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The Medical Journal of Malaysia

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Palliative care in Malaysia: the need to do much more

Sivalingam Nalliah, MBBS, FRCOG[1], Richard Lim Boon Leong, MBBS, MRCP[2], Lekhraj Rampal, MBBS, DrPH[3]

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INTRODUCTION

The World Health Organization (WHO) defines palliative care (PC) as an approach that improves the quality of life of patients and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial, or spiritual.[1] Hospice care focuses on the palliation of pain and symptoms of terminally ill patients, in addition to attending to emotional and spiritual needs till the end of life. Care is extended to provide emotional support to both client and family, apart from assisting decision- making about needed treatments.[2] In 2010, Temel JS et al., published a landmark study that showed how early PC approaches, when compared to standard cancer care, led to less aggressive treatments with improved quality of life, less depression and increased survival in stage 4 non-small cell lung cancer patients.[3] Despite the known benefits of PC, WHO reported that worldwide, only 14% of people requiring it have access to it.[1] This situation can be improved with greater commitment of governments working in partnership with corporate bodies and Non-Government Organisations (NGOs).[4] Governments must therefore create national policies to steer the design and development of models of PC to suit the country's needs. With the rapidly ageing global population and the exponential rise in non-communicable chronic diseases (NCDs), the demand for PC services is ever increasing. WHO's 2019 survey of 194 member countries indicated that only 68% had somefunding for PC and 39% reported that the services reached only 50% of the people in need.[5]

Scope and Practice of Palliative Care

As defined by the WHO, PC is applicable early in the course of an illness in conjunction with other therapies that are intended to prolong life, both in children and adults.[1] It was also explicitly stated in the WHO Global Action plan for Non-communicable diseases (NCDs) that comprehensive care of NCDs requires the access to PC services.[6] Hence, PC is needed by all people who suffer from NCDs which are life-threatening including cancers, end-organ failures, neurodegenerative diseases as well as frailty in the elderly.[5,7-9] Its role is not merely confined to those who are dying but should include those with longer illness trajectories but severe disease morbidity. Beyond NCDs, the role of PC is also recognised for communicable diseases such as HIV/AIDS, multidrug-resistant tuberculosis and most recently severe COVID-19.[5] In 2014 the World Health Assembly passed resolution WHA67.[19] to impress upon its members to integrate PC within their healthcare systems to provide a continuum of care across all levels including hospital care, primary care, community and home-based care.[7] Hence the practice of PC must be wide and far-reaching to provide equitable care to all in need both in rural and urban settings. It has been argued that PC is a human rights issue and is part of universal health coverage.[5,9,10] In reality, however, worldwide there exists gross inequity with a lack of funding, human resource and essential medications to provide PC in poorer countries particularly in rural settings. The National Palliative Care Policy and Strategic Plan (NPCPSP) is an initiative by the Malaysian government to address this inequity and integrate PC into its local healthcare system.[4]

Lancet Commission on Palliative Care and Pain Relief

In 2018 the Lancet Commission on Palliative Care and Pain Relief used a methodology to assess the global need for PC called 'serious health-related suffering (SHS)' using mortality data for 20 conditions, adjusted for the prevalence of both physical and psychosocial symptoms. It reported that 25.5 million of 56.2 million people who died in 2015 experienced SHS and another 35.5 million experienced SHS due to life-threatening conditions. Majority (i.e., 80%) of these 61 million individuals lived in low -income and middle-income countries. These countries had very little access to any PC, and oral morphine for pain relief. More than 90% of paediatric deaths are associated with SHS and annually, 2.5 million terminally ill children around the world are in need of PC and pain relief. The report highlights the growing need for services to be developed equitably extending beyond urban centres.[11]

Palliative care in Malaysia

In November 2019, the Malaysian Ministry of Health (MOH) launched the NPCPSP 2019-2030. The plan highlighted the development of PC in Malaysia since the field's inception in 1991 and the need for much greater efforts to be made in order to provide effective, equitable and sustainable PC throughout the country. The report documented that only seven hospitals under the MOH had resident specialists in palliative medicine and of these , only four had in-patient PC units. Apart from the MOH, four public teaching hospitals and five private hospitals also provide specialist PC services, all of them are located in urban areas. The NPCPSP recognises that, despite significant progress in the development of PC, it does not cover the full scope of PC; progress has been sporadic and lacking standardisation. In fact, services in rural areas are non-existent. There is no equity of PC in Malaysia.[4]

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It is recognised that a large proportion of PC services should be community-based, in order to facilitate care at home as research has shown that majority of people prefer home as their place of care and death.[12,13] There are also many benefits of community-based care including improved quality of life and reducing overall cost of healthcare and hospitalisation.[14,15] Despite this insight, community-based PC has received very little support for its development and at present most of this care is provided by 30 PC by NGOs that have been voluntarily established throughout the country. While these services are a blessing to the nation, the coverage is grossly inadequate serving again, mainly urban areas. To improve the situation, in 2016, the MOH initiated the development of domiciliary PC programmes at their health clinics, piloted in the states of Selangor, Perak, Penang, and Kedah.[4] This is an important development but progress is slow in this due to the lack of funding and human resource.

The NPCPSP estimated the cost for developing eight new PC units in major hospitals with 160 domiciliary care team (not including operational cost in the MOH is expected to be RM38 million. It is estimated that twice this amount is needed to form such units throughout the whole nation. Specific annual funding for PC in the MOH is RM 7.5 million, with only RM 0.8-1.2 million awarded for PC as government grants to NGOs. This funding is insufficient to put in place a comprehensive integrated PC in Malaysia and an estimated increase of annual funding of upto 30.4 million RM for human resource, infrastructure, and purchase of drugs is required.[4] PC services provided by nursing homes is very limited. The standard of practice of such services has neither been evaluated or documented in a central registry. There is a need to evaluate competencies of staff, availability of medications and resources for PC in these care centres.

Provision of palliative care: Models of care

The WHO public health model for PC is the primary framework for developing PC services. It emphasises the need for essential drug availability, PC education and implementation of PC services under an umbrella of government policy.[16] Expanding upon this is also the need for human resource and funding.

There are many models of delivery of PC service and in general these models are built around the major areas of ambulatory clinics, home-based programs, inpatient PC units, and inpatient consultation services.[17,18] These service delivery models may provide care at various levels of skill and complexity beginning with the basic PC approach which can be delivered by any healthcare service and evolving to generalist , specialist services and finally the PC reference centre.[19] Luckett et al., conducted a rapid review of the elements of effective PC models and concluded that effective population-based PC models should include supporting case management through the integration of specialist PC with primary and community care services, and enable transitions across care settings, including residential aged care.[20]

Lim LC et al., reported developing a community- based PC services in Kuala Lipis Hospital, Malaysia. They adopted the traditional public health care model which highlighted the need to foster greater leadership among health personnel and community leaders in increasing accessibility of PC to the community.[21] If this model is effective and sustainable, such a strategy could be extended to support home care in Malaysia.

Beyond service provision, novel models for funding are also important as the implementation of a national PC policy needs to be sustainable without relying entirely on government infrastructures alone. Greater corporate involvement and collaboration with other agencies, local government and NGOs are essential. A successful model in Uganda has demonstrated how a smart partnerships between NGO-run PC centres and the government, wherein the government provides essential medications, training and payment of taxes, has encouraged development and sustainability of PC services.[22] In Malaysia, PC NGOs are estimated to raise some RM 7-8 million annually for maintaining operations while only about RM one million was given out as government grants.[4] Much more needs to be done to support PC NGOs providing such essential services.

BURDEN OF DISEASE IN MALAYSIA

The National Health and Morbidity Survey (NHMS) of 2019 reported that NCDs in Malaysia, contributed up to 71% of premature deaths. The prevalence of diabetes was 18.3%; hypercholesterolaemia 38.1% and hypertension, 30% in 2019.[23] With the increasing prevalence of diabetes, hypertension and hypercholesterolaemia, it is unlikely that Malaysia will achieve target 3.4 of the United Nations Sustainable Development Goals in reducing premature mortality due to NCDs.[24] It can be inferred that this situation, cumulatively will add to the increasing need for rehabilitation and PC services.

Currently, about 150,000 people require PC services in Malaysia, and this is estimated to rise to 240,000 by 2030.[25] Using the serious SHS formula, it is estimated that 220, 000 people would require PC annually. Similar estimates for children with SHS in Malaysia is around 30,000 annually.[4,11] Only a small proportion of these children are cancer cases; a larger proportion being those with cerebral palsy, neurodegenerative, muscular dystrophy, and congenital malformations as well as inborn errors of metabolism who require longer term care. Paediatric PC which started developing in 2012 is lagging behind adult PC in Malaysia and to date only 4 paediatricians have specialised in the field.[4,26]

NEED FOR FURTHER INTEGRATION AND GOVERNMENT SUPPORT

The WHO Global Action Plan for NCDs includes the integration of PC into the healthcare system to meet the goals of Universal Health Coverage stated in the UNSDG Target 3.8, as well as the goals of Primary Health Care in the Declaration of Astana, 2018.[6,24] This plan is supposed to be adopted by the MOH of Malaysia.

Due to the isolated provision of PC services and inequitable care provided to the population, Malaysia was ranked 38 out of 80 countries in the Global Quality of Death Index study in

2015 falling behind countries such as Mongolia and Uganda.[27] In the recent second edition of the *'Global Atlas of Palliative Care'* Malaysia was categorised as a level 3A nation meaning there has been limited progress in integrating PC into the healthcare system while our neighbours Singapore and Thailand have already achieved level 4A which are approximating integration.[5]

The NPCPSP report 2019-2030, admits there is much more to do, as Malaysia still 'lacks equitable and effective PC services to meet the acute needs of the Malaysian population'.[4] Malaysia, as a signatory of WHA 67.19 resolution, urgently requires strategic implementation of workable processes, especially in the rural and remote areas.[7]

Working models aside, other gaps identified by MOH are the availability and dispensing of essential medicines, especially morphine , infrastructure, and human resources. In order to bridge these gaps, the NPCPSP has suggested an expanded healthcare framework with seamless merging of private and public sectors. It identifies 7 key strategies to integrate PC into the healthcare system which includes i) recognising PC as part of universal health coverage; ii) identifying PC needs of patients; iii) creating access to care and essential medications; iv) creating networks for continuity of care; v) investing in PC education at all levels; vi) encouraging community participation in PC provision and vii) establishing standards of care.[4] These strategies are in line with recommendations by the WHO and Worldwide Hospice Palliative Care Alliance (WHPCA) in their blueprint for building integrated PC programmes and services which highlights the models and experiences of countries around the world where integration has been successful.[19] While these strategies are very appropriately documented in the NPCPSP, there is an urgent need for all of this to be implemented as soon as possible.

Proposed Palliative Care Model in Malaysia

Fig.1 shows a proposed model of care to provide an integrated and comprehensive PC in Malaysia irrespective of place of care. The level of PC accessed will depend on the index case, which can range from hospital care to primary care and care in the home. For patients managed at home, the pattern of care may follow fluctuating phases in the progression of disease with spurts of higher level of service (including consultation with specialists) accessed from time to time. This would justify a seamless integration of levels of care to provide personalised and customised care. Current models of PC in Malaysia will need to be extended to rural and remote sites, including care of children. To support such services, the six pillars shown in Fig. 1 are to be enhanced. It is clear that to provide an integrated and comprehensive model, infrastructure and resources should be developed based on an analysis of needs of patients and family. One of the four foundation domains reflected in the figure would be appropriate funding. Greater political commitment and policy development will need to be the basis of effective and accessible PC services. Any design and development of a model of care needs to be integrated into the existing Malaysian health care system, with a smart partnership with public and private health facilities, to be sustainable in meeting the goals of the WHO.

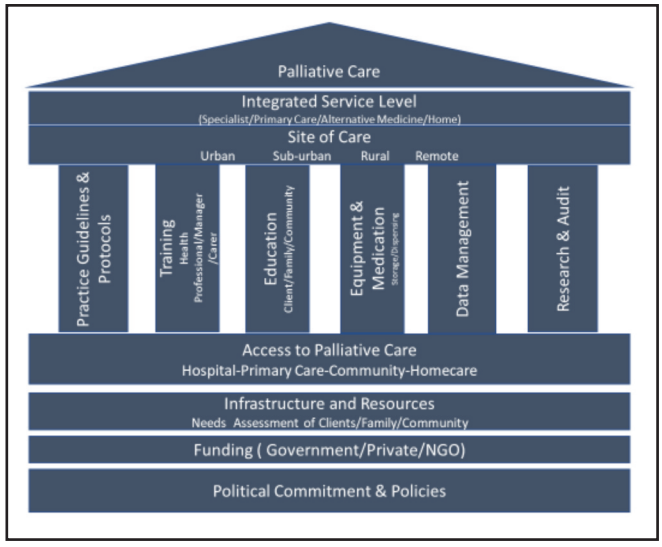

Fig. 1: Proposed Palliative Care Model in Malaysia.

Education and training for GPs, volunteers, and other stakeholders

Education and training are one of the key elements of the public health model for PC.[16] In order to integrate PC into the healthcare system, education needs to be provided at every level beginning from public awareness to primary, secondary and tertiary healthcare levels.[28] Over the years, formal and informal training programmes have been conducted by the MOH, the Universities, PC NGOs, the Malaysian Hospice Council (MHC) and the local PC fraternity. However, this has hardly been enough to create sufficient human capital for the PC needs of the residents in the country. Public awareness about PC is grossly inadequate and in a study conducted by Hospis Malaysia, only 17.2% of respondents were able to describe PC correctly.[12] At the primary care level, all general practitioners (GPs) should have some basic knowledge and skill to care for patients needing PC. There is a dire need for more institutes of higher learning in Malaysia to offer formal training in PC. At the secondary level, hospitals offering basic specialist care should also be equipped to manage the PC needs of patients seeking surgical or medical care. Dedicated teams with more in-depth training in PC can provide this. Ultimately formal specialist training will provide centres of excellence where research and development can also be conducted.[19,28]

At present, Malaysia has developed a fair amount of expertise in the field of PC with PC specialists, PC nurse specialists, an internationally acclaimed Hospice Centre (Hospis Malaysia) and even associate professors in PC in the universities. Hence much of the resources to train and educate others in PC already exist to some extent. What needs to be done is to bring these resources together to systematically provide a comprehensive PC education programme. An integrated blended learning approach with digital online learning is advocated in many developed countries and Malaysia must capitalise on this as well. Recently, University Malaya and the MHC commenced the Extension for Community Healthcare Outcomes Project

(Project ECHO) in Malaysia to reach out to PC NGOs throughout Malaysia. Project ECHO is a tele-mentoring programme developed by the University of New Mexico and is currently being shared throughout the world with the intention of helping clinicians to learn as they practice even when in remote areas.[29] As the COVID-19 pandemic has encouraged the use of virtual platforms for conducting webinars and conferences, the opportunities for tapping into international expertise has also become much more accessible and there is a myriad of online learning portals offering PC education to anyone.

One should not forget the training of volunteers who are also an important resource. With appropriate skills-building and coping enhancement they can help to provide a range of services including managerial, social, emotional, and physical care. It has been suggested that if a community can come together and provide care for one another at times of health crisis, this can significantly reduce the burden on healthcare systems and even reduce the cost of healthcare. This is the concept of *"compassionate communities"* and is an idea that must be looked into for Malaysia.[30]

DATA MANAGEMENT

Robust data on PC services and the social and emotional impact on their family members is needed. Davies JM et al alluded to the value of routine data collected at personal, service, and geographical area level, drawn from death registry data, primary and secondary data, and other health parameters with particularities of the community at personal and family level. With digitalisation and documentation, MOH can draw uniform templates for generation of standard data that would help in analysis and service provision. Home deaths, specialist service, patient characteristics and healthcare processes will lend to measuring both gaps in service provision and measuring quality indices at all levels of care.[31]

The MOH e-Health programme will hopefully enable such data collection and if longitudinal medical records from the primary care setting can be collated electronically, it will provide enormous assistance for PC services, especially in continuing medical care from hospital- based treatment to PC at home.

CONCLUSION

The NPCPSP 2019-2030 launched by the MOH, though timely, needs urgent support and leadership to incorporate PC into the national health system. The current PC services in Malaysia are not sufficiently comprehensive to meet current needs and greater integration is required in a systematic manner to cover rural and urban areas.[4,5,27] An urgent review of provision of pain relief and opioid availability is required.[4,23] The power of individuals, families, and communities as partners- in- care needs to be further harnessed. Enhanced private-public partnership with greater contribution by GPs and primary care physicians is warranted. The institutes of higher learning in Malaysia should offer formal instructional training in PC all levels of personnel involved in the PC team. More research is warranted in Malaysia to provide robust data on patients requiring PC, including the social and emotional impact on their family members. The systematic measurement of patient-reported indicators is an essential step towards people-centred health systems.[4,31] In addition to a smart partnership, corporate bodies in Malaysia should also support public awareness. A comprehensive health economic study is urgently required by MOH to justify increasing budget needs for PC services beyond what is currently being provided and to find sustainable models of funding to incorporate PC provision by GPs, private healthcare facilities and NGOs. As serious health-related suffering will continue to rise, action must be taken now to ensure that proper care and support will be available to all peoples in Malaysia in the near future.

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ORIGINAL ARTICLE

Paediatric surgical response to an 'adult' COVID-19 pandemic

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ABSTRACT

Introduction: The Coronavirus Disease 2019 (COVID-19) has dramatically affected global healthcare systems. We aimed to determine the response of our paediatric surgical fraternity to a disease that overwhelmingly affects adults.

Materials and Methods: We conducted a cross-sectional questionnaire-based study over 6 weeks during a federally mandated lockdown. Using snowball sampling, we recruited paediatric surgeons, trainees and medical officers from paediatric surgical units in Malaysia. The anonymous online questionnaire covered sociodemographic information, changes in patient care, redeployment, concerns regarding family members, and impact on training. Mental well-being was assessed using the Depression, Anxiety and Stress Scale (DASS-21). Kruskal-Wallis, ANOVA and multiple regression analysis was used, with significance level 0.05.

Results: Of the 129 eligible participants, 100(77%) responded. Junior doctors had clinically higher levels of depression, anxiety, and stress. Age <30 years was significantly associated with anxiety. Junior doctors believed that redeployment led to loss of surgical skills ($p<0.001$) and trainees felt that clinical application of knowledge had reduced ($p<0.020$).

Conclusion: Specific to our paediatric surgical community, this study highlights areas of concern, particularly among junior doctors. It is likely that recurrent cycles of the pandemic will occur soon. These issues must be addressed to preserve the mental and emotional well-being of all health care workers.

KEYWORDS:
Pandemic; training; psychosocial impact; health care workers; mental well being

INTRODUCTION

The novel coronavirus disease Covid-19 was initially identified in December 2019 as a case of pneumonia in Wuhan, China and has since become a global pandemic, affecting more than 150 countries around the world. To date, it has infected up to 79 million people worldwide and caused up to 1.7 million deaths.[1,2] The World Health Organization declared the outbreak a pandemic on March 11, 2020 and called for coordinated mechanisms to support preparedness and response to the infection across health sectors.[2] A restricted movement order (lockdown) was announced by the Malaysian federal government on 18 March 2020, by which time there was an average of 170 new cases per day, with a total of approximately 1800 cases nationwide.[3]

All areas of health care have been impacted by the Covid-19 pandemic, including paediatric surgery. Since the onset of the crisis, surgical care practices have been adapted in many hospitals, each institution adopting the strategy believed to be the most appropriate according to their available manpower, hospital resources, and limitations.[4] Normalcy of the medical professional and personal lives has changed completely.[5]

In Malaysia, the daily working activities of paediatric surgery services have drastically modified due to the pandemic. These include changes in clinical interaction, where video or phone call follow up became the method of choice in reducing the number of patients coming for face-to-face follow-up.[5] Only a minimum number of essential personnel were involved in daily ward rounds, and surgical procedures were temporarily halted with only emergency cases performed according to strict local triage criteria. In some units, paediatric surgery trainees were redeployed to other critical areas, such as adult emergency and intensive care. Training programs were also overhauled to minimize trainee exposure to Covid-19, and clinical rotas were adjusted to allow for backup teams in the event that health care workers (HCW) became ill, thus leading to decrease in quality of training.[6]

The primary aim of this study was to determine the response of healthcare workers in the paediatric surgical fraternity to the Covid-19 pandemic, a disease that overwhelmingly affects adults compared to children. The secondary aim was to explore the psychosocial implications of Covid-19 on our community, using the Depression, Anxiety and Stress Scale score (DASS-21).

MATERIALS AND METHODS

Study setting

This study was carried in Malaysia and included all hospitals providing paediatric surgery services. The hospitals consist of publicly funded hospitals, private hospitals, and university-affiliated academic centres. A total of 8 hospitals are recognised as training centres for paediatric surgery, staffed

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by HCW consisting of approximately 40 fully trained paediatric surgeons, 39 trainees, and 50 non-trainee medical officers (MO). In addition, during the Covid-19 pandemic, 23 hospitals were designated as Covid-19 hospitals, with the facilities to provide the full range of care for Covid-19 patients, including intensive care.

Study design and sampling method
A cross-sectional study design was used. This study was carried out between 1st April to 15th May 2020, in the midst of a federally mandated national lockdown. A self-administered electronic questionnaire was distributed to all paediatric surgical units. Participants were recruited via snowball sampling and representative sampling.

We categorised our respondents as follows.
1) Paediatric surgeons: those who had completed specialist training in paediatric surgery. When evaluating the impact of the pandemic on surgical training, this group was referred to as 'Trainers'.
2) Trainees: All those registered in a paediatric surgery training programme at the time of the survey.
3) Medical officers (MO): Non-specialist and non-trainee doctors whose primary duties were in a paediatric surgical unit.

Respondents were contacted via a number of different channels, including the national paediatric surgical association, local trainee representatives, hospital and social network. A web-based data collection tool (Google Forms), which was anonymous was used to collect data.

Questionnaires
We devised the questionnaire based on our literature review of issues highlighted by HCW in previous pandemics to guide the areas of focus.[7-9] The questionnaire was pilot tested on 10 respondents prior to full execution.

The questionnaire consisted of 4 parts:
Part 1: Sociodemographic data
Part 2: Respondent response towards (a) changes in provision of patient care, (b) redeployment to other departments and (c) concern about family members. Five-point Likert scale questions, with response options ranging from 'strongly agree' score '5' to 'strongly disagree' score '1', were utilised to assess respondents' agreement with statements.
Part 3: Exploration of the impact of Covid-19 on training and education from perspectives of different roles – trainer, trainee and non-trainee medical officer.
Part 4: Psychological assessment using the Depression Anxiety Stress Scale-21 (DASS-21 score). The DASS-21 is a 21-item scale that provides independent measures of three self-report subscales such as depression (7 items), stress (7 items), and anxiety (7 items). Scores for each subscale were calculated by summing the scores for the relevant items and then multiplied by 2 to calculate the final score (Table I).[10] The DASS-21 score has been validated in multiple studies around the globe.[11-13]

Content validity was checked with experts regarding attitudes towards provision of patient care, redeployment of manpower to other departments, concern about patient care and family members, research regarding COVID-19 pandemic as well as attitudes towards training among consultants and attitudes towards skills, learning, clinical application knowledge among trainee and MO. Face validity was also checked with the participants in the aspect of clarity of the questions, likelihood the target audience would be answering the questions, and layout and styles off the questionnaire. Cronbach's alpha coefficient was calculated for internal consistency of the questionnaire. The Cronbach's alpha coefficient of attitudes towards provision of patient care was 0.516, attitudes towards redeployment of manpower to other department during the pandemic was 0.258, concern about family was 0.619, and attitudes towards research regarding COVID-19 pandemic was 0.283. The Cronbach's alpha coefficient of attitudes towards skills, learning, clinical application knowledge among trainee and medical officer was 0.690

Data processing and analysis
SPSS version 18.0 was used for data analysis. Descriptive statistics such as frequency and percentage, median and quartiles (1st and 3rd) were calculated. Kruskal-Wallis test was used to determine the difference of attitudes between surgeon, trainee and medical officer, towards provision of patient care, redeployment of manpower to other department, concern about patient care and family member, ANOVA was calculated to determine the difference of stress, anxiety and depression between groups. Multiple regression analysis was also used to determine the factors associated with depression, anxiety, and stress. Level of significance was set at 0.05.[10]

Ethics Approval
This study was approved by the Medical Research Ethics Committee, University of Malaya Medical Centre (UMMC) (No 2020515-8625)

RESULTS

A total of 100 respondents participated in the study, consisting of surgeons (n=28), trainees (n=34) and MOs (n=38), representing approximately 77% of all eligible participants (Table II). The majority of trainees (97.1%) were aged 31-40 years. The majority of all respondents (64%) were from public hospitals, and nearly half (47%) were not living with vulnerable household members.

Table III describes the responses to the areas covered in the questionnaire. Of note, trainees and MOs were more likely to report concern regarding loss of surgical skills due to manpower redeployment, and more likely to find it important to have preferential Covid-19 testing for their family members.

Stress was three times more likely to be present among trainees and MOs in comparison to surgeons, while anxiety and depression were two times more likely (Figure 1). Multiple linear regression analysis of factors associated with depression, anxiety and stress in all the groups found only age <30 years was significantly associated with anxiety. No other factors such as sex, marital status, and place of practice showed significant association with depression, anxiety, and stress.

When surveyed for their opinion on the impact on training, trainers were happy with how the academic programme was coping with the changes demanded. Trainees were significantly more concerned than MOs that the clinical application of knowledge was reduced (Figure 2).

DISCUSSION

Paediatric surgery around the world has been profoundly impacted by the Covid-19 pandemic. To our knowledge, this is the first study exploring the response of the paediatric surgical fraternity to the pandemic. The key finding in our study was that the prevalence of stress was three times more likely to be present in surgical trainees and MOs in comparison to surgical trainers while anxiety and depression were two times more likely. Although this did not reach statistical significance, we believe that it is clinically significant. Similar patterns of psychosocial impact have been reported in many other studies done during previous pandemics.[14,15,16] A few factors are possible reasons. Junior doctors are prone to be redeployed to non-surgical areas, with little autonomy over their daily clinical duties compared to senior surgeons, taking them to unfamiliar clinical environments. Younger doctors are also more likely to have domestic obligations such as the care of smaller children.[7] We recommend that hospital administrators recognize the challenges faced by junior doctors and provide practical support, such as childcare and mental well-being care. In UMMC, regular online townhall sessions were organised to provide HCW an avenue to obtain updates, provide feedback and put forth questions to the management.[17] Unsurprisingly, none of the doctors working in non Covid-19 hospitals were affected psychosocially as their daily activities remained unchanged[9,15,19] We also explored the issue of manpower redeployment to other non-paediatric surgical areas, which was a practice commonly described in other centres.[20-22] Some were also assigned for specific tasks such taking pre-procedural swabbing in children which would normally be out of their scope of training but was necessary during the pandemic.[18] While the majority agreed that this was appropriate in these unique circumstances, a concern about losing surgical skills was significantly higher (P< 0.001) among paediatric surgical trainees and MOs (Table III). This is unsurprising as junior doctors are in the process of developing surgical skills. Moulton et al reported that consistent exposure to skills training in smaller aliquots over time resulted in superior retention of surgical skills, compared to intense and concentrated exposure over a short period. On the other hand, expert or trained personnel usually have superior retention of surgical skills.[23]

With regards to views on the impact of Covid-19 on the surgical training programme, paediatric surgeons agreed that operative volume was reduced. In UMMC our operative

Table I: DASS 21 score

	Depression (D)	Anxiety (A)	Stress (S)
Normal	0 – 9	0 – 7	0 – 14
Mild	10 – 13	8 – 9	15 – 18
Moderate	14 – 20	10 – 14	19 – 25
Severe	21 – 27	15 – 19	26 – 33
Extremely Severe	28+	20+	34 +

Table II: Demographic profile of respondents

Variables	Surgeon n (%)	Trainee n (%)	Medical officer n (%)
Age			
≤30	0 (0)	1 (2.9)	16 (42.1)
31-40	12 (42.9)	33 (97.1)	22 (57.9)
>40	16 (57.1)	0 (0)	0 (0)
Sex			
Male	15 (53.6)	19 (55.9)	16 (42.1)
Female	13 (46.4)	15 (44.1)	22 (57.9)
Place of practice			
Private	5 (17.9)	0 (0)	0 (0)
Public	20 (71.4)	16 (47.1)	28 (73.7)
University Hospital	3 (10.7)	18 (52.9)	10 (26.3)
Working in a COVID-19 hospital			
Non COVID-19 hospital	7 (25.0)	3 (8.8)	1 (2.6)
COVID-19 hospital	21 (75.0)	31 (91.2)	37 (97.4)
Marital status			
Single	9 (32.1)	9 (26.5)	16 (42.1)
Married	19 (67.9)	24 (70.6)	22 (57.9)
Divorced/widowed	0 (0)	1 (2.9)	0 (0)
Currently living in a household with			
Senior members	4 (14.3)	6 (17.6)	3 (7.9)
Children	15 (53.6)	10 (29.4)	11 (28.9)
Immunocompromised/ chronic medical condition	2 (7.1)	0 (0)	2 (5.3)
None of the above	7 (25.0)	18 (52.9)	22 (57.9)

Table III: Attitudes towards provision of patient care, redeployment of manpower to other department, concern about patient care and family member

No	Variables	Median (Q1, Q3)			p value
		Consultant (n=28)	Trainee (n=34)	Medical Officer (n=38)	
	Changes in provision of patient care				
1.	My daily working schedule has changed	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)	4.0 (2.0, 5.0)	0.703
2.	There are changes to my routine patient care (eg. ward rounds, clinic, operating time)	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)	4.0 (2.0, 5.0)	0.912
3.	I think the quality of patient care I provide is not affected	3.0 (1.25, 3.0)	2.0 (2.0, 3.25)	2.0 (2.0, 3.25)	0.865
4.	Lack of face to face patient interaction during follow up is detrimental for my patient care	4.0 (3.0, 4.0)	4.0 (3.0, 4.0)	4.0 (2.0, 4.0)	0.931
5.	Patients can be followed up optimally by phone/video call	4.0 (3.0, 4.0)	4.0 (3.0, 4.0)	4.0 (2.0, 4.0)	0.810
6.	I feel that multidisciplinary care of my patients is compromised	4.0 (2.25, 4.0)	4.0 (2.0, 4.0)	4.0 (2.0, 4.0)	0.859
7.	I feel that some patients are not getting the care that they need	4.0 (2.25, 4.0)	4.0 (3.0, 4.0)	3.5 (2.0, 4.0)	0.069
	Redeployment of manpower to other department during the pandemic				
8.	I think redeployment is appropriate during the covid-19 pandemic	4.0 (4.0, 4.0)	4.0 (3.0, 4.0)	4.0 (3.0, 4.0)	0.139
9.	I prefer to choose where I am redeployed as I know where I will be useful	4.0 (4.0, 4.0)	4.0 (4.0, 4.25)	4.0 (4.0, 4.0)	0.978
10.	Hospital authorities have the right to decide where I am deployed	2.0 (2.0, 3.75)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	0.232
11.	I will lose my skills if I am redeployed	2.0 (1.0, 2.75)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	<0.001
12.	I do not feel confident in treating patients out of my specialty	4.0 (2.25, 4.0)	4.0 (4.0, 4.0)	4.0 (2.0, 4.0)	0.167
	Concern about family members				
13.	Due to concerns regarding covid-19, I try to avoid direct contact with senior family members	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)	0.262
14.	Due to concerns regarding covid-19 I avoid direct contact with children	4.0 (2.0, 4.0)	4.0 (4.0, 5.0)	4.0 (3.0, 5.0)	0.094
15.	I am not concerned about interacting with my family members	4.0 (2.0, 4.0)	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)	0.074
16.	I have changed my routine on arrival home after work to avoid infecting my family members	4.0 (3.0, 5.0)	4.0 (4.0, 4.0)	4.0 (3.0, 5.0)	0.926
17.	Priority testing for covid 19 should be given to family members of healthcare workers	3.5 (2.0, 4.0)	4.0 (4.0, 4.25)	4.0 (3.0, 4.0)	0.036
18.	Treatment for covid 19 should be prioritised for family members of healthcare workers	3.0 (2.0, 4.0)	4.0 (3.0, 4.0)	4.0 (3.0, 4.0)	0.171
	Research regarding covid-19 pandemic				
19.	I am involved in covid-19 research	2.0 (1.0, 30)	2.0 (1.0, 2.0)	2.0 (2.0, 3.0)	0.186
20.	I feel that covid-19 related research is important	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)	0.481
21.	I think it is not important to do research regarding covid 19 pandemic	4.5 (4.0, 5.0)	4.0 (4.0, 5.0)	4.5 (4.0, 5.0)	0.361

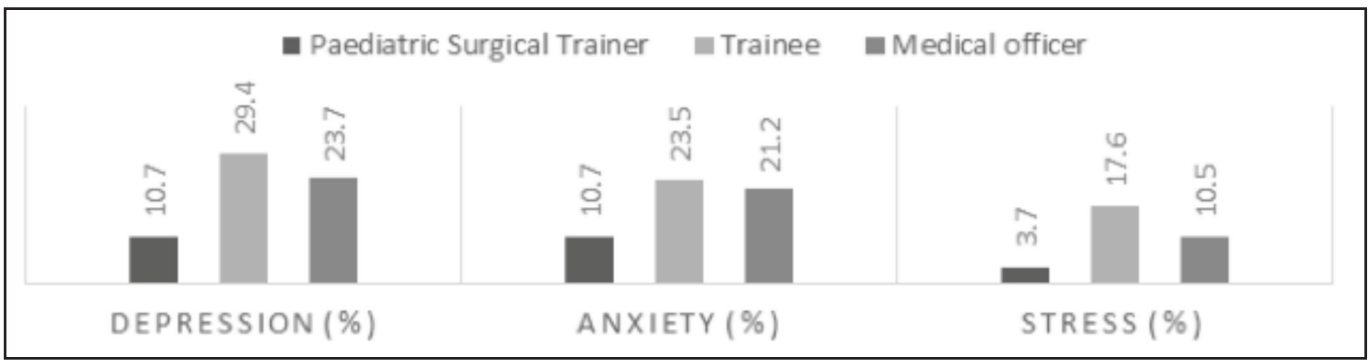

Fig. 1: Prevalence of depression, stress and anxiety among respondents.

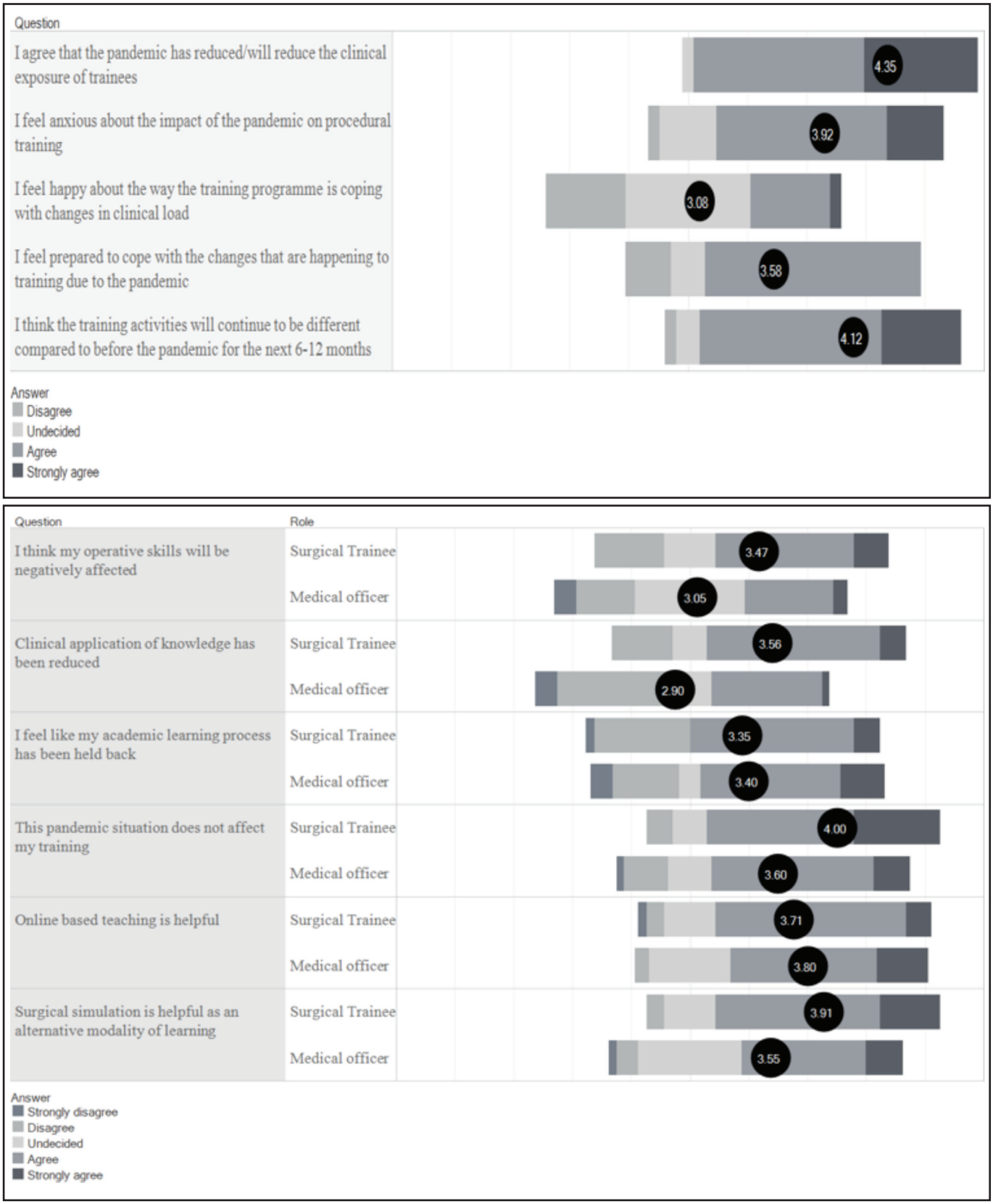

Fig. 2: Attitudes towards training programme and skills, learning, and clinical application of knowledge among paediatric surgeons, paediatric surgical trainees and medical officers with the mean value in circle.

load was reduced by more than 80%.[17] There were no significant differences between trainees and MOs in terms of attitudes towards surgical training except that trainees agree that clinical application of knowledge had been reduced (p=0.02). This current Covid-19 pandemic has provided trainees and MOs with opportunities to explore different virtual learning options, including surgical simulation-based training as an adjunct to other teaching tools for surgical training.[24]

We also found that trainees and MOs were more concerned about transmission of Covid-19 to family members, especially the elderly, the immunocompromised, or those with chronic medical conditions.[25] This is similar to other previous outbreaks such as the H1N1 influenza in the United Kingdom in 20077 and China's severe acute respiratory syndrome (SARS) outbreak in 2003.[26] However, adequate PPE provision can help to alleviate anxiety levels. we could A study conducted in UMMC reporting early results of routine pre procedural swabbing for all operative cases, showed that no low risk patients were positive for COVID. Dissemination of these results would also reduce the level of anxiety.[18]

Trainees and MOs were significantly more likely (p=0.036) to agree that their family members should receive priority testing for Covid-19 compared to the surgeons (Table I). This might be because paediatric surgeons consist of senior doctors who are less likely to be on the clinical frontline, while trainees and MOs are deployed to critically need areas such as the emergency department. All participants agreed that provision of patient care has been affected during the Covid-19 pandemic. Many from other countries have described measures similar to those practised in the UMMC setting which have affected patient care, such as limiting the number of HCW performing clinical duties, postponement of elective surgeries, and conversion of clinic sessions from face to face to telemedicine.[5] A study by the CovidSurg collaborative projected that up to 70% of electives surgeries were postponed and that it would need up to 45 weeks to clear the backlog.[27]

While it was necessary for the protection of HCW and for resource preservation, some of these measures also profoundly affected academic training activities. There were restrictions placed on the number of HCW in the operating theatre, and face-to-face teaching was replaced by video-conferencing sessions. Similar changes have also been seen in other countries e.g. in UK, US, China, European, Italy, Latin America, Finland.[6]

There are several limitations in the present study. Firstly, this is a cross sectional study, and we therefore cannot determine the temporal relationship of the exposure to Covid-19 pandemic and the outcome or response towards it. On-response bias is a limitation in conducting a survey-based data collection. It must be recognised that inherent bias present in surveys may have selected those with more interest in this outbreak, inflating the levels of reported knowledge and confidence. The small sample size of 100 respondents clearly affected our statistical analysis; however, it reflects the small paediatric surgical fraternity in Malaysia and represents 77% of them.

CONCLUSION

During this challenging time changes are inevitable, but the outcome will be defined by our action and ability to adapt today. Specific to our paediatric surgical community, this study highlights areas of concern, particularly among junior doctors. It is likely that recurrent cycles of the pandemic are likely to occur in the near future, and these issues must be addressed to preserve the mental and emotional well-being of all health care workers. Thus, we suggest for a follow up study once there is restoration of services. This pandemic is far from over despite many countries being able to rebuild their economy. Issues that we have highlighted here, such as the differences in response by roles have to be addressed more vigilantly to be prepared to respond to future new public health threats.

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Cardiovascular risk factors of Alzheimer's disease and other neurocognitive disorders in Malaysia

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ABSTRACT

Introduction: Risk factors for cardiovascular disease (CVD) have been increasingly implicated in the development of dementia but little is known about the effects in a Malaysian population. We aimed to determine the interaction between sociodemographic and CVD risk factors among the dementia and mild cognitive impairment (MCI) patients in Malaysia.

Materials and Methods: A cross-sectional study was conducted in the memory clinic at Hospital Kuala Lumpur (HKL). Medical records data from 2014 to 2019 were extracted. Mini Mental State Examination (MMSE) test was used to assess the neurocognitive function of patients.

Results: A total of 298 patients (30 MCI, and 268 dementia) were evaluated, with dementia patients consisting of 78 Alzheimer's disease (AD), 93 Vascular dementia (VaD), 94 Mixed dementia, 2 early-onset Alzheimer's disease (EOAD) and 1 Logopenic Progressive Aphasia type of AD (LPA). MCI and dementia were significantly associated with a history of CVD, particularly stroke (p=0.023).

Conclusion: Given that stroke significantly predicted the risk of developing vascular dementia among the patients in a central Malaysian population, lifestyle modifications are recommended to alleviate these risk factors of CVD.

KEYWORDS:
Alzheimer's disease, vascular dementia, cardiovascular, hypertension, Malaysian

INTRODUCTION

Dementia or major neurocognitive disorders (NCD) refers to the collection of heterogeneous disorders that occur because of progressive neurodegeneration and other pathologies of brain cells. Based on the Diagnostic and Statistical Manual for of Mental Disorders, Fifth Edition (DSM-5), the commonest major NCD is Alzheimer's disease (AD) that involves disturbances in the cognitive cerebral domains, such as memory, language, and executive functions.[1] On the other hand, mild cognitive impairment (MCI), which is a mild NCD, has been implicated in the spectrum of NCDs, and refers to a transitional state between normal ageing and dementia.[2] MCI is characterised by a decline in one's cognitive abilities in the memory domain of cognitive functions compared to the previous level of performance, provided the activities of daily living remain intact and the subject does not fulfil the criteria for AD.[3] Typically, AD accounts for more than 70% of all cases of dementia and most patients have late onset AD (LOAD) but some are also identified with early-onset AD (EOAD) that is likely hereditary in aetiology.[4] A survey in 2016, reported that AD affects nearly 40-50 million people worldwide, out of which approximately 23 million of them live in Asia, and more than 123,000 reside in Malaysia.[5] The second most prevalent form of dementia is vascular dementia (VaD),[6] and the third most common dementia subtype is mixed dementia, which is usually caused by a co-existence of AD and VaD. Other forms of dementias include fronto-temporal dementia (FTD) and Lewy-body dementia (DLB).[7,8] In addition, atypical AD subtypes such as language variant AD, known as the Logopenic variant of Primary Progressive Aphasia (lv-PPA) also exist.[9]

For VaD, the clinical presentation is dependent on the causative agent. Specifically, a cerebrovascular accident or stroke may localise the area and extent of the brain injury, whereas VaD due to cardiovascular disease (CVD) is highly diffuse in its involvement and presents with a reduced rate of information processing, cognitive dysfunction, and an inability to perform tasks that require complex attention.[10] Apart from memory loss, VaD has been implicated in gait apraxia, and urinary incontinence.[11] Additionally, mixed dementia, presents with a combination of the symptoms of AD and VaD; namely memory loss, together with executive impairment and attention dysfunction.[9]

Clinical conditions such as stroke, atrial fibrillation, coronary heart disease (CHD), and heart failure are examples of CVDs. The CVDs have been increasingly implicated in the development of dementia.[12] It is postulated that there is a direct causal association between CVD and AD as cardiac disease leads to cerebral hypoperfusion and micro-emboli.[13] These mechanisms can cause neuronal damage, which along

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with beta amyloid deposition and tau pathology, lead to the neurocognitive deficit of AD.[7,14] Stroke, which is a major type of CVD, can lead to 'post-stroke dementia' or VaD. Lacunar strokes caused by cerebral small vessels disease are known to cause VaD and can also increase the risk of developing AD.[15] Furthermore, ischemic brain damage, which is evidenced by white matter lesions on magnetic resonance imaging (MRI), is also associated with dementia.[15,16]

A previous community-based study conducted among elderly Malaysians revealed that the risk factors for dementia included older age, lack of formal education, female gender, very poor level of self-rated health quality, and Malay or Bumiputera ethnicity.[17] There is, however, a lack of information regarding the sociodemographic information and related risk factors pertaining to dementia patients in a hospital-based setup in Malaysia. In particular, it is of interest to identify the sociodemographic information and associated risk factors for patients having dementia at HKL, which is one of the largest tertiary referral centres in Malaysia that attends to dementia cases at a regular basis in their memory clinic.

To the best of our knowledge, to date only community-based studies pertaining to dementia have been conducted in Malaysia. Therefore, the present study is aimed to achieve the following objectives i.e., to estimate the frequency of MCI and the different subtypes of dementia among Malaysians attending the memory clinic HKL, to determine the differences in MMSE scores among the MCI and dementia patients and to determine the association between MCI or dementia with the sociodemographic and CVD risk factors.

MATERIALS AND METHODS

Study design and settings

A retrospective study was carried out using secondary data from the medical records of 298 patients (30 MCI and 268 dementia) attending the memory clinic of HKL between 2014 and 2019. The patients are residents of an urban region in Malaysia, specifically Kuala Lumpur.

The Memory Clinic at the Geriatric Unit, HKL has been operating since 2003. Patients who attend the clinic here are first screened by nurses who are well-trained in the assessment of cognitive function. Several cognitive assessment tools such as the Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), the Saint Louis University Mental Status exam (SLUMS) were used to assess the' level of daily living activities of the patients before they were evaluated by the geriatricians. Furthermore, since 2013, the memory clinic incorporated a multidisciplinary approach involving allied health workers in the care of patients. For example, occupational therapists, pharmacists, speech and language therapist, physiotherapist, dietitians, special-need dentists, social workers and neuroradiologist were instrumental in providing the necessary services to the patients. This kind of multidisciplinary approach is thus essential in providing good quality of care for the patients.

Sample size determination

The sample size calculated was estimated based on the assumption that retrospective studies use statistical power instead of measuring sample sizes (also called post hoc power analysis).[18] Consequently, the GPower software was used to predict the actual sample size needed by choosing the effect size of 0.25, power (1-β err prob) of 0.95 and 4 number of groups for the ANOVA, the results yielded 280 NCD patients' data was needed to be recorded retrospectively based on the a study with similar endpoint.[19] However, during the data collection, 298 patients were found in the hospital records and hence all were considered for the analysis.

Patients selection

The inclusion criteria included Malaysian patients at the HKL memory clinic, having all the relevant clinical data, i.e., the diagnosis of the type of NCD was available, the age, gender, education level, marriage status, and comorbid disease. Foreigners and patients who were not diagnosed with dementia between the periods of 2014 to 2019 were excluded from the study.

Secondary source of data

The data was collected manually by going through the files of the patients that met the inclusion criteria for our study. The primary data extracted from the files of patients included age, gender, race, marital status, level of education, occupation, and the Mini Mental State Examination (MMSE) test scores. The MMSE test is an example of a widely used tool for the objective assessment of dementia.[20] It is comprised of 30 questions aimed at evaluating memory, registration, recall, calculation, language, attention, and orientation, as well as visuospatial abilities.[21] Normally a total score of 24 and below indicates significant cognitive impairment and dementia. However, sociodemographic factors such as age, duration of formal education and other factors affect the scores at an individual level.[22]

Diagnostic criteria

The patients were diagnosed with the specific subtypes of NCDs by the clinicians based on the standardised criteria using DSM-5 and MMSE test scores. Although there is no consensus for the diagnosis of mixed dementia, several international references such as the Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) and the National Institute of Neurological Disorders and Stroke and *Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (NINDS-AIREN) have proposed diagnostic criteria that differ from each other. Therefore, mixed dementia was diagnosed following the harmonization of criteria outlined by the ADDTC and NINDS-AIREN, such as the presence of focal neurological symptoms and evidence of significant CVD.[23]

Ethical Approval

This study was approved by the Medical Research Ethics Committee (MREC) of National Medical Registration Registry (NMRR) Malaysia (NMRR-19-2719-49105) and the Ethics Committee for Research Involving Human Subjects of Universiti Putra Malaysia (JKEUPM-2019-328)

Table I: Association between socio-demographic risk factors and neurocognitive disorders among the memory clinic patients at Hospital Kuala Lumpur, Malaysia

	MCI (n=30) (10.24%)	AD (n=78) (26.62%)	VaD (n=93) (31.1%)	Mixed dementia (n=94) (32.1%)	Total (n=293) (100%)	F/X2	p value
Age (years)	74 (7.22)	75.47(8.90)	75.48 (7.77)	77.35 (7.49)	75.93 (7.98)	1.77	0.153
Gender							
Male	17 (56.7)	35 (44.9)	44 (47.3)	36 (40.4)	133 (46)	2.24	0.524
Female	13 (43.3)	43 (55.1)	49 (52.7)	53 (59.6)	156 (54)		
Race							
Malay/Bumiputera	5 (16.7%)	21 (27.3)	32 (34.8)	27 (28.7)	85 (29)	4.55	0.603
Chinese	17 (56.7)	37 (48.1)	37 (40.2)	46 (48.9)	137 (46.8)		
Indian	8 (26.7)	19 (24.7)	23 (25)	21 (23.3)	71 (24.2)		
Years of education:							
≤ 6 years	9 (34.6)	39 (54.9)	45 (57)	55 (62.5)	148 (56.1)	6.39	0.094
≥ 6 years	17 (65.4)	32 (45.1)	34 (43)	33 (37.5)	116 (43.9)		
Marital status:							
Unmarried	7 (29.2)	13 (22)	18 (25.4)	28 (35)	66 (28.2)	3.23	0.358
Married	17 (7.3)	46 (78)	53 (74.6)	52 (65)	168 (71.8)		
Employment							
Yes	18 (78.3)	40 (80.0)	47 (77.0)	52 (75.4)	157 (77.3)	0.369	0.946
No	5 (21.7)	10 (20.0)	14 (23.0)	17 (24.6)	46 (22.7)		
Diabetes mellitus							
Yes	10 (33.3)	29 (37.2)	46 (50)	41 (43.6)	126 (42.9)	4.077	0.253
No	20 (66.7)	49 (62.8)	46 (50)	53 (56.4)	168 (57.1)		
Hypertension							
Yes	17 (56.7)	47 (60.3)	68 (73.9)	64 (68.1)	196 (66.7)	5.051	0.168
No	13 (43.3)	31(39.7)	24 (26.1)	30 (31.9)	98 (33.3)		
Hypercholesterolemia							
Yes	1 (3.3)	3 (2.8)	1 (1.1)	2 (2.1)	7 (2.4)	1.53	0.676
No	29 (96.7)	75 (96.2)	91 (98.9)	92 (97.9)	287 (97.6)		
Stroke							
Yes	1 (3.3)	3 (3.8)	15 (16.3)	13 (13.8)	32 (10.9)	9.374	0.023*
No	29 (96.7)	75 (96.2)	77 (83.7)	81 (86.2)	262 (89.1)		
Heart disease							
Yes	0 (0.0)	1 (1.3)	1 (1.1)	4 (4.3)	6 (2)	3.574	0.311
No	30 (100)	77 (98.7)	91 (98.9)	90 (95.7)	288 (98)		

Note: Data were expressed as n (%) or mean ± SD; Significant difference between risk of MCI and de¬mentia was determined by One-way ANOVA test or Chi-square test ($\chi 2$) at 0.05 level of significance; *p<0.05

Statistical Analysis

All statistical tests were conducted using the Statistical Package for the Social Sciences (SPSS software Version 23.0, SPSS Inc., Chicago, IL, USA) and the level of significant was set at p value less than 0.05. Chi-square test was used to determine the association between socio-demographic risk factors among patients with NCDs while One-way ANOVA test was used to determine the means difference in terms of age of the patients with NCDs. Simple descriptive statistic and one-way ANOVA were employed in analysing the MMSE test scores among various subtypes of NCD patients.

RESULTS

As shown in Figure 1, the distribution of the patients based on the NCDs showed that mixed dementia was the highest type of NCD (Figure 1). This was closely followed by VaD (31.2%), and AD (26.2%). MCI patients made up 10.1% of the patient population. We also identified 2 patients with EOAD and one patient with LPA, respectively. There were no patients diagnosed with FTD during our study period.

To compare the mean MMSE scores among patients with NCDs, One-way ANOVA test was used and revealed a statistical significance [F (3, 263) = 17.28, p < 0.001] mean difference between the scores in the MCI and the dementia groups. Moreover, the results from the post hoc Dunnett's C test revealed that there is a significant means difference (p < 0.05) between MMSE scores of patients with MCI and those with AD, VaD and mixed dementia. MCI patients had the highest MMSE scores (mean 24.88±4.84), followed by VaD (mean 18.28±6.49), mixed dementia (mean 14.98±7.28), and the lowest score was among the AD (mean 14.81±7.26) as shown in Figure 2.

To determine the association between the sociodemographic and CVD risk factors and NCDs, Chi-square and One-way ANOVA tests were performed. The results indicate that only a history of stroke was significantly associated with NCDs (p=0.023) (Table I). All other factors did not significantly associate with NCDs.

DISCUSSION

We have identified that the frequency of mixed dementia and VaD exceeded that of AD cases and that of EOAD, whereas LPA type of dementia presented with the least frequency in HKL. Hence, it is evident from our study that the

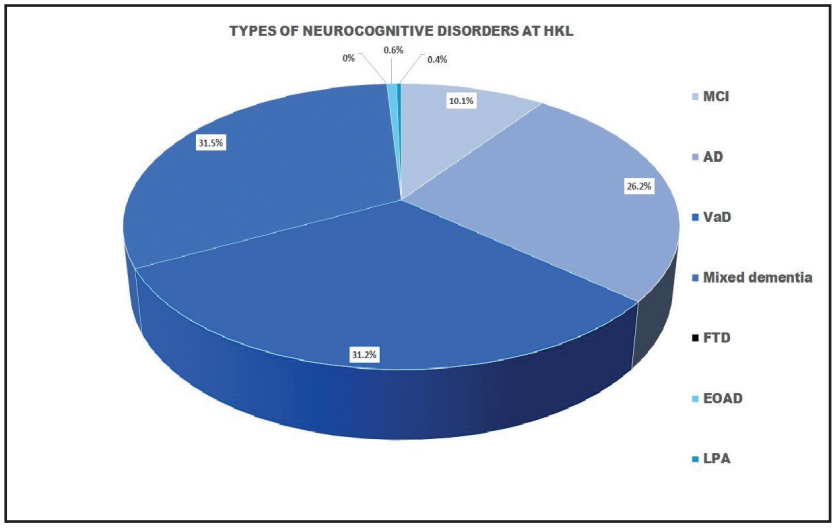

Fig. 1: Distribution of the patients with Neurocognitive disorders attending the memory clinic in Hospital Kuala Lumpur, Malaysia. AD=Alzheimer's disease, EOAD= Early-onset Alzheimer's disease, LPA = Logopenic Progressive Aphasia type of AD, MCI = Mild cognitive impairment, NCD= neurocognitive disorder, VaD= Vascular dementia

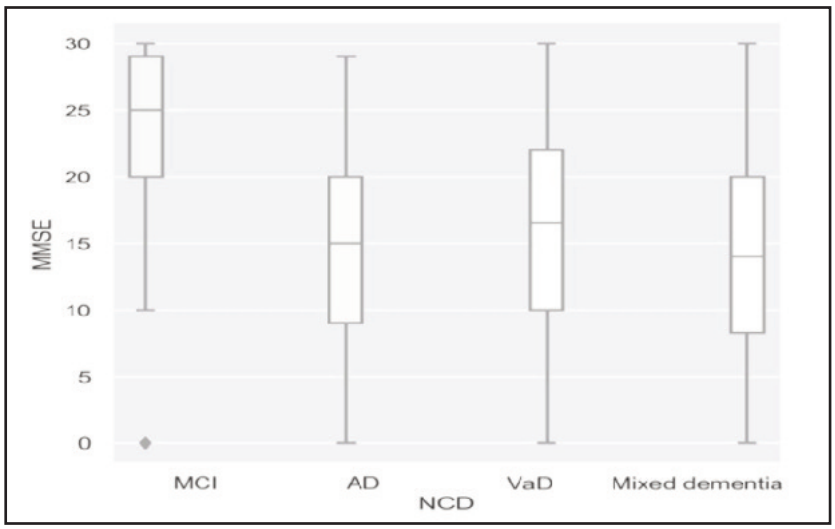

Fig. 2: Mean difference between the Mini Mental State Examination test scores for the various neurocognitive disorders subtypes of the patients attending the memory clinic in Hospital Kuala Lumpur, Malaysia. (MCI=Mild cognitive impairment, AD=Alzheimer's disease, VaD=Vascular dementia).

prevalence of VaD and mixed dementia, i.e., the NCDs with a vascular pathology, are more common than the primary degenerative dementia or AD among the urban Malaysian hospital-based population. Unlike other studies in the Western countries that indicated AD was the more prevalent type of dementia in their population,[21,22,24] our results showed that VaD and mixed dementia are more common among Malaysians living in Kuala Lumpur. This may be due to the comorbidity of hypertension as a major risk factor for CVD and the inherent excess dietary salt intake that is prevalent in many Asian populations, specifically in Malaysia.[25,26]

The MMSE scores of patients with MCI differed significantly ($p < 0.001$) from those with dementia, whereby MCI patients had overall higher scores compared to patients with dementia. This result agrees with previously published studies proving the usefulness of MMSE test in classifying healthy control from patients with MCI and dementia.[27,28] The MMSE test is normally administered to patients as the first line screening tool to determine the level of cognitive impairment in patients. Ordinarily, patients with less severe cognitive impairment tend to have higher scores in this neurocognitive test and conversely those at moderate and advanced stage of disease would normally have lower scores. Nevertheless, the interpretation of the test scores also depends on the age and level of education of the patients.[29] Therefore, our result agrees with previous evidence indicating that MMSE test scores, either taken alone or in combination with other tools for testing cognitive impairment, can help clinicians make prompt decisions for the early referral or therapeutic intervention of NCDs.[28,29]

Our study also revealed that lower levels of education was positively associated with dementia but failed to achieve statistical significance. This may be due to better educated individuals were more likely to seek hospital treatment and thus our patient population was skewed towards urban families with better knowledge and resourcefulness to seek treatment for their afflicted family members. Previously, population-based research supported the understanding that lower level of education correlated with dementia and MCI.[17,30] It is hypothesised that a lower levels of education, or no formal education, tends to be correlated with dementia due to less involvement in complex brain activity, which affects one's cognitive reserve and exposes one to early brain cells pathological insult.[31] However, the association between the level of education and dementia was said to vary between developed and developing countries, whereby low level of education in dementia is more pronounced in the latter countries.[32]

Moreover, a low level of education (not statistically significant in our study) and a history of stroke (statistically significant in our study) were associated with dementia in our population. These results are comparable with a previous study conducted among the urban population in Beijing China, whereby the elderly people with a lower level of education, having limited physical activity and a history of stroke were noted to have a higher risk for developing dementia.[33] Furthermore, similar to what has been observed in our study among the urban Malaysian population, a study in China also revealed that multi-infarct dementia or VaD was relatively more common than AD with a ratio of 3:2.[33]

Low average educational attainment and high CVD risk profile have been postulated to be the cause of VaD being more prevalent in developing countries.34 Nevertheless, an excellent explanation for educational level affecting the development of dementia can be derived by the Lifespan Developmental Model proposed by Sharp and Gatz, 2011, whereby educational factor is deemed as a surrogate indicator of cognitive development in a two-stage approach, i.e., (i) pre-education factors, e.g., parental socioeconomic status (SES), genetics, and socio-emotional influences and (ii) post-education factors, e.g., adult SES (particularly in developed regions), which is associated with occupational and environmental exposures, including the type of food intake, exercise and lifestyle habits.[32] Thus, this model indicates that the level of education does not directly affect the risk for developing dementia directly, but acts as a proxy through its influence on a multitude of factors across the lifespan of the patients.[32]

Hypertension being one of the modifiable risk factors in the spectrum of CVD, was noted to significantly predicted the development of VaD in our study population. This finding is corroborated by the results from a review conducted by Kalaria et al., 2018 whereby hypertension, diabetes mellitus, and obesity were implicated in the increased risk of developing dementia.[35] Additionally, a study among patients having VaD in India reported that stroke, hypertension, and diabetes mellitus, acting by the mechanism of causing small vessel disease, were important risk factors that gave rise to predominantly a subcortical type of VaD.[36]

The implication of this study is on improving the healthcare services by educating the public regarding lifestyle modifications and optimising the control of hypertension and diabetes mellitus, which are modifiable risk factors of CVD.

LIMITATIONS

The MMSE was used in this study as a screening tool to identify dementia and MCI among the patient population. However, other studies have suggested that the MoCA is a better screening tool for MCI.[37-39] Thus, future prospective studies may consider MoCA for evaluating their subjects. Additionally, our study has a relatively small sample size. Thus, future multicentre studies may reveal more significant modifiable risk factors for dementia. Furthermore, comparison with age and gender-matched cognitively healthy controls will allow more sophisticated statistical evaluation of the predictors of dementia in this population. Another limitation is that the diagnosis of the dementia subtypes was based on the expertise of the clinicians and not by the gold standard such as a biopsy. Alternatively, diagnostic imaging can play a role in the management of dementias, whereby the structural and functional information can be availed to exclude potential secondary causes and offer additional information to differentiate the dementia subtypes, especially in atypical cases.[40] Nevertheless, our clinicians followed the criteria developed by the ADDTC and NINDS-AIREN. Understanding the mechanisms that lead to dementia is crucial in the planning of interventional strategies, hence futures studies will need to evaluate the complete risk factors profile that includes physical examinations of neuropsychological deficits, food intake, physical activity, biochemical indices, genetic profiling, together with a complete panel of comorbidities and medications.

CONCLUSION

Vascular dementia and mixed dementia are more common than Alzheimer's disease in our urban HKL population. Modifiable risk factors for cardiovascular disease are significantly associated with dementia. Hence, lifestyle modifications, optimised blood pressure control, and monitoring other CVD risk factors are recommended to delay the development of dementia.

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CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest to disclose.

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ORIGINAL ARTICLE

Self-sampling in Human Papillomavirus screening during and post-COVID-19 pandemic

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ABSTRACT

Introduction: Cervical cancer is the third most common cancer among Malaysian women. Sarawak, the largest state in Malaysia has consistently recorded the highest cervical cancer rate in the country where nearly half of its population still live in the rural areas and is at increased risk of the disease due to inequitable access to healthcare. The countrywide lockdown due to the COVID-19 pandemic had halted the accessibility to cervical cancer screening programme. The aim of the study is to determine the feasibility of providing primary HPV DNA test using the self-sampling method to the hard-to-reach population in the interior of Sarawak during the COVID-19 pandemic.

Materials and Methods: This is a cross-sectional study where women aged between 20-80 years were recruited via convenient sampling from villages in Long Banga, Sarawak over a five-day outreach programme. Cervicovaginal self-samples were obtained and screened for the presence of high-risk human papillomavirus DNA (HR-HPV) using the careHPVTM Test. A self-administered questionnaire was also administered to determine the sociodemographic and perception towards the self-sampling method.

Results: The 55 women recruited consist of ethnic backgrounds of Penan (58.18%), Kenyah (25.45%), Iban (5.45%), Saban (3.64%), Kelabit (3.64%), Malay (1.82%) and Chinese (1.82%). The prevalence of HR-HPV was 1.85% (n=1/55). Nearly 80% of the women were unemployed, and more than half have had attended primary education. Nine (16.4%) have heard about HPV, and seven (13%) knew HPV infection could cause cervical cancer. Three of them had HPV vaccination, and only one (1.85%) knew the brand of the HPV vaccine. Although 40% preferred self-sampling over clinician-collection, only ten (18.2%) women have completed the self-collection perception questionnaire.

Conclusion: Primary HPV DNA screening using the self-sampling method can be carried out in the remote areas during the COVID-19 pandemic without compromising mobility restriction.

KEYWORDS:
Self-sampling, Human papillomavirus, indigenous population, rural, COVID19 pandemic

INTRODUCTION

Cervical cancer (CC) is the second cause of death among Malaysian women after breast cancer. It is ranked as the third most common female cancer in Malaysia. CC is linked to the persistent infection by one or more of the high-risk human papillomavirus (HR-HPV), although other cofactors such as multiple sex partners, early sexual debut, smoking, and co-infection with Chlamydia trachomatis, have catalytic effects on the oncogenic progression of HRHPV infection to precancer and cancer.[1,2] Currently, more than 200 human papillomaviruses have been identified, with approximately 40 of them are sexually transmitted and 14 of them (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) are oncogenic and known as the HR-HPV.[3]

Cervical cancer is one of a few preventable cancers by early cervical cancer screening and effective vaccination. Cervical cancer screening through Pap smear was begun in Malaysia since 1969, and was gradually incorporated into the postnatal care programme. Three decades later, the national coverage is stagnant at around 22%, far below the recommended coverage of 80% by the World Health Organization (WHO).[4,5]

The strong association of HR-HPV infection with cervical cancer has triggered the paradigm shift in CC prevention strategies worldwide. For example, population-based HPV vaccination using the bivalent HPV vaccine in many countries has shown significant success in reducing the rate of CC.[6] In addition to this, the more sensitive molecular assays detecting the HRHPV genomic DNA are gaining market share and is actively replacing Pap smear as the primary cervical cancer screening tool in many countries such as the Netherlands, Turkey, United Kingdom, Norway, Italy, Sweden, Germany, and Finland, while many more are in the transition state.[7-9]

Sarawak is the largest state in Malaysia with approximately 2.4 million people living on a 124,450 km^2 land, making it the least densely populated state. Nearly half the population still lives in the rural areas and some in the remote villages[10] with inequitable access to healthcare. It is not surprising that Sarawak has consistently recorded the highest rate of CC in the country, with the Age-Standardised Rate (ASR) of 12.1/100,000 compared to the national ASR of 6.2/100,000.[11] Our study site was Long Banga (3.2015N, 115.4018E), a town

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within the district of Bario that lies in the deep interior of Sarawak. Long Banga is located south of Bario and consists of villages such as Long Lamei, Lio Mato, Long Spigen, Long Kerong, and Long Sait. All these villages will be referred to as Long Banga here. Due to its geographical location and economic development, Long Banga is still devoid of road access but is linked to Miri city via a 16-seat Twin Otter plane. Its surrounding villages are connected to the main towns (including Bario town) via logging trails and/or a network of rivers.

