours after surgery and reached stable levels at 36-72 hours after surgery. Other studies showed that cortisol levels decreased in patients who underwent scalp block with bupivacaine 0.5%, baseline 12.5±2.24 and after skin incision 9.9±2.63, after skin incision 8.6±2.74, after dura mater closure 9.2±1.72 compared to the group receiving fentanyl 2 µg/kg (during maintenance of general anaesthesia).[1] In the scalp block study with bupivacaine 0.25% with the addition of clonidine 2 µg/kg (group III), the group adding clonidine 1 µg/kg (group II), was compared with group I (control) at each time of hemodynamic calculation, both times pin placement, skin incision and duramater incision show that scalp block administration with up to clonidine 2µg/kg is safe for craniotomy patients.39 Sensory block scalp block study on bupivacaine 0.25% supplemented with clonidine 2µg/kg 887.97±398.21 minutes, longer than the group that only received bupivacaine 0.25% (408.17 ± 209.81 minutes). Through a prospective cohort study showed that the addition of clonidine 2 µg/kg to bupivacaine 0.25% in scalp block resulted in rapid onset time, improved quality of anaesthesia and prolonged duration of sensory block.[14,20,21]

Clonidine, an α2 agonist, is an option for administering adjuvants to scalp blocks. Clonidine acts on centrally acting presynaptic α2 adrenoreceptors, α2 mediating a decrease in systemic vascular resistance and an increase in vagal tone resulting in a decrease in mean arterial pressure and heart rate. This also causes a decrease in norepinephrine secretion from peripheral nerve endings thereby reducing the stress response. Clonidine inhibits the larger C-fibere action potential component of the A-α fibres through hyperpolarising the activation of cationic currents. The effect of clonidine on Na+ currents in the dorsal root ganglia decreases the amplitude of sodium currents. Hyperpolarization of nucleotide-gated ion channels results in prolonged nerve block by local anaesthetic.[13-15]

In this study, cortisol levels in the test Group 2 of bupivacaine 0.25% and dexamethasone 8 mg showed an increase 12 hours after scalp block (T1) ΔT0-T1= 9.10 (±11.50), and 24 hours after scalp block (T2) ΔT0-T2 = 17.83 (±27.84). The addition of dexamethasone 4 mg to bupivacaine 0.5% can cause an increase in the quality of anaesthesia and a prolonged duration of sensory block.1 Scalp block patients at craniotomy with ropivacaine 0.2% added to dexamethasone 8 mg experienced sensory block for 760 minutes. The addition of 4 mg perineural dexamethasone to an interscalene brachial plexus block with ropivacaine 0.75% prolonged the duration of motor and sensory block compared to the group receiving ropivacaine 0.75% + 1 ml isotonic saline and ropivacaine 0.75% + 1 ml isotonic saline + dexamethasone 4 mg intravenously.[22]

CONCLUSION

The administration of scalp block with 0.25% bupivacaine and 2 mcg/kg clonidine is more effective in reducing NRS scores and suppressing the increase in cortisol levels compared to using 0.25% bupivacaine and 8 mg dexamethasone in patients undergoing craniotomy for tumour resection.

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Posterolateral tibial plateau bone bruises in anterior cruciate ligament (ACL) injuries and its association with lateral meniscal injuries

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ABSTRACT

Introduction: This study examined the prevalence of posterolateral tibial bone bruising in isolated anterior cruciate ligament (ACL) injuries, prevalence of meniscal injuries in ACL injuries, as well as the association between posterolateral tibial bone bruising and lateral meniscal tears among those with ACL injury undergoing Primary ACL Reconstruction.

Materials and Methods: Retrospective data on 130 patients who underwent primary ACL reconstructions was analysed. Their preoperative magnetic resonance images (MRI) were reviewed for the presence of posterolateral tibial bone bruise. The presence of meniscal injuries was recorded based on the arthroscopic findings from the operative records.

Results: 95 patients were recruited into the study. The prevalence of posterolateral bone bruise in this study was 41%. There was a statistically significant difference when comparing the prevalence of bone bruising to the time of injury to MRI ($p<0.001$). The prevalence of an injury to at least one meniscus at the time of ACLR surgery was 83.2%. The prevalence of lateral meniscus injuries in patients with bone bruise was found to be 53.9%. The crude odds ratio of a patient having a lateral meniscal tear in the presence of bone bruising was 1.56 (0.68, 3.54). This figure was even higher when it was adjusted for time to MRI and was 2.06 (0.77, 5.46).

Conclusion: Prevalence of posterolateral tibial bone bruising in our study was 41%, and the prevalence of meniscal injury to either meniscus at the point of surgery was 83.2%, out of which the lateral meniscus tears were identified during ACLR surgery in 47.3% of the patients. We found there was no association between posterolateral tibial bone bruising to sex, age and mode of injury, but was sensitive to the interval between time of injury and MRI. The overall prevalence of lateral meniscal tears was higher in patients with posterolateral bone bruising but was not statistically significant with a P value of 0.31; however, the Crude odd ratio was 1.56 (0.68, 3.54) and was higher when adjusted to time of injury to MRI 2.06 (0.77, 5.46). We suggest for MRI to be done as soon as possible after injury in regard to bone bruising identification. We should be vigilant to look for lateral meniscal tears and anticipate for its repair in ACL injuries, especially so when we identify posterolateral tibial bruising on the preoperative MRI.

KEYWORDS:
Bone bruise, ACL injury, Meniscus tear, Bone Edema, Posterolateral tibia

INTRODUCTION

The anterior cruciate ligament (ACL) is a band of dense connective tissue which courses from posterior medial aspect of the lateral femoral condyle in the intercondylar notch to the anterior aspect of the intercondylar eminence of the tibia.[1] The ACL is a key structure in the knee joint, as it resists anterior tibial translation and rotational loads.[2,3] The ACL has a critical role in the stability of the knee.[4] Anterior cruciate ligament (ACL) injuries represent more than 50% of knee injuries and affect more than an estimated 200,000 people in the United States each year, with direct and indirect costs of more than $7 billion annually.[5,6] Most of these ACL injuries occur during sports activity, and up to 70% of all incidents are non-contact injuries.[7-9]

The terms bone bruise and bone contusion have been used synonymously and represent a spectrum of occult bone injuries, including bleeding, infarction and oedema due to microscopic compression fractures of cancellous bone.[10] It is sometimes referred to as occult or non-displaced impaction fracture.[11] Its occurrence in the knee is commonly associated with more serious ligament injuries such as rupture of the ACL where bone bruises are commonly found in the lateral compartment of the knee and are theorized to indicate a higher energy pivoting injury.[11-15] The location of bone bruises within specific compartments of the tibia and femur can provide evidence about the potential injury mechanism.[16]

Bone bruise is best diagnosed by the increased signal intensity seen on T2-weighted images, with decreased signal intensity on T1-weighted images. T2-weighted images reflect the presence of free water (oedema, hemorrhage or inflammatory response) and therefore are useful to determine how acute the injury is. Clinically, it can cause pain and tenderness.[15] MRI studies of acute ACL injury have reported bone bruises, contusions or edema in the subchondral tibia and femur in more than 80 % of subjects with a complete ACL disruption.[12,13,16] In a study by Mink and

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Deutsch, bone signal abnormalities were present laterally in 92% of ACL tears (tibia or femur) [17] and in 100% (tibia or femur) in another study by Murphy et.al.[18] Avulsion fractures of the posterior aspect of the lateral tibial plateau were present in 40% of the acute ACL tears in the study by Stallenberg et al.[19] Bone bruises that were depicted in these regions were usually in accordance with acute ACL tears.

During ACL injury, large external forces in combination with the patient's ligament vulnerabilities during certain loading conditions cause a violent impact between the tibial and femoral articular cartilage that is transferred to the bone, resulting in bone bruises.[16] The typical pattern of bone bruising during ACL rupture involves the lateral femoral condyle (LFC and the lateral tibial plateau (LTP). This pattern of distribution reflects the mechanism of injury during ACL rupture, with the lateral plateau subluxating more laterally than medially, which causes an impact on the anterolateral rim of the femur and the posterolateral rim of the tibia.[20,21] These resultant bone bruises are seen on MRI of the ACL-injured knee as hyperintense signals in the subchondral tibia and femur.[16] When the knee is imaged longer after the ACL injury has occurred, the incidence of bone bruising decreases, ranging from 40-56 % on MRI.[22-24]

Bone bruises evolve over time from the acute injury time and intensify or resolve after varying periods of time. Significant time differences between time of injury and date of MRI collection could potentially lead to inaccurate comparisons of bone-bruise prevalence and location among studies. Tung et al. reported an average MRI collection period of 4.3 weeks for all subjects who demonstrated at least one bone bruise on their MRI[24] while in another study by Graf et al., it was reported that their subjects only expressed bone bruises when MRIs were collected within six weeks post-ACL injury[22] Bone-bruise studies classify ACL injury mechanisms by the location of bone bruises within the anterior, posterior and/or middle aspects within each lateral and medial compartment of the tibia and femur.[25,26]

Isolated ACL tears are uncommon, with approximately 55-65% accompanied by meniscal tears due to the close anatomic and functional relationships of these structures.[27] The menisci are important structures within the knee, with complex biomechanical functions. They are thought to carry 40-70% of the load across the knee, and they have a role in shock absorption, proprioception, and enhancement of stability.[28] The lateral meniscus is injured more often in acute ACL tears, and the medial meniscus is more likely involved in chronic ACL tears.[13,29] Some studies have demonstrated unique gender and sport-specific meniscal injury patterns associated with acute ACL tears.[30-32]

The objectives of this study were to determine the prevalence of posterolateral tibial bone bruises in isolated ACL injuries, the prevalence of meniscal injuries in ACL injuries and to determine the association between between posterolateral tibial plateau bone bruising and lateral meniscal tears among those with ACL injuries.

MATERIALS AND METHODS

Retrospective demographic information and data from the medical records were collected on all patients who underwent primary ACL reconstructions by a single surgeon (M.M.) between the 1st January 2013 and 31st August 2022 at Hospital Sultan Abdul Halim, Kedah, Malaysia. The presence of meniscal injury was recorded based on the arthroscopic findings during the surgery only as obtained from the operative records (meniscal tears confirmed by arthroscopy). Patients whose preoperative magnetic resonance imaging (MRI) images or digitized MRI were unavailable in the local hospital Information system, patients who had sustained more than one ligament injury, and patients who underwent any previous tibial plateau fractures or surgery which could possibly alter the findings of the bone bruise had been excluded from this study. For patients who had met the criteria, their preoperative MRI scans were analyzed via CentricityTM Universal Viewer Zero Footprint Client (GE Healthcare) software and reviewed to determine the presence of posterolateral tibial bone bruise. Bone bruising was considered as present when there was increased signal present specifically in the subcortical or cancellous bone of the Posterolateral tibial condyle on T2-weighted images. Approval for the study was obtained from the Malaysian Research and Ethical Committee, Ministry of Health Malaysia.

RESULTS

A total of 130 patients were recruited into the study of which 35 of them were excluded from the study as they did not meet the inclusion criteria (Figure 1). Of the 95 patients included in the study, 76 of them were males and 19 were female. The mean age of the study patients was 26.6 years, and their ages ranged from 15 to 50 years. (Table I). Sports-related injuries were the main cause of the ACL injury in the study participants accounting for 69.5% (Table I). Field soccer accounted for 60% of the study patients with sports injuries. Other sports-related injuries included futsal, badminton, netball, rugby and other sports accounted for the remaining 40 %. Non-sports injuries, such as motor vehicle accidents and traumatic falls, accounted for the remaining 30.5% of injuries. The median time from the time of injury to the time the MRI was performed was 5 months (Q1–Q3) 2–12 (Table I). Out of 95 patients, 35 patients (37.2%) had their MRI performed within 3 months,16 patients (17%) had their MRI performed between 4 and 6 months after the injury and 22.3% between 6-12 months post-injury. Out of 95 patients, 22 patients (23.4%) had their MRI performed 12 months after the injury (Table I).

The prevalence of posterolateral tibia bone bruising in this study was 41% (39/95) (Table II). The prevalence of posterolateral bone bruising was 42.1 % in females and 40.8 % in males (Table II). There was no statistically significant difference in the prevalence of posterolateral tibia bone bruising patients when compared for sex, age and mode of injury. There was, however, a statistically significant difference when comparing the prevalence of bone bruising to the time of injury to MRI. There was no statistically significant difference between the time intervals <3 and >3–6 months, with a prevalence of 62.9% and 62.5%, respectively.

Table I: Demographic data of the patients including mechanism of injury and the time lapse between the injury and date of MRI

Characteristics	n (%)
Sex	
Female	19 (20.0)
Male	76 (80.0)
Age (years), mean±SD	26.6±8.6
Sports injury	
No	29 (30.5)
Yes	66 (69.5)
Type of sports	
Field Soccer	40 (60.6)
Futsal	8 (12.1)
Badminton	4 (6.1)
Netball	4 (6.1)
Rugby	3 (4.5)
Sepak Takraw	2 (3.0)
Other sports	5 (7.6)
Time to MRI	
Median (Q1-Q3)	5 (2-12)
≤3 months	35 (37.2)
>3-6 months	16 (17.1)
>6-12 months	21 (22.3)
>12 months	22 (23.4)

Table II: Prevalence of posterolateral tibial bone bruise by age, sex, mode and time of injury

	Posterolateral tibial bone bruise		P value
	No, n (%)	Yes, n (%)	
Overall	56 (59.0)	39 (41.0)	
Sex			0.99
Female	11 (57.9)	8 (42.1)	
Male	45 (59.2)	31 (40.8)	
Age, mean±SD	26.6±8.9	26.6±8.4	0.99
Mode of injury			0.82
Other	18 (62.1)	11 (37.9)	
Sports-related	38 (57.6)	28 (42.4)	
Time of injury			<0.001
≤3 months	13 (37.1)	22 (62.9)	
>3-6 months	6 (37.5)	10 (62.5)	
>6-12 months	17 (81.0)	4 (19.0)	
>12 months	20 (90.9)	2 (9.1)	

Table III: Prevalence of meniscal tears at time of ACL reconstruction surgery

Presence of meniscal tear	n (%)
No	16/95 (16.8)
Yes	79/95 (83.2)
Medial meniscus torn	61/95 (64.2%)
Lateral meniscus torn	45/95 (47.3%)
Only involving medial meniscus	34/79 (43.0)
Only involving lateral meniscus	18/79 (22.8)
Both menisci torn	27/79 (34.2)

Table IV: Prevalence of lateral meniscus tear and its association with posterolateral tibial bone bruise

Posterolateral tibial bone bruise	Prevalence, n (%)			Associations, OR (95% CI)	
	No	Yes, n (%)	P value	Crude	Adjusted*
Lateral Meniscus Tear			0.31		
No	32 (57.1)	18 (46.1)		1.00	1.00
Yes	24 (42.9)	21 (53.9)		1.56 (0.68, 3.54)	2.06 (0.77, 5.46)

*Adjusted for time of injury to time of MRI.