During the current COVID-19 pandemic, China has taken a controversial measure to contain the spread of SARS-CoV-2 by locking down the entire 19 million population in Wuhan city at the end of January 2020. Malaysia followed suit and enforced a nationwide lockdown termed the Movement Control Order (MCO) on the 18th March, 2020. The National Cervical Cancer Screening Programme came to a halt. If this situation remains, the delay in accessing essential healthcare will likely see an increase in women presenting with late-stage cervical cancer, a situation which will contribute to both direct and indirect mortality from this preventable and treatable disease.[17-19] Even before the pandemic, as high as 76% of cervical cancer patients were only diagnosed at Stage 2 or worse.[20]

During the current MCO due to the COVID-19 pandemic, the whole small district of Bario, including its surrounding villages were cut off. Malaysia had eased the lockdown restriction on the 4th May, 2020 under the Conditional Movement Control Order (CMCO), restoring the courier service to Bario. With this, we took the opportunity to study the feasibility of providing primary HPV screening using the self-sampling method to the hard-to-reach population in the interior of Sarawak during the COVID-19 pandemic.

The HPV genotyping, follow-up testing, and the cytological screening results are beyond the scope of this manuscript.

MATERIALS AND METHODS

Reaching the hard-to-reach communities

A convenient sampling method was employed in this population-based HRHPV prevalence study, and we envisaged to recruit as many participants as possible over the 5-day outreach programme during the CMCO period in May 2020. Recruitment in Long Banga includes non-virgin females living in villages such as Long Banga itself, Long Lamei, Lio Mato, Long Spigen, Long Kerong, and ends at Long Sait (see Figure 1).

Self-sampling kit

The self-collection kits were sent from Kota Samarahan to Bario town using the national courier service. Every self-collection kit consisted of a reusable ziplock bag containing a careBrush (Qiagen, Shenzhen, China), one vial of careMedium (Qiagen, Shenzhen, China), self-sampling instruction, a patient information sheet with a questionnaire and consent form.

The pictorial self-sampling instruction was adapted from the Guidelines for Primary HPV Testing in Cervical Cancer Screening in Malaysia 2019 (http://ogsm.org.my).

A questionnaire was included that consisted of questions grouped in three parts: (1) sociodemographic and socioeconomic factors like name, age, race, the highest level of education, employment status - 5 questions; (2) awareness and knowledge of about HPV infection - 4 questions; and post-sampling - 4 questions. The questionnaire was pretested on 90 women before being used.

Self-sampling

Participants were given time to go through the patient information sheet, self-collection instruction, and complete the questionnaire. Verbal instruction was given whenever necessary. Women were allowed to perform self-collection in their privacy. The instructions were the person was to take off her undergarments and place one leg on a support such as a chair or a toilet bowl. She then was to hold the free end of the careBrush's handle and gently push the other end with the brush to the top of the vagina. When the careBrush was inserted in her vagina, the woman was to turn the handle two or three turns, remove the careBrush completely from her vagina, and put it back into the careHPV™ Collection Medium, snap the careBrush handle to break it, cap the tube, and seal it with parafilm. Finally, she was to put the specimen and other documents into the ziplock bag and return it to the health volunteers. The specimens were then consolidated and brought back to Bario town, air-flown to Miri and couriered back to the Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak at room temperature.

HPV DNA Test and reporting

Samples were screened for HR-HPV DNA using the careHPV™ Test (Qiagen, Shenzhen, China) on 20th May, 2020. Results were reported back to the health volunteers in Bario via email, and the results are communicated to the participants in-person. The HRHPV positive woman was triaged for further screening according to the National Cervical Cancer Screening Guideline, and those negative for HRHPV infection were advised rescreening in 3-5 years later.

This study was approved by the Universiti Malaysia Sarawak Medical Ethics Committee (UNIMAS/NC-21.02/03-02 Jld.3(17). All participation was voluntary, and the participants were briefed about the study, and they all provided written informed consent before their participation.

RESULTS

The mean and median age of the participants was 40.5 and 39.5 years, respectively. The cohorts from 20-29, 30-39, and 40-49 years old represented 83.6% (n=46/55) of the sample size. There was only one HRHPV positive woman detected, which gives the prevalence of 1.85% in the population. The sole HRHPV positive case was an unemployed Penan woman in the 30-39 age cohort and had only attended primary education (Table I). Only 5.5% (n=3/55) had attained tertiary education; while 40% (n=22/55) and 54.5% (n=30/55) had attended secondary and primary education (Table I).

Unemployment was high at 76.4% (n=42/55) as most of them are housewives. Some 16.4% (n=9/55) are self-employed or engaged in agricultural activities, and only 7.3% (n=4/55) were employed and having a stable payroll (Table I).

Table I: Demographic information on the consenting women according to age cohorts, Ethnicity, Employment and education status

Age	Negative	Positive	Total
20-29	13	0	13
30-39	13	1(1.85%)	14
40-49	19	0	19
50-59	5	0	5
60-69	2	0	2
70+	2	0	2
Total	**54**	**1(1.85%)**	**55**
Ethnic	**n (%)**		
Penana	32(58.18)		
Kenyaha	14(25.45)		
Ibanb	3(5.45)		
Sabana	2(3.64)		
Kelabita	2(3.64)		
Malay	1(1.82)		
Chinese	1(1.82)		
Education	**Primary**	**Secondary**	**Tertiary**
	30(54.5%)	22(40.0%)	3(5.5%)
Employment	**Unemployed**	**Self-employed**	**Employed**
	42(76.4%)	9(16.4%)	4(7.3%)

[a] classified under ethnic Orang Ulu (people of the interior)
[b] classified under ethnic Dayak

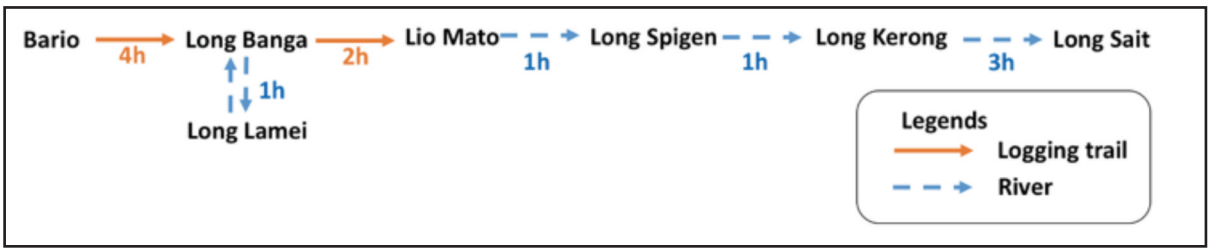

Fig. 1: The sampling journey in Long Banga, Small District of Bario, Sarawak. [The duration is approximate in hour(h)].

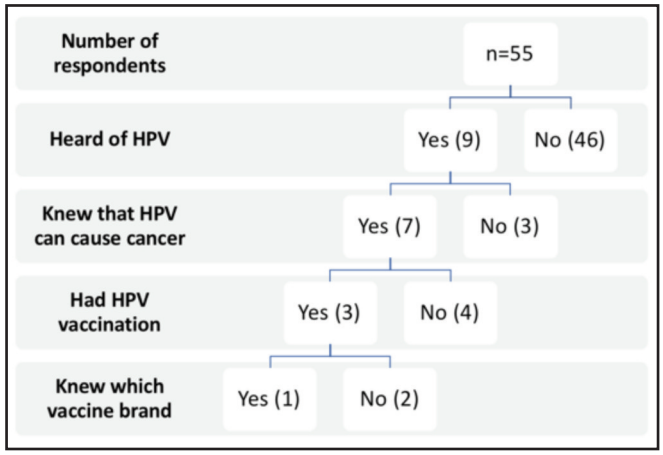

Fig. 2: HPV literacy survey completed by 55 (100%) of the respondents.

All participants had completed the HPV literacy survey, with most of them (83.6%; n=46/55) stated that they had never heard about HPV. Only 16.4% (n=9/55) had heard about HPV, with seven of them knew that HPV infection could lead to cervical cancer. Of the 7 women who knew the oncogenic nature of HPV, three had received HPV vaccination, but only one knew the brand of the vaccine (Figure 2).

As for the self-sampling perception survey, only 10 (18.2%) of the participants provided their responses. Only 40% (n=4/10) stated that they preferred self-sampling, and half of them stated that self-sampling was easy to perform while the other half found it difficult. The two participants who found self-sampling easy provided self-collected vaginal samples without expressing any concern. One of the other two

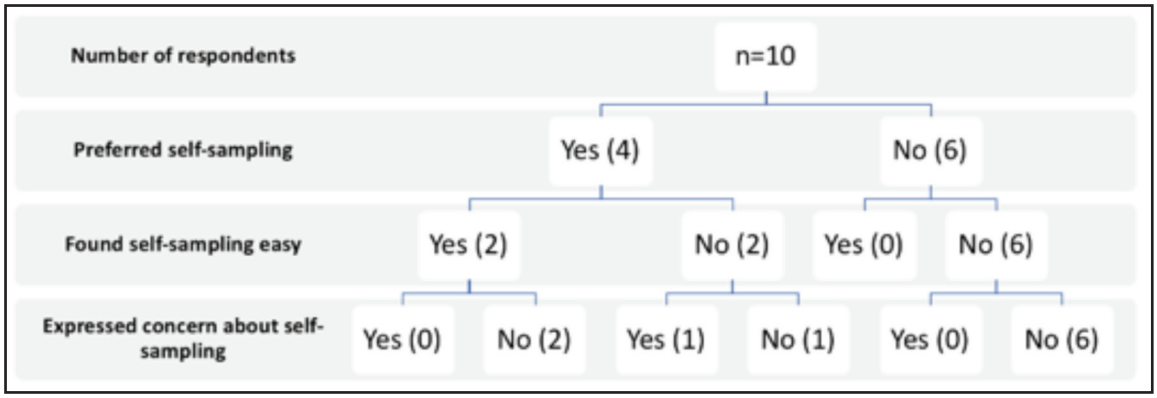

Fig. 3: Self-sampling perception survey completed by 10 (18.1%) of 55 women.

participants who found self-sampling to be difficult and was concerned if she had done it right, but the other did not express any concern. Majority of the participants (60%; n=6) who have responded mentioned that they preferred clinician-collection over self-sampling, and all of them found self-sampling to be difficult and expressed concern whether they have done the procedure correctly (Figure 3).

DISCUSSION

This is an active population-based HRHPV prevalence study where sampling was carried out at the remote villages in Long Banga rather than hospital-based as done by other researchers. The prevalence of HRHPV in Long Banga was determined to be 1.85% (n=1/55), which is much lower than the prevalence of 8% (n=6/75) in Bario town, using the same assay in 2019.[21] Considering both studies, the updated prevalence of HRHPV in the small district of Bario would be 5.38% (n=7/130), similar to the population-based HRHPV prevalence in other states in Malaysia such as Sabah (4.6%)[22] and Selangor (6.5%).[23] However, other researchers have reported a much higher prevalence in Peninsular Malaysia, ranging between 25.6-46.7%.[24-26]

The sole HRHPV positive woman was a Penan in the age-cohort 30-39, which is consistent with the national cervical cancer incidence trend, which increases at age >35 years and peaks between 50-74 years old.[11] However, we are not able to determine if the positivity correlates with cervical intraepithelial neoplasia as we did not follow-up with cytological test in this study.

All participants had attended some level of formal education. More than half of the women had reported attending at least primary education, which was not surprising as primary education is mandatory in Malaysia. Public-funded schools are being offered to citizens for free, even in the deep interior of Sarawak.[27] Furthermore, the retention of females in school is relatively high, at least true for primary education,[28] and we see that only 40% of the women have attended secondary education. The three participants who had attended tertiary education were government officials serving in the area, and their higher level of awareness about HPV may have distorted the actual HPV and cervical cancer awareness in the study population.

The awareness of HPV was found to be inferior among the women in Long Banga, which may be attributed to the lower education level of the participants. Most other HPV awareness studies had been carried out among the university students and consistently found that higher education level correlates with higher awareness on HPV and cervical cancer,[29-30] but even so, gaps exist such as the methods for prevention, symptoms, and consequences of HPV infection. Thus, intentional and targeted campaigns are required to bring HPV and cervical cancer education to the hard-to-reach populations to improve their awareness level.

The majority of the participants who have responded to the questionnaire prefer clinician-collection over self-sampling. This is an expected response from rural women who have never been offered such a new method before. Their possible unfamiliarity with their reproductive anatomy may increase their fear of inflicting self-injury due to performing the sampling technique incorrectly. However, they were still willing to undergo self-sampling, indicating that self-sampling can be an acceptable new norm and outweigh the women's potential shyness to be inspected by medical personnel. This is not surprising as a longitudinal study conducted by Hood et al., have revealed that 47% of women have initially indicated their unwillingness to perform self-sampling. However, when given an opportunity, they would seize the opportunity, meaning that offering an opportunity is more important than the acceptability of self-sampling method.[31] Furthermore, population-based randomised trials have also shown that self-sampling has resulted in a four-fold increase in cervical cancer screening uptake,[32,33] and HPV education on the safety of self-collection can improve the acceptance rate of the self-collection method.[34]

Self-sampling has provided the women in Long Banga with accessibility to cervical cancer screening. It allows them to have their cervicovaginal samples collected in their privacy and at the time of COVID-19 pandemic without compromising the strict standard operating procedures imposed by the government. This study may not have accomplished the screen and treat strategy recommended by WHO, but the 55 women were successfully screened using a more sensitive method than the traditional cytology offered under the National Cervical Cancer Screening Programme. At the time of writing, the small district of Bario and the rest of the villages remained free from SARS-CoV-2 infection.

This study has several limitations.[1] The sample size represents approximately 8.73% (n=55/630) of the female population in Long Banga,[35] and larger sample size is desired to improve the significance of the data. We must highlight that postal service is not available to the villagers and postal delivery of self-sampling kit to individual addresses as described by Kobetz et al., is impossible.[36] We cannot discount the possibility of improper sampling technique as it was carried out in privacy of participants but other studies have shown high-concordance between clinician-collection and self-sampling;[37-39] The careHPVTM Test lacks a housekeeping gene such as beta-globin for internal control and, therefore not possible to validate the adequacy of the starting material. However, we must bear in mind that vaginal swab differs from cervical swab as it targets free virions secreted into the cervicovaginal fluid rather than cell-bound or genome-integrated HPV DNA. Lastly, self-administered questionnaire is open to self-report bias which could have been minimised by having a full-time interviewer.

FUNDING

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ORIGINAL ARTICLE

Liver fibrosis associated with adipose tissue and liver inflammation in an obesity model

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ABSTRACT

Introduction: Obesity, the main risk factor for type 2 diabetes mellitus (T2DM), affects the secretion of various hormones that lead to change in metabolism. Visceral adipose tissue accumulation may contribute to Non-alcoholic Fatty Liver Disease (NAFLD) and induce liver injury. This study was aimed to investigate the association between adipose tissue inflammation and liver fibrosis.

Materials and methods: Wistar male rats (3 months old, 160-230 grams) were divided into 4 groups that consisted of six rats in each group. The obesity model was induced through the administration of high-fat diet for a month (OB1), two months (OB2), and four months (OB4). Standard chow was provided for the control group for four months. After the specified date the rats were euthanized and the liver and retroperitoneal white adipose tissue (RWAT) were harvested. We performed RT-PCR to assess the mRNA expressions involved in proinflammatory mediators, fibrosis and anti-fibrosis signaling. Sirius red staining was performed to assess liver fibrosis. Data were analyzed with SPSS 23 for Windows with significance set as $p<0.05$.

Results: Obesity-induced high-fat diet stimulated an increase of body mass index (BMI) in the OB groups ($p<0.05$) compared to the control group. Increased BMI was followed by upregulation of proinflammatory mediators (MCP-1, CD68, TLR4, and NFκB) of the RWAT and liver in the obese groups ($p<0.05$), which promoted hepatic fibrosis in triad portal areas and upregulation of TGFβ ($p<0.05$) mRNA expression as well as downregulation of HGF and c-Met ($p<0.05$). In addition, hepatic ppET1 and EDNRB mRNA level expressions ($p<0.05$) were obviously upregulated in the obese groups followed by downregulation of eNOS ($p<0.05$) mRNA expressions.

Conclusion: Obesity enhanced inflammation in RWAT and was associated with inflammation and fibrosis of liver.

KEYWORDS:
Obesity; retroperitoneal white adipose tissue; liver injury; inflammation; fibrosis

INTRODUCTION

Obesity is associated with an increased risk for type 2 diabetes mellitus (T2DM) which is characterized by insulin resistance and hyperglycemia. Around 80% of people with T2DM are also obese. The prevalence of obese people has significantly increased during every decade. It was reported that about 30% of Americans were obese.[1] It is estimated that the prevalence of diabetes mellitus in adults aged 20-79 years has reached 285 million and will increase to 439 million people globally in 2030.[2,3] In obese people, the adipose tissues undergo hypertrophy and hyperplasia resulting in increased secretion of leptin, glycerol, adiponectin, non-esterified fatty acids (NEFA), various proinflammatory cytokines and chemokines, which produce lipotoxicity.[4,5]

Obesity is a condition characterized by the presence of excess adipose tissue, and additionally, it consists not only of adipocyte cells but also stromal vascular fractions.[6] Adipose tissue is an endocrine organ that produces hormones which will affect metabolism. Hypertrophy of fat tissue causes an imbalance of hormone secretion and secretion of various proinflammatory cytokines with various factors that cause insulin resistance.[4,6,7] Hypertrophy of adipocyte cells triggers an increase in leptin secretion and a decrease in adiponectin secretion. In obesity there is an increase in leptin receptors mainly in the brain. Increased receptors and ligands from leptin will induce an increase in fatty acid oxidation, increased corticotropin secretion, increased thermoregulation, and various changes in the metabolism of the body through several signal transduction pathways.[8] Hyperleptinemia increases the ability of leptin to bind to the promoter side of Peroxisome Proliferator-Activated Receptor-α (PPARα) and Sterol Receptor Element Binding Protein-1c (SREBP-1c) that affect mitochondrial work functions.[9,10]

Metabolic alteration due to obesity affects the endothelial function. An increase of various hormones, such as resistin and leptin, stimulates an increase of reactive oxygen species (ROS) and inflammatory cytokines in *in vivo* models of endothelial cell culture which then leads to an elevation of endothelin-1 (ET-1) release and extrication of proinflammatory mediators.[11–14] Moreover, obesity reduced nitrite oxide (NO) bioavailability in endothelial cells resulting in endothelial dysfunction. It is known that obesity causes cardiovascular disease due to an elevation of ET-1.[12] It has been observed that upregulation of the ET-1 serum correlates with the development of liver fibrosis in patients with non-alcoholic steatohepatitis (NASH).[15] However, the impact of obesity induced liver injury has not been clearly understood.

Liver is one of the organs that severely suffers in obesity. Hepatosteatosis is a common feature of histological changes

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due to an increase of fatty acid oxidation (FAO) and release of fatty acid (FA). Hepatocyte growth factor (HGF) is a mitogen that contributes to cell growth, cell motility, and morphogenesis.[16] In conditions of liver cancer HGF/c-Met plays a role in the process of liver regeneration and inhibits cellular senescence.[17] However, the relationship between liver fibrosis due to an increase in sterile inflammation caused by adipocyte cells has not clearly understood.

MATERIALS AND METHODS

Animal experiments

Wistar male rats (3 months old, 160-230 grams) were divided into 4 groups that consisted of six rats in each group. The groups were: control (Control, n=6), Obesity 1 month (OB1, n=6), Obesity 2 months (OB2, n=6), and Obesity 4 months (OB4, n=6). The control group received AIN76A, while the obesity groups were fed High-Fat Diet (HFD) for 1 month (OB1), 2 months (OB2), and 4 months (OB4). After the specified date, the rats were injected using the lethal dose of ketamine (Ivanes, 250201) and euthanized. Then, their liver and retroperitoneal adipose tissue (RWAT) were harvested. Finally, the harvested organs were immersed in RNA Later for mRNA assay (Ambion, 7021) and kept in Neutral Buffer Formalin (NBF) for paraffin making and histological examination.

The obesity criteria was determined according to the body mass index (BMI; weight (grams)/length (cm^2)) and Lee Index formula (($\sqrt[3]{}$weight (grams))/nasoanal length (mm)). This research was based on the guidelines for animal care of the Universitas Gadjah Mada and we obtained a license from Ethical Committee of Medical Research and Health of Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada with ethical expediency number KE/FK/0490/EC/2018.

RNA Extraction, cDNA synthesis and Reverse transcriptase-PCR (RT-PCR)

Liver and RWAT was extracted using Genezol RNA Solution (GENEzol™, Cat. No. GZR100) based on the protocol from the manufacturer. The RNA concentration was quantified using nanodrop. The RNA was synthesized into cDNA using Revertra-Ace kit (Toyobo, Cat. No. TRT-101), random primer (TAKARA, Cat. No. 3801), and deoxyribonucleotide triphosphate (dNTP) (Takara, Cat. No. 4030), with PCR condition: 30°C for 10 min, 42°C for 60 min, and 99°C for 5 min.

Reverse Transcriptase-PCR was performed to examined these following genes with specific primer. The inflammatory mediators were assessed using cluster of differentiation 68 (CD68) (forward 5′- TGTGTCCTTCCCACAAGCAG-3′ and reverse 5′- AAGAGAAGCATGGCCCGAAG-3′), nuclear factor kappa-B (NFκB) (forward 5′-CACTCTCTTTTTGGAGGT-3′ and reverse 5′- TGGATATAAGGCTTTACG-3′), Toll-like receptor4 (TLR4) (forward 5′- CAGGGAGCACGAGGCTTCTAACC-3′ and reverse 5′- CTTGTGCCCTGTGAGGTCGTTGA-3′) Monocyte Chemoattractant Protein-1 (MCP-1)(forward 5′-GCTGTAGTATTTGTCACCAAGCTC-3′ and reverse 5′-ACAGAAGTGCTTGAGGTGGTT-3′). Fibrosis marker, Transforming Growth Factor Beta (TGFβ), was assessed using the following primers (forward 5′-CGAGGTGACCTGGGCACCATCC-3′ and reverse 5′-GCTCCACCTTGGGCTTGCGACC-3′). The mRNA expression of Hepatocyte Growth Factor (HGF) was assessed using (forward 5′- ACAGCTTTTTGCCTTCGAGC-3′ and reverse 5′-TGTCGGGATATCTTTCCGGC-3′) and cMET (forward 5′-CCAAGCCGCGTATGTCAGTA-3′ and reverse 5′-GCAGGGTCCTATTGAAACAGTG-3′). The mRNA expression of endothelial nitrite oxide synthase (eNOS) (forward 5′-CCGGCGCTACGAAGAATG-3′ and reverse 5′-AGTGCCACGGATGGAAATT-3′), ppET-1 (forward 5′-GTCGTCCCGTATGGACTAGG-3′ and reverse 5′-ACTGGCATCTGTTCCCTTGG-3′), and Endothelin receptor B (EDNRB) (forward 5′-TCTCAGCCTTTTGTCCGAGC-3′ and reverse 5′-CGCCGTTTTCAGTCTCGCA-3′) was performed to assess the endothelial dysfunction. The housekeeping gene, β-actin (forward 5′- GCAGATGTGGATCAGCAAGC-3′ and reverse 5′- GGTGTAAAACGCAGCTCAGTAA-3′), was used to normalize the expression.

The cDNA was mixed with Taq Master Mix (Promega, GoTaq Green, M7122) and primers, then incubated in 94°C denaturation for 10 s, annealing at 60°C for 30 sec and extension 72°C for 1 min final extension phase end with the conditions of 72°C for 10 minutes for 35 cycles. The PCR products were separated using 2% agarose gel along with 100 bp DNA ladder (Bioron, Germany, Cat. No. 306009). The expression of the genes was quantified with a densitometry analysis using the ImageJ software.

Immunohistochemical (IHC) staining of CD68 and MCP-1

The liver and RWAT of the rats were embedded in paraffin blocks and cut into 4 µm in thickness. Then the slides were deparaffinized using xylene and rehydrated using 100%, 90%, 80%, and 70% alcohol, followed with antigen retrieval and blocking peroxidase using H_20_2 3% in PBS solution. The slides were then incubated using background sniper, rabbit 1st monoclonal antibody MCP-1 (Abcam®, ab25124; 1:200) and mouse 1st polyclonal antibody anti-CD68 (Abcam®, ab955; 1:300), TrekAvidin-HRP, 2ndantibody Trekkie Universal Link (Biocare Medical®, STUHRP700L10), and diaminobenzidine tetrahydrochloride (DAB) (Biocare Medical®, STUHRP700L10). The macrophage number was quantified using ImageJ software, examined with light microscope (Olympus CX22®), and portrayed with the Optilab software with 400x magnification.

Statistical analysis

The SPSS 23 software for windows was used for the analyses of data. Data normality test were conducted using Shapiro-Wilk and One-Way ANOVA for normal data distribution. The p-value less than 0.05 ($p<0.05$) was considered as statistically significant.

RESULTS

High-fat diet enhanced obesity and increased of SGOT level

We were able to show that high-fat diet feeding significantly induced obesity in the obese groups compared to the control group. The increased BMI was shown in the OB1 group (0.41±0.01; $p=0.009$), OB2 (0.57±0.02; $p=0.047$), and OB4 (0.61±0.03; $p=0.028$) compared to the control group. Meanwhile, determination of obesity according to the Lee

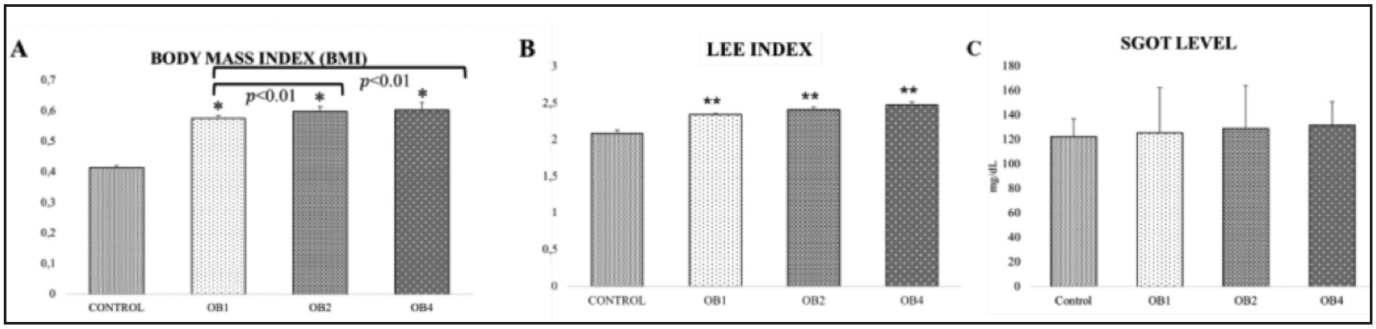

Fig. 1: Porto-venous phase computed tomographic angiography (Angio-CT) of abdomen and pelvis. Labelled image with long arrows shows filling defect within the SMA and SMV suggestive of emboli with non-enhancing bowel loop (short arrow).

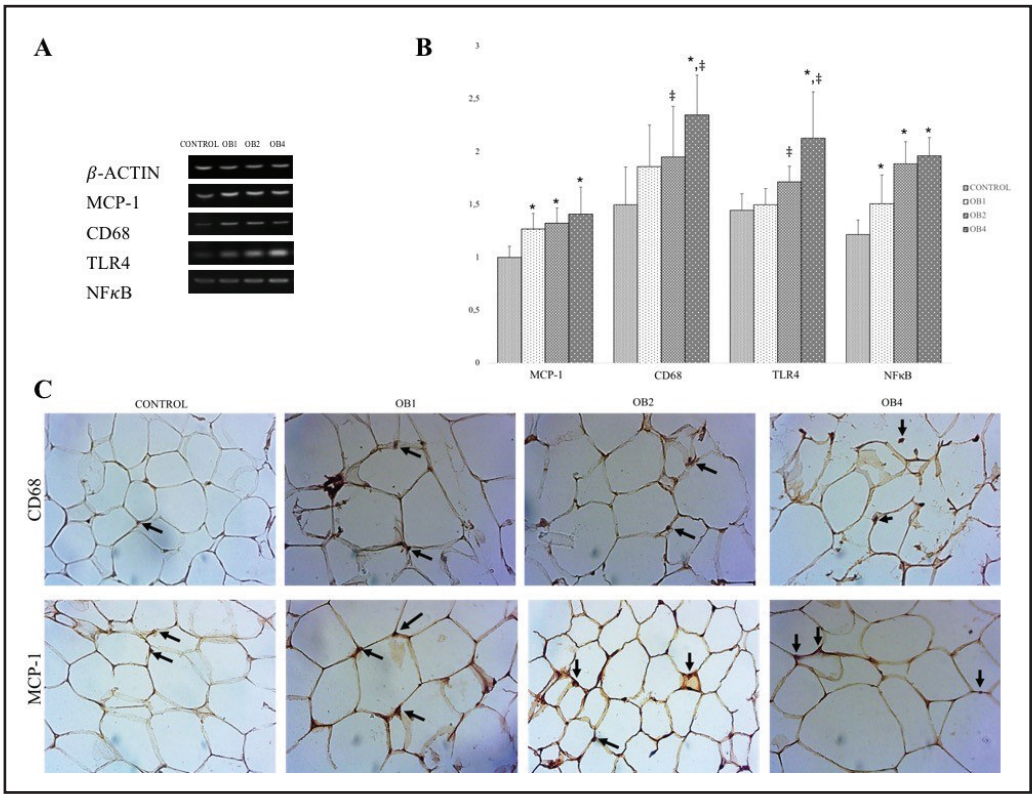

Fig. 2: Obesity induced RWAT inflammation. A-B. Upregulation of the pro-inflammatory mediators mRNA expression. C. Immunohistochemistry of CD68 and MCP-1 protein expression with 400X magnification. The black arrows showed positive-staining cells. *=<0.05 vs Control; ‡ p<0.05 vs OB1.

Index formula demonstrated that the obese groups which consisted of OB4 (2.48±0.04; p=0.002), OB2 (2.41±0.03; p=0.001), and OB1 (2.34±0.01; p=0.000) groups had higher scores compared to the control group (2.08±0.04). However, this alteration was not sufficient to induce an elevation of Serum Glutamic Oxaloacetic Transaminase (SGOT) level (p>0.05) in the obese groups.

Long-term obesity induced retroperitoneal adipose tissue inflammation

Regarding obesity stimulated inflammation of RWAT, we found that the mRNA expressions of MCP-1, CD68, TLR4, and NFκB mRNA expressions were significantly higher in accordance with an increase of BMI. The elevation of MCP-1, CD68, TLR4, and NFκB was obviously seen in the OB4 group (p<0.05). Moreover, the alteration of MCP-1 and CD68 were followed by an upregulation of protein expression as shown by the immunohistochemistry staining (Figure 2).

Obesity induced hepatic inflammation

The increase of the inflammation in RWAT was followed by an increase of inflammatory mediators in the liver which was clearly shown in an elevation of the TLR4 and CD68 mRNA expressions compared to the control group (p<0.05). The mRNA expression of TLR4 was markedly increased in the OB4 group (2.08±0.37; p=0.002) which was then followed by OB2 (1.52±0.35; p=0.022) and OB1 (1.39±0.05; p=0.019) compared to the control group (0.62±0.20). In addition, the CD68 mRNA expression and the macrophage number were significantly upregulated in the obese groups which was significantly seen in the OB4 group with (2.12±0.09; p=0.006) and (32.27±1.81; p=0.000), respectively, compared to the control group (1.46±0.02) and (23±1.17), respectively.

Liver fibrosis occured in obese groups

Subsequently, we assessed the histological changes which involved markedly increased areas of fibrosis in the portal

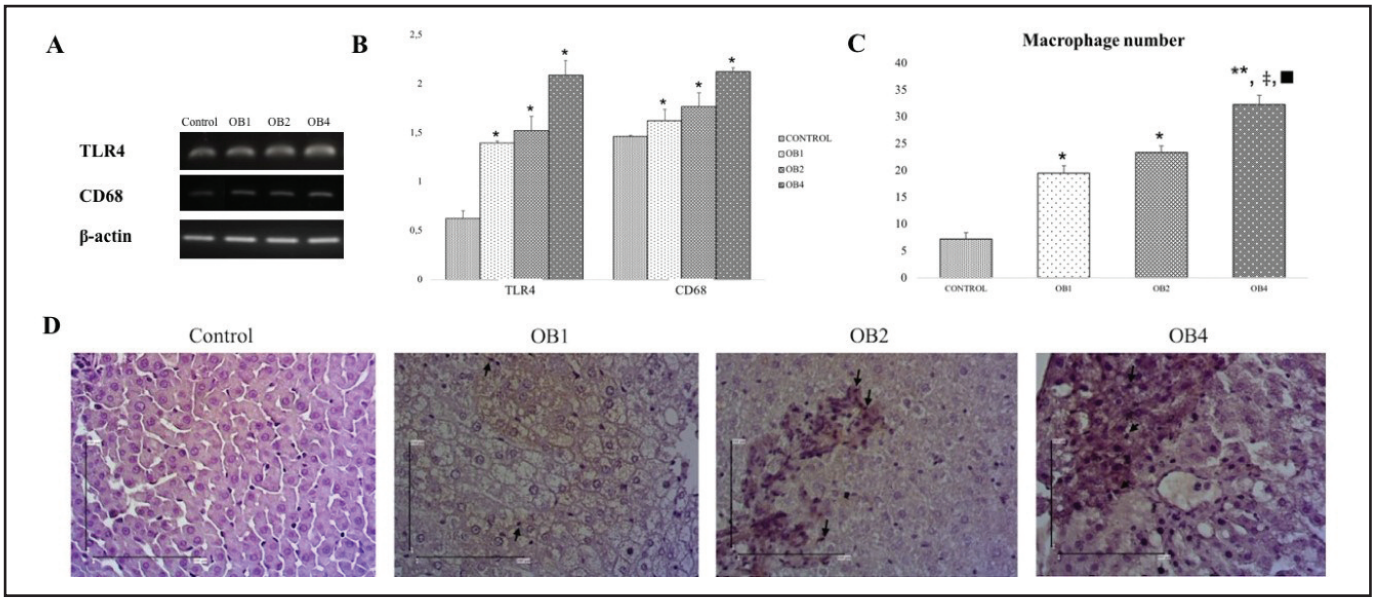

Fig. 3: Obesity triggered hepatic inflammation. A-B. Upregulation of CD68 and TLR4 mRNA expressions using Reverse Transcriptase PCR (RT-PCR) in obese groups. C. Immunohistochemistry staining of CD68 protein expression in the liver with 400X magnification. *p<0.05 vs Control, **p<0.01 vs Control, ‡ p<0.05 vs OB1, ■■ p<0.01 vs OB2.

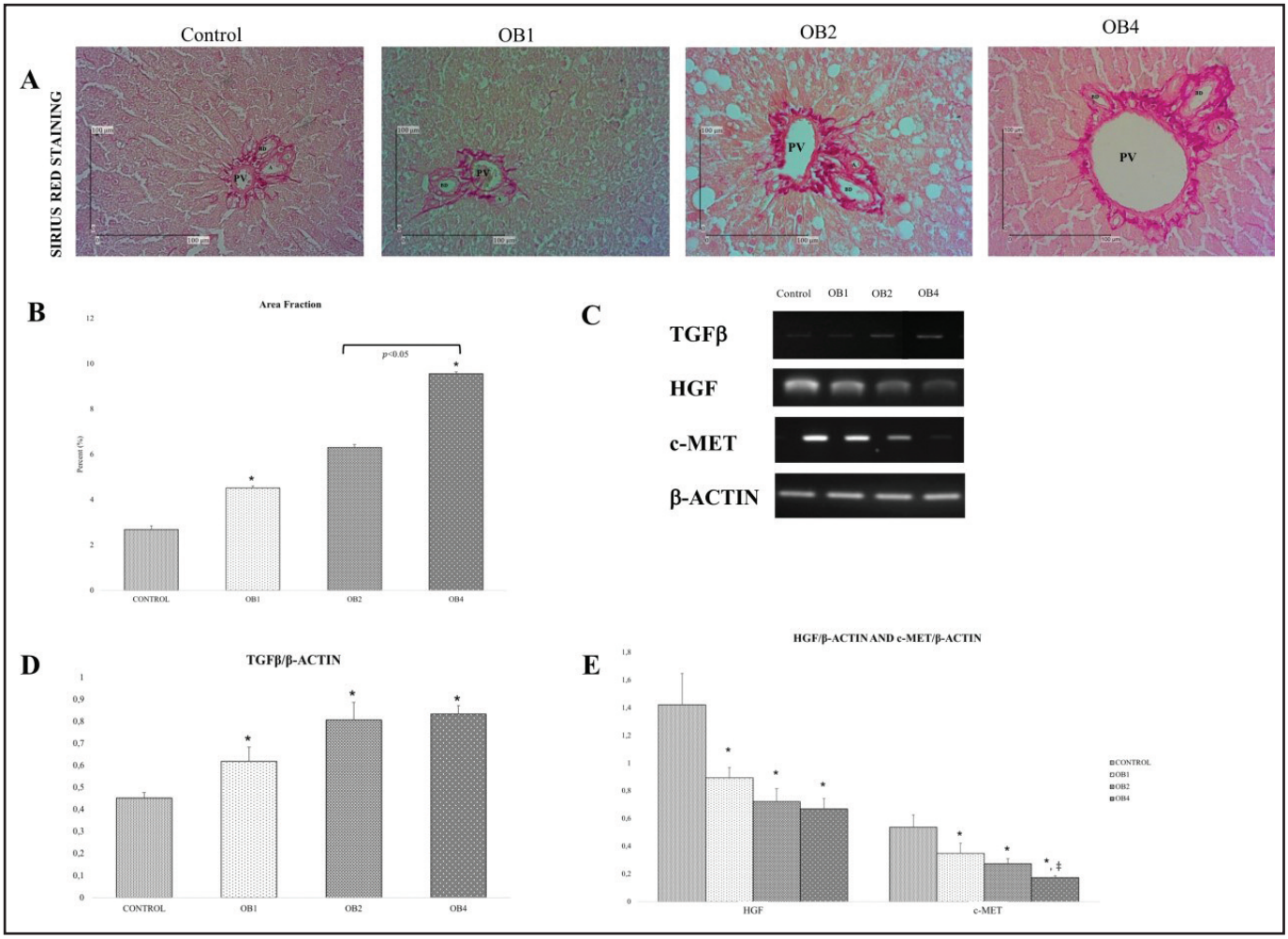

Fig. 4: Obesity provoked liver fibrosis. A-B. Sirius Red staining in 400X magnification and fibrosis area fraction quantification. C-E. The representative picture and quantification of TGFβ, HGF, and c-Met mRNA expressions. *=*p*<0.05 vs Control; ‡ p<0.05 vs OB1. PV (portal vein), A (hepatic artery), BD (bile duct).

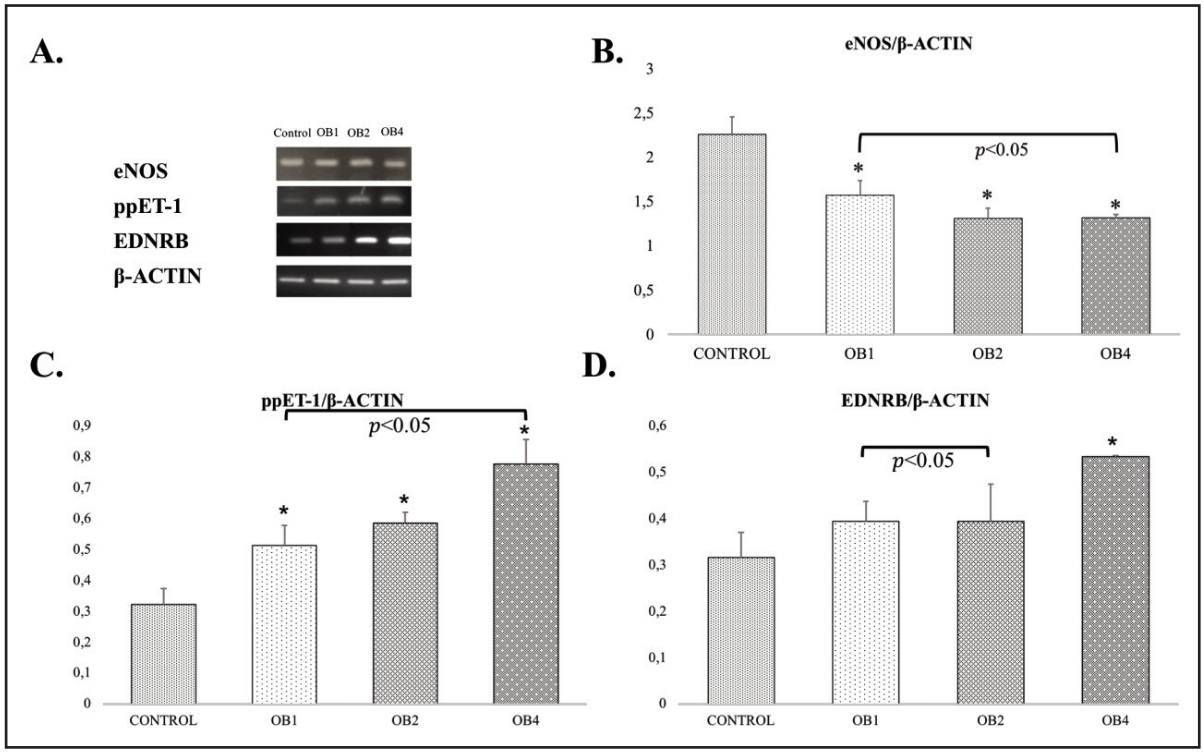

Fig. 5: Obesity enhanced imbalance of ppET-1 and eNOS mRNA expressions.A-D. Reverse transcriptase PCR demonstrated upregulation of ppET-1 as well as EDNRB and downregulation of eNOS mRNA expression. *=p<0.05 vs Control.

triad of the obese groups compared to the control group. This alteration was supported by a significant higher expression of TGFβ mRNA in all of the obese groups compared to the control group. The fibrosis area fraction was quantified around the portal triad that showed high deposition of collagen in the obese groups, OB4 (9.57±0.40; p=0.000), OB2 (6.29±0.33; p=0.000), and OB1 (4.52±0.20; p=0.000) compared to the control group (2.69±0.40). The TGFβ, known as a fibrosis agent, was upregulated in the obese groups along with an increase of fibrosis area fraction. We demonstrated that the TGFβ mRNA expression can only be significantly seen in OB2 (0.80±0.19; p=0.030) and OB4 (0.83±0.08; p=0.006) groups compared to the control group (0.45±0.06).

Besides, the antifibrotic agents', HGF and cMET, mRNA expressions were lower in the obese groups following an increase of the obesity periods (p<0.05). The HGF, known as an anti-fibrosis agent, was remarkably downregulated in the obese groups, OB1 (0.89±0.07; p=0.000), OB2 (0.72±0.09; p=0.000), and OB4 (0.67±0.07; p=0.000), compared to the control group (1.42±0.22). The receptor of HGF, cMET, was notably reduced in the OB4 group (0.17±0.01; p=0.000) compared to the control group (0.54±0.08).

Obesity induced hepatic vasoconstrictor and vasodilator

The obesity groups demonstrated significantly higher ET-1 and EDNRB mRNA expression in the liver compared to the control group that was followed by the reduction of eNOS mRNA expression. The ET-1 was known as potent vasoconstrictor agent markedly increase in OB4 group (0.77±0.14; p=0.000) compared to the control group (0.32±0.09). Interestingly, the EDNRB was remarkably upregulated in the OB4 group (0.53±0.01; p=0.044) compared to the control group (0.31±0.09).

In addition, the eNOS mRNA expression was downregulated in the OB groups. However, this alteration was obviously seen in the OB4 group (p<0.05). In addition, the upregulation of vasoconstrictor agents promoted vasodilatation disturbance which was shown by downregulation of eNOS at the same time (p<0.05).

DISCUSSION

This study reveals that the upregulation of inflammatory mediators in adipose tissue during obesity which leads to liver fibrosis. Obesity has long been correlated with liver steatosis, insulin resistance, and inflammation. However, 4 months of high-fat diet feeding was not adequate to induce liver steatosis. The extrication of cytokines and chemokine released by enlarged white adipose tissue leads to sterile inflammation and insulin resistance. The inflammatory mediators released by adipose tissue were upregulated in the obese groups compared to the control group (Figure 2). Adipocyte tissue plays an important role as a bridge connecting between immunological properties and metabolic alteration. Macrophages are thought to contribute in an increase of inflammation, since they are recruited from the bone marrow and form crown-like structure (CLS). Then, macrophages surround the moribund adipocyte cells. Consequently, more than 50% of immune cells in adipose tissue are macrophages. Meanwhile, approximately less than 10% of immune cells in lean adipose tissue are macrophages.[18,19]

Our study revealed that upregulation of TLR4, NFκB, CD68, and MCP-1 signalling in adipocyte tissue that leads to low-grade chronic inflammation (Figure 2). The TLR4 in adipose and others tissues, including liver and muscles, recognized the free fatty acid (FFA) secreted by hypertrophy adipocyte cells, then caused binding to myeloid differentiation (MD2) and CD14 complex. Next, the dimerisation of this complex stimulates the adaptor protein, myeloid differentiation88 (Myd88) to activate the NFκB to produce various proinflammatory cytokines and chemokines, including MCP-1 and TNF-α. Infusion of lipids dramatically induced upregulation of NFκB, IL6, and MCP1 protein and mRNA expressions in adipose tissue as shown in LPS-induced activation of NFκB.[20,21]

We highlight that the upregulation of inflammatory mediators in the retroperitoneal adipose tissue which is in accordance with upregulation of TLR4 and CD68 in the liver. It has been known that obesity elevates hepatic NFκB activity that leads to hepatic inflammation due to an increase of FFA. In addition, it alters hepatic metabolism resulting in NAFLD. Kupffer cells play an important role in clearing damage-associated molecular patterns (DAMPs). FFA recognized by Kupffer cells triggers sterile inflammation and activates pattern recognition receptors (PRRs), such as TLR4 in the hepatocyte cells.[22–24] Deficiency of TLR4 is associated with decrease of atherosclerosis and vascular inflammation.[25] The number of macrophage-expressed CD68 was higher in the obesity groups compared to the control group. It seems that inflammation in the liver aligns with inflammation in RWAT, although we cannot establish direct evidence in this study. Shared circulation models, such as parabiosis may provide a much more complete study for elucidating the correlation between the two organs in the next future research. It obviously can be seen in the fibrotic liver induced by 4 months of high-fat diet feeding that aligns with RWAT.

As the Kupffer cells were activated due to inflammation, the hepatic stellate cells (HSCs) become activated which is mediated by TGFβ leading to liver fibrosis and increased secretion of extracellular matrix. Activation of the TGFβ has been considered to contribute to the development of fibrosis in the kidney, lungs, heart, and other organs. The adipocyte-derived hormone, such as leptin, contributes to sensitize the Kupffer cells producing collagen.[26] We found that augmentation of TGFβ is followed by the downregulation of anti-fibrosis also assessed by the antifibrotic factor, HGF, and its receptor, c-Met during obesity. Our results demonstrate that obesity promotes augmentation of TGFβ mRNA expression and portal triad hepatic fibrosis which was followed by downregulation of HGF and c-Met as anti-fibrotic factors. HGF/c-Met plays an important role in contributing to lipid accumulation in the liver. HGF transgenic mice demonstrated low lipid accumulation through microsomal transfer protein (MTP) and apolipoprotein B (ApoB).[27] In this research, the findings suggest that FFA which is produced by white adipose tissue and is transported to the liver through the hepatic artery and portal vein. Then, the circulating mesenchymal cells, cholangiocytes, resident fibroblast, or even endothelial cells may undergo myofibroblast formation that contributes to the development of triad portal fibrosis during obesity.[24,26,28]

The transformation of endothelial cells into mesenchymal cells known as endothelial to mesenchymal transition (EndoMT) is promoted by upregulation of TGFβ and perhaps by ET-1.[29] The endothelin system is thought to contribute to the activation and proliferation of HSCs and collagen synthesis. The ET-1 was released by hepatic vascular smooth muscles, endothelial cells, stellate cells and mesenchymal cells during the injury process. Upregulation of serum ET-1 level was markedly correlated to the severity of liver fibrosis in NASH patients and this elevation was accomplished by an increase of ALT serum level.[15] More than 80% of ET-1 was secreted abluminally toward the vessels, and in consequence, the ET-1 promotes endothelial dysfunction, cardiovascular disease, and portal hypertension.[30,31] Interestingly, we found that in obesity, the mRNA expression of EDNRB was upregulated. The EDNRB expressed by vascular smooth muscle cells increased in cerebral ischemia, subarachnoid hemorrhage, and ischemia-reperfusion injury.[32–35] The EDNRB mRNA and protein expressions were upregulated in intestinal mucosa of obese rats due to inflammation, including in the liver.[36] We hypothesize that upregulation of ppET-1/EDNRB promotes liver fibrosis in obesity-induced rats.

Imbalance of vasoconstrictors and vasodilators was markedly observed in the OB4 group which was shown by downregulation of eNOS. In obese patients there are decreasing bioavailability of NO in small vessels which promotes the generation of free radicals and pro-inflammatory mediators. Endothelial dysfunction promoted deterioration of eNOS due to decrease of phosphorylation of eNOS in serine 1177 in the blood vessels of obese patients which was accompanied by an increase of proinflammatory mediators.[37] Therefore, we suggest that the downregulation of hepatic eNOS was associated with an elevated level of pro-inflammatory mediators. We highlight that adipose tissue inflammation may be associated with inflammation and fibrosis in the liver which may be mediated by ET-1 and TGF-B1 signalling.

We highlight here that adipose tissue inflammation directly promotes liver inflammation in high-fat diet feeding for 4 months and led to the development of liver fibrosis that was mediated by TGFβ and endothelial dysfunction.

CONCLUSION

In conclusion, our results indicated that chronic obesity contributes to the development of liver fibrosis through upregulation of TGFβ and downregulation of HGF that caused by sterile inflammation. Furthermore, this condition promotes endothelial dysfunction of the liver.

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Relationship between cellular communication network factor 1 (CCN1) and carotid atherosclerosis in patients with rheumatoid arthritis

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ABSTRACT

Background: The cellular communication network factor 1 (CCN1) is one of the matricellular proteins of the CCN family involved in chronic inflammatory disorders like rheumatoid arthritis (RA) and involved in human atherosclerotic lesions. This study was aimed to assess the levels of serum CCN1 in patients with rheumatoid arthritis (RA), evaluating its relation to carotid intima-media thickness (CIMT) and predisposition to subclinical carotid atherosclerosis and its impact on activity of RA disease.

Materials and Methods: This is a case-control study that included 105 RA patients classified into active and inactive groups according to disease activity score (DAS28) with 50 healthy matched controls. Clinical and laboratory assessments were done including enzyme-linked immunosorbent assay (ELISA) measurement of CCN1 with a bilateral assessment of CIMT using high resolution-ultrasonography. Comparison of CCN1 between RA patients and controls, a correlation between CCN1, DAS28, swollen joint count (SJC), tender joint count (TJC), and CIMT were analyzed.

Results: There was significant elevation of CCN1 in RA patients compared to controls (235.62±62.5 vs. 73.11±18.2, respectively). The cut off value of CCN1 was 99.25 pg/ml, with an area under the curve (AUC) =0.995, p<0.001, 98 % sensitivity and 95% specificity. CCN1 was inversely correlated with DAS28 and its components in both active and inactive RA patients (r=- 0.92, r=- 0.94, p<0.001). CCN1 was inversely correlated with SJC (r= -0.64, r= - 0.67, p<0.001), TJC (r=- 0.56, r= - 0.63, p<0.001), and with Larsen x-ray score (r=- 0.68, r= - 0.78, p<0.001) in both active and inactive RA patients, respectively. The CCN1 levels in active RA patients were significantly lower than that in patients with low disease activity. A significant positive correlation between CCN1 levels and CIMT in RA patient groups (r=0.88, r=0.47, p<0.001, respectively) was found.

Conclusion: Serum CCN1 could be a helpful biomarker in the diagnosis of RA, associated with RA remission. Disruption of serum CCN1 is engaged in the pathogenesis of atherosclerosis in RA patients which could be a clue for a future treatment strategy of atherosclerosis in RA by controlling CCN1 disruption. Regular follow-up of RA patients is recommended for early detection of subclinical atherosclerosis. New research ideas for controlling CCN1 disruption as new aspects of atherosclerosis treatment in RA patients are needed.

KEYWORDS:
Atherosclerosis; the cellular communication network factor 1 (CCN1); disease activity; rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune chronic inflammatory disorder of unknown cause with a female to male ratio of 3:1 manifested with articular damage and disability in addition to extra-articular manifestations affecting multiple organs like the heart, lungs, eyes, and mouth.[1-4] Atherosclerosis is an important complication of RA mostly due to chronic inflammation, which requires continuous follow up of those patients.[5,6]

RA involves symmetric small and large synovial joints causing pain, swelling, and stiffness.[1] Gradual onset polyarthralgia with symmetrical, intermittent, and migratory joint involvement, especially in the hands and feet are the most typical clinical presentations of RA.[3,4] The chronic pain leads to joint destruction and disability that usually progresses from peripheral to more proximal joints.[3]

Clinical symptoms in combination with an erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), Anti-cyclic citrullinated peptide (Anti-CCP), and X-ray are the main lines of RA diagnosis and follow up.[4,7,8] For the detection of RA, combined RF and anti-CCP have sensitivity and specificity of 90.2% and 83.3% respectively. However, they cannot differentiate patients with the active disease from those in remission.[8]

Thus, there is a need to establish an accurate diagnostic biomarker for RA.[7] The matricellular protein cellular communication network factor 1 (CCN1) is a novel extracellular matrix protein of the CCN family that consists

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of six distinct members (CCN1–6) encoded by immediate early gene due to growth factor response.[9] Specific integrins and heparin cell surface sulfate proteoglycans co-receptors mediate the function of CCN1.[10] Several studies reported high expression of CCN1 protein in synovial fluid, fibroblast-like synoviocytes (FLS), and peripheral blood mononuclear cells of RA patients.[11] So, it can be used as a diagnostic marker to distinguish RA patients from healthy controls and patients with other autoimmune diseases.[11]

CCN1 which is also called Cysteine-rich angiogenic inducer 61 (Cyr61) has multiple well-established functions including the ability to regulate a wide range of cell functions like cell growth and adhesion and participates in inflammation, neovascularization, and thrombosis. Disruption of CCN1 leads to several disorders and leads to the bad prognosis of vascular diseases, cancers, and chronic inflammatory diseases like RA.[10,11] At the same time, CCN1 could strongly inhibit the migration of immune cells, having anti-osteoclastogenic and anti-inflammatory properties.[11]

At the cellular level, purified CCN1 supports cell adhesion, stimulates cell migration, enhances mitogenesis, promotes cell survival, and induces chondrogenic differentiation in limb mesenchyme.[12] Also, the expression of genes involved in angiogenesis and matrix remodeling is induced by CCN1, So, the control of these processes might underlie the biological roles of CCN1 in several disorders, such as vessel morphogenesis, skeletal development, wound repair, and tumor growth.[11]

In RA, it was reported that CCN1 mRNA was strongly increased in lymphoblastoid B cell lines derived from RA discordant monozygotic twins, being one of the three most overexpressed genes.[11] Also, it was found that CCN1 could not only stimulate IL-6 production by FLS via the CCN1/αvβ5/Akt/NF-κB signaling pathway but also promote neutrophil infiltration via upregulation of IL-8 production in RA-FLS.[13] A recent study demonstrated that CCN1 promoted vascular endothelial growth factor expression in osteoblasts through negative regulation of miR-126 via the PKC-α signaling pathway and increased endothelial progenitor cell angiogenesis in RA.[14]

Recently the relationship between CCN1 and vascular diseases has been reported. CCN1 immunoreactivity was significantly associated with myocardial ischemia, interstitial edema, and coronary arteries atherosclerosis.[11,15] Few studies have explored the relationship between RA disease activity and serum CCN1 levels demonstrating that CCN1 is inversely correlated with DAS28 in RA patients and all disease activity indices including swollen joint counts (SJC) and tender joint counts (TJC), ESR, and CRP. The CCN1 levels were observed highest in the low TJC/SJC group and decreased in patients with a high number of TJC/SJC.[11] So, this study aimed to assess the levels of serum CCN1 in patients with RA, evaluating its impact on disease activity and its relation to carotid intima-media thickness (CIMT) and predisposition to subclinical carotid atherosclerosis.

The *in vitro* effect of CCN1 on cell cultures was explored previously in several studies, where it was founded that IL-6 production was decreased by CCN1 knockdown in fibroblast-like synoviocytes (FLS). Also, these studies showed that IL-6 production is activated by CCN1 via the avb5/Akt/NF-kB signaling pathway. A co-culture system was used consisting of purified CD4+ T cells and RA FLS and it was founded that RA FLS stimulated Th17 differentiation, and the pro-Th17 differentiation effect of RA FLS can be attenuated or stimulated by CCN1 RNA interference or addition of exogenous CCN1, respectively.[16-18]

The *in vitro* effect of CCN1 in atherosclerosis was also reported in previous studies where it was founded that CCN1 had an in vitro effect on smooth muscle rich tissues demonstrating that mechanical strain-dependent induction of the CCN1 gene involves signaling cascades through RhoA-mediated actin remodeling and the p38 stress-activated protein kinase (SAPK).[19,20]

MATERIALS AND METHODS

Study design and patient population

This case-control study included 105 RA patients according to Fan et al., 2019 with at least 80% power at two-sided 95% significance level and the ratio of case/control 2:1. Recruited from the rheumatology clinic in Menoufia University (MU), Egypt, from December 2018 to December 2019 with 50 healthy age and gender-matched controls.

Study participants

RA patients fulfilled the 2010 American College of Rheumatology (ACR) classification criteria for RA and their age was > 18 years.[21] 50 healthy subjects with matched age and gender were recruited as a control group.

Subjects with peripheral vascular disease, familial dyslipidemia, and subjects with conditions known to affect serum CCN1 levels including cancer, infection except after 3 to 6 months, liver diseases, coronary heart diseases, hypothyroidism, renal disorder (serum creatinine: ≥3.0 mg/dl or creatinine clearance: ≤30 ml/min), and other autoimmune diseases were excluded from this study.

Ethical approval and informed consent

This study was approved by the Institutional Review Board of MU, Egypt (approval IRB no.19102018INTPH1) and was carried following the Declaration of Helsinki ethics. Informed consent was taken from all subjects included in this study.

Clinical assessment

All patients underwent history taking including disease duration, special habits, cumulative steroid dose in the previous year, and clinical atherosclerosis symptoms like intermittent claudication, chest pain, fatigue, or confusion.

Clinical and physical assessment including morning stiffness, TJC, SJC and visual analogue scale during the last week on a scale between 0 and 10 mm, where 0 is no pain and 10 is the highest level of pain was done for RA patients.[22] Disease activity was assessed by disease activity score including 28 joint counts (DAS28) categorising the disease activity into high, moderate, low disease activity, and remission.

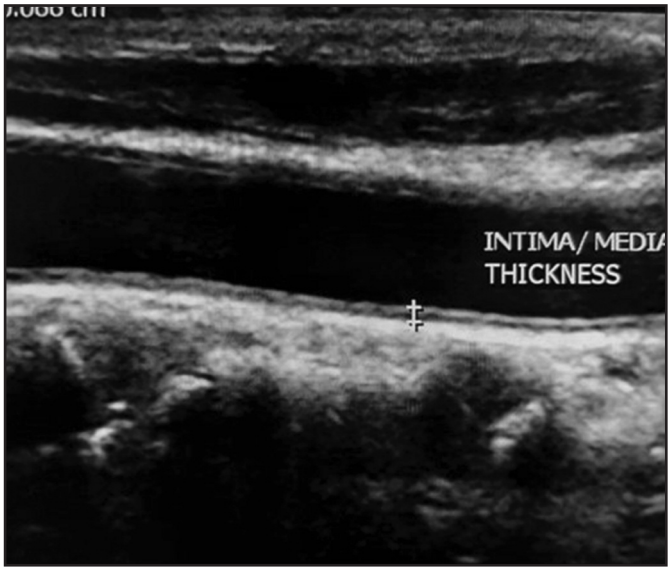

Fig. 1: Longitudinal grayscale ultrasound image at the level of common carotid artery showing intima/ media thickness = 0.66 mm.

RA patients were divided into two groups according to DAS28: patients with moderate to high disease activity (DAS28 ≥3.2 defined as active RA patients) and patients with low disease activity to remission (DAS28< 3.2 defined as inactive RA patients).[11]

Laboratory assessment and immunoassays
Complete blood picture, blood urea, serum creatinine, and ESR (by Westergren pipette)[23] were done. Lipid profile was done including total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG).[24] Serum samples of the patients were analyzed for Anti-CCP antibodies by enzyme-linked immunosorbent assay (ELISA) (Immunoscan RA CCP2, Euro-Diagnostica, Arnhem, the Netherlands) according to the manufacturer's instructions. The results for the Anti-CCP antibody were reported qualitatively where it is considered positive at serum levels ≥20.0U/ml.[25]

RF titer was obtained using the latex agglutination method (RF Direct Latex; EDALAB, France) and the normal range for RF is less than 14 IU/ml.[25] Laboratory assessment for CRP titer (SPINREACT, S.A/S.A.U Ctra. Santa Coloma.7 E-17176, and Spain) was done.

Undiluted serum samples were obtained to assess serum CCN1 by ELISA kit [ELISA Kit for Cysteine Rich Protein, Angiogenic Inducer 61(CYR61) – Cloud –Clone Corp, Katy, Texas, USA] following all internal manufacture procedure. The absorbance was measured at 450 nm and a standard curve was used to calculate serum CCN1 concentration.[26]
Radiological assessment:

Plain x-rays on both hands, wrists, and feet was done and graded by Larsen score from 0 where the joints are normal to 5 where there are mutilating abnormalities.[27] The radiological findings were graded by the same radiologist who was blinded to DAS28.

CIMT assessment:
Bilateral assessment of CIMT was done using high-resolution ultrasonography (Philips-HD11XE with multi-frequency linear 7-12 MHz transducer) after 15 minutes rest and the participants were examined in a supine position with neck extension and the chin turned contralateral to the side being examined. All patients and controls underwent the same scanning technique (Figure. 1). An average of CIMT of right and left common carotid arteries were used. CIMT ranged from 0.59-0.95mm is considered abnormal and 1.0 mm or more is considered high risk.[1,28]

Statistical analysis
SPSS version 20 with IBM compatible computer was used for statistical analysis. Number and percent for qualitative data and mean, standard deviation, and range for quantitative data were used. For comparison between groups having quantitative variables and comparison between two groups not normally distributed Student's t-test and Mann-Whitney test (U) were used, respectively. A one-way ANOVA test was used to compare between more than two groups having quantitative variables. A comparison between more than two groups with unequal distribution having quantitative variables was done using the Kruskal Wallis test. To study the association between two qualitative variables Chi-squared test (χ^2) was used. To correlate between two quantitative variables, the Pearson correlation coefficient test was used. Spearman correlation was used to correlate between not normally distributed quantitative variables. For all statistics, a p-value of ≤0.05 was statistically significant and ≤0.001 was highly significant. The receiver-operating characteristic (ROC) curve was used to determine the cutoff point of CCN1 in terms of sensitivity and specificity.[29]

RESULTS

A total of 105 RA patients classified into active and inactive groups according to DAS28 with fifty age and gender-matched controls were included.

Demographic and clinical characteristics of the studied groups
Active RA patients included 14 males (31.1%) and 31 females (68.9%) with a mean age of 48.62±13.33 years. Inactive RA patients included 18 males (30 %) and 42 females (70 %) with a mean age of 43.55±12.19 years. Controls were 17 males (34%) and 33 females (66%) with a mean age of 46.72±11.63 years with no statistically significant difference (p>0.05) between them regarding demographic characteristics, ensuring homogeneity of both groups (Table I).

A significant increase in the ESR, VAS, cholesterol, LDL, CCN1, and CIMT in RA patients compared to controls was found with significant differences regarding DAS28, SJC, TJC, Larsen x-ray score, and disease duration between both RA groups (active & inactive). The mean disease duration for RA patients was 96.26±56.76 months for the active group and 65.70±47.93 months for the inactive group. RF was positive in 77 RA patients (73.3%) and 78 RA patients had positive Anti-CCP antibodies (74.3%) (Table I).

Table I: Demographic and clinical characteristics of the studied groups

Demographic characteristics	Studied groups			Test of significance	P-value	Post Hoc test
	Active RA (n=45) Mean±SD	Inactive RA (n=60) Mean±SD	Controls (n=50) Mean±SD			
Age (years)	48.6±13.33	43.5±12.19	46.7±11.63	F=2.27	0.11	___
Sex: No. (%)						
female	31 (68.9%)	42 (70%)	33 (66%)	χ^2 = 0.2	0.90	___
male	14 (31.1%)	18 (30%)	17 (34%)			
Disease duration (months)	96.26±56.76	65.70±47.93	__	U=2.83	0.005	___
DAS 28	4.59±0.79	2.36±0.55	___	t=16.91	<0.001	___
SJC 2.42±0.81	1.50±0.56	___	U = 6.85	<0.001	___	
TJC 4.40±0.91	2.38±0.86	___	U = 11.53	<0.001	___	
X-RAY SCORE (Larsen score)	3.31±0.70	1.20±0.73	___	U = 14.88	<0.001	
RF positive No. (%)	35 (77.8%)	42 (70 %)	___	χ^2 = 0.45	0.51	
Anti-ccp Positive No. (%)	36 (80%)	42 (70%)	___	χ^2 = 0.87	0.34	
ESR (mm/hour)	62.75±21.96	14.61±2.86	10.42±1.65	K= 113.82	<0.001	P1< 0.001 P2 < 0.001 P3= 0.002
VAS	6.42±1.55	3.45±1.36	1.60±0.74	K= 98.15	<0.001	P1 < 0.001 P2 < 0.001 P3 < 0.001
CCN1 (pg/ml)	200.82±37.21	261.73±65.14	73.11±18.24	F=188.34	<0.001	P1 < 0.001 P2 < 0.001 P3 < 0.001
Cholesterol (mg/dl)	172.75±31.98	163.17±21.09	142.15±20.53	F=16.71	<0.001	P1= 0.05 P2 < 0.001 P3 < 0.001
HDL (mg/dl)	41.62±2.46	41.55±3.42	42.15±2.38	F=0.57	0.56	___
LDL (mg/dl)	112.51±17.44	120.58±17.45	107.28±17.59	F=7.33	0.002	P1= 0.02 P2 = 0.17 P3 < 0.001
Triglycerides (mg/dl)	83.95±20.53	88.71±21.79	87.7±21.78	F= 0.66	0.51	___
Mean CIMT (mm2)	0.79±0.16	0.72±0.19	0.35±0.03	F=113.16	<0.001	P1= 0.04 P2 < 0.001 P3 < 0.001

t= t-test, U= Mann-Whitney test, F: Anova test, K: Kruskal Wallis test, χ2: chi-square test, P1: between active RA group and inactive RA, P2: between active RA group and control, P3: between inactive RA group and control group. HDL= high-density lipoproteins, LDL= low-density lipoproteins, CIMT= carotid intima-media thickness, ESR= erythrocyte sedimentation rate, VAS= visual analogue scale, RF= rheumatoid factor, DAS28= disease activity score, SJC= swollen joint count, TJC= tender joint count.