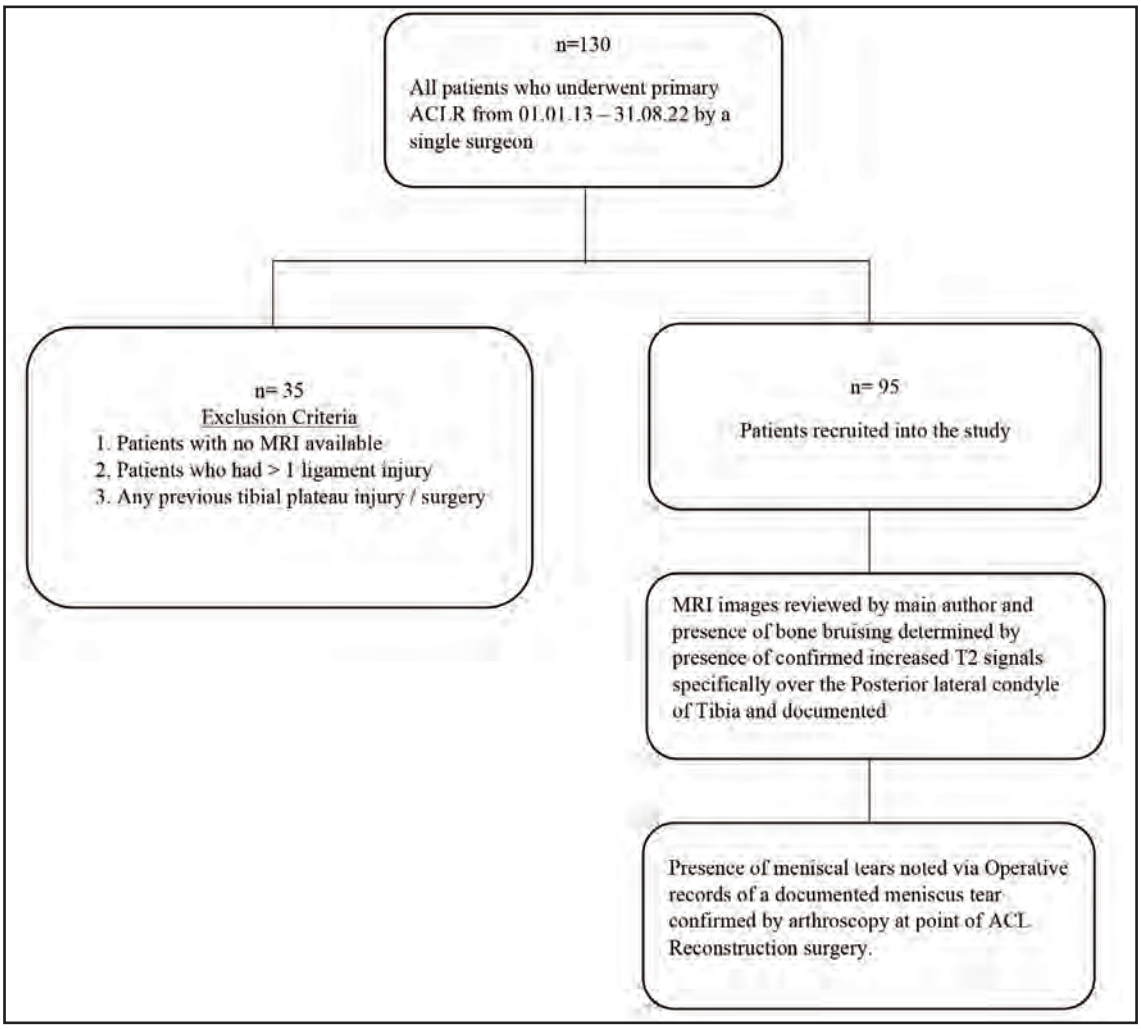

Fig. 1: Flowchart of patient selection.

The prevalence of bone bruising reduced significantly with time to MRI between 6 and 12 months (19.1%) and further reduced with time to MRI above 12 months (9.1%) (Table II).

Prevalence of an injury to at least one meniscus at the time of ACLR surgery was 83.2%. In 28.4% (27/95) of the patients, both the medial and lateral menisci were injured (Table III).

The prevalence of lateral meniscus injuries in patients with bone bruise was 53.9% (Table IV). Although this was higher compared to patients without bone bruise (46.1%), it was statistically not significant with a P value of 0.31 (Table IV). However, when comparing the association between the presence of lateral meniscus tear in posterolateral bone bruising using Fischer's Analytical testing, it was noted that the crude odds ratio with (95%CI) was 1.56 (0.68, 3.54) and was even higher when it was adjusted for time of injury to MRI 2.06 (0.77, 5.46) (Table IV).

DISCUSSION

The prevalence of posterolateral tibia bone bruising in the patients in this study was found to be 41%. Other similar studies have reported a prevalence of bone bruise of 48% with approximately 30% of them in the lateral tibial plateau.[22] A systematic review also reported that ACL-injured subjects showed an increased prevalence of lateral compartment bone bruises, more specifically in the posterior aspect of the lateral tibial plateau and lateral compartment of the femur.[16] This study showed no statistically significant difference in the prevalence of posterolateral tibia bone bruising when compared for sex, age and mode of injury (p>0.05). However, Fayad et al.,[33] and Engebretsen et al.,[34] reported a higher percentage of females demonstrated lateral tibial and medial tibial plateau bone bruises compared to males.

There was no statistically significant difference between the time to MRI intervals <3 and 3-6 months, which both showed a prevalence of about 62%. Other MRI studies have reported bone bruises, contusions or edema in the subchondral tibia and femur in more than 80 % of subjects with a complete ACL disruption.[12,13,16] However, the prevalence of bone bruising was significantly reduced for the group of patients with time to MRI performed between 6 and 12 months after injury to 19.1%. This prevalence was even lower for those patients in which MRI was performed after 12 months from

time of injury (9.1%). This is consistent with the fact that bone bruising is a haemorrhagic/oedematous response to the traumatic injury during an event resulting in ACL tear. These injuries tend to heal over time and may resolve within a year but may persist longer in some cases. These time differences between the time of the injury and the time MRI were performed may lead to inaccurate comparisons of bone-bruise prevalence and location among studies. Some studies have reported bone bruise on MRI performed in a period of 4-6 weeks after the injury[24,22] while other studies have identified persistent bone bruising up to 14 weeks after the injury.[35] The results from this study, however, showed a decline in the incidence of bone bruising after 6 months. 45.7% of the patients had an MRI performed >6 months from the time of injury and this could be a contributing factor for the lower overall prevalence of bone bruising among the patients in this study. The average waiting time for an MRI at the study hospital ranged from 1 to 6 months depending on the number of MRI requests, and this was one of the limitations of this study.

The prevalence of meniscal injury at the time of ACLR surgery among the patients in this study was 83.2% (79/95), of which involving the medial meniscus was 77.2% and that involving the lateral meniscus was 57%. The overall incidence of lateral meniscal tears in this study was 47.3% at the time of ACLR surgery. These findings are consistent with other studies which have shown the presence of lateral meniscal tears between 38.2 and 49.5%.[32,36] The higher incidence of medial meniscus tears in this study patients of 64.2% may be attributed to the chronicity of these injuries. Most of the surgeries for these patients were performed after 1 year from the initial ACL injury. The risk of developing a medial-sided meniscus injury in an ACL-deficient knee increases with time as demonstrated by the findings in this study. In a study of associated injuries in paediatric and adolescent ACL tears, it was also concluded that a delay in surgical treatment was associated with a higher incidence of medical meniscal tears.[36] Chhadia et al.,[37] and Vavken et al.,[38] also similarly reported a significant association between delayed surgery and the risk of medial meniscal injuries as well. The overall prevalence of lateral meniscus injuries in patients with bone bruise was 53.9% compared to 46.1% in patients without bone bruise. Although the percentage was higher, it was statistically not significant with a P value of 0.31. However, when comparing the association between the presence of lateral meniscus tear in posterolateral bone bruising, it was found that the crude odds ratio with (95% CI) was 1.56 (0.68, 3.54) and was even higher when it was adjusted for time of injury to MRI 2.06 (0.77, 5.46).

CONCLUSION

Prevalence of posterolateral tibial bone bruising in our study was 41%, and the prevalence of meniscal injury to either meniscus at the point of surgery was 83.2%, out of which the lateral meniscus tears were identified during ACLR surgery in 47.3% of the patients. We found there was no association between posterolateral tibial bone bruising to sex, age and mode of injury, but was sensitive to the interval between time of injury and MRI. The overall prevalence of lateral meniscal tears was higher in patients with posterolateral bone bruising but was not statistically significant with a P value of 0.31; however, the Crude odd ratio was 1.56 (0.68, 3.54) and was higher when adjusted to time of injury to MRI 2.06 (0.77, 5.46).

We suggest that an MRI has to be done as soon as possible after injury regarding bone bruising identification. We should be vigilant to look for lateral meniscal tears and anticipate for its repair in ACL injuries, especially when we identify posterolateral tibial bruising on the preoperative MRI.

FUNDING OF STUDY

This study is not funded by any organisation.

CONFLICT OF INTEREST

This study has no conflict of interest.

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A model of acceptance for family caregivers in the management of severe mental disorders

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ABSTRACT

Introduction: Managing severe mental disorders at home by family members as caregivers is considered the most efficient option compared to hospital care. However, on the other hand, it can lead to the emergence of physical and psychological burdens on the caregiver. To improve their role optimally in caregiving, families will undergo psychological adaptation, reaching the highest level of acceptance. Other factors, such as stigma, social support, social norms, caregiving experience and personal characteristics, influence family acceptance. This study aims to determine a family acceptance model to enhance the role of the family.

Materials and Methods: The research instruments used included The McMaster Family Assessment Device Adaptation, IEXPAC, and S.N.Q. 22, F.Q., P.S.Q., Social Support Questionnaire shortened version, The Family Focused Mental Health Practice Questionnaire and extraversion personality questionnaire. The questionnaire was distributed to caregivers with a population of 175 individuals. The sample size of this study was 133 individuals selected through proportional random sampling. The data were analysed using Structural Equation Modeling Partial Least Square (SEM-PLS) with Amos software v.26.0.

Results: The phase one research showed that intention and satisfaction are the leading indicators of family acceptance that can influence family roles. At the same time, family acceptance is influenced by personal character (p≤0.001), care experience (p≤0.001), social support (p≤0.001), social norms (p=0.004), symptom severity (p≤0.001), and stigma (p≤0.001). Additionally, family acceptance significantly impacted the family's caregiving role (CR=6.573, p≤0.001).

Conclusion: It was found that the family acceptance model to improve the family's role in the care of patients with severe mental disorders focuses on the acceptance that the family has to be able to carry out its role well in patients. To improve family acceptance, families still lack the personal character expected in caring for patients with severe mental disorders at home. It is necessary to increase commitment to care and positive values in life.

KEYWORDS:
Family, caregiver, family acceptance, severe mental disorder

INTRODUCTION

Mental disorder is a medical condition affecting a person's thoughts, mood, emotions and ability to interact with others and perform daily functions.[1] Mental disorders are categorised into mild and severe mental disorders based on symptoms that disrupt an individual's functioning.[2] The number of individuals with severe mental disorders such as schizophrenia, bipolar disorder, major depression, panic disorder and obsessive-compulsive disorder has been increasing yearly.[3]

Severe mental disorders have become one of the 'burden diseases' that are an exciting topic of discussion at the annual conferences of the American Psychiatric Association in Miami, Florida, United States of America since 1995.[4] The prevalence of severe mental disorders is significant worldwide, particularly among the adult population. Individuals with these disorders experience impairments in brain function, involving numerous changes in brain structure, chemistry and genetic factors.[5] As a result, significant clinical symptoms arise, including disturbances in emotions, thoughts and behaviours, leading to distress and suffering.[6]

A report from the World Health Organization (WHO) in 2018 showed that more than 430 million individuals experience mental health problems. In Indonesia, the prevalence of severe mental health disorders is currently around 7 per 1000 people or about 1,652,000 people. In 2013, the number of individuals experiencing mental health disorders in East Java reached around 1.4% of the total 38,318,791 people or about 53,646 people. Meanwhile, in Surabaya, the rate of mental health disorders was about 0.2% of the total population of 1,602,875 people, roughly equivalent to 3,206.[7]

In Indonesia, specifically in the Bantur Primary Health Center area, Bantur District, Malang Regency, the reported number of individuals with severe mental disorders until May 2023 is 225. In that area, all individuals with severe mental disorders receive home-based management or community-based care, known as Community Mental Health Nursing (CMHN), which aims to save costs associated with high hospital care expenses.[8] Individuals with severe mental disorders often experience complex disabilities and require assistance from others to carry out their daily functional activities.[10,11] It burdens various parties, including the

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government, society and families. A burden on the family can occur due to prolonged treatment, frequent recurrence of symptoms, prolonged use of medications and the need for assistance in daily life.[12] The various limitations mentioned ultimately become reasons for families to manage medical care at home under the supervision of the Primary Health Center through the Community Mental Health Nursing program.[13] In this home care management, the family acts as caregivers who are considered experts in mental health, while the responsible doctor carries out the medical treatment management at the Primary Health Center.[12]

The optimisation of care for severe mental disorders through home-based family management requires a holistic and integrated approach involving mental health services at the Primary Health Center, the community and the family.[14] The home care of individuals with mental disorders by their families emphasises the importance of community strength, family support and the empowerment of the individuals in the care and recovery process. In this program, the family plays a central role in organising the care of the individuals while they are at home,[15] with tasks such as supervising medication intake, providing motivation, involving the individual in social interactions, teaching activities and providing vocational training.[11,16]

Home care management for individuals with severe mental disorders by families is not limited to Indonesia. In Sweden, this type of care is also provided by family members living in the same household, such as partners, children, parents or close relatives. Managing care for people with mental disorders at home has many advantages. In addition to lowering treatment costs, it can improve patients' social skills because they live with their families. However, ensuring that this form of care is complemented by increased resources and a well-developed healthcare service system to support the families and individuals involved adequately is crucial.[17] The role of the family in shouldering the primary responsibility for the healthcare of an ill family member is significant.[18] It will also bring other impacts, namely emotional and economic burdens on the family.[4]

The quality of care the family provides to the person with the illness can indicate the level of family concern. The family's involvement in delivering high-quality healthcare and utilising various available resources for the individual's care is a form of family acceptance.[1,19] However, not all families reach the acceptance stage in the psychological adjustment process. Personal and structural factors can influence family acceptance. Individual factors include demographic characteristics, the relationship with the person with the illness, self-confidence, experience and coping strategies during caregiving. Meanwhile, structural elements encompass social values and norms, social support and social pressure. These factors interact with each other and influence an individual's acceptance of others.[20]

The influence between latent and observed variables in this study will be measured in terms of their direct and indirect relationships using structural equation models (SEM) within the framework of the family acceptance model. The novelty of this research is that a newly developed family acceptance model was found to have a more substantial construction in explaining the family acceptance process, aiming to improve the family's role in caring for individuals with severe mental illness, compared to previously existing models.