Table II: Comparison between RA patients and controls regarding Cyr61, lipid profile, and CIMT

Studied parameters	Studied groups		Test of significance	P-value
	RA (n=105) Mean±SD	Controls (n=50) Mean±SD		
CCN1 (pg/ml)	235.62±62.53	73.11±18.24	24.07	<0.001
Cholesterol (mg/dl)	167.28±26.60	142.15±20.53	5.38	<0.001
H.DL(mg/dl)	41.58±3.03	42.15±2.38	1.06	0.28
L.D.L(mg/dl)	117.12±17.82	107.28±17.59	2.98	0.003
Triglycerides (mg/dl)	86.67±21.29	87.67±21.78	0.25	0.80
mean CIMT (mm2)	0.75±0.24	0.35±0.03	U=10.49	<0.001

U= Mann-Whitney test, HDL= high-density lipoproteins, LDL= low-density lipoproteins, CIMT= carotid intima-media thickness.

Table III: Clinical performance of Cysteine-rich 61 (Cyr61), RF, & Anti-CCP in RA patients

Studied parameters	Optimal cutoff point	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Diagnostic accuracy (95%CI)	DOR (95%CI)
CCN1 (pg/ml)	99.25	19.62 (5.08-75.76)	97% (93–99)	95% (82–99)	98% (93–100)	95% (82–99)	98% (93–100)
RF (mg/dl)	8.11	73% (64–81)	82% (67–92)	92% (83–96)	54% (41–67)	76% (68–82)	12.96 (5.15–32.64)
Anti-CCP (u/ml)	17.08	74% (65–82)	78% (61–89)	90% (81–95)	53% (40–66)	75% (67–82)	9.95 (4.20–23.55)

95% CI= 95% confidence interval, PPV=Positive predictive value, NPV= Negative predictive value, DOR= diagnostic odds ratio.

Table IV: Correlation between CCN1, disease duration, DAS 28, ESR, VAS, and CIMT in active and inactive RA patients

Studied parameters	CCN1 (pg/ml)			
	Inactive RA (n=60)		Active RA (n=45)	
	P value	r	P value	r
Disease duration (months)	- 0.07**	0.66	- 0.27**	0.03
DAS 28	- 0.92*	<0.001	- 0.94*	<0.001
SJC	- 0.67*	<0.001	- 0.64	<0.001
TJC	- 0.63	<0.001	- 0.56	<0.001
Larsen score	- 0.78	<0.001	- 0.68	<0.001
ESR (mm/hour)	- 0.44*	0.002	- 0.82*	<0.001
VAS	- 0.65*	<0.001	- 0.49*	<0.001
CIMT (mm2)	0.88*	<0.001	0.47*	<0.001

*Pearson correlation coefficient, **Spearman correlation coefficient, VAS= visual analogue scale, DAS28= disease activity score, SJC= swollen joint count, TJC= tender joint count, ESR= erythrocyte sedimentation rate, CIMT= carotid intima-media thickness, RA= rheumatoid arthritis.

According to DAS 28, there were 45 (42.85%) active RA patients and 60 (57.14%) inactive RA patients. 32 active RA patients (71.1%, p<0.001) and only 2 inactive RA patients (3.3%, p<0.001) were on corticosteroid treatment (Table I).

CCN1 levels, lipid profile, and CIMT measurements in RA patients and controls

There were significant differences regarding Cholesterol and LDL between RA patients and controls (p<0.001 and p=0.003, respectively) with no significant differences regarding HDL (p=0.28) and triglycerides (p=0.80). Serum levels of CCN1 were significantly higher in RA patients compared to healthy controls (235.62±62.53 vs. 73.11±18.24, p<0.001, respectively). CIMT was increased in RA patients compared to controls (0.75±0.24 vs. 0.35±0.03, respectively). This means that the CCN1 could differentiate RA patients from controls and is associated with atherosclerosis development risk (Table II).

Clinical performance of CCN1, RF & Anti- CCP in RA

Table III illustrates the clinical performance of CCN1, RF, & Anti-CCP in RA patients. Serum CCN1 can discriminate RA patients from healthy controls with an area under the curve of 0.995 (95% CI 0.98 to 0.100, p<0.001). The optimal cutoff point of CCN1 equals 99.25 pg/ml with a sensitivity of 98% and specificity of 95% with positive predictive value (PPV) of 98% and negative predictive value (NPV) of 95 % (Table III).

CCN1and CIMT in active and inactive RA patients

Serum levels of CCN1were significantly higher in inactive RA patients compared to active RA patients (261.73±65.14 vs. 200.82±37.21, p<0.001, respectively). Pearson correlation showed that CCN1 serum levels were inversely correlated with DAS28 (r= - 0.94, r= - 0.92, p<0.001), SJC (r= - 0.64, r= - 0.67, p<0.001), TJC (r= - 0.56, r=- 0.63, p<0.001), Larsen score (r= - 0.68, r= - 0.78, p<0.001), ESR (r=- 0.82, p<0.001), and VAS (r=- 0.49, p<0.001), in active and inactive RA patient groups respectively (Table IV).

CIMT was significantly high in RA patients compared to controls (0.75±0.24 vs. 0.35±0.03, respectively) and Pearson correlation showed that CCN1 serum levels were positively correlated with CIMT in active and inactive RA patient groups (r=0.47, p<0.001, r=0.88, p<0.001), respectively (Table IV).

DISCUSSION

The matricellular protein, CCN1 is encoded by an immediate-early gene induced by growth factor and it is transcriptionally activated within minutes of stimulation by injury stimuli especially inflammation. However, it is expressed at low levels in quiescent cells.[11]

CCN1 controls the cell cycle, stimulates chemostasis, and augments the growth factor effects.[30] It also has an important role in angiogenesis by promoting the survival of the endothelial cells and stimulating pro-angiogenic factors.[13] The expression of CCN1 was found to be high in peripheral blood mononuclear cells fibroblast-like synoviocytes (FLS) and synovial fluid of RA patients.[13,31]

In this study, a high expression of CCN1 in RA patients was reported compared to the healthy control group exploring its value in discriminating RA patients from healthy controls. This was consistent with previous preclinical studies showing overexpression of CCN1 in the synovial fluids and peripheral blood mononuclear cells of RA patients.[10,31]

RA patients are twice likely to develop sudden cardiac death attributed mostly (50%) to cardiovascular disease. The histochemical analysis in individuals who died of sudden cardiac death revealed that CCN1 was significantly elevated (80%) and associated with myocardial ischemia and atherosclerosis of coronary arteries.[6,32] Rawla et al., supported this hypothesis reporting that the prevalence of cardiovascular diseases in patients with RA is high and multifactorial.[6]

CCN1 was significantly high in RA patients compared to controls with a statistically significant positive correlation with CIMT. Studies by Rawla et al., and Deng et al., are consistent with our results reporting the important role of CCN1 in atherosclerosis pathogenesis.[6,32]

Several studies have demonstrated the association between CCN1 and various aspects of atherosclerosis demonstrating that it is highly expressed in atherosclerotic plaques, contributing to the development of cardiovascular and cerebrovascular diseases and peripheral arterial diseases.[14,33] Besides, CCN1 levels were associated with rapid mortality in acute heart failure (AHF) patients and coronary heart disease (CAD) and could be a potential marker of myocardial ischemic injury and prognosis in patients with the acute coronary syndrome (ACS).[34,35]

Furthermore, CCN1 expression in human atherosclerotic lesions was significantly elevated.[32] This comes in agreement with our study reporting that CCN1 is a predisposing factor for atherosclerosis in RA patients in combination with hyperlipidemia and other factors including the chronic inflammatory nature of the disease.

Interestingly, serum CCN1 was more elevated in inactive RA patients than those with active disease. Spearman correlation analysis revealed that CCN1 levels were negatively correlated with almost all disease activity indices in statistics [Tables I, IV]. When RA patients were stratified by numbers of TJC and SJC, the CCN1 levels were the highest in patients with a low number of TJC and SJC and decreased in active patients with an increasing number of TJC and SJC. These results were supported by Fan et.al., and Woo et al.,[11,36] who reported significantly high levels of CCN1 in RA patients compared to controls (211.57 vs. 37.24, respectively) with negative correlation with DAS28 ($r = -0.174$, $p = 0.010$).

There was also a negative correlation between CCN1 and DAS28 which is complicated in its explanation. In this study, the negative correlation of CCN1 with disease activity is attributed to the strong anti-inflammatory protective activities of CCN1 promoting tissue repair which is accompanied by inflammation resolution.

To explore the role of CCN1 in pulmonary hypertension associated with systemic lupus erythematosus, a multi-center study revealed that patients with higher CCN1 levels had better survival than those with lower levels.[12] However, the significant-up regulation of CCN1 expression in the development and progression of arthritis in RA was reported.[31,37]

CCN1 has a critical role in promoting recovery and mucosal healing in colitis.[38] Exogenous administration of CCN1 accelerated mucosal restitution of colitis in wild type, suggesting a therapeutic potential for CCN1 in inflammatory bowel disease (IBD).[38] IBD and RA share important pathogenesis mechanisms, especially the contribution of the Th1/Th2 cytokine balance.[39]

Regarding both sensitivity and specificity, ROC analysis revealed that CCN1 had higher sensitivity and specificity (98 % and 95%, respectively) compared to both RF and Anti-CCP with a cutoff point of 99.25 pg/ml (AUC of 0.995, 95% CI 0.98 - 0.100, p-value <0.001) exploring the ability of CCN1 to discriminate RA patients from healthy controls and supporting our hypothesis that CCN1 could be used as a diagnostic tool of RA (Table III). These results are consistent with Fan et al., who reported CCN1 sensitivity of 92.09% and specificity of 98.00 in RA patients.[11]

This study explored that serum CCN1 levels had a positive correlation with CIMT predisposing to atherosclerosis as a RA comorbidity. Serum CCN1 levels were significantly elevated in RA patients compared to healthy controls with a negative correlation with RA disease activity. To the best of our knowledge, this study is one of the early studies exploring the effect of CCN1 on CIMT in RA patients. However, further research suggestions for controlling CCN1 disruption as new aspects of treatment of atherosclerosis in RA are needed.

LIMITATIONS OF THE STUDY

This study has some limitations, firstly, the protective role of CCN1 in RA needs to be further assessed by using more precise animal experiments and clinical studies with a larger sample size. Secondly, a long-term follow-up duration in order to evaluate the CCN1 level and its correlation with CIMT in RA patients is needed. Lastly, patients with hyperlipidemia should have been excluded from this study to explore the effect of CNN1 on CIMT.

CONCLUSIONS

Serum CCN1 can be a helpful biomarker in RA diagnosis, associated with RA remission. Disruption of serum CCN1 is involved in the pathogenesis of atherosclerosis in RA patients which could be a clue for a future treatment strategy of atherosclerosis in RA by controlling CCN1 disruption. Regular follow-up of RA patients is recommended for early detection of subclinical atherosclerosis.

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AVAILABILITY OF DATA AND MATERIALS

The data sets during and/or analyzed during the current study available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

A 5-year clinicopathological study on microscopic colitis at a Malaysian tertiary hospital

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ABSTRACT

Introduction: Microscopic colitis (MC) is a well-recognised cause of chronic diarrhoea in Western countries. It is classically associated with normal endoscopic findings and a higher prevalence among patients with autoimmune disease. Local information regarding this disease remains scarce. We identified patients diagnosed with MC over a five-year period, and then proceeded to analyse the clinical characteristics of these cases.

Materials and Methods: A retrospective study was conducted by identifying all histologically confirmed colitis cases diagnosed at Hospital Universiti Sains Malaysia from January 2015 until December 2019. Clinicodemographic data was retrieved from case notes of patients.

Results: Of the 299 cases with histological colitis, 23 (7.7%) were initially identified as MC. Two cases had incomplete data, while two others were excluded as the diagnoses were revised to inflammatory bowel disease. An incidence of 14 MC cases/1000 case-year was obtained using the 21 MC cases seen within the five-year period. MC subtypes for the 19 analysed cases i.e., lymphocytic colitis and collagenous colitis accounted for 13 (68.4%) and 6 (31.6%) cases, respectively. Eleven patients (57.9%) were females (M:F ratio 1:1.5) with a median age of 51 years. Only nine (47.3%) presented with diarrhoea; one subject (5.4%) had an autoimmune condition (Hashimoto thyroiditis). Normal endoscopic findings were found in 89.5% of patients.

Conclusion: Approximately half of the subjects in our study who had histologically confirmed MC did not present with diarrhoea. Adequate biopsy samples despite normal colonoscopy findings are important in order to not miss the diagnosis of MC.

KEYWORDS:
Collagenous colitis, Colonoscopy, Inflammatory bowel disease, Lymphocytic colitis, Microscopic colitis

INTRODUCTION

Microscopic colitis (MC), which consists of collagenous and lymphocytic colitis is a common cause of chronic non-bloody diarrhoea. Apart from diarrhoea, this entity is characterised by a macroscopically normal colonic mucosa observed during gastrointestinal endoscopy; however, diagnosis relies on characteristic histopathological findings.[1] Since MC was first described in the 1970's, it is recognised as one of the commonest causes of chronic diarrhoea in the West with a reported incidence of between 3-14 cases per 100,000 person-years in Europe.[2] MC has a female preponderance, with a median age of 65 years at diagnosis.[3] The number of MC cases is on the rise worldwide, mostly attributed to a greater awareness among physicians of this disease.[4]

The diagnosis of MC depends on findings of characteristic histopathologic features in colonic mucosal biopsies. As stated earlier, MC has two main histological subtypes i.e., lymphocytic colitis (LC) and collagenous colitis (CC). However, incomplete forms of MC (incomplete MC – MCi) have also been recognised.[5] Tong et al. in his systematic review and meta-analysis of 25 studies from North America and Europe found that the pooled incidence rate of CC and LC to be 4.14 and 4.85 per 100,000, respectively.[3] Nevertheless, as patients with MC often have normal endoscopic mucosal findings, the diagnosis may be missed unless clinically-indicated random biopsy samples are obtained during endoscopy.

The pathogenesis of MC remains unclear. It is thought to be due to a specific pathological reaction of the colonic mucosa towards luminal noxious agents in predisposed individuals and this eventually leads to an inappropriate immune response. Concomitantly, it has been shown that those with MC had higher rates of autoimmune conditions such as autoimmune thyroid disease, coeliac disease, and rheumatoid arthritis.[6-8] Common medications such as non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs) and statins have also been implicated as a cause for MC.[9-11]

The majority of published reports on MC are data from the West, very few being from the Southeast Asian region including Malaysia. Only two published articles on MC from Malaysia were identified: The first was a histological analysis of nine patients who were diagnosed with MC published in 1994.[12] The second, from 2013 was of a 63-year-old woman who had histologically confirmed MC among a cohort of 74 patients with diarrhoea-predominant irritable bowel

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Table I: Demographic and clinical data of microscopic colitis patients over 5-year period

No.	Age	Sex	Presenting symptom	Colonoscopy finding	Biopsy site	Histopathology finding	Concomitant diseases	Treatment	Follow up
1	42	F	Diarrhoea	Polyps	Left only	LC	HTN, gastritis, uterine fibroid	Prednisolone	Asymptomatic
2	51	F	Diarrhoea	Normal	Right & left	CC (segmental)	HTN, DM, IHD, gastritis	Mesalazine, azathioprine	Asymptomatic
3	41	F	Diarrhoea	Normal	Right & left	LC	HTN	Nil	Asymptomatic
4	66	M	Diarrhoea	Normal	Right & left	LC	HTN, HPL, IHD, gastritis, multinodular goitre	Nil	Asymptomatic
5	56	F	Diarrhoea	Normal	Right & left	LC	GERD, bipolar disorder	Nil	Asymptomatic
6	57	M	Diarrhoea	Polyps	Right & left	LC	HTN	Nil	Asymptomatic
7	68	F	Diarrhoea	Normal	Right & left	CC	HTN, HPL, IHD, DM, CKD, GERD	Nil	Lost to follow up
8	54	F	Diarrhoea	Normal	Right & left	LC with infectious colitis	Asthma	Ciprofloxacin, metronidazole	Lost to follow up Lost to follow up
9	52	F	Diarrhoea	Normal	Right & left	LC (segmental)	HTN, HPL, asthma, gastritis	Nil	Lost to follow up
10	17	F	Constipation	Normal	Left only	LC	Gastritis	Nil	Asymptomatic
11	42	M	Constipation	Normal	Left only	CC	HTN, HPL, GERD, allergic dermatitis	Nil	Partial relief
12	45	M	Constipation	Normal	Right & left	CC (left only)	Functional constipation	Nil	Partial relief
13	64	M	Constipation	Polyps	Right & left	LC	HTN, gastritis, benign prostatic hyperplasia	Prednisolone	Lost to follow up
14	30	M	Constipation	Normal	Left only	LC	Nil	Nil	Lost to follow up
15	27	F	Blood in stool	Patchy inflammation	Right & left	LC	Hashimoto thyroiditis, GERD	Nil	Asymptomatic
16	33	F	Blood in stool	Normal	Right & left	LC	Nil	Prednisolone	Lost to follow up
17	52	F	Anaemia	Normal	Right & left	CC	GERD	Nil	Asymptomatic
18	59	M	Anaemia	Normal	Right & left	CC (segmental)	HTN, DM, CKD, gout	Nil	Asymptomatic
19	29	M	Abdominal pain	Patchy inflammation	Right & left	LC	GERD	Nil	Asymptomatic

LC: Lymphocytic colitis CC: Collagenous colitis HTN: Hypertension DM: Diabetes mellitus HPL: Hyperlipidaemia
IHD: Ischaemic heart disease GERD: Gastroesophageal reflux disease CKD: Chronic kidney disease

syndrome (IBS-D).[13] As the diagnosis of MC is based on histopathology, many cases could be missed as patients may present with minimal clinical and endoscopic findings. This study aimed to describe and analyse the clinicopathological findings of patients with MC over a 5-year period.

MATERIALS AND METHODS

We conducted a retrospective study on all cases of histologically confirmed MC diagnosed at Hospital Universiti Sains Malaysia (HUSM) over a period of five years from 1st January 2015 to 31st December 2019. A total of 299 colitis cases were collected.

Cases were identified from the Lab Information System (LIS) of the pathology department using the keywords "colitis", "microscopic colitis", "collagenous colitis" or "lymphocytic colitis". We included all colonic biopsies reported as MC or any of its subtypes.

Histopathological findings of all included cases were collected from the LIS database, clinical and demographic information were obtained from the case notes of subjects. The variables collected included age, sex, symptoms, colonoscopy findings, histological findings, comorbidities, concomitant medications, treatment administered and clinical course. Descriptive analysis of all collected data was performed.

Ethical approval was obtained from the Human Research Ethics Committee (USM/JEPeM/20020091) in accordance with the Helsinki Declaration of 1975, as revised in 2008.

RESULTS

Epidemiology

Of the 299 cases of colitis collected; 23 were reported as MC. From these 23 cases, four were excluded from the study, two cases due to incomplete online information and another two cases due to a revised diagnosis of IBD. In all 19 MC cases were therefore included for study analysis.

Lymphocytic colitis was diagnosed in 13 (68.4%) and collagenous colitis was diagnosed in six (31.6%) An annual incidence of 14 MC cases/1000 case-year was obtained using the 21 MC cases seen within the five-year period.

TABLE 1 summarises the characteristics of the 19 subjects with MC. Eleven (57.9%) were females, (male to female ratio of 1:1.5). The median age at diagnosis was 51 years and age ranged from 17 to 68 years (FIGURE 1). Fourteen (73.7%) patients were Malays. The presenting symptom in nine cases (47.3%) was diarrhoea. Other presenting symptoms were constipation (5, 26.3%), blood in stool (2, 10.5%), anaemia (2, 10.5%) and abdominal pain (1, 5.4%).

Endoscopic and histologic findings

Majority of the subjects (17, 89.5%) had normal colonic mucosa on endoscopic examination with three of them having small hyperplastic polyps which were confirmed in biopsy samples. Two cases displayed mucosal hypervascularity which involved several segments of the colon. Fifteen (78.9%) had random mucosal biopsies taken from both the right and left sides of the colon. The remaining cases only had colonic biopsy samples obtained from the left side of the colon.

Histologically, 12 (63.1%) were diagnosed as LC, the remaining seven (36.8%) as CC (Figures 2A and 2B). One of the cases displayed only left-sided CC with normal histology reported from the right side of the colon. Three cases showed histology consistent with MC in several segments of the colon, biopsies from the remaining colonic segments were reported as non-specific chronic colitis (NSC).

Concomitant diseases and medications

Two patients had no previous medical illness and no history of taking regular medications. One (5.4%) patient had underlying autoimmune disease, namely Hashimoto thyroiditis. The majority of patients (12, 63.1%) had concomitant gastritis or gastroesophageal reflux disease (GERD), ten (52.6%) with hypertension and three (15.8%) with type 2 diabetes mellitus. Medications was strongly associated with MC – PPIs, statins and NSAIDs were used by ten (52.6%), five (26.3%) and one (5.4%) patient(s), respectively. The number of subjects on each of these medications and their MC subtypes are shown in Figure 3.

Treatment and clinical follow up

Only four (21.1%) patients received treatment for MC upon diagnosis, either with steroid (prednisolone), mesalazine or azathioprine. One was found to have concomitant infectious colitis on histology, and therefore received a course of antibiotics (ciprofloxacin and metronidazole). Fourteen (73.7%) patients were treated conservatively. Almost 60% (11/19) of these patients reported resolution of symptom during clinic follow up, which were conducted at 3- or 4-monthly durations. Six were lost to follow up, while two others had partial relief of symptoms. Of three patients receiving prednisolone in tapering doses, only one returned to follow up and reported improvement, while two others defaulted. The only patient who received mesalazine and azathioprine responded to the treatment. All patients with an initial complaint of diarrhoea reported resolution of symptom on follow-up, even those who were treated conservatively.

DISCUSSION

Clinicopathological information regarding MC from Southeast Asia, specifically from Malaysia has not been updated since 2014. This lack of published reports could be influenced by the historical presumption that MC is rare among Asian patients, as supported by low reported incidences in East Asian countries.[14] One meta-analysis found that patients of East Asian descent living in the United States of America were affected by MC at a much lesser extent than those of other ancestries (odds ratio of 0.2), which reflects a possible presence of genetic factors.[14]

However, a small retrospective study in Japan on patients with chronic diarrhoea who had biopsies during colonoscopy showed that nearly 45% (12/27) of them had MC.[15] Likewise, in South Korea, a prospective study found that 22% of 100 patients investigated for chronic diarrhoea were diagnosed with MC, a figure which is almost similar to data from

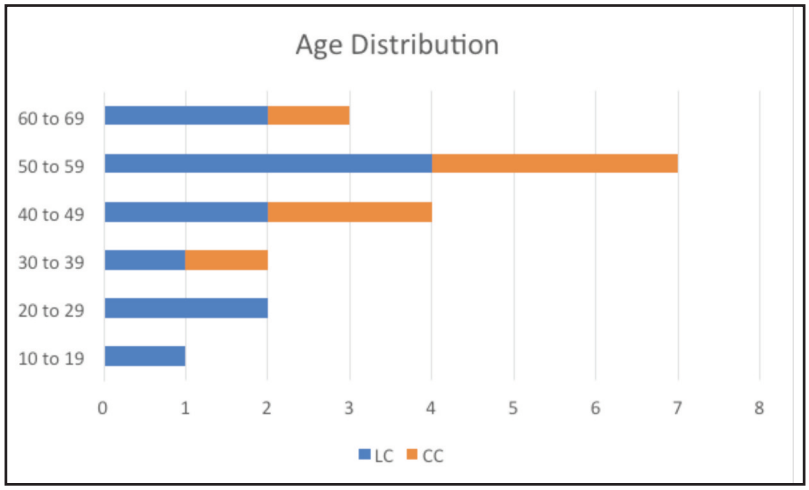


Fig. 1: Age distribution of patients according to MC subtypes (LC: lymphocytic colitis, CC: collagenous colitis)

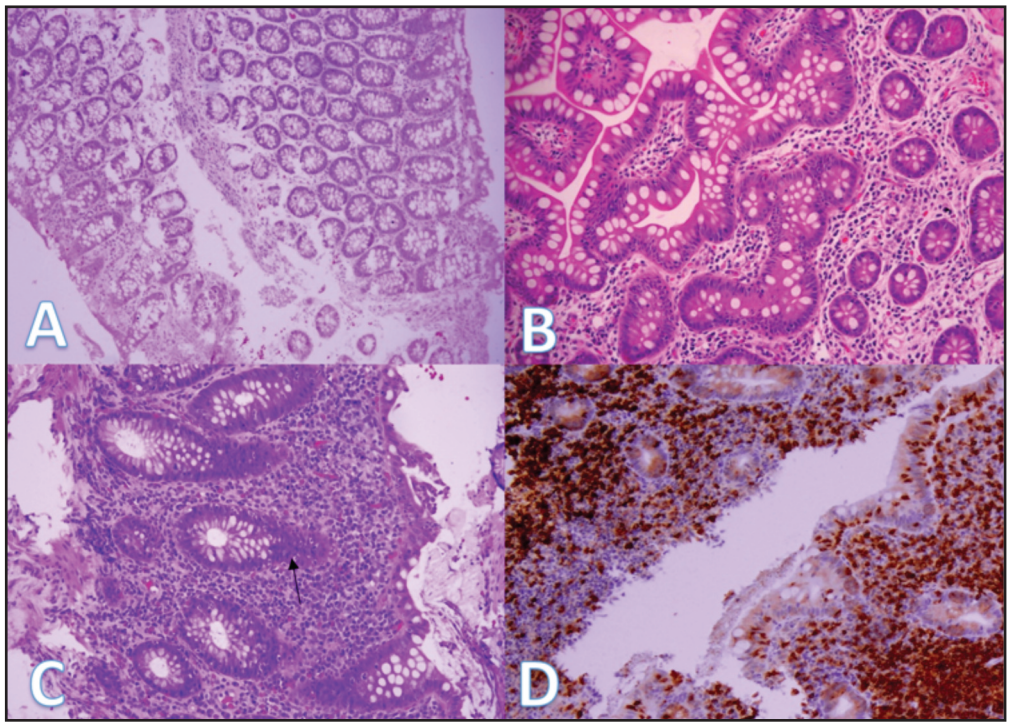


Fig. 2a: Microscopic pictures of lymphocytic colitis. (A) HPE image shows mucosal tissue is composed of well-spaced glands (100x magnification, H+E stain). (B) Some of the crypts appear branched (100x magnification, H+E stain). (C) Lamina propria is densely infiltrated by lymphoplasma cells with evidence of cryptitis seen (arrow) (200x magnification, H+E stain). (D) The increased epithelial lymphocytosis is confirmed with immunohistochemistry stain CD3 (200x magnification).

Western countries.[16] A larger prospective study of 613 patients with chronic diarrhoea in Southern China revealed that 9.6% and 4.5% of patients had LC and CC, respectively.[17] The results of these studies suggest that MC might not be as rare in Asian populations as it was initially thought.

Our study shows that the majority of patients with MC were aged more than 50 years, with a median age of 51 years. The incidence of MC is higher in the elderly, with a median age at diagnosis of over 60 years old.[3] Nevertheless, up to a quarter of patients with MC were aged 45 years or younger when first diagnosed, and cases were also seen among children.[1] The younger median age at diagnosis in our study may also reflect the age distribution of the local population; the proportion of elderly patients may not be as high as those seen in studies from the West. There were more female patients than males with MC, and this matches the current knowledge that MC has a higher female preponderance. Physical examination and thyroid function tests were unremarkable in all our patients. Subjects who presented with diarrhoea had stool samples which were sent for cultures and examined for parasites, ova, and cyst, all were reported as negative.

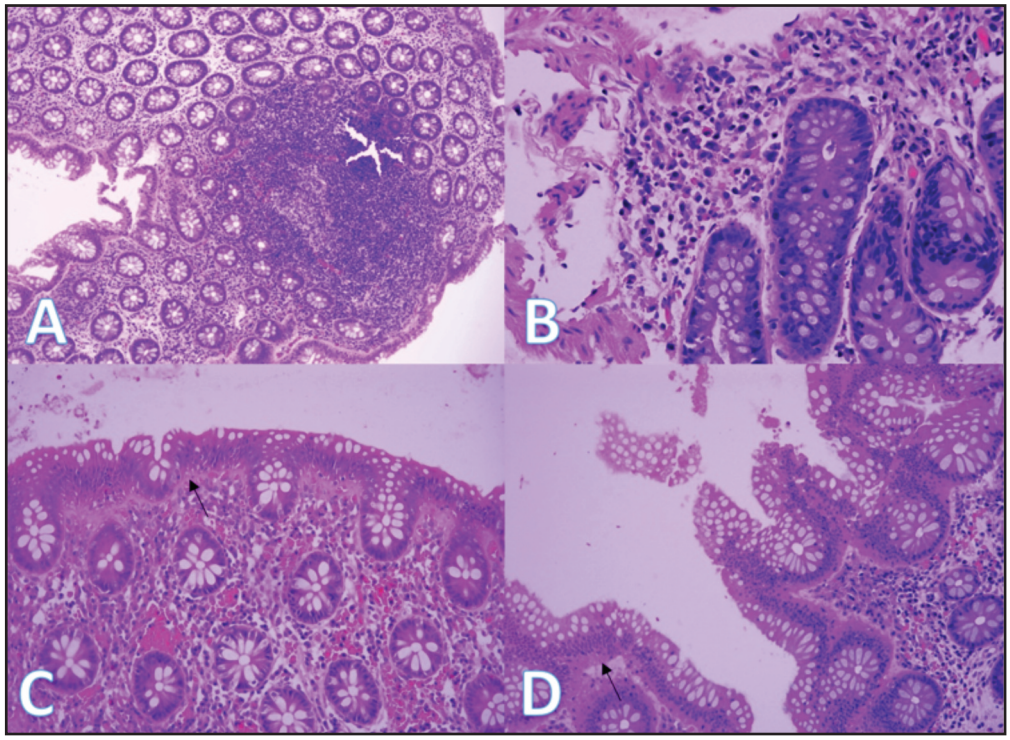
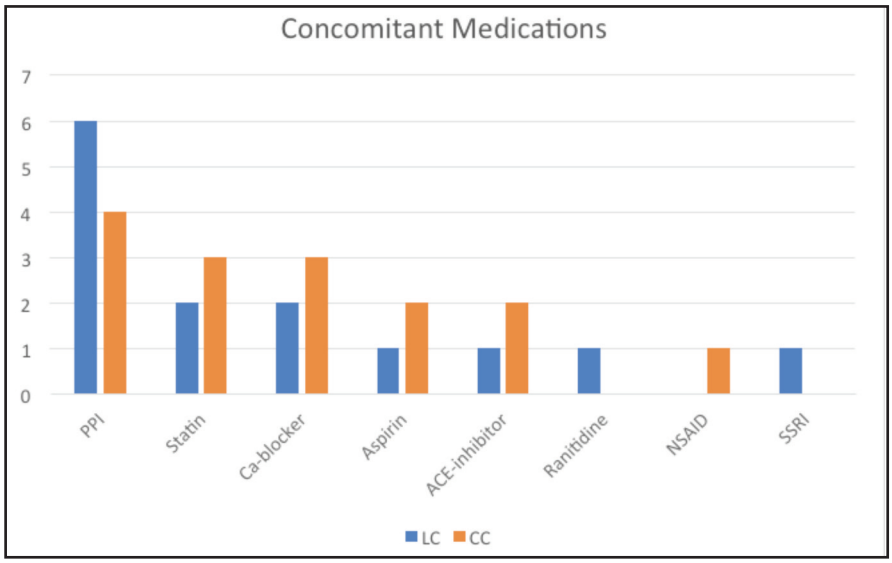


Fig. 2b: Microscopic pictures of collagenous colitis. (A) At 100x magnification, the mucosa is composed of well-spaced glands. Lymphocytic aggregates with germinal centre can be appreciated (H+E stain). (B) Lamina propria show moderate increase in lymphoplasma cells with cryptitis seen (200x magnification, H+E stain). (C&D) Presence of mild thickened subepithelial collagen layer (arrows) that entrap small capillaries and inflammatory cells (200x magnification, H+E stain).



PPI: proton pump inhibitor, Ca-blocker: calcium channel blocker, ACE-inhibitor: angiotensin converting enzyme inhibitor, NSAID: non-steroidal anti-inflammatory drugs, SSRI: selective serotonin receptor inhibitor

Fig. 3: Concomitant medications of patients according to MC subtypes (LC: lymphocytic colitis, CC: collagenous colitis)

It is an accepted notion that MC always presents as a chronic, watery, and non-bloody diarrhoea accompanied by weight loss, abdominal pain, nausea, or faecal incontinence. The exact mechanism of diarrhoea in MC is less understood and is likely to be multifactorial in nature; mucosal inflammation leading to secretory diarrhoea, bile salt malabsorption and mucosal injury from luminal contents may all play a role.[10]

In our case series though, only nine patients complained of diarrhoea while the others did not have diarrhoea-related complaints with five of them having constipation.

Nevertheless, CC and LC cases that present with constipation have been documented. Most of the time the constipation is of a short duration. Chronic constipation does occur,

however.[18] Barta et al., reported 43% of their patients (23/53) with histologically proven MC had constipation as a presenting complaint.[19] In our study, one of the five patients who complained of constipation was known to have functional bowel disease. In one meta-analysis, overall prevalence of MC among patients with all types of functional bowel disorders was 7%, and prevalence with diarrhoea-dominant irritable bowel syndrome (IBS) was not significantly higher compared to constipation-dominant IBS or mixed-type IBS.[20] However, one of the latest guidelines states that MC should not be diagnosed in patients that fulfil the criteria for functional bowel disease; this is still open to debate as the studies that form the basis for this statement had heterogenous results.[1] Two of our patients had bloody stools as the presenting complaint, with both being diagnosed as having LC. At least two studies reported a similar presentation; the superficial mucosal inflammation of LC was thought to be a possible explanation for the bleeding.[21,22] As for the presence of MC among those with concomitant autoimmune disease, we only had one female patient who was diagnosed as having Hashimoto thyroiditis in 2013 and was investigated for per rectal bleeding. The patient was found to have LC; at the time of MC diagnosis she was euthyroid on thyroxine replacement.

MC is classically associated with normal appearance of colonic mucosa during endoscopy. However, Park et al. reported half of their cohort of LC cases (7/14) had mucosal lesions, namely hypervascularity, exudative bleeding and mucosal oedema.[23] There was also a case report of CC that presented with skip lesions mimicking Crohn's disease and was complicated by intestinal obstruction.[24] A large Swedish study of 795 patients reported endoscopic abnormalities in 37% of patients with CC and 25% of patients with LC.[21]

Two of our patients exhibited significant mucosal hypervascularity involving only several segments of the colon. One patient showed diffuse changes, while the other had clear demarcations between diseased and normal mucosa. Interestingly, this was our patient that had underlying autoimmune disease. It is uncertain whether these two findings correlate.

To a certain degree however, this underlines the importance of having an awareness of the disease and the significance of obtaining multiple random biopsies despite normal colonoscopy mucosal findings. There have been many instances when no biopsy sample was taken during colonoscopy if the visual findings were deemed normal by the endoscopist, regardless of the indication for the procedure.

We recognise that this is a significant limitation of our study as MC may be missed if mucosal biopsies were not obtained during visually-normal colonoscopies. Virine et al. proposed the use of a Western protocol to assist in the diagnosis of MC where two biopsies should be taken from the ascending colon, and another two from the descending colon.[25] European guidelines, however, recommend ileocolonoscopy with biopsies from at least the right and left side of the colon.[5] Nevertheless, Andrews et al. showed that endoscopists with an academic practice, gastroenterologists and those with lower annual endoscopy volumes were more likely to make a diagnosis of MC.[26] Thus, in HUSM based on clinical suspicion the majority of cases would have had random colonic biopsies obtained despite having normal colonoscopy findings as the histological report would be of valuable assistance in determining the underlying pathology.

Approximately half of the subjects in our study were on proton-pump inhibitors; a quarter were on statins. These medications have been known to be strongly associated with MC. One common theory proposes that certain drugs act as luminal antigens, increasing immune system activity in the colonic mucosa and thus resulting in MC.[27] Several hypotheses for PPI-induced MC have been suggested, including colonic intraepithelial lymphocytosis following PPI exposure,[28] impaired colonic barrier function contributed by acid suppression related dysbiosis,[29] and possible idiosyncratic type drug reaction.[30] Identification and subsequent withdrawal of the offending drug contributes to spontaneous remission of MC, as demonstrated in this study. However, discontinuation of statins can be associated with an increased risk of cardiovascular event in high risk individuals;[31,32] before this is decided a cardiology consultation should be obtained and alternatives offered to the patient regarding lipid lowering therapies. Some of our patients reported symptom resolution with discontinuation or dose reduction of the PPI pantoprazole; it has been shown that PPI use is associated with an increased risk of MC (OR 2.68, 95% CI 1.73–4.17).[3]

As for treatment, locally acting budesonide, released in the terminal ileum and right colon, is preferred over systemic corticosteroids as first line treatment for MC due to its efficacy and favourable side effect profile.[10] Due to unavailability of budesonide, three of our patients were treated with a tapering prednisolone dose. One patient had reported success, but two others defaulted follow up. Despite reports that immunosuppressive agents have no clear effects in MC,[4] one of our patients showed therapeutic response to azathioprine and aminosalicylate. It has been shown that those who had spontaneous disease remission had better long term outcomes than those who needed medications for treatment of MC; 93% of MC patients who had spontaneous reduction in disease will have sustained remission after one year, while only 60.5% of those with drug-induced remission will still be in remission a year later.[33]

In the context of MC, since both CC and LC have distinct histological characteristics, Geboes et al. found many cases not fitting into these two subtypes were generally classified as non-specific colitis.[34] In the early 2000's, the terms "incomplete MC" and "MC not otherwise specified" (MC-NOS) were introduced to describe a subgroup of patients not completely fulfilling the classical criteria for MC diagnosis. Later on, several authors proposed expanding the MC spectrum further into five subtypes, adding "minimal change colitis" and "MC with giant cells".[35] By and large however, the majority of studies from Asia only consider LC and CC in the context of MC diagnosis.

According to Mantzaris et al., factors leading to categorisation failure and thus NSC include a) endoscopist-related factors e.g., inadequate biopsies, timing of biopsies vs

course of inflammation, and having incomplete clinical data; and b) pathologist-related factors e.g., handling and sample processing issues as well as personal interest and experience in examining colonic mucosa.[36] These may explain differing histologic diagnoses of biopsies which were obtained from various colonic segments.

During our screening, there were two patients who had histologically confirmed MC, but were subsequently excluded as they were treated as IBD after further investigation and follow up. There is still no conclusive answer whether IBD and MC are two separate entities, or a same disease at occurring at a different spectrum of progression. Freeman et al. for example, reported a case of CC refractory to treatment but later progressed to ulcerative colitis requiring surgical resection.[37] One case series highlighted patients with Crohn's disease whose colonic biopsies showed focal morphology of either LC or CC.[38] Jegadeesan et al. reported a series of six ulcerative colitis patients under complete remission whose surveillance colonoscopy biopsies were consistent with either LC or CC.[39] More recent evidence from a study on the clinicopathological significance of MC in IBD reported that MC may occur either before or after the onset of IBD. It also suggested that MC may be an initial presentation of IBD, especially in older IBD patients.[40]

Active smoker status has been associated with an increased risk for MC.[5] Although there is insufficient evidence to strongly recommend smoking cessation as a means to alter MC disease activity, advice to quit smoking may still be given for its health benefits. Due to the nature of this study however, this was not analysed as there was limited information on subject smoking status.

CONCLUSION

We demonstrated that a significant percentage of cases diagnosed as MC at HUSM did not present with diarrhoea. Therefore, a high clinical suspicion is needed, which requires an awareness of the disease by the clinicians involved. The variety of symptoms MC can present with means that it is very likely that a significant proportion of patients with MC remain undiagnosed. Adequate biopsy samples despite normal colonoscopy findings are important in order to not to miss a diagnosis of MC.

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ORIGINAL ARTICLE

Characteristics of ovarian malignancy in Bali province, Indonesia

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ABSTRACT

Introduction: The aim of this study was to describe the characteristics of ovarian cancer (OC) diagnosed in a tertiary referral centre in Bali, Indonesia, according to several risk factors.

Materials and Methods: This is a descriptive retrospective study using data from the medical records of patients diagnosed with primary OC who underwent surgery at the Department of Obstetrics and Gynecology, Sanglah General Hospital Denpasar, Bali from January 2018 to December 2019.

Results: A total of 94 OC or 19.4% from total gynecologic cancer (484 cases) were diagnosed. The characteristics of the majority of OC were as follows: 1. Socio demography: median age 46.5 years (*interquartile range*: 16.5) and 47.9% (45/94) had low educational level; 2. Hormonal factor: 48.9% (46/94) were multiparous, 59.6% (56/94) were premenopausal, and 97.9% (92/94) had never used oral contraceptive pills; 3. Genetic: all patients did not have a family history of ovarian cancer; 4. Clinical characteristics: 76.6% (72/94) with histologic type of epithelial tumors, 61.7% (58/94) with advanced stage, 74.5% (70/94) with unilateral tumor, and 44.7% (42/94) with mass sized 11-20 cm. In advanced OC, 63.8% (37/58) presented with ascites and omental carcinomatosis, 87.9% (51/58) without liver metastasis; and 5. Surgical outcome: 55.3% (52/94) underwent primary cytoreductive surgery and 78.8% (41/52) had suboptimal surgical outcome.

Conclusions: The characteristics of OC in the study population were different compared with the developed countries and the global population, i.e. the incidence of OC was most common among younger and premenopausal women. The majority of patients with advance OC had suboptimal surgical outcome.

KEYWORDS:
Primary ovarian cancer, developing country, characteristics

INTRODUCTION

In 2018 worldwide? approximately 4.4% of cancer-related mortality in women was attributed to ovarian cancer (OC).[1] Although the prevalence of OC is lower than breast cancer, it is three times deadlier.[2] It has been known that there isappears to be a? geographical variation in the incidence, clinical characteristics, morbidity and mortality rate of OC. In developed countries, the incidence is significantly higher than in developing countries. However, the 5-years survival rate for all stages OC in developed countries has been increasing from 33.6% in 1975 to 44.2% in 2003-2009 and to 48.6% in 2010-2016.[3] The incidence of OC also varies according to age groups and race.[4] It is estimated that 30% of OC occurs in European countries.[5] Among the Asian countries, the highest incidence was found in Singapore, Kazakhstan, and Brunei Darussalam, respectively.[6]

The geographical variation in the incidence, clinical characteristics, morbidity and mortality rate of OC are attributed to the difference in the risk profile of patients, socioeconomic status, and access to the medical care. In countries with higher human development index (HDI), the incidence of OC is also higher but however, the mortality is lower.[6] Understanding the difference in risk profile and clinical characteristics of OC patients can assist in the efforts in prevention, early detection and treatment. Thus, data from specific population or geographical area is needed.

Indonesia is a developing country in the South East Asian region with a total population of over 270 million. The life expectancy at birth for Indonesian female is 73.7 years.[7] Published reports on epidemiologic data of OC among Indonesian women is still lacking. This study is aimed at describing the epidemiology of OC among Indonesian women.

MATERIALS AND METHODS

This is a descriptive, retrospective study involving all cases of OC diagnosed within the period of January 2018 to December 2019 in Sanglah General Hospital. Sanglah General Hospital is a tertiary referral hospital in the capital city of Denpasar, Bali Province, Indonesia, that serves as gynecologic oncology referral centre for Bali and Nusa Tenggara region. The inclusion criteria were all newly diagnosed cases of primary OC proven by official histopathology reports and recorded within the study period. The exclusion criteria were cases with incomplete data. Two cases with incomplete data (CA 125 level and the presence of liver metastasis) were excluded. Data regarding the socio demographics (age, educational

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Table I: Sociodemographic and clinical characteristic of the study population

Characteristics	N	%
Age group		
11-20 years	6	6.4
21-30 years	10	10.6
31-40 years	15	16.0
41-50 years	31	33.0
51-60 years	24	25.5
>60 years	8	8.5
Educational level		
Low	45	47.9
Moderate	43	45.7
High	6	6.4
Occupation		
Unemployed/housewives	39	41.5
Self-employed	35	37.2
Private employee	16	17.0
Medical personnel	2	2.1
Government officer	2	2.1
Histologic type		
Epithelial	72	76.6
Germ cell	18	19.1
Sex cord stromal	4	4.3
Stage		
I	19	20.2
II	17	18.0
III	51	54.4
IV	7	7.4
Bilaterality		
Yes	24	25.5
No	70	74.5
Tumor size		
≤ 10 cm	17	18.1
11-20 cm	42	44.7
21-30 cm	26	27.7
>30 cm	9	9.6
Total	**94**	**100**

Table II: Clinical characteristics of the advanced ovarian cancer

Characteristic	N	%
Histologic type		
Epithelial	44	75.9
Germ cell	11	19.0
Sex cord stromal	3	5.1
Bilaterality		
Yes	20	34.5
Tumor size		
≤ 10 cm	13	22.4
11-20 cm	28	48.3
21-30 cm	13	22.4
>30 cm	4	6.9
Ascites		
Yes	37	63.8
Omental carcinomatosis		
Yes	37	63.8
Liver metastasis		
Yes	7	12.1
CA125 level		
≤500 IU/ml	35	60.3
>500 IU/ml	23	39.7
Total	**58**	**100**

Table III: Critically ill patients' care after primary cytoreduction

Characteristics	N	%
ICU (Intensive Care Unit)		
With ventilator	15	28.8
Without ventilator	18	34.7
HCU (High Care Unit)	7	13.5
Ward	12	23
Total	**52**	**100**

Table IV: Treatment after primary cytoreduction

Characteristics	N	%
Chemotherapy 6 series (Adjuvant)	11	21.2
Immunotherapy	0	0
Radiotherapy	0	0
Second look laparotomy	15	28.8
Palliative setting		
Medically unfit to do second look surgery	9	17.3
Refuse to do second look surgery	7	13.4
Progressive disease	10	19.3
Total	**52**	**100**

level, occupation), hormonal factors (parity, menopausal status, use of oral contraceptive pills), genetic factors (family history of ovarian cancer), clinicopathology (histologic types, stages, laterality, sizes, ascites, omental carcinomatosis, liver metastasis), type of surgery, and surgical outcome were all extracted from the medical records. Information about family history of OC in the first and second degree relatives was obtained from a thorough history taking during the initial visit at the outpatient clinic or confirmed through telephone calls within the during the study period. Surgical outcomes after primary cytoreduction was defined using the criteria from Gynecologic Oncology Group and categorized as optimal if there was no residual mass (R0) or mass <1 cm after cytoreduction and suboptimal if there was residual mass >1 cm after cytoreduction.[8] The presence of ascites, omental carcinomatosis, and liver metastasis was inferred from findings on imaging (ultrasonography or abdominal CT) as well as the intraoperative evaluation by the gynecologic oncology surgeons? and confirmed by the histopathologic evaluation. The minimal volume of ascites that was defined as a significant marker of advanced ovarian cancer was set to be 500 ml. Data were analyzed using SPSS version 24.0.

This study was approved by the Institutional Review Board of Faculty of Medicine, Udayana University/Sanglah General Hospital, Denpasar, Bali, Indonesia (Ethical Clearance No. 1833/UN14.2.2.VII.14/LT/2020).

RESULTS

A total of 484 new cases of gynecologic cancer were diagnosed in our center in 2 years. OC accounted for 19.4% of the total cases (94/484) and all cases were referred cases from satellite hospitals within and outside Bali Province, Indonesia.

Sociodemographic

The median age of patients with OC in our centre was 46.5 years (IQR: 16.5 years). Age group of 41-50 years was the most common in which OC was diagnosed. Majority of the patients in the low socioeconomic status (Table I). Healthcare was accessible to all patients, including the primary health care that were available in every village. However, majority of the patients (76%) felt reluctant to seek advice from the medical professionals in a health care setting.

Hormonal and genetic factors

Median number of parities in our study population was 1.0 (IQR: 3.0). The proportion of nulliparous, primiparous and multiparous women were 36.2% (34/94), 14.9% (14/94) and 48.9% (46/94), respectively. Postmenopausal women only constituted 40.4% (38/94) of the total cases. Only two patients reported the use of oral hormonal contraceptives in the past (2.1%). No patient reported the family history of OC (first- or second-degree relatives).

Clinical characteristics

Abdominal enlargement was the most common symptoms present in this population (55/94 patients, 58.5%), followed by loss of weight (50/94, 53.2%), bloating (30/94, 31.9%), and abdominal pain (21/94, 22.3%).

Epithelial OC was the most common histologic type diagnosed in our center (76.6%). The distribution of epithelial subtype was as follows: 26 cases of serous carcinoma (27.7%), 15 cases of mucinous carcinoma (16.0%), 13 cases of clear cell carcinoma (13.8%), 11 cases of endometrioid carcinoma (11.7%), 5 cases of mixed epithelial tumor (5.3%) and 2 cases of undifferentiated type tumor (2,1%). Among the non-epithelial type, immature teratoma was the most common type (10/94, 10.6%), followed by germ cells tumor (mixed germ cells: 3/94, 3.2%; endodermal sinus or yolk sac tumor 3/94, 3.2%; dysgerminoma: 2/94, 2.1%), and sex cord stromal tumor (adult granulosa cell tumor: 2/94, 2.1%; malignant Sertoli-Leydig cell tumor: 1/94, 1.0%; mixed sex cord stromal cell tumor: 1/94, 1.0%).

Most cases were diagnosed in the advance stage, had unilateral mass, and sized 11-20 cm. Most of all types of

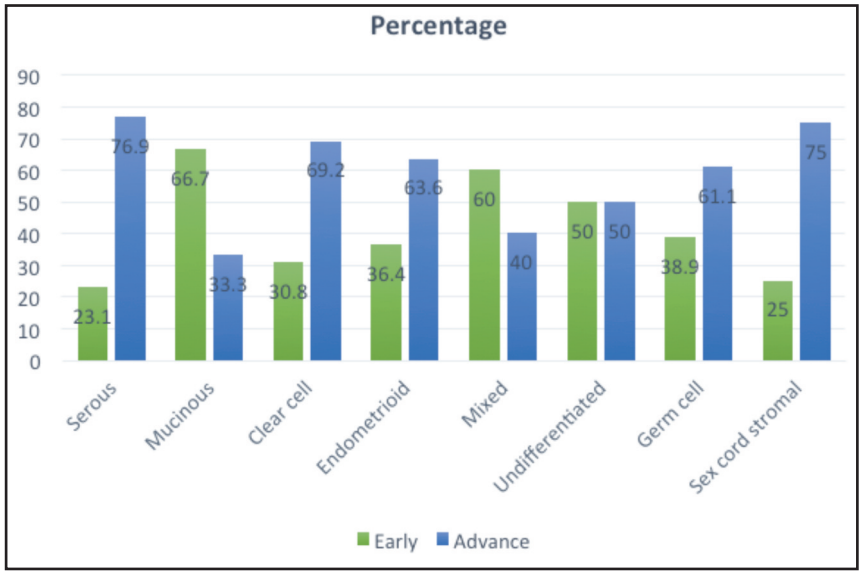

Fig. 1: A repeated CT scan of the neck showing compressed thrombus in the left internal jugular vein (blue arrow) with multi-loculated abscess measuring 2.1 x 1.9 x 2.5 cm (red arrow). Trachea is displaced to the right.

histology were diagnosed in advance stages (Figure 1). The clinical characteristics of advanced OC are summarized in Table II.

A total of 52 cases (55.3%) underwent primary cytoreductive or debulking procedure, while 27 cases (28.7%) underwent complete surgical staging, 8 cases (8.5%) underwent conservative surgical staging, and 7 cases (7.4%) underwent tumour biopsy. Among the cases that underwent primary cytoreduction, 8 cases (15.4%) were in stage IIB, 2 cases (3.8%) in stage IIIB, 36 cases (69.2%) in stage IIIC, and 6 cases (11.5%) in stage IVB. Among those who underwent primary cytoreductive, 41 cases (78.8%) had suboptimal outcome.

Post-operative care of critically ill patients and treatment after primary cytoreductive are as table III and table IV.

Transfusion facilities in our hospital are as part of Indonesia Red Cross Organization. This institution could facilities transfusion for emergency situation in 15-30 minutes.

Seven patients underwent laparotomy biopsy, three patients were given neoadjuvant chemotherapy for three series, followed by interval debulking. Due to medically unfit condition four patients underwent symptomatic palliative treatment.

For suboptimal cases after primary cytoreductive were given three cycle of chemotherapy and performed evaluation. Patients who were eligible to undergo operation, were continued with second look laparotomy. In the case of progressive disease, symptom palliative treatment was done, whether medical or operative, based on primary cause of the symptoms.

DISCUSSION

In this study, OC contributed to 19.4% of the total new cases of gynecologic cancer diagnosed within the two year period. During the study period, OC contributed to 17.0% of total new cases of gynecologic cancer in Indonesia.[9] It was the second commonest type of gynecologic cancer after cervical cancer (68.4%) but much more prevalent than endometrial cancer (8.5%), gestational trophoblastic neoplasia (3.9%), vulvar cancer (1.5%) and vaginal cancer (0.6%). This finding differs from the epidemiologic pattern seen in developed countries. For example, in the United States of America (USA), OC was more common than cervical cancer. There were 24.469 new cases of OC in 2018, as compared to 14.046 new cases of OC.[10] The higher incidence of OC in developed countries may be attributed to higher socioeconomic level, and thus, better access to healthcare services including early detection of.[6]

OC was commonly diagnosed in the age group of 41-50 years in our study population. Modi et al reported the same findings in India, where 46.2% of OC was diagnosed in the age group of 41-50 years.[11] However, data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry reported that the mean age of OC patients in USA during 2004-2014 was 53.5-64.7 years.[12,13] Global data shows that the median age at the time of diagnosis for OC is 50-79 years.[1] Thus, OC was diagnosed at a relatively younger age in our study population. The similar figures were reported by Modi et al in India might strengthen the fact that OC tends to occur in younger age groups in developing countries.

More than 40% of patients in our study population were in the low socioeconomic level. Indonesia is a developing country with moderate human development index (HDI) level. There was a positive and significant correlation between HDI level and the incidence of OC.6 However, HDI level did not correlate with the mortality due to OC. Alberg et

al.,[14] reported that there was a negative association between the educational level and the risk of OC. The lower socioeconomic level also correlated with more severe morbidity of OC.[15]

The peak incidence of ovarian cancer among Caucasian women occurs in the postmenopausal age.[1] However, among the Asian women OC tends to exhibit a different trend. Shen et al reported that among Chinese women, the prevalence of OC in the premenopausal group was 46%.[16] In our study, the prevalence of OC in the premenopausal group was 59.6%. This? number was relatively higher than the Caucasian women. The reason for the difference may be due to the racial difference in the genetic susceptibility for OC. Han et al reported that genetic polymorphism (rs6983267 in chromosome 8q24) among Chinese women increases the risk for OC in the premenopausal age group (adjusted OR=1.62, 95% CI:1.18-2.23, P = 0.003).[17]

More than 20% of OC are hereditary in origin.[18] Approximately 65-85% cases of hereditary OCare associated with BRCA mutation. Mutation of other tumor suppressors or oncogenes are also involved in the pathogenesis of OC, such as mutation of TP53, BARD1, CHEK2, RAD51 dan PALB2. Lynch syndrome contributes to 10-15% of hereditary OC.[19] In this study, no patients reported a family history of OC. Genetic testing for OC risk is still a very rare option offered in this population. In fact, information about genetic testing is seldomly discussed by the healthcare professionals. However, some physicians will offer genetic testing if the patients present with a strong family history of ovarian or breast cancer. Studies evaluating the epidemiology of genetic susceptibility for OC among Indonesian women are also lacking.

Epithelial OC was the most common histologic type in this study, followed by germ cell tumour and sex cord stromal tumour, respectively. Patel et al[20] report the same distribution pattern of OC in India. Serous carcinoma was the most common type of epithelial OC in this study. This is in accordance to the study reported by Modi et al[11], Gupta et al[21], and Yogambal et al[22] in India. Data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry in USA during 2004-2014 reported that high-grade serous carcinoma was the commonest type of epithelial ovarian cancer (63.4%), followed by endometrioid carcinoma (9.9%), clear cell carcinoma (9.6%), mucinous carcinoma (9.4%), carcinosarcoma (4.9%), low-grade serous carcinoma (2.5%), and malignant Brenner tumors (0.3%).[12] Although there is a difference in the risk profile of OC, the distribution of histologic type seems to be similar between our population and the global population.

In this study, the more than half of epithelial OC were diagnosed at the advance stage. The same observation was also found for germ cell and sex cord stromal ovarian tumour. Among the epithelial OC diagnosed in our study, serous, clear cell, and endometrioid type of OC were diagnosed in advance stage while mucinous carcinoma was diagnosed in the early stages. Data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry in 2004-2014 also reported the same pattern of distribution.[12] Recent data from the 2018 National Center for Health Statistics registry in the USA reported that mucinous carcinoma tend to be diagnosed in the advance stages while germ cell and sex cord stromal ovarian tumour were diagnosed at early stage.[4] Advance stage at diagnosis is associated with late recognition of OC. More importantly, there is often a long waiting time before primary treatment (months, rather than weeks), which might be too long for this kind of tumours. In developing countries, other factors that may also contribute to the more advance stage at diagnosis are lower socioeconomic levels.

As for the advance stage OC diagnosed in this study, majority of cases were epithelial type, with unilateral tumor, ascites and omental carcinomatosis. The median size of tumour at presentation was 20 cm (IQR:15.0 cm). Only a small portion of cases present with liver metastasis or CA125 level above 500 IU/ml. Chesnais et al.,[23] reported in their study that the proportion of advance OC patients who presented with ascites was 60.7%, while those who presented with omental carcinomatosis was 40.5% and liver metastasis was 24.3%. Many studies have proposed that the presence of ascites, omental carcinomatosis, liver metastasis and high level of CA125 (>500 IU/mL) can predict the surgical outcomes for advanced OC.[23-28] It was reported that advanced OC with ascites, omental carcinomatosis, liver metastasis and high level of CA125 tend to have suboptimal outcome after cytoreductive surgery.[23,24,28] In this study, the proportion of advanced OC patients who presented with ascites and omental carcinomatosis was quite high (>50%). However, hospital related factors such as availability of adequately trained staff, operating theatres and ICU facilities as well as waiting lists were also the important factors determining the outcomes of patients. In our hospital, the waiting list can be as long as one month.

Majority of cases in our study underwent primary cytoreductive surgery (55.3%), while a small proportion underwent conservative surgical staging (8.5%). The majority of those who underwent cytoreductive surgery had suboptimal outcome (78.8%). A lower percentage of suboptimal outcome was reported in a study by Chesnais et al23 in France (62.3%) and Rosendahl et al[29] in Denmark (50%). Suboptimal outcome is correlated with the larger extend of tumour spreading.[23] It has been widely accepted that residual mass after cytoreductive surgery is one of the most important prognostic factor for OC.[30] An increase in the proportion of patients who achieved optimal cytoreduction as minimal as 10% was a significant and independent predictor for an increase in medial survival for 1.8 months (95% CI 0.6-3.0, p=0.004).[8] Clinical predictors for surgical outcome of advanced OC would be beneficial in developing countries where costly imaging modalities (e.g., CT, PET scan) or laparoscopy are not widely available.

Important achievements have been made in terms of targeted therapies in the management of OC, including in cases after debulking surgery. In Indonesia, addition of targeted therapy is an option for the patient. Moreover, the treatment is not yet covered by national insurance program and to benefit from this targeted therapy, we should continue our efforts to identify and testing patients who are may potentially benefit from targeted therapy.

We are aware that tertiary hospitals like our hospital have a highly selected population of patients and their characteristics may differ considerably from the Indonesian national databases. However national data of OC that was based on population-based study is currently unavailable.

CONCLUSION

It is known that disease patterns like gynaecological cancers appear earlier in developing and under-developed countries because of the lack of screening tools, residing far from health facilities, transportation difficulties and financial strains in contrast to patients from the developed world.

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ORIGINAL ARTICLE

Development and validation of pelvic floor muscles exercise intervention for urinary incontinence among pregnant women

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ABSTRACT

Introduction: The prevalence of urinary incontinence among pregnant women is high in Malaysia. However, healthcare providers appear to pay little attention to it along with a limited local intervention that addresses the continence health during pregnancy. This study aims to develop and validate intervention with pelvic floor muscle exercise (PFME) for pregnant women.

Materials And Methods: The development of PFME intervention was guided by the Medical Research Council Framework for Developing and Evaluating Complex Intervention (MRC Framework). This involved four phases: identification of current research evidence, expert opinion, validation via focus group discussions with physiotherapists and pregnant women, and piloting the intervention using a single group pre-post design among 30 pregnant women at Maternity Hospital Kuala Lumpur to assess the feasibility of the intervention by evaluating changes in knowledge and attitude. The qualitative approach was used to analyse the first three phases, while non-parametric methods were used to analyse the pilot pre-post test results.

Results: Based on research evidence and guidelines found during the literature review, a PFME intervention was developed using a new paradigm incorporating two theories, the Health Belief Model and Motivational Interviewing that have been shown to be important in continence promotion and exercise adherence. The contribution of the panel of experts in refining the intervention to meet the local context, endorses the achievement of the intervention's content validity. While, the focus group discussion with pregnant women and physiotherapists revealed the face-validity of the intervention. The findings of the pilot pre-testing showed that PFME knowledge ($p<0.001$) and attitude ($p=0.011$) improved significantly immediately following the intervention.

Conclusions: Evidently, this is a pioneer study that illustrates the development of a Malaysian context-adapting PFME intervention on the basis of recommended steps using the MRC Framework. Incorporating a theory-based and rigorous validation approach into the development of the PFME intervention brought novel perspectives to the intervention. Given the promising preliminary results of the pre-testing pilot study, the PFME intervention could be implemented in the planned randomised control trial to validate the robustness of the results.

KEYWORDS:
Urinary incontinence, Pelvic floor muscle exercise, Intervention, Pregnant women

INTRODUCTION

Urinary incontinence (UI) is defined as involuntary or uncontrolled urinary leakage, is the most common bladder problem diagnosed in women.[1] Women are at greater risk of developing UI during the pregnancy.[2,3] The overall prevalence rate of UI during pregnancy revealed to be between 40% and 65% in the population of European, Asian and United States of America, regardless of parity and gestational age.[2] Onset of UI during pregnancy, tends to become an ongoing burden for most women, which may have an impact on all aspects of life of a woman and her wellbeing from the physical, social and psychological aspects.[2-4] It may be considered to be a silent maternal problem as many pregnant women perceive UI as a normal physiological change during pregnancy and fail to report it to their obstetricians or midwives as a potential health problem.[5-7]

The physiological and anatomic changes that occur during pregnancy with additional risk factors such as maternal age, multiparity, pre-pregnancy UI, overweight and obesity, constipation, smoking and other risk factors associated with childbirth may result in the weakening of pelvic floor muscles.[3,4,8-10] These changes may disrupt the normal mechanism of continence and increase the risk of UI during pregnancy.[11] UI, however is readily preventable and treatable where pelvic floor muscle exercise (PFME) or training in early pregnancy offers an opportunity to control the UI that can mitigate the need for more invasive intervention in the future.[12,13]

In Malaysia, current public health initiatives or recommendations place less emphasis on the prevention of UI and control it specifically during pregnancy, despite the

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prevalence of UI among pregnant women increases significantly between 19% and 84.4%.[5,7,14] Simultaneously, there are limited UI screenings during antenatal visits and not all women are informed about the implication of UI during pregnancy.[5,7,14,15] This may be due to lack of awareness or empathy among healthcare providers along with a limited local intervention that addresses the continence health. Regardless of the availability of Antenatal and Postnatal Exercise Manual that informs PFME, the information regarding PFME in this manual is very brief with minimal focus on the details associated with PFME related to UI.[16]

There is a need for structural intervention that focuses on PFME in prevention and control of UI that not only guides the local healthcare provider to educate antenatal women, but also aid the pregnant women to make informed decisions regarding their continence health.[5,7,14,16] A randomized controlled trial (RCT) was carried out to evaluate the effectiveness of the PFME intervention in terms of improving knowledge, attitude, practice and self-efficacy of PFME and continence status amongst the pregnant women. This study reports the development of PFME intervention on the basis of recommended steps using the Medical Research Council Framework for Developing and Evaluating Complex Intervention (MRC Framework).[17]

MATERIALS AND METHODS

This study is part of main RCT study, formal ethical approval for the main RCT was obtained from the Malaysia Ministry of Health Medical Research Ethics Committee (MREC) (NMRR-16-2029-28782) and the Universiti Putra Malaysia Ethic Committee for Research involving Human Subject (FPSK [MREC 17] P015).

The development of the PFME intervention was carried out in four phases which were guided by the MRC Framework.

Phase 1: Identifying the Evidence

The first phase was the integration of evidence and knowledge to draft the intervention through a literature review and clinical experience of the primary researcher in women's health and continence. In identifying the UI related antenatal PFME intervention components, theories, and relevant clinical guideline, a search was performed in several online databases: namely MedlinePlus, ScienceDirect, PubMed, Cumulative Index to Nursing, and Allied Health Literature (CINAHL), Scopus, Physiotherapy Evidence Database (PEDro) and Cochrane Central Register of Controlled Trials (CENTRAL).