Hypotheses

Hypothesis 1 (H1): Symptom severity significantly affects stigma.
Hypothesis 2 (H2): Stigma significantly affects social support.
Hypothesis 3 (H3): Social support significantly affects personal character.
Hypothesis 4 (H4): Stigma significantly affects personal character.
Hypothesis 5 (H5): Social support significantly affects family acceptance.
Hypothesis 6 (H6): Stigma significantly affects family acceptance.
Hypothesis 7 (H7): Symptom severity significantly affects family acceptance.
Hypothesis 8 (H8): Personal character significantly affects family acceptance.
Hypothesis 9 (H9): Personal character significantly affects the caregiving experience.
Hypothesis 10 (H10): Experience caregiving significantly affects family acceptance.
Hypothesis 11 (H11): Social norms significantly affect family acceptance.
Hypothesis 12 (H12): Personal character significantly affects family roles.
Hypothesis 13 (H13): Social norms significantly affect family role.
Hypothesis 14 (H14): Family acceptance significantly affects family role.

Figure 1 represents an image that depicts the hypotheses and the relationships among variables as a structural equation model (SEM).

MATERIALS AND METHODS

Participants and Data Collection

This research was conducted in the Bantur Primary Health Center, Bantur District, East Java Province, Indonesia. The research instrument used was a questionnaire distributed directly to the respondents after checking and verification by the researcher. The research was conducted in April 2023, and all returned questionnaires were checked for data completeness, resulting in 133 respondents.

Sample Size Calculation

The sampling technique used was proportional random sampling, where the researcher obtained the total number of families with family members with severe mental disorders that met the criteria in all villages within the Bantur Primary Health Center area. The study population consisted of families caring for individuals with severe mental disorders and living together with them, providing direct care. The researcher excluded families who were not living together, totalling 175 individuals. After calculating using the minimum sample size formula based on Slovin's recipe, adding a 10% anticipation for dropouts or non-response, the sample size of 133 respondents was obtained. Then, it was

calculated proportionally using the random sampling formula, where ni (the number of sample members per stratum) is Ni (the population size per stratum) divided by N (the total population size) multiplied by n (the full sample size). The proportionate numbers for each village are as follows: Village Bandungrejosari with 36 individuals, Sumber Bening with 27 individuals, Bantur with 41 individuals, Wonorejo with 10 individuals and Srigonco with 19 individuals.

Consent to Participate and Ethics

All participants in this study voluntarily participated in the research activities and signed informed consent on the questionnaire sheet by providing their signatures directly. The ethical approval for this research has been obtained from the Ethics Committee of Brawijaya University, Malang, Indonesia, through an approval letter with the number No.39/EC/KEPK-S3/03/2023 dated 10 March 2023, following the Helsinki Declaration guidelines.

Instruments

The instrument used in this study is a questionnaire. The first questionnaire measures personal character and comprises 10 items adopted from the Extraversion Personality Questionnaire.[21] The second questionnaire is about social support and consists of six items adapted from the Social Support Questionnaire shortened version.[22] The third questionnaire is about stigma and consists of 12 items modified from the Perceived Stigmatization Questionnaire (PSQ).[23] The fourth instrument is about symptom severity and consists of 15-item questions modified from The Family Questionnaire (FQ).[24] The fifth instrument is a questionnaire about social norms, consisting of 8-item questions modified from The Social Norms Questionnaire (SNQ22).[25] The sixth instrument is a questionnaire about caregiving experience, consisting of six item questions adopted from the Instrument To Evaluate The Experience of Patients With Chronic Diseases (IEXPAC).[26] The seventh instrument is a questionnaire about family acceptance, consisting of 10 item questions adopted from the modified version of The McMaster Family Assessment Device Adaptation.[27] The last instrument is a questionnaire about family roles, consisting of 21 items adapted from The Family Focused Mental Health Practice Questionnaire (FFMHPQ).[28] The instruments used in this study have gone through a process of language adjustment that is easy to understand and adapted to local culture. All instruments were measured using a Likert scale, where "never" is scored as 1, 'sometimes' as 2, 'often' as 3 and 'very often' as 4. The responses were then categorised as follows: poor (<25%), fair (26-50%), good (51-75%) and excellent (>75%). The instruments were also tested for validity using the Pearson product–moment correlation method, which correlates the item scores on the questionnaire with the total scores. The obtained correlation coefficient (r) was compared with the critical value from the Pearson product–moment correlation table at a significance level of 5%. The item is considered valid if the received r is greater than or equal to the table value (0.361, n=30). Furthermore, the reliability of the variables was tested using Cronbach's alpha coefficient, where a value greater than 0.6 indicates reliability. It was found that all questions and variables were both valid and reliable.

Data Analysis

The data analysis consists of descriptive analysis, hypothesis testing and testing the structural model using SEM. The data analysis was conducted using IBM SPSS Statistics 26.0 software. Descriptive analysis presented information about the respondents' socio-demographic data, such as age, education and occupation. Next, a goodness-of-fit test was performed to assess the fit of the observed data to the predicted model. The goodness-of-fit test was conducted using AMOS 26.0 software. Following the goodness-of-fit trial, the indicators were examined to reflect the latent variables through confirmatory factor analysis (CFA) based on the Standardized Regression Weight output. All hands were found to reflect the variables, with estimate values greater than 0.5. The next step was hypothesis testing, which aimed to analyse the relationships within the structural model. The results of hypothesis testing were analysed based on the significance level of the causal relationships between constructs, using the critical ratio (CR) values. A critical ratio value greater than or equal to 1.96 at a significance level of 5% indicated a significant relationship. Finally, the model fit of family acceptance was obtained by testing the Structural Equation Model (SEM).

Indicators of Model Fit

The goodness-of-fit test was conducted using IBM AMOS 26.0 software. This model-fit test is used to assess the adequacy of the observed input with the predictions from the proposed model. The test yielded the following results: CMIN/DF value of 5.710 (good fit), GFI value of 0.447 (good fit), as a higher GFI value indicates a better model fit, and AGFI value of 0.363 (good fit). Therefore, it can be concluded that the overall model is a good fit, and no modifications are necessary. Other data are presented in Table III.

RESULTS

Characteristic of Participants

Nearly half of the respondents fall into pre-elderly (45-59), with 85 people (64%). Almost half of all the respondents have a distance to the Primary Health Centers ranging from 1 to 4 km, with a total of 39 people (29.3%), while a small portion of them travel a distance of more than 16 km to the Primary Health Center, with a total of 17 people (12.8%).

Furthermore, more than half of the respondents have a family size ranging from 1 to 3 members, with 71 people (53.4%). More than half of the respondents have an income of 1-2 million rupiahs, comprising 75 people (56.4%). Regarding gender, more than half of the respondents are female, with 79 people (59.4%). Most respondents have completed junior high school education, with 82 people (61.7%). Nearly all respondents work in miscellaneous occupations, totalling 95 people (71.4%). Other data are presented in Table I.

Structural Equation Models Analysis

The results of the SEM analysis indicate several significant relationships between variables, with critical ratio (CR) values greater than or equal to 1.96, showing a considerable influence. The positive (+) or negative (–) signs indicate the direction of the result, whereas a negative sign indicates a

Table I: Characteristics of socio-demographic participants (n=133)

Characteristic	Frequency	Percentage
Adult (19-44)	28	21
Pre-elderly (45-59)	85	64
Elderly (>60)	19	15
Total	133	100
Distance to health center		
1-4 km	39	29.3
5-8 km	25	18.8
9-12 km	27	20.3
13-16 km	25	18.8
>16 km	17	12.8
Total	133	100
Number of family members		
1-3 people	71	53.4
4-6 people	60	45.1
>6 people	2	1.5
Total	133	100
Income		
<65.50 USD	53	39.8
65.50-131.00 USD	75	56.4
> 131 USD	5	3.8
Total	133	100
Gender		
Male	54	40.6
Female	79	59.4
Total	133	100
Education		
No formal education	17	12.8
Elementary school (SD)	82	61.7
Junior high school (SMP)	27	20.3
Senior high school (SMA)	6	4.5
Higher education (College/University)	1	.8
Total	133	100
Occupation		
Unemployed	14	10.5
Entrepreneur	10	7.5
Private sector employee	13	9.8
Freelancer	95	71.4
Civil servant	1	0.8
Total	133	100
Ethnicity		
Javanese	131	98.5
Maduranese	2	1.5
Total	133	100
Duration of caregiving		
<1 year	3	2.3
1-3 years	19	14.3
4-6 years	31	23.3
7-10 years	32	24.1
>10 years	48	36.1
Total	133	100
Relationship with the patient		
Husband	8	6.0
Wife	9	6.8
Child	41	30.8
Parent	29	21.8
Sibling	46	34.6
Total	133	100

Note: Age categories according to the Indonesian Ministry of Health, 2019.

Table II: Critical ratio, probabilities and estimate among variables (n=133)

Variable	CR	p-value	Estimate	Influence
Symptom severity (X4) → Stigma (X3)	-0.432	0.666	-0.26	No significant
Stigma (X3) → Social Support (X2)	-0.608	0.543	-0.96	No significant
Social Support (X2) → Personal Character (X1)	5.382	<0.001	0.407	Significant
Stigma (X3) → Personal Character (X1)	5.109	<0.001	0.725	Significant
Social Support (X2)→ Family Acceptance (Y2)	8.206	<0.001	1.795	Significant
Stigma (X3) → Family Acceptance (Y2)	4.289	<0.001	1.465	Significant
Symptom Severity (X3) → Family Acceptance (Y2)	-4.683	<0.001	-0.465	Significant
Personal Character (X1) → Family Acceptance (Y2)	-4.345	<0.001	-1.743	Significant
Personal Character (X1) → Experience caregiving (Y1)	2.171	0.030	0.436	Significant
Experience caregiving (Y1) → Family Acceptance (Y2)	3.512	<0.001	0.205	Significant
Social Norms (X5) → Family Acceptance (Y2)	2.906	0.004	0.167	Significant
Personal Character (X1) → Family role (Y3)	3.714	<0.001	0.451	Significant
Social Norms (X5) → Family role (Y3)	4.971	<0.001	0.283	Significant
Family Acceptance (Y2) → Family role (Y3)	6.573	<0.001	0.380	Significant

Table III: Model fitness index

Index	Recommended values	Value of model	Meaning
Chi-square	<341.95	5.7	Good fit
Probability level	≤0.05	0.000	Good fit
CMIN/DF	<2.00/3.00	5.710	Enough fit
GFI ≥0.90	0.447	Enough fit	
AGFI	≥0.90	0.363	Enough fit
RMSEA	≥0.90	0.189	Bad fit
TLI ≥0.90	0.453	Enough fit	
NFI ≥0.90	0.454	Enough fit	

Note: χ2, chi-square; GFI, goodness of fit index; AGFI, adjusted goodness-of-fit index; CFI, comparative fit index; df, degrees of freedom; NFI, normed fit index; PGFI, parsimony goodness of fit index; NFI, normed fit index; RMSEA, root-mean square error of approximation

reverse effect. The significance level between variables is determined by values with a significance level of <0.05, marking a significant relationship. (Table II)

Based on the standardised regression weight, in the family acceptance model, it is known that symptom severity does not have a significant influence on stigma (CR= -0.432, p=0.666), stigma does not have a significant effect on social support (CR = -0.608, p=0.543), social support has a significant influence on personal character (CR = 5.382, p<0.001), stigma has a significant effect on personal character (CR=5.109, p<0.001), social support has a significant influence on family acceptance (CR=8.206, p<0.001), stigma has a significant influence on family acceptance (CR=4.289, p<0.001), symptom severity has a significant effect in the opposite direction on family acceptance (CR= -4.683, p<0.001), personal character has a significant effect in the opposite direction on family acceptance (CR= -4.345, p<0.001), personal character has a significant influence on caregiving experience (CR=2.171, p=0.030), caregiving experience has a significant effect on family acceptance (CR=3.512, p<0.001), social norms have a significant influence on family acceptance (CR=2.906, p=0.004), personal character has a significant effect on family role (CR=3.714, p<0.001), social norms have a significant influence on family role (CR=4.971, p<0.001) and family acceptance has a significant effect on family role (CR=6.573, p<0.001).

DISCUSSION

This study aimed to identify the influence of social support, personal character, stigma, social norms, caregiving experience, symptom severity, family acceptance and family caregiving roles on caring for individuals with severe mental disorders in Bantur, East Java, Indonesia. The research findings indicate that all the mentioned variables have a significant relationship with family acceptance and caregiving roles, except for the relationship between symptom severity and stigma and between stigma and social support, which were not found to be significant (Figure 2).

The figure above explains the statistical model of family acceptance. It is an analytical approach to understanding the factors that influence families of people with severe mental illness. This model seeks to identify the relationship between various independent variables or predictive factors, including social norms, social support, stigma, personal characteristics, and symptom severity, with the dependent variable, family acceptance. The aim is to provide a deeper understanding of these factors in influencing family acceptance to improve the role of the family. This structural model is built by correlating the variables through hypothesis proving, which is discussed as follows:

1. **The Influence of Symptom Severity on Stigma**
   In the final model, symptom severity does not influence stigma in family acceptance.29 Stigma is one of the main reasons families caring for individuals with severe mental disorders do not seek help. This fact can explain the

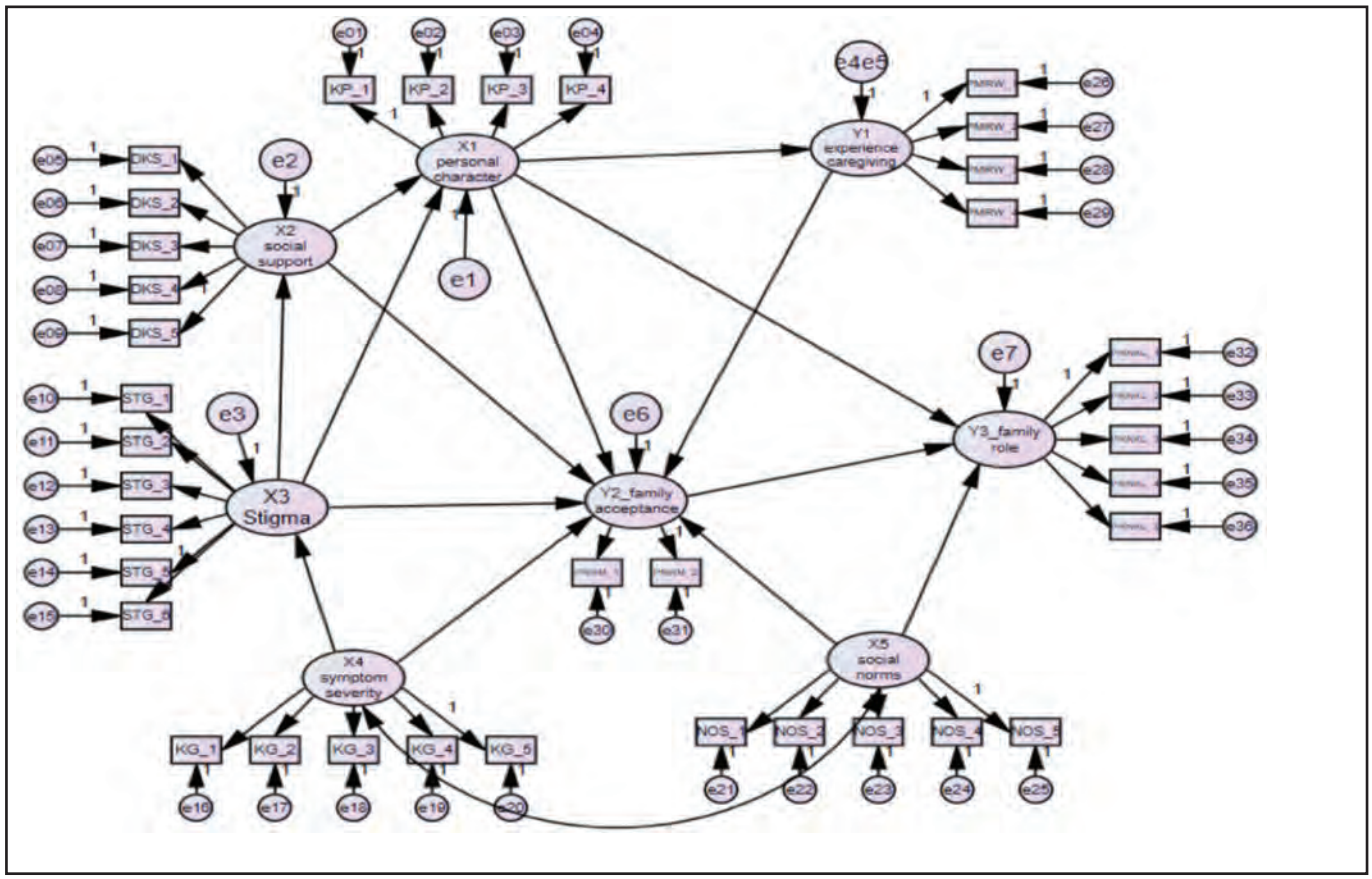

Fig. 1: The original hypothetical model (M1) was performed using IBM SPSS Statistics and Amos 26.0 statistical software.

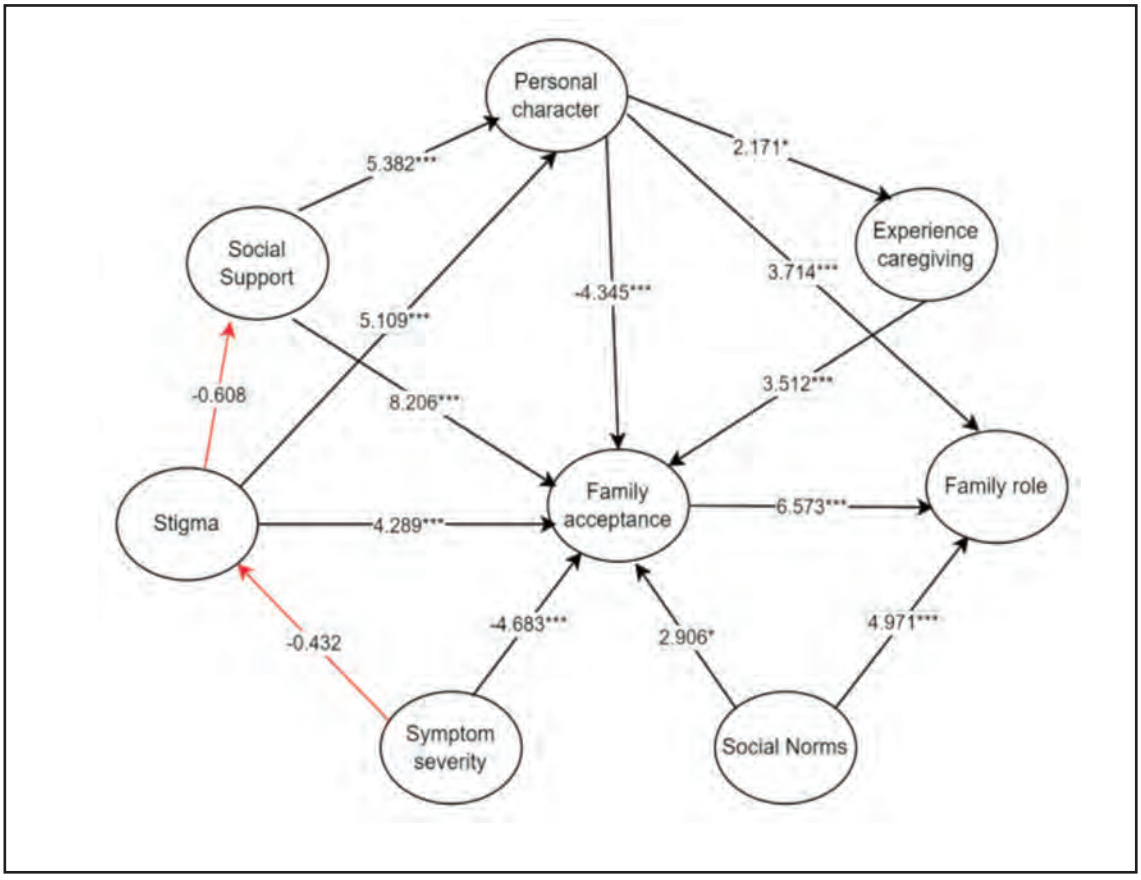

Fig. 2: The final model (M2) with standardised regression weights, ***p<0.001; **p<0.01; *p<0.05

findings of this study, which suggest that families may anticipate and prepare for stigma by considering the symptoms of the affected individuals as tolerable. Thus, it is hypothesised that higher symptom severity experienced by the patients would not necessarily lead to increased stigma. Because the families have already taken anticipatory measures to prevent the occurrence of stigma.[30] This assumption is supported by research findings stating that public stigma in Latin America in 2018 remains high, ranging from 40.5% to 70%. Furthermore, an individual's education level significantly influences their understanding of the severity of severe mental disorders. Education level is associated with a person's ability to recognise signs and symptoms or the severity of severe mental disorders. Therefore, a lack of knowledge and information may lead families to perceive the symptoms experienced by the affected individual as less serious.[31]

2. **The Influence of Stigma on Social Support**
   Stigma does not affect social support; according to theory, stigma is a multifaceted construction built from three separate but interrelated structures: perceived, anticipated and internalised stigma.[13] Perceived stigma is the stigma received based on the past or the family is currently experiencing. Meanwhile, anticipated stigma reflects an individual's prediction of future stigma.[32] Based on this theory, it can be explained by the researcher that the stigma that has been felt or will be felt by the family results in the family no longer expecting support from other people. So, with low stigma, it does not also make the family feel increasing support because there are already limitations from the family itself that there is no hope for support from other people.[33]

3. **The Effect of Stigma on Personal Character**
   As previously explained, stigma in the family, whether it is felt, anticipated or internalised directly, significantly affects personal character. As previously described, stigma makes a person no longer have hope for patient care or recovery. However, this hope is one indicator of personal character. This fact is in line with the results of research that the higher the stigma, the lower the personal character.[31]

4. **Social Support's Significant Effect on Personal Character and Acceptance**
   Social support has a significant effect on personal character and family acceptance. The results of this study indicate that the higher support received by the family can affect the personal characteristics of the family, such as beliefs and expectations for caring for people with severe mental disorders. This statement aligns with Taylor et al.,[34] which states that social support is a material or psychological resource from an individual's social network that can help them face challenges. The social support that the family receives from other people can develop the family's sense of purpose and purpose in caring for others. Further research states that perceived social support can significantly predict one's feelings and expectations in the future. The existence of hope, belief and willingness to care shows that it directly affects family acceptance of patients.[15,35]

5. **Personal Character's Significant Effect on the Experience of Caregiving, Family Acceptance, and Family Roles**
   The Personal character significantly affects the experience of caring for, family acceptance, and family roles. This study's results align with the previous theory that beliefs and individual expectations can increase patients' acceptance. This character also gives the family a positive personal basis in developing themselves to face challenges in caring for patients. A person's ability to use knowledge and other positive self-sufficiency is called experience in caring. This statement is consistent with Metzelthin et al. and Nguyen,[36] which state that the family as a caregiver can feel a loss of role when experiencing changes in responsibility, distance, or other changes that occur. Included in this context is when the family loses the experience of caring for or changes in experience, it will affect its role.[37] It is in line with research results, which show that the experience of managing will affect the function of the family to patients. It is necessary to develop personal character to develop acceptance and a "sense of role".[38]

6. **Social Norms' Significant Effect on Acceptance and Family Roles**
   Social norms significantly affect the acceptance and role of the family. Social norms can help or, on the contrary, burden individuals who are in the environment of these social norms.[36] Actions taken by people with severe mental disorders in the form of collective and individual behaviour allow society to change disliked or liked norms.[37,39] Social norms can reduce a person's autonomy to do or do something. Suppose this social norm is considered discouraging to the family. In that case, it can influence the family not to accept patients, so it can ultimately affect the role of the family in care.[40]

7. **Family Acceptance's Significant Effect on Acceptance and Family Roles**
   Acceptance has a significant effect on the role of the family, and family acceptance is defined as a condition in which the family is voluntarily involved and actively participates in the care of people with severe mental disorders.[39] From this theory, it can be explained that individuals who want to live in the same house and even care for these patients either directly or indirectly cause individuals to take responsibility for the treatment and activities of patients with severe mental disorders every day.40 And conversely, individuals who do not accept patients will lead to reduced family behaviour in administering drugs and involving patients in daily activities.

CONCLUSION

The conclusions from the results of this study focused on variables such as stigma, social support, social norms, personal characteristics, caring experiences, acceptance, and family roles. Stigma and social support have no effect, and social support also has no impact on personal character. What has the most significant effect is social support on family acceptance and personal character, as well as family acceptance of family roles. We can suggest the results of this

study to families to emphasise improving personal character because this personal character can change our perception and mindset to gain social support and reduce stigma. Good personal character will directly affect family acceptance so that the family can carry out its role properly. In addition to supervising taking medication, the family can involve patients in daily activities and teach them to work or be productive.

Application of Research Ethics

This study was approved by The Health Research Ethics Commission, Faculty of Medicine, Universitas Brawijaya, protocol number No.39/ EC/ KEPK – S3/ 03/ 2023

Informed Consent

All participants in this study agreed and signed informed consent.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

The clinical implications of *Porphyromonas gingivalis* and its detection methods – a systematic review

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ABSTRACT

Introduction: Mounting evidence has shown the significant correlation between periodontitis and the development of other comorbidities, such as cardiovascular disease due to periodontopathogenic bacterial migration and colonisation. As the main etiologic agent of periodontitis, the role of *Porphyromonas gingivalis (P. gingivalis)* has been widely explored as the main culprit and its early detection is crucial to control the exacerbation of diseases. This review aims to identify and summarise all clinical diseases that potentially developed due to the presence of *P. gingivalis* and discover all its detection methods that have been developed.

Materials and Methods: Full-text articles of case report, case control, cohort and cross-sectional studies that were published from 1st January 2012 until 30th June 2022, were searched using PubMed, CINAHL and Scopus. Periodontal related diseases were excluded in this review due to its well-known associated disease with *P. gingivalis*. A comparison studies of detection methods were also excluded in this review.

Results: Out of 612 articles that were screened, only 106 met the eligibility criteria to be selected for further review. Risk of bias was performed using FEAT principles and reviewers' discussion. A total of 21 final articles that were reviewed showed significant correlation with *P. gingivalis* and were classified into several clinical domains. Twelve out of 13 detection methods showed high sensitivity and specificity with short duration analysis.

Conclusion: Due to asymptomatic periodontal disease and the high prevalence of *P. gingivalis*-associated clinical diseases, this review suggests the need for oral public health awareness and early screening for the bacterium detection especially among elderly groups to maintain their quality of life.

KEYWORDS:
Clinical implication, Porphyromonas gingivalis, diseases, periodontal disease, detection method, systemic impact

INTRODUCTION

Porphyromonas gingivalis (P. gingivalis) is known to be the keystone and aetiologic agent in the progression of irreversible periodontitis, a chronic form of periodontal disease and had gained much interest globally due to its pathogenicity and virulence factors that cause destruction in the gingival and periodontal tissues.[1] In the early phase, periodontal disease is asymptomatic and painless, which could be the reason for most patients not seeking a dental treatment, subsequently becoming the site for bacterial colonisation, and leading to chronic periodontitis. The global prevalence of periodontitis demonstrated high occurrence in elderly group (82%) compared to adults (73%) and adolescents (59%), and thus, the disease is predicted to increase by years due to the increasing older population.[2] In the Indian population, *P. gingivalis* was highly detected in chronic periodontitis patients at 79.16%, and 29% in the healthy group.[3]

Over the last two decades, periodontal disease has been strongly associated with several systemic diseases such as cancer, atherosclerosis, rheumatoid arthritis, thus reducing individual performance and quality of life.[4] Numerous findings had revealed the role of *P. gingivalis* in the progression and exacerbations of existing disease by migrating from the bloodstream to the distant sites such as heart, liver, brain and placenta, then manipulating the immune system, causing immunosuppression and tissue damage.[5] Therefore, early detection of *P. gingivalis* is crucial to address the progression of other diseases and control their aggressiveness. Several advanced techniques have been developed such as polymerase chain reaction (PCR) and magnetic-nanobead based assay to detect the infection. Different sampling techniques were believed to affect the results.[6]

Most of the previous article reviews were only focused on the relationship between *P. gingivalis* and one specific disease or one class of disease, while the relationship between the bacterium and overall health, as well as the bacteria detection methods are still lacking. Therefore, in this review, our main objectives are: 1) to identify all the clinical diseases that are potentially due to the presence of *P. gingivalis* and 2)

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to identify all types of detection methods that have been developed for *P. gingivalis* detection.

MATERIALS AND METHODS

Criteria of selected studies in our review are as described as below:

1) Type of clinical disease: *P. gingivalis* is the main culprit and must be significant with a particular disease.
2) Type of detection: Multiple bacterial detection and comparison of detection method articles were excluded.

Search methods for identification of studies (including PRISMA 2009 flowchart)

Case report, case control, cohort and cross-sectional studies that was published from 1st Jan 2012 until 30th June 2022, were searched using PubMed, CINAHL and Scopus. A total of 612 full text articles were selected. Books, monograph, conference abstracts, editorials, letters, comments and reviews were excluded.

The search terms used were (*P. gingivalis* and clinical), (*P. gingivalis* and clinical), (*P. gingivalis* and health), (*P. gingivalis* and health), (*P. gingivalis* and disease), (*P. gingivalis* and disease), (*P. gingivalis* and importance), (*P. gingivalis* and importance), (*P. gingivalis* and significance), (*P. gingivalis* and significance), (*P. gingivalis* and implication), (*P. gingivalis* and implication), (*P. gingivalis* and association), (*P. gingivalis* and association), (*P. gingivalis* and detection), (*P. gingivalis* and detection), (*P. gingivalis* and culture), (*P. gingivalis* and culture), (*P. gingivalis* and isolation), (*P. gingivalis* and isolation), (*P. gingivalis* and cultivation), (*P. gingivalis* and cultivation), (*P. gingivalis* and cultivate), (*P. gingivalis* and cultivate), (*P. gingivalis* and identification), (*P. gingivalis* and identification), (*P. gingivalis* and methods), (P. gingivalis and methods), (*P. gingivalis* and ways), (*P. gingivalis* and ways), (*P. gingivalis* and technique), (*P. gingivalis* and technique), (*P. gingivalis* and techniques), (*P. gingivalis* and techniques), (*P. gingivalis* and assays), (*P. gingivalis* and assays), (*P. gingivalis* and assays), (*P. gingivalis* and assays). The results of each search terms were generated in Mendeley Reference Manager. From the main reference master page, subsequent subgroups references were generated based on the series of search terms mentioned. Any duplicated articles were deleted. Three independent reviewers checked and reviewed the articles independently.