The search was conducted from January of 2010 till January of 2017 with an extended search in 2019. To avoid the search being too restrictive, general search terms were used which included other synonyms, spelling variants and acronyms: ("pelvic floor muscle" or "pelvic floor" or "Kegel") AND ("exercise" or "training") AND ("pregnant women" or "pregnancy" or "antenatal" or "expectant mother" or maternal or gravida or gestation) AND (urinary incontinence or urinary leakage).

Phase 2: Expert Opinion

In the second phase, the opinions of experts were used to review and validate the initial draft of PFME intervention. Three senior consultants from UPM's Faculty of Medicine and Health Sciences, each with a speciality in Family Medicine, Public Health, Psychology, and one senior physiotherapist from Hospital Kuala Lumpur (HKL) formed a panel of experts which reviewed the initial draft of PFME intervention and provided qualitative suggestions and comments on a number of aspects such as the accuracy of the content, organisation of information, application of the theory and relevance of the intervention and comprehensibility. Two of the experts had experience in clinical counselling techniques. In response to the comments and suggestions by the experts, the content of the intervention was revised and modified to meet the Malaysian context.

Phase 3: Focus Group Discussion

The third phase involved validation of the PFME intervention through focus group discussion (FGD) to elicit and obtain feedback on the initial draft of PFME intervention. Two FGDs were conducted to evoke discussion among pregnant women and physiotherapists to gather more in-depth information, feedback and suggestions about PFME intervention following a "mock" PFME intervention that demonstrated the key elements of the intervention. In addition, the FGD with physiotherapists was used to explore the current practices and needs of the PFME intervention. The focus group participants, pregnant women, and physiotherapists were recruited using purposive sampling from the antenatal clinic, Maternity Hospital Kuala Lumpur (MHKL) and Physiotherapy Department, HKL respectively.

No specific inclusion criteria were applied in selecting participants as long as they voluntarily agreed to participate. Written consent was obtained from participants and separate demographic data was collected from participants in both groups. These FGDs were conducted and led by the primary researcher and two facilitators, one of whom documented the discussion and another one of whom tape-recorded the group discussion. A semi-structured, open-ended questions were used to facilitate discussion. Both FGDs took approximately an hour and they were audiotaped and transcribed. The results of each focus group were then summarized and these findings were used to revise the development of PFME intervention.

Phase 4: Pilot Pre-Testing

In the final phase, once the validation was completed, a pilot study was conducted using a single-group pre-test/post-test design among 30 pregnant women in MHKL using a convenience sampling method. The inclusion criteria of the study: pregnant women with a singleton pregnancy without complications or contraindications to practice the physical activity and has given consent to participate in this study. This pilot study aimed to assess the feasibility of the intervention by gauging the potential immediate effect of the PFME intervention in terms of changes in knowledge and attitude.

The PFME intervention was delivered in a single session that focused predominantly on the educational session of the PFME intervention. The participants were assessed at baseline

and immediately post-intervention using a validated and standardised questionnaire.[14] The percentage of score of each 18 knowledge items with correct answers and 8 attitude items with positive response were computed. McNemar's test was used to estimate the significant difference in proportion of correct knowledge and positive attitude pre-test and post-test. The Wilcoxon matched-pairs signed-rank test was subsequently conducted to analyse changes in percentage score observed between pre-test and post-test. All the analysis performed using Statistical Package for Social Sciences (SPSS) Version 23 and a p-value of less than 0.05 were considered to be statistically significant.

RESULTS

Summary of findings from the literature review

Nine intervention studies focused on antenatal PFME linked to UI prevention and treatment were discovered through a literature search.[18-26] Despite the fact that existing PFME interventions have shown demonstrable effectiveness, the components that contributed to the observed effects of interventions in terms of improving continence status, behaviour or adherence were not clear. Notably, in each of the existing antenatal PFME studies, there are many variations in the intervention components with a lack of theoretical clarification. The key intervention component described in the existing antenatal PFME study includes strategies related to the transmission of UI-related PFME information or knowledge, the prescription of adequate exercise dosage (frequency, intensity, duration), the teaching of correct pelvic floor muscle contraction and adherence support to prescribed intervention.[18-26]

There is, however, a lack of strategy targeting on healthy lifestyle behaviour or healthy bladder habits in existing PFME intervention. This is an important strategy for UI prevention and control during pregnancy and postpartum according to recommendations based on systematic review or expert consensus and international guidelines such as the European Association of Urology guideline, National Institute for Health and Clinical Excellence guideline, NICE, and the Continence Foundation of Australia pregnancy guideline on healthy bladder and bowel habits and Dutch Clinical practice guideline.[3,8,27-32] Mostly all the intervention strategies were conveyed using traditional lecture-based approach or didactic approach which is a clinician centred approach with frequent supervision of practical sessions.

Although the effectiveness of PFME intervention depends on the component of supervised training, few studies have shown that poor compliance with such supervised clinical intervention is responsible for non-significant results in reducing UI prevalence and UI severity.[18,19,24] In other words, clinical based supervised training may be perceived to be too intensive with frequent follow-up, costly and time-consuming not only for pregnant women, but also for health care providers.[18]

Despite this, three studies have shown that a combination of both short-term supervised pelvic floor muscles training and non-supervised home-based as well as provision of adequate information and skills training on PFME was likely to be more effective, not only in the prevention and treatment of UI, but also in behavioural changes related to PFME.[21,25,26] These approaches seem to demand less time, incur fewer costs, and possibly offer more motivation to adhere with PFME in real clinical practice.

Development of PFME intervention

All the findings and gaps identified from the literature review and clinical guidelines together with clinical experience were translated into the development of a PFME intervention. The development of PFME intervention involved developing the intervention manual which included an information booklet for pregnant women as a take-home guide. The PFME intervention was developed on the basis of a new paradigm incorporating two theories, the Health Belief Model (HBM) and Motivational Interviewing (MI), as proposed by McClurg et al.[33] HBM tends to be widely used in continence promotion primarily for preventive health behaviour and public programmes, while MI is the unexposed theory that could benefits in optimising commitment or adherence to intervention.[33] The content of the PFME intervention was guided by HBM that uses MI techniques as a tool for delivering information.

The PFME intervention content was structured on the basis of six HBM constructs that were proposed as motivating factors to commence and adhere to PFME.[34,35] In this context, pregnant women are more likely to be motivated to practice PFME if they believe that they are susceptible to incontinence (perceived susceptibility), that severity of present incontinence is likely to worsen, or incontinence has a negative impact on their health (perceived severity) and that PFME is effective in improving continence status (perceived benefit). Moreover, pregnant women would be further motivated to practice PFME if they had experience of the actual practice of PFME by overcoming barriers to adherence (perceived barrier), feelings of competence in performing PFME correctly (perceived self-efficacy), and identifying appropriate cues or triggers in taking action in practicing PFME (cue to action).[34,35]

With regards to the method of information delivery, the Elicit-Provide-Elicit ("Ask-tell-ask") approach of motivational interviewing was utilized, using five "core skills" to elicit change talk which consisted of asking open-ended questions, affirming, reflecting, summarizing, and informing and advising.[36] By employing this approach, the educator is immediately able to elicit the person's understanding and need for information, then provides information or feedback with permission.[37] Following that, questions about what this knowledge meant to clients and what else they needed were elicited. This client-centred approach may allow for a conversation for strengthening a person's motivation by fostering the individual's intrinsic motivation that addresses an individual's desire, opinions and feeling to modify behavioural changes.[36,37]

The structure of PFME intervention was designed, according to the Hay Smith et al., recommendations which include education session, message reminders, and booster sessions.[38] All of the intervention schedules were planned to coincide with the schedule of antenatal clinical visits, so that no

Table I: Summary of Findings from the Focus Group Discussion with Physiotherapists and Pregnant Women

Focus Group Discussion with Physiotherapists	
Topic	**Physiotherapist's Responses and Feedback**
Current practice	• Antenatal classes are held on every Tuesday • The class comprises midwife, physiotherapist and audiologist sessions focusing on preparation for labour, postnatal care, and early parenthood. • One-hour physiotherapy session includes a talk and practical session that specifically targets breathing exercise, relaxation during labour, back exercises, circulatory exercise and kegel exercise.
Needs of intervention	• We felt good to have a standard manual so that everyone communicates in the same language and using the same terms. • This manual ensured all the important information are shared to all the women. • Currently, we conduct the class in our own way and the information that is shared in the class may vary.
Intervention content	• Very informative and simple to understand, referring to the manual and information booklet. • Very systematic and the flow of content continuously links. • Comprehensive patient information booklets available in both Malay and English.
Intervention delivery and Implementation	• Feasible to implement, as it is group intervention. • Time constraint if it is an individual consultation in a busy clinical setting. • May need to assess the practicality of text messaging in current clinical practise.
Improvement or suggestion	• We require training for physiotherapists on how to use the therapist manual.

Focus Group Discussion with Pregnant Women	
Topic	**Pregnant Women's Response and Feedback**
Knowledge on urinary incontinence	• I felt it normal to have urinary incontinence during pregnancy. • I used to go to toilet very often during pregnancy "it is normal" during pregnancy. • I felt the baby pressing on the bladder. • I am not really bothered about it because I got it during every pregnancy and it subsided after delivery.
Knowledge on PFME	• Kegel exercise and squeeze around private area like stopping the urine. • It is like stop and start the urine. • I just learned the exercise during antenatal class "squeeze around private area while holding the breath". • I learned the exercise from a lady masseur during confinement "postnatal traditional massage".
Perceived susceptibility and severity of urinary incontinence	• I had urinary leakage in the first pregnancy but it doesn't bother me and disappeared after childbirth. • I only have it when I have a bad cough • I feel it is normal to have urinary leakage • It is normal to wee often during pregnancy • Growing baby presses on the bladder so its normal during pregnancy
Perceived benefit of PFME	• Yes, it is important because the Malay lady masseur told me to do this exercise to prevent womb from coming down or dropping. • To keep the private area stronger for the next pregnancy.
Perceived confident in performing PFME	• I know how to do but don't know whether I am doing the exercise correctly. • Confident level less than 5 out of 10.
Perceived barrier to adhere to PFME	• I never do it after my confinement. • I only do it when I remember. • I do it when urinating, stop and start the urine. • I more concern on abdominal exercise after delivery
Overview of the intervention, understandability and suggestion	• I am delighted to join this excellent programme. • I like the way we discuss and exchange opinions. • Very informative programme and the explanation is very simple and easy to understand. • I gained new knowledge about exercise and urinary leakage. • I never initially believed this muscle to be so important. I learned a lot. • I had urinary leakage in my first pregnancy, but it didn't bother me and disappeared after childbirth. Now I know the importance of doing the exercise • Good! Both Malay and English version brochures are available and easy to visualize and understand • We sincerely hope this program will be provided to all pregnant women

Table II: Participants' Correct Responses on Knowledge Based Questions

Knowledge Items	Participant's Correct Response		
	Pre-test	Post-test	p-value
	n (%)	n (%)	
Muscles involved in pelvic floor muscle exercises are situated at pubic region.	21 (70)	30 (100)	0.004*
Pelvic floor muscle exercises involve muscles at anal region.	13 (43.3)	30 (100)	<0.001*
Vagina muscles are not involved in the pelvic floor muscle exercises.	12 (40)	27 (90)	<0.001*
Muscles involved in pelvic floor muscle exercises are known as pelvic floor muscles.	13 (43.3)	30 (100)	<0.001*
Pelvic floor muscles are important in controlling urinary bladder function.	13 (43.3)	30 (100)	<0.001*
Pelvic floor muscles are not involved in controlling the anus.	5 (1.7)	25 (83.3)	<0.001*
Pelvic floor muscles are not involved in tightening the vagina	8 (26.7)	25 (83.3)	<0.001*
Pelvic floor muscles have a function in the sexual relationship between husband and wife.	12 (40)	16 (53.3)	0.481*
Buttock muscles may be tightened by performing pelvic floor exercises.	17 (56.7)	30 (100)	<0.001*
Pelvic floor muscle exercises may prevent urinary incontinence during laughing, sneezing or lifting weight.	7 (23.3)	23 (76.7)	<0.001*
Pelvic floor muscle exercises may also prevent or treat pelvic organ prolapse such as bladder prolapse.	13 (43.3)	29 (96.7)	0.001*
Pelvic floor muscle exercises may be done at anytime.	19 (63.3)	30 (100)	<0.001*
Perform pelvic floor muscle exercises can be done while holding the breath.	3 (10)	28 (93.3)	<0.001*
Pelvic floor muscle exercises involve squeezing inward in the vagina and anus.	17 (56.7)	30 (100)	<0.001*
Pelvic floor muscle exercises may be done during performing daily routine activities such as cooking and landing.	11(36.7)	30 (100)	<0.001*
Muscles involved in the pelvic floor muscle exercises should be contracted for 6 - 8 seconds before being released	14 (46.7)	30 (100)	<0.001*
Pelvic floor muscles should be contracted for 8 - 12 times in a row each time when performing the pelvic floor muscles exercise.	9 (30)	28 (93.3)	<0.001*
Pelvic floor muscle exercises should be done at least 3 times a day which are in the morning, afternoon and night.	5 (16.7)	29 (96.7)	<0.001*
Percentage of correct answers	38.4	92.6	<0.001‡

*McNemar's Test; ‡Wilcoxon Signed Rank Test; n (%) = number of participants (percentage); p-value<0.05 is significant

Table III: Participants' Positive Responses on Attitude Based Questions

Attitude Items	Participant's Positive Response		
	Pre-test	Post-test	p-value
	n (%)	n (%)	
Pelvic floor muscle exercises should be done by all females, especially pregnant women and postnatal women, regardless whether they have any urinary leakage symptoms or not.	22 (73.3)	30 (100)	0.008*
I should practice pelvic floor muscle exercises to prevent or treat urinary leakage.	23 (76.7)	30 (100)	0.016*
I should practice pelvic floor muscle exercises to prevent pelvic organ prolapse such as bladder prolapse.	26 (86.7)	30 (100)	0.125*
I feel that pelvic floor muscle exercises are boring.	22 (73.3)	30 (100)	0.008*
I believe that pelvic floor muscle exercises should be taught to all antenatal mothers at the antenatal clinic.	21 (70)	29 (96.7)	0.008*
I support those who want to perform pelvic floor muscle exercises.	24 (80)	29 (96.7)	0.125*
I believe that pelvic floor muscle exercises can increase sexual satisfaction.	21 (70)	29 (96.7)	0.008*
I will make the effort to search for information on pelvic floor muscle exercises.	23 (76.7)	29 (96,7)	0.031*
Percentage of positive responses	75.8%	98.4%	0.011‡

*McNemar's Test; ‡Wilcoxon Signed Rank Test; n (%) = number of participants (percentage); p-value<0.05 is significant

additional clinical attendance was necessary for pregnant women when participating in the study. As the first eight weeks of PFME is crucial for the prevention and reduction of UI symptom, the first eight weeks of the intervention were designed to deliver the main education session at one appointment.[12] This was followed by weekly exercise reminders and one booster session to keep motivating pregnant women to practice PFME. In addition, two booster sessions were added during routine antenatal clinical visits in the early third trimester and late third trimester to maintain the impact of the initial eight-week PFME intervention session.

Expert Opinion

A positive comment on the intervention was provided by all the experts in terms of relevance of the content, organisation of information, application of the theory and comprehensibility. Nevertheless, a few suggestions on the use of MI techniques, wording and terminologies used were given. In response to the experts' comments and suggestions, the content of the intervention was revised and modified to meet the Malaysian context. Following expert review, the information booklet and text messages that were prepared in English were translated into Bahasa Malaysia following a standard forward-backwards translation.

Focus Group Discussion

The detail of FGDs results is presented in Table I. A total of six nulliparous and multiparous pregnant women aged between 25 and 30 years old at 20 to 36 weeks of gestation participated in a FGD that evoked discussion from both experienced and first-time mothers. During the discussion in eliciting the participant's understanding about knowledge, belief, perceived benefit, perceived barrier and self-efficacy of PFME before sharing information during the mock intervention, most of the participants showed low general awareness of all these aspects. Majority of the participants demonstrated less details of prior knowledge of UI and PFME and about the benefit of the exercise. Moreover, only three pregnant women responded that they had some confidence in doing pelvic floor muscle exercises with rating range 4 to 5 out of 10 scale point. Following a mock PFME intervention, all pregnant women in the focus group held a favourable view of the PFME intervention. They also claimed that the information provided during the intervention and in the booklet was easily understood and helpful in increasing awareness of UI and practice of PFME. The participants also indicated that all pregnant women should in future be given this intervention during the antenatal visit.

The FGD, involved five physiotherapists with clinical experience ranging from 2 to 20 years, addressed the need for a standardised and structured PFME intervention. The physiotherapists claimed that the antenatal physiotherapy classes typically focussed on mat-based exercise sessions mainly aimed at breathing exercises and relaxation during labour, back exercises and circulatory exercises. They also highlighted that current antenatal education pertaining to PFME is less comprehensive and the information shared varied according to the education guided by traditional slide-based presentations.

Generally, the participants in the focus group agreed with the content, delivery method, and implementation of the PFME intervention. Despite the concerns of the physiotherapists about the feasibility of a weekly text message reminders, they all agreed that such a technique was crucial in empowering pregnant women to exercise and change their behaviours on a consistent basis. In addition, physiotherapists expressed their desire for training in using the manual. No further alterations were made following FGD with physiotherapists and pregnant women, as there were no contradictory comments on PFME intervention including the manual and information booklet.

Pilot Pre-Testing

A total of 30 healthy pregnant women age 22 to 39 years (mean age 29.7 ± 4.7) between 18 and 22 weeks gestation were included in this pilot pre-testing. The respondents were predominantly Malays (n=29, 96.7%), had completed high school and college/university (n=29, 96.7%), were employed (n=21, 70%), and were non-smokers. Regarding their parity, more than half of the respondents reported being multiparous or women who had given birth once or more times (53.3%). In relation to continence status, ten (33.3%) respondents reported having UI.

The results of the pilot test (shown in Table II and III) indicate that there was a significant improvement in the PFME knowledge, and attitude immediately after the intervention. The scores on the knowledge items ranged from 38.4% correct at baseline to 92.6% at immediate post-intervention ($p<0.001$). The results on the favourable attitude towards PFME ranged from 75.8% at baseline to 98.4% at immediate post-intervention ($p=0.011$).

DISCUSSION

The development process results in pioneering intervention components that incorporate the best available evidence from international trials and clinical guidelines in combination with clinical experience and expert opinions. Integrating clinical experience with expert opinions strengthens the content validity of the PFME intervention. In particular, the participation of local experts ensures that the intervention includes elements that suit the local context and preferences. The findings of FGDs have shown that intervention users/physiotherapists and intervention recipients/pregnant women have acknowledged and accepted the intervention well. These FGDs findings demonstrated the face-validity of the intervention, which is an important criterion for the further implementation of the intervention. The FGD with physiotherapists has also addressed and verified the need for PFME intervention, which further reaffirms the rationale for developing a PFME intervention which indirectly expresses the physiotherapist's desire in providing quality care.

With regards to pilot pre-testing, only the knowledge and attitude of the participants were assessed at post-intervention, as other behavioural change outcomes such as practice and self-efficacy were not reliable at this juncture. Other behaviour changes need time to define the improvements and were accordingly, not assessed. The baseline data illustrate the need for intervention to enhance the awareness of these participants on UI and PFME as less than half of the participants were able to correctly answer each question. The immediate positive effect of PFME intervention on knowledge and attitude is considered to be the most important prerequisite for behavioural change relevant to the practise or adherence to PFME.[33,38] While these findings indicated that the intervention could be viable in the proposed full-scale RCT, the effect of the intervention on other indicators of behavioural and clinical outcomes could not be verified. Therefore, the results from this pre-test pilot should be interpreted and generalised with caution.

The key strength of this research was the use of the evidence-based and rigorous methods to develop the PFME intervention. Beside using a robust method, the intervention schedules are defined on the basis of evidence and also on the basis of practicability that does not impose additional resource burden on healthcare providers and intervention recipients, including time and cost, to carry out and comply with the intervention.

Notwithstanding, there were some inherent limitations in spite of the strengths of this study. Firstly, only a single FGD was performed involving physiotherapists and pregnant women, which does not reflect the view of the target population as a whole. A second limitation related to the pilot testing. Using convenience sampling, the single arm

pre-post design with no control group can theoretically increase the risk of bias. The absence of a control group limits the interpretation of the potential for causal effects. The way the pilot pre-test was conducted in this study does not discuss the practicalities of the recruitment, randomization, fidelity, adherence and completeness of the evaluation which is necessary to inform the planned full-scale RCT study.[39] Moreover, not all sessions of the PFME intervention were introduced during the pilot pre-test due to budgetary, logistical, and time constraints Therefore, all these limitations need to be considered when interpreting the results of the pilot study.

In spite of the limitations, the development of PFME intervention in this study may be considered as an initial step in continence health initiatives in the absence of specific guidelines, manuals, or modules in this field locally. If the intervention is found to be effective in main RCT study, the physiotherapist should be encouraged to use this manual as a guide for educating pregnant women during perinatal care. By using this manual, physiotherapists may enable the quality of care to pregnant women in line with Malaysian efforts to improve maternal health care according to the Millennium Development Goals 5.[40]

CONCLUSION

As far as we know, this is a first study which illustrates the development in the Malaysian context-adapting PFME intervention on the basis of recommended steps using the MRC Framework. This paper describes the development of a PFME intervention based on current available evidence that combines clinical knowledge and clinical expert review with the intervention recipients/pregnant women and users/physiotherapists preference, along with assessment of the preliminary effect of the PFME intervention. Incorporating a theory-based and rigorous validation approach into the development of the PFME intervention brought novel perspectives to the intervention. Given the promising preliminary results of the pre-testing pilot study, the PFME intervention could be implemented in the planned randomised control trial to validate the results' robustness.

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ORIGINAL ARTICLE

Distance vision, near vision and quality of life between preferred emmetropia and residual myopia in monofocal intraocular lens implantation - A Comparative study

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ABSTRACT

Introduction: This study was done to evaluate the visual acuity and quality of life in predicted emmetropia (EM) and predicted residual myopia (RM) patients following phacoemulsification with monofocal intraocular lens implantation.

Materials and Methods: This prospective comparative study was conducted in the ophthalmology clinic of the Universiti Sains Malaysia Hospital, Kelantan, Malaysia. Overall, 139 patients with senile cataract were randomised into EM and RM groups. At three months post-operatively, patients were assessed for distance and near vision, as well as quality of life using a modified VF-14 questionnaire.

Results: Thirty-six patients (64.3%) in the EM group and 30 patients (52.6%) in the RM group (p = 0.209) showed good distance vision (LogMAR 0.3 or better). Fifty patients (87.7%) in the RM group and 27 patients (48.2%) in the EM group gained significantly higher satisfactory near vision (p < 0.05). The quality of life in both groups was good, with a mean modified VF-14 score of 94.5 (SD 2.68) for the EM group and 95.1 (SD 3.19) for the RM group (p = 0.286). Female patients scored significantly higher than males for total activities (p = 0.010) and distance vision-related activities (p = 0.001). The RM group had significantly better patient satisfaction for near vision-related activities compared to the EM group (p = 0.001). In particular, the item 'reading small print' was significantly better in the RM group (p = 0.003).

Conclusion: Patients in the predicted RM group gained more satisfactory near vision than patients in the EM group, with significantly better quality of life for near vision activities.

KEYWORDS:
Quality of life, post-cataract operation, residual myopia, near vision

INTRODUCTION

Cataract is the main cause of preventable blindness worldwide, contributing to 51% of the total incidence.[1] In Malaysia, 58.6% of preventable blindness cases are caused by unoperated cataracts.[2] Currently, there is no effective prevention for cataracts, and the only treatment is to remove the cloudy lens.[3]

Intraocular lens (IOL) implantation is the commonest practice of visual rehabilitation after cataract surgery. Monofocal or fixed focal IOLs have only one focus at distance; thus, the placement of a monofocal IOL requires corrective lenses (spectacles) after surgery for near vision-related tasks. Although no statistical difference was found between multifocal (MFIOL) and monofocal IOL with respect to achieving a post-operative best-corrected visual acuity (BCVA) of 6/6, near vision was often found to be better with MFIOL.[4] However, MFIOL is costly and would be a luxury for most people in poor and developing countries. In the Malaysian set up, monofocal IOL is still more popular than multifocal partly because it is more affordable. The final refractive result depends on the accuracy of biometric data and the appropriate use of IOL power calculations.[5] The target for residual refractive result post-operative slightly varies among ophthalmologist. Some ophthalmologists recommend emmetropia, while others routinely prefer residual myopia up to –1.00 dioptres (D).[6] However, there is still lack of evidence on the impact of these target final refractive result post-operative to the quality of life of the patients.

The post-operative outcome of functional vision is classified according to both objective and subjective findings. Objective parameters include uncorrected visual acuity, contrast sensitivity, glare disability, visual field and colour vision. Subjective parameters are best evaluated through interviews or questionnaires since the domains covering daily activities can be tailored to local populations. Several questionnaires are available for this purpose, such as the Visual Function Index 14 (VF-14)[7,8,9], European Quality of Life 5 Dimensions (EQ-5D) questionnaire,[10] the National Eye Institute Refractive Error Quality of Life Instrument-42 (NEI RQL-42),[11] and the Glasgow Benefit Inventory.[12] VF-14 questionnaire is a self-reported outcome-based questionnaire which was initially designed for cataract patients. However it has now been widely used in glaucoma, retina and corneal diseases. It has been modified to include activities that are more relevant to the local population in other languages.[13,14] This

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questionnaire was translated into Bahasa Malaysia and Malaysian activities such as reading fine print such as Quran, sewing, wood carving and carpentry were added. The modified Malaysian VF-14 questionnaire has been used by previous authors.[15] VF-14 was preferred due to the simple format and easily administered thus increasing patient compliance.

This study was aimed to evaluate the visual acuity and quality of life (QOL) in predicted emmetropia (EM) group and predicted residual myopia (RM) group following phacoemulsification with monofocal IOL using a modified VF-14 questionnaire. The VF-14 is used for the assessment of QOL in post-operative cataract patients. A previous study suggested that VF-14 is a dependable and effective measure of QOL.[16] This study compares EM and RM with QOL as a measure of the functional vision post-phacoemulsification with IOL implantation.

MATERIALS AND METHODS

Patients

A total of 139 patients were selected for this study. Patients were recruited from the eye clinic of the Universiti Sains Malaysia Hospital, Kubang Kerian, Kelantan, Malaysia. Ethical approval was obtained from the Ethical Research Committee of the Universiti Sains Malaysia. Written consent was obtained from the participants. All senile cataract patients undergoing phacoemulsification with monofocal IOL were enrolled in the study. The predictive refractive power of intraocular lens selection was done by simple randomization method. The patients were divided into two groups using closed envelope method. They were given an envelope containing a paper written either Group A or Group B. Group A (predicted emmetropia) were patients that using intraocular lens with predicted refractive power of 0.00 to -0.50 D and Group B (predicted residual myopia) were patients that using IOL with predicted refractive power of -0.51 to -1.00D. At 6 weeks post-operatively, distance and near vision were recorded, and questionnaires were given to evaluate patient QOL.

Clinical evaluation

Patients were subjected to full ophthalmic examinations including anterior segment, intraocular pressure measurement and fundus examination, by either ophthalmologists or medical officers. Patient with any ocular pathology were excluded at pre-operative stage. Biometry was performed by two trained ophthalmic technicians using a Sonomed A2500 contact A-scan (Sonomed, Florida, USA). To reduce bias, multiple axial length measurements were taken, and the most reproducible with the lowest standard deviation was taken as the value. Keratometry was performed using an automated keratometer for horizontal and vertical K values. The average K reading was used in the SRK II formula for IOL calculation.

Surgery

Phacoemulsification was performed using a standardised technique. In brief, a 2.75-mm clear corneal incision was made, followed by capsulorhexis, using the 'divide and conquer' technique and a phacoemulsification system (Infiniti, Alcon Surgical Inc., Forth Worth, Texas, USA). Implantation of a monofocal IOL (AcrySof IQ SN60WF, Alcon Laboratories Inc., Forth Worth, Texas, USA) was performed by three ophthalmologists.

Data collection

Post-operative exclusion criteria included any intra operative or post-operative complications, spherical equivalent differing from predictive refractive power more than + 0.50 D and astigmatism more than -2.00D either pre-existing preoperatively or surgically induced postoperatively. At 10–12 weeks post-operatively, patients were interviewed for demographic data, followed by evaluation for distance vision using a LogMAR chart. Patients with a LogMAR of 0.3 or better were grouped as 'satisfactory distance vision', and those with a LogMAR of less than 0.3 were grouped as 'non-satisfactory distance vision'. Subjective refraction using Red green filter, Jackson Cross Cylinder and Binocular Balancing was performed to obtain the BCVA and spherical equivalence. Near vision was checked using a Jaeger chart. Patients who scored J3 or better were grouped as 'satisfactory near vision,' and those who scored less than J3 were grouped as 'non-satisfactory near vision'.[17]

QOL (modified VF-14 questionnaire)

Post-operative QOL evaluates the perception of the effectiveness of their surgery of patients via the use of a health related QOL questionnaire. This study used a modified Bahasa Malaysia version VF-14 questionnaire which assessed the post-operative satisfaction of the patients with their visual function in three domains: near, intermediate and distance. The questionnaire was modified from English to Malaysian, and some activities relevant to the local population were added. A score was given with a scale of 0 to 100. Scores on all activities that the patients could perform or could not perform were then averaged, yielding an average score between 0 and 4. This average score was then multiplied by 25, resulting in a possible final score ranging from 0 (unable to do all applicable activities due to vision problems) to 100 (able to do all applicable items without difficulties). Patients with a VF-14 score between 95.01 and 100.00 were considered 'satisfied', while those who had a VF-14 score of 95.00 or less were considered 'not satisfied'. For individual items, patients who scored 4 were considered 'satisfied', and those who scored less than 4 were considered 'not satisfied'.

Statistical analysis

The data were analysed using the Statistical Package for Social Sciences version 18.0 (SPSS Inc., Chicago, IL, USA). Statistical analyses were performed using Pearson's chi-squared test for sociodemographic data, and descriptive analysis was used for visual acuity and QOL. The differences between the two groups were analysed using Pearson's chi-squared test, independent t-test and one-way ANOVA with post hoc Tukey test. A p value of < 0.05 was considered statistically significant.

RESULTS

Of the 139 patients, 26 patients were excluded because their post-operative refractive power difference was more than +0.50 D compared to the prediction. No patients had surgically induced astigmatism of more than –2.00 D.

Table I: Distribution of sociodemographic data

	EM		RM		*p-value
	n=56	(%)	n=57	(%)	
Sex					
Male	28	(50.0)	34	(59.6)	0.303
Female	28	(50.0)	23	(40.4)	
Race					
Malay	48	(87.5)	48	(82.5)	0.453
Chinese	7	(12.5)	10	(17.5)	
Education					
Less than primary education	14	(25.0)	17	(29.8)	0.794
Primary school	13	(23.2)	13	(22.8)	
Secondary school	15	(26.8)	11	(19.3)	
Higher education	14	(25.0)	16	(28.1)	
Occupation					
Housewife	21	(37.5)	21	36.8)	0.934
Government servant	4	(7.1)	6	(10.5)	
Self-employed	17	(30.4)	17	(29.8)	
Pensioner	14	(25.0)	13	(22.8)	

EM = Predicted emmetropia, RM = Predicted residual myopia
*Pearson's chi-square test, p-value < 0.05

Table II: Distribution of distance and near vision

	EM (n=56)		RM (n=57)		*p-value
	S n (%)	NS n (%)	S n (%)	NS n (%)	
Distance vision					
LogMAR	36 (64.3)	20 (35.7)	30 (52.6)	27 (47.4)	0.209*
Near vision					
Jaeger chart	27 (48.2)	29 (51.8)	50 (87.7)	7 (12.3)	0.001*

EM = Predicted emmetropia, RM = Predicted residual myopia
S = LogMAR 0.0–0.3; J3 or better
NS = LogMAR worse than 0.3; J worse than J3
*Pearson's chi-squared test, p-value < 0.05

Table III: Comparison of actual and predictive refractive power

	EM Mean (SD)	RM Mean (SD)	Mean differences (95% CI)	*p-value
Actual refractive power (D)	–0.39 (0.31)	–0.78 (0.30)	0.39 (0.28, 0.50)	<0.05
Predictive refractive power (D)	–0.37 (0.11)	–0.69 (0.14)	0.31 (0.26, 0.36)	<0.05

EM: Predicted emmetropia; RM: Predicted residual myopia
*Independent t test, p-value < 0.05

Table IV: The mean VF-14 scores in male and female patients

VF-14 score	Male Mean (SD)	Female Mean (SD)	Mean differences (95% CI)	*p-value
Total	94.2 (3.08)	95.6 (2.60)	–1.42 (–2.50, -035)	0.010
Near vision	91.3 (7.67)	92.7 (6.51)	-1.38 (–4.07, 1.30)	0.310
Intermediate vision	99.6 (1.54)	99.0 (2.30)	–3.47 (–0.14, 1.30)	0.115
Distance vision	91.7 (5.88)	95.2(4.76)	–3.47 (–5.49, –1.47)	0.001

*Independent t test, p-value < 0.05

Table V: Patients' satisfaction for near, intermediate, and distant vision and overall satisfaction using VF-14 Questionnaire

	EM (n=56)		RM (n=57)		*p-value
	S n (%)	NS n (%)	S n (%)	NS n (%)	
Overall	28 (50.0)	28 (50.0)	30 (52.6)	27 (47.4)	0.780*
Near	12 (21.4)	44 (78.6)	29 (50.9)	28 (49.1)	0.001*
Reading small print (Font 8–9)	14 (25.0)	42 (75.0)	30 (52.6)	27 (47.4)	0.003*
Reading small print (Font 10–12)	28 (50.0)	28 (50.0)	37 (64.9)	20 (35.1)	0.109*
Reading small print (Font > 14)	54 (96.4)	2 (3.6)	54 (94.7)	3 (5.3)	1.000**
Writing	37 (69.8)	16 (30.2)	44 (78.6)	12 (21.4)	0.295*
Intermediate	56 (89.3)	6 (10.7)	51 (89.5)	6 (10.5)	0.974*
Recognizing faces	54 (96.4)	2 (3.6)	55 (96.5)	2 (3.5)	1.00*
Climbing stairs	52 (50)	28 (92.9)	56 (98.2)	1 (1.8)	0.26*
Sewing, knitting	46 (92.0)	4 (8.0)	52 (94.5)	3 (5.5)	0.706*
Recognizing money	54 (96.4)	2 (3.6)	52 (91.2)	5 (8.8)	0.438*
Cooking	52 (92.9)	4 (7.1)	56 (98.2)	1 (1.8)	0.164*
Distance	28 (50.0)	28 (50.0)	24 (42.1)	33 (57.9)	0.400*
Reading signboard	34 (60.7)	22 (39.3)	26 (45.0)	31 (54.4)	0.108*
Gardening	46 (93.9)	3 (6.1)	53 (94.6)	3 (5.4)	1.00*
Watching TV	48 (95.7)	8 (14.3)	50 (87.7)	7 (12.3)	0.753*
Driving (day)	19 (65.5)	10 (34.5)	22 (68.8)	10 (31.2)	0.788*
Driving (night)	1 (34.4)	28 (96.0)	4 (12.5)	28 (87.5)	0.357*

EM: Predicted emmetropia; RM: Predicted residual myopia
S: satisfactory; NS: non-satisfactory
*Pearson's chi-squared test, p value < 0.05
**Fisher's Exact test, p value < 0.05

Demographic data
Sex, race, education level and type of occupation among the EM and LM groups were compared, and no significant differences were found (Table I).

Distance and near vision
Out of 113 patients, 7 patients (12.5%) from the EM group obtained a LogMAR of 0.0, while no patient from the RM group obtained a LogMAR of 0.0 (Table II). Thirty-six patients (64.3%) in the EM group and 30 patients (52.6%) in the RM group obtained a LogMAR of 0.0–0.3 (p = 0.209). However, 50 patients (87.7%) from the RM group gained satisfactory near vision, compared to only 27 patients (48.2%) from the EM group (p < 0.05).

Predictive and residual refractive power
Table III shows the comparison of predictive and residual refractive power between the EM and LM groups. Predictive and residual post op is lower in RM compared to EM group. This shows that the 2 groups were significantly different, a fact achieved by the randomisation process. Therefore, the 2 group would be valid for the subsequent evaluation of QOL questionnaire. The two predicted refractive power groups were significantly distinct by the randomisation process. The mean actual refractive power for the EM group was –0.39 D (SD 0.31), which was lower than that of the RM group (–0.78 D, SD 0.30; p < 0.05).

QOL
The VF-14 scores among the EM and RM groups ranged from 86.1 to 100.0, with a mean score of 94.8 (SD 2.95), skewed toward the higher score chart. Only five patients (4.4%) scored less than 90.01. At least 50% of the patients from each group scored more than 95.00. The mean VF-14 score in the EM group was 94.5 (SD 2.68), while the mean VF-14 score in the RM group was 95.1 (SD 3.19), a difference which was not statistically significant (p = 0.286). Female patients scored significantly higher than males for total activities (p = 0.010) and distance vision-related activities (p = 0.001), as shown in Table IV.

Patient's vision satisfaction
Comparisons between the EM and RM groups for near, intermediate, distance and overall vision satisfaction were evaluated using the VF-14 questionnaire, as demonstrated in Table V. The RM group had better patient satisfaction in near vision-related activities than the EM group (p = 0.001). In particular, the item 'reading small print (font size 8–9)' was better in the RM group (p = 0.003). The comparison between intermediate, distance and overall vision activities was not significantly different (p = 0.974, p = 0.400 and p = 0.780, respectively).

DISCUSSION

Our study indicated that a significant numbers of RM patients gained satisfactory near vision following monofocal IOL implantation, which was translated into significantly better QOL in near vision-related activities on the VF-14 questionnaire, especially regarding reading small print (font size 8–9). This finding is comparable with a previous study, which also showed good vision in cases of mild myopia following cataract surgery.[18] Previous published reports regarding post-operative spectacles dependence also suggested that patients with RM can be independent from wearing glasses.[19]

The ability to have good near vision was very important in our cohort of patients. Approximately 85% of patients were elderly Malay Muslims who are enthusiasts in learning and reading the Quran daily. In this social setting, a rural area in northeast Malaysia, elderly people live with their children, and most of their needs are taken care of by their offspring. Elderly females commonly stay indoors as compared to their male counterparts. In our study, males and females were equally distributed, whereas a female predominance (62%) was noted in a previous study conducted in Auckland.[20] We compared the VF-14 scores between the female and male patients in our study and found that there was a statistically significant difference in the VF-14 scores between males and females. This difference can probably be attributed to the gender-related activities listed in the questionnaire. The questions about sewing and knitting revealed 105 responses since males do not perform needlework. The questions about driving had 61 responses, which were mainly from male patients. This probably contributed to the low satisfaction rates for distance vision in both EM and RM groups.

Earlier study evaluated that the impact of visual impairment on health-related QOL in a cohort of persons over the age of 64 demonstrated contrary mean VF-14 values between the sexes. The mean VF-14 score using the original version was consistently inferior for women than for men for all categories of visual acuity.[21]

Literature review has shown the importance of predictive refractive power in patients with normal axial length undergoing uneventful phacoemulsification surgery and their visual acuity outcome.[22,23] In our study, we found statistically significant differences for both groups predictive and residual refractive power. This suggests that we are evaluating patients in two distinct groups. At 3 months post-operatively, both groups gained unaided distant vision ranging from LogMAR 0.0 to 0.7. The predictive refractive power in previous studies[17,22] was comparable to that of the EM group in our study. Improvements in visual function and QOL have been demonstrated following cataract surgery.[24-27]

Other reports have observed improvements in the various domains of QOL.28 VF-14 questionnaires have been extensively used to assess QOL[15,17,26,29] and the VF-14 questionnaire has been translated into various languages, including Arabic,[17] Dutch,[30] German[31] and Bahasa Malaysia.[15] The questionnaire in this study were administered 3 months after the surgery to allow for proper healing and for stabilisation of astigmatism. Subjective refraction was performed within 10 to 12 weeks post-operatively, allowing for a more appropriate assessment of the gains that patients were likely to achieve.[25] The gains in visual function related to QOL are apparent within 4 months of cataract surgery.[25]

Modified VF-14 questionnaires were used to assess the vision-related QOL in our study. The use of other patient-reported outcome questionnaires may help to evaluate QOL following cataract surgery.[12] Newer questionnaires may be able to explore the signs and symptoms that are demonstrated in pseudophakia. There are suggestions that reading speed should be incorporated as a parameter to evaluate reading performance, as well as reading acuity, distance reading, near reading and reading small print.[32] The results of this study are tailored to the needs of the local community.

CONCLUSION

The modified Bahasa Malaysia version of VF-14 QOL questionnaire was successfully used in this study to evaluate functional vision in post-operative cataract patients implanted with monofocal IOL. Both EM and RM patients gave high scores on the QOL questionnaire. However, predicted RM achieved more satisfactory near vision and near vision-related activities compared to EM. Monofocal IOL implantation is a cheaper alternative to multifocal IOL and it is a highly acceptable choice measured by QOL suited to the local population's routine QOL activities. A newer questionnaire could be constructed to explore other relevant post-operative visual functions and activities. This study was limited by its sample size and may not be applicable to a wider general population. A longer follow-up period (e.g. up to 6 months post-operatively) would provide more comprehensive QOL data interpretation.

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CONFLICTS OF INTEREST/COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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ORIGINAL ARTICLE

Determinants of colorectal carcinoma screening amongst patients attending a public primary care health centre in Johor Bahru

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ABSTRACT

Introduction: Colorectal cancer (CRC) is one of the major causes of cancer-related mortality in Malaysia. Early screening has proven to be effective in reducing mortality due to CRC. The Malaysian CRC Clinical Practice Guidelines (2017) recommends that immunochemical faecal occult blood test (iFOBT) as the best non-invasive method for screening CRC in asymptomatic or average risk population. Outcome data on CRC screening program in the community is scarce. This study was to evaluate the prevalence and determinants of CRC among patients attending a public primary care health centre who underwent the screening program.

Materials and Methods: Reviews of CRC Screening Registry and medical case record were conducted on patients who underwent CRC screening program at Klinik Kesihatan Mahmoodiah, Johor Bahru (KKMJB) from 2016 to 2018 period. Sociodemographic data, clinical profile of patients, iFOBT results and colonoscopy outcomes were extracted for analysis. Descriptive and inferential statistics were performed using IBM SPSS version 25.

Results: Out of 591 registered patients, 584 were included for analysis. Majority of the screened individuals were males (2016-2017) compared to females (2018). Chinese were most screened individuals in 2016 [94 (46.8%)] and 2017[87 (61.7%)]. Percentage of patients with appropriate indicators for screening and underwent colonoscopy for positive iFOBT were highest recorded in 2018 (74.7%, 58.8% respectively). Prevalence of CRC among those screened with iFOBT was 1 per cent for 2017 and 2018. Adherence to annual screening with iFOBT ranged between 1.1% (2016)-2.2% (2018). Significant association observed between gender and iFOBT results, $\chi 2(df)= 4.747$, $p=0.029$ (2018). Median age and ethnicity were not significantly associated with iFOBT results ($p>0.05$)

Conclusion: Screening for CRC among average risk groups in primary care should focus on recruiting female patients/clients as an organised activity. Prevalence of CRC detected from screening with iFOBT was 1 per cent. CRC screening programs should focus on proportion of iFOBT positive patients progressing to receive definitive colonoscopy and complying to annual surveillance screening.

KEYWORDS:
Colorectal cancer, screening, iFOBT, Primary care

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related death globally.[1] CRC is the second most commonly diagnosed cancer worldwide among females and the third in males. The global burden of CRC has been increasing consistently over the years, with approximately one to two million new diagnoses reported annually, and the majority are reported from Asian countries.[2,3] The Malaysian National Cancer Registry Report 2012-2016 (MNCRR) reported a 13.3% rise compared to the 2007-2011 period. The age-standardized incidence rate in men and women from 2012 to 2016 was reported as 14.8 and 11.1 per 100,000 population respectively. The incidence of colorectal cancer was noted to be the highest among the Chinese for both sexes in terms of differences among multi-ethnic Malaysians. Among men, the lifetime risk for Chinese was 1 in 43, significantly higher than that in other ethnic groups; 1 in 65 for Malays and 1 in 70 for Indians. The same lifetime risk was also reported in females, i.e., among Chinese 1 in 57, Malays 1 in 89 and Indians 1 in 95. The incidence of CRC is higher in both sexes and peak at the age of 70 and above.[4] The disease is accountable for 12.3% of all cancer-related mortality in Malaysia,[5] and contributes to 13% of cancer-associated disability-adjusted life year (DALY).[6]

Earlier studies have reported that the majority of Malaysians were diagnosed with late-stage CRC due to the absence of national CRC screening programs.[7-9] The disease causes an increase in Malaysian economic burden as the treatment costs increase with the advanced cancer stages. Thus, it was suggested that the implementation of screening programs may reduce the mortality through early detection of CRC, leveraging on screening in patients with no known risk or categorized as average risk at primary care facilities.[10] Screening using the immunochemical faecal occult blood test (iFOBT) is recommended at ages 50 to 70 years old, on an annual basis.[11] An early colonoscopy is recommended if screening with iFOBT is found to be positive.

The Malaysian Health Technology Assessment Section (MaHTAS), Ministry of Health Malaysia (MOH) reported that annual screening using iFOBT can be effective for preventing advanced CRC (i.e., reducing the risk of developing advanced

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CRC by 28-46% and reduce the mortality by 23-60%). Regular iFOBT can detect pre-cancerous lesions and when detected in early stages, will reduce CRC-related mortality. iFOBT followed by colonoscopy is the most cost-effective screening strategy compared with no screening or colonoscopy alone. The recommended screening program estimated an incremental cost-effectiveness ratio of RM9,377.65 compared to no screening.[12]

The sensitivity and specificity for iFOBT is 67% and 85% respectively.[13] Although the sensitivity and specificity are only moderate, the acceptability of iFOBT as a screening tool is still very high for detecting CRC owing to its noninvasive procedure and the ease in collection of specimens by patients. Furthermore, early diagnosis of CRC would potentially reduce the economic burden and mortality rates in the country.

The MOH implemented the CRC screening programs using iFOBT for screening of average risk population at public primary care health centres, since 2016. To date, studies assessing the outcomes of this screening program is scarce. This study was to evaluate the prevalence and factors associated with CRC among patients attending a public primary care health centre who underwent the screening programme.

MATERIALS AND METHODS

Study design and setting

This cross-sectional study was conducted at a public primary healthcare centre, the Klinik Kesihatan Mahmoodiah in Johor Bahru (KKMJB) district. The KKMJB CRC Screening Registry began when the CRC screening program was initiated in 2016 on the directive of the Johor Bahru District Health Office. The CRC screening program initially catered to patients' risk stratification profile by the primary care provider (PCP). The program is also available on a walk-in basis; where clients can request for this service (self-referral), with the staff nurse in charge at the clinic registration counter (Figure 1). The criteria for the latter included adults who are asymptomatic or no known risk for CRC. Hence, a clinic-based registry was formed. The clinic-based registry captured 11-items: socio-demographic data of clients (4 items), date of iFOBT test kit issued, reviewed by Clinician (medical officer or Family Medicine Specialist), iFOBT results, referral to Surgical Outpatient Department (SOPD) (i.e., patient agreed or refused), appointment date at SOPD, colonoscopy results, staging of CRC. The data of patients /clients registered during 1st January 2016 till 31st December 2018 were analysed.

Study tool

A data extraction form was used to consolidate the information from CRC registry and information verified from Surgical Clinic, Hospital Sultanah Aminah Johor Bahru (HSAJB) (i.e., colonoscopy findings and histopathological examination reports). All patients/clients listed in the KKMJB CRC registry in the study period were included, while patients with non-traceable results or iFOBT samples rejected by laboratory for any particular reason (e.g., sample leakage) were excluded from analysis. All data were entered into SPSS spreadsheets, using pre-defined codes to ensure patients' anonymity was maintained throughout the study and the subsequent period.

Statistical Analysis

Descriptive statistics was used to summarise the data. Frequencies and percentages were used to describe quantitative variables. Median and interquartile range were used to describe non-normally distributed data. Univariate non-parametric analysis such as Mann Whitney U and Fisher's exact tests were applied to determine differences and associations between sociodemographic variables and iFOBT results. Statistical Package for the Social Sciences (SPSS version 25) was used to perform analysis. The data from patients who had samples rejected by the clinical diagnostic laboratory due to technical /sampling errors were excluded from analysis.

Operational definition of terminologies used in this study include: Appropriate indication for CRC screening refers to asymptomatic patients aged 50-70 years old.[11] Compliant to annual CRC screening program refers to yearly CRC screening using iFOBT for asymptomatic patients.[11] Average risk population refers to a person who is asymptomatic and does not have family history of CRC, personal history of colorectal cancer or certain types of polyps or inflammatory bowel disease, confirmed or suspected hereditary colorectal cancer syndrome, e.g., familial adenomatous polyposis (FAP) or Lynch syndrome (hereditary non-polyposis colon cancer or HNPCC).[11]

Written consent from the patients was not obtained in the study since the study utilised secondary data from the primary care clinic records. However, all patients who registered at the clinic were notified during registration that the data collected during the clinic visits could potentially be used to improve the clinic services and performance, i.e., audit evaluations. Access to the database was restricted to the co-investigators only. The original electronic data was electronically encrypted, and password protected.

The ethical approval was obtained from Research Ethics Committee in Universiti Kebangsaan Malaysia (JEP-2019-554, FF-2019-403), Medical Research & Ethics Committee's (MREC) KKM/NIHSEC/P19- 1739 (5), Ministry of Health Malaysia and as well the Johor State Health Director. This study was self-funded by the research team.

RESULTS

A total of 591 patients, were screened for CRC during the 2016-2018. However, seven (7) patients were omitted from the final analysis. Three (3) patients were excluded due to non-traceable iFOBT results. Four (4) patients were rejected due to leakage of samples. Altogether 584 patients were included for the final analysis. Overall, the median age of the patients who underwent CRC screening was 58 (10) years old (range 50.0-70.0 years). Most of the screening tests were performed in the year 2017 with 242 patients followed by 201 patients in 2016 and 141 in 2018. The profile of the patients screened are summarised in Table I.

Patients/clients meeting the recommended age-criteria for CRC screening were from 2018, (74.7%) compared to only 42.7% in 2017 and 46.8% in 2016.

Table I: Profile of CRC screened patients according to year

Characteristic	2016		2017		2018		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Gender								
Male	121	60.2	129	53.3	64	45.4	314	53.8
Female	80	39.8	113	39.8	77	54.6	270	46.2
Ethnicity								
Malay	64	31.8	99	40.9	87	61.7	250	42.8
Chinese	94	46.8	108	44.6	35	24.8	237	40.6
Indian	40	19.9	34	14.0	19	13.5	93	15.9
Others	3	1.5	1	0.4	0	0.0	4	0.7
iFOBT results								
Negative	163	81.1	208	86.0	125	88.7	496	84.9
Positive	38	18.9	34	14.0	16	11.3	88	15.1
Completed colonoscopy*								
No	19	50.0	19	54.3	7	41.2	47	51.1
Yes	19	50.0	16	45.7	10	58.8	45	48.9
Period prevalence (Prevalence of CRC/year)	0		3/242=0.01		1/141=0.01			
Compliant to annual CRC screening program								
No	199	98.9	238	98.3	138	97.8	575	98.5
Yes	2	1.1	4	1.7	3	2.2	9	1.5

*Confirmed from SOPD records

Table II: Association between sociodemographic variable and iFOBT test results.

Year	Variable	Negative	Positive	χ2	(df)	P value
		n (%)	n (%)			
2016	**Age, Median (IQR)**	61 (12.0)	61 (16.0)	16075.5a		0.939
	Gender					
	Male	101 (62.0)	20 (52.6)	1.120	(1)	0.290
	Female	62 (38.0)	18 (47.4)			
	Ethnicity					
	Malay	53 (32.5)	11 (28.9)			0.770b
	Chinese	75 (46.0)	19 (50.0)			
	Indian	33 (20.2)	7 (18.4)			
	Others	2 (1.2)	1 (2.6)			
2017	**Age, Median (IQR)**	58 (12.0)	60 (10.0)	3094.5[a]		0.277
	Gender					
	Male	105 (50.5)	24 (70.6)	4.747	(1)	0.029
	Female	103 (49.5)	10 (29.4)			
	Ethnicity					
	Malay	86 (41.3)	13 (38.2)			0.822b
	Chinese	93 (44.7)	15 (44.1)			
	Indian	28 (13.5)	6 (17.6)			
	Others	1 (0.5)	0 (0.0)			
2018	**Age, Median (IQR)**	58 (9.0)	57 (17.0)	988[a]		0.938
	Gender					
	Male	54 (43.2)	10 (62.5)	2.132	(1)	0.144
	Female	71 (56.8)	6 (37.5)			
	Ethnicity					
	Malay	80 (64.0)	7 (43.8)			0.182[b]
	Chinese	28 (22.4)	7 (43.8)			
	Indian	17 (13.6)	2 (12.5)			
	Others	0 (0.0)	0 (0.0)			

a Mann Whitney U, b Fisher's exact test

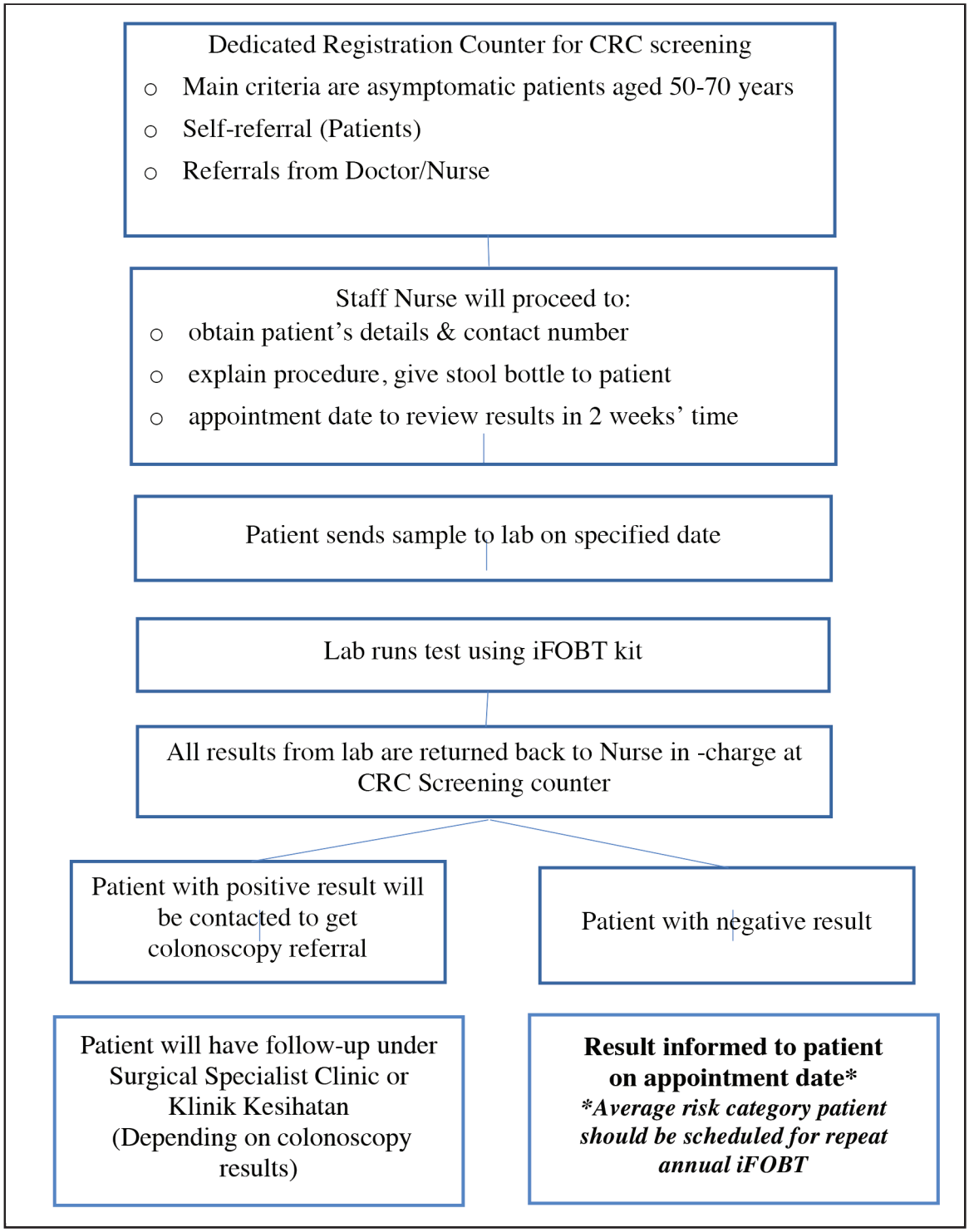

Fig. 1: CRC Screening Program at KK Mahmoodiah, Johor Bahru.

In general, 15.1% of patients/clients screened during the 2016-2018 period were iFOBT positive. The highest percentages of positive iFOBT test were in 2016, [38(18.9%)] and the count was lower over the years. Altogether, a total of 88 patients required referral for colonoscopy (Table I). However, colonoscopy was performed for 43 out of 45 patients (95.6%). The histopathological examination results indicated that 29.7% had Adenomatous Polyps. The CRC screening program diagnosed four patients with CRC during the study period. The number of cases confirmed with CRC from colonoscopy alone were 3 cases in 2017 and one in 2018. This makes the period prevalence, which is the proportion of patients with CRC in particular year, i.e., 0.01 in 2017 and 2018 respectively.

There was no significant difference in the median age of patients tested ($p>0.05$). iFOBT results were not associated with ethnicity ($0.182<p<0.822$). As for gender, no significant

association was observed with iFOBT result, χ^2(df)= 1.120(1), p=0.290 in 2016 and 2018, χ^2(df)= 2.132 (1), p=0.144. However, for 2017, gender was significantly associated with iFOBT result, χ^2(df)= 4.747 (1), p=0.029. Despite almost homogenous gender distribution of the patients screened in 2017, more males tested positive for iFOBT [24 (70.6%)] compared to female patients [10 (29.4%)].

DISCUSSION

To our knowledge, this is a first study to evaluate the CRC screening program from a public primary care health centre in Malaysia. Our study provided an overview of the outcomes of a CRC screening program conducted at a public primary care healthcentre. For the 2016 – 2018 period, an overall of 15.1% of the patients screened had positive iFOBT test. However, only half of the patients who tested positive for iFOBT proceeded with colonoscopy for further investigation and diagnosis. Since the majority of patients tested 'negative' for iFOBT, we are unable to conclude if the screening in these individuals have been able to safely reassure both patients/clients and the primary care team have succeeded in ruling out CRC.

The Clinical Practice Guidelines on CRC management (2017) by the Malaysian Ministry of Health emulated the American and European CRC screening guidelines, recommends the age of 50 as the starting age for screening.[14-15] However, the consensus from the Malaysian Society of Gastroenterology and Hepatology, suggested that screening for colorectal cancer in Malaysia should start earlier than that of Europe and the United States of America.[16] This is based on Malaysian studies which reported approximately 90% of the CRC incidence occurred among those aged over 40 years old and geriatrics people above 60 years of age[17] Moreover, the Malaysian National Cancer Registry reported that adults younger than 40 diagnosed with CRC, accounted for only 7% of the CRC incidence in Malaysia.[10] Hence the recommendation was made for screening to be done among those aged 50-70 years only. However, in our study, slightly more than half of the patients were not in the recommended age range for the 2016-2017 period. This could be due to the fact that the CRC KKMJB Registry combined patients who were referred by the primary care team (i.e., symptomatic or had risk factors for CRC) as well as patients who may be from the asymptomatic or average risk. The proportion of age-appropriate patients screened in 2018 was higher at 74.7% and this could be due to the publication of the first CRC CPG in November 2017, offering a better guide to primary care team. The prevalence of CRC per year in our study was 1:100 among patients who had no or average risk for CRC based on our study.

Consequently, our study found the proportion of patients who returned for annual iFOBT screening was dismal, ranging from 1.1-2.2% compared to 34.6% in Canada.[18] Once tested negative for iFOBT for that year, Malaysian patients/clients are required to repeat the test annually, if they are in the 50 to 70-year-old age group. This suggests that the majority of the patients screened negative with iFOBT did not return to continue with the surveillance for CRC. Appropriate mechanisms should be put in place to educate and re-enforce the staff as well as patients, that annual screening is advised even if the iFOBT screen is negative for that particular year. Methods to increase the screening rate such as sending out reminders to patients annually via post or short messaging service or one-to-one patient interaction when informing results.[19] The percentage of patients who comply with annual screening compliance should be the key performance index for the CRC screening program. Hence, it is our postulation that the screening program did not meet its objective for early detection of CRC in a cost-effective manner as per the original intention of this program. In terms of improving the CRC screening program at KKMJB, patients/clients in the average risk category should be given a reminder or assigned an annual repeat iFOBT appointment, after receiving results of the iFOBT for that particular year. The primary care team should also include safety netting measures for patients/clients should they develop symptoms of CRC at any time.

Due to diversity and ethnicity of the residents of Malaysia, the demography of CRC could differ from the developed countries. Despite this, the risk of CRC by gender is the same worldwide as the age-standardized incidence is higher among males than females.[2,17] However, the current recommendation by CPG does not differ by gender even though the screening outcome differs. This study demonstrated a slightly higher proportion of positive iFOBT in males than in females, although the association between gender and screening results is not significant except for in 2017. Contrastingly, studies from UK and US indicated that individuals subjected to CRC screening were higher in women than men.[20-21] Meanwhile, a study in Malaysia has suggested that women have a 59% higher chance of being screened for CRC than men when adjusted for age and ethnicity.[22] Although the possible reasons are inconclusive, improvement in the CRC mortality perception among male could be reflecting the result of this study.[23] Our study implies that perhaps CRC screening should be included among the female patients aged 50-70 years who attend primary care facilities, as an additional organised preventive health advise together with screening for cervical cancer (Papanicolaou test) and breast cancer screening (Mammogram).

In terms of ethnicity, the incidence of CRC is reported to be highest among the Chinese, followed by Malays and Indians in Malaysia.[9,17] In studies conducted in Malaysia and Canada, the utilisation of healthcare services is known to be low among the Chinese compared to other ethnicities, for various reasons such as refusal to seek specialist care for chronic or age-related conditions, socio-cultural taboos or due to under reporting.[24-25] On the contrary, in our study, the majority of the patients screened in the primary care clinic in 2016 and 2017 were Chinese. However, the proportion of Chinese patients was lower, almost 50% in 2018. There is no clear explanation for this finding. However, it must be taken into consideration that screening of CRC in private health care facilities may play a significant role in utilisation of healthcare facilities, as the demand for private healthcare services has increased in Malaysia, even though the cost of screening is significantly higher than in the public sector. Screening programs for malignancy may be offered as 'package deals" for wellness programs organised by private

hospitals or private clinical diagnostic labs. These screening packages may be conducted in better surroundings and include multiple cancer screening programs in one setting, at competitive prices. As opposed to screening programs conducted in public healthcare facilities, various factors may deter the patient from returning for annual CRC screening. Factors such as availability of test kits, laboratory facilities and long waiting time at the public primary care health centres are some of the significant barriers to CRC screening in Malaysia.[26-27]

The limitation of this study is the retrospective analysis of data obtained from the program, and the limited variables extracted for analysis from the KKMJB CRC screening program database. The results from this study may not be generalised to all public primary care healthcentres in Peninsular Malaysia. However, despite the introduction of screening campaigns, the CRC incidence in Malaysia is still on the rise with most cases still being diagnosed at late stages.4-6 Hence, remedial measures are required to ensure the quality of CRC screening programs achieves its intended objectives and more importantly prevent wastage of resources. Our study suggests that the CRC screening program in asymptomatic or average risk population could be further improved with participation of positive iFOBT who proceeded for colonoscopy and the returning of negative iFOBT patients for annual screening. iFOBT positive patients must be encouraged to undergo colonoscopy for further diagnosis. As such, our study found close to one third of the patients who underwent colonoscopy had adenomatous polyps, which had potential for malignant change, hence requiring closer monitoring. By performing colonoscopic polypectomy for higher risk population, the incidence of CRC will be reduced and thus prevent mortality due to CRC. We recommend a more focused delivery of the pre iFOBT counselling on the interpretation of results should be included for all patients/clients undergoing screening for CRC to improve patients/client's compliance to the screening program.

Future studies should include data analyses from more public primary care health centres across Malaysia, representative of urban, suburban and rural facilities as well as private healthcare facilities. Serial analyses of CRC screening programs conducted after the release of the CPG CRC and its impact on the program should be assessed, especially in ensuring the better compliance to annual screening in the average risk group in the population who attend primary care health centres.

CONCLUSION

Screening for CRC among average risk groups in primary care should focus on recruiting more female patients/clients as an organised activity. Prevalence of CRC detected from screening with iFOBT was 1 per cent. Evaluation of CRC screening programs should focus on proportion of iFOBT positive patients progressing to receive definitive colonoscopy and complying to annual surveillance screening.

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CONFLICT OF INTEREST

The authors declare they have no competing interest.

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Clinical characteristics and factors associated with diagnoses of ventilator and non-ventilator associated pneumonia in Intensive care unit

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ABSTRACT

Introduction: Ventilator-associated pneumonia (VAP) is a significant cause of morbidity and mortality in ventilated patients in intensive care units (ICUs) worldwide. This study was conducted to identify the proportion, associated factors and outcomes of patients who developed VAP.

Materials and Methods: This was a retrospective, cross-sectional study involving 111 ventilated patients admitted to the ICU at Hospital Universiti Sains Malaysia (HUSM) from 1 April 2018 to 30 June 2019. The patients were categorised into VAP and non-VAP groups using the clinical scoring for VAP at the end of the stay in ICU. Logistic regression analysis was performed to determine the factors independently associated with VAP and its outcomes.

Results: Thirty-three patients were categorised into the VAP group and the remaining 77 patients were categorised into the non-VAP group. The proportion of patients who developed VAP was 30.0%. The VAP rate per 1000 people according to the Johansen, Clinical Pulmonary Infection Score (CPIS), and Center for Disease Control and Prevention (CDC) criteria were 6.9, 6.1 and 0.4, respectively. There was an association between duration of mechanical ventilation (MV; odds ratio [OR] = 1.22; 95% confidence interval [CI] 1.12, 1.34; $p < 0.01$) and length of ICU stay (OR = 1.213; 95% CI 1.107, 1.32; $p < 0.01$) and VAP. However, there was no difference in the patients between VAP and non-VAP groups in terms of mortality.

Conclusion: The VAP rate differs according to the diagnostic criteria. The factors associated with VAP in our centre were increased duration of MV and increased length of ICU stay. There was no difference in the mortality rate between the VAP and non-VAP groups.