The geographical area covered are all countries and the language of the publication was restricted to English in all databases. The PRISMA flow diagram for the search strategy is summarised in Figure 1 below.

Data Collection and Analysis

Data collection was done by two reviewers (MSES & NANS) and checked by three reviewers (SA, EMA&, HAH) independently. After finalising the studies to be included for analysis, full texts of all the eligible studies were retrieved. Two reviewers (RM & MSES) independently screened titles and abstracts for eligible studies, followed by full-text reading for methodological validity. If multiple publications of the same study were retrieved, only the most recent relevant data was included from these publications.

Qualitative synthesis was done by descriptive comparison of the reviewed articles for the clinical implications of *P. gingivalis* in overall health, the detection methods of the bacterium and risk of bias comparison. The risk of bias is evaluated based on the author's judgement using FEAT principles and discussion with other reviewers.[7] Four core principles that risk of bias assessments must meet (FEAT: assessments must be Focused, Extensive, Applied and Transparent) to enable the risk of bias to be low. If one component is not fulfilled, the risk is considered moderate. Meanwhile high risk is equivalent to the study that is unable to meet two or more of the core principles. Meta-analysis was not performed due to difficulty in obtaining some of the estimates which were not reported in the articles.

RESULTS

P. gingivalis is associated with numerous clinical diseases and involves multiple systems in the human body. As summarised in Table I, the organism is responsible for gingivitis, carcinoma progression, cognitive deterioration, arthritis development, abnormal sugar control, cardiovascular diseases and fatty liver formation. The presence of *P. gingivalis* antibodies also increases the odds of having intracranial aneurysms and diabetic retinopathy. Antenatally, those with the presence of *P. gingivalis* are 6.7 times more likely to have a preterm birth and 2.8 times more likely to have a foetus with intrauterine growth restriction.

Detection Methods of *P. gingivalis*

Most of the detection methods of *P. gingivalis* used in all studies were just reused the established protocol, especially the primers used for the molecular detection technique, that sometimes were not reproducible by time due to the fact that primers are not 100% conserved. Numerous detection methods for *P. gingivalis* have been developed with the main objective to detect the species at a fast rate of detection, but with high specificity and sensitivity. A comparative table as shown in Table II representing the advantages and disadvantages of all developed detection techniques for *P. gingivalis*. Different sampling techniques were believed to affect the results.[6]

Risk of Bias in Included Studies

There were 26 studies with low risk of bias and seven articles with moderate risk category as highlighted in Table III. Methodologically, these studies were conducted cross sectionally, retrospectively or in a cohort study. Some are in the form of a case report in which the biases were looked at from the detailed description of the case and its objectives. Majority of the studies have low selection bias as the study population and eligibility criteria were clearly mentioned. Most of the articles highlighted a novel and standard way of performing the bacteria detection. However, one study by Brun et al.,[38] has high selection bias as within the study, different samples were taken from different specimen sites, without making the methodology to be homogenous to all sampling processes. Nevertheless, this study can be considered low to moderate bias as other categories of bias assessment were considered low.

Table I: List of reviewed articles on P. gingivalis, their characteristics and clinical importance

Authors	Study design	Sample size	Population	Period	Clinical importance of *P. gingivalis*	Clinical domain	Odds ratio (OR)/Relative risk (RR (confidence interval) [*p*-value]
Kong et al. (2021)[8]	Retrospective analysis	50 cases	Patients attending to the First Affiliated Hospital of Henan University of Science and Technology	Data collection between January 2012 and December 2018	*P. gingivalis* was highly detected in the late stage of oesophageal squamous cell carcinoma (ESCC)(64.7%) and showed positive correlation with lymph node metastasis, where *P. gingivalis* was also detected in lymphatic metastasis tissues of ESCC patients at 60%.	Oncology	[p<0.05]
Liu et al. (2021)[9]	Retrospective study	309 cases	Subjects were primarily obtained from Henan province, including the First Affiliated Hospital of Henan University of Science and Technology, Hospital of Zhengzhou University, and Anyang Tumor Hospital Patients were recruited from	Data collection between 2010 and 2013. Next follow up within 5 years.	The detection of *P. gingivalis* was significantly higher in lung squamous carcinoma tissues, compared to adjacent lung tissues.	Oncology	(CI:17.609-28.995) (χ2:6.365) [p<0.05]
Chang et al. (2019)[10]	Case control	61 cases, 30 controls	Affiliated Stomatological Hospital of China Medical University.	Data collection between 2013 and 2014.	*P. gingivalis* has been detected in the oral squamous cell carcinoma tissues at 60.7%, compared to healthy tissues, 13.3%.	Oncology	[p<0.05]
Ahn J et al. (2012)[11]	Prospective study	7852 participants	The participants were obtained from the National Health and Nutrition Examination Survey III (NHANES III) survey-based USA population.	Data collection between 1991 and 1994.	High levels of antibody *P. gingivalis* accompanied with an excess orodigestive cancer mortality.	Oncology	RR3.03 (CI: 0.99-9.31) [p=0.006]
Sansores-España et al. (2022)[12]	Case control	20 cases 10 controls	Control patients were recruited from the Faculty of Dentistry, Autonomous University of Yucatan.	Data collection from June and December 2019.	80% of Alzheimer's disease patients had a chronic periodontitis, with high abundance of *P. gingivalis* and its presence had negative correlation with Montreal cognitive assessment (MoCA) test values, suggesting the severe cognitive impairment patients tend to have a higher P. gingivalis load.	Neurology	-
Rasheed et al. (2013)[13]	Case report	1 case	34-years old-male patient admitted at Thammasat University Hospital, Thailand.	-	Patient was presented with subdural empyema and sinusitis. *P. gingivalis* was detected in the subdural empyema's patient in his yellowish purulent.	Neurology	-
Hallikainen et al. (2021)[14]	Case-control	227 cases, 1096 controls	Patients were recruited from Kuopio University Hospital (KUH). Controls were obtained from cross-sectional Finnish Health 2000 Health survey study	-	IgA antibodies against *P. gingivalis* were 1.5 times higher in intracranial aneurysms cases compared to control	Neurology	OR:1.4 (CI:1.1-1.8) [p≤0.003]
Wisutep et al. (2022)[15]	Case report	One case	80-years-old woman from Hospital of Mahidol University, Bangkok, Thailand.	-	Patient was presented with an acute stroke-like syndrome and *P. gingivalis* was detected in the pus aspirate sample. The patient was fully recovered after 8 weeks of taking antimicrobial treatment and dental therapy.	Neurology	-

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Table I: List of reviewed articles on P. gingivalis, their characteristics and clinical importance

Authors	Study design	Sample size	Population	Period	Clinical importance of *P. gingivalis*	Clinical domain	Odds ratio (OR)/ Relative risk (RR (confidence interval) [*p*-value]
Mougeot et al., (2017)[16]	Retrospective study	42 cases	-	Data collection between 2022 and 2003.	Among 245 species detected in the coronary and femoral arteries, *P. gingivalis* was the most abundance detected (46.8%), followed by another species, 19.3%.	Cardiology	[p=0.0005]
Totaro et al. (2013)[20]	Case-control	69 cases, 26 controls	Patients from the division of Rheumatology of the Catholic University of the Sacred Heart of Rome	From October 2010 to February 2012	High detection of *P. gingivalis i*n synovial tissue of rheumatoid arthritis patients (33.3%) suggested its role in the progression of disease.	Rheumatology	[p<0.01]
Ceccarelli et al, (2018)[21]	Case-control	143 cases, 94 controls	Patients were enrolled at the Rheumatology unit, La Sapienza University of Rome	-	P. gingivalis was significantly higher in rheumatoid arthritis patients compared to the control group.	Rheumatology	[p=0.01]
Arvikar et al. (2013)[22]	Cohort study	50 cases	Early rheumatoid arthritis patients were obtained from the Rheumatology clinic at Massachusetts General Hospital.	-	Rheumatoid arthritis patients tended to have a higher *P. gingivalis* antibody and the levels of anti-Pg antibodies were directly correlated with anti-cyclic citrullinated protein level. Moreover, patients with positive *P. gingivalis* had greater rheumatoid factor values and higher disease activity score (DAS) values.	Rheumatology	[p<0.01]
Kharlamova et al. (2016)[24]	Case control	1974 cases, 377 controls	Swedish population based	-	The autoantibodies *P. gingivalis* were more frequently detected in anti-citrullinated protein antibodies (ACPAs) positive rheumatoid arthritis patients.	Rheumatology	-
Radhakrishnan et al. (2019)[25]	Prospective study	37 cases	Patients attending to the outpatient clinic, in the tertiary care hospital of India.	-	Diabetes mellitus (Type 2) and periodontitis is closely associated and early detection of *P. gingivalis* is suggested to control glycaemic status.	Endocrine - diabetes	-
Al-Rawi & Al-Marzooq. (2017)[26]	Cross-sectional study	78 cases	Patients attending the University of Sharjah Dental Hospital, Sharjah, UAE.	From December 2015 to April 2016	The high levels of periodontopathogenic bacteria could trigger the release of salivary resistin in obese people, and the most prevalent bacterial species detected was T. denticola (100%), followed by *P. gingivalis* (97.4%).	Endocrine diabetes	-
Gogeneni et al. (2015)[27]	Case control	-	Patients attending the Endocrinology and Metabolism outpatient clinic, Aydın State Hospital, Aydın, Turkey.	Data collection between September 2012 to March 2013	Women with gestational diabetes mellitus (GDM) are more likely to have higher periodontopathogen, and *P. gingivalis* was detected at the most top three abundance bacteria at 52.6%	Endocrine - diabetes	-
Chiu et al. (2021)[28]	Cohort study	116 cases 116 controls	Patients were selected randomly from the US Third National Health and Nutrition Examination Survey.	The survey was conducted between 1988 and 1994.	Patients with high *P. gingivalis* IgG antibody levels had a high risk for developing early diabetic retinopathy over 60%.	Endocrine - diabetes	OR:1.64 (CI: 1.36-1.97) [p=0.0053]

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Table I: List of reviewed articles on P. gingivalis, their characteristics and clinical importance

Authors	Study design	Sample size	Population	Period	Clinical importance of *P gingivalis*	Clinical domain	Odds ratio (OR)/Relative risk (RR (confidence interval) [*p*-value]
Yoneda et al. (2012)[29]	Case control	150 cases, 60 controls	Nara City, Hospital, Japan.	-	The detection of *P. gingivalis* was significantly higher in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) patients compared to control, suggesting its role in the progression of NAFLD and NASH.	Hepatology	OR:3.16
Omura et al. (2016)[30]	Case report	One case	45-years-old woman who died from sepsis	-	*P. gingivalis* was detected in NASH patient's hepatocytes, highlighting its significance in the progression of cirrhosis to NASH.	Hepatology	-
Andonova and Iliev. (2021)[31]	Case control	60 cases 50 controls	-	-	The presence of *P. gingivalis* in pregnant women showed a higher complication in pregnancy, where pregnant women with positive *P. gingivalis* were 6.7 times more likely to have a preterm birth and 2.8 times to have a foetus with intrauterine growth restriction.	Obstetric	RR: 6.65 (CI:1.38-32.11) [p<0.05]
Tellapragada et al. (2014)[32]	Cross-sectional study	390 pregnant women	Patients attending antenatal clinic at the Dr. TMA. Pai Hospital, Udupi, Karnataka, India.	Between July 2012 and June 2013.	Out of total pregnant women selected, 10% of patients were having periodontitis and 38% were diagnosed with gingivitis. The most bacterial species detected was *P. gingivalis* (36%).	Obstetrics	OR: 2.6 (CI: 1.35-5.15) [p< 0.05]

Table II: Detection methods for *P. gingivalis*, their advantages and limitations

Authors	Methods	Method group	Sample	LOD	Duration analysis	Advantages	Limitations
Rajaram et al. (2016)[33]	Culturing on blood and kanamycin agar.	Culture-based	From root canal	-	Up to 3 days	Able to distinguish species in mixed microbial communities.	The method is time-consuming and has low rate of detection (44%). The sensitivity indicated as low, due to low rate of detection (44%) as stated in the table.
Mendes et al. (2016)[35]	PNA-FISH Technique	Direct detection methods	Subgingival plaque	-	Few hours	The method (peptic nucleic acid, FISH) is very high sensitive (100%), and very high specific (100%)	Need to pre-treat the sample and the assay is quite costing for microscopic visualisation.
Gu et el. (2020)[37]	Direct qPCR	Nucleic acid-based methods	Swabbing inside the cheek	1000 copies/ mL	1.5 hours	The method is highly sensitive (95.24%), and very high specificity (100%). Besides, the method is cost effective, and no DNA extraction is required.	Inconsistent results due to low level of DNA copies.
Brun et al. (2020)[38]	Nested PCR	Nucleic acid-based methods	-	-	-	Increased specificity by 22% from previous conventional PCR	Need a longer time for optimisation
Hamzan et al. (2018)[39]	Loop mediated isothermal amplification assay.	Nucleic acid-based methods	Subgingival plaque and saliva	1 ng of DNA	3 hours	The method was 10 times more sensitive than conventional PCR and needed fewer operations steps compared to PCR.	Complicated primer designs (six primers)
Kitano et al. (2016)[40]	LAMP combined with PCR	Nucleic acid-based detection method	Periodontitis tissue	21 copies/tube	20 minutes	Higher sensitivity and specificity than PCR technique.	Complicated design primers (need eight primers)
Ge et al. (2022)[41]	Isothermal amplification and Lateral Flow Strip Methods	Nucleic acid-based methods	-	9.27 CFU/rxn	30 minutes	The method is highly sensitive (95%), and highly specific (93.3%).	Good antibody preparation is obligatory
Imamura et al. (2015)[42]	Immunochro matographic assay	Immunologic al methods (IMs)	Subgingival plaque	10^4 copies/2 paper points	15 minutes	The method is highly sensitive (96.2%), and highly specific (91.8%). No expensive laboratory equipment is required and the portable device is suitable for point-of-care detection.	Inaccurate sample volume may reduce the accuracy.
Lee et al. (2021)[43]	Colorimetric membrane immunoassay	Immunologic al methods (IMs)	-	10^3 cells/mL	-	Cheap, easy to prepare, and can be observed by naked eyes.	Takes more times than other molecular techniques. It is easy to prepare as immunological methods, but the method takes more time compared to molecular techniques such as PCR assay.