KEYWORDS:
Ventilator-associated pneumonia; intensive care unit

INTRODUCTION

Ventilator-associated pneumonia (VAP) is one of the leading causes of healthcare-associated infection (HAI) in adult intensive care units (ICUs) and is linked to increased ICU days, mechanical ventilation (MV) days and mortality.[1,2] However, while there have been many proposals for a definition of VAP, there is no consensus on the meaning of this term. Furthermore, a 'gold standard' guideline to diagnose VAP or test the accuracy of the current clinical scoring and parameters used is lacking.[3] A new term used for ventilation-associated lung infection that does not meet the VAP criteria is ventilator associated tracheobronchitis. This encompasses infection arising in the larynx, trachea, and bronchus.4 However, the diagnosis, treatment and outcome are similar to VAP.[4]

As the mean duration of MV and hospital stay becomes longer in the VAP group of patients, the resource utilisation burden increases to almost 1.5-fold compared with patients who do not develop VAP.[5] Further studies on the incidence and risk factors of VAP can help physicians minimise VAP occurrence through the implementation of simple, economically safe preventive measures. Overall, the eradication of this preventable nosocomial infection would save lives and conserve health care resources.[6]

The aim of this study was to determine the proportion of various definitions of VAP throughout the study period in HUSM and comparing of clinical characteristics and associated factors of three different criteria in diagnosing ventilator associated pneumonia versus non - ventilator associated pneumonia in the ICU. The number depends on the formula used to calculate and types of definition used to diagnose VAP. The denominator used in our study consisted of patients who underwent MV days in the ICU per 1000 people. Indirectly, the results will reduce unnecessary antibiotic prescriptions, which may eventually lead to decrease in antibiotic resistance in HUSM.

MATERIALS AND METHODS

This was a retrospective, cross-sectional study approved by the Medical Research and Ethics Committee (JEPeM) of USM (JEPeM Code: USM/JEPem/18040218). Patients aged 16 years and above who were intubated and requiring MV for at least 48 hours were included. A total of patients who were

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admitted to the General ICU and Surgical ICU at HUSM from 1 April 2018 to 30 June 2019 were screened. The sample was then narrowed by selecting patients labelled as having pneumonia in the admission and discharge ICU medical record book. The patients were excluded from the study if their medical records could not be traced at the record office or the final diagnosis was community-acquired pneumonia. A precision of 4.5–5% with a significance level (α) 0.05 and 10% dropout was used to calculate the sample size for this study.

Sampling method
The participants were divided into VAP and non-VAP groups. A data collection sheet was used to collect and record the following information: demographic data, for example, ages, sex and clinical data, including the date of ICU admission; cause of admission (medical or surgical); associated comorbidities; primary diagnosis (the reason for initiation of ventilation); level of consciousness according to the Glasgow Coma Scale (GCS); duration of MV; length of ICU stay; occurrence of VAP; causative organisms of VAP; duration of antibiotic use (up to 48 hours before MV); positioning of patients (supine or semi-recumbent); re-intubation; requirement of non-invasive ventilation (NIV); tracheostomy; and the outcome (survival or death). VAP was defined based on clinical, radiological, and microbiological criteria as described in Clinical Pulmonary Infection Score (CPIS), Johansen and Center for Disease Control and Infection (CDC) criteria. VAP was considered if pneumonia occurred after 48 hours of MV to fulfil the criteria of various definitions in our study. Those who did not fulfil these criteria were assigned to the non-VAP group. Permissions were obtained from the director of HUSM and head of the ICU.

Diagnostic criteria for VAP
Diagnosis of VAP was made using three different clinical scores, namely, the CPIS, Johansen and CDC criteria for VAP.

CPIS criteria
In the CPIS, the diagnosis of VAP was made using clinical variables. This instrument uses a score of 0–2 for the ventilation-perfusion ratio, chest radiography, tracheal secretions, tracheal aspirate culture, temperature, and leucocytosis. The maximum score that could be obtained is 12, and a score > 6 is diagnostic of VAP.[7]

Johansen criteria
According to the Johansen criteria, VAP can be diagnosed based on a new persistent infiltrate on a chest radiograph and at least two of the following: fever of ≥ 38 °C, leucopoenia (<4000 white blood cells [WBC]/mm3) or leucocytosis (≥12 000 WBC/mm^3) and purulent respiratory secretions, worsening gas exchange (PaO_2/FiO_2 < 240).[8]

CDC criteria
The CDC's new definition of VAP consists of a hierarchical approach that identifies ventilator-associated events (VAE). The first tier is a ventilator-associated condition (VAC). This is defined as the deterioration of respiratory function for 48 hours after a period of 48 hours of stability or improvement. Subsequent tiers are infection-related ventilator-associated complications (IVACs), defined as a temperature >38 °C or <36 °C or a white cell count >12 000 mm3 or ≤4000 mm3 and one or more antibiotics started within 2 days before or after the onset of VAC and continuing for at least 4 days. The third tier is possible occurrence of pneumonia. The patient must fulfil the VAC and IVAC criteria with purulent secretion or positive culture. The last tier is probable pneumonia, in which both purulent secretion and positive culture are present.[9] The probable VAP criteria can also be met by positive pleural fluid culture, lung tissue with histological evidence of infection and positive diagnostic tests for Legionella or selected respiratory viruses.[9]

Calculations of incidence
The VAP incidence density was calculated as follows: (Number of cases with VAP/Number of ventilator days) x 1000 = VAP rate per 1000 ventilator days.[9-12]

Data collection
Data were collected using a data collection sheet that was prepared and filled in by the researcher once a patient had been identified. In the HUSM, a patient is followed up for 30 days via the hospital informative system after discharge from/death in the ICU or discharge from the hospital (based on the medical record and ICU chart of the patients).

Data analysis
Statistical analysis was performed using IBM SPSS version 24.0 statistical software. The quantitative variable was expressed as mean and standard deviation (SD), while qualitative data were presented as a number with a percentage. Continuous data were compared using the Student t-test or Mann–Whitney test as appropriate. A categorical variable was compared using the Chi-square test or Fisher's exact test. A logistic regression model was performed to determine factors independently associated with risk factors for developing VAP and the related outcomes. Variables with a p-value < 0.25 in univariate analysis were subjected to the multivariate regression model. The adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated. A double-sided p-value < 0.05 was considered statistically significant.

RESULTS

Of the total of 796 MV patients admitted to the ICU, a total of 156 patients with the diagnosis of pneumonia were considered for the study. Another 30 patients were excluded because they were found to have community-acquired pneumonia while the remaining 15 patients were excluded because their medical records could not be traced or there were incomplete data at the records office. Therefore, 111 patients were included in the final analysis. The total ventilator days for patients who were mechanically ventilated during the study period was 4589 days. The total mean duration of mechanical ventilator days was 5.7 days. There were 73 (66.7%) male patients and 37 (33.3%) females. The mean age of the patients was 53.94 years. The main causes of admission were surgical (65.8%), and others medical (34.2%). Most patients had underlying comorbidities (70.2%), while the others (29.7%) had no underlying comorbidities. The mean GCS score for the patients was 11. Thirty-three per cent of patients with VAP presented with septic shock, while 43.6% of the non-VAP group had septic shock. The mean Acute Physiology and Chronic Health

Table I: Comparison between demographic factors associated with VAP

Variables	VAP (n = 33) n (%)	Non-VAP (n = 78) n (%)	p-value
Gender			
Male	24 (72.7)	50 (64.1)	
Female	9(23.3)	28 (35.9)	0.378[f]
Age (years) [a]	55.97 (13.279)	53.09 (18.868)	0.361[c]
Race			
Malay	31 (93.9)	75 (96.2)	
Non-Malay	2 (6.1)	3 (3.8)	0.633[f]
GCS[b]	12 (8)	14 (7)	0.095[d]
Comorbidities			
Yes	24 (72.7)	54 (69.2)	
No	9 (27.3)	24 (30.8)	0.713[f]
Admission category			
Medical	11 (33.3)	22 (66.7)	
Surgical	27 (34.6)	51 (65.4)	0.896[e]
Septic shock			
Yes	11 (33.3)	34 (43.6)	
No	22 (66.7)	44 (56.4)	0.314[e]
Position of patient			
Supine	3(9.1)	3 (3.8)	
Semi-recumbent	30 (90.9)	75 (96.2)	0.360[f]
APACHE II score[a]	14.30 (6.197)	14.064 (7.848)	0.877[e]
SOFA Score[a]	9.455 (4.790)	8.744 (5.113)	0.494[e]

[a] Mean (SD), b Median (IQR), c Independent t-test, d Mann–Whitney test, e Chi-square test, f Fisher exact test

Table II: Comparison between treatment-associated factors and VAP

Variables	VAP (n = 33) n (%)	Non-VAP (n = 78) n (%)	p-value
Antibiotic exposure			
Single	4 (12.1)	19 (25.7)	
Multiple	29 (87.9)	55 (74.3)	0.115[b]
Duration of antibiotic (days)a	29 (23.5)	12 (12.5)	<0.001[c]
Tracheal Suctioning			
Open method	31 (93.9)	75 (96.2)	0.633[d]
Closed method	2 (6.1)	3 (3.8)	
Duration of mechanical ventilation (MV; days)[a]	21 (15.5)	5 (7)	<0.001[c]
Length of ICU stay (days)[a]	24 (16)	7 (7)	<0.001[c]
Length of hospital stay (days)[a]	34 (27)	14 (14.3)	<0.001[c]
Adverse reaction			
Require NIV > 2 hours	7 (58.3)	9 (69.2)	
Re-intubation	5 (41.7)	4 (30.8)	0.571[b]

a Median (IQR), b Chi-square test, c Mann–Whitney test, d Fisher exact test

Evaluation (APACHE) II score at admission for the VAP group was 14.3, and the non-VAP group was 14 (p = 0.877). The mean Sequential Organ Failure Assessment (SOFA) score was 9 in the VAP group, whereas the non-VAP group had a mean SOFA score of 8 (p = 0.494; Table I). None of the sociodemographic factors analysed showed any significant difference in terms of the development of VAP in our cohort. The three most common organisms associated with VAP in our centre were Klebsiella pneumoniae, Acinetobacter spp. and Pseudomonas aeruginosa.

The number of study subjects fulfilling the three types of criteria for VAP in our 111 study patients was 33, which accounted for 29.7%. As for the diagnosis of VAP, 32 out of 33 patients fulfilled the Johansen criteria (97%), 28 patients (85%) fulfilled the CPIS criteria and only 2 (6%) fulfilled the CDC criteria. The proportion of VAP according to each diagnostic tool varied; for the CDC criteria, it is 1.8%, whereas the proportional incidences of VAP according to the CPIS and Johansen criteria were 25.2% and 28.8%, respectively. The total VAP rate was 7.1. The VAP rates for the Johansen, CPIS and CDC criteria were 6.9, 6.1 and 0.4, respectively.

The VAP population required a significantly longer duration of antibiotic therapy during the total admission days (p < 0.001), with a median duration of 29 days. However, there was no significant difference in the requirement of single or multiple types of antibiotics (p = 0.115). Open or closed tracheal suctioning was not associated with VAP (p = 0.633; Table II).

Patients with a longer duration of MV were prone to developing VAP (OR 1.22; 95% CI 1.12, 1.34; p < 0.01). Those

Table III: Factors associated with VAP using simple logistic regression

Factors	b	Adjusted OR (95% CI)	p-value[a]
Age (years)	-0.01	0.990 (0.954, 1.027)	0.59
Gender	-0.464	0.629 (0.239, 1.656))	0.348
Race	0.373	1.451 (0.581, 3.626)	0.425
Comorbidity	0.17	1.185 (0.48, 2.928)	0.713
Admission category	0.057	1.059 (0.448, 2.506)	0.896
GCS	-0.522	0.594 (0.236, 1.496)	0.268
Septic shock	-0.623	0.535 (0.201, 1.425)	0.211
Position	-0.667	0.513 (0.089, 2.960)	0.456
APACHE II	0.008	0.993 (0.919, 1.071)	0.847
SOFA	0.54	1.055 (0.939, 1.185)	0.367
Duration of antibiotic (days)	0.025	1.026 (0.973, 1.081)	0.346
Duration of MV (days)	0.205	1.228 (1.121, 1.344)	< 0.01
Re-intubation	1.353	3.869 (0.95, 15.75)	0.059
Requiring NIV post-intubation	0.879	2.407 (0.799, 7.267)	0.119
ICU mortality	0.689	1.991 (0.869, 4.563)	0.104
30-day mortality	-0.177	0.170 (0.009, 3.257)	0.24
Length of ICU stay (days)	0.193	1.213 (1.107, 1.328)	< 0.01
Length of hospital stay (days)	0.017	1.018 (0.971, 1.066)	0.464

OR = odds ratio, a simple logistic regression test, MV = mechanical ventilation, NIV = non-invasive ventilation

Table IV: Associated factors for VAP (n = 111) using multiple logistic regression

Factors	b	Adjusted OR (95% CI)	p-value[a]
Septic shock			
No		1	
Yes	-1.538	0.215 (0.044, 1.041)	0.056
Duration of mechanical ventilation (MV; days)	0.590	1.803 (1.232, 2.638)	0.002
Adverse event 1 (requiring NIV)	1.920	6.821 (1.230, 37.824)	0.028
Adverse event 2 (re-intubation)	-0.502	0.605 (0.048, 7.674)	0.698
Length of ICU stay (days)	-0.328	0.72 (0.510, 1.017)	0.063

[a] Multiple logistic regression, NIV = non-invasive ventilation
Constant = -3.611
Backward LR method was applied
No multicollinearity and no interaction
Hosmer—Lemeshow test, p-value = 0.241
Classification table, 86.5% correctly classified
Area under the ROC curve 93.9% (95% CI: 0.897, 0.981)

Table V: Comparison of outcomes from VAP

	VAP (n = 33) n (%)	Non-VAP (n = 78) n (%)	p-value
ICU mortality	20 (37)	34 (63)	0.10[a]
30 days mortality	1 (12.5)	7 (87.5)	0.432[b]

[a] Chi-square test, b Fisher exact test

who stayed longer in the ICU were at risk of VAP (OR 1.21; 95% CI 1.10, 1.32; p < 0.01; Table III). The median durations of ICU stay were 24 days in the VAP group and 7 days in the non-VAP group. At the same time, the VAP population required significantly longer hospital stays ($p < 0.001$). The VAP group had a median hospital stay of 34 days, and the non-VAP group had a median of 14 days. There was no significant difference in the requirement of NIV or re-intubation in either group ($p = 0.571$; Table II).

A backward stepwise linear regression model was conducted to explore the significance of VAP predictors. Variables entered in the first step were the presence of septic shock, duration of MV, requirement of NIV, re-intubation, ICU mortality, 30-day mortality, and length of ICU stay (Table III). The last step revealed that only duration of MV (OR = 1.803; 95% CI 1.232, 2.638; $p = 0.002$) and post-intubation requirement of NIV (OR = 6.821; 95% CI 1.230, 37.824; $p = 0.028$) were factors significantly associated with VAP (Table IV).

The next step in the analysis was checking the fitness of the model. Firstly, using the Hosmer–Lemeshow goodness-of-fit test, the p-value was found to be 0.241, which is not significant. The classification table showed that the data were 86.5% correctly classified for the model. Finally, the area

under the receiver operating characteristic (ROC) curve was 93.9%. A value in the ROC curve of less than 0.5 means that the model is of no use for discrimination. The recommended area under the ROC curve is at least 70%. These three tests supported the claim that the model fit the data. Therefore, it can best describe the association between the factors associated with the proportion of VAP in the ICUs of HUSM.
Out of the 111 patients, 54 died in the ICU, and a further eight patients died after ICU discharge within 30 days of enrolment. However, there was no significant difference in ICU mortality (p = 0.101) or 30-day mortality (p = 0.432) between the groups (Table V).

DISCUSSION

Our study population consisted of various surgical and medical cases in view of the sampling frame taken from both surgical and medical ICUs. The proportion of VAP in our study was 29.7%. The denominator used was the total number of study population (111). There were three established criteria used in our study, namely, the Johansen, CPIS and CDC criteria. It was crucial to differentiate among them to ensure the standardised incidence was obtained, especially for quality assessment and performance indicator evaluation in ICUs.

Many studies have been published regarding the incidence of VAP; however, there is a difference in the denominators used to calculate it. In our study, two different numbers were used as denominators. The first denominator used was the number of study populations which was 111. A total of 33 out of 111 gives a proportion or incidence of 29.7%, which was similar to that found 10 years ago in our institution by Kathereson et al.[13] However, the incidence of VAP per 1000 ventilator days was 7.1, which was below the national key performance indicator of 10. The incidence even differs if the individual criteria were used in the ICU. The incidences for the Johansen, CPIS and CDC criteria were 6.9, 6.1, and 0.4 per 1000 ventilated days, respectively. It is exceedingly difficult to establish a VAP diagnosis based on CDC criteria because the first tier on the hierarchy requires the patient to be maintained in a stable mechanical ventilator setting for 2 days. The Malaysian ICU registry also reveals dramatic improvement in terms the VAP rate in 2017, after implementation of the CDC criteria. The VAP rate reported in the Malaysian Registry of Intensive Care Report 2017 is 1.7, whereas it was 5.4 in 2013.[14] Inter-observer variability criteria such as chest radiography, should be given priority to ensure accuracy of data used to diagnose VAP. Therefore, modified CDC criteria up to the tier of IVAC represent a standardised tool to define VAP for surveillance. The advantage of CDC criteria is that no chest radiography is included in the criteria.

Traditionally, it has been acknowledged that VAP diagnosis is based on a combination of clinical, radiological and microbiological criteria. However, the diagnosis brings a challenge to physicians because there is a wide range of clinical conditions that mimic VAP in chest radiography results of ventilated patients, including acute respiratory distress syndrome, pneumonia, pulmonary oedema, pulmonary contusion, pulmonary haemorrhage, and lung carcinoma. Some of the clinical conditions used in the diagnosis of VAP (e.g. change in the amount, consistency, and colour of tracheal secretion) are subjective and may vary according to inter-individual variation in interpretation. The combination of clinical findings, radiological findings and laboratory parameters may increase the specificity and sensitivity of VAP diagnosis, but limitations persist.[10] As there are no pathognomonic radiological features for VAP, the interpretation may overlap with other diseases. For obtaining microbiological specimens, invasive technique (eg. bronchoalveolar lavage [BAL]) and non-invasive techniques (i.e. tracheal aspirate [TA] culture) can be used. Both techniques are the more common sample obtaining method used when required to guide in terms of diagnosis and treatment of pneumonia in HUSM. Both reflect low sensitivity because bronchoscopic sampling cannot guarantee that the sample is taken from the lung area that is the most affected. The TA specimen may be contaminated with normal flora from the oropharyngeal area.

In a 2012 meta-analysis study comparing invasive and non-invasive techniques, it was concluded that the methods exhibited no differences in terms of survival, length of ICU stay, or duration of MV.[11] In 2017, the guidelines issued by the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESCIM), European Society of Clinical Microbiology/Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT) expressed a preference for invasive sampling techniques, such as mini-BAL, bronchoscopic BAL or protected specimen brush (PSB) to diagnose VAP as Pneumonia-1 (PNEU-1).[12] In 1991, Pugin and colleagues developed the CPIS to aid the diagnosis of VAP using clinical variables.[7] This scale gives a score of 0–2 for each of TA culture, tracheal secretions, chest radiography, ventilation-perfusion (PF) ratio, leucocytosis and temperature. A score of more than 6 is diagnostic of VAP. The interpretation of chest radiography and tracheal secretions are prone to being affected by inter-observer variability.

The Johansen criteria from 1999 allow VAP to be diagnosed based on the presence of new or progressive infiltrates on serial chest radiographs associated with at least two of three clinical findings of infection, such as temperature >38°C, purulent secretions or leucocytosis. Fabregas and colleagues compared the validity of the diagnosis by these criteria with immediate post-mortem lung biopsies and found that the sensitivity was only 69%, while the maximum specificity was 75%.[8]

In 2013, the United States of America, CDC introduced a new definition of VAP.[9] It was initially designed as a surveillance instrument for HAI, and it was not meant for the diagnosis of pneumonia. It has low specificity compared with bronchoscopic cultures. Neither is it specific for VAP. The agreement between VAP and VAC and IVAC was poor (less than 0.2).[15]

The definition of VAP was noted to be fulfilled mainly by the Johansen criteria, followed by CPIS scoring and CDC criteria in our study. Klompas, who suggested routine bedside evaluation coupled with radiographic information, provided suggestive but not definitive evidence for VAP. Clinicians should consider an additional test to provide further evidence

for VAP or establish another diagnosis.[16] Ventilator-associated tracheobronchitis (VAT) is a term used if chest radiograph results do not meet the criteria.[17] The organisms identified to be associated with VAP are similar to those in previously reported studies, namely, Klebsiella pneumoniae, Acinetobacter spp. and Pseudomonas aeruginosa.[14,18-20]

The prolonged duration of MV carried 1.8 times the risk of developing VAP in our study. A study by Trouillet et al. supported our finding that MV duration is an important risk factor for the development of VAP.[21]

The use of NIV prior to re-intubation in patients who fail extubation carries the greatest risk (6.8 times) of developing VAP. However, a meta-analysis and systematic review by Hess found that non-invasive weaning significantly reduced mortality and length of stay in intensive care and hospital, consistent with the observed reduction in VAP.[22]

In Malaysia, Katherason et al. (2009) reported that the incidence of VAP was 27.0%. Among the risk factors identified were aspiration pneumonia, cancer, leucocytosis and duration of MV.[13] It was found that potentially modifiable independent risk factors were aspiration and exposure to paralytic agents. In 1998, Cook et al. reported that exposure to antibiotics conferred protection, resulting in low rates of early-onset VAP.[23] A study by Charles et al. in 2013 showed chronic lung failure, H2 blocker usage and supine head position were significant risk factors for VAP.[24] In our study, positioning was not a significant factor in developing VAP; however, a total of 95% of the study subjects were in a semi-recumbent position. The study showed that supine patient positioning may facilitate aspiration, a possibility that is potentially decreased by semi-recumbent positioning. Drakulovic et al. reported a 3-fold reduction in VAP incidence in patients treated while in a semi-recumbent position compared with patients treated while completely supine.[25] A Spanish ICU, ventilator care bundle practice reduced the VAP rate by 50% (from 9 to 4.5) within 3 months of implementation.[20] However, our study did not find a significant association between supine or semi-recumbent positions and the VAP incidence.

Awareness of the various risk factors will reduce the morbidity and mortality associated with VAP. Supine head position, stress ulcer prophylaxis, surgery, burns, chronic renal failure, trauma, steroid therapy and duration of MV of more than 5 days were documented as risk factors in 2003.[26] The reported VAP-associated mortality ranges from 20 to 70%. In France in 2016, the mortality rate was reported as 25%.[27] Patients with VAP are often critically ill, with multiorgan involvement. Survival may be affected both by other underlying conditions and sepsis because of a new-onset VAP. A recent study demonstrated a relatively limited attributable (1–1.5%) ICU mortality of VAP when adjusting for the severity of co-existing diseases.[19]

The role of systemic antibiotics in the development of VAP remains unclear. A study by Trouillet et al. showed that recent antibiotics usage (within 15 days) predisposes patients to infection with antibiotic-resistant organisms.[21] In contrast, prior exposure to antibiotics protects against the development of early-onset VAP.[13] However, our study showed no significant association between antibiotic exposure and VAP incidence. The VAP populations had an increased need for a longer duration of antibiotics (mean = 29 days; SD = 23.5), which may reflect an increase in the cost of treatment for patients.

LIMITATIONS OF THE STUDY

Since this was a retrospective study, our main limitation was tracing the patients' medical records. The medical records and ICU charts were kept separately at the record office, and this caused difficulty in obtaining some of the data needed, especially the ventilator setting and arterial blood gas results, which could not be traced elsewhere. In addition, some of the medical records of patients could not be traced because the patients were already deceased or the clinic kept the records for follow-up purposes. This caused a lower number of patients to be included in the study. We were unable to predict the new incidence of VAP due to the cross-sectional nature of the study. However, we were able to identify VAP-associated factors. Diagnosis of VAP using the new CDC definition is limited because most of the information needed relates to the daily ventilator setting, which was recorded in the ICU chart but could not be traced. Furthermore, not all intubated patients were subjected to bronchoscopy because this is an invasive procedure that requires skilful personnel and carries a risk to the patient. Thus, sputum BAL was not obtained from all patients as per the requirement to diagnose pneumonia or probable pneumonia in the new CDC definition of VAP.

CONCLUSION

The proportion of VAP during the study period in HUSM was 29.7%. The rate of VAP was 7.1 per 1000 ventilator days. The factors associated with VAP were increased duration of MV and length of ICU stay. There was no significant difference in mortality between intubated patients who developed VAP and those who did not in our ICU.

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ORIGINAL ARTICLE

Effective connectivity between precuneus and supramarginal gyrus in healthy subjects and temporal lobe epileptic patients

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ABSTRACT

Introduction: The effective connectivity (EC) when the brain is resting and how a neuronal system exerts influence over other regions of the brain, in different groups of subjects are still being investigated. Limited information was seen about the relationship between precuneus (PRE) which is a well-known resting state hub with supramarginal gyrus (SMG) in healthy subjects (HS) and temporal lobe epilepsy (TLE) participants.

Materials and methods: Fourteen HS and 14 TLE patients with age and gender matched underwent resting state functional magnetic resonance imaging (rsfMRI) scanning using a 3-Tesla MRI machine to investigate the EC and percentage of amplitude fluctuation (PerAF) involving SMG and PRE. The rsfMRI data were analysed using Statistical Parametric Mapping (SPM12) and Spectral Dynamic Causal Modelling (spDCM) from which causal models were specified, estimated and inferred.

Results: Model with bidirectional connections between PRE and SMG was chosen as the winning model. The EC from PRE to SMG is positive but the EC from SMG to PRE is negative in both hemispheres and in HS and TLE. Based on the findings from the EC analysis, there is an excitatory effect shown by PRE to SMG connection indicating a dominant role of PRE over SMG in both groups.

Conclusion: There is important evidence showing that PRE might also have influence on areas outside resting state network and the influence changes in the presence of brain abnormality.

KEYWORDS:
Bayesian, effective connectivity, temporal lobe epilepsy, supramarginal gyrus, precuneus

INTRODUCTION

Temporal lobe epilepsy (TLE) is a condition characterized by recurrent, unprovoked seizures originating from either medial or lateral temporal lobe. Recent research shows that longstanding TLE is associated with extra-temporal damage. These findings relate to the importance and relevance of the study of the effective connectivity of other extra-temporal areas of the brain in TLE. Both precuneus (PRE) and supramarginal gyrus (SMG) is located in the extra-temporal area which is a major hub in default mode network (DMN).[1] Precuneus is located at the postero-medial region of parietal lobe while SMG is located in the lateral surface (Wernicke's area) at the inferior parietal lobule region.[2] Based on our preliminary analysis on the most active areas of the brain in both healthy and TLE participants during resting, it was found that the highest brain activity present in the PRE and SMG areas which was represented by the highest number of voxels. Precuneus (PRE), is an area in resting state network, has received attention due to its role as a resting-state hub while SMG in the parietal area is well known as a visual word recognition area. We proposed that PRE which has highly integrated function has a greater influence on SMG would have connectivity changes between two areas in the presence of TLE. Little attention has been given to the relationship between these two areas before especially in the presence of brain abnormality such as TLE. Based on a previous study, it was found that in brains of TLE patients, there is reduced connectivity at the region outside the temporal lobe particularly from the posterior to the anterior DMN during rest.[3]

Effective connectivity (EC) is a measurement on neuronal units in one part of the brain which communicate and influence other parts of the brain. It is causal in nature, that is, the influence one region to over another which is caused by some external stimulations generated within an experimental context.[3,4,5]

Initial study used stochastic DCM (sDCM) to model the observed BOLD time series of each node and to estimate the model parameters and any hyper-parameters that parameterize the random fluctuations.[6,7] Later, a DCM analysis of resting-state fMRI (rsfMRI) data, known as spectral DCM (spDCM) was introduced.[8,9] The spDCM uses a neuronally plausible power-law model of the coupled dynamics of neuronal populations to generate complex cross spectra among measured responses. It estimates the time-invariant parameters of their cross spectra and models the

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observed endogenous random fluctuations between nodes to obtain the cross spectra density which was then used in estimating the EC between the DMN nodes.

Given the fundamental cognitive functions of both regions when the brain is in an active state, it is important to obtain more information about their connectivity and the changes that could occur in the presence of brain abnormality such as TLE when their brain is at rest. To our knowledge, not many studies have focused on resting state connectivity in patients with TLE. Furthermore, there is no study available comparing the EC of specific extra-temporal areas in healthy subjects (HS) and TLE participants during resting state.

Thus, in our study we had investigated the forward and backward connections EC between PRE and SMG in both healthy subjects and temporal lobe epileptic patients. In this study, the causal models that show the best presentation of the EC between PRE and SMG in two groups of subjects (healthy and TLE patients) was developed. We hypothesised that PRE which is known as an area of highly integrated function has a greater influence on SMG and their connectivity changes in the presence of TLE.

Temporal lobe epilepsy is a disease with morbidity in which patient suffers from unpredictable seizure which reduce their quality of life. Thus, our study could give a valuable information on the neuronal electrical circuit that happens in the brain of TLE patient particularly involving PRE and SMG which may give insight to prediction of seizure for better management of this disease. The information gained is valuable in indicating the extent of spread of seizure to both sides of the brain from the focal onset and might be able to trigger a warning that another seizure will happen.

MATERIALS AND METHODS

Subjects

This was an experimental study in which two groups of subjects were involved.

One group consisted of 14 healthy subjects (11 females 3 males) (average age ± standard deviation = 36.93 ± 8.75 years) and another group also consisted of 14 patients (11 females 3 males) with TLE (average age ± standard deviation = 37.00 ± 8.79 years). The subjects from the two groups were matched by their age and gender. Clinical history of their temporal lobe of epilepsy in TLE participants is shown on Table I(a).

The healthy subjects in this study were recruited from persons who accompanied patients (relatives) who went for treatment at polyclinic Hospital Universiti Sains Malaysia (HUSM). HUSM staff were also among the healthy participants who were involved in this study. The inclusion criteria of the healthy subjects where that they were free from medical and/or surgical illness based on history taking done by the medical officer in-charged. Once patients consented to participate, they were screened for MRI compatibility. Then, they underwent preliminary scanning by MRI producing T1-weighted images (T1WI) and T2-weighted images (T2WI). A radiologist was present during the MRI scanning to interpret the MRI findings, and all patients who had normal T1 and T2-weighted images (which were one of the inclusion criteria) were included.

The 14 patients with TLE who were recruited were diagnosed to have TLE by the neurology team and under neurology clinic follow-up. The patients were diagnosed to have TLE based on clinical semiology features of the seizure and the EEG findings that fit the diagnosis. The EEG was also done with video monitoring. All subjects agreed to involve in this study by signing the consent form after being given full explanation about the study including the nature and risks of the research. This study was approved by the Institutional Ethics committee (IEC) of HUSM number USM/JEPeM/16050175. The exclusion criteria of the participants include patients with brain abnormality caused by surgery or injury, tumors, significant malformation of cortical development leading to distortion of brain anatomy, patients who had previous history of brain injuries and psychiatric disorders.

Resting State MRI Scanning

Patients underwent MRI scanning in the Department of Radiology, HUSM using a 3-T Phillips Achieva MRI scanner equipped with 32-channel head and neck system. Particular MRI protocol was executed to ensure that the images taken were in the resting state.

The first three scanned images from the patients were discarded by the BOLD imaging protocol to eliminate the magnetic saturation effect. The echo planar imaging (EPI) parameters for acquiring functional T2* weighted images are echo time (TE) = 33 ms, repetition time (TR) = 1700 ms, flip angle (α) = 75°, slice thickness = 4 mm, slice gap = 0 mm, field of view (FOV) = 192 × 192 mm, matrix size = 64 × 64, voxel size = 2 × 2 × 4 mm, number of scans = 250 and total imaging time = 425 s.[10]

Resting state

To ensure that the patients were in resting state, they were requested not to move their heads during the scan. They were required to be relaxed, empty their mind and passively focus on a fixation point "×" symbol on the screen throughout the session. Subjects were not to fall asleep during the scan because "sleeping brain" is very different from the "resting brain".[11]

Data analysis:

The analysis of the fMRI data involved a number of steps including spatial processing, signal extraction, correlation analysis, modelling and percentage of amplitude of fluctuation.

1. Spatial Processing

A total of 247 functional images were analyzed using Statistical Parametric Mapping (SPM12), Functional Imaging Laboratory (FIL), and Wellcome Trust Centre for NeuroImaging (WTCN), in the Institute of Neurology (ION) at the University College London (UCL), UK – which runs on MATLAB R2016b (The Mathworks, Inc. USA) platform.[12] The functional images of each measurement was first entered into a slice timing module for acquisition time correction. They were then realigned using the 6-parameter affine transformation in translational (x, y and z) and rotational

Table I(a): Clinical history of temporal lobe of epilepsy

Side and cause of TLE	Last seizure attack	Treatment
1) Not known	1 year before scan	Y
2) L	6 months before scan	Y
3) L	2 weeks before scan	Y
4) R temporal mesial sclerosis	3 years before scan	N
5) R temporal mesial sclerosis	4 days before scan	Y
6) Bilateral mesial temporal sclerosis	1 months before scan	Y
7) L	2 years before scan	Y
8) L mesial temporal sclerosis	3 months before scan	Y
9) R	1 month before scan	Y
10) Not known	11 days before scan	Y
11) L	1 year before scan	Y
12) R	1 year before scan	Y
13) R mesial temporal sclerosis	1 year before scan	Y
14) L	1 year before scan	Y

Y = Yes; N = No; R=Right; L=Left; TLE = Temporal lobe epilepsy

Table I(b): Healthy subjects' and TLE patients' percentage of amplitude fluctuation obtained from all regions

	PerAF/% ($p<0.05$)			
	LPRE	LSMG	RPRE	RSMG
Healthy subjects				
1	0.74	0.73	0.58	0.50
2	0.73	0.67	0.68	0.57
3	0.48	0.28	1.00	0.93
4	1.09	0.44	1.44	1.83
5	0.83	0.50	1.40	0.82
6	0.52	0.40	0.45	0.30
7	0.40	0.69	0.82	0.55
8	0.70	0.30	0.39	0.80
9	0.62	0.33	0.65	0.55
10	0.52	0.33	0.44	0.26
11	0.44	0.50	0.46	0.44
12	0.42	0.39	0.37	0.33
13	0.52	0.49	0.43	0.46
14	0.79	0.40	0.59	0.81
Average	**0.63**	**0.46**	**0.69**	**0.65**
Healthy subjects				
1	0.74	0.73	0.58	0.50
2	0.73	0.67	0.68	0.57
3	0.48	0.28	1.00	0.93
4	1.09	0.44	1.44	1.83
5	0.83	0.50	1.40	0.82
6	0.52	0.40	0.45	0.30
7	0.40	0.69	0.82	0.55
8	0.70	0.30	0.39	0.80
9	0.62	0.33	0.65	0.55
10	0.52	0.33	0.44	0.26
11	0.44	0.50	0.46	0.44
12	0.42	0.39	0.37	0.33
13	0.52	0.49	0.43	0.46
14	0.79	0.40	0.59	0.81
Average	**0.63**	**0.46**	**0.69**	**0.65**

(pitch, roll and yaw) directions to reduce the effects on the overall signal intensity from movements of the participants. After realigning the data, a mean image of the series was used to estimate some warping parameters that mapped it onto a template that already conforms to standard anatomical space (EPI template provided by the Montreal Neurological Institute-MNI).[12] The normalization procedure used a 12-parameter affine transformation. The images were then smoothed using a 6-mm full-width-at-half-maximum (FWHM) Gaussian kernel. Low-frequency responses caused by aliased biorhythms, cardiac effects and other oscillatory signal variations were removed using high-passed filter.

2. Signal Extraction

A general linear model (GLM) containing the time corrected, realigned, normalized and smoothed images was chosen for each subject and a design matrix was constructed. This design matrix was then estimated and was used in extracting the time series signals from cerebrospinal fluid (CSF) and white matter (WM) centered at (0, -40, -5) and (0, -24, -33) of a 6-mm radius volume of interest (node) respectively. The extracted signals from the two regions were then used to construct a second design matrix. This new design matrix was then estimated.

The second design matrix was later used to extract signals from the 8-mm radius node of the four DMN nodes; left precuneus (PRE) centered at -9, -78, 36, right PRE centered at 10, -73, 39 [9], left supramarginal gyrus (SMG) centered at -52, -28, 23 and right SMG centered at 55, -28, 28.[10] The time series signal extracted from all the nodes were entered into a third design matrix, together with the extracted signals from CSF and WM, six realigned parameters and global. This newly constructed design matrix was used to generate activation for left and right PRE, left SMG and right SMG for each subject by means of t-contrast (t-test) looking for the effects these nodes would have during which the brain is at rest. Group activation was later produced using one-sample t-test at the second level, in the random-effects framework, corrected for multiple comparisons ($p < 0.05$), testing for the effects against no activation.

3. Correlation analysis

The EC between left PRE and left SMG as well as from right PRE and right SMG was also investigated by means of correlation analysis to determine the distribution of EC between the activated areas across all subjects. The EC obtained from PRE vs. SMG plot for both groups of subjects were averaged and were compared by means of independent t-test. Comparisons in the slopes were also made between the two hemispheres. Similar treatment was also done for SMG vs. PRE plot. Only intra hemispheric connectivity was considered in this study. All the results were reported based on significant level (α) of 0.05 with a 95% confidence interval.

4. Modelling

The time series signals for each node were then used in specifying and constructing the causal models in DCM analysis. Left hemisphere causal models comprising of left PRE and left SMG; and right hemisphere causal models comprising of right PRE and right SMG were constructed using dynamic causal modelling.[13] Based on Figure 1, model 1 has a one directional connection from PRE to SMG. Model 2 has a one directional connection from SMG to PRE and model 3 has a bidirectional connection between PRE and SMG. No input was specified as this study was motivated by resting state condition and all models are assumed to have self-connection on each region, shown by the curved arrows.

The causal models were then estimated using spectral DCM (spDCM) to obtain the coupling parameters, the effective connectivity (EC) between nodes. Their endogenous fluctuation of activity was recorded and analyzed to generate complex cross spectra. The time invariant covariance of the random fluctuations between nodes was then estimated to obtain the cross spectra density which was then used in estimating the EC between the DMN nodes. The EC among coupled neuronal responses was then estimated using a plausible power-law model.[14]

The inverted models were then compared by means of Bayesian model selection (BMS) for group studies under the FFX framework[15], to test the null hypothesis that no single model is better than any other competing models and to obtain a model that has the best balance between fit/accuracy and complexity.

Upon obtaining the most optimum model, the EC values among the DMN nodes were then averaged over the subjects using Bayesian parameter averaging. In Bayesian framework, a connection is considered significant if its posterior probability value is equal or larger than 0.9.[16]

Percentage of amplitude of fluctuation

The percentage of amplitude of fluctuation (PerAF)[17,18] for the left and right hemisphere PRE and SMG were computed for every healthy subject and TLE patient. This is done by first extracting the signal (random fluctuation) from the highest intensity voxel of the main cluster of activation for each region. The SPM maximum intensity projection (MIP) was used to locate the respective voxel. A series of time points (n) on the random fluctuation, denoted as Xi, was used to calculate the average of the fluctuation amplitude (μ) as given by equation (1).

$$\mu = \frac{1}{n}\sum_{i=1}^{n} X_i$$

The PerAF was then computed for each region using μ obtained from equation (1) by means of equation (2).

$$\mathrm{PerAF} = \frac{1}{n}\sum_{i=1}^{n}\left|\frac{X_i - \mu}{\mu}\right| \times 100\%$$

RESULTS

Dynamic causal models and effective connectivity

Figure 2 shows the results of model comparisons obtained from Bayesian model selection (BMS) for left and right hemispheres in healthy subjects and TLE participants. The structure for Models 1, 2 and 3 are shown in Figure 1. From Figure 2, it can be seen that Model 3 is the winning model among the three competing models which has the highest

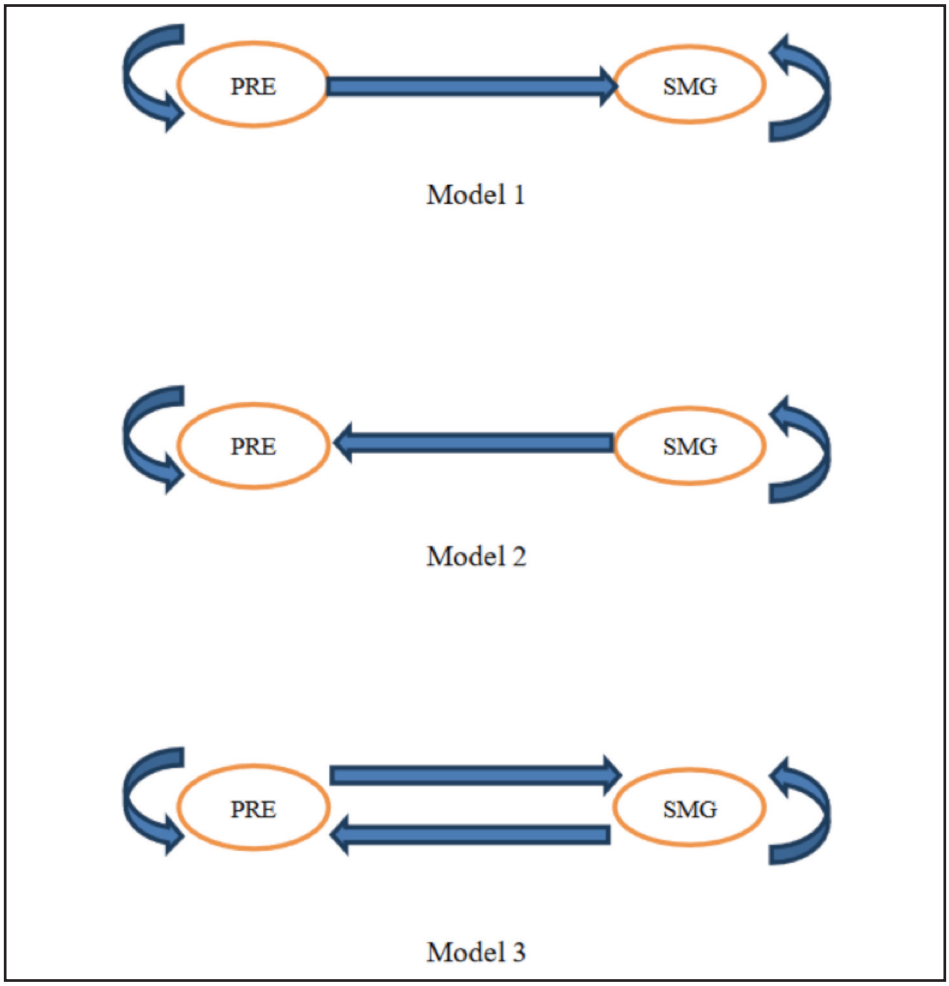

Fig. 1: Dynamic causal model specified to all subjects in this study. Straight arrows represent coupling while curved arrows indicate self-connection.

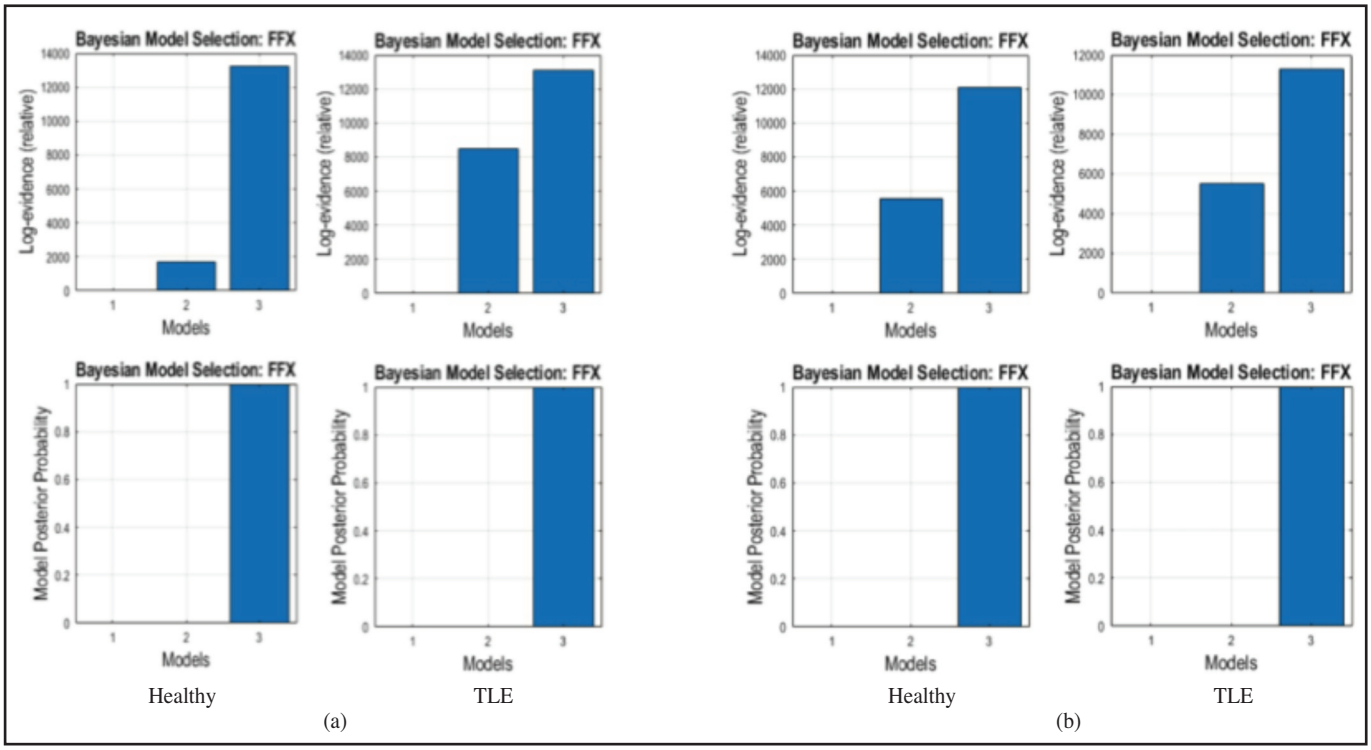

Fig. 2: Model comparison results using BMS for healthy subjects and TLE patients; (a) left hemisphere (b) right hemisphere.

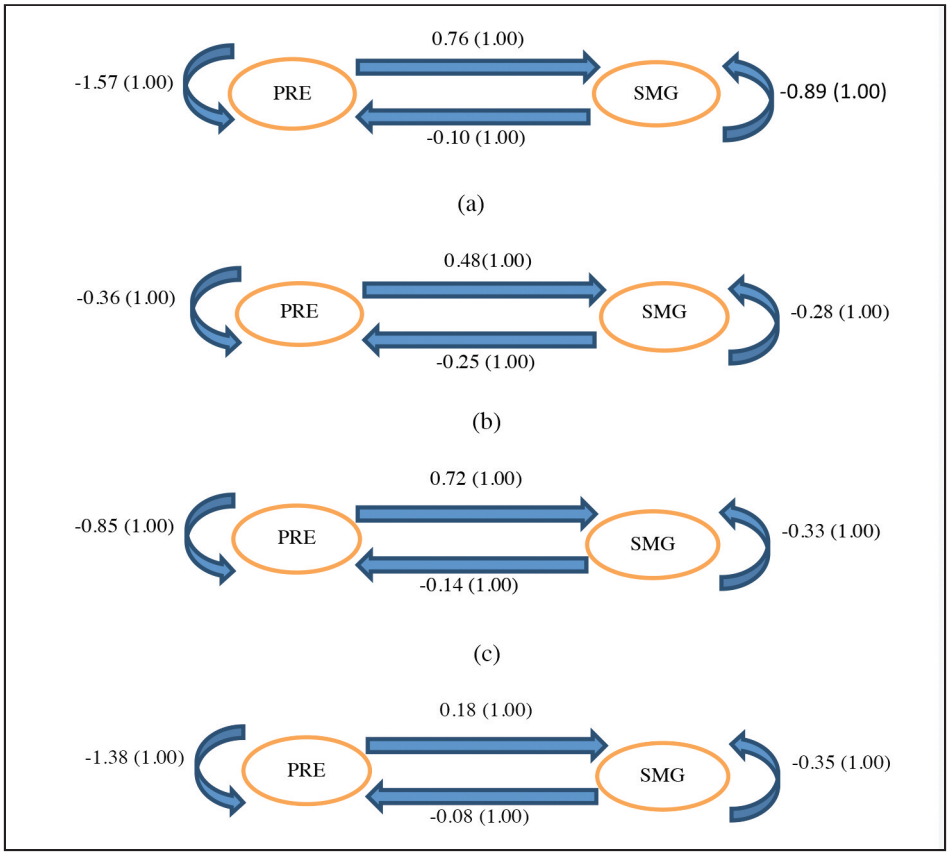

Fig. 3: The EC between PRE and SMG for (a) healthy subjects' left hemisphere, (b) TLE patients' left hemisphere, c) healthy subjects' right hemisphere and d) TLE patients' right hemisphere. Straight arrows represent coupling while curved arrows indicate self-connection. All connectivity values are in Hz. All values are significant (posterior probability > 0.9); ($p < 0.05$; 95% CI).

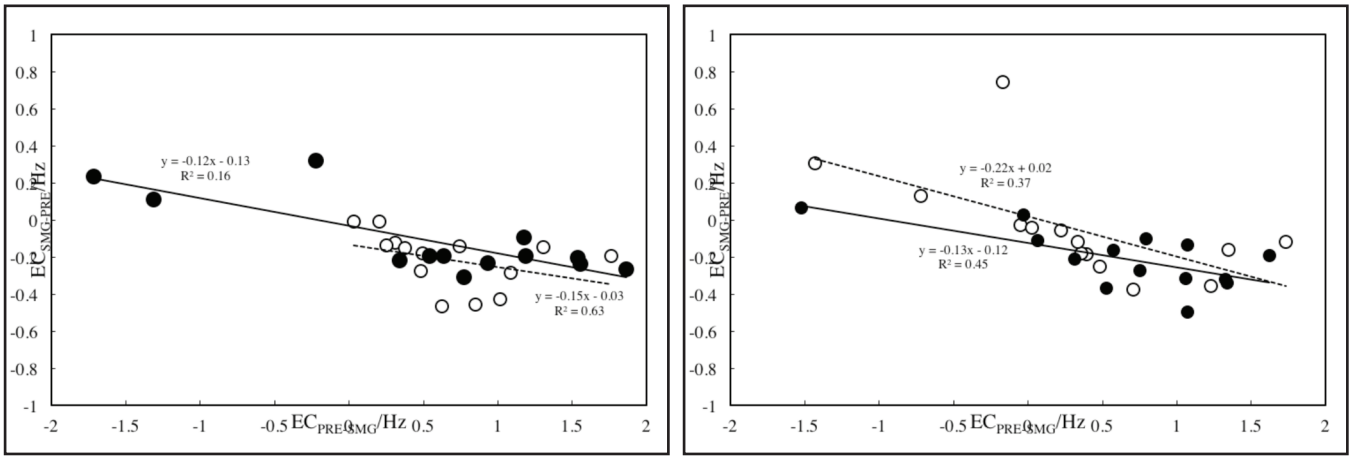

Fig. 4: The EC from SMG to PRE (ECSMG-PRE) plotted against the EC from PRE to SMG (ECPRE-SMG) for healthy subjects (open circle and broken line) and TLE patients (solid circle and solid line); left hemisphere (top) and right hemisphere (bottom).

model evidence and posterior probability. The results are consistent for both hemispheres in healthy subjects as well as in TLE participants. From the results, it can be said that the form of connectivity between PRE and SMG during resting state for both left and right hemispheres is the same in both groups of subjects with bidirectional connectivity between the two regions.

The average EC values and their posterior probabilities (in brackets) for Model 3 obtained from BPA for both groups and hemispheres are shown in Figure 3. Also shown in the figure is the self-connection for both regions. All values are significant (posterior probability > 0.9).

Based on Mann-Whitney U test, it was found that the PRE to SMG connection for HS is no different with that of TLEP ($p > 0.05$; 95% CI) in both the left and right hemispheres. Similar analyses conducted on SMG to PRE connections using similar tests also show insignificant difference ($p > 0.05$; 95% CI).

Based on Mann-Whitney U test, it was found that the PRE to SMG connection for the left hemisphere is no different with that of the right hemisphere ($p > 0.05$; 95% CI) in both the HS and TLEP. Similar analyses conducted on SMG to PRE connections using similar tests also show insignificant difference ($p > 0.05$; 95% CI).

Both the PRE and SMG have negative self-connectivity as can be seen in Figure 3. Statistical analysis conducted using the non-parametric Wilcoxon Signed Rank test revealed significant ($p < 0.05$; 95% CI) differences in the self-connectivity between both regions with PRE having a larger self-connection than SMG for all cases.

In Figure 3, the structures for model 1, 2 and 3 are shown. It shows the connectivity between PRE and SMG during resting state for both left and right hemispheres in both groups of subjects with bidirectional connectivity between the two regions. The average EC values and their posterior probabilities (in brackets) for Model 3 obtained from BPA for both groups and hemispheres are shown in Figure 3. Also shown in the figure is the self-connection for both regions. All values are significant (posterior probability > 0.9).

Figure 3 shows that the magnitude of EC for PRE→SMG connection is larger than for SMG→PRE connection for both hemispheres in healthy subjects and TLE patients. Based on Wilcoxon signed-rank test, the median of differences between PRE→SMG and SMG→PRE connections equals zero indicating a significant difference between the two values ($p < 0.05$; 95% CI) in all cases, rejecting the null hypothesis of no difference. The PRE→SMG connection is positive while the SMG→PRE connection is negative for all cases indicating non-reciprocal behavior of connectivity that could possibly be due to the inhibitory-excitatory interactions between the two regions.

Based on Mann-Whitney U test, it was found that the PRE→SMG connection for healthy subjects is no different from that of TLE patients ($p > 0.05$; 95% CI) in both the left and right hemispheres. Similar analyses conducted on SMG→PRE connections using similar tests also show insignificant different ($p > 0.05$; 95% CI).
Based on Mann-Whitney U test, it was found that the PRE→SMG connection for the left hemisphere is no different from that of the right hemisphere ($p > 0.05$; 95% CI) in both the healthy subjects and TLE patients. Similar analyses conducted on SMG→PRE connections using similar tests also show insignificant different ($p > 0.05$; 95% CI).

Both the PRE and SMG have negative self-connectivity as can be seen in Figure 3. Statistical analysis conducted using the non-parametric Wilcoxon signed rank test revealed significant ($p < 0.05$; 95% CI) differences in the self-connectivity between both regions with PRE having a larger self-connection than SMG for all cases.

Figure 4 is the distribution of PRE→SMG (and SMG→PRE) connections in the left (top) and right (bottom) hemispheres across healthy subjects and TLE patients. All graphs show a negative linear correlation between EC from PRE to SMG and from SMG to PRE from which it can be said that an increase in connectivity from PRE to SMG results in a decrease in connectivity from SMG to PRE. This non-reciprocal behaviour of connectivity is similar in both the left and right hemispheres and the correlation were found to be small to moderate but significant ($p < 0.05$; 95% CI) for all cases, as tested using Spearman correlation test.

Percentage of amplitude fluctuation (PerAF)
The PerAF computed for all regions for healthy subjects and TLE participants are tabulated in Table I(b). The average value for each region is shown in bold-face numbers at the bottom of the table. Statistical analyses conducted within healthy subjects by means of 2-way Friedman's ANOVA by ranks showed no significant difference ($p > 0.05$) in the median of PerAF among regions of interest. This concluded that the distribution of PerAF among left hemisphere PRE and SMG as well as right hemisphere PRE and SMG in both groups of subjects are the same. However, for TLE participants, Friedman's ANOVA indicated a significant difference ($p = 0.041$) in PerAF between one pair of regions; that is between left hemisphere SMG and right hemisphere PRE .

Between groups comparisons (matched region-to-region e.g. PRE for healthy participants vs. PRE for TLE participants conducted using Wilcoxon signed-rank test found no significant difference ($p > 0.05$) in the median of PerAF of all regions between healthy participants and TLE participants. The findings concluded that the fluctuation of signal amplitude is no difference between healthy participants and TLE participants for all regions of interest.

DISCUSSION

The spatial activations that were obtained at a stringent significant level corrected for family wise errors (FWE) for supramarginal gyrus (SMG) and precuneus (PRE) during resting state fMRI is an evidence of higher brain activity (as compared background) that took place in PRE and SMG when the brain is in its default mode.

From the results of our study, it was found that both healthy subjects and TLE patients activated SMG and PRE at rest and both regions were significantly connected in the respective hemisphere. Furthermore, the effective connectivity between SMG and PRE was similar in both the right and left hemispheres, from which the bidirectional model is the model of choice to explain the information exchange between SMG and PRE.

From the spDCM results obtained, it seemed that higher self-connection in PRE is accompanied by higher excitatory (positive EC) connectivity strength from PRE to SMG which in turn return a lower inhibitory (negative EC) connectivity value from SMG to PRE.

In DCM analysis, self-connection parameters are dimensionless and scale up or down the default self-

connection of -0.5 Hz.17 If the values of the self-connections are positive (or more positive), they indicate increased in self inhibition and if negative (or more negative), the values indicate self-disinhibition (or self-excitation).[18] For the between regions connection, positive values indicate excitation and negative values indicate inhibition. In view of the dynamic causal models shown in Figure 2, it can be said that PRE is more negative than SMG in all cases indicating self-excitation whereas SMG is more positive which means that it indicates self-inhibition. It is thought that this self-excitation of PRE drives positive excitatory connectivity from PRE to SMG. To achieve a balanced state of information transfer, the self-inhibitation of SMG then drives negative inhibitory connectivity from SMG to PRE.[16] At the neurophysiological level, this may be seen as non-reciprocal connectivity between two neuronal systems of a network.

The similarity in the model structure for the healthy subjects and TLE participants as well as for the left and right hemispheres for both groups of subjects was validated by the average PerAF values for the respective regions shown in Table I(b). There was significant difference in the median PerAF between left hemisphere SMG and right hemisphere PRE. However, there was an insignificant difference in PerAF values among the regions within both groups due to small differences in each node's activity. Therefore, the EC (that parameterized the model) was not much changed because it was derived from within one region neuronal activity. Furthermore, the abnormality within the TLE participants brain were mainly located at the temporal lobe which is situated outside the regions of interest in this study. Both PRE and SMG are located in the extra-temporal area which is grossly anatomically normal similar to healthy participants. In terms of distance, the epileptic center is at another part of brain which might not significantly affect the connectivity to the PRE and SMG area. Upon MRI screening during selection of the samples, both control and study subjects did not show significant structural abnormality in the brain. Perhaps, the medication taken by TLE participants might have reduced the effects of TLE in the brain. A firm conclusion regarding the relationship between EC and PerAF require confirmation with studies having a larger set of data.

The behaviour (or pattern) of the influence of the activity of one region on another in the form of EC in Figure 4 supports the above discussion. Left and right hemisphere PRE and SMG for both groups of subjects show similar negative correlation of effective connectivity influences. The relationship is non-reciprocal as can be seen from the negative slopes on the graphs. More importantly, the graphs represent the distribution of data from the whole subjects that comprise the group. Non-reciprocity in the EC between two regions has been observed in many previous studies.[16,17,18] Non-reciprocity could be caused by different responses or fluctuations in each region. The difference in brain activity fluctuation, such as delay and amplitude, can be attributed to different responses in particular brain region. This difference could impose influence on the information encoded in another region.

There were several limitations noted in this study. One was the number of participants in our study. However the preliminary results obtained is still meaningful. Larger sample size give more reliable results with greater precision and power, but they also cost more time and money which was limited in our study. The TLE patients recruited in this study were mainly from patients who had been treated with anti-epileptic drugs. This could affect the brain activity and thus EC. We would like to suggest that in future in order to get more findings, patients could stop the treatment 24-hours before the scanning time to see the brain activation without the effect of drug.

Non-homogenous sample size in which varieties of causes of TLE included in our study was due to limited number of cases obtained from in-patient data only. We suggest in future, a homogenous cause of TLE only were recruited in the study as it will create more specific findings related to the group.

CONCLUSION

The resting state fMRI technique via statistical parametric mapping and dynamic causal modeling is able to summarize the connectivity behavior between PRE and SMG in healthy subjects and TLE participants. The winning model in both groups is a bidirectional connection model in which the influence of PRE on SMG is excitatory while the influence of SMG on PRE is inhibitory. The connection strength from PRE to SMG is inversely correlated in which when there is an increase in unidirectional strength from PRE to SMG, there will be a decrease in the unidirectional strength from SMG to PRE, hence explaining the inhibitory nature of SMG to PRE connection. Even though SMG seldom being reported as the main area of DMN in the human brain as much as PRE, it's connectivity at rest to one prominent region of DMN in this study is very significant. Statistical analysis indicates the dominance of PRE as compared to SMG. In this study, even though unidirectional connection from PRE to SMG for HS seemed to be larger than that of TLEP in both the left and right hemispheres, the difference was not significant. TLEP differs significantly with HS only on the PerAF value of RPRE and LSMG.

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The efficacy of intense pulse light among patients with skin type III-IV in acute facial acne: The Malaysian experience

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ABSTRACT

Twenty-seven adult patients, skin type III -V with mild to moderate acne, were recruited. IPL at wavelengths range of 420 - 600nm with triple pulses was administered every two weeks for a total of 3 sessions. Assessment of acne severity and improvement of treatment was based on Global Acne Grading System (GAGS), scoring before and after treatment for each session and patient satisfaction's using a 5-item Likert scale range at the end of session three.

Results: Of the 27 patients, 77.8% were female. Their ages group ranged from 18 to 35 years, and all patients had skin type III or IV. There were 14 mild acne patients and 13 moderate ones. There was a statistically significant improvement in mean acne severity score from 18.1± 4.3 at baseline to 14.3 ± 4.6 after two weeks post-IPL and 12.3 ± 4.9 after four weeks post-IPL. The result on satisfaction level of patients showed 'satisfied' in 3 patients, "very satisfied" in 5 patients; and, half of the patients (11) answered "fair" at the end of the study. Most patients tolerated well the procedure, and only 5 patients developed either post-inflammatory hyperpigmentation or skin hyperpigmentation.

Conclusion: The IPL of wavelength of 400-600nm offers effective, safe, and well-tolerated treatment of mild to moderate acne lesions in Malaysians with skin types III-IV. The majority of subjects had a fair score on treatment satisfaction. It is recommended that reasonable expectations for clinical results be addressed with patients before hands to prevent over-expectation.

KEYWORDS:
Intense pulse light; acne; Malaysian, Fitzpatrick skin type III-IV

INTRODUCTION

Acne is a well-known inflammatory disease of the pilosebaceous units that affect adolescents more often than adults. The two acne lesions are non-inflammatory acne lesions (closed comedones, open comedones) and inflammatory acne lesions (papules, pustules, nodules, and cysts). The disease predominantly affects the areas of skin with a large number of sebaceous glands, including the face, neck, chest, and back. Acne pathogenesis is now thought to be triggered by inflammatory pathways caused by factors such as genetic predisposition, diet, sebaceous gland involvement, inflammatory mediators, and their target receptors, as well as Propionibacterium acnes proliferation.[1-2] Depending on its severity, different methods of treatments have been suggested, and one of the methods is to use treatment with intense pulsed light therapy (IPL).

When a chromophore (melanin, red blood cells, and water) on our skin is exposed to the light of a specific wavelength or colour, it absorbs the energy and self-destructs, resulting from the enormous heat produced by the absorbed energy.[3] IPL is a light source with polychromatic (all visible colour or all visible wavelength from 400nm to 700nm), non-coherent, and non-collimated light waves that spread out as they pass. IPL (400–1200 nm) is thought to disrupt sebaceous gland function by causing direct phototoxic and thermal damages4 and bactericidal effects on P. acnes by inducing reactive free radicals.[4,5] Porphyrins such as coproporphyrin III and protoporphyrin IX formed by P. acnes within sebaceous follicles absorb light wavelengths between 400 and 700nm, with the 415nm wavelength in the blue light spectrum being most effectively absorbed.[6,7] Blue light, on the other hand, has inadequate penetration depth into the skin. Red light, which is longer wavelengths such as 660nm, can, in addition to its deeper penetration, have anti-inflammatory properties by influencing cytokines released from macrophages.[8] IPL was also effective in treating inflammatory acne in darker-skinned patients as a monotherapy, with reduced side effects and better patient compliance.[9] There are currently no proven guidelines for the number of sessions necessary for IPL acne treatment, and the majority of studies used three treatment sessions at two-week intervals.[10,11] Though IPL is effective in treating acne in people in other countries, no research has yet been done in Malaysia on its effects. As a result, this research was aimed to establish the efficacy of IPL as a monotherapy in treating acne in Malaysians.

MATERIALS AND METHODS

Study design and population

This prospective open-label study was conducted from September 2020 to October 2020. The study obtained ethical approval from the Research Ethics Committee of MAHSA

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University (code: RMC/EC36/2020). All participants were recruited through convenient sampling from MAHSA Avenue Clinic, Petaling Jaya, Malaysia. This clinic provides medical services to all its students, staff, and community nearby, consisting of a multi-ethnic population. Adolescent and middle-aged women are the main populations who come to this clinic for getting treatment, especially skin conditions.

Using the reported IPL effectiveness by Patidar MV et al. (2016) and Faul F et al. (2007) as a reference, the largest sample size required to detect a difference between matched sample population (level of significance (α) of 0.01, power of 95% with mean + standard deviation of 24.1 and 20.5), was 15. Considering a 50% possible dropout rate, a total of 31 adult patients aged 18 – 45 years with mild to moderate acne skin type III -V (Fitzpatrick classification) were invited to participate in the study. Patients were excluded from the study if they had severe acne, pregnant, taking oral isotretinoin, immunocompromised patients, receiving light & laser therapies within the last three months, or any acne & cosmetic treatments within the previous six months. During the recruitment, patients were given explanation about the study and their rights. Patients were informed that they would receive the intervention at no cost. Upon agreement to participate, they were asked to sign the informed consent form to allow their demographic information and photos to be used in this study.

Measuring tools

The Global Acne Grading System (GAGS) was used in this study as a subjective tool for assessing the severity of acne based on the presence or absence of inflammation and the degree of involvement.[12] The GAGS, a reliable[13] tool of assessment, considers six areas of the face and chest/upper back with a factor at each area based on the surface area, distribution, and density of pilosebaceous units (Figure 1). The hairline, jawline, and ears define the boundaries of the face. The six areas were graded separately depending on the type of lesion as the following: no lesion =0, one comedone = 1, papule=2, one pustule = 3, one nodule = 4. The lesion score then was multiplied by the factors area, which performs as the weightage score to produce the local scores for each face area. The sum of local scores gives the global score of between 0 and 52 (Table I).