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Table II: Detection methods for *P. gingivalis*, their advantages and limitations

Authors	Methods	Method group	Sample	LOD	Duration analysis	Advantages	Limitations
Witkowska et al. (2021)[44]	SERS-Based Magnetomicr ofluidic sensor	Biosensor methods	Saliva	10^3 CFU/mL	-	Able to detect multiple strains of *P. gingivalis*	Moderate accuracy of 82% and need further optimisations
Alhogail et al. (2018)[45]	Magnetic-nanobead based assay.	Biosensor methods	Saliva	49 CFU/mL	30 seconds	The method is highly sensitive and highly specific. Applicable for on-site detection	Requires minimal detection platform manipulation
Park et al. (2021)[46]	Electrochemic al sensor	Biosensor methods	Saliva	5×10^5 CFU/mL	-	The method is able to determine the exact concentration of *P. gingivalis* and applicable for point-of-care detection	Personnel trained is required to analyse the results from an instrument. and the detectable range was lower than qPCR
Yamanaka et al. (2018)[47]	Electrochemic al DNA sensor + PCR	Biosensor methods	Gingival crevicular fluid, saliva	10^4 CFU/mL	Few hours	Measurement principle is simple and applicable to other targets	Personnel trained is required to analyse the results from an instrument. and the detectable range was lower than qPCR

Table III: Risk of bias in reviewed articles

Author	Selection bias	Exposure assessment bias	Confounder	Other bias	Overall risk of bias
Kong et al. (2021)[8]	Low	Low	Moderate Other possible factors did not include such as family history, diet history, occupation which could lead to the development of malignancy.	Data were collected from medical records - information not verified with patient	Low
Liu et al. (2021)[9]	Low	Low	Low	Nil	Low
Chang et al. (2019)[10]	Low	Low	Low	Nil	Low
Ahn J et al. (2012)[11]	Moderate Subset of national health survey	Non-communicable diseases were not assessed directly but by patient self-reported	Moderate Family history/job exposure not included in co-variates	Nil	Moderate
Sansores-España et al. (2022)[12]	Moderate Small sample size	Nil	Other modifiable and non-modifiable risk factors were not included	Nil	Moderate
Rasheed et al. (2013)[13]	Moderate - one case report	Nil	Diabetes and immunocompromised status were not mentioned	Other relevant investigations were not included in the case report	Moderate
Hallikainen et al, (2021)[14]	Low	Low	Low	Nil	Low
Wisutep et al. (2022)[15]	Moderate - one case report	Low	Low	Nil	Low
Mougeot et al. (2017)[16]	Low	Low	Moderate - demographic information is too little. Other relevant modifiable and non-modifiable risk factors were not included.	Nil	Low
Totaro et al. (2013)[20]	Low	Low	Low	Nil	Low
Ceccarelli et al. (2018)[21]	Low	Low	Low	Nil	Low
Arvikar et al. (2013)[22]	Moderate - sample size questionable (relatively low for cohort study)	Low	Low	Nil	Low
Kharlamova et al. (2016)[24]	Low	Low	Low	Nil	Low
Radhakrishnan et al. (2019)[25]	Moderate - small sample size	Low	Low	Nil	Low
Al-Rawi & Al-Marzooq. (2017)[26]	Low	Low	Low	Nil	Low
Gogeneni et al. (2015)[27]	Low	Low	Other cofactors are not studied/ included	Nil	Low
Chiu et al. (2021)[28]	Moderate Subset of national health survey	Non-communicable diseases were not assessed directly but by patients self-reported.	Low	Low	Moderate
Yoneda et al. (2012)[29]	Low	Low	Other factors not included (alcohol, physical activity, diet, smokers)	Low	Low
Omura et al. (2016)[30]	Moderate - solely a case report	Low	Low	Dyslipidaemia status was not verified.	Moderate
Andonova & Iliev. (2021)[31]	Low	Low	Mothers with concomitant non-communicable diseases or co-morbidities were not excluded	Nil	Low
Tellapragada et al. (2014)[32]	Low	Low	Low	Nil	Low

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Table III: Risk of bias in reviewed articles

Author	Selection bias	Exposure assessment bias	Confounder	Other bias	Overall risk of bias
Rajaram et al. (2016)[33]	Low detailed recruitment and methodological process has been spelled out	Low	Low	Nil	Low
Mendes et al. (2016)[35]	High name of strain providers were mentioned in the methodology - which may lead to conflict of interest and bias.	Low	Low	Low	Moderate
Gu et al. (2020)[37]	Low	Low	Low	Nil	Low
Brun et al. (2020)[38]	High - different sample sites for different studies	Low	Low	Nil	Moderate
Hamzan et al. (2018)[39]	Low	Low	Low	Nil	Low
Kitano et al. (2016)[40]	Low	Low	Low	Nil	Low
Ge et al. (2022)[41]	Low - detailed methodology steps	Low	Low	Nil	Low
Imamura et al. (2015)[42]	Moderate - detailed of the person responsible to differential and classify to groups are not clear	Low	Low	Nil	Low
Lee et al. (2021)[43]	Supplier of bacterial strains were highlighted	Low	Low	Nil	Low
Witkowska et al. (2021)[44]	Low	Low	Low	Nil	Low
Alhogail et al. (2018)[45]	Low	Low	Low	Nil	Low
Park et al. (2021)[46]	Low	Low	Low	Nil	Low
Yamanaka et al. (2018)[47]	Low	Low	Low	Nil	Low

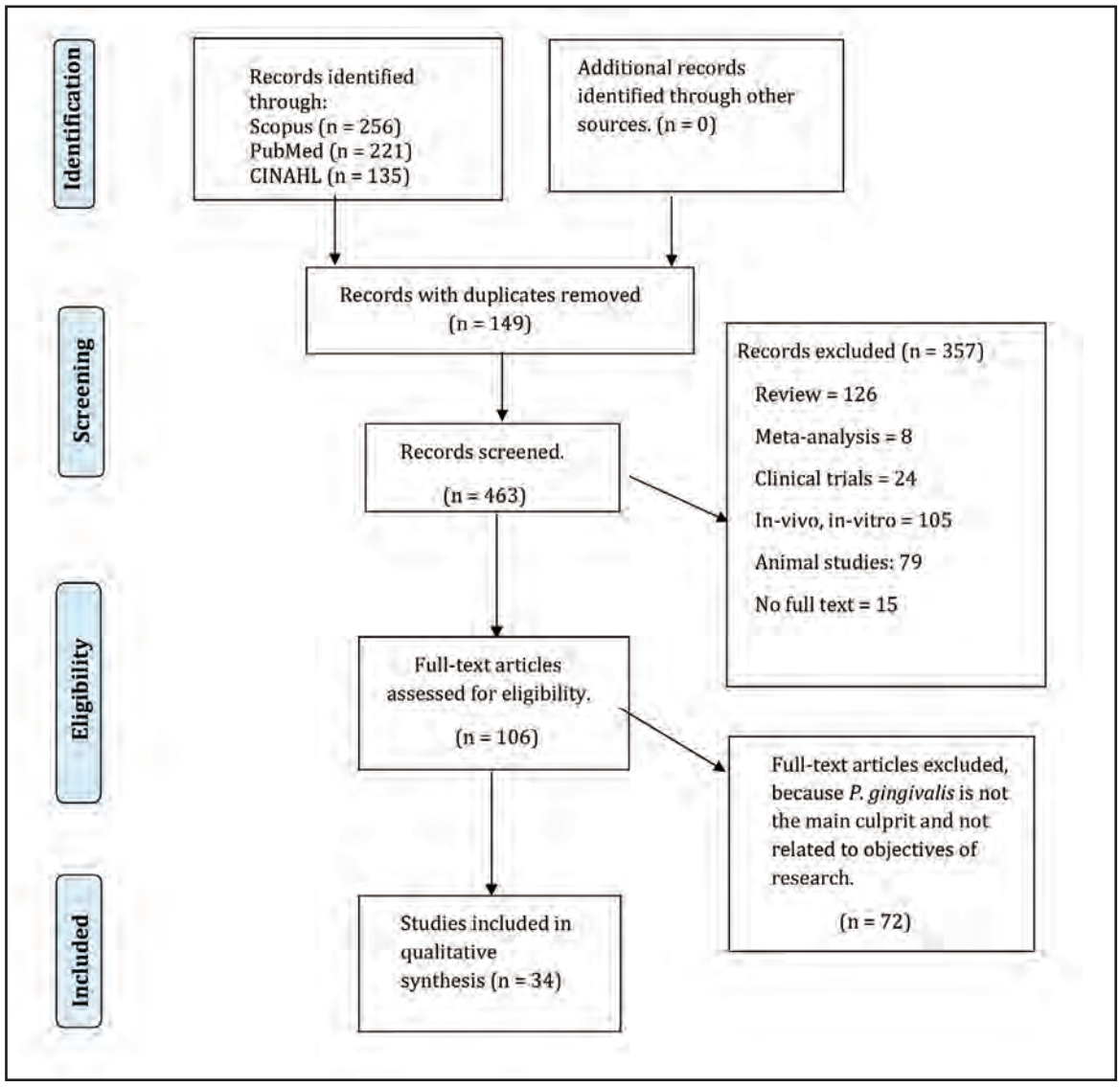

Fig. 1: PRISMA 2009 Flow Diagram.

In terms of confounding factors, they are present in the form of background of the patients recruited. For example, the study conducted by Kong et al.,[8] Ahn et al.,[11] Sansores-España et al.,[12] and Rasheed et al.,[13] the sociodemographic factors and patient related profiles were not captured completely. These include family history, diet history, comorbidities, and some important results.

In the form of data collection, the study by Kong et al.,[8] has high risk of bias as the information was gathered from self-report which can lead to recall bias and cannot be verified. Overall, 16 studies have low risk in all categories of bias risks.

DISCUSSION

A. Clinical Importance of *P. gingivalis* and Disease Implications

Due to growing evidence, *P. gingivalis* has been an important risk factor in the exacerbations of a particular disease as shown in Table I either via its virulence factors or *P. gingivalis* alone.

(i) Oncology

Upper Gastrointestinal Malignancy

As both oesophagus and oral cavity are structurally closed to each other, the oral microbiome is more likely to infect oesophagus compared to other parts in the digestive system and *P. gingivalis* has been confirmed to have a strong correlation with oesophageal cancer. Previous study demonstrated that *P. gingivalis* was highly detected in the late stage of oesophageal squamous cell carcinoma (64.7%) compared to those in the early stage (30.3%). Furthermore, it must be noted that there was no significant correlation between positive *P. gingivalis* detection and other factors including smoking history, alcohol status, age and gender in the oesophageal squamous cell carcinoma (ESCC) patients. In addition, the detection of *P. gingivalis* in the ESCC showed positive correlation with lymph node metastasis, where *P.*

gingivalis was also highly detected in lymphatic metastasis tissues in ESCC at 60%. These findings suggested the specific role of *P. gingivalis* as an etiologic agent and could be a potential prognostic indicator in the progression of esophageal cancer.[7]

Lung Cancer

Due to the clinical importance and close association between *P. gingivalis* and oesophageal cancer that has been discussed in previous discussion, it has been suggested that *P. gingivalis* also could migrated and colonised into the lung cells as the oesophagus and trachea are anatomically closed to each other. To support this speculation, Liu Y et al. 2021,[9] found a significantly higher detection of *P. gingivalis* in the carcinoma tissues of patients with lung adenocarcinoma (26.89%), lung squamous cell carcinoma (39%), and small cell lung cancer (35%), compared to the adjacent lung tissues (3%, 3% and 4%, respectively). Importantly, the 5-years survival rate of these three types of lung cancer patients with positive *P. gingivalis* were significantly lower than those survival rates of patients with negative *P. gingivalis*. Hence, the authors suggested that *P. gingivalis* infection is closely associated with survival rate of lung cancer patients. Besides, the highest detection rate of *P. gingivalis* in lung squamous cell carcinoma was frequently observed in many patients with smoking history, suggesting that smoking habit may increase the risk of *P. gingivalis* infection, subsequently promoting the progression of lung cancer. In fact, long-term smoking could damage the body's immune function, and thus, allowing a better colonisation of *P. gingivalis* and the bacterium may induce invasion, proliferation, and metastasis of lung cancer.[8]

Oropharyngeal Cancer

Oral squamous cell carcinoma (OSCC) is the most common oral malignancy that occurs due to the mutation of squamous cell that lining up the lips, mouth, tongue and gums. Besides alcohol consumption, poor dietary, and other environmental factors, several studies have indicated the significance of oral microbes in the carcinogenesis of OSCC, where high abundance of P. gingivalis has been detected in the OSCC tissues at 60.7%.[9] Next, *P. gingivalis* also has been suggested to be a biomarker for bacterial-associated risk of death in orodigestive cancer. Previous study had found that greater levels of serum *P. gingivalis*-IgG was associated with an increased orodigestive cancer mortality. *P. gingivalis* that is associated with orodigestive mortality was also detected in patients without periodontal disease, suggesting a strong association of *P. gingivalis* in the orodigestive cancer mortality regardless of periodontal health.[10]

(ii) Neurology

Neurodegenerative Disorder

Research interests in exploring the association of periodontal microbes and neurodegenerative disorder such as Alzheimer's disease (AD) has increases in recent decade, suggesting that the presence of microbes could lead to the overproduction of amyloid-β peptides in the brain which may clumps into plaque and cause neuroinflammation. A statistical data showed that 80% of AD patients had a chronic periodontitis, with higher abundance of *P. gingivalis* and its pro-inflammatory molecules, compared to non-AD patients, where only 20% had a chronic periodontitis. Moreover, it has been identified that the more *P. gingivalis* is present in AD patients, the lower their Montreal Cognitive Assessment (MoCA) test values are, suggesting that the severe cognitive impairment patients tend to have a higher *P. gingivalis* load.[11]

Subdural Empyema

Although *S. pneumoniae* is the most common species to cause subdural empyema, the first case study in 2013 by Rasheed et al.,[13] had discovered that *P. gingivalis* could be the main culprit in the disease progression where an adult male patient was presented with precedent dental and sinus infection. After microbiological examinations, the subdural empyema's patient was positive *P. gingivalis* in his yellowish purulent. Meanwhile, no organisms were observed in an aerobic environment. Hence, the author and his colleagues suggested *P. gingivalis* should be considered in differential diagnostic measure of subdural empyema or CNS abscesses.[12]

Intracranial Aneurysms

Previous study had found that patients with intracranial aneurysms (IAs) were more likely to have gingivitis and severe periodontitis (2 times and 1.5 times, respectively) as compared to the control. Interestingly, the *P. gingivalis* epitope was found to be present in the IA wall, suggesting its role in the IAs formation and rupture. Moreover, further examinations have confirmed that the IgA antibodies level against *P. gingivalis* in both ruptured and unruptured IAs patients was 1.5 times higher than control patients. Meanwhile, the IgG antibodies against *P. gingivalis* were 1.8 times lower than control patients. Thus, exposure to *P. gingivalis* and dysfunctional acquired immune response against the bacterium could exacerbate the risk of IAs formation and rupture.[13]

Stroke

Odontogenic infection, including periodontitis is one of the commonest sources of brain abscess formation. A recent case study has reported that a patient who had a brain abscess and presented as an acute stroke-like syndrome was having multiple periodontal infection sites during oral examination. Further microbiological diagnostic was confirmed that the pus aspirate sample isolated from that patient was positive with oral anaerobes, *P. gingivalis* and Filifactor alocis. Interestingly, that patient was fully recovered after 8 weeks of taking antimicrobial treatment and dental therapy. Therefore, the authors speculated that both *P. gingivalis* and *F. alocis* were suspected to be the main culprits for the brain abscess formation.[14]