Two well-trained researchers, AI and SK evaluated the severity of acne lesions, who received a 2-hour training on acne assessment and GAGS scoring in all sessions. Both researchers scored the acne lesions independently and gave a global scoring. If the acne severity global score between two researchers had a difference of more than 10%, a consensus was achieved through a discussion. Facial photos of the acne area were taken upon consented by the patients (five angles) at the baseline (week 0) and final follow-up (week 4).

The patient satisfaction throughout the IPL treatment was conducted using a self-administered survey. At the end of the session, patients were asked to score their satisfaction with the treatment provided using a 5-item Likert scale ranging between very disappointed to very satisfied.

The IPL procedure

All patients in this study received three sessions of IPL at baseline (week 0), week 2 and week 4. The three sessions of the two-week interval were utilized in this study following the procedure reported in previous studies.[14,15] The same intervention procedures were provided in all three sessions. During the intervention, appropriate goggles were worn by both the patients and clinicians. A cut-off filter of 420-600nm was used. Test shots were performed on the forearm of patients, and the maximum tolerated dose was selected. The procedure was continued when there was no adverse effect, such as erythema observed after 3-5 minutes. According to the skin type of patients, a range of fluence 10 to 15J/cm^2 with triple pulses was used, in which higher fluence was used for fairer skin type III to IV. Lower fluence was used for darker skin type V. Treatment areas were applied with clear ultrasound gel (approximately 1-2 mm thickness). Two overlap shots of IPL were administered once over each acne lesion. To avoid treating the unwanted area, a wooden spatula was used to cover part of the IPL handpiece tip. The immediate endpoint was observed as mild erythema. Post-procedure, the patient was advised to protect from the sun and to never pick scabs, if they appear. Moisturiser was applied over the treated site immediately after the procedure in all patients, followed by sunscreen (>SPF 35). Post-procedure side effects such as erythema, blistering, scarring, hypopigmentation, or hyperpigmentation were noted and treated with topical steroid-antibiotic cream. Patients received the same procedure in the second and third sessions with a degree of improvement, assessed using GAGS, were conducted for every session.

Data Analysis

The demographic characteristics of the patients, such as age, gender, ethnicity, and satisfaction towards the treatment, were analyzed and presented as a number, percentage, mean and standard deviation where appropriate. The scoring for pre and post-treatment of IPL was done using the Global Acne Grading System (GAGS) and analyzed using paired t-test. A p-value of < 0.05 was considered significant.' Satisfaction of patients towards the treatment was assessed using patient subjective responses at the end of the follow-up visit using questionnaires that rated satisfaction.

RESULTS

A total of 31 patients were recruited, with 27 agreeing to take part in the study. The mean age ± standard deviation (SD) of patients is 20.5 ± 3.6 (range between 18 and 35). There were a total of 19 Malay and 12 Indian patients in this study. The majority of the respondents were females (n=21, 77.8%) and had Fitzpatrick's skin type III (n=16) followed by type IV (n = 11).

During the baseline visit, a total of 14 patients had mild acne condition of score between 1-18 and 13 had moderate acne condition of score between 19-30. The mean baseline acne severity score according to GAGS was 18.1 ± 4.3. There was a significant difference in terms of acne severity score pre-intervention (mean = 18.1, SD 4.3) and two weeks post-intervention (mean = 14.3, SD = 4.6) with t-value (26) = 5.2, $p < 0.0001$. A significant difference was also noted between

Table I: The Global Acne Grading System (GAGS)

Area	Factor	Most severe lesion score*	Local score
Forehead	2		
Right cheek	2		
Left cheek	2		
Nose	1		
Chin	1		
Chest and upper back	3		
GLOBAL SCORE			

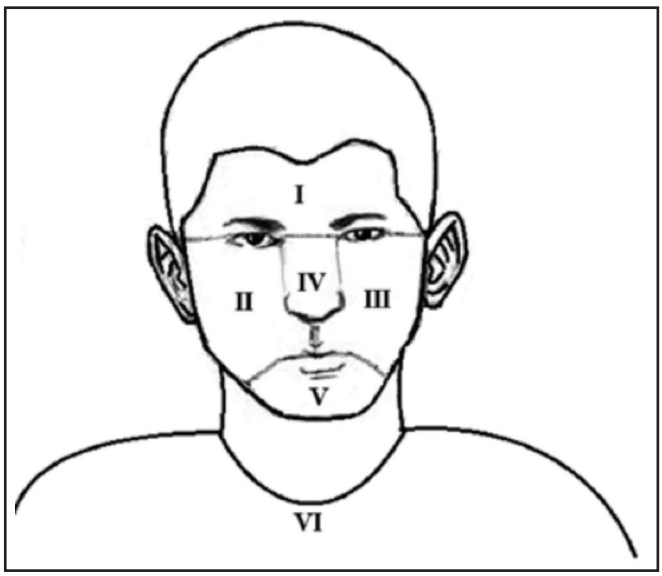

Fig. 1: Visual representation of GAGS scoring for acne.

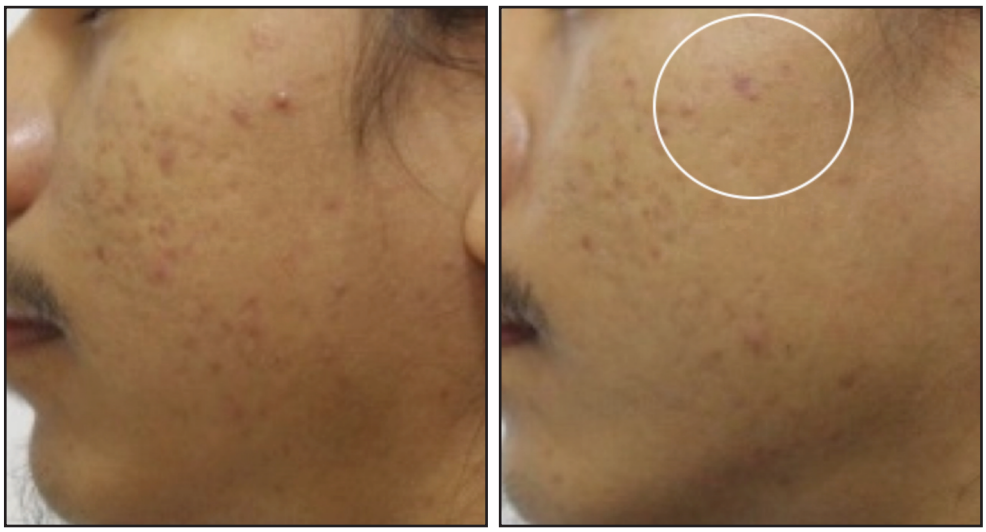

Fig. 2: A 20-year-old male showing clearance of pustules following three sessions of IPL.

pre-intervention (mean = 18.1, SD 4.3) and four weeks post-intervention (mean = 12.3, SD 4.9) with t-value (22) = 6.8, p < 0.0001. For the acne score between week 2 (mean = 14.3, SD = 4.6) and week 4 post-intervention (mean = 12.3, SD 4.9) the results also showed to be significantly different with t-value (22) = 2.4, p = 0.03. According to our subgroup analysis, patients with mild acne improved significantly after four weeks of treatment (pre-intervention: mean = 14.5, SD 2.7; post four weeks intervention: mean = 10.4, SD 3.9) with t-value (11) = 3.1, p = 0.01. Similarly, significant improvement was also observed among patients with moderate acne post 4 weeks of the intervention (pre-intervention: mean = 21.5, SD 2.7; post four weeks intervention: mean = 14.2, SD 4.9) with t-value (12) = 7.07, p <0.01. When the effectiveness of IPL was

Fig. 3: A 21-year-old female showing a reducing number of papules following three sessions of IPL.

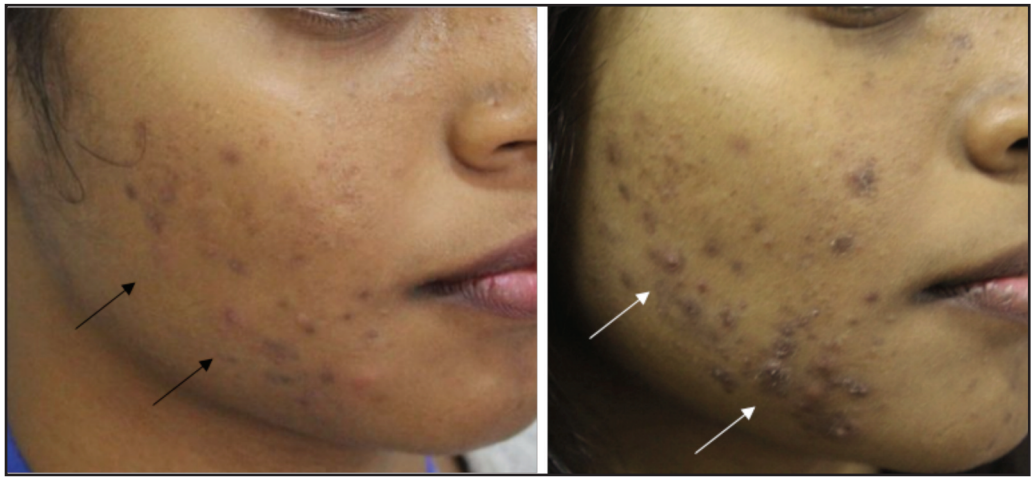

Fig. 4: A 22-year-old female showing post-inflammatory hyperpigmentation following IPL.

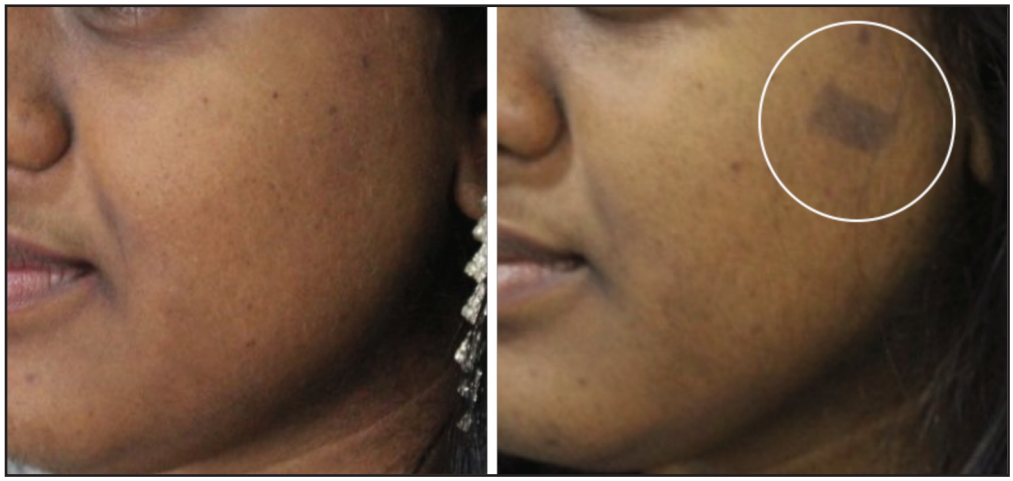

Fig. 5: A 21-year-old female of Fitzpatrick skin type IV showing skin hyperpigmentation following IPL.

evaluated against the demographic information and ages of patient's there was no significant association with the changes of acne severity score pre-and post-intervention (rs = -0.06577, p-value = 0.77). No significant difference in IPL effectiveness was found between males and females (t = 0.56, p = 0.57) and Malay and Indian patients (t = -0.89, p = 0.38). After three sessions of IPL therapy, 81% of patients showed improvement in acne lesions, as shown in Figures 2 and 3. Nonetheless, 2 weeks after IPL, 18% (n= 5) of patients had side effects such as post-inflammatory hyperpigmentation (PIH) and hyperpigmentation, as seen in Figures 4 and 5. In those who developed PIH and hyperpigmentation following IPL, downtime varied from one to two weeks, although it usually took longer for complete resolution of the lesion.

The mean score of satisfaction of patients upon completion of the treatment is 3.4 ± 0.9 of the total score of 5. Three patients were very satisfied at the end of treatment; 5 were

satisfied, 11 were fair, one was disappointed and very disappointed with their treatment. Six patients did not fill in their satisfaction evaluation form at the end of the study.

DISCUSSION

In this study, the mean age of our patients was 20.5 + 3.6, and the majority of them were females. Most of our patients had Fitzpatrick skin type III, where half of them had mild acne and the other half have moderate acne. Based on demographic data, patient ages, and gender, there was no significant effect of IPL has been reported.

A few known methods like topical regimens and systemic acne therapies are scientifically proven and widely accepted as an effective treatment for acne. Nevertheless, their level of effectiveness and satisfaction with the treatment given are varied. IPL may be an alternative treatment option when topical or systemic therapies either had not been effective, were contraindicated, or are not preferred by the patients. The photothermal activity of IPL at wavelengths of 400-420nm helps minimize active acne lesions and new lesions by heating the sebaceous gland and photochemical inactivation.[3,5] This mechanism supports our finding that IPL therapy showed better therapeutic effects for moderate acne patients than mild acne patients. Generally, mild acne is due to the formation of comedones (blackheads or whiteheads). At the same time, the growth of bacteria such as P. acnes remained relatively limited compared to the case of moderate acne. Hence, IPL therapy is more effective for moderate acne cases, which the prominent cause is the formation and growth of Cutibacterium colonies and inflammation.[3,5] The study conducted by Mathew et al. also showed that IPL is an effective treatment for acne-induced post-inflammatory erythema (PIE) in Fitzpatrick's skin type III and type IV.[16]

IPL can be delivered by splitting the energy into two, three, or four pulses with different pulse delays, which allow the skin to be cooled between pulses, thus preventing adverse effects. Kumaresan et al. compared burst-pulse and single pulse mode of IPL and found that burst-pulse mode had a better result in clearing acne than the single-pulse mode.[4] Patients with darker skin types are more likely to have hyperpigmentation and skin burning post-IPL.[4,17] Our study used a range of fluence 10 to 15J/cm^2 with triple pulses to minimize the risk of skin burning, erythema, and PIH. However, five (18 percent) of our patients with Fitzpatrick skin type III-IV experienced skin burning and PIH despite using sub-pulses mode with longer pulse width and off-time between 20ms to > 30ms. Our results were consistent with the research conducted by Mathew et al. and Kawana et al., who noticed that Fitzpatrick skin type III - V was more likely to have an adverse effect.[16,17] However, Patidar et al. found that both normal(35J/cm^2) and subnormal fluence(20J/cm^2) were equally effective in reducing side effects. None of their patients experienced hyperpigmentation and scarring following IPL.[18]

IPL for acne treatment is not without complications, and recent studies have shown that it induces more side effects and complications in patients with skin types III-V.[17,16] According to our study, five patients with skin type IV experienced side effects. This may be one reason why most of our patients were moderately satisfied with the free IPL treatment given. Other causes could include the differing perceptions of patients and/or higher expectations of clinical outcomes, resulting in a reasonable degree of satisfaction with the treatment. Six patients failed to turn up for their final assessment visit, by which time the survey was expected to be handed out. Patients may not have shown up for the last visit evaluation due to concerns about the COVID-19 disease outbreak, which hit countries near the end of the study.

CONCLUSION

The intense pulse light therapy of wavelength of 400-600nm offers effective, safe, and well-tolerated treatment of mild to moderate acne lesions with skin types III-IV. It may be an attractive option for treating acute facial acne, with a low risk of side effects in the Malaysian population. The majority of subjects responded noting a fair score on treatment satisfaction. In order to prevent over-expectation by patients, it is recommended that this be addressed with patients before hand.

LIMITATIONS

The main limitation of this study is a short-term follow-up period because of the COVID-19 outbreak. We should extend the study by six to twelve weeks to collect more data on the recurrence rate of facial acne and patient satisfaction.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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Amelioration of inflammation in young men with cardiovascular risks participating pedometer-based walking programme

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ABSTRACT

Introduction: Inflammation plays a central role in the pathogenesis of cardiovascular events. The lack of exercise among Malaysians and the increasing cardiovascular diseases among young men are of concern. The aim of this study was to evaluate the reducing of inflammation by measuring C-Reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α).

Materials and Methods: A total of 70 young men (20 - 40 years) who were sedentary, achieving less than 5,000 steps/day in casual walking with 2 or more cardiovascular risk factors were recruited in Institute of Vocational Skills for Youth (IKBN Hulu Langat). Subjects were randomly assigned to a control group (CG) (n=34; no change in walking) and pedometer group (PG) (n=36; minimum target: 8,000 steps/day). All parameter was measured at baseline, at 6 weeks and after 12 weeks.

Results: At post intervention, the CG step counts were similar (4983 ± 366vs 5697 ± 407steps/day). The PG significant increased step count from 4996 ± 805 to 10,128 ±511 steps/day (p<0.001). The PG showed significant improvement in anthropometric variables and lipid (time and group effect p<0.001). After intervention, CRP, IL-6 and TNF-α were significantly reduced for time and group effect (p<0.001). However, no changes were seen in CG.

Conclusion: The pedometer-based walking programme improved health status in terms of improving inflammation and arterial stiffness.

KEYWORDS:
Pedometer based walking programme, inflammation, young men, cardiovascular risks.

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of mortality and disability that challenges humankind in both health and wealth in developing countries including Malaysia and the prevalence of CVD is still rising.[1] Among the CVD, more than 50% were due to ischemic heart disease (IHD). Twenty-three per cent of these patients were reported to be less than 50 years old. Most of the Acute Coronary Syndrome (ACS) cases involved men.[2] The increased in the prevalence of IHD may be due to increase in CVD risk factors such as lack of physical activity, smoking, hypertension, dyslipidaemia, obesity, and diabetes mellitus.[3] Atherosclerosis may develop with the presence of cardiovascular risk factor. Atherosclerosis is a chronic and progressive inflammatory disease of the artery which develops in the intima layer of the artery. Atherosclerotic plaques contain various cells (inflammatory, endothelial and smooth muscle cells), connective tissue and fat.[4] The initial steps involved in the formation of fatty streak which consist of foam cells, which are actually macrophages that engulf fat.

Atherosclerosis will develop if a diet high in cholesterol mainly low-density lipoprotein (LDL) is taken. LDL in the blood would enter the intima layer of the arterial wall and with the presence of free radicals it will become oxidized LDL. Oxidized LDL will stimulate release of phospholipids and further activate the expression of vascular cell adhesion molecule–1 (VCAM-1) and intercellular cell adhesion molecule-1 (ICAM-1) in the endothelial cells. VCAM-1 and ICAM-1 on the surface of endothelial cells may attract leucocytes in the blood to bind with endothelial cells and enter the intima layer. These leucocytes will release a lot of cytokines that enhance inflammation in this area. Oxidized LDL will be taken by macrophages via scavenger receptors and produce foam cells that make macrophage less mobile and start to accumulate in this region. Foam cells are still active and can produce inflammatory cytokines such as macrophage chemoattractant protein-1 (MCP-1).[5] These activities will enhance the inflammatory process and produce various inflammatory mediators such as tumour TNF-α, Monocyte Colony Stimulating factor (MCSF), MMP-1 and Interleukin-18. These mediators further stimulate release of IL-6 and this mediator will enter the bloodstream and stimulate the liver secretion of CRP. CRP will enhance more inflammatory mediators release by macrophages and worsen the inflammation in that area. CRP may also impair

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bioavailability of nitrous oxide (NO) in the arterial wall and lead to vasoconstriction.[6]

Overcoming the sedentary lifestyle by engaging in sustainable daily physical activity (PA) is a practical approach in reducing the risk of developing CVD. The National Institute for Health and Clinical Excellence (NICE), 2006[12] guidelines highlights the contribution of regular physical activity in promoting to the health of communities. It is recommended that every adult accumulates the recommended 30 minutes of moderate physical activity on five days of the week or to accumulate 150 minutes per week in at least bouts of ten minutes of sustained physical activity. Besides, the Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) also recommends adults to walk 10,000 steps/day on most days of the week . These recommendations have been shown to promote and maintain health and significantly reduce the risk for CAD.[13]

Walking is a form of exercise that is very acceptable to many people and may be integrated easily into daily routine. However, NICE indicates that there is currently insufficient evidence to recommend the promotion of organised walking schemes, and that the effects of low levels of exercise are poorly documented.

Thus, the aim of the present study was to determine the effects of pedometer-based walking programme at workplace on reducing reducing of inflammation by measuring CRP, IL-6 and TNF-α. Up to now, there are only a few reports of adherence within unsupervised walking programme in reducing cardiovascular risks.[14,15] Furthermore, there are gaps in evidences in relation to the effects of varying doses of exercise using pedometers as an adjunct to other interventions. In addition, pedometer-based health promotion is gaining in popularity but data on its role in intervention for health is lacking.

MATERIALS AND METHODS

Subjects

This prospective randomized controlled trial study was conducted in the Institute of Vocational Skills for Youth (IKBN) Hulu Langat, Selangor, Malaysia. The inclusion criteria were young men aged 20-40 years old, sedentary lifestyles with less than 5000 steps per day and have 2 or more cardiovascular risk factors such as hypertension, dyslipidemia, abdominal obesity, smoking, and family history (FH) of CVD. Exclusion criteria were those with diabetes mellitus (DM) and other chronic disease such as CVD, peripheral vascular disease, lung disease, liver disease, and inflammatory disease. Adults above 40 years old were excluded to prevent bias since the body changes may differ either between men and women or young and adults people. DM was excluded since this disease is equivalent to coronary artery disease (CAD), and subjects may have advanced vascular properties compared to other CV risk factors.[16] Criteria for young Malaysian males for various CV risk factors was observed as per reference given with each of the following: 1) Hypertension: systolic blood pressure ≥140 and/or diastolic ≥90 or on antihypertensive medication. 2) Diabetes mellitus: fasting plasma glucose ≥7mmol/L.[17] 3) Smokers: a habit of daily smoking continued at the time of recruitment for study. 4) Abdominal obesity: waist circumference >90 cm. 5) Family history (FH) of premature CAD: when parents had CAD at <55 (father) or <65 (mother) age. 6) Dyslipidemia: when TC >6.2mmol/L, TG >1.7mmol/L, LDL >4.2mmol/L, or HDL <1.04mmol/L.[18] In this study, a total of eligible 70 young men (20 - 40 years) who were sedentary, achieving less than 5,000 steps/day in casual walking with 2 or more cardiovascular risk factors were recruited.

Pedometer-based walking programme

The research design was approved by the Research and Ethics Committee of Universiti Kebangsaan Malaysia (FF-2019-139). The protocol as well as the potential risks and benefits of participating in this programme were explained to each subject before he gave written consent. Once enrolled in the program, subjects underwent a complete medical history and physical examinations to ensure that they were fit for the exercise intervention. During the trial phase, each subject was exposed to the self-monitoring pedometer programme which needed full commitment from each subject. The subjects were informed that the programme involved a self-monitoring-based pedometer intervention, and they were expected to give full commitment and must be mentally and physically prepared to go through the next phases. In the trial week, the subjects were instructed to assess their average number of daily steps with a pedometer for five days including four working and one non-working day. The average number of daily steps was used as the baseline for the further step goals. Subjects with less than 5000 steps per day were recruited in this programme. In this 4-week trial, subjects are required to gradually increase their walking by 1000 steps/day over 4 weeks. At the end of the trial phase, they were to achieve a mean daily step count of 3000 steps/day on at least 5 days of the week, so that a total minimum number of 8000 steps/day is needed before the start of the actual intervention phase. The most important goal was the improvements above the baseline values. No instructions were given regarding nutritional intake or dietary habits.

Then, subjects were randomly assigned to either a control or pedometer group. Seventy random numbers obtained through Microsoft Excel 2007. Each random number representing the two groups, either pedometer or control group. Each subject was required to select a random number without knowing which group represented the number. The subjects were divided into groups according to a random number assigned either a CG or PG. Those subjects assigned to the PG were followed a 12-week pedometer-based walking programme using pedometers (Yamax Digi-Walker SW-200)[19] for monitor the number of steps initiated by them from wake-up to bed time every day (five days per week) and the numbers of step were keyed in into diary book. Flow of chart of the study is summarized in Figure 1.

Subjects assigned to the CG were maintained their habitual lifestyle and not to change their activity throughout this programme. There were three sessions of cardiovascular markers assessments: at baseline, at 6-weeks intervention (short-term effects) and at 12-weeks intervention (post intervention).

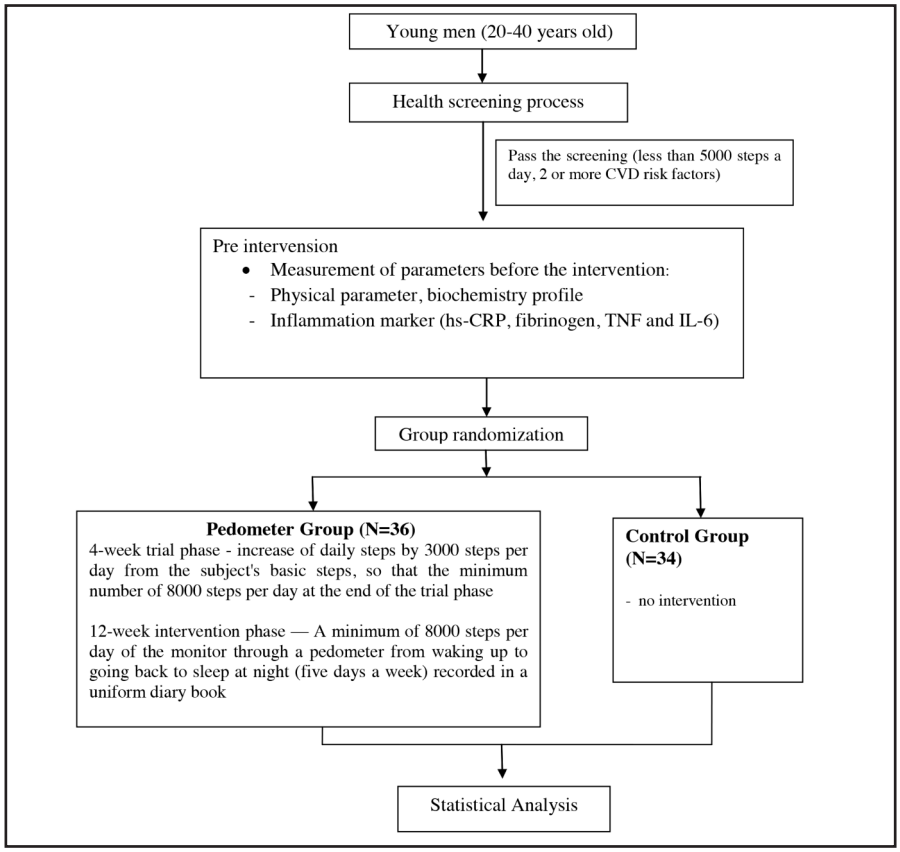

Fig. 1: Flow chart of the study.

Measurement of Physical parameters.
Heights of subjects was measured by a wall-mounted stadiometer (SECA, Hamburg, Germany) and weight was measured by using a digital scale (SECA, Hamburg, Germany). Body mass index was then calculated as weight (kg)/height (m2). Waist circumference was measured by a measuring tape on the horizontal plane, midway between the anterior superior iliac spine and lower rib after normal expiration.[18]

Measurement of blood parameters.
About 5 ml of blood was withdrawn from the antecubital vein after fasting for a minimum of 8 hours. Blood samples were then sent to Gribbles pathology laboratory (Petaling Jaya, Selangor, Malaysia) for further analysis of lipid profiles, CRP, and glucose. This laboratory obtained International Organization of Standardization (ISO: MS ISO 15189) in compliance with the standard quality. The serum TG, HDL cholesterol, and TC were measured using enzymatic methods (Advia 2400 Chemistry Analyzer, Siemens, Tokyo, Japan). The blood glucose was measured by enzymatic method using hexokinase and glucose-6-phosphate dehydrogenase enzymes (Advia 2400 Chemistry Analyzer, Siemens, Tokyo, Japan). For lipids profile, the inter-assay coefficient of variant (CV) ranged from 1.4-3.5%. The inter-assay CV for CRP ranged between 2-2.4%, and CV for glucose ranged from 1.6-1.7%. The TNF-α & IL-6 were conducted using enzyme immunoassay (ELISA) method.

Statistical analysis
Visual inspection of the histogram (plotted as the distribution frequencies) and acceptable level of skewness (-1 to 1) and kurtosis (-1 to 1) were used to determine the normality of the data. All the data were normally distributed except for CRP, TNF-α & IL-6 which were skewed. The values of CRP were logarithmically transformed to improve the skewness and were used in data analysis. All the data were in mean (95% CI) except for CRP, TNF-α & IL-6 which was in median [inter quartile range (IQR)]. The levels of cardiovascular parameters between groups were compared by general linear model (GLM) repeated measures. The significant results were accepted as $p<0.05$. All the data were analyzed using the Statistical Package for Social Sciences Version 20 (SPSS Inc., Chicago, IL, USA).

RESULTS

The characteristics of the subjects for the whole and each groups is summarized in Table I. They were young males (n=70), with mean BP, WC, lipid profile, blood sugar and PWV within normal range. The CRP level was considered to be in the average risk. The prevalence of hypertension was 4.0%, abdominal obesity 51%, dyslipidemia 67 %, smoker 74 %, and FH of CAD 10%. None of them had DM or prediabetes (6.1 mmol/L, <FBS <7mmol/L).

In following intervention, the number of steps for PG significant increase for time and group effect ($p<0.05$).

Table I: Subject`s characteristics

Parameter	Pedometer Group(N=36)	Control Group(N=34)	p value
Age (years)	26.17 ± 6.68	26.62 ± 7.393	0.937
Weight (kg)	73.32 ±18.47	68.94 ± 14.15	0.271
Height (m)	1.67± 0. 056	1.68 ± 0. 056	0.818
BMI (kg/m2)	26.13± 5.99	24.49± 4.54	0.202
Waist circumference (cm)	86.56± 15.09	83.75±14.01	0.422
SBP rest (mmHG)	120.22± 8.97	122.12±8.23	0.361
DBP rest (mmHG)	64.70± 8.84	67.52± 8.31	0.172
HR rest (bpm)	70.81±12.09	70.32± 14.20	0.879
Cholesterol level (mmol/L)	5.01± 0.80	5.10 ± 1.26	0.732
Triglyceride level (TG) (mmol/L)	1.81 ± 0.90	1.82±1.24	0.939
HDL level(mmol/L)	1.17± 0.17	1.18± 0.19	0.718
LDL level(mmol/L)	3.07±0.76	3.28± 1.04	0.314
Fasting Blood Glucose(mmol/L)	4.94± 0.85	4.77± 0.42	0.293
CRP (mg/L)	2.23 ± 2.32	2.49 ± 2.25	0.729
TNF-α (pg/ml)	22.00± 7.75	21.50 ± 8.00	0.520
IL-6 (pg/ml)	12.50 ± 10.47	11.25 ± 6.96	0.590

Data is presented as mean± SD, except for hs-CRP, TNF-α & IL-6 data are presented as median± interquartile range (IQR)
*p< 0.05 is considered significant

Table II: Number of steps per day

	Pedometer group(N=36)		Control Group(N=34)	
	Week 1	Week 12	Week 1	Week 12
STEPS/DAY	4996 ± 805	10128 ± 511**#	4983 ± 366	5697 ± 407 NS

*p< 0.05 (time interaction*group) ** p< 0.01 (time interaction*group) # p<0.05(time effect)

Table III: Changes characteristics of the subjects

	Pedometer group(N=36)			Control Group(N=34)		
	Week 1	Week 6	Week 12	Week 1	Week 6	Week 12
Weight (kg)	73.32± 18.47	72.62± 18.37**	71.35± 16.47**#	68.94± 14.15	69.71± 13.47	69.69± 13.69
BMI (kg/m2)	26.13± 5.99	25.88± 5.93**	25.43± 5.27**#	24.49± 4.54	24.56± 4.51	24.54± 4.57
Waist circumference (cm)	86.56± 15.09	84.87± 13.94**	83.62± 13.53**#	83.75±14.01	84.46±13.79	84.01± 13.11
SBP rest (mmHG)	120.22± 8.97	116.39± 9.71*	116.33± 9.62**#	122.12±8.23	118.62±10.57	118.71± 10.63
DBP rest (mmHG)	64.70± 8.84	63.89± 8.83	63.83± 8.73*	67.52± 8.31	67.44± 9.69	67.82± 6.68
HR rest (bpm)	70.81±12.09	67.92± 12.50	66.89±10.83*	70.32± 14.20	71.18±14.33	71.23± 12.87
Total cholesterol	5.01± 0.80	4.92 ±1.02	4.62± 1.08*	5.10 ± 1.26	5.17± 1.11	5.29± 1.08
TG	1.81 ± 0.90	1.31± 0.91*	1.16± 0.59**#	1.82±1.24	1.75± 0.69	1.77± 1.31
HDL	1.17± 0.17	1.24± 0.21*	1.29± 0.24**#	1.18± 0.19	1.17± 0.16	1.16 ± 0.16
LDL	3.07±0.76	3.05±0.82	2.87± 0.85*	3.28± 1.04	3.35±0.82	3.6± 1.35
FBS	4.94± 0.85	4.99± 0.98	4.84 ± 0.83	4.77± 0.42	4.61±0.34	4.68± 0.53

*p< 0.05 (time interaction*group) ** p< 0.01 (time interaction*group) # p<0.05(time effect)

Table IV: Changes of inflammation markers

	Pedometer group(N=36)			Control Group(N=34)		
	Week 1	Week 6	Week 12	Week 1	Week 6	Week 12
CRP(mg/L)	2.23 ± 2.32	1.44 ± 2.13*#	0.95 ± 1.58*#	2.49 ± 2.25	2.55 ± 2.15	2.99 ± 3.40
TNF-α (pg/ml)	22.00± 7.75	20.00 ± 7.00*#	14.00±16.50**#	21.50 ± 8.00	22.00± 10.50	23.35 ± 9.75
IL-6 (pg/ml)	12.50±10.47	7.37± 7.33*#	5.25± 3.47**#	11.25 ± 6.96	11.55 ± 6.79	11.56 ±7.13

*p< 0.05 (time interaction*group) ** p< 0.01 (time interaction*group) # p<0.05(time effect)

However no change seen in CG (Table II). In term of physical parameter , after pedometer-based interventions for 12 weeks, the body weight and waist circumference were significant decreased for PG (time and group effect, $p<0.05$) and significant improved for lipid profiles in PG (Table III).

The median CRP changes significantly decreased in PG for time and group interaction, $p<0.05$ (Table IV) as well as significant reduced noted for TNF-α & IL-6 (time and group effect, $p<0.05$). No change seen in CG (Table IV).

DISCUSSION

The pedometer is a validated instrument to measure steps, and it encourages increased physical activity effecting health-related quality of life.[21] Pedometers allow ambulatory populations to track their steps, which influences motivation through goal-setting. The current study noted better compliance and more accumulated steps in the subjects treated with pedometers and a daily step-recording log.

The results of our study suggest exercise interventions decrease body weight, BMI, WC, total cholesterol, increase high-density lipoproteins (HDL), decrease low-density lipoproteins (LDL) and lower blood pressure . The current study did not produce significant changes in fasting blood glucose (FBG). The lack of changes in FBG in this study may have been attributed due to baseline value was in normal range. The blood lipid results from our study compliment prior studies that have shown that physical activity effectively increases HDL and decreases both LDL and total cholesterol. Leon and colleagues (2000) reported that 20 weeks (5 months) of supervised exercise significantly improved HDL.[22] Our study showed an increase in HDL for PG in 12 weeks duration. The increased HDL increase in this study, may be attributed to: the 5 days exercise vs. 3 times per week in the Leon et al. study, to the self-selected exercise intensity in the current study, higher self-selected volume of exercise, or to a random effect of our smaller sample size, gender, or ethnicity. Walking exercise training programs can result in modest decreases in body weight and fat stores, blood pressure (particularly in persons with elevated resting blood pressure), serum triglycerides, and low-density lipoprotein cholesterol, and increases in the "protective" high density lipoprotein cholesterol.

Both SBP and DBP were found to be reduced in the first 6 weeks and maintained over the second six weeks. The physical conditioning achieved by regular walking exercise decreases the heart rate and blood pressure at rest and at given level of exercise.[23] Consequently, the workload on the heart is reduced and angina symptoms may be alleviated. Regular exercise also improves muscle function and increases the cardiac ability of the patients to take in and use oxygen. This is commonly referred to as the maximal oxygen consumption or aerobic capacity. As the ability of the body to transport and deliver oxygen improves, the patient has added energy and less fatigue. This benefit is important for patients with cardiovascular risk whose aerobic fitness is typically less than that of healthy adults of similar age. Moreover, moderate exercise on overall cardiovascular risk, when combined with other lifestyle modifications (such as proper nutrition, cessation of smoking, and medication use), can be dramatic.

Inflammatory markers in cardiovascular risks

The study showed a significant reduction in CRP, TNF-α and IL-6 in the pedometer group after the intervention, and no significant change for the control group.[24,25] There are significant differences and the interaction effects between the two groups pedometer and control. A reading of fibrinogen, TNF-α and IL-6 in both groups respectively but still within the normal range in the direction of the border beyond the normal. However, the pedometer group showed a significant decrease in the pattern of TNF-α and IL-6 at the end of the intervention. CRP readings for the two groups are in a moderate risk range of between 1 to 3 mg / L. For the pedometer, the overall decline of 0.65 mg / L is equivalent to 57% is a very large and so makes reading Hs-CRP less risky belongs to a group at the end of the intervention. According to a study conducted by[26] as much as 16-41% decrease in CRP after undergoing regular physical activity can reduce the risk of heart disease.

As stated previously, the production of CRP is stimulated by IL-6 and also of IL-1 and TNF-α. Hiperinsulin factors contributing to obesity and increased production of inflammatory markers. Inflammatory process that occurs starting from adipose tissue leads to obesity due to excessive adipocyte cell hypertrophy and infiltration of macrophages.[27] The increased number of fat cells that trigger an inflammatory response. Production of proinflammatory cytokines trigger inflammation in the arterial wall. Primary cytokines (interleukin- 1 [IL-1], tumour necrosis factor - α [TNF-α]) mediates attraction and migration of inflammatory cells into the vascular tissue. It is also encouraging intermediary other cytokines such as interleukin- 6 (IL-6), which is released into the systemic circulation, causing the liver to increase the production of acute phase reactants, such as CRP. IL-6 is a cytokine primary procoagulant. It can increase the plasma concentration of fibrinogen and CRP that strengthens the inflammatory response and procoagulant.[28]

Thus, through physical activity such as walking in this study can reduce the mass of adipose tissue and indirectly reduce inflammation or inflammation. This study is in line with another by Mayer et al. (1998)[29] that has shown that physical activity lowers the level of IL-6, TNF-α and CRP reduction in line with the reduction of obesity and insulin sensitivity. Physical activity also reduces inflammation through repair of endothelial function. As is well known endothelial cells secrete IL-1 and IL-6, and activated endothelial cells will increase the production of interleukins and adhesion molecules that promote inflammation. Therefore, constant physical activity lowers peripheral inflammatory markers associated with endothelial dysfunction, for example, intracellular and vascular adhesion molecules and MCP-1.[30] In addition, moderate-intensity physical activity such as walking continued this can improve endothelial function by maintaining or increasing nitric oxide and increase anti-oxidant defence through up-regulation of anti-oxidant enzymes. Furthermore, the anti-oxidant effect of physical activity can reduce LDL other than

their more oxidized, which in turn can help prevent endothelial dysfunction and inflammation. In summary, this continuous physical activity can reduce CRP directly through cytokine reduction in fat, muscle and mononuclear cells and indirectly through increased insulin sensitivity, repair of endothelial function and weight reduction.

CONCLUSION

A pedometer-based walking programme may be an effective strategy for promoting increased daily physical activity which reduces inflammatory processes and improving arterial stiffness which can be seen as early as 6 weeks and normalized after 12 weeks and thus improve cardiovascular health. Findings from this study will provide future direction for community based physical activity. Physical health and work performance of the employee are directly related. Healthy work environment will help in improving his productivity. It helps in giving job satisfaction to the employees and to motivate the employees to work better and in safer manner such as work hard and play safe.

AUTHOR CONTRIBUTIONS

Conceptualization, N.O and M.S.M.S.; data curation, N.O.; investigation, N.O.; methodology, N.O., AA., and K.C.; original draft preparation, N.O.; writing—review and editing, N.O., R.Z., M.S.M.S., A.A., and K.C. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Factors predicting clinical outcomes of continuous ambulatory peritoneal dialysis associated peritonitis – A single centre study

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ABSTRACT

Background: Peritonitis is the common complication among Continuous Ambulatory Peritoneal Dialysis (CAPD) patients. This study is aimed to identify the factors predicting clinical outcomes of peritonitis in patients undergoing CAPD and the demographic, clinical and microbiological features of CAPD patients who were diagnosed with peritonitis.

Materials and Methods: This is a retrospective observational study conducted to identify factors predicting clinical outcomes of CAPD associated peritonitis over a four-year period in Taiping Hospital, Malaysia.

Results: A total of 109 episodes of CAPD associated peritonitis in 54 patients was enrolled with a median age being 56.5 years. In all 43.1% of these were complicated peritonitis. About half (n=54, 49.5%) of the peritonitis was caused by a single gram-positive organism. Coagulase negative *Staphylococcus (CoNS)* and *Escherichia coli* was the most often isolated gram-positive and gram-negative microorganism, respectively. We observed that less likelihood of developing complicated peritonitis in presence of abdominal pain (Odd ratio, OR 0.25, 95% confidence interval, 95%CI: 0.10, 0.63). In contrast, presence of more than one previous episode of peritonitis (OR 2.79, 95%CI: 1.11, 7.04) and previous migration and readjustment of Tenkchoff catheter (OR 7.48, 95%CI: 1.39, 40.41), were factors significantly associated with complicated peritonitis.

Conclusion: Presence of abdominal pain, more than one previous episode of peritonitis, and previous migration and readjustment of Tenkchoff catheter, were found as significant factors in predicting clinical outcomes of CAPD associated peritonitis.

KEYWORDS:
Complicated episode; Continuous Ambulatory Peritoneal Dialysis; Factors; Peritonitis

INTRODUCTION

Peritoneal dialysis (PD) is a home-based therapy and offers clear advantages over haemodialysis (HD), such as simplicity, minimal technical support requirements, non-dependence on electricity and issues regarding water purification, in addition to cost saving.[1] A study reported approximately one-fourth of total population of PD in the world are from the Asia Pacific region.[2]

Peritonitis remained the main reason for PD patients to drop out of the PD modality[3-5] and a common cause of catheter loss and subsequent transfer to HD temporarily or permanently.[6] Based on data from Malaysian registry, excluding death as a cause for drop-out from PD, peritonitis remained as the most common cause of treatment failure over the last decade, and contributed to 18% of PD dropout in the year of 2016.[7]

Strategies such as dissemination of risk factors, publication and adherence to guidelines, development of new techniques, and implementation of more effective therapies have led to a reduction in the prevalence of PD associated peritonitis globally. However, studies done in Malaysia on factors predicting clinical outcomes are limited and published data have only listed demographic factors, clinical characteristics of peritonitis and the spectrum of microorganism as potential risk factors for PD associated peritonitis.[8,9]

We conducted this retrospective observational study to identify the demographic characteristics of Continuous Ambulatory Peritoneal Dialysis (CAPD) patients who were diagnosed with peritonitis, to identify the clinical characteristics and microbiological features of the peritonitis and the factors that can predict the clinical outcomes of peritonitis in patients undergoing CAPD.

MATERIALS AND METHODS

The study was performed at Taiping Hospital, Malaysia which is a 608-bedded multidisciplinary public hospital. All episodes of CAPD associated peritonitis diagnosed in Taiping Hospital from October 2015 until October 2019 as referred to the census were enrolled in the study. Peritonitis was defined as the presence of at least two of the following criteria: (a) clinical features consistent with peritonitis, for example abdominal pain and/or cloudy dialysate effluent; (b) presence of white blood cells (WBC) in the dialysate effluent in excess of 100 cells/mm^3 with more than 50% polymorphonuclear cells and; (c) positive dialysate culture.[10] Peritonitis that occurred before patient underwent the intended CAPD training, patient with concurrent presence of malignancy or concurrently on any immunosuppressant were excluded. All data were retrieved manually from the

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medical record file of eligible patients and entered into a predesigned data collection form. The data collection form included patient demographic data, medical history data, patient's dialysis treatment data, and information regarding the pre-initiation of CAPD of patients. Additionally, for each episode of peritonitis, data regarding clinical characteristics, microbiological data, antibiotic treatment, clinical outcome, and length of hospitalisation were collected.

The clinical outcomes of patients were divided into two groups: those with curable episodes and those with complicated episodes. An episode was considered curable when resolution occurred with an appropriate duration of antibiotic therapy as recommended by the International Society for Peritoneal Dialysis (ISPD) guideline 2016, without catheter removal.[10] An episode was considered complicated if there were recurrent episodes, relapsed, repeated, catheter removal took place and/or there was a need for temporary or permanent HD and/or death. Episodes due to a different organisms occurring within four weeks period after completion of therapy were defined as recurrent, while episodes due to a same organism or one sterile episode occurring within a four week period after completion of therapy was defined as relapsed.[10] An episode considered as repeated if it was due to the same organism but occurred after the four week period following the completion of therapy.[10] Death was defined as fatal event with active peritonitis within the four week period of a peritonitis episode or during hospitalisation for a peritonitis episode.[10] In the Taiping Hospital, CAPD patients are implanted with double cuff coiled Tenckhoff catheter. For each episode of peritonitis, specimens were collected for aerobic, anaerobic, fungal and mycobacterium cultures. This study protocol was registered with the National Medical Research Register (NMRR), and ethical approval was obtained from the Medical Research & Ethics Committee (MREC) with reference KKM/NIHSEC/P19-2398(7). Informed consent is waived since this is a retrospective study looking into the patient's medical record.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Science Software version 26.0. Descriptive statistics, such as mean and standard deviation, median and interquartile range (IQR), frequencies, and percentages, were used to explore, summarize, and describe the parametric and non-parametric data, respectively. Between-group comparison analysis was carried out using Pearson Chi-Square (χ^2) or Fisher's exact test for categorical variables. While for continuous variables, normality of the data was tested by using Kolmogorov-Smirnov statistic with a Lilliefors significance level for sample sizes ≥100, or by referring to Shapiro-Wilks statistic for sample size <100. Any differences between continuous variables were tested by using Independent t-test for normally distributed data, while the Mann Whitney U test was used for non-normally distributed data. Variables with a p-value of <0.05 were considered statistically significant. Those variables which were found statistically significant were taken forward to the next stage, whereas repeated measure simple logistic regression with Generalised Estimating Equation (GEE) was conducted to assess the factor predicting the complicated outcomes of CAPD associated peritonitis and the results were expressed as the odds ratio (OR) with a 95% confidence interval (95%CI).

RESULTS

A total of 123 episodes of CAPD associated peritonitis were identified. After excluding ten episodes which did not fulfill the diagnostic criteria of CAPD associated peritonitis, and four episodes that happened before the intended CAPD training, a total of 109 episodes of CAPD associated peritonitis were identified in 54 patients and included in this study. The demographic characteristic of the included subjects is summarised in Table I. The median age of patients was 56.5 years (IQR 44-60.6), with a minimum age of 22.6 years and a maximum of 82.5 years. There were 22 males (40.7%) and 32 females (59.3%), with a majority of patients of being Malays (85.2%) followed by Indians (9.3%) and Chinese (5.6%).

Diabetic nephropathy (44.4%) and hypertensive nephrosclerosis (42.6%) were the two main primary renal diseases that caused end-stage renal disease (ESRD). Among the 54 patients, 88.9% of them had hypertension, 44.4% had diabetes mellitus, and 18.5% had ischemic heart disease. The majority (63%) of them received PD as their first renal replacement therapy (RRT) modality, while others (37%) were transferred from HD. More than half of the patients were on the Fresenius CAPD system, while the others were on the Baxter CAPD system. All the patients underwent the intended CAPD training before they proceeded with CAPD at home. The median duration of CAPD training of seven days (IQR 6-9) were recorded. The majority of the patients (61.1%) required assistance while doing CAPD.

Clinical history, clinical symptoms, and laboratory findings of 109 episodes of CAPD associated peritonitis is summarised in Table I. The median duration of CAPD with the onset of CAPD associated peritonitis was 10.6 months (IQR 5-19). A total of 20 episodes (18.3%) had a history of migration and readjustment of Tenckhoff catheter, and 27 episodes (24.8%) had a history of exit site infection (ESI). There were 53 episodes (48.6%) being the first episodes of peritonitis, while other episodes were relapsed, repeat or recurrent ones. There were 94.5% (n=103) and 69.7% (n=76) of the peritonitis presented with turbid dialysate and abdominal pain, respectively.

Overall, the peritonitis presented with raised in dialysate WBC count on day one (median 940 cells/mm^3, IQR 322.5-2000) and on day three (median 180 cells/mm^3, IQR 45.25-592.50), while the median of day five dialysate effluent WBC count was lower than 100 cells/mm^3 (median 60 cells/mm3, IQR 0-352.50). The median of 4 days (IQR 3-7) was required for the dialysate effluent WBC count to be less than 100 cells/mm^3. Hypoalbuminemia (mean±SD, 26.26±7.47g/L), low serum total protein (60.14±8.86g/L), normokalaemia (3.79±0.82mmol/L) and raised serum C-Reactive Protein (CRP) level (123.13±82.68 mg/L) was noted in these patients. Table II lists the causative organisms of the 109 episodes of CAPD associated peritonitis. About half (n=54, 49.5%) of the peritonitis was caused by a single gram-positive organism, 15.6% (n=17) caused by a single gram-negative organism, and 6.4% (n=7) was caused by a fungal infection. The culture was sterile in 27.5% (n=30) of the cases, and one case caused by polymicrobial infection. Coagulase negative Staphylococcus (CoNS) were accounting for almost two-thirds of the gram-positive episodes. Methicillin-resistant CoNS was

Table I: Demographic characteristics of the 54 patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) and clinical characteristics of 109 episodes of CAPD associated peritonitis.

	Value
Demographic characteristics of the 54 patients	
Age, years old, median, (IQR)	56.5 (44-60.6)
Distance of residence to CAPD centre, km, median, (IQR)	8.4 (5-36.7)
BMI, kg/m^2, median, (IQR)†	23.02 (20.44-28.37)
Gender, n (%)	
Male	22 (40.7)
Female	32 (59.3)
Ethnicity, n (%)	
Malay	46 (85.1)
Chinese	3 (5.6)
Indian	5 (9.3)
Marital Status, n (%)	
Single	8 (14.8)
Married	41 (75.9)
Widowed	5 (9.3)
Education Level, n (%)	
No formal education	2 (3.7)
Primary	15 (27.8)
Secondary	28 (51.9)
Tertiary	9 (16.6)
Family Monthly Income, n (%)	
<RM1000	29 (53.7)
RM1000-RM3000	19 (35.2)
RM3001-RM5000	5 (9.3)
RM5001-RM10000	1 (1.9)
Smoking status, n (%)	
Smoker	2 (3.7)
Ex-smoker	1 (1.9)
Non-smoker	51 (94.4)
Primary renal disease, n (%)	
Diabetic nephropathy	24 (44.4)
Hypertensive nephrosclerosis	23 (42.6)
Obstructive uropathy	2 (3.7)
Glomerulonephritis	2 (3.7)
Unknown etiology	3 (5.6)
Diabetes mellitus, n (%)	
Yes	24 (44.4)
No	30 (55.6)
Hypertension, n (%)	
Yes	48 (88.9)
No	6 (11.1)
Ischemic heart disease, n (%)	
Yes	10 (18.5)
No	44 (81.5)
First renal replacement therapy, n (%)	
Haemodialysis	20 (37)
Peritoneal dialysis	34 (63)
CAPD system, n (%)	
Fresenius	33 (61.1)
Baxter	21 (38.9)
Duration of CAPD training, days, median, (IQR)†	7 (6- 9)
CAPD care, n (%)	
Self-care	21 (38.9)
Assisted	33 (61.1)
Number of peritonitis episodes, n (%)	
1	32 (59.3)
2	10 (18.5)
3-4	8 (14.8)
≥5	4 (7.4)
Clinical characteristics of the 109 episodes of CAPD associated peritonitis	
Duration of CAPD with the onset of CAPD associated peritonitis, months, median, (IQR)	10.6 (5-19)
History of migration and readjustment of Tenckhoff catheter, n (%)	
Yes	20 (18.3)
No	89 (81.7)
History of ESI, n (%)	
Yes	27 (24.8)
No	82 (75.2)

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Abdominal pain, n (%)	
Yes	76 (69.7)
No	33 (30.3)
Turbid dialysate effluent, n (%)	
Yes	103 (94.5)
No	6 (5.5)
Fever, n (%)	
Yes	26 (23.9)
No	83 (76.1)
Diarrhoea, n (%)	
Yes	18 (16.5)
No	91 (83.5)
Nausea or vomiting, n (%)	
Yes	12 (11.0)
No	97 (89.0)
Number of previous peritonitis episodes, n (%)	
0	53 (48.6)
1	23 (21.1)
2	12 (11.0)
3	7 (6.4)
4	4 (3.7)
≥5	10 (9.2)
Use of antifungal for secondary prophylaxis, n (%)	
Yes	26 (23.9)
No	83 (76.1)
Day one dialysis effluent WBC count, cells/mm^3, median, (IQR)	940 (322.5-2000)
Day three dialysis effluent WBC count, cells/mm^3, median, (IQR)†	180 (45.25-592.50)
Day five dialysis effluent WBC count, cells/mm^3, median, (IQR)†	60 (0-352.50)
Days for dialysis effluent WBC count < 100 cells/mm^3, median, (IQR)†	4 (3-7)
Serum albumin, g/L, mean±SD†	26.26±7.47
Serum total protein, g/L, mean±SD†	60.14±8.86
Serum potassium, mmol/L, mean±SD†	3.79±0.82
Serum CRP level, mg/L, mean±SD †	123.13±82.68

CAPD = continuous ambulatory peritoneal dialysis; BMI = body mass index; RM = ringgit Malaysia; ESI = exit site infection; WBC = white blood cells; CRP = C-reactive protein; IQR = interquartile range; SD = standard deviation., †Missing data were excluded from analysis

the most commonly isolated microorganisms leading to CAPD associated peritonitis. Escherichia coli was the most common gram-negative organisms isolated.

The type of peritonitis episode and clinical outcomes of all cases included in the study is summarised in Table III. More than half (n=62, 56.9%) of the peritonitis was cured with antibiotic treatment. 43.1% (n=47) were considered complicated which included relapsed peritonitis (9.2%), repeat peritonitis (9.2%) and recurrent peritonitis (2.8%). Of these, 17.4% required removal of catheter and 4.6% resulted in death. 79 episodes (72.5%) of peritonitis required hospitalisation and the median length of hospitalisation was seven days (IQR 5-13).

The possible factors predicting the clinical outcomes of CAPD associated peritonitis have been divided into categorical factors and numerical factors. The factors and their effect on the complicated episodes are listed in Table IV. Males were significantly associated with lower complicated peritonitis compared with the females (27.8% vs. 50.7%, p<0.05). The presence of abdominal pain was found significantly lower in the complicated course compared with episodes without the presence of abdominal pain (32.9% vs. 66.7%, p<0.05). History of migration and readjustment of Tenckhoff catheter (p<0.001), the presence of dialysate effluent WBC counts more than 100cells/mm^3 on day five (p<0.05), history of peritonitis (p<0.05) and fungal peritonitis (p<0.05) was associated with a complicated course. There was a difference between curable and complicated episode in regard to the number of previous episodes of peritonitis (p<0.05).

Repeated measure simple logistic regression analysis (Table V) revealed that history of migration and readjustment of Tenckhoff catheter (OR 7.48, 95%CI: 1.39, 40.41), history of more than one episode of peritonitis (OR 2.79, 95%CI: 1.11, 7.04) are significant factor predicting a complicated course of CAPD associated peritonitis, while presence of abdominal pain (OR 0.25, 95%CI: 0.10, 0.63) were associated with lower risk. However, history of peritonitis (OR 2.23, 95%CI: 0.94,5.31), presence of dialysate effluent WBC count more than 100cells/mm^3 on day five (OR 2.71, 95%CI: 0.98, 7.50) and male gender (OR 0.37, 95%CI: 0.13, 1.04) did not demonstrate any relationship with a complicated course of CAPD associated peritonitis.

DISCUSSION

Peritonitis is an important complication of CAPD.[9] PD patients in the age group of 55 to 64 years have greater preponderance towards peritonitis based on data from the Malaysian registry.[7] This is consistent with patients in the Taiping Hospital who were mostly older adults (median 56.5, IQR 44.0-60.6). However, two studies conducted in Malaysia observed higher proportion of younger patients being diagnosed with CAPD associated peritonitis.[11,12]

Table II: Causative organisms of 109 episodes of Continuous Ambulatory Peritoneal Dialysis (CAPD) associated peritonitis

Causative organism	Number of episodes, n (%)
Gram-Positive	**54 (49.5)**
Coagulase-negative Staphylococcus (CoNS)	
Methicillin-resistant	21 (19.3)
Methicillin-sensitive	12 (11.0)
Staphylococcus Aureus	
Methicillin-resistant	4 (3.7)
Methicillin-sensitive	4 (3.7)
Bacillus spp.	7 (6.4)
Streptococcus spp.	2 (1.8)
Vancomycin-resistant Enterococcus faecium (VRE)	1 (0.9)
Enterococcus spp.	1 (0.9)
Diphtheroids	1 (0.9)
Rotria dentocariosa	1 (0.9)
Gram-Negative	**17 (5.6)**
Escherichia coli (E. coli)	
ESBL (-)	3 (2.8)
ESBL (+)	1 (0.9)
Amp C beta lactamase (+)	1 (0.9)
Carbapenem resistant	1 (0.9)
Escherichia hermanii	1 (0.9)
Klebsiella pneumoniae	
ESBL (-)	1 (0.9)
ESBL (+)	1 (0.9)
Acinetobacter baumanii	4 (3.7)
Stenotrophomonas maltophilia	2 (1.8)
Pseudomonas aeruginosa	1 (0.9)
Pseudomonas stutzeri	1 (0.9)
Fungal	**7 (6.4)**
Candida spp.	4 (3.7)
Candida parapsillosis	1 (0.9)
Cryptococcus laurenti	1 (0.9)
Rhodorula glutinitis	1 (0.9)
Polymicrobial	**1 (0.9)**
Culture negative	**30 (27.5)**

ESBL = extended spectrum beta-lactamase.

Table III: Type of peritonitis episodes and clinical outcomes of 109 episodes of Continuous Ambulatory Peritoneal Dialysis (CAPD) associated peritonitis

Outcomes	Value
Curable episodes, n (%)	**62 (56.9)**
Complicated episodes, n (%)	**47 (43.1)**
Relapsed peritonitis, n (%)	10 (9.2)
Repeat peritonitis, n (%)	10 (9.2)
Recurrent peritonitis, n (%)	3 (2.8)
Catheter removal required, n (%)	19 (17.4)
Death, n (%)	5 (4.6)
Hospitalised, n (%)	**79 (72.5)**
Length of hospitalisation, days, median, (IQR)	**7 (5-13)**

IQR = interquartile range.

Patients with assisted CAPD has significantly higher risk in developing peritonitis.[7] Our study found that most patients lack self-care capabilities due to advancing age and low levels of literacy. In fact, the presence of medical and social conditions were potential barriers to self-care PD, especially in the elderly, thus contributing to elevated complication risk.[13] Performing this RRT modality is perceived as tedious process, involving proper handwashing technique and hygiene, CAPD exchange procedures, exit-site care, recording of blood pressure, weight and ultrafiltration, in addition to recognition of peritonitis and management.[11] Such added responsibility may provoke reduced self-confidence leading to reliance on partial or complete assistance when carrying out CAPD.[14]

The microbiological spectrum observed in CAPD associated peritonitis in our study population did not show discrepancies with other studies. The main causative microorganisms were gram-positive bacteria which were reported in numerous studies[5,7-9,15,16] often with CoNS presenting as the most ubiquitous gram-positive pathogen, while Escherichia coli was more often isolated in gram-negative peritonitis.[3,5,7,9,12,16]

Table IV: Categorical and numerical factors and their effect on 109 episodes of CAPD associated peritonitis

	Complicated episode if factor present, n (%)	Complicated episode if factor absent, n (%)	p-value*
Demographic data			
Male gender	10 (27.8)	37 (50.7)	0.023
Self-care CAPD	23 (53.5)	24 (36.4)	0.078
Comorbidities			
Diabetes mellitus	20 (43.5)	27 (42.9)	0.948
Hypertension	42 (44.7)	5 (33.3)	0.410
Ischemic heart disease	5 (25.0)	42 (47.2)	0.070
Clinical history			
History of migration and readjustment of Tenckhoff catheter	16 (80.0)	31 (34.8)	<0.001
History of peritonitis	29 (52.7)	18 (33.3)	0.041
History of ESI	10 (37.0)	37 (45.1)	0.462
Clinical findings			
Abdominal pain	25 (32.9)	22 (66.7)	0.001
Turbid dialysate effluent	45 (43.7)	2 (33.3)	0.619
Fever	9 (34.6)	38 (45.8)	0.316
Diarrhoea	5 (27.8)	42 (46.2)	0.150
Nausea and vomiting	5 (41.7)	42 (43.3)	0.914
Clinical findings			
Dialysate effluent WBC counts >1000cells/mm^3 on day three†	10 (55.6)	28 (37.3)	0.139
Dialysate effluent WBC counts >100cells/mm^3 on day five †	19 (57.6)	16 (33.3)	0.030
Gram-positive peritonitis	24 (44.4)	23 (41.8)	0.782
Gram-negative peritonitis	7 (41.2)	40 (43.5)	0.860
Culture negative peritonitis	9 (30.0)	38 (48.1)	0.088
Fungal peritonitis	7 (100.0)	40 (39.2)	0.002**
Age at the onset of peritonitis, years old, median, (IQR)	55.8 (37.8-60.5)	56.6 (51.8-61.8)	0.702
Distance of residence to CAPD centre, km, median, (IQR)†	6.4 (3.2-36.6)	9.6 (9.6-45.4)	0.126
BMI, kg/m^2, median, IQR†	23.28 (19.63-28.91)	22.83 (21.91-28.32)	0.967
Duration of CAPD training, days, median, (IQR)†	7 (6-10)	7 (5-8)	0.057
Number of previous episodes of peritonitis, median, (IQR)	0 (0-1)	1 (0-3)	0.002
Duration of CAPD, months, median, (IQR)	10 (3.2-19)	11.3 (6.5-18.8)	0.482
Day one dialysate effluent WBC count, cell/mm^3, median, (IQR)	1000 (365-2000)	560 (260-2000)	0.376
Days for dialysate effluent WBC counts <100cell/mm^3, median, (IQR)†	5 (3-7)	4 (3-6)	0.329
Serum albumin, g/L, mean±SD†	27.1±7.72	25.05±7.04	0.229##
Serum total protein, g/L, mean±SD†	60.92±9.08	59.03±8.54	0.359##
Serum CRP, mg/L, mean±SD†	118.76±68.31	129.78 ± 102.29	0.640##
Length of hospital stay, days, median, (IQR)	5 (0-7)	6 (0-14)	0.184

CAPD = continuous ambulatory peritoneal dialysis; ESI = exit site infection; BMI = body mass index; WBC = white blood cells; CRP = C-reactive protein; IQR = interquartile range; SD = standard deviation, *Pearson Chi-Square; **Fisher exact test; #Mann-Whitney U Test; ##Independent T-test, †Missing data were excluded from analysis.

Table V: Factors predicting the complicated course of CAPD associated peritonitis

Variables	OR	95%CI	p-value
Male	0.37	0.13, 1.04	0.060
History of migrated and readjustment of Tenkchoff catheter	7.48	1.39, 40.41	0.019
History of peritonitis	2.23	0.94, 5.30	0.070
Presence of abdominal pain	0.25	0.10, 0.63	0.004
Presence of dialysate effluent WBC counts >100 cells/mm^3 on day five†	2.71	0.98, 7.50	0.054
History of > one episode of peritonitis	2.79	1.11, 7.04	0.029

CAPD = continuous ambulatory peritoneal dialysis; WBC = white blood cells; OR = odds ratio; CI = confidence interval; †Missing data were excluded from analysis.

Meanwhile, culture-negative peritonitis rate (27.5%) was comparable with local studies,[11,12] but was slightly higher than the national value of 24.5%.[8] Culture-negative rates were lower in studies involving Australian and Canadian PD patients,[5,9] thus fulfilling the standard of not more than 20% suggested by ISPD guidelines.[10] There were no cases of mycobacterium peritonitis being identified during this study period. High incidence of culture-negative may warrant further review and improvements on existing diagnostic methods in order to achieve the ISPD cut-off value.

In contrast to bacterial peritonitis, fungal peritonitis is uncommon.[17] We report here a rate of 6.4% which exceeded published values by other authors and the national report, ranging from 2.5% to 4.5%.[5,7,8,11,12,15,17] Limited prescription of antifungal for secondary prophylaxis, whereby only 23.9% of peritonitis events received antifungal prescription, as well as history of previous peritonitis episodes, prior use of antibiotics, immunosuppressed state, diabetes mellitus, malnutrition, prolonged time on PD[18] and presence of gastrointestinal disorder[17], were possible contributors of more

fungal peritonitis events in our patient population. Further analysis is required to identify the risk factors unique to this infection which was beyond the scope of the current study due to insufficient sample size and other limitations.

Our study found complicated episodes of peritonitis, was 43.1% compared to 26% in a single centre study in Greece.[8] This could be attributed to higher incidence of fungal peritonitis and around 26% isolated microorganisms were drug resistant. Other clinical outcomes such as mortality and hospital admission were found to be similar with numbers reported by other investigators. Fatality rates ranged from 2.3% to 5.7%,[3,8,9] hospitalisation frequencies were approximately 70%.[3,5] In order to reduce the need for admission and length of stay, our current practice allows for some clinically stable patients to be administered intraperitoneal antibiotics and assessed regularly for treatment response in the outpatient setting.

The first occurrence of peritonitis, and subsequently repeated episodes may cause pathological changes in the peritoneal membrane by inflicting severe injury to mesothelial cells. These are specialised epithelial cells that line the peritoneal membrane and play a crucial role in peritoneal host defence.[19,20] In their paper, Kofteridis and colleagues reported that a history of peritonitis and not the number of previous episodes was associated with a complicated episodes,[8] while we showed a statistically significantly higher risk of developed complicated episode in those with history of more than one episode of peritonitis.