(iii) Cardiology

Atherosclerosis (AS) is a progressive disease that develops due to lipid accumulation in the arterial walls that may harden and narrows the arteries and could lead to occlusion. Although periodontopathogens may not be the main factor in the inflammatory diseases associated with AS, but it may be considered as a potential risk factor. The association between the *P. gingivalis* and AS may be supported by the evidence of its DNA detection in the healthy arterial tissues, where P. gingivalis was the most abundant species detected at 79.2% of all bacterial species counts. These findings suggested the possible role of P. gingivalis in the initiation or exacerbation of early atherosclerosis where the bacterium

may invade the arterial walls from the subgingival tissues and survive intracellularly.[15]

(iv) Rheumatology

Rheumatoid arthritis (RA) is an autoimmune and chronic inflammatory disease that causes destruction, pain and swelling in the joints. Periodontitis is known to be one of the risk factors of RA, where both shared the same histopathological characteristics, inflammatory pathways and risk factors for susceptibility, such as cigarette smoking and genetic factors by HLA-DRB1 shared epitope (SE) alleles.[16] Moreover, several studies have highlighted that periodontitis is more frequent in RA patients compared to healthy subjects.[16-18] A previous study had demonstrated that *P. gingivalis* could migrate to the joints and its persistent exposure may exacerbate the chronicity of inflammation in arthritis progression. The authors found a higher detection of *P. gingivalis* in the synovial tissue of RA patients at 33.3% compared to healthy subjects at 5.9%.[19] Additionally, Ceccarelli and his colleagues reported that there was a significant association between *P. gingivalis* composition and RA disease activity score in 28 joints (DAS28), where the higher DAS values was observed frequently in *P. gingivalis*-positive patients (8.2%) compared to *P. gingivalis*-negative patients (1.7%). The authors also found that the RA patients in remission state had a lower prevalence of *P. gingivalis* compared to non-remission RA patients, indicating the presence of *P. gingivalis* may trigger an autoimmune system regardless of whether periodontitis is present or not.[20]

The autoantibodies against citrullinated proteins, also known as anti-citrullinated protein antibodies (ACPAs) or its subset namely anti-cyclic citrullinated protein (anti-CCP) is highly specific for RA and became one of an important diagnostic measure for the disease. The citrullinated proteins could be catalysed by peptidylarginine deiminase (PAD) enzyme, where *P. gingivalis* is the only known bacteria that generates PAD.21 Moreover, it has been reported that people at high risk of RA with positive anti-CCP were having a dysbiotic microbiome, and the *P. gingivalis* was found to be higher in the risk group compared to other groups. Therefore, it is suggested that the *P. gingivalis* infection could contribute to the progression of RA by generating citrullinated proteins via PAD enzymes.22 Others, the glutaminyl cyclases (QC) expressed by *P. gingivalis* also has been proposed to play important role in maintaining inflammatory conditions and destructions of RA, where the QC mRNA was detected more frequently in the gingival crevicular fluid of RA patients.[23]

Although both periodontitis and RA shared the same risk factor which is a cigarette smoking, it has been revealed that the anti-P gingivalis arginine gingipain type B (anti-RgpB) antibody level and RA had even stronger association as compared to the association between smoking and RA. Moreover, the increased anti-RgpB antibody levels, as well as smoking and HLA-DRB1 SE alleles were only observed in ACPAs positive patients only. These findings supported that P. gingivalis is an etiologic agent in RA progression, along with smoking and HLA-DRB1 SE alleles as a well-established risk factor.[24]

(v) Diabetology

Diabetes is commonly associated with periodontal disease and recently *P. gingivalis* was detected at 30% in diabetic patients with periodontal disease.[25] In addition, previous study had suggested that the release of salivary resistin (resist insulin) could be upregulated by high abundance of periodontopathogenic bacteria in obese patients, where *P. gingivalis* was detected at 97.4% associated with high amount of salivary resistin. It is speculated that *P. gingivalis* could trigger the release of salivary resistin due to its lipopolysaccharide (LPS) virulence factor based on previous in-vitro studies.[26]

Previously, *P. gingivalis* was detected at the most top three among periodontopathogenic bacteria at 52.6% in gestational diabetes mellitus (GDM) patients or a pregnant woman who had been diagnosed with diabetes for the first-time during pregnancy with the presence of gingivitis.[27] Besides, recent findings also demonstrated that a high amount of *P. gingivalis*-IgG serum was measured in early diabetic retinopathy patients over 60%.[28] Based on this evidence, *P. gingivalis* may be a risk factor in the development of diabetes, and further studies on the mechanisms on how the bacteria involved in the disease progression are needed.

(vi) Hepatology

Non-alcoholic fatty liver disease (NAFLD) also known as metabolic (dysfunction) associated fatty liver disease (MAFLD). The higher prevalence of *P. gingivalis* infection in the NAFLD patients (46.7%) compared to healthy subjects (21.7%) suggested that the *P. gingivalis* may be involved in the progression of onset of NAFLD. The study findings showed that there is no significant difference in the persistence of diabetes mellitus (DM) was noted between both positive and negative *P. gingivalis* in NAFLD subjects. Thus, it is suggested that the high detection of *P. gingivalis* in NAFLD patients was not due to the presence of DM, as reported by some previous studies due to the correlation between NAFLD and DM. However, there is a significant difference in the persistence of DM between positive and negative *P. gingivalis* among non-alcoholic steatohepatitis (NASH) subjects. These findings suggested that the presence of both DM and *P. gingivalis* may cooperatively contributed to the risk of the progression of NAFLD to NASH. In addition, the prevalence of *P. gingivalis* in NASH patients (52.0%) was higher than NAFLD patients.[29] Interestingly, previous case study has reported that the *P. gingivalis* was detected in the hepatocytes of NASH patients who died from sepsis. Further autopsy found that the NASH patients had progressed to cirrhosis. Therefore, this case suggested that the *P. gingivalis* does contribute to the progression of NASH to cirrhosis.[30]

(vii) Obstetrics

Most findings have been focused on bacterial vaginitis as a primary infection in pregnant women with an adverse pregnancy outcome. However, since pregnant women were more susceptible to periodontal disease, oral anaerobic bacteria had gained much interest among researchers as a distant site of infection that could reach the fetoplacental unit, leading to pregnancy complications. Among oral bacterial species detected, *P. gingivalis* was the most abundant species detected in pregnant women at 56%.[31,32] Recent study

also discovered that a group of pregnant women with positive *P. gingivalis* in their oral swabs were 6.7 times more likely to have a preterm birth compared to those negative *P. gingivalis*, and 2.8 times to have a foetus with intrauterine growth restriction.[31]

B. Detection Methods

(i) Culture-Based Technique

Bacterial culture is considered as a gold standard detection method due to its ability to identify a wide range of unexpected species in the mixed microbial communities in a clinical sample. However, the cultivation of *P. gingivalis* may take several days at minimum of three to four days and need further biochemical tests for identification. Furthermore, *P. gingivalis* is an anaerobic and fastidious organism that needs specific conditions to grow and sometimes are uncultivable. Based on our literature, although the cultivation process was done with proper and adequate precautions, the highest detection rate of *P. gingivalis* through culture was only 44%.[33]

(ii) Direct Detection Methods

This method can visualise the desired organism directly by using a microscope or an optical instrument where the amplification efficiency is not considerable. However, these direct detection methods need a longer time to pre-treat the sample and require an expensive instrument.[34] The highest specificity and sensitivity for direct detection method was 100% for both that was done by a fluorescence in situ hybridisation (FISH) technique. The developed technique is also able to localise the organism and observe the spatial distribution of polymicrobial communities in the clinical sample.[35] However, the FISH technique usually takes around two to three days and takes some time to set up the reaction.[36]

(iii) Nucleic Acid-Based Detection Methods

These identification methods are based on the amplification of single-stranded DNA that binds to its complementary strand.[34] The current nucleic acid-based detection methods for *P. gingivalis* are PCR and a loop-mediated isothermal amplification (LAMP) method. Based on our literature, the detection of *P. gingivalis* by PCR assay has been greatly evolved over time. The study by Gu et al. 2020,[37] had performed a direct qPCR assay without DNA extraction and only took 1.5 hours when compared to DNA extraction-based qPCR (kit-qPCR). Although the specificity was 100%, the positivity of P. gingivalis by direct qPCR was inconsistent and the retest results also showed weak positive to negative results compared to kit-qPCR. These might be due to low levels of target DNA and the presence of inhibitors.[37] Next, a nested PCR for *P. gingivalis* detection involving two primer sets has been developed, where the large fragments outside the targeted DNA were amplified first by one set of primer (first PCR), allowing a specific amplification of the 16s rRNA gene by the second primer set. The protocol had successfully improved the specificity of the amplification by 22.2%.[38]

LAMP is an alternative PCR method that provides a better sensitivity and specificity by using six to eight primers compared to only two primers by PCR. The detection of *P. gingivalis* by LAMP method was proven to be ten times more sensitive than a conventional PCR.[39] Nucleic acid-based methods can be combined each other, such as done by Kitano et al. 2016[40] that demonstrated a great combination between LAMP and PCR assay (LAMP-PCR), and the combination was much more sensitivity where only two or more copies of *P. gingivalis* DNA were needed for the detection, compared to 21 copies by LAMP assay alone.[40] Another successful combination was done by Ge et al.,[41] where a recombinase polymerase amplification (RPA) is combined with a lateral flow strips assay (RPA-LFS), where the amplification time was two times more rapid than qPCR assay, and the accuracy showed 100%.[41]

(iv) Immunology-Based Methods

An immunology-based detection method is a highly portable and rapid method by visualising the antigen-antibody interactions in the clinical specimens.[34] Some developed immunology-based methods for *P. gingivalis* detection include an immunochromatographic device and colorimetric membrane enzyme immunoassay (EIA) technique.[42] The highest sensitivity of immunology-based methods was established by EIA technique where the sensitivity was 100 times more sensitive than other lateral flow immunoassay. In addition, no device is needed for the visualisation as the results can be observed by naked eyes.[43] However, this immunology-based method is at high risk of giving false negative results if the antigens are partially denatured and need pre-enrichment to expose the surface of antigens, thus, extending the detection time. Moreover, this method was also less employed in detecting the desired organism due to its lower sensitivity compared to other molecular techniques.[34]

(v) Biosensor-Based Methods

Biosensor-based detection method is an analytical platform that comprises a bio-receptor to recognise the desired targets. Once recognised, the transducer will convert the bioreaction into a measurable electrical signal such as electrochemical, magnetic, or optical. There are many biosensor devices that have been developed for *P. gingivalis* detection that can process many specimens at once and is suitable for point-of-care detection.[34] The first study of surface-enhanced Raman spectroscopy (SERS) technique for *P. gingivalis* detection has been successfully developed, where the microfluidic and magnetic separation were employed that allows multiple strains of *P. gingivalis* detection. However, the accuracy of the developed protocol was only 89% and needed further optimisations.[44] Based on our overall literature, the magnetic nanobead-based assay is one of a notable assay where the method had the fastest detection rate which is only within 30 seconds with high specificity.[45] Next, an electrochemical biosensor done by Park et al.,[46] had demonstrated that the developed device is highly specific and sensitive, although washing and separating steps were not included in processing their saliva samples, thus reducing the detection time to only 30 minutes.[46] A newly quantitative electrochemical analysis for *P. gingivalis* detection was developed where a portable electrochemical DNA sensor was linked with PCR. This method was primarily developed to quantify the *P. gingivalis* load in an easier way compared to conventional real-time PCR (RT-PCR) by using disposable electrodes, which may reduce cross-contamination. However, this method had a lower dynamic range compared to RT-PCR and the detection limit was just the same as RT-PCR.[47]

LIMITATION AND RECOMMENDATION

This review has some limitations. First, there was no review of the association between the presence of systemic implications and periodontal disease. Second, the mechanism or the way on how the bacterium contributed to systemic implications was not explained clearly. Therefore, we suggested reviewing the association between particular systemic diseases, such as rheumatoid arthritis and periodontal disease, in the future. Lastly, we also recommended a review of the mechanisms involved in the development of the particular systemic diseases due to the presence of *P. gingivalis*.

CONCLUSION

In this review, the modulation effect of *P. gingivalis* on the major clinical diseases, as well as the established detection methods for the bacterium have been summarised. The high prevalence of *P. gingivalis*-associated diseases suggests the need for oral public health awareness and encouragement for oral screening regularly, although there are no apparent symptoms developed. Almost all detection methods were able to detect the desired organism at a fast detection rate, while maintaining the high sensitivity and specificity for more accurate results. Therefore, it is recommended for health practitioners to take oral samples from patients who attend for medical help with a chronic inflammatory disease and employ the suitable detection methods based on availability, convenience, and patients' concern, as each method has its own benefits and drawbacks.

DISCLOSURES

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: Fundamental Research Grant Scheme (FRGS); FRGS21-211-0820 FRGS/1/2021/SKK05/UIAM/03/1. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organisations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Teaching clinical toxinology in medical schools: The need, challenges and opportunities

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ABSTRACT

Clinical toxinology is an essential subject that should be included in undergraduate medical curricula. By equipping students with the knowledge and skills to identify and treat venomous animals and use antivenom appropriately reduces the risk of medical negligence and delays in treating and transporting these patients. Unfortunately, given the packed curriculum of undergraduate medical programs, it is important to focus on providing students with essential knowledge and skills to function as competent house officers. Student-centered learning approaches, such as gamification and community service projects, can be effective in enhancing learning and promoting awareness of appropriate toxin-related public measures.

KEYWORDS:
Clinical toxinology, snake envenomation, bites and stings, medical education, student-centered learning, gamification, community services

INTRODUCTION

Defined as 'the medical discipline that encompasses the diagnosis, treatment, and prevention of toxin diseases caused by exposure to venomous and poisonous animals, plants, and mushrooms'[1], clinical toxinology should be an important subject to be included in undergraduate medical curriculum. At least three reasons can be advocated for this inclusion.

THE NEED

First, Malaysia's high operating expenditure of healthcare budget means that one needs to be prudent in stocking up the right amount of the right types of anti-venom depending on the geolocation.[2,3] Overstocking without proper species identification is not only expensive but also wasteful.[2,3] Clinical toxinology provides medical students with the knowledge and skills necessary to identify different types of venomous animals and the appropriate anti-venom needed to treat their bites or stings.

Second, with an ongoing crisis in emergency departments with lengthy wait times increases the risk of medical negligence and delays in transporting patients who need anti-venom in a tertiary facility. Due to a surge of non-COVID patients coupled with staff shortages, some Malaysian general hospitals' emergency departments are experiencing excruciatingly long waiting times of up to 6–7 days for ward admission. The delay in admission and treatment can lead to medical negligence and worse outcomes for patients with bites or stings. Clinical toxinology equips medical students with the necessary knowledge and skills to recognise and manage such cases in the prehospital stage and reduce the risk of medical negligence and delayed transportation.

Third, the increasing integration of artificial intelligence (AI) in healthcare means that there is a need to be more aware of the inherent biases in these AI algorithms. Artificial intelligence bias is a phenomenon that arises when an algorithm systematically delivers biased results due to erroneous assumptions in its machine learning processes.[4] For example, during a reverse Google image search performed by the author on some of the local snake photos that had bitten our patients, most of these snakes were not accurately identified by the search engine. Whilst this may be due to the crushed anatomical structures of the dead snakes rendering identification difficult, this could also be due to the insufficient image data of local snakes from this region in the Google algorithm's training set compared to data from other regions of the world.