The higher proportion of study subjects without presenting complaint of abdominal pain in the complicated CAPD peritonitis group may influence treatment outcomes. Data from two study centres namely in Canada and Thailand showed higher treatment success rates in patients with abdominal pain, though the figures were not statistically significant.[9,15] Apart from abdominal pain, another common clinical symptom of CAPD associated peritonitis is turbid dialysis effluent. While the former is usually the early presenting symptom when dialysate effluent might initially be clear, the latter may become turbid after the next exchange or on the very next day.[21] Hence, this earlier presenting symptom may result in early treatment, thus potentially lowering the incidence of complicated peritonitis. Migration of Tenckhoff catheter can impair dialysate outflow in peritoneal dialysis[22] resulting in subsequent catheter readjustment and increased preponderance to complicated episodes of peritonitis in our study. There is a lack of published reports examining the relationship between this phenomenon with clinical outcomes of CAPD associated peritonitis. Surgical readjustment of the catheter via laparoscopic surgery is a common practice in the Taiping Hospital setting for cases of migrated catheter. Hence, this may increase the risk of secondary or tertiary peritonitis. Besides, constipation is one of the predisposing factors of catheter migration,[23] which can be alleviated by prescribing laxatives and ensuring patient adherence to such treatment.

Dialysate effluent WBC count may be an index of peritonitis severity and a prognostic factor for CAPD associated peritonitis clinical outcome.[8,9,15,24,25] Dialysate effluent WBC counts exceeding 100 cells/mm^3 on day five were indicative of a complicated episode, a finding which was supported by Nochaiwong and colleagues.[15] There was association between the number of days with dialysate effluent WBC counts >100cells/mm^3 with the occurrence of complicated peritonitis, more so if such counts persisted beyond five days.[8,9,24,25] Meanwhile, early dialysate effluent WBC counts of >1000cells/mm^3 on days three to four was associated with higher treatment failure risk.[15,24] Conversely, we report no statistically significant differences for day one and day three dialysate effluent WBC counts between curable and complicated episodes, as well as no evidence of increased complicated disease risk in patients with dialysate WBC count >100cells/mm^3 on day five. Nevertheless, clinical relevance of early dialysate WBC count has resulted in less treatment delay because most of the causative organisms, if any, will likely be cultured after five days of incubation. Published guidelines have also recommended catheter removal in patients with unresolved turbid dialysate effluent after five days of appropriate antibiotics.[10]

This study found that male gender does not associated with lower risk of developing complicated peritonitis. The finding is consistent with numerous studies which have shown that gender did not influence the course and clinical outcomes of peritonitis.[8,9,15] While the type of causative organisms (gram-positive or gram-negative) were not proven to influence infection outcome apart from fungal peritonitis in our patients and another study,[8] several authors have reported significant association between cultured pathogens with overall course of peritonitis.[9,15,26,27] The time taken for the identification of organism, which involved the process of culture and sensitivity, may delay the management of CAPD associated peritonitis.[15] As such, its clinical value remained limited in the initial stage of treatment where physicians will more likely to adopt early dialysate cell count, effluent appearance and other parameters to diagnose CAPD associated peritonitis and initiate prompt antibiotic treatment.

Long-term PD therapy has been linked to alteration of peritoneal membrane structure and peritoneal macrophage function, resulting in decreased peritoneal host defence.[8,9] Our study did not demonstrate any relationship between duration of PD with the clinical outcomes of peritonitis, which was consistent with other papers.[8,28] Several studies with duration of PD ranging from 28.8 to 60 months (versus a median of 10 months in our study) described that the occurrence of unsatisfactory outcomes was related to longer time on this RRT modality.[9,29,30] Due to conflicting results, duration of CAPD should not be used as the only parameter to ascertain patients' risk of developing complicated peritonitis.

In terms of serum CRP, those with poor clinical outcomes were presented with higher baseline values.[23,28] Our study did not show significant association between serum CRP and clinical outcomes. Besides, in CAPD associated peritonitis, many researchers were unable to establish a relationship between serum albumin and disease outcomes[8,9,15] which is consistent with our study finding. On the other hand, Zhen and colleagues reported significantly lower serum albumin levels in fatal peritonitis, patients with catheter removal, and those experiencing relapsed peritonitis.[30] Therefore, serum CRP and serum albumin monitoring at baseline and during the course of peritonitis may be considered in the clinical management of CAPD peritonitis.

This study was conducted at the current point of time where locally published reports on factors predicting clinical outcomes of CAPD associated peritonitis was noticeably lacking. The findings will set the pace for future research and establishment of clinical practice guidelines to focus on development and implementation of new strategies, and improvement of existing disease management. Incomplete data, small number of patients and retrospective data are limitations noted in this study.

CONCLUSION

In conclusion, presence of abdominal pain, more than one previous episode of peritonitis and previous migration and readjustment of Tenkchoff catheter were found as significant factors in predicting clinical outcomes of CAPD associated peritonitis.

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CONFLICT OF INTEREST

We have no conflicts of interest.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Reconsideration of planned vaginal breech delivery in selected cases

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ABSTRACT

Introduction: The debate surrounding the management of term breech presentation (BP) has resulted in the presence of a multitude of guidelines, reviews, and directives. The vaginal delivery of a breech baby requires sound obstetric skills since approximately 3-4% of babies at term are breech presentations. BP is the commonest of all malpresentations. However, expertise required to deliver breech babies vaginally has virtually disappeared. There is no convincing evidence that Caesarean Section (CS) is better than assisted vaginal delivery when conducted in appropriate settings, with experienced obstetricians and strict prevailing protocols. Unfortunately, planned vaginal breech delivery (VBD) is becoming an uncommon event. This has led to fewer opportunities for obstetric residents to master the skills of vaginal birth of breech presentations.

Materials and Methods: The BP has always been a challenge for obstetricians, due to special skills required to deliver the breech safely. In addition, the immediate perinatal outcome, in terms of APGAR scores and acid-base status of the breech babies is of great concern. Thus, in 2000, in order to provide more evidence-based data, the Term Breech Trial (TBT) was published which compared the outcome of VBD with planned CS. In their 2003 Clinical Guideline, the National Institute for Health and Clinical Excellence (NICE) recommended external cephalic version (ECV) for breech presentation at 36 weeks of gestation a ns elective CS if the procedure is declined or failed.

The first edition, Green-top Guidelines by the Royal College of Obstetricians and Gynaecologists (RCOG) regarding the breech delivery was first published in 1999 and revised in 2001, 2006 (Nos. 20a and 20b) and March 2017. In 2020, the Guideline Committee meeting decided on a further revision and deferred the decision for further 3 years (2023). The aim of this Guideline is to aid decision making regarding the route of delivery and choice of various techniques used during delivery. In March 2005, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) issued a formal statement concerning breech delivery at term.

Through their Committee on Obstetric Practice, the American College of Obstetricians and Gynecologists (ACOG) issued a Committee Opinion paper on "Mode of term singleton breech delivery" in 2006.

Results: Almost immediately, the medical community all over the world embraced the conclusions of the trial highlighting the superiority of outcomes in planned CS compared to VBD in terms of maternal, neonatal mortality and morbidity. Clinicians, in consultation with their patients, must make the final decisions regarding mode of breech delivery in the light of the updated clinical guidelines and committee opinions for a rational choice for the mode of delivery.

Conclusion: There is a place for planned VBD, the pre-requisites are: strict case selection, operator skills and vigilant intrapartum monitoring. Provision of basic skills training by utilizing birthing pelvic models and mannikins, hands-on practice of External Cephalic Version (ECV) in clinical settings, may result in larger reduction in the risk of CS.

KEYWORDS:
Term Breech Trial, External Cephalic Version, Perinatal mortality, Perinatal morbidity, Severe maternal morbidity

INTRODUCTION

Caesarean section (CS) as the sole mode of delivery for breech presentations (BP) carry additional health risks in future pregnancies, such as placenta previa, rupture uterus and morbidly adherent placentae.[1] All these morbid factors are associated with an increased risk of severe peripartum haemorrhage and emergency hysterectomies.[2] Repetitions of CS is also associated with an increased risk for injury to the bladder and bowel.[3] The risk of uterine scar rupture during vaginal birth after one CS is approximately 0.5%.[4] However, in under- resourced countries where healthcare is lacking,[5] the effect on maternal outcome is likely to be undesirable.

Breech presentation occurs in 3-4% of pregnancies at term[6]. The incidence is more in preterm deliveries. A breech presentation is defined as a fetus in a longitudinal lie with the buttocks or feet in the lower segment of the uterus. Here the approach to delivery appears debatable. Vaginal breech births were previously the norm until 1959 and thereafter,[7] it was decided upon that all breeches should be delivered via CS.[8] This concept was further strengthened by the appearance of Term Breech Trial (TBT) in 2000. It remains concerning that the scarcity of experienced clinicians to tutor junior residents in training leads to the desertion of vaginal breech deliveries.

The lead researchers of TBT headed by Hannah et al 2000[9] at the University of Toronto in Canada conducted a randomized trial at 121 centers in 26 countries. In that trial, 2183 women

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at term, singleton fetuses in a frank or complete breech presentation were randomly assigned for planned CS or planned vaginal birth. Perinatal mortality, neonatal mortality or serious morbidity were significantly lower for CS group than for planned vaginal birth group. The maternal morbidity or mortality was similar in both groups. This single piece of randomized TBT in 2000, profoundly and ubiquitously changed obstetric practice globally. This effectively removed planned vaginal breech delivery (VBD) in both the Western world and South Asian countries. In the Netherlands, the CS rate for breech presentation has increased from 57% in 2000 to 81% in 2001 after the TBT. It came as no surprise that, instantaneously, obstetricians reverted enthusiastically to the conclusions of the trial. It is obvious that CS requires less skills and the obstetricians feel more protected medico-legally if he/she performs CS without taking into cognizance the increased maternal morbidity, longer hospitalization, a four-times higher risk of blood transfusion and an over ten-times higher risk for endometritis.[10]

Unfortunately, the TBT had methodological flaws and discussing its generalizability and applicability is questionable with adequately staffed and well-resourced Australian and New Zealand hospitals. Hence, unfounded conclusions drawn should no longer be considered as valid.[11] Malaysia is a rapidly developing country in Southeast Asia, with a multi-ethnic, conservative and predominantly Muslim population. The latter prefer larger families and normal vaginal deliveries if given a choice. This is an observation of us (the authors) over the past four decades.

MATERIALS AND METHODS

The Green-top Guideline (Table I), No. 20 (April 2001) RCOG recommended offering all women with an uncomplicated BP, ECV at (term 37-42 weeks) provided there were no contraindications.[12] In December 2006 Guidelines 20a and 20b were further updated,[13] outlining less rigid approach to compulsory elective CS. Furthermore, the reports highlighted about advising women of the safety factors and details of intrapartum management and delivery of the breech vaginally.

The ACOG issued a Committee Opinion paper on "Mode of term singleton breech delivery" in 2006,[14] asserting that planned VBD may be applicable under hospital specific protocol guidelines including importance on documentation, informed consent issues related to ECV and VBD. RANZCOG guideline 2005, reiterated that maternal preference and consideration in the mode of delivery. The Guideline further emphasized that the level of risk to the foetus is higher in planned VBD than in elective CS, but it does not exclude as an alternative decision. In their 2003 Clinical Guideline, NICE[15] recommended ECV for breech presentation at 36 weeks gestation and elective caesarean section if the procedure fails. The document concluded that clinicians must make the final decision in consultation with their patients for ECV and mode of delivery.

In addition, The Cochrane Review[16] (2003), one of the opinion-making institutions endorsed the recommendations soon after the publication of the TBT has now modified their recommendations and support the VBD, provided the institution is equipped with stringent measures to meet the final point made in this Guideline; maternal preference should be sought.[17] The PREsentation of MODe d' Accouchment (PREMODA) study group published in 2006 designed a prospective observational multicenter study incorporating antenatal radiological pelvimetry.[18] The role of antenatal pelvimetry is unclear, convincing evidence supporting this as a reliable screening tool has not been established, although it was employed in 82.5% of planned vaginal births in the same study. The study included over 8 000 women with breech presentation at term (four times as many as included in the TBT, which were recruited in 174 French and Belgian centers over a 12-month period. The study appraised the safety of VBD using strict criteria for selecting patients for a trial of labour. The authors did not observe differences in perinatal morbidity or mortality in breech babies delivered by CS or vaginal delivery.

Since the publication of TBT two decades ago, generations of residents in both the Western world and South Asian countries have completed training, with scarce expertise and experience in VBD. The significance of this situation is many fold, unavoidable CSs, with substantial morbidity to mothers and increased risk to the breech foetuses, who need to be delivered by vaginal route. A partial solution to this is to include simulation training to residents and availability of standby experienced obstetricians. This should be treated as an obligatory simulation courses for residents and those doing postgraduate training in Malaysia. Provision of basic training with availability of childbirth, birthing simulators and mannikins in the market can be in-cooperated and used to teach and train basic skills for delivering breech babies[19] In addition, in-house training of ECV should also be made an integral part of training and offered to all pregnant mothers with a breech who have no contraindications or a potential pathological fetal condition for this procedure. In this way, the parturient is given a fair choice to deliver a breech baby vaginally. Under these circumstances, trainees in the long run would be able to master required maneuvers for VBDs and handle unforeseen complications.

RESULTS

The BP has always been a challenge for obstetricians, due to special skills required to deliver the breech safely. In addition, the immediate perinatal outcome, in terms of APGAR scores and acid-base status of the breech babies is of great concern. In the light of the Green-top Guidelines (RCOG) on further management of BP, the NICE Guidelines recommending ECV at 36 weeks, the RANZCOG and ACOG view points must be taken into account along with consultations and informed consent of patients, management plans must be carefully designed.

Table I: A summary of guideline and directive recommendations on breech delivery

Royal College of Obstetricians & Gynaecologists (Better to write country name) [10-12]	**Green-top Guideline No. 20 (2001)** • Recommended offering all women with uncomplicated breech presentation an external cephalic version (ECV) at term (37-42 weeks), provided there were no contraindications. If not performed or unsuccessful, elective caesarean section at term should be offered. • It is still important that clinicians and hospitals are prepared vaginal breech delivery. • Recommended that any woman delivering a breech presentation vaginally should be cared for by an attendant with suitable experience. **Green-top Guideline Nos. 20a and 20b (2006)** • More information on benefits, risks and the role of ECV • A less rigid approach to elective caesarean section • More information on short and long-term benefits and risks of modes of planned delivery and on advising women of them. Safety factors and details of intrapartum management of breech presentation and delivery • Training, counselling and documentation highlighted
American College of Obstetricians & Gynaecologists [14]	• Planned vaginal breech delivery may be reasonable under hospital specific protocol guidelines • Documented, informed consent, clearly outlining the increased short-term serious risk to the infant, is a prerequisite
Royal Australian & New Zealand College of Obstetricians & Gynaecologists [17]	• States that the risk is higher in planned vaginal breech delivery than in elective caesarean section but does not exclude it as an option. • Maternal preferences should be considered
National Institute for Health and Clinical Excellence (NICE) (Better to write country name)[15]	• Recommended ECV for breech presentation at 36 weeks of gestation and elective caesarean section if the procedure declined or fails

Source: The Risk Management Planned vaginal breech delivery: should this be the mode of Choice. The Obstetrician & Gynaecoloist 2007; 9: 171-176

Table II: Studies supporting vaginal delivery for breech presentation

Study	Study design	Study population	Outcome measures	Summary of findings
Alarab et al (2004) [23] Dublin, Ireland	Retrospective Review	All breech presentations > 37 weeks; n=641; selection for vaginal delivery was based on clear pre-labour and intrapartum criteria	Obstetric and perinatal outcomes	298 had a trial of vaginal delivery, 49% delivered vaginally. Fewer nulliparous women achieved vaginal delivery than multiparous (37% vs 63%, P<0.001). Significantly more infants >3.8 kg were selected for prelabour and intrapartum caes-arean section than vaginally. No non-anomalous perinatal deaths
Doyle et al (2002-03) [24], Texas, USA	Retrospective review	All single breech deliveries; n=150	Obstetric and perinatal outcomes	41 vaginal breech deliveries. 109 caesa-rean sections. Mean birthweight was signi-ficantly lower and parity significantly higher in vaginal group. No differences in neonatal outcomes
Kumari et al (1997-2000) [25] Abu Dhabi	Retrospective population based cohort study	Women with breech presentation at term; 128 women for whom a vaginal delivery was planned compared with 122 women who had an elective caesarean section	Neonatal morbidity and mortality, Maternal morbidity	No difference betwe-en neonatal mortality and morbidity betwe-en the two groups. Fewer maternal com- plications. In the plan ned vaginal delivery group 70% of multi-parous and 85% of grand multiparas delivered vaginally compared with 50% of nulliparous
Goffinet et al (200102)[18], Paris, France	Observational prospective study	8105 women; singleton breech presentations in 138 French and 36 Belgian units	Fetal and neonatal mortality; severe neonatal morbidity	Of the 2526 women with planned vaginal deliveries , 71% delivered vaginally. No significant differe-nce in neonatal out-come measures between the delivery groups
Irion et al (1984-1996) [26], Geneva, Switzerland	Observational prospective study	705 consecutive singleton breech presentations:385 planned vaginal and 320 elective caesarean sections	Neonatal mortality and morbidity; maternal morbidity	No difference in neonatal morbidity between groups. Fewer maternal com-plications in the planned vaginal delivery group

Source: Review The case for and against vaginal breech delivery. The Obstetrician & Gynaecologist, 2008; 10:139-144

DISCUSSION

There is a continued disapproval of the TBT from all over the world. The allegations are: Poor antepartum and intrapartum fetal monitoring; the inclusion criteria were not followed to and a large group of women were recruited in labour.[20-22] Table II alludes to the results from planned VBD comparing with planned CS. The PREMODA study- group[18] published in 2006, this was a prospective study in 2001-02, recruiting just over 8000 women in maternity units in France and Belgium (138 French and 36 Belgian respectively) comparing vaginal delivery with elective caesarean section, whereby 71% achieved successful VBD with no significant differences in neonatal outcome measures between the delivery groups. This was primarily due to their strict selection criteria, antenatal radiological pelvimetry and their stringent management guidelines.

On a similar note (Table II), other authors have published studies showing comparable outcomes in smaller populations. In Dublin Alarab et al[23] published data on 641 deliveries (343 elective cesarean section deliveries and 298 trials of vaginal deliveries, of which 146 were successful), using strict selection criteria for allowing a trial of vaginal delivery. They reported only 2 neonates born vaginally with Apgar scores of 7 at 5 minutes (both were neurologically normal at 6 weeks) and no non-anomalous perinatal deaths. Doyle et al (2002-03),[24] from Texas, USA in a retrospective review of 150 singleton breech deliveries (41 were vaginal breech deliveries, 109 were caesarean sections) did not find any difference in neonatal outcomes. Kumari et al (1997-2000)[25] in Abu Dhabi, found no difference neonatal mortality or morbidity between multiparous (85%) and nulliparous (50%) women who delivered breeches vaginally. Goffinet et al[18] published in 2006 the PREMODA study which was a prospective observational multicenter study evaluating the safety of vaginal breech birth by strict criteria.

Irion et al in 1984-1996,[26] Geneva, Switzerland, in an observational prospective study-design of 705 consecutive singleton breech presentations compared 385 planned vaginal deliveries and 320 elective caesarean sections. There was no difference in corrected neonatal morbidity between groups. There were fewer maternal complications in the planned vaginal delivery group.

Additionally, data obtained, on the long-term sequelae of the neonates born by vaginal breech delivery was rebutted by the original authors of TBT, published a subgroup analysis in 2004.[27] This showed that the prevalence of death or abnormal neurodevelopment at 2 years did not differ between the vaginal and caesarean groups.

However, in contrast to these studies, several others[28-31] conducted retrospective studies not in favour of vaginal breech deliveries. For instance, a review of the Dutch perinatal database showed the rate of planned elective CS for term breech changed from 49% in the 33 months before the publication of TBT to 80% in 25 months thereafter.[28] This change led to a halving of the perinatal mortality rates, low APGAR scores and rates of birth trauma that declined three-quarters.[30] Neonatal mortality was even lower in data from California where planned CS rates were even higher at 95%, in a population of 100,000 term breeches.[29] In another population-based study, the Swedish Collaborative Breech Group[30] published findings of a national cohort study[31] of more than 22,000 breech deliveries. They found that perinatal or infant mortality of planned vaginal breech delivery was significantly higher than planned CSs.

In addition, the TBT had been subject to an economic evaluation.[32] The costs were lower in the planned elective CS group than the vaginal delivery group ($7165 verse $8042 (Canadian dollars). The high costs of vaginally delivered group were due to the hospital and physician costs as well as higher costs of epidural anaesthesia, the costs of neonatal intensive care for women and babies allocated to vaginal breech delivery.

Another inference of an "elective section caesarean for all" policy is the negative impact on training, thus reducing the number of doctors with the skills and experience required to deliver a breech vaginally and safely.

CONCLUSION

Although the multicenter TBT found an increased rate of perinatal mortality and serious immediate perinatal morbidity, however the long-term outcome of these neonates born by vaginal breech delivery is reassuring. Long term assessment (2 years) of composite morbidity/mortality showed no difference in outcome between infants delivered by planned CS or by VBD.[9]

There is a place for planned VBD. However, the prerequisites include: more robust and stringent selection criteria of cases, management guidelines, close intrapartum monitoring, family consent and availability of expertise in vaginal breech delivery. These requisites can be difficult to achieve in many clinical settings. If the amenities are adequate and the parturient is fully informed of the risks and benefits, this option should be offered. On the other hand, if the criteria cannot be met, it would be prudent to refer the parturient to a center that can meet them.

The concept of specialized centers (supra institutional centers) where safe planned VBD is offered has not evolved yet in Malaysia. On the other hand, simulation training with pelvic models and videos, in strictly selected cases trial of ECV, provision of standby teams of experienced physicians can be explored for safe planned VBD. Otherwise, obstetrical skills, expertise and experience vanishes thus resulting in the abandonment of vaginal breech deliveries altogether.

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Gut microbes - Early immunity and health

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ABSTRACT

Introduction: Microbes in the human gut impact holistic health. Modifiable events can steer immunity through commensal microbial action. This protects from acute diseases and lays foundation for enduring health benefits. Timely modulation of immune development by correct feeding choices negate consequences of microbial dysequilibrium.

Materials and Methods: Review and critical analysis of relevant literature integrated to the core understanding of facets of microbial existence in the gut , their roles in early immunity , and impact on health were done. Known deficiencies in newborn immunity integrated to the actions of microbes in human milk permitted some conclusions to be drawn through logical extrapolations.

Results: Deficiencies in early immunity can, at least partially, be surmounted by an optimal gut microbial milieu provided for by human milk which also enhances gut immunity and holistic health.

Limitations: This is a narrative review and articles chosen were subjectively analysed for suitability according to relevance, however, analysis by statistical methods was not done.

Conclusions: There are clear pathways linking gut microbes, intestinal epithelia, microbial metabolites and early immune maturation. The immature immune system is guided towards proper development and maturation by breastmilk factors and milk microbes for immediate and enduring holistic health. Utilising this knowledge, research must be energised on possible mutualistic benefits of gut microbes to counter the current health challenges. The counselling of breastfeeding must not overlook the unique microbial environment endowed by the mother as a gift of health.

KEYWORDS:
gut, feeding , microbes, mucosal , immunity

INTRODUCTION

Contemporary scientific information indicates that microbial seeding of the gut during the first few years of life is an opportunity for early "programming" of immune responses with support that natural feeding can lay foundation for optimal modulation of microbes to provide the infant holistic health.[1]

Culture based assessments, molecular biology and genomic data indicate that gut microbes show remarkable heterogeneity among individuals.[2] Despite this, certain constant variables influence gut health and can provide important advantages.

A state of 'eubiosis', is coexistence of diverse microorganisms, together with oral tolerance to commensal bacteria and innocuous antigens.[3] This is quite different from the state of 'dysbiosis' which essentially refers to microbial imbalances ,scenarios that alter microbial communities due to changes in the nature and quantity of the gut microbial composition.[4] Dysbiosis increases susceptibility to a number of diseases.[5]

On early events in immune development,[5,6] while the intrauterine milieu is now known to be no longer completely germ-free, the comparatively low exposure to antigenic stimulation and the relatively quiescent intrauterine immune environment, do not stimulate the production of robust immune factors in the foetus,[5] a state that favours foetal in - utero survival.

At birth, the newborn has some immune capacity, but this is immature and not fully functional.[6] The development of early gut microbiota[7] helps optimal immune maturation in the face of muted immunity in the newborn.[8] It is driven and modulated by substances in early feeding, of which breastfeeding supports selective microbial colonization for positive health and neurocognition.[1,9]

This article focuses on how newborn immunity is impacted by gut microbial action. It integrates early immunity and microbial effects, mainly those passed on from the nursing mother to her infant. This is rather crucial because gut colonization is completed within approximately three years of life and is an early event with great potential for far-reaching and holistic health impact.[9]

MATERIALS AND METHODS

This article is divided into four subtopics. In the first area of newborn immunity, literature searches used keywords such neonatal, newborn, immune, innate and adaptive. In the second subtopic, search words were gut, gastrointestinal, immune, commensals, microorganisms, barrier, intestine and epithelium. The third area used search words such as secretory immunoglobulin A (sIgA), mucosal, immunity , secretory, while in the fourth area microbes, products, metabolites and health were search words used.

With regards to experimental studies, animal experiments were important due to ethical difficulties for such studies to be conducted on human subjects, as well as because of the challenges and ethical considerations in conducting in vivo dynamic studies of breastmilk.

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250 related articles were perused in accordance with the MeSH search strategy, in the PubMed, Scopus, Embase and other databases. The articles were analysed, sometimes extrapolated, and integrated. Deficiencies in one area were integrated to developments that surmount them in another.

Publications characteristics:
Original articles, systematic reviews, meta-analyses, narrative reviews, experimental studies, prospective studies, retrospective studies and case reports were included.

Excluded were letters to editor and publications in foreign language. Unpublished papers were also excluded. A total of 45 articles were chosen.

Topic characteristics:
The articles that satisfied the following inclusion criteria on topics reviewed included newborn immunity, infant immunity, gut barrier maturity, sIgA, mucosal immunity and microbial products.

Excluded were articles that focused only on adolescent and adult immunity and on maturation of mucosal surfaces other than that of the gut and respiratory tract. Animal experiments that were felt to be unsuitable for extrapolation to humans based on pathophysiology were excluded

RESULTS

Immunity of the newborn

Issues in the immature immunity of the newborn involves various arms of immunity. Innate and adaptive immune responses of the newborn have a number of recognised differences compared to the immunity in adults.[10] The newborn system must develop the ability for defences, tissue repair, wound healing, cancer cells surveillance,[10] and must learn to coexist through immune tolerance with commensal gut microbes.

The role of gut microbes in the evolution of immunity by induction of useful responses and by guiding host immune maturity, are now recognised.[1] In health, the mature immune system is in symbiosis with the host and with diverse microbes.[11] The developing immune system is exposed to commensals during passage through the birth canal and together with other variables, steer immune development.[1]

Effective mucosal barriers are necessary to defend against pathogen entry at all mucosal surfaces, most specifically, in the gut and respiratory tract. Innate responses, barrier immaturities of newborn gut epithelium with incompletely developed chemical barriers increase risks of diseases.[8,10] Defective barriers involve composition and glycosylation of the vital mucous layer; and microbial modulation of early defenses[12], are explored here.

Serum concentrations and biological activity of almost all circulating immune substances in the newborn are lower than in adults. Cord blood contains fewer specific dendritic cells for T cell presentation, affecting development of adaptive and innate immune responses, and the links between the two.[10] There are restricted responses of interferon production for adequate viral defences and natural killer cells do not respond briskly to interleukin -2 (IL-2) and interleukin -15 (IL-15), as they would, in the older child or adult.[10]

Adaptive B cell responses are not fully effective either. B cell maturity , antibody formation and antibody class switching are of particular consequence to the preterm infant.[14,15,16] T cell functions are impaired, although they may still remain responsive, because of defective cytokine production particularly in relation to Th1 cytokines that support cell mediated immune responses, hence affecting a spectrum of T cell reactions[14,15,16,17,18,19]

In the fetus and the newborn, T cell responses are skewed towards Th2 immunity,encouraging immune tolerance, decreased recognition of allo-antigen and generally, weaker responses to most foreign antigens.[10] However, the newborn has some capacity for T cell recognition of antigens relevant to MHC molecules with potentials for interleukins to link innate to adaptive immunity.[10]

A newborn faces many novel immune challenges. Antibody responses to specific vaccines such as the polysaccharide protein conjugate vaccines require T cell interaction. However, the repertoire of neonatal B cells are not equipped with sufficient co-receptors, necessary for this, impairing such important responses.[10]

Despite such deficiencies, neonatal immunity may have some elements of responsiveness.[18] Neonatal T cells are broadly reactive with potential to rapidly evolve immune cell types for prompt protection against pathogens, and tolerance to self-antigens.[18] If this is so, responsive immunity could well be advantageously modulated by specific modifiable variables with inherent immune potential, such as exclusive breastfeeding.

Cell mediated immunity in the adult controls immune responses mainly through regulatory T cells (Treg) and Th1 cells and enhances humoral and allergic responses through Th2 cells.[19] This is not the case in early life, where T cells are polarised to dominant Th2 responses under most conditions, impairing cytokine production and regulation. T cells also respond by a number of ways to the antigen in order to balance protection and the closely associated immune-mediated tissue destruction.[20]

There are intrinsic differences in the newborn, culminating in weaker B cell antibody responses as a result of greater numbers of immature cells and unclear verdict on function of individual B cell subsets.[14] As a consequence, immunoglobulins in circulation are low in quantity, except for immunoglobulin G (IgG) passed by transplacental transfer. Immunoglobulin A (IgA) is almost undetectable and Immunoglobulin M (IgM) levels are low but increase with antigen exposure. Neonatal B cells can produce Immunoglobulin E (IgE) in the presence of cytokines, but with cytokine production affected, IgE levels are limited, and relative immaturity of yet other immunoglobulin subclasses could persist even up to 10 years of age.[14,15,16]

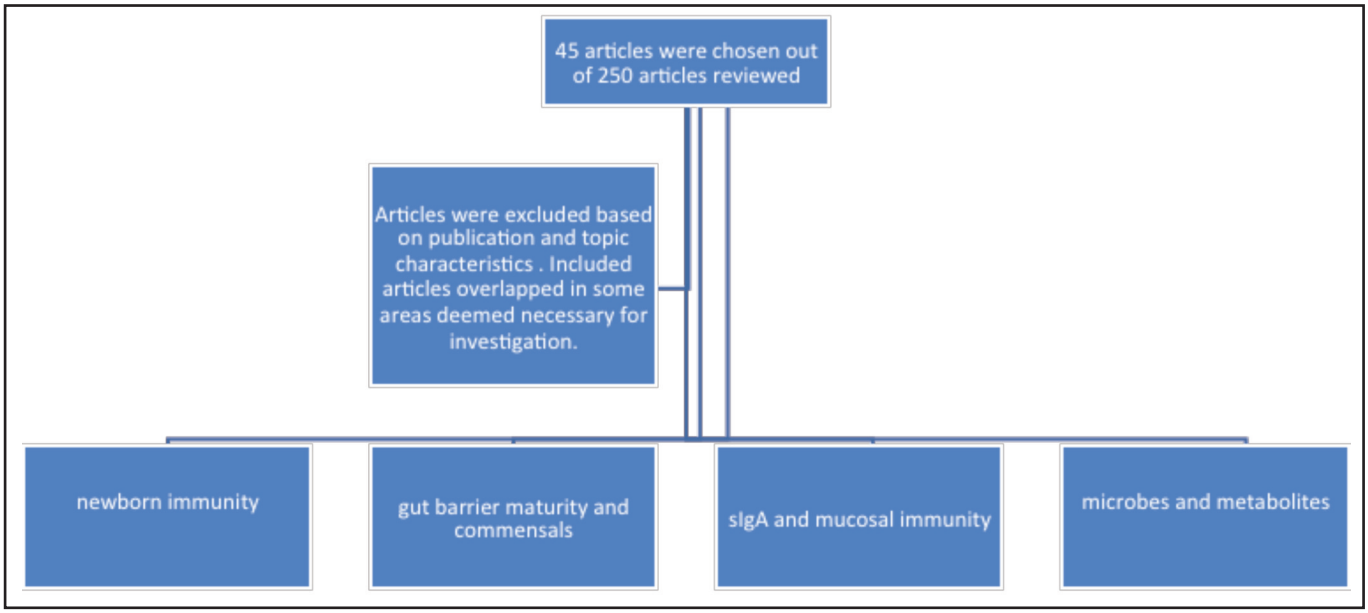

Fig. 1: Choosing articles by inclusion and exclusion characteristics.

Neonatal B cells show severely impaired class-switching, a biological mechanism that alters B cell production from one type to another, generating different antibody classes. This deficiency is most striking with IgG and IgA responses and these are linked to increased expression profiles of specific micro-ribonucliec acids (miRNA). Such responses emphasise intrinsic qualitative deficits in neonatal B cell immunity.[14]

IgA class switching after B cell activation, is crucial for effective immunity. Different affinities of sIgA maintain mucosal homeostasis and sIgA responses independent of T cells resemble innate immunity, with broad antigen specificity. T cell dependent (TD) responses, in contrast, are more specific adaptive responses, elicited by many mucosal pathogens and vaccines.[21]

Impaired innate immunity, adaptive immunity and immature gut epithelial barriers, weak Th1 and antibody responses, predispose to infection risks in the neonate, stressing emphasis on ways to enhance immunity in this crucial period.

A greater role for gut microbes in immunity

The importance of the role of gut microbes in health and disease is emphasised and microbes offer quite a different concept to early life predisposition to allergies and diseases in later life.

Most gut microbes are either innocuous or beneficial to the host. Despite marked microbial variation in individuals, three groups or enterotypes exist, the Bacteroides, Prevotella, and Ruminococcus, further identifiable by genera.[4]

The nexus that determines the development and responses of the immune system and immune mediated diseases have been considered in relation to the Th1/Th2 paradigm as well as the hygiene hypothesis.[22,23]

The hygiene hypothesis argues that patterns of microbial exposure in early life are crucial determinants of the prevalence and severity of allergic diseases in later life.[19,22,23] Early life infection exposures drive immunological responses towards a balanced cytokine profile whereas fewer intercurrent infections in the modern environment skew immunological reactions to reduce their capacity for protection against allergies.[19,24] The extended hypothesis, on the other hand, proposes that commensal intestinal microbiota, healthy host microbial interactions together with immunomodulatory and immunosuppressive responses may all be of greater importance compared to infection exposure alone, in order to stimulate immunity.[25]

Frequent infections , while probably usefully stimulating the immune system and protecting from allergies also potentially interfere with growth and development whereas commensal microbial nurture and their immunomodulation may be enhanced by behaviour patterns and safe health practices. Immunity modulated by intestinal microbes may thus be an essential tool against modern diseases.

Gut commensals , barrier maturity and immunity

From birth, many gut commensal microorganisms provide a useful "living" shield of protection against pathogens, drive metabolism needed as energy in the young and confer some important nutrients, while breaking down toxins and drugs.[9]

Microbes enter the infant's gut through various routes[26,27] and influence it as a prime organ of immune maturity. Microbes in breastmilk may be a mother's early priceless vaccination from her very own microbiota found in her mammary gland or in her gut via the entero-mammary route or the oro-mammary route. Exogenous sources such as retrograde intramammary milk inoculation through the infant's mouth or by milk contamination through the use of breast pumps,[26,27] highlight that different feeding methods impact milk microbial composition. Additionally, the mammary gland itself may autonomously regulate immune and microbial environments.[28]

Irrespective of the origin of microbes, exclusive breastfeeding provides a sustained microbial flow to the infant's gut and stabilises immature gut micro-communities.

A spectrum of bacteria such as staphylococci, streptococci, bifidobacteria and lactic acid bacteria are found in the breastfed infant. This process is sequential and orderly, where the gut may first be colonised by predominantly facultative anaerobes such as enterobacteria, coliforms and lactobacilli, then by anaerobes such as Bifidobacterium, Bacteroides, Clostridium and Eubacterium.[29] It is also notable that gut microbial colonisation is rich in signals that extend beyond the gut, influencing vital organ systems.[30,31]

Intestinal immunity depends on its barrier integrity for homeostasis and disease prevention. Epithelial translocation of pathogenic microbes or their products from the gut lumen into the systemic circulation can spread diseases.[4] Microbes influence immature epithelial barriers through their actions[9] and products. Substances such as short chain fatty acid (SCFA) augment intestinal barriers and stimulate mucus and antimicrobial peptides.[32] In this way, microbes support barrier integrity, and enhance mucus, strengthening innate immunity.

Preterm infants less than 33 weeks gestation monitored for intestinal permeability and faecal microbiota show improved intestinal permeability and barrier maturation correlating with significant increases in microbial diversity, particularly, members of the Clostridiales and Bifidobacterium. Early exclusive breastmilk feeding, shorter duration of antibiotic exposure and early microbial gut colonisation by members of the Clostridiales improved intestinal barrier function in this cohort.[33]

Intestinal barrier integrity activates intestinal immunity and this is critical to the preterm infant. Intestinal microbes within the gut lumen, in proximity to immune cells and the epithelial barrier, modulate immunity.[34] A link between commensal bacteria and optimal development of gut-associated lymphoid tissues (GALT), a part of the mucosa associated lymphoid tissues (MALT), "unifying" mucosal sites in immune responses to antigens, may clarify this role.[35] They activate immune cells of the innate and adaptive system such as macrophages, neutrophils, innate lymphoid cells 3 (ILC3), B and T cells, to produce antimicrobial factors.[4]

In the immature systems commensals guide the development of immunity. A typical molecule of commensal bacteria is bacterial polysaccharide (PSA) important for maturating the immune system by modulating T cells , Th1/Th2 imbalances and guiding lymphoid organogenesis. PSA presented by dendritic cells , the specialised sentinel cells of immunity, activates CD4+ T cells for cytokine production.[36] Integrating, it is appreciated that commensal activity can surmount some features of newborn immune immaturity.

The cells in the gut mucosa are unique , balancing pathogen responses and modulating immune tolerance towards commensal microbes. Instead of a proinflammatory milieu as occurs against pathogens, specialised intestinal cells namely the dendritic cells (DCs) at mucosal surfaces stimulate tolerance-inducing reactions, moderated responses without the unnecessary side effects of inflammation , when they encounter commensal bacterial antigens.[37]

In the gut, antigen presenting cells, (APCs) express low levels of toll-like receptors (TLRs) and microbe-associated molecular patterns (MAMPs) expressed on commensals do not trigger inflammatory reactions. Such responses not only foster microbial tolerance but may also importantly contribute to host development and health.[36]

Additionally, commensal bacteria themselves help create a tolerant immune environment. By stimulation of pattern-recognition receptors (PRR) present in intestinal epithelial cells (IEC), such as Toll-like receptor (TLR) and other receptors, by commensal bacteria, there is production of thymic stromal lymphopoietin (TSLP), for immune proliferation and modulation of host- microbial interactions.[4]

Angiogenesis is fundamental to intestinal epithelial growth and development. Commensal microbes also have impact on blood vessel development[34,35] contributing to a robust mosaic of villus capillaries in the intestinal wall.[37,38] This is corroborated by the comparisons of germ-free and colonized rodents where indigenous microbes that colonize mucosal surfaces regulate the underlying microvasculature by signaling mechanisms.[38]

The microbiota cross talk with macrophages produces regulatory molecules for intestinal homeostasis. Transforming growth factor-beta (TGF-β) is an important immune regulatory cytokine produced abundantly by IEC in the intestines for a degree of immune tolerance in the gut which help nurture commensal microbes and an intestinal milieu that can potentially prevent the growth of pathogenic microbes, through a process of commensal microbial selection deemed necessary for optimal immune development and health.[4]

Regarding adaptive immune response, the intestinal lamina propria contains T cells that stimulate T regulatory (Treg) cells which express the transcription factor forkhead box P3 (Foxp3), a transcriptional regulator in development.[39] Microbe-induced Treg cells also prevent inflammation through immune mechanisms.[40]

Gut microbial profiles influence the immune maturation of the gut , but the immune equilibrium by cytokines induced by microbes and their individual contribution to the immune balance is yet unfolding and not completely elucidated.[40,41,42] The human symbiont *Bacteroides fragilis* encourages the formation of Treg cells and suppresses proinflammatory immune responses.[40] Such responses are mediated by specific T cell subsets such as the T-helper 17 (Th17) cell, a T helper cell that produces a highly inflammatory cytokine with role in pathogenesis of immune mediated diseases,[41] whereas colonization by segmented filament bacteria (SFB) induces Th1, Th2, Th17, and Treg cells and this balance contributes to maturation of gut immunity.[42]

Breastmilk also provides factors with indirect supportive roles towards commensal growth in the gut. Human milk oligosaccharides, (HMOs) which mostly escape digestion play multiple roles , they help fortify intestinal barriers , can act as decoy receptors for pathogens and enhance innate and adaptive immunity. Some HMOs are prebiotics , providing metabolic substrate for specific commensal microbes.[1]

sIgA

A tight -knit association exits between microbes , the lining of epithelial cells of the gut and the underlying mucosal immune system (MALT), of which sIgA is key. Homeostasis at gut mucosal surfaces ensures cooperation between the three and induces production of sIgA.[34,35,36]

Specific microbes that colonise the intestine shortly after birth induce the generation of IgA antibodies of which there are two types, IgA 1and IgA 2.[43] Through mechanisms involving a proliferation-inducing ligand (APRIL), bacteria trigger IgA(2) class switching[43] This seems to be an important function of mucosal immunity, as IgA2 is more resistant to bacterial digestion[43], and such microbial actions could overcome some of the inherent deficiencies of newborn immunity. IgA, produced by lamina propria B cells is secreted into the intestinal lumen, where it is able to perform "immune exclusion",[35] a process of entrapment, agglutinating and clearance of pathogens , as well as influence gut microbiota composition and function.[4,40]

The unique structural components of the sIgA molecule and its dynamics in the mucous contribute to potent mucosal immune action.[44] In its multimeric form it is transported across mucosal surfaces and secretions by a polymeric Ig receptor (pIgR), in epithelial cells. During the synthesis of pIgR, a conformational change occurs in the molecule so that a covalent bond between polymeric IgA (pIgA) and pIgR is formed. The pIgR, which transports pIgA, also contributes to a very important part of the molecule, the secretory component (SC). SC not only protects sIgA from proteolysis resisting digestion by intestinal juices, but also contributes towards intestinal homeostasis, directly interacting with intestinal bacteria, possibly via binding them.[44]

Additionally, through T cell independent mechanisms, bidirectional responses between commensal gut microbes and host , induce the production of low affinities of sIgA,[43,44] whereas through T dependent mechanisms , high affinity sIgA defend against pathogens.[44] The suggestion that despite immaturity, neonatal T cells are capable of responsive action,[18] maybe pertinent here. Early exposure to commensals could train the immune system for a more modulated T cell development.

Microbes, products and links

There is wide individual diversity of commensal gut microbes that regulate epithelial development and guide innate immunity. A study of an impressive number of prokaryotic ribosomal RNA gene sequences from the gut of healthy subjects indicate that bacterial sequences corresponded to uncultivated species and varying novel microorganisms between subjects.[45]

Distant microbial links are supported by evidence such as of liver disease associated with gut dysbiosis, gut toxins affecting renal function and gut microbiomes influencing progression of atherosclerosis and congestive heart failure.[30,31]

CONCLUSION

Newborn immature immunity can be influenced by modifiable events such as feeding choices. Microbes in breastmilk, at least partially, help to overcome this immaturity and to guide early immunity through immune factors and biological links to positively modify the health fabric. Developing this, research on novel microbial communities can continue to be effective tools for health intervention, both at the individual level as well as at the community.

Exploring microbial balances, conferred by the wisdom in natural feeding, as in this article, is a good place to begin.

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Electroencephalography-detected neurophysiology of internet addiction disorder and internet gaming disorder in adolescents - A review

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ABSTRACT

Introduction: Internet Addiction Disorder (IAD) is an umbrella term for various types of Internet-based behavioural addiction, whereas Internet Gaming Disorder (IGD) addresses a specific type of IAD that is postulated to be due to a lack of control in impulse inhibition. IGD is an area of concern in the Diagnostic and Statistics Manual of Mental Disorders (DSM-5), which can be objectively assessed by dysfunctional behaviour and the increasing time of being online, particularly during the COVID-19 pandemic. Electroencephalography (EEG) identifies amplitude changes in the evoked response potential (ERP) among IGDs, correlated with underlying comorbidities.

Materials and Methods: A scoping review was performed to elaborate on the research regarding resting-state EEG and task-based EEG, particularly for Go/No-go paradigms pertaining to subjects with IAD or specifically IGD. The role of EEG was identified in its diagnostic capability to identify the salient changes that occurred in the response to reward network and the executive control network, using resting-state and task-based EEG. The implication of using EEG in monitoring the therapy for IAD and IGD was also reviewed.

Results: EEG generally revealed reduced beta waves and increased theta waves in addicts. IGD with depression demonstrated increased theta and decreased alpha waves. Whereas increased P300, a late cognitive ERP component, was frequently associated with impaired excessive allocation of attentional resources of the IAD towards addiction-specific cues. IGD had increased whole brain delta waves at baseline, which showed significant reduction post therapy.

Conclusion: EEG can identify distinct neurophysiological changes among Internet Addiction Disorder and Internet Gaming Disorder that are akin to substance abuse disorders.

KEYWORDS:
EEG, ERP amplitude, impulsivity, inhibitory control, P300, resting-state EEG

INTRODUCTION

Internet addiction disorder (IAD) can be defined as a non-chemical, behavioural addiction that involves human-machine interaction.[1] Whereas, electroencephalography (EEG) is a modality that identifies cortical electrical impulses of the brain, hence enabling the detecting of brainwave patterns during rest and thought processing.[2] IAD is comprised of generalised Internet addiction (GIA) and specific Internet addictions (SIA). SIAs are comprised of distinctive online activities such as Internet Gaming Disorder (IGD), social networking sites (SNS) addiction, cyber-pornography addiction, and online shopping addiction.[1] IGD has been proposed as a type of addiction similar to substance use disorders (SUDs).[3] Specifically, IGD can be considered a pathological behavioural addiction, provided that the gaming causes significant impairment or distress in several aspects of a person's life.[3]

The development of tolerance has been implicated in the diagnosis of IGD as it is a progressive and chronic condition. Some of the objective assessment for an individual to be diagnosed with IGD include increased time of being online and having a tendency to download faster software to run their gaming applications.[3] Clearly with the advent of mobile smartphones, problematic smartphone use and internet addiction have become more prevalent among young adults.[4] Moreover, during these challenging times of the novel coronavirus disease 2019 (COVID-19) pandemic and movement restriction orders imposed by governments to enforce social distancing, the urge to be constantly online has become stronger among the adolescents and young adults, as evidenced by a three-fold increase in online mobile gaming and 35% higher usage for multiplayer modes in a survey conducted in India.[5]

Internet Addiction Disorder

The phenomenon of IAD, also known as Problematic Internet Use (PIU), is defined as a behavioural addiction involving a psychological dependence to internet applications and sites, with resultant adverse consequences.[1] IAD is attributed to an impairment of the frontal executive control network (ECN), which leads to a diverse set of behavioural addictions that may comprise of specific applications and activities, such as online pathological gambling, online social networking addiction, cybersex addiction, e-shopping, and online information seeking.[1] The lack of inhibitory impulse control leads to a compulsive behaviour to constantly seek gratifying activities.[2] Thus, understanding the neurophysiology of the mechanisms underpinning this condition can be critical in implementing a proper treatment plan. The theory driven

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model for IAD assumes a similarity with SUDs, whereby the 'positive' reinforcement factor is the cravings for rewarding stimuli (impaired response to reward in the limbic system); and the 'negative' factor is the impulsiveness or lack of inhibitory control that leads to withdrawal and tolerance (lack of impulse control in the ECN).[2,3]

Internet Gaming Disorder

Playing videogames online provides a conducive platform for gaining mastery of skills needed to win the games, escaping from the realities of life, and achieving socializing needs while providing anonymity, all of which are vastly appealing to adolescents and young adults.[4] Nevertheless, the downside of this is the development of dependence and tolerance, particularly among adolescents and young adults. The neurobiology of IGD is deemed analogous to the pathways involved in SUDs.[3] Neuroimaging studies and epidemiological studies point to a dual processing model of digital technology addictions characterized by an imbalance between the reflective ECN, which is 'hijacked' by the over-reactive cortico-limbic reward system.[3,6-9] Moreover, by using cue-reactivity paradigms, e.g., presenting game-related stimuli, activations of the ventral striatum, amygdala and hippocampus were noted in IGD cases compared to controls.[3]

Neurophysiological evaluation using electroencephalography

There is growing recognition that the EEG activity, which is recorded under either the resting-state eyes-closed (EC) or eyes-open (EO) condition or simultaneously during the presentation of a task-based stimulus, acts as a brain-activity correlate of behaviour and cognition.[7] The high temporal resolution, mobility, non-invasive scanning, and relatively low cost of EEG make it a valuable tool to study addictive behaviours compared to neuroimaging techniques.[2] Current scalp EEG systems are typically 64-channel electrodes placed in several predetermined positions on the scalp of the subjects (Figure 1a). The interpretation of EEG waves is categorized into frequency bands that denote different degrees of brain activity. Commonly discernible frequency bands include the delta wave, δ wave (0.3–3.5 Hz), theta wave, θ-wave (4–7.5 Hz), alpha wave, α-wave (8–13 Hz), beta wave, β-wave (14–30 Hz) and gamma wave, γ-wave (>30 Hz).[2] Beta band activity are high-frequency waves that are related to exerting inhibitory control, whereby the activation of attention will cause an increase in β-wave amplitude in the frontal area and a decrease in the β-wave amplitude in the posterior regions.[2] The α-wave amplitude increases with an increase in cognition, memory and attention, and is reduced when an inhibitory control is exerted by the ECN.[2] Contrarily, an increase in θ-wave amplitude indicates cognitive dysfunction.[2]

Concerning task-based EEG, several evoked response potentials (ERPs) are implicated in the neurophysiology of addiction. The ERPs are defined by the amplitude, latency, polarity, and scalp distribution of the electrical wave recordings. A fronto-central negative wave that peaks at 200 to 350 ms after the onset of the stimulus is termed the N2 or N200 wave.[6] The N200 amplitude has a negative deflection from the baseline EEG recordings and is larger during negative feedback and perceived adverse outcomes in neuropsychological tasks.[6] Figure 1b shows an example of the N200 wave. In Go/No-go tasks, the N200 is observed predominantly in the fronto-central regions and is caused by infrequent/ 'target' stimuli in the No-go task. The N200 amplitude is noted to increase as the frequency of the eliciting stimulus decreases.[6] This is inferred to be caused by the mental need to control incorrect responses and involved in the automatic novelty sensing process.[6] Accentuated novelty sensing process has been implicated in IAD due to increased impulsiveness.[22] Whereas, the feedback related negativity (FRN) wave reflects the monitoring process associated with feedback inputs and is often elicited by negative stimuli. This negative potential of FRN is predominantly distributed over the fronto-central scalp area and occurs at a latency of 200–300 ms after the feedback (Figure 1c).

FRN is defined as the negative deflection of the EEG recording produced by the subtraction of the waveform for the positive feedback from that for the negative feedback, or purely from the negative waveform obtained from the negative feedback.[2] Studies have revealed reduced amplitude and prolonged latency of the FRN in pathological conditions related to impaired attentional states.[2] Then, there is the P300 or P3 wave, which is an ERP that corresponds to activations of the anterior cingulate cortex (ACC) is postulated to reflect premotor decisional processes, including updating of memory, providing cognitive closure, and activation of inhibitory processes over widespread cortical areas.[2] The P300 ERP is a large positive amplitude waveform, having a maximum amplitude over the parietal area with a peak latency of about 300 - 350 ms (auditory stimulus) and 350 - 450 ms (visual stimulus) (Figure 1c). The P300 is involved in the activation of cortical inhibitory processes. Its amplitude is affected by the level of difficulty of the task, motivation, significance of the stimulus, and vigilance.

The hypotheses of IAD and IGD are that they are similar to SUDs, i.e., both are influenced by (i) impaired inhibitory control exerted by the ECN/ increased impulsivity and (ii) overactive response to addiction-specific cues that are perceived as rewards.[2,3] However, little is known regarding the underpinnings of the neurophysiological changes that are involved in these disorders. EEG can provide an excellent temporal resolution in detecting abnormal brain wave patterns. Thus, this scoping review aims to identify relevant articles that have evaluated the role of resting-state and task-based EEG in determining the neurophysiological changes that occur in IAD and IGD. Subsequently, this review aims to summarize recommendations to improve this technique and to propose a conceptual framework regarding the role of EEG in evaluating the neurophysiology of IAD and IGD.

MATERIALS AND METHODS

This review adopted the framework of scoping reviews proposed by Arksey and O'Malley's, 2005.[26] The initial research questions were identified, relevant studies were sourced, studies that fulfilled the inclusion criteria were selected, the data was plotted in tables, and the report and finally a summary of the salient findings and recommendations were presented in the discussion section.

Identifying the initial research questions
This review aimed to identify critical neurophysiological changes that occur in IAD and IGD subjects using resting-state EEG and task-based EEG, respectively. We also aimed to determine trait features of IAD and IGD, while identifying potential trait features of comorbid conditions such as Attention Deficit Hyperactivity Disorder (ADHD), which is also an impulse control disorder and depressive symptoms that can co-exist with IAD or IGD.

Identifying relevant studies
A wide range of keywords and their combination was used to source the published literature in Scopus and PubMed databases. Advanced search tools and the use of Boolean operators were employed to broaden the scope to cover the specific objectives of this review. The search terms included a combination of the keywords 'Internet Addiction Disorder', 'IAD', 'Internet Gaming Disorder', 'IGD', 'electroencephalography', 'EEG', 'resting-state EEG', 'evoked response potential', and 'inhibitory control'.

The inclusion criteria were all peer-reviewed, original research articles, written in the English language, evaluating the role of EEG in determining the neurophysiological changes that occur in IAD or IGD, compared with healthy controls (HC) or any other suitable, comparable group. The exclusion criteria were all articles that were not original research articles, e.g., review papers, proceedings, technical reports, and case series. Furthermore, the exclusion criteria involved full texts that were not written in the English language, articles that did not evaluate IAD or IGD, and studies that did not utilise EEG as the primary investigation to evaluate IAD or IGD. We did not apply any time constraint for our search strategy. Review of the literature was completed over four months, ending in January 2021.

Articles selection
The initial search of the databases identified 114 articles by applying the inclusion criteria. Deduplication was done and 59 articles were removed. Fifty-five articles were evaluated based on the title and abstract, and subsequently 14 articles were removed. A review of the abstracts revealed large numbers of articles that were not original articles (n=10). The full texts of a further 41 articles were screened using the exclusion criteria. The Preferred Reporting of Items for Systematic Reviews and Meta-Analyses (PRISMA) method was utilised for the whole process of evaluating the articles. Finally, 35 studies were identified as being relevant to the research topic, as shown in the PRISMA flowchart (Figure 2). We did not evaluate the potential bias of the eligible articles as this process is not considered essential for scoping reviews.

RESULTS

Overall, our search of the databases identified 12 eligible resting-state EEG articles and 23 eligible task-based EEG articles that evaluated IAD or IGD. Of the former 12 articles, five evaluated IAD[7-8,10-12] and seven evaluated IGD.[13-19] Of the latter 23 articles that utilised task-based EEG, 16 evaluated IAD[6,20-33] and seven evaluated IGD,[9,34-39] respectively.

Resting-state Electroencephalography in IAD and IGD
The frequency bands detected from the EEG recordings can be evaluated for their power spectral density (PSD) or absolute power, representing the power distribution of the EEG series in the frequency domain. Additionally, the scalp recording sites can also be statistically correlated using coherence analysis to estimate the functional connectivity between areas of the brain cortices in the temporal domain of IGD subjects.[16] The data can be recorded using either the eyes closed (EC), or eyes open (EO) condition, whereby the EC condition permits the evaluation of a functional baseline because there are no external tasks demands that can distract the subjects' attention. Alternatively, the EO condition allows the subjects to engage passively with an external visual input without performing a specific task. Fast Fourier Transformation (FFT) is used to convert the continuous EEG data recordings into the frequency domain, and subsequently, the data from each scalp electrode will be computed for the respective frequency bands.[16]

Studies that have evaluated the resting-state EEG coherence among IAD and IGD have identified similarities with SUD regarding the regional brain connectivity abnormalities. It is postulated that the altered γ phasic synchrony is explained by the abnormal excitatory system and hyper-aroused sensory system in addicts.[10]

Decreased absolute β power is a consistent finding among subjects with IAD and IGD and is significantly correlated with the severity of the addiction and impulsivity.[13] It is also postulated that the resting-state EEG findings of IAD patients with comorbid depression are altered because of the effect of depression, whereby an increased relative θ-wave power was found in these cases.[8]

A summary of studies that evaluated resting-state EEG in IAD and IGD can be found in Table I.

Electroencephalography and event related potentials
EEG responses that are time-locked to more complex processing of a given stimulus is defined as the event-related potential (ERP).[2] As mentioned earlier, the commonly identified ERPs, namely the N200, P300 and FRN, occur after a stimulus is presented, and can provide detailed measures of the processes that occur between the stimulus input and response output.

The N100 and P200 peaks are auditory cortical responses that reflect bottom-up information such as stimulus features.[9] Frequently, the P300 wave is elicited by two types of ERP tasks, namely the oddball task and the Go/No-go task. The subject's response is typically recorded by eliciting the button-pressing response. Furthermore, the P300 is sensitive to the occurrence probability of a stimulus as well as task complexity.[9] The P300 amplitude is increased when a more salient and relevant event is observed that produces an automatic attentional response.[9] Hence, an increased P300 amplitude is considered as a biomarker of inhibitory deficit in IAD.[9] This is frequently observed in the Go/No-go task, whereby the No-go stimulus is considered as the rare one, in which the subjects are required to avoid it. Thus, the presence of an increased P300 amplitude during the No-go task is a marker for response inhibition.

Table I: Studies that assessed Internet Addiction Disorder / Internet Gaming disorder using resting-state EEG

(A) Internet Addiction Disorder

Author (Year)	Region	Type of tests to diagnose IAD/ IGD and comorbids	Participants, Sample size	Findings
1. Choi JS et al. (2013)[10]	South Korea	- IAT - BIS-11 test	• IAD (n=21) • HC (n=20)	-↓ absolute power on the β band, ↑ absolute power on the γ band among IAD - increased impulsivity and impaired inhibitory control among the IAD
2. Lee J et al. (2014)[8]	South Korea	- IAT - SCID - BDI - BAI	• IAD (N=35; IAD with MDD: n=18, IAD without MDD: n=17) • HC (N=34)	- IAD without MDD had ↓ absolute power of δ and β waves - IAD with MDD had ↑ θ but ↓ α waves - This indicates that changes in the δ and β waves can act as a neurobiological marker of IAD. Whereas ↑ absolute power of θ waves may represent trait markers of IAD with comorbid MDD because θ waves are predominantly associated with emotional memory retrieval and meditative states.
3. Kim JW et al. (2017)[11]	South Korea	- DISC-IV - CDI - K-scale	• Pure ADHD (n=22) • ADHD with depression (n=11) • ADHD with PIU (n=19)	- ADHD with PIU showed ↓ absolute θ power at the central and posterior zones compared to pure ADHD - ADHD with depressive symptoms did not show any significant changes. - This indicated that ↓ absolute θ power at fronto-parietal regions may represent trait markers for PIU.
4. Wang GY et al. (2018)[7]	New Zealand	-IAT	• Healthy subjects using the Internet for recreational purposes	- IAT score was positively correlated with α power obtained during eyes closed resting-state EEG recordings - There was a positive correlation between BDI score with α asymmetry at mid-frontal regions
5. Kamaruddin N et al. (2021)[12]	Malaysia / Indonesia	- validated questionnaire for cyber-pornography addiction - EEG pattern derived classification of learning disorders	• Not having porn addiction (n=7) • Not addicted to porn (n=7)	- ADHD was identified as those with high θ/β ratio in frontal regions - ASD was identified as those with high α/β ratio in frontal regions - Dyslexia was identified by ↑ power of θ on the left hemisphere of the brain including the frontal regions - ASD was significantly correlated with risk for cyber-pornography.

(B) Internet Gaming Disorder

Author (Year)	Region	Type of tests to diagnose IAD/IGD and comorbids	Participants, Sample size	Findings
1. Son KL et al. (2015)[13]	South Korea	-IAT	• IGD (n=34) • AUD (n=17) • HC (n=25)	- ↓ absolute β power among IGD - ↑ absolute power on the γ band in AUD - No significant correlation between severity of IGD with QEEG
2. Kim YJ et al. (2017)[14]	South Korea	- IAT at baseline and and post SSRT therapy	• IGD (n=20) • HC (n=20)	- there was ↑ absolute power of θ at central zone and whole brain δ bands at baseline, which showed significant ↓ at 6 months post SSRT - the extent of θ band reduction correlated with the change in IAT scores
3. Park JH et al. (2017)[15]	South Korea	- YIAS - K-ARS	• ADHD only (n=15) • ADHD with IGD (n=15) • HC (n=15)	- ADHD only group showed ↑ power of θ at the frontal regions - ADHD and IGD showed ↑ power of β at the temporal regions - interhemispheric coherence was ↑ in ADHD with IGD (likely due to repetitive activation of the brain reward and working memory systems during continuous gaming can result in an ↑ in neuronal connectivity within the temporal and parieto-occipital regions

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4. Park SM et al. (2017)[16]	South Korea	- DSM-5 - IAT - AUDIT	• IGD (n=30) • AUD (n=30) • HC (n=32)	- AUD showed ↑ θ band - IGD showed ↑ interhemispheric γ coherence compared to AUD and HC regardless of psychological features evaluated such as depression, anxiety, and impulsivity - Right fronto-central coherence predicted the IAT scores
5. Youh J et al. (2017)[17]	South Korea	- DSM-5 - IAT	• MDD (n=15) • MDD + IGD (n=14)	- MDD+IGD had ↓ α band coherence between the interhemispheric frontal regions - MDD+IGD had ↑ intra-hemispheric coherence for α band between parietal and occipital regions - MDD+IGD had ↑ intra-hemispheric β band coherence between fronto-temporal regions
6. Park S et al. (2018)[18]	South Korea	- DSM-5 - YIAS	• IGD (n=30 out of which 18 completed treatment) • HC (n=12)	- At baseline recording, IGD showed ↑ β and γ inter-hemispheric coherence, and ↑ δ intra-hemispheric coherence of the right hemisphere - At 6 months post SSRI interventional therapy, IGD did not demonstrate any significant EEG changes compared to baseline but continued to show ↑ β and γ inter-hemispheric coherence despite improvements in IGD symptoms (likely to indicate that ↑ β and γ inter-hemispheric coherence are neuro-physiological trait markers of IGD.
7. Hong JS et al. (2020)[19]	South Korea	- DSM-5 - Beck Depression Inventory - Beck Anxiety Inventory - K-ARS	• IGD with no comorbids, treated with CBT and PE (n=25) • IGD with no comorbids, treated with CBT only (n=25)	-↑ FAA, addiction score, and ↓ depression scores that were more marked in the CBT and PE group, which indicates greater left PFC activation during PE alleviates the mood of IGD subjects

Footnote: ↓: reduced, ↑: increased, ADHD: attention deficit hyperactivity disorder, ASD: autism spectrum disorder, AUD: alcohol use dependence, AUDIT: Alcohol Use Disorders Identification Test, BAI: Beck's Anxiety Inventory, BDI: Beck's Depression Inventory, BIS-11: Barratt's impulsiveness scale, DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, FAA: frontal alpha asymmetry, CBT: cognitive behaviour therapy, PE: physical exercise, PFC: prefrontal cortex, K-ARS: Korean version of ADHD Rating Scale, YIAS: Young's Internet Addiction Scale, IAT: Internet Addiction Test, MDD: major depressive disorder, DISC-IV: ADHD Diagnostic Interview Schedule for Children Version IV, CDI: Children's Depression Inventory, K-scale: Korean Internet Addiction Self-scale, SSRT: selective serotonin inhibitor, SCID: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV, CPz: central-parietal zone. QEEG: quantitative EEG.

Table II: Studies that elicited evoked response potential in Internet Addiction Disorder /Internet Gaming Disorder during task-based EEG

(A) Internet Addiction Disorder

Author (Year)	Region	Type of stimulus	Participants, Sample size	Findings
1. Yu H et al. (2009)[20]	China	Auditory oddball task with simultaneous 19-channel scalp electrodes EEG monitoring	• young adults with IAD (n=10) • HC (n=10)	- PIU showed ↓ P300 amplitude and ↑ P300 latency in all electrodes. - γ oscillation occurred at 300 ms after stimuli presentation at 40–50 Hz on the CPz electrode. - PIU affects information coding and integration in the brain.
2. Dong G et al. (2010)[21]	China	Go/No-go task	• IAD (n=12) • HC (n=12)	- IAD had ↑ P300 amplitude, which indicated that more cognitive endeavours were required to complete the inhibitory task because of impaired inhibitory control - longer P300 peak latency noted in IAD, indicated less efficient information processing due to impaired inhibitory control towards No-go tasks - N200 amplitude was ↓ in IAD, likely due to poor attentional resources
3. Zhou ZH et al. (2010)[22]	China	Visual Go/No-go task	• IAD (n=26) • HC (n=26)	- BIS-11 total scores, attentional key, and motor key scores in IAD group were higher than that of the HC group. - N200 amplitude was significantly ↓ in the frontal regions during the No-go task among the IAD and correlated with impulsivity scores. - This indicates that IAD shares neuropsychological and ERPs characteristics of compulsive-impulsive spectrum disorder.
4. Ge L et al. (2011)[23]	China	Auditory oddball task	Middle-aged adults: • IAD (n=38) • HC (n=48)	- ↓P300 amplitude and longer P300 latency in IAD, was postulated to be due to attentional resource allocation of cognitive processing being of greater importance in the development of IAD in older people compared with younger people. - shorter/ reduced latency of P300 after CBT may be indicative of quicker response and improved attentional resource allocation.
5. Zhou Z et al. (2013)	China	Erikson flanker task	• IAD (n=23) • HC (n=23)	- IAD made ↑ total error rates than HC - IAD had ↓ Reactive times for total error responses - IGD had ↓ mean ERN amplitudes of total error response conditions at frontal and central electrode sites (likely to indicate deficient response monitoring function characteristics, i.e. compulsive-impulsive spectrum disorder characteristic.
6. Ling Z et al. (2015)[25]	China	Visual oddball task	• IAD (n=10) • HC (n=10)	- IAD showed ↓ P300 wave amplitude and longer latency period when tested for addiction-related stimuli (likely due to impaired memory abilities of the IAD)
7. Yau YHC et al. (2015)[26]	USA	BART task	• PIU (n=39) • HC (n=27)	- PIU showed ↓ FRN and P300 amplitudes to both negative and positive feedback (implying that impaired feedback processing can be a neural correlate of PIU).
8. Zhang F et al. (2016)[27]	China	Face vs. non-face object	• IAD (n=20) • HC (n=20)	- The N110 and the P200 ERP amplitude in response to faces were ↑ in the IAD group than HC group. - The N170 to faces ↓ in the IAD group than in the HC group.
9. Balconi M et al. (2017)[28]	Italy	Attentional inhibitory task (Go/No-go task)	- High IAT scores (n=12) -Low IAT scores (n=13)	- High-IAT young participants had specific responses to IAD-related cues (videos representing online gambling and videogames) in terms of cognitive performance (↓ Response Times, and Error Rates) with ↓ FRN and increased P300.
10. Jiao C et al. (2017)[29]	China	Visual stimuli (person's hands/ forearms/feet in painful or non-painful situations)	• IAD (n=16) • HC (n=16)	- Painful pictures elicited ↑ N200 and P300 amplitudes than the non-painful pictures only in the HC group but not in the IAD group. - Both early automatic and of the later cognitive processes of pain empathy may be impaired in IADs. - Psychophysical evidence of empathy deficits in association with IAD.