THE CHALLENGES

Due to the packed curriculum of most undergraduate medical programs in Malaysia, the extent and depth of clinical toxinology that should be taught to medical students should be carefully considered. In this regard, it is crucial to remember that the overarching goal of any undergraduate medical curriculum is to ensure that students have obtained sufficient clinical competency to function effectively as future house officers. In this regard, the focus should be on providing students with the essential knowledge and skills that a house officer is expected to know and perform when managing patients with bites or stings. These include basic interventions such as administering copious irrigation on bite wound, immobilisation of the bite wound, rapid transportation to a facility with anti-venom availability, positively identifying the snakes, taking a proper history of the patient, examining the patient for signs of envenomation and knowing where and how to seek help (such as expert consultation from clinical toxinologists using the remote envenomation consultation services, or RECS).[2,5]

THE OPPORTUNITIES

When considering how to teach clinical toxinology, it is important to note the recent pedagogic shift from teacher-centered to student-centered learning.[6] In the traditional

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approach, the instructor delivers information through lectures and textbooks ('sage of the stage'), whereas in student-centered learning, the instructor encourages students to take ownership of their own learning processes through active engagement ('guide on the side').[7]

One fun approach to promote student-centered learning is through gamification.[8] In the context of clinical toxinology, the classical snake-and-ladder game can be creatively modified to make it an engaging way for students to learn about snake envenomation and other toxin-related illnesses. To turn the game into a learning tool, for example, players who are 'bitten by a snake' would be relegated to a lower position, and the player must then pick a card with a picture of a snake and be tasked to correctly identify it and administer appropriate first aid measures. Correct answers will allow the player to move forward. A 'ladder' can transport them more quickly to an anti-venom facility. In fact, the snake-and-ladder game can also be customised for public health education with an appropriate level of difficulty of the card questions tailored to suit different age groups, such as school children.

Another student-centered learning activity related to clinical toxinology that students can participate in is community service projects. For example, students can embark on projects aimed at dispelling myths and harmful practices such as cut and suck, electric shocks and herbal remedies that can cause more harm than good[2] and research on understanding the socio-cultural reasons behind these harmful practices. Inspired by the chain of survival for cardiac arrest victims, perhaps a novel concept known as the 'chain of snake envenomation management' can be developed to identify and strengthen the weaknesses within the chain. This is because the strength of the chain is only as good as its weakest link. This chain would consist of (1) early identification of the snake species and call for help, (2) early first aid, (3) early resuscitation, (4) early anti-venom administration and (5) early post-resuscitation care and monitoring.

CONCLUSION

In conclusion, clinical toxinology is an important subject that can equip medical students with the knowledge and skills to manage bites and stings, reducing the risk of negligence and transporting patients to the right facilities. Student-centered learning approach, such as gamification and community service projects, should be incorporated to enhance the learning processes and promote the awareness of appropriate toxin-related public measures.

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Screening for lung cancer in high-risk non-smokers: A step too far or time to address an unmet need?

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Globally, two million new cases of lung cancer are diagnosed annually with approximately 1.8 million deaths each year. Over 60% of all cases and mortality occurs in Asia with a preponderance of non-small cell lung cancer (NSCLC), predominantly adenocarcinoma. In Malaysia, lung cancer is the second most common male cancer, marginally surpassed by colorectal malignancy with an age-standardised incidence rate (ASR) of 13.2 per 100,000 of the population and accounts for 15% of all cancers in men. It is the leading cause of cancer-related mortality. In women, it is the fourth most common cancer (ASR of 5.9 per 100,000) but only breast cancer is more fatal.[1] In Malaysia overall 5-year relative survival for lung cancer across all stages is only 11%, largely driven by late stage diagnosis in the vast majority of victims with almost 95% of cases detected in stage III or IV.[1,2] The treatment and prognosis for NSCLC is very stage dependant. Early stage NSCLC has a 5-year survival of 70-90%. In contrast, survival for advanced or late stage disease is approximately 5-10%.[3] Despite tremendous recent advances in the treatment landscape for NSCLC including bespoke oral-targeted therapies (tyrosine kinase inhibitors) for tumours with actionable driver mutations (e.g. epidermal growth factor receptor, EGFR), the emergence of antibody drug conjugates and systemic immunotherapies with potentially game-changing pathological tumour regression in patients with a high PDL-1 expression, locally advanced (stage III) and metastatic (stage IV) NSCLC presently, remains incurable.

Detection of early-stage lung cancer remains elusive and challenging as many are asymptomatic or have mild non-specific symptoms. Several landmark randomised trials[4,5] have demonstrated unequivocal benefit of low-dose computed tomography (LDCT) screening in terms of a risk reduction in lung cancer-specific mortality, largely driven by impactful stage shift with detection of more early-stage tumours, which can be treated with a curative intent and more cost-effectively. These trials however have understandably focused on high-risk groups defined by a significant tobacco history.

The demographics and tumour biology of lung cancer in Asia is different from the West with an alarming rise in the incidence of lung cancer amongst non or never smokers, mainly women. The smoking prevalence in Malaysian adults is approximately 43% and <2% for men and women respectively, but the use of e-cigarettes and vapes amongst adolescents is on the rise.[6,7] The long-term health implications of the latter remain unknown. Over 90% of male lung cancer victims here have a smoking history. Conversely, at least 60% of Malaysian women diagnosed with lung cancer are never smokers.[8] Put simply, lung cancer is no longer a male smokers disease. It has been suggested that women may be more susceptible to cigarette smoke or air pollution, perhaps due to hormonal differences including differing immune response but compelling data to support this is lacking. Exposure to second-hand smoke, air pollution including the annual transboundary haze, indoor high temperature wok-frying, chronic lung diseases like chronic obstructive pulmonary disease (COPD) and pulmonary infections including tuberculosis and possibly even COVID-19, may all increase the risk of a future lung cancer in the non-smoker. Chronic cumulative exposure to pollutants (PM 2.5) is thought to trigger an interleukin-mediated inflammatory process at a cellular level that 'activates' pre-existing dormant cancer-causing genes (e.g., EGFR) in genetically susceptible individuals.[9] EGFR is a glycoprotein involved in cell proliferation and apoptosis. The prevalence of EGFR mutations in NSCLC in Asia (40-55%) is considerably higher than in the West (15-25%).[8] This genetic predisposition is supported by data from Taiwan which demonstrated that a family history of lung cancer is a significant risk factor in never smokers. The risk is incremental, as the more first-degree relatives one has with lung cancer, the higher the risk. The TALENT study confirmed the effectiveness of LDCT screening in a pre-defined, never-smoker high-risk population with an impressive early lung cancer detection rate of 2.6%, superior to both the NLST (1.1%) and NELSON (0.9%) data.[10] A rigid adherence to existing Western derived screening criteria of high risk populations based on a tobacco history only, will be erroneous as it excludes a sizeable subgroup of at-risk non-smokers, mainly Asian females with a family history of the disease.

Despite being a dominant cancer with a high burden of late stage presentation and the leading cause of cancer-related mortality here, Malaysia does not have a national lung cancer screening programme, yet.[11] Currently, screening is opportunistic and conducted ad hoc, mostly in the private sector. Barriers to screening for lung cancer include poor awareness, fear of a cancer diagnosis, stigma, traditional cultural beliefs including fatalism, overdiagnosis, concerns of radiation exposure and financial cost due to low insurance penetration and lack of reimbursement. A previous privately funded pilot screening project (PEARL study) initiated by lung specialists here utilising LDCT was terminated prematurely

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due to poor enrolment due to a combination of poor awareness and reticence of smokers to be screened.[12] More recently, Lung Cancer Network Malaysia (LCNM) pioneered a community-level screening project with deep learning artificial intelligence (AI) algorithm enabled-chest radiography (CXR) imaging of over 10,000 individuals which demonstrated a diagnostic rate of approximately 2.5 % for detection of an indeterminate pulmonary nodule which may represent possible early stage NSCLC.[13] However, despite provision of free scans and patient navigators to guide individuals with suspicious CXRs through the screening process, uptake for the subsequent definitive LDCT was similarly poor, perhaps in part due to the fact that much of the screening was done during the COVID pandemic.

The alarming rise in lung cancer in non-smokers mandates serious consideration for screening of high risk non-smokers. This should be based primarily but not exclusively, on a family history of the disease, as second-hand smoke exposure including air pollution is difficult to quantify accurately. Women, who make up the majority of non-smokers with lung cancer, tend to have better health seeking behaviour and hopefully this will translate into better screening uptake. Screening with a CXR initially may be more palatable and affordable as a prelude to an interrogative LDCT in individuals with an abnormal or equivocal CXR, surmounting historical barriers of cost, accessibility and low specificity (false positives), from upfront LDCT imaging. It is possible future screening initiatives could be further refined with incorporation of biomarkers like plasma circulating tumour DNA or exhaled breath (volatile organic compound) analysis. The National Cancer Institute (IKN) has recently launched a similar AI-CXR lung cancer screening project as part of a broader lung health check.[14] It is a step in the right direction to 'widen the net' for early and widespread screening to facilitate effective lung cancer control in our country. The IKN project is similar to LCNM's pilot initiative (in 2020-2022) which demonstrated adoption of such AI technology to be user friendly, affordable and scalable. A similar initiative is currently underway at several NHS hospitals in the United Kingdom.[15] AI-enabled chest radiography has superior diagnostic accuracy for detection of malignant nodules, over trained radiologists.[16]

Poor uptake for lung cancer screening is a global phenomenon not unique to Malaysia. Public educational awareness campaigns coupled with appropriate sustained funding for subsidised or free screenings, ideally on a single visit at a one-stop tertiary centre can help remedy this. A hybrid sequential strategy of AI-CXR to identify and funnel the right individuals for complementary LDCT imaging may be pragmatic and transformative in large-scale timely detection of early-stage lung cancer. Screening-enabled stage shift will allow for more cost-effective therapies and save many more lives. We must acknowledge the changing face of lung cancer here with a rising number of cases in never smokers and the importance of a significant family history for the disease. Failure to embrace and utilise innovative technology with broader screening criteria is a significant missed opportunity for Malaysia that will result in more preventable deaths from lung cancer due to continued late-stage diagnosis.

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Safeguarding against potential injury from an eye drops bottle

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SUMMARY

We describe a potential cause of eye injury, its concerns and ways to prevent it. The first author underwent a left cataract operation and was prescribed eye drops postoperatively. While applying one of the eye drops, he felt an object hitting the lower eyelid. A serrated plastic piece had fallen off the bottle. Had it fallen on the operated site, it might have caused serious untoward complications. Nurses, carers and patients need to be educated to remove the serrated piece from the bottle before applying eye drops. Manufacturers of eye drops should design safer bottles without such serrated pieces to prevent such eye injuries.

INTRODUCTION

Cataract surgery is one of the most commonly performed eye surgeries. Cataract is one of the world's leading causes of treatable blindness in the elderly. Cataract surgery is a relative core procedure with minimal risk and complications post-operatively, provided patients are selected appropriately and the procedure is carried out carefully.[1] Postoperatively, patients are given a range of eye drops for a few weeks. Either patients themselves or their caretakers instil the eye drops.[2] Issues with the instillation of eye drops impede their successful administration and may lead to untoward consequences.[2-4] We describe a potentially serious cause of eye injury due to a serrated cover of a plastic eye drops bottle.

The first author underwent left eye cataract surgery. Post-operatively, the nurse explained the different types of eye drops to be instilled. She also gave an educational pamphlet on the precautions to be taken for a few weeks postoperatively. While instilling drops from one of the bottles, the author felt an object hitting the lower eyelid, and it subsequently fell on the floor. The author was aware that he should not rub the eye. No injury was sustained.

On further investigation, a serrated piece of the plastic bottle cover had fallen off the bottle (Figure 1). It would have remained on the bottle after the seal was broken.

Had it fallen on the cornea or conjunctiva of the operated eye, it would have caused intense itching and rubbing of the eye. This could cause abrasion of the skin or conjunctiva, leading to introduction of infection at the operated site. Staphylococcus epidermidis, which is found in normal eyelid skin and conjunctiva, is the most common infecting microorganism in this instance.[1,5] Infection has been identified as an important factor causing endophthalmitis, the most feared complication of intraocular surgery. Based on 7-year data from the Malaysian Ministry of Health Cataract Surgery Registry (MOH CSR), the incidence of post-operative endophthalmitis (POE) was 0.08% (131/163,503).6 Issues

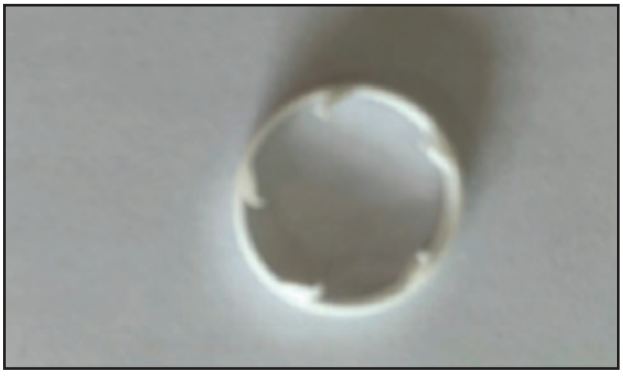

Fig. 1: Serrated piece of the plastic seal of the eyedrops bottle.

Fig. 2: Bottle with serrated piece.

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encountered while instilling the eye drops such as difficulty in squeezing or opening the bottle and lack of a partner or carer are factors that may decrease the compliance to ocular eye drops.[2,3,7,8] The potential risk of injury may further augment this issue.

If the serrated piece was routinely removed from the bottle after the seal was broken, this incident would not have happened (Figure 2). Nurses and patients alike may not be aware of the intricacies of the plastic bottles and its seal. Ocular surface injuries have been reported with eye drops bottle tips while instilling ocular medications.[2,3,7,9]

In this instance, the manufacturer was notified of the incident and injury risk. The manufacturer initially replied that they would investigate the incident. Subsequently, they replied that no similar complaint was reported earlier. They had also performed 'in-process functionality test' on eight samples. No deviations were reported, and no material deviations were reported for the cap and bottle. Obviously, these tests were carried out by informed personnel who knew that the serrated piece had to be removed. We contend that if a large number of patients were observed while opening the bottle, some would 'forget' to remove the serrated piece. A majority of the elderly would need cataract surgery at some point in their lives and almost all patients with eye conditions need some sort of drops for treatment. Hence, we deduce that a large number of patients would be exposed to such bottles with serrated pieces. Even if a small proportion of these patients do not follow the exact procedure, there would be a considerable number of patients who are needlessly exposed to the risk of injury.

The most effective way to reduce the potential for such injuries is the use of safer plastic bottles without such serrated pieces. While manufacturers take care of this issue, such bottles with serrated pieces will still exist in the market. Healthcare personnel and patients should be educated on risks and potential injuries with the use of eye drops with serrated seals. Nurses and pharmacists could demonstrate the first application of the eye drops with emphasis on removing such pieces before use.

We suggest widespread education of health care personnel (doctors, nurses, pharmacists, etc) and patients through a step-by-step, clear, instructional video to increase the safety of use of eye drops and overall compliance.

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