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11. Lai C et al. (2017)[30]	Italy	Visual task of viewing pictures with Internet themes and emotional images having neural, positive, and negative themes as conditions	• IAD (n=16) • HC (n=14)	- there was no significant difference between IAD and HC when presented with Internet themed cues (likely due to heterogeneous group of IAD, who may have different motivations for their Internet addiction) - IAD subjects had ↑ activations detected using the somato-sensorial cortex on LoRETA software (likely due to dissociative symptoms in pathological Internet use, i.e., disruption of the normal psychological functioning caused by the IAD.
12. Gao et al. (2019)[31]	China	Go/No-go task	• excessive SNS users (n=23) • HC (n=20)	- N100 amplitude was ↑ following SNS images than control images in excessive SNS users. - Excessive users showed ↑ N200 amplitude and ↓ No-go P300 amplitude than non-excessive users irrespective of stimuli. - Excessive SNS users are inefficient in allocating monitoring resources in the No-go task (reflected by enhance N200) and showed difficulty in late inhibitory control procedure (reflected by ↓ No-go P300) compared to non-excessive users. - Excessive SNS users pay more attention to SNS-related images compared to non-SNS-related images (reflected by the N100).
13. Karapetsas AV et al. (2020)[32]	Greece	IAD related visual stimuli	• IAD (n=14) • HC (n=14)	- longer latency of P300 that normalised in post rehabilitation EEG recordings in the IAD - Improved IAT score was observed post rehabilitation programme and correlated with shorter latency period of P300.
14. Killian C et al. (2020)[33]	Germany	Go/No-go task and response to reward assessment Flanker task	• HBW (n=35) • NBW (n=33)	- Internet entertainment programmes streaming binge watching subjects who were HBW showed ↑ P300a and P300b during response inhibition and ↑ MMN/ERN for Flanker task errors.
15. Wang J et al. (2020)[6]	China	Two-choice Oddball task (neutral stimuli and deviant pornographic images)	• TCA (n=36) • HC (n=36)	- TCA showed ↓ N200 and P300 waves amplitude for deviant compared to neutral stimuli. - TCAs were more impulsive/ showed lack of inhibitory control and shared similar neurophysiological ERP changes with substance use disorder and other behavioural addictions.

(B) Internet Gaming Disorder

Author (Year)	Region	Type of stimulus	Participants, Sample size	Findings
1. Duven ECP et al. (2015)[34]	Germany	Cue induced reactivity/ Monetary reward computer game task	• IGD (n=14) • HC (n=13)	- IGD showed ↑ N100 amplitude, ↓ P300 amplitude, likely caused by an initial ↑ attention status that required more cognitive capacity to process the gaming reward, but later evaluating that the reward required less attention (this is contradictory to other findings but is explained by the maintenance phase of addiction, whereby habitual processing of the addictive stimuli might lead to less attentional processing of the addiction-specific cues).
2. Kim SN et al. (2018)[35]	South Korea	Gaming related cues	• IGD: 20 • OCD: 20 • HC: 23	- IGD group showed ↑ amplitude of P300 at the CPz in game-related cues (indicating ↑ arousal/attentional resources to gaming-related cues).
3. Kim J et al. (2019)[36]	South Korea	Comparison of band power during playing online games	• IGD (n=24) • HC (n=35)	- IGD showed ↓ left frontal θ, α, and β band activities - left frontal θ power negatively correlated with IGD severity. - Proposed that left frontal θ power could be used as a neurophysiological biomarker for the detection of diminished cognitive control in IGD.
4. Park M et al. (2017a)[9]	South Korea	Auditory oddball task	• IGD (n=26) • AUD (n=22) • HC (n=29)	- IGD and AUD groups had ↓ P300 amplitudes at the midline central and parietal area compared with the HCs. - IGD had ↓ N100 amplitudes at the midline frontal area compared with the HCs. - ↓ P300 was correlated with a higher spatial span error rate in the IGD.

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5. Park M et al. (2017b) [37]	South Korea	Auditory oddball task at baseline and 6 months post SSRI interventional therapy	• IGD (n=18) • HC (n=29)	- At baseline recording, IGD had ↓ P300 amplitude and longer latency at the CPz - At post treatment recording, although there were no significant changes in EEG waves, there was significant reduction in the symptoms and improvements in the addiction scores - This indicates that ↓ P300 amplitude and longer latency at the CPz are likely to be candidate endophenotypes in the pathophysiology of IGD.
6. Ha J et al. (2020)[38]	South Korea	Cue induced reactivity towards watching preferred gaming video vs. control	• IGD (n=20) • HC (n=20)	- When watching the preferred type of gaming video (addiction-specific stimulus), the IGD showed ↑ absolute θ power and ↓ absolute β power at the parieto-occipital region that correspond to cravings related features.
7. Raiha S et al. (2020)[39]	South Korea	Response to reward cue reactivity task	• IGD (n=35) • HC (n= 39)	- IGD showed blunted FRN for losses vs gains - when presented with high-risk choices, there was increased FRN amplitude in HC, but not in IGD (likely to represent impaired risk avoidance tendency/ inability of the ECN to exert an inhibitory control).

Footnote: ↓: reduced, ↑: increased, AUD: alcohol use disorder, BART: Balloon Analogue Risk Task, CBT: cognitive behaviour therapy, CPz: central-parietal zone, DISC-IV: ADHD Diagnostic Interview Schedule for Children Version IV, CDI: Children's Depression Inventory,DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, ECN: executive control network, ERN: error related negativity, FRN: feedback related negativity, MMN: mismatch negativity, HBW: high binge watching, NBW: no binge watching, PE: physical exercise, PFC: prefrontal cortex, K-ARS: Korean version of ADHD Rating Scale, IAT: Internet Addiction Test, MDD: major depressive disorder, K-scale: Korean Internet Addiction Self-scale, SSRT: selective serotonin inhibitor, SCID: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV, BDI: Beck's Depression Inventory, BAI: Beck's Anxiety Inventory, ADHD: attention deficit hyperactivity disorder, ASD: autism spectrum disorder, SSRI: selective serotonin receptor inhibitor, TCA: tendencies towards cybersex addiction.

The neurobiology of this observation correlates with the hypothesis that the ECN fails to exert an inhibitory effect in addicts, often causing decreased P300 amplitude.[2] Nevertheless, the P300 amplitude increases with the rarity of the stimulus, is sensitive to changes in the working memory, and is affected by the preferential allocation of attentional resources.[9] In SUD, particularly alcoholics, P300 ERP is observed to have a reduced amplitude and a delayed latency, particularly in the parietal region.[9] In fact, a reduced P300 has been observed in both Go and No-go tasks in alcoholics, indicating a dysfunction of the response to reward among addicts.[2] Additional data is available pertaining to the P300 amplitude in SUD, whereby a larger P300 amplitude was provoked by alcohol-related pictures in alcohol dependent patients but not in controls.[9] Conversely, reduced P300 amplitudes and delayed P300 latency periods have been noted in the centro-parietal zone (CPz) among IGD subjects compared with healthy controls.[9]

The feedback related negativity (FRN) is an ERP, which can elucidate the neurocognitive correlates of decisional behaviour in addiction. FRN effects are characteristically negative amplitude deflections that occur at the mediofrontal regions and peak at approximately 200–350 ms after the onset of the feedback stimulus, which codes for reward predicting error.[9] FRN acts to monitor performances and is generated at the medial prefrontal cortex (mPFC) and ACC.[2] Varying results have been observed pertaining to the significance of the FRN, however there is consensus that this ERP is an adaptive mechanism that analyses the outcome expectancies and provides a feedback control mechanisms that alters the rewarding power of responses.[9] In combination, the P300 and FRN act as biomarkers of the increased inability to adopt an adequate cognitive strategy in response to a decisional context. This occurs in the presence of some rewarding bias, which occurs concomitantly with an anomalous automatic attentional response.[9]

A summary of studies that evaluated task-based stimuli with simultaneous EEG in IAD and IGD can be found in Table II.

Electroencephalography during stimulus presentation

The main components of working memory are visuo-spatial scratchpad and attention allocation. Many neuropsychological paradigms assess for working memory, the cues are often visual cues and preferably are addiction-specific cues.[2] Stroop Colour and Word Test (SCWT), also known as the Stroop Test for short, is an example of a neuropsychological test, which is extensively used to assess the ability to inhibit cognitive interference. A Stroop task is administered with alternating 'congruent' and 'incongruent' stimuli, whereby a congruent stimulus occurs when what the words say, compared to what the displayed colours of words portray are matched (congruent), hence the frequency of the congruent and incongruent stimuli can be designed to form a Go/No-go task. Conversely, an incongruent stimulus is when the words and displayed colours are mismatched/contradictory. Notably, a previous Stroop task study has detected that children had longer reaction time (slower to respond) and more inferior results accuracy (made more mistakes) compared to adults when they had mixed tasks, i.e., neutral, congruent, and incongruent trials all mixed in every block of the paradigm.[17]

The oddball task, which is used to detect short-term memory retrieval, is performed by requiring the subject to respond mentally or physically to an infrequent target presented amidst frequently occurring standard stimuli and infrequently occurring distracters.[6] He et al., 2018 also utilised an oddball paradigm in an ERP experiment that induced mismatch negativity (MMN).[40] MMN was significantly induced in the subjects with IAD as evidenced by more significant negative deflection of the waveform occurring at the timing of the amplitude at the time of display of the Internet-related pictures.[40]

In a study by Park et al. 2017a, IGD exhibited reduced N100 amplitudes at the midline frontal area compared with the controls.[9] Among the IGD, the reduced P300 was associated with a higher spatial span error rate. However, the reduced P300 and N100 amplitudes were not correlated with the Internet addiction severity scores in the IGD. These results indicate that IGD is associated with abnormalities in the P300 comparable to those with alcohol use disorder.[9]

Zhou et al., 2010 evaluated Problematic Internet Use (PIU), which is like IAD, and its association with impulsivity by performing a Go/No-go task along with simultaneous EEG.[22] It was identified that the N200 amplitude was significantly decreased in the frontal regions during the No-go task among the PIU and correlated with impulsivity scores. This indicates that PIU shares similar neuropsychological characteristics of compulsive-impulsive spectrum disorder.[28] Zhang et al. 2016 conducted an ERP experiment to evaluate dysfunctional face processing in IAD patients and identified that the underlying mechanism of processing faces could be different in IAD compared to healthy individuals.[27]

Role of electroencephalography in monitoring treatment response

A study by Lai et al., 2017 recorded EEG data while presenting images related to the internet and visual emotional cues among IAD patients undergoing psychological treatment.[30] The study utilised a software, i.e., the GeoSource (version 2.0; EGI, Eugene, OR) that is based on the standardized Low Resolution Electromagnetic Tomography (LoRETA). LoRETA is a software that enables the identification of the neural sources of the measured scalp potentials.[2,30] Probabilistic maps are generated and averaged in the Talairach space using an anatomical atlas, then the mean intensity of the Brodmann Areas are extracted based on the identified ERP components. Prior to therapy, IAD patients have a higher primary somatosensorial cortex and lower paralimbic, temporal, and orbito-frontal activation in response to both internet and emotional images as compared to the healthy population.[30]

DISCUSSION

Internet Addiction Disorder comprises of a broad range of addictive online stimuli that induce cravings and reveal a lack of inhibition among both genders of addicted adolescents and young adults. Conversely, Internet Gaming Disorder, which is a specific type of internet addiction, particularly afflicts young males. Teenagers are in the most vulnerable age group, as they develop more severe complications compared to other age groups when addicted to the internet. The deterioration of the inhibitory control

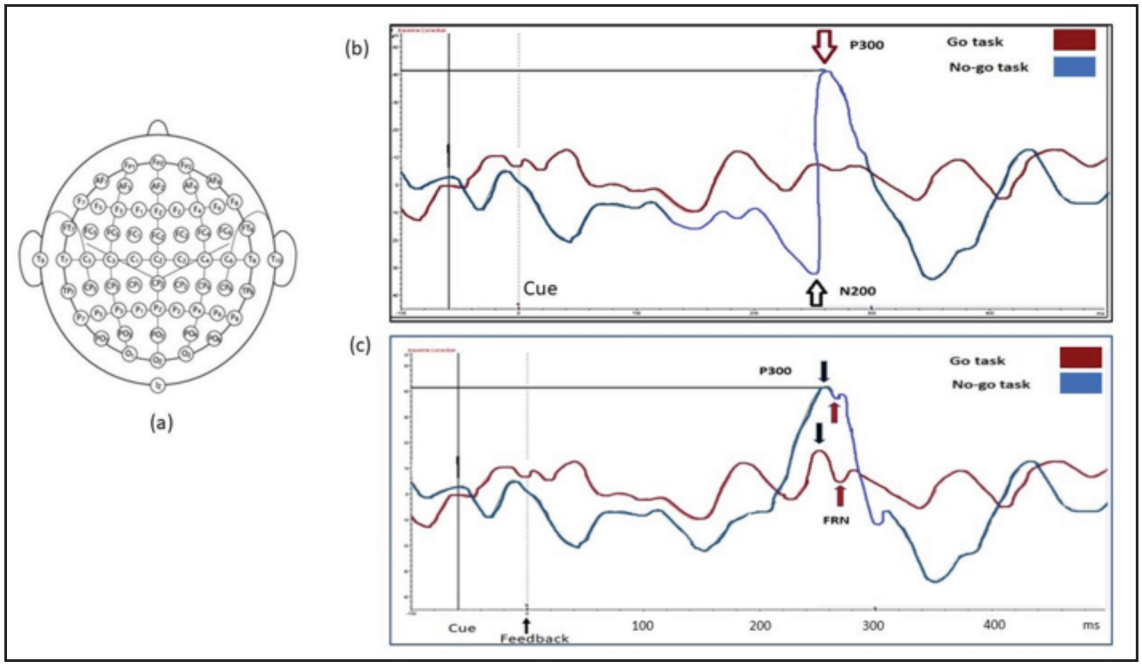

Fig. 1: (a) EEG electrodes designated positions for 64-channels setup. (b) Task-based EEG recording at the central electrodes demonstrated the negative deflection of N200 wave occurring at approximately 220-260 ms from the time of cue presentation, with significantly larger amplitude when performing the No-go task (addiction-specific task) compared to the Go task. The P300 positive deflected wave, occurring at approximately 280-320 ms, also showed a larger amplitude when performing the No-go task compared to the Go task. (c) Task-based EEG recording at the frontal electrodes, demonstrated the P300 positive deflected wave, occurring at approximately 280-290 ms from the time of feedback presentation, which showed a larger amplitude when performing the No-go task (addiction-specific task) compared to the Go task. The feedback related negativity (FRN) evoked response potential demonstrated the negative deflection at approximately 2280-300 ms from the time of feedback presentation, with significantly larger amplitude when performing the No-go task compared to the Go task.

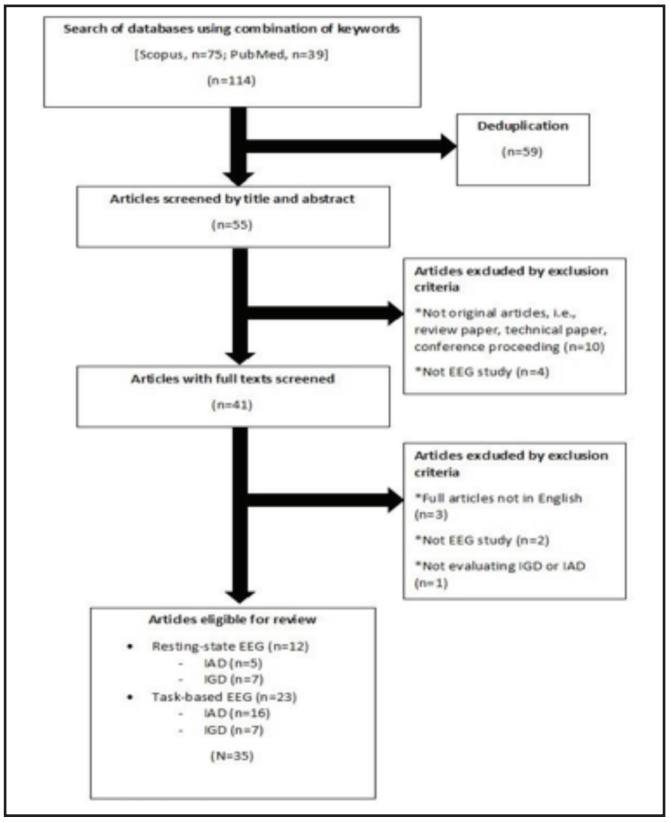

Fig. 2: PRISMA flowchart for selection of eligible articles in this scoping review.

exerted by the ECN, coupled with an inherent risk approach caused by impulsivity, make the IGD subjects susceptible to seeking rewarding stimuli persistently.

Resting-state EEG commonly demonstrates increased θ band activity in the frontal brain regions of the addicts. Hence, a decreased absolute power of the θ band in the frontal brain region may be a trait marker of IAD and IGD, which can act as a biomarker for detecting diminished cognitive control.[11,36] Alternatively, increased absolute power of the θ band has been hypothesized to represent trait markers of IAD with comorbid MDD, because θ waves are predominantly associated with emotional memory retrieval and meditative states.[8]

Furthermore, abnormal ERPs, i.e., the N200, P300 and FRN, were observed in both the IAD and IGD subjects. Nevertheless, there is conflicting evidence from various task-based EEG studies regarding the influence of IAD and IGD on the P300 and FRN amplitude waveforms. Essentially, ERPs on cue reactivity, such as the P300 and FRN, can be utilised as biomarkers for IGD. Deficits in behavioural feedback are believed to be related to rewarding bias, whereby the modulations of FRN and P300 are postulated to be affected by salience detection and motivational states of the subject.[534,39] The subjects' anticipation and prediction of the rewarding stimuli is believed to exert a significant FRN amplitude reduction.[39]

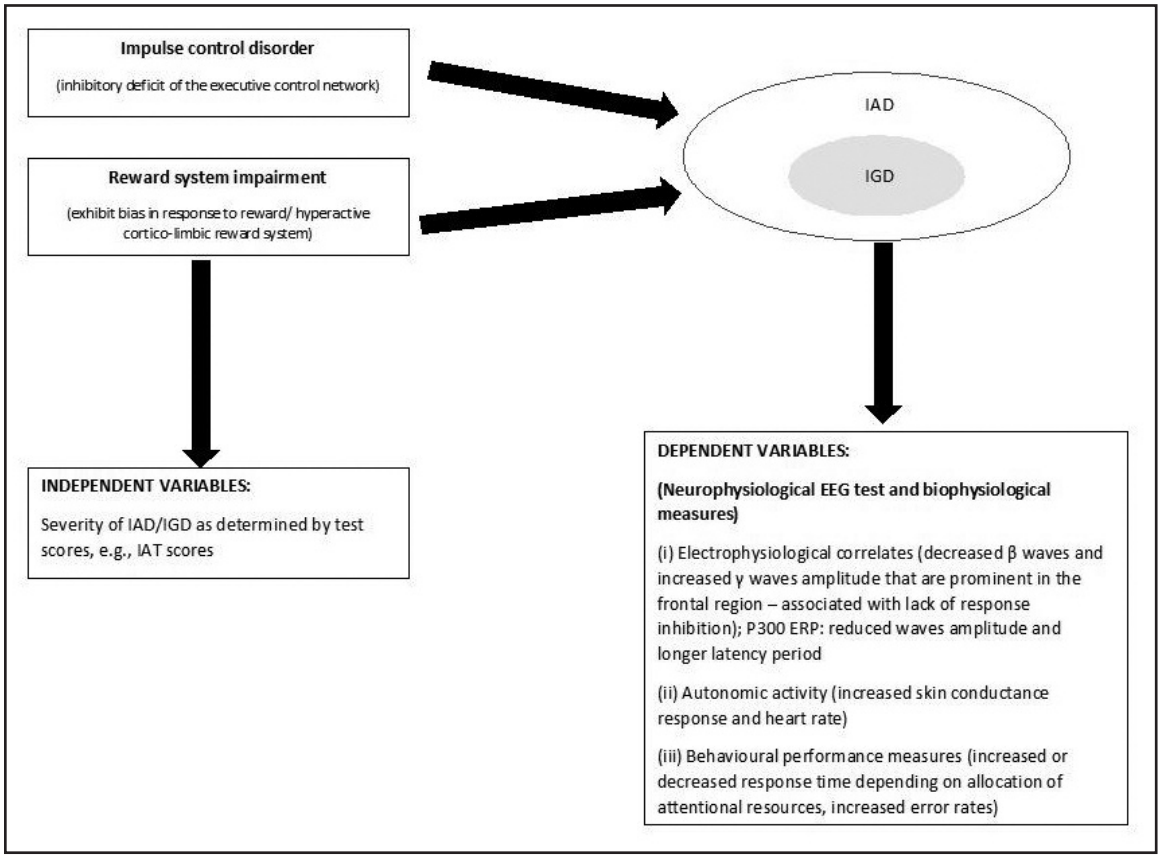

Fig. 3: Conceptual framework of the role of EEG in identifying the neurophysiological underpinning of IAD and IGD.

Implicitly, altered P300 modulations, specifically reduced amplitude, can act as a biomarker of IGD that identifies impaired attentional states when presented with perceived rewarding stimuli in comparison with the non-rewarding stimuli for these subjects.[9,34,37] On the contrary, larger P300 amplitudes have been observed in both IGD and IAD subjects after the presentation of the perceived rewarding cues, which is hypothesized to be caused by an impaired salience assignment and increased arousal or attentional resources to addiction-related cues.[21,33,35]

It is also important to note that comorbid conditions such as ADHD may affect the EEG waveforms, e.g. IGD with concomitant major depressive disorder (MDD) had reduced α band coherence between the interhemispheric frontal regions.[17] As for ADHD only subjects, there is increased power of θ at the frontal regions, however for the ADHD with IGD there is increased power of β at the temporal regions, likely caused by the repetitive activation of the brain reward and working memory systems during continuous gaming.[15]

The conceptual framework regarding the role of EEG in evaluating the neurophysiological changes that occur in IAD and IGD is elucidated by this scoping review (Figure 3). It is hypothesized that the underlying neural mechanism of the overactive cortico-limbic reward system and the deficient inhibitory control exhibited by the ECN collectively give rise to IAD and IGD. Both the conditions share similar neural underpinnings of impulsivity but differ in the type of rewarding stimuli that the addicts respond to.

The limitations include the fact that most studies were performed in either South Korea (mainly for IGD) or China (mainly for IAD). Hence, the recognition of IGD as a true pathological condition is still controversial. More multinational studies are needed to evaluate this disorder to evaluate the consistency of the findings. Another limitation includes the lack of standardisation of the diagnostic criteria and cut-off values to identify the subjects at risk of IAD and IGD. There is also heterogeneity in the observed P300 wave deflections, whereby some studies observed reduced wave amplitude and others observed increased wave amplitude of the P300.[6] The former observation is believed to be caused by reduced attentional resources, whereby habitual processing of the addictive stimuli might lead to less attentional processing of the addiction-specific cues, particularly in the maintenance phase of the addiction. The latter observation can be frequently seen in addicts because of the increased arousal and recruitment of attentional resources towards addiction-specific cues. The interpretation of these findings can be harmonised if the selection of the test subjects is made with care, having considered the phase of addiction that they are currently in.

Moreover, many previous EEG studies pertaining to IAD and IGD have focused on assessing male participants. Hence,

more effort needs to be made to evaluate females, despite the challenges that are associated with performing scalp EEG testing in this group. Additionally, although EEG provides excellent temporal resolution and can provide a gross localization of the neural source using LoRETA, the incorporation of simultaneous EEG-correlated functional magnetic resonance spectroscopy (EEG-fMRI) may pave the way for the improved understanding of the neurophysiology and neuropathology of this condition.[2]

CONCLUSION

EEG can identify distinct neurophysiological changes among Internet Addiction Disorder and Internet Gaming Disorder in adolescents and young adults that are akin to substance abuse disorders.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest to declare.

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SHORT COMMUNICATION

Fluctuation of *BCR-ABL1* qPCR^{IS} level beyond 0.1%^{IS} after stopping tyrosine kinase inhibitor in chronic myeloid leukaemia patients with deep molecular response for at least two years

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SUMMARY

Fluctuation of *BCR-ABL1* real-time quantitative polymerase chain reaction in International Scale (qPCR^{IS}) level below major molecular response (MMR) (0.1%^{IS}) is a known phenomenon after stopping tyrosine kinase inhibitor (TKI) in chronic myeloid leukaemia (CML) patients who are attempting treatment free remission (TFR). We report here four cases of fluctuation beyond MMR during conduct of a Malaysia Stop TKI Trial (MSIT) to examine the validity of the commonly used relapse criterion – loss of MMR for one reading – aiming to provide evidence in setting relapse criteria for future CML patients who want to attempt TFR.

KEYWORDS:
chronic myeloid leukemia, treatment free remission, BCR-ABL1, tyrosine kinase inhibitor, major molecular response

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that originates from an abnormal pluripotent bone marrow stem cell and is consistently associated with *BCR-ABL1* fusion gene[1], which can be quantitated using real-time quantitative polymerase chain reaction (qPCR) and standardized using International Scale (IS) (qPCR^{IS}).[2] One of the many advancements in the field of CML is the concept of treatment free remission (TFR), arguing the necessity of life long tyrosine kinase inhibitor (TKI). About 40% of CML patients, who had achieved deep molecular response (DMR) (molecular response (MR) of 4-log reduction (MR4) (0.01%^{IS}) or deeper) for at least two years, were able to stop TKI safely and remain in TFR, while 60% relapsed molecularly.[3-6] Criteria of relapse used in majority of stopping TKI trials are loss of major molecular response (MMR) (0.1%^{IS}) for one reading.[7,8] Fluctuation of qPCR level below MMR (0.1%^{IS}) is a known phenomenon after stopping TKI[4], probably due to interplay between the persistence of leukaemic stem cells and immunosurveillance.[8] To our knowledge, there no detail report on fluctuation that exceeding MMR, which is probably the reason it is recommended as a criterion of relapse[9] and used in most of the stop TKI trials.[7,8] During the conduct of Malaysia Stop TKI Trial (MSIT), we observed fluctuation of qPCR^{IS} levels beyond MMR that we feel think it is worth reporting to define safe and practical relapse criteria in CML patients who attempt TFR. Four cases of fluctuation exceeding MMR here.

MATERIALS AND METHODS

MSIT (Malaysia National Medical Research Register (NMRR): NMRR-13-1186-15491; ClinicalTrials.gov: NCT02381379) is a multi-center trial in Malaysia aiming to compare the outcomes of peginterferon (pegIFN)-α-2a for a year followed by observation versus observation after stopping TKI in CML patients with DMR for two years or more. Relapse was defined as: 1) one reading of loss of MMR (0.1%^{IS}), or 2) positivity of *BCR-ABL1* transcripts in qPCR^{IS}, as confirmed by a second analysis point, indicating the increase (≥ 1 log) in relation to the first analysis point at two successive assessments. The qPCR^{IS} test was sent monthly for the first 12 months, 2-monthly for subsequent 12 months, and 3-monthly thereafter and done in a central laboratory.

RESULTS

Two patients (P1 and P2) in the observation arm, both from the same study site (Sultanah Aminah Hospital) relapsed according to the relapse criteria no.1, i.e. loss of MMR (see Table I). TKI was reinitiated as per protocol. However, a repeated qPCR^{IS}, which was not prohibited in the study protocol, was done prior to the initiation of TKI, which showed DMR. Investigations showed no evidence of wrong sampling or laboratory error. After discussion, investigators decided to stop their TKI after two months of TKI intake.

These two "relapse" cases challenge MMR as a relapse criterion and raise doubt on the four relapse cases (R1 to R4, see Table I) prior to the incidence. We re-examined these four cases and could only truly confirm relapse in one case, in which the previous two successive readings showed 1-log increment, fulfilled our trial relapse criterion no.2, before loss of MMR.

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Table I: The four cases with fluctuation of qPCR^{IS} beyond MMR (P1 to P4) and four relapse cases prior to P1 and P2 (R1 to R4)

Patient (sex)	Arm	Four successive readings of qPCR^{IS} (%^{IS}) as per protocol prior to relapse as loss of MMR				Relapse as loss of MMR			Retrospectively confirm relapse	Outcome in Nov 2020
						qPCR^{IS} (%^{IS})	Months after stopping TKI	Date		
P1 (F)	Observation	0.0003	0.0070	0.0133	0.0001	0.2512	12	Dec 2017	Repeat 0.0028%^{IS}, not relapse	Relapse at 45 months after stopping TKI
P2 (F)	Observation	0.0057	0.0035	0.0222	0.0051	0.8765	14	Feb 2018	Repeat 0.0062%^{IS}, not relapse	In TFR
P3 (M)	pegIFN	0.0098	0.0274	0.0108	0.0337	0.1046	22	Jan 2020	Repeat 0.0232%^{IS}, not relapse	Pending for review
P4 (M)	pegIFN	0.0286	0.0541	0.0816	0.0795	0.1100	46	May 2020	Repeat 0.0679%^{IS}, not relapse	Treating physician continued TKI, in DMR$_2$
R1 (M)	Observation	-	-	0.0059	0.0896	0.2594	2	Jun 2016	Confirmed relapse	Restarted TKI and in DMR$_2$
R2 (F)	Observation	0.0300	0.0637	0.0117	0.0774	0.1931	12	Aug 2016	Unable to confirm relapse	
R3 (F)	pegIFN	0.0281	0.0354	0.0225	0.0680	0.1085	10	Jun 2016		
R4 (F)	pegIFN	0.0083	0.0121	0.0203	0.0664	0.1653	27	Nov 2017		

DMR, deep molecular response, also equivalent to 0.01%^{IS} or better; F, female; M, male; MMR, major molecular response, also equivalent to 0.1%^{IS}; pegIFN, peginterferon; qPCR^{IS}, real-time quantitative polymerase chain reaction in International Scale; TFR, treatment free remission; TKI, tyrosine kinase inhibitor

Following the incidence, study protocol was amended to include a repeated qPCR^{IS} on the time of restarting TKI after loss of MMR, which means relapse criteria no. 1 – loss of MMR – must be confirmed by two successive readings. The TKI would be given for two months and re-stopped if the repeated qPCR^{IS} does not confirm the loss of MMR. After the change of protocol, we had two more patients (P3 and P4) who experienced fluctuation of qPCR^{IS} beyond MMR. In Jan 2020, P3 in pegIFN arm experienced such fluctuation (see Table I). He was restarted on TKI for two months, just like the previous two cases of fluctuation, but had not returned to us for review due to the Malaysia and Singapore lock-down during COVID-19. In May 2020, P4 in pegIFN arm experienced such fluctuation, too. However, the treating physician decided to continue his TKI after two months and withdrawn from trial.

DISCUSSION

From the four cases reported here, the fluctuation of qPCR^{IS} occurred after 12 months of stopping TKI. This is probably the phenomenon caused by interplay between leukaemic stem cells and immunosurveillance[7,8] compared to fast rising qPCR^{IS} without fluctuation in most relapse cases within 6 months of stopping TKI. Retrospectively, patients R2 and R4 were probably experiencing the same fluctuation beyond MMR.

Is there an outcome difference between the loss of MMR for one reading and two readings? Up to Nov 2020, P1 and P2 have been follow-up for 47 months. P1 had true relapse (0.1235%^{IS}) at 45 months after stopping TKI with prior increasing trend of qPCR^{IS} and the repeated qPCR^{IS} after relapse was 0.5324%^{IS}. There was differences of opinion among the investigators that maybe it does not matter whether loss of MMR for two readings is needed to confirm relapse because maybe loss of MMR for one reading predicts the relapse later. This awaits more data. For Malaysia setting at the moment, considering the availability and turn-around-time of qPCR^{IS} result in hospitals of Ministry of Health of Malaysia outside of clinical trial, we would not recommend attempting TFR in our eligible CML Malaysian patients outside of clinical trial.

CONCLUSION

In view of the four cases reported, treating physician could consider fluctuation of qPCR^{IS} beyond MMR before diagnosing relapse in CML patients who are attempting TFR and already stopping TKI for 12 months or more. It is safer to restart TKI once there was a loss of MMR while awaiting the result of the repeat qPCR^{IS}.

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Fertility preservation opportunities for cancer patients in Malaysia

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ABSTRACT

Fertility preservation is significant for oncology patients to maintain their ability to start a family when they are ready. Onco-fertility, as a discipline, exists at the intersection of oncology and reproductive medicine that safeguards and expands the fertility options for cancer survivors, by facilitating early intervention and suitable treatment with favourable outcomes. Successful fertility preservation requires a comprehensive networking among the gynaecologists, oncologists, pathologists, imaging and other specialists, involved in diagnosing and treating cancer in the reproductive age group. There are several ways in which fertility can be preserved, like role of gonadotrophin releasing hormone analogues, in vitro maturation, and cryo-preservation.

KEYWORDS:
Fertility preservation, gonadal cryopreservation, ovarian tissue cryopreservation, oncofertility, oncology

SUMMARY

Cancer affects patients of all ages and those in the reproductive age group are not spared. With the availability of newer modalities for early diagnosis and treatment, the survival of patients has improved affording a fulfilling life and start of a family when desired. Cancer treatment can potentially diminish fertility due to its effects on the gonads. Unless safeguards are put in place most of the cancer survivors seeking fertility treatment, unfortunately, are left with poor gonadal reserves crashing their hopes for successful treatment. The scope for the full range of fertility preservation options, including the technology for the ovarian tissue cryo-preservation, are now available in Malaysia. For this new facility to be of optimal benefit for the patients, a new awakening needs to be generated among the clinicians in the frontline of cancer diagnosis and treatment, so that they go beyond cancer treatment and preserve fertility wherever possible.

INTRODUCTION

The 25th of July, 1978 is a landmark date in the advancement for fertility treatment with the birth of Louise Brown, the world's first in vitro fertilisation (IVF) live birth.[1] Malaysia soon joined this advancement, with the country's first live birth from IVF documented in 1986.[2] Fertility treatments have progressed by leaps and bounds since.

Fertility preservation (FP) essentially means maintaining the ability of an individual or a couple to start a family when they are ready. It is a fundamental concern for women in the reproductive as well as preadolescent age groups, when future fertility may be compromised. The most usual reason for FP intervention is cancer therapy.[3] Other conditions that affect fertility potential include advancing age, chromosomal, autoimmune and metabolic disorders, and specific surgical interventions.[4]

Oncofertility is a new field coined for FP in patients suffering from cancer. This involves an interdisciplinary approach at the intersection of oncology and reproductive medicine that expands fertility options for cancer survivors.[5] There are several ways in which this can be achieved, including gonadotrophin releasing hormone analogues, in vitro maturation, and cryopreservation.

There are several categories of cryopreservation. The embryo, oocyte and, sperm cryopreservation methods is well established for more than 20 years, with research on ovarian tissue cryopreservation (OTC) being greatly refined. In 2005, the first live birth from an ovarian tissue transplant was achieved.[6] This was followed 10 years later with a birth from an ovarian tissue that had been cryopreserved from a pre-pubertal patient.[7] Globally more than 100 babies have been born from this technology, and there are calls for it to be it an established treatment rather than experimental.

In the current medical practice in Malaysia, gynaecologists and fertility specialists rarely see any fertility preservation referral cases prior to treatment of cancer patients that may be detrimental to the gonads either by chemotherapy or radiotherapy. Referrals are more common years after treatment, once patients have found a partner and are ready to start a family. Alas, here lies the problem, as at this point, the damage to the gamete reserves has already been done. A greater awareness among the medical fraternity is the first step in overcoming late referrals. This will subsequently lead to earlier discussion with patients on the availability of such an option and making them understand the importance of early intervention in order to preserve their fertility potential. Patients are being diagnosed with cancer at younger ages, and with the advancement of treatment, survival has generally improved.[8] Thus, currently the time a patient spends in the reproductive age is longer. Once the primary disease has been controlled, opportunities to start a family improve. With this in mind, the opportunity to preserve or

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protect the gonadal tissue to increase the chances of conceiving for this group of patients should not be overlooked.

There is a general lack of awareness within the medical community regarding options for FP, observed from the lack of referrals from the front line physicians treating cancer in those patients of the reproductive age.[9] These include haematologists, oncologists, paediatric oncologists, breast and endocrine surgeons, and urologists to name a few specialities.

The Malaysian Fertility Society for Preservation (MSFP) has championed this cause to create awareness amongst the medical fraternity and public. On the 2nd of July 2020, the Society was formed by reproductive experts and representatives from the specialties involved in treating cancer patients. On the 26th of August 2020, Malaysia welcomed the launch of its first oncofertility centre by the Health Minister of Malaysia in Hospital Canselor Tuanku Muhriz, operating in the Advanced Reproductive Centre (ARC) of the hospital. The centre has been registered with the Northwest Oncofertility Consortium, which is an international interdisciplinary initiative designed to explore the reproductive future of cancer survivors and champion the cause of oncofertility. ARC provides a full range of fertility preservation options, including ovarian tissue cryopreservation (OTC). In Asia, OTC is still largely considered experimental. With the equipment and media obtained, along with ethical approval from the Ministry of Health, the centre began its services. The centre has thus far performed four cases of OTC since August until the time this editorial was written.

CONCLUSION

The future for these fertility preservation opportunities in Malaysia hinges on the next two years in terms of how the MSFP can form a network and generate awareness so that the offerings of this service can be ingrained in the practices of health care providers. It is difficult enough breaking the devastating news of cancer diagnosis, but fertility preservation should not be disregarded.

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Scrofuloderma: A diagnostic dilemma in primary care

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SUMMARY

A 35-year-old lady presented at the Klinik Kesihatan Bandar 32 Bera, Pahang with a one-month history of multiple cervical swelling and ulcers over her neck area. The lesions began as papules and later progressively developed into nodules and pustules. She also had low grade fever associated with weight loss for one month duration. Chest x-ray revealed normal findings and sputum direct smear for acid fast bacilli was noted to be negative. Histopathologic finding of skin biopsy revealed central epidermal necrosis surrounded by granulomatous tissue forming an abscess and histiocyte infiltrates, confirming the diagnosis of Scrofuloderma. In view of the report of the fine needle aspiration cytology (FNAC) of the cervical lymph nodes suggestive for tuberculous lymphadenitis, the patient was given anti-tuberculosis therapy. Fortunately, six months later, the ulcers began to solve and heal gradually.

INTRODUCTION

Global Burden of Disease Study has reported that tuberculosis (TB) is the second leading cause of death in the world.[1] TB is a chronic granulomatous infectious caused by *Mycobacterium tuberculosis*, an acid-fast bacillus whose route of transmission is via the inhalation of airborne droplets. The most common extra pulmonary tuberculosis is tuberculous lymphadenitis. Cutaneous tuberculosis (CT) on the other hand is a very rare case accounting for only 1-2% of TB cases worldwide.[2] Scrofuloderma is a form of cutaneous tuberculosis normally affecting children and young adults. Scrofuloderma also known as *tuberculosis colliquativa cutis* which occurs due to the direct spread from endogenous source who have been infected with *M.tuberculosis bacilli*, predominantly lymph nodes and other structures such as joint, tendon, bone and synovial fluid are infected.[3] Suppurative ulcers are commonly found in cutaneous tuberculosis because of severe and chronic inflammation. Among the areas that most commonly affected are neck, chest and axilla.[3]

Clinical characteristics of Scrofuloderma generally starts with multiple or solitary painless lymph node enlargement.[3] Over time, the basal part eventually become softened forming cold abscess. The abscesses will become suppurated and finally rupture, creating a linear and irregular ulcers. The differential diagnosis of CT comprise of atypical mycobacterial infection (NTM), sarcoidosis, verrucous vulgaris, blastomycosis, leprosy, and tertiary syphilis.[4] Treatment of Scrofuloderma is similar to the treatment of pulmonary tuberculosis i.e. by using oral anti-tuberculosis regimen containing isoniazid, rifampicin, pyrazinamide and ethambutol.[5]

CASE REPORT

A 35-year-old woman presented to the health clinic, Klinik Kesihatan Bandar 32 Bera, Pahang with one-month history of multiple cervical swellings and ulcers over her neck and upper chest region. Examination revealed that there were initially two lesions around her neck, which began as papules but gradually increased in size and progressed to pustules leading to ulcerations with the drainage of pus. She also had low grade fever with weight loss and loss of appetite for one month. There was no history of haemoptysis, prolonged cough, trauma, or any similar presentations among family members. She had sought medical treatment a few times previously and was prescribed several courses of antibiotics. However, the lesions did not improve and became worse progressivley.

Physical examination revealed multiple ulcers with suppurative surface, along with nodule measuring 3 cm x 0.5 cm as shown in Figure 1. Around her neck, some crusts were found measuring 2 cm x 0.5 cm typical of Scrofuloderma. There were also mobile and painless lymph nodes enlargement in the right and left anterior cervical region measuring 2x2cm.

In view of her complaints of weight loss and lack of appetite, we proceeded with investigations for tuberculosis. Chest X-ray was performed but noted to be normal. However, tuberculin skin test revealed positive finding with 15mm induration. However, direct smear of sputum specimen was noted to be negative for acid fast bacilli. In view of chronicity of the presentations and persistent lesions despite being given several courses of antibiotic at primary care, we referred the patient to the Dermatology Clinic in Hospital Tengku Ampuan Afzan, Kuantan for shared care. Skin biopsy was performed in which the histopathology results showed epidermal necrosis in the central region surrounded by granulomatous tissue with Langhan's type of giant cells peripherally, forming abscess with histiocytic infiltrate around the lesion. These reports confirmed the diagnosis of Scrofuloderma. The swabs from the discharging fluid were tested positive for acid fast bacilli. Furthermore, fine needle aspiration cytology (FNAC) of the enlarged cervical lymph nodes was done which was suggestive for tuberculous lymphadenitis.

Once the final diagnosis of Scrofuloderma was confirmed, the patient was started on standard regimen of anti-tuberculosis drugs containing Rifampicin (R), Isoniazid (H), Pyrazinamide (Z), and Ethambutol (E) for two months continued by Rifampicin (R), Isoniazid (H) for the next four months. During the second month, our patient showed remarkable

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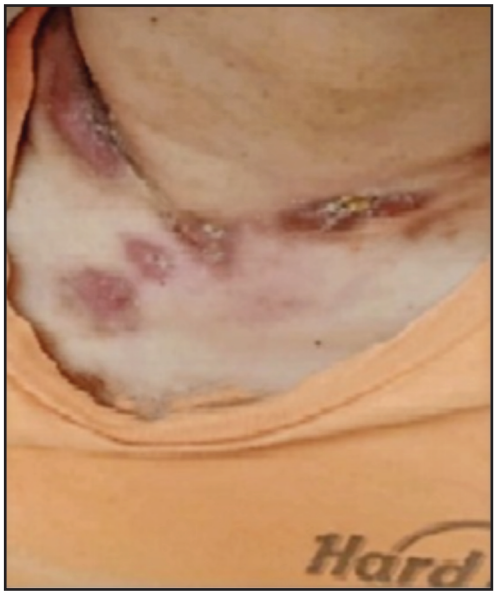

Fig. 1: Multiple ulcers with suppurative surface and crusts over her neck area.

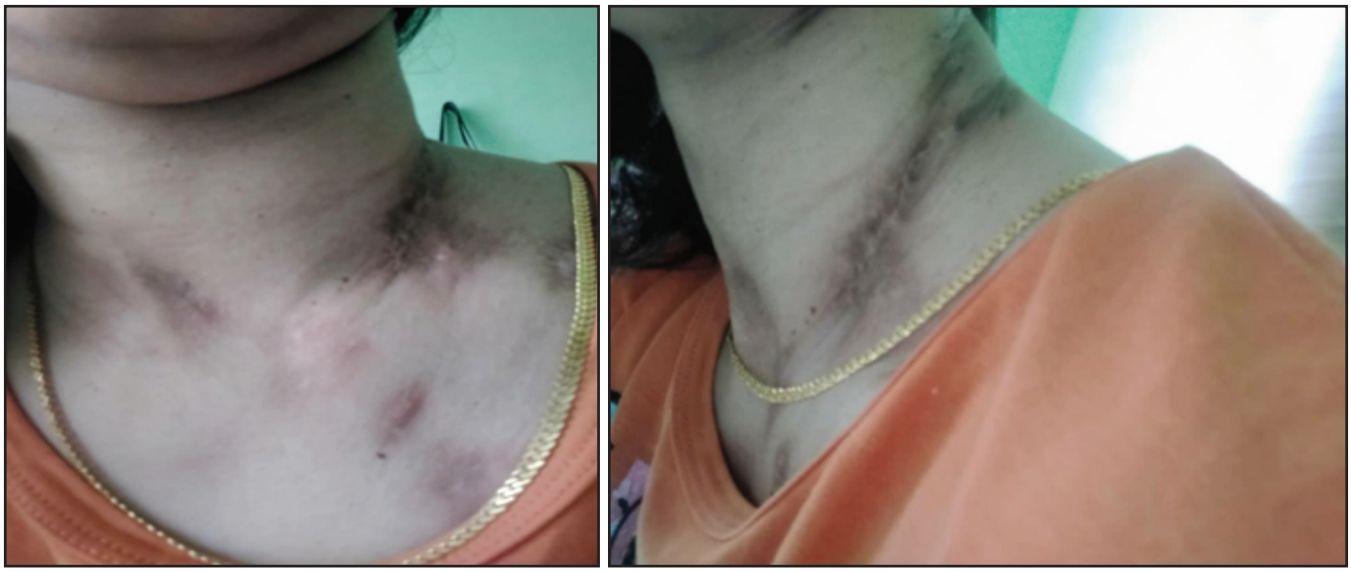

Fig. 2: Pictures show healing ulcers with scar tissue following six months post anti-tuberculosis therapy.

improvement as the cervical lymph nodes enlargement were reduced in size significantly. In the fourth month, the ulcers in the neck region began to resolve gradually leaving scar tissue. Overall, she showed a remarkable satisfying response with the anti-tuberculous therapy.

DISCUSSION

The prevalence of tuberculosis (TB) is projected to be around 9.6 million worldwide. It has been challenging time for clinicians in diagnosing cutaneous tuberculosis due to varieties of presentations that are like other cutaneous lesions. CT was recognized by Beyt at al. in 1981.[4] It was described that the most common type of cutaneous TB is scrofuloderma which is predominantly found in children. However, in our case it was found in a 35 year old adult. Typically, it occurs commonly in the neck, chest, and axilla region. Scrofula is an old term representing tuberculosis infection of lymph nodes in the neck, known as cervical tuberculosis lymphadenopathy.[4] It is frequently the result of primary tuberculosis infection of the lymph node. *M. tuberculosis* bacilli can disseminate through lymph node and blood (hematogenously). Scrofuloderma represents a condition manifested by a bluish-red nodule overlying an infected lymph gland, joint or bone that ruptures to form an undermined ulcer with a granulating tissue at the base. Irregular adherent masses, densely fibrous tissue and discharging sinuses can occur as a result of the disease progression.[3,4]

Chest X rays are mandatory to rule out systemic TB. Tuberculin sensitivity usually is marked but has a very low specificity. Histopathological examination is confirmatory, which reveals the presence of tubercular granulomas with epitheloidal cells, Langhan's giant cells and lymphocytes. According to various reports, only a small percentage of histopathological specimen's stain positive for acid fast bacilli. A combined effort of using the available clinical, radiological, and microbiological modality to reach early diagnosis can go a long way to avoid misdiagnosis and unnecessary delay in the treatment, especially in cases, without the pulmonary involvement. Various other conditions can clinically mimic scrofuloderma and should be correctly identified and differentiated. Differential diagnosis for discharging sinuses can be atypical mycobacterial infection due to mycobacterium scrofulaceum and *M. avium intracellulare*, actinomycosis, sporotrichosis, botryomycosis, nocardiosis.[4] Other common conditions at primary care level that may presented with similar lesions include chronic eczema and recurrent impetigo. However, these conditions are not associate with alarming symptoms such as weight loss and loss of appetite which are present in our case. Therefore, the decision to have a shared care with the physician or dermatologist is indeed important in this case.

The treatment of cutaneous TB is crucial and universal measures should be taken to tackle any concomitant illness causing immunosuppression; and people in close contact with the patient such as the family members should undergo testing for TB. World Health Organization (WHO) and Clinical Practice Guidelines Management of Tuberculosis by Ministry of Health Malaysia recommends treatment for cutaneous tuberculosis which is anti-tuberculosis regimen containing Rifampicin (R), Isoniazid (H), Pyrazinamide (Z) and Ethambutol (E) for two months known as intensive phase followed by Rifampicin (R) and Isoniazid (H) for the next four months which is the maintenance phase.[5] This treatment generally uses directly observed treatment short course (DOTS) approach to ensure compliance and successful treatment.

CONCLUSION

We report here a rare case of Scrofuloderma in a 35 year old lady which was successfully treated with anti-tuberculosis therapy. This form of CT is quite challenging to diagnose due to its similarity to many other skin lesions as it may be misdiagnosed. Therefore, a thorough history taking, complete examination and various relevant investigations should be carried out for early diagnosis and initiation of treatment for comprehensive recovery. In addition, the importance of completing the treatment should be emphasised to the patient to ensure successful therapy.

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CASE REPORT

Long term outcome of Omalizumab Therapy in childhood severe allergic asthma

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SUMMARY

Childhood severe asthma is different from adult asthma and little is known about the use of biologics in children in Malaysia. Uncontrolled severe asthma has significant morbidity and impact on the quality of life of the children and their families as well as increase healthcare burden. Anti-IgE therapy is known for its efficacy and safety for severe allergic asthma phenotype, both in adults and children. We describe our experience using omalizumab therapy in two pediatric cases of severe allergic asthma and the journey of these patients before and after omalizumab therapy.

INTRODUCTION

Severe asthma affects 5–7% of children worldwide[1] and it has significant morbidity and even mortality. Thus, children are at risk for asthma exacerbations, emergency visits, asthma related hospitalization, impairment in their quality of life, missing school and high economic burden.[2] There are limited therapeutic options in children with severe asthma, despite maximal guideline-based therapy and treatment of contributory factors. Omalizumab, a humanized recombinant monoclonal anti-IgE antibody, is the only approved biologic agent in Malaysia for children with severe allergic asthma. This therapy is approved for treatment of moderate to severe allergic asthma (SAA) and Chronic Idiopathic Urticaria (CSU) with good clinical efficacy and safety profile.[3] The experience of using omalizumab in pediatric patients has been very limited with almost no published report from Malaysia. Our aim is to share our experience of using omalizumab in two pediatric patients of severe allergic asthma (SAA) with multiple comorbidities, describing their profile, financial challenges and long term outcomes, including the dilemma faced during tapering/weaning off Omalizumab in our local setting.

Case 1

An 8-year-old Malay boy was referred from a district hospital for uncontrolled severe asthma to our center in 2010. He was the seventh of 11 siblings with family history of severe asthma where his father died due to an asthma exacerbation. The patient had daytime cough and chest tightness throughout the day, along with frequent nocturnal awakenings due to wheezing and breathlessness. His school performance had deteriorated as he was absent from his school most of the days. He was mainly confined to his house and his mother remained awake at night, worrying about his asthma. He was on Step 5 GINA {high dose Metered Dose Inhaler (MDI) Inhaled Corticosteroid and Long-Acting-Beta2-Agonist (ICS-LABA), oral anti-leukotriene, MDI salbutamol PRN and long course tapering to alternate low dose oral prednisolone (OCS)} and treatment for his allergic rhinitis (intranasal steroid, anti-histamine PRN). Through 2009 to 2011, the patient had in all 26 exacerbations, some that required hospitalizations but none required intubation, non-invasive ventilation support or intensive care (ICU) admission. He did not develop side effects for OCS but a decision to initiate Omalizumab was made in late 2012 at the age of 10 years old, as he still has frequent exacerbations that required hospitalizations despite good adherence, proper inhaler technique (via spacer) and avoidance of triggering factors. The baseline characteristics before and during Omalizumab therapy is shown in Table I.

In summary, this is a very severe case of childhood allergic asthma which showed a rather delayed, but a very good response to using omalizumab as an add on therapy for a period of 5 years. The low alternate dose of OCS was then possible to stopped by 16 months of Omalizumab therapy, a slower response than we predicted due to severe baseline asthma profile and multiple confounding factors, including irregular supply of Omalizumab especially during the initial 2-3 months of therapy. Despite no clear recommendation on how to taper Omalizumab, we initiated stepwise tapering as per Table I in view of good asthma control, budget constraint, and excellent quality of life achieved at 3.5 years of therapy. Omalizumab was then discontinued after 5 years of therapy. With a total of almost 20 months of symptoms and exacerbation free period after Omalizumab discontinuation, the onset of three exacerbations required the re-initiation of omalizumab therapy (Table I). His asthma remained well controlled after re-initiation of therapy.

Case 2:

An 8-year-old Malay girl was referred to us in early 2012 with a history of uncontrolled asthma of 2 years, chronic spontaneous urticaria (CSU), seafood allergies and persistent allergic rhinitis. Presenting complaints were persistent daytime and night time symptoms, frequent school absenteeism due to asthma exacerbations, exertional dyspnoea and frequent recurrent urticaria (skin redness and itchiness). She was on high dose Metered Dose Inhaler (MDI) Inhaled Corticosteroid and Long-Acting-Beta2-Agonist (ICS-LABA) via a spacer, oral anti-leukotriene, MDI salbutamol PRN, fluticasone nasal spray and anti-histamine, plus avoidance of triggering factors. Due to recurrent exacerbations, she was initiated with tapering dose of prednisolone until low alternate daily dose. Her childhood

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Table I: The clinical course of case 1 on Omalizumab through 9 years

Baseline	Initial Follow up	Tapering & Withdrawal	Discontinuation & Re-initiation
• FEV_1/FVC = 68%, FEV_1 = 77% predicted Positive reversibility ≥ 12% • Total IgE = 1091 IU/ml Specific IgE high for Shrimp • Baseline cACT = 5 • Asthma: uncontrolled (frequent exacerbations, school absenteeism, no sports) • Medications: o high dose ICS+LABA o anti-leukotriene o maintenance low dose OCS • Omalizumab initiated at 300mg every 2 weeks (27 August 2012) • Co-morbid: allergic rhinoconjunctivitis • HRCT Thorax; normal	• **3 months:** Partial response • **1 year:** 5 exacerbations • **16 months:** controlled asthma : o no exacerbations o FEV1: 106% of predicted o No daytime or nocturnal symptoms o No exercise-induced symptoms o Discontinued OCS. o Regular school and sports. o ACT = 25	• Omalizumab starting dose: 300 mg/2 weekly • tapered dose: o **3.5 years:** 300mg/4 weekly o **4.0 years:** 300mg/6 weekly o **4 years 8 months :** 300mg/8 weekly o **5 years:** Patient symptom free, no rescue medication use, no exacerbations thus Omalizumab discontinued (19 September 2017) • No asthma controller for 2 years (non-adherent) • Rhinoconjunctivitis controlled on antihistamine.	• **7 years:** asymptomatic for 23 months after discontinuation. o Not on controller ICS for 23 months • **7.5 years:** re-initiation of Omalizumab (6 August 2019) (3 mild exacerbations until July 2019, outpatient treatment with short course OCS) • Asthma controlled since then.

Table II: The clinical course of case 2 on Omalizumab through 8 years

Baseline	Initial Follow up & clinical course	Tapering & Withdrawal	Discontinuation
• FEV_1/FVC = 69% FEV_1 = 73% predicted Positive reversibility ≥ 12% • Total IgE = 1140 1U/ml • Specific IgE high for *Dermatophagoides pteronyssinus and Dermatophagoides farinae,* crab, shrimp and cockroach • Baseline cACT = 7-14 • Asthma : uncontrolled (School absenteeism, exercise induced, frequent exacerbations, nocturnal and daytime symptoms) • Medications: high dose ICS-LABA, anti-leukotriene , maintenance low dose OCS • Omalizumab initiated at 300mg /4 weekly (13.12.2012) • However, she developed pharyngitis within 24 hours thus subsequent dose was reduced to 150 mg/4 weekly • **Co-morbid:** o CSU o sea- food allergies o allergic rhinitis	• **1 months:** good response • OCS discontinued after second dose o FEV1: 103% predicted o Asthma: controlled (Regular school, sports, no daytime or nocturnal symptoms, no exacerbations) • cACT = 27 • 13 months; • Step down to ICS only • 2.5 years: • one mild exacerbation treated with prednisolone as outpatient. • CSU : full remission • Allergic rhinitis: controlled	• Omalizumab starting dose: 300 mg/4 weekly • tapered dose: o **1 month:** 150mg/4 weekly o **2.5 years:** 150mg/6 weekly o **4.0 years:** 150mg/8 weekly o **4 years 8 months:** step up 150 mg/6 weekly* o (*due to recurrence of CSU although asthma was controlled) o **5 years:** step up 150mg/ 4 weekly- for CSU	• **5 years 10 months:** Discontinuation of Omalizumab (15 Oct 2018) • **28 months post discontinuation:** o Asthma remained controlled o Recurrence of her CSU, but milder and controlled with high dose anti-histamine.

asthma control test (cACT) improved from 7 to 14 but her asthma was still uncontrolled with very poor quality of life. Baseline spirometry showed mild obstructive lung disease with significant reversibility post-bronchodilator. Her total IgE was remarkably high of 1140 IU/ml with raised specific IgE for house dust mites, seafood and cockroach (Table II). We initiated omalizumab 300 mg every 4 weeks based on weight and IgE level at the age of almost 9 years old. After the first injection, an episode of pharyngitis was reported within 24 hours, which required observation in hospital for one day. Omalizumab was adjusted at 150mg/4 weekly. Remarkably her asthma and CSU became completely controlled after first dose and oral prednisolone was discontinued after the second dose. Her cACT was 27 and her spirometry normalized. She was a very fast responder to Omalizumab. We were able to discontinue OCS after the second dose of Omalizumab and subsequently reduce ICS-LABA combination to ICS only after 13 months of therapy. She had one mild asthma exacerbation 2.5 years later that required prednisolone as outpatient basis. The clinical course of the patient is summarized in Table II.

For both patients, the funding for Omalizumab was from limited hospital's budget. Omalizumab were supplied by the company for the initial 2 months while waiting for approval from the Malaysian Director-General of Health.

DISCUSSION

Omalizumab is one of the recommended options in GINA Step-5 severe allergic (IgE-mediated) asthma phenotype for patients aged ≥ 6 years.[3,4] It is indicated in patients with following characteristics:

i. High IgE (≥30-1500 IU/ml)
ii. Positive skin test or in vitro reactivity (radioallergosorbent test [RAST]) to a perennial aeroallergen.
iii. Reduced lung function (FEV1 < 80%).
iv. Frequent daytime symptoms or night-time awakenings.
v. Multiple documented severe asthma exacerbations.
vi. Receiving daily high-dose ICS-LABA and other controller (GINA Step 4/5)

The other indication is uncontrolled Chronic idiopathic urticaria (CSU) despite standard therapy in patients ≥ 12 years old.

Omalizumab inhibits the binding of IgE to Fc3RI receptors on mast cells, basophils and dendritic cells, thus preventing release of cytokines and subsequent eosinophilic airway inflammation. It reduces free-IgE and downregulates high-affinity IgE receptors on multiple cells in the airway mucosa, thereby reduce early and late phase inflammatory cell recruitment, tissue remodelling and functional changes in the airways.[3]

Omalizumab has been shown to reduce asthma exacerbation, emergency visits, provide control of symptoms, reduce oral corticosteroid (OCS) burden and improve patient's quality of life.[3] An excellent clinical response was observed in our patients with good asthma control, cACT score, reduction in exacerbation rate, reliever use, atopic symptoms, ICS doses, OCS usage, and normalization of lung functions. Studies have shown that IgE levels correlate with disease severity[3] and clinical data suggests that the patients who are the best 'responders' to anti-IgE treatment are those with more severe asthma, like our two patients.[5]

We also report a period up to almost two years of preservation of good clinical response post-cessation of Omalizumab in the first patient, despite ICS-free for almost 4 years duration (Table I). This is consistent with findings that ICS use was withdrawn completely in a greater percentage of omalizumab-treated patients versus placebo without compromising asthma control.[6] He developed mild exacerbations requiring outpatient treatment only after 20 months later. The second patient had recurrence of non-asthma atopic symptoms (i.e. CSU) earlier than symptoms of asthma, post discontinuation of omalizumab. The two cases illustrate the clinical efficacy of omalizumab used for a long term, the first of its kind in childhood severe asthma in Malaysia. From the safety perspective, we did not identify any severe adverse events, although upper respiratory tract infection was noted in the second patient. None of them developed anaphylaxis.

These two patients had a significant duration of uncontrolled symptoms and OCS use burden before we initiated omalizumab, showed delayed initiation of biologic in eligible patients. Many factors including lack of early access of drug, affordability by poor patients, issues with availability, delay in referral, low awareness level among patients/caregivers could result in this delay of initiating right treatment for these eligible patients for omalizumab in our healthcare scenario. We identified that lack of centers with adequate experience and availability of omalizumab, will pose additional challenge for the patients to get the best quality of care. The frequent visits for the injections and the need to travel to limited number of referral centers (in this case, our hospital) may pose an additional hurdle towards compliance of patients.

The cost and duration of Omalizumab treatment significantly affects the selection of patients for this therapy. Although with initial success in our cases, we needed to taper down and subsequently stop omalizumab once their treatment reached 5-6 years duration. The recurrence of symptoms post cessation of omalizumab would also require us to evaluate the need for omalizumab re-initiation. Financial access determines initiation as well as re-initiation of omalizumab in our setting. Although there is lack of evidence on re-initiation and tapering regimen, affordability of the drug requires us to consider tapering while monitoring clinical parameters. We describe the tapering regimen in the Malaysian context based on symptoms control and spirometry, and adjusting the dosages and interval based on its impact on asthma control in patients. Our experience with the use of omalizumab has demonstrated a life changing situation in our patients.

We recommend a holistic approach to improving childhood asthma care in Malaysia which includes:

i. Early referral from peripheral centers to specialized/experienced center,
ii. Facilities for phenotyping related investigations,
iii. Increased awareness among population and physicians,
iv. Dedicated fund for biologic access,
v. Financial support for patients to enable long term therapy,
vi. Severe childhood asthma registry to understand the problem statement, and
vii. Consideration of biologic in selected patients earlier than current practice,
viii. Multidisciplinary approach to severe asthma care.

We recommend early phenotyping of the patients uncontrolled on GINA step 4/5 treatment (blood eosinophils, allergy profile by skin prick or specific IgE or equivalent tests, total IgE, FENO (fractional exhaled nitric oxide) in childhood asthma to identify patients eligible for biologic therapy, enabling them to live life to the best.

CONCLUSION

Anti Ig-E therapy is a safe and efficacious in pediatric patients with severe allergic (IgE-mediated) asthma and atopic comorbidities. To improve the access of anti IgE therapy, we recommend a holistic approach in Malaysia to overcome the existing challenges of the delay in treatment. More data is needed to guide tapering, cessation and re-initiation of anti-IgE therapy.

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CASE REPORT

Intestinal adaptation in fluid restricted cardiac failure following extensive bowel resection

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SUMMARY

Acute mesenteric ischemia (AMI) is an emergency associated with a high mortality rate. A high index of clinical suspicion, prompt diagnosis and treatment is necessary to improve the patient outcome. The principle of damage control surgery should be adopted in the management of critically ill surgical patients with AMI. Strategic planning by resecting the ischemic bowel, physiological restoration and planned reassessment of remnant bowel with a definitive procedure is recommended. The resection of a long segment ischemic bowel may result in morbidity such as that of short bowel syndrome.

We report here a case of decompensated cardiac failure in a 56-year-old lady, presented with one-day history of severe acute epigastric pain and abdominal distension. She presented with extensive bowel ischemia involving most of the superior mesenteric artery distribution. Damage control surgery followed by entero-colic anastomosis was performed 48 hours later. The patient recovered with remarkable intestinal adaptation without exhibiting short bowel syndrome symptoms despite the postulated theory of altered intestinal permeability in decompensated cardiac failure.

INTRODUCTION

Acute mesenteric ischemia (AMI) is commonly due to mesenteric artery embolism, thrombosis and venous thrombosis. A high index of clinical suspicion, prompt investigation and treatment is necessary to diagnose this condition. Mortality rate range from 54.1% to 77.4% is associated with the condition.[1,2] The resection of a long segment ischemic bowel may result in short bowel syndrome. Management of short bowel syndrome is challenging, and an estimated 13.3% of patients would require long-term parenteral nutrition.[3] Intestinal adaptation of the remnant small bowel and colon may take a significant duration before weaning off parenteral nutrition.

CASE REPORT

A 56-year-old lady, presented at the Sarawak General Hospital, Malaysia with one-day history of severe acute epigastric pain and abdominal distension. She had atrial fibrillation with congestive heart failure. She was on fluid restriction of 500ml per day. She appeared toxic, dehydrated and abdominal examination revealed generalised peritonitis. Laboratory results showed that total white blood count 13.8 X 10^9/L (normal range 4 - 11 X 10^9/L), serum creatinine 153µmol/L (normal range 45 - 90µmol/L), serum lactate 3.8mmol/L (normal range 0.5 – 1 mmol/L) and compensated metabolic acidosis. Chest and abdominal X-ray revealed no free air or bowel dilatation. Transthoracic echocardiography showed left ventricular ejection fraction of 40% and absence of thrombus or vegetation. Computed tomography angiography of the abdomen was performed, which revealed non-opacification of superior mesenteric artery and vein suggestive of embolus with extensive bowel ischemia (Figure 1). High-risk surgery consent was taken given the underlying co-morbidities and nature of the disease.

Urgent laparotomy was performed after fluid resuscitation and broad-spectrum antimicrobial coverage. Intraoperative findings revealed extensive small bowel and ascending colon infarct sparing the duodenum and 40cm of the proximal jejunum (Figure 2). Damage control surgery strategy applied by resecting the ischemic segment and left in discontinuity with temporary abdominal closure. The patient was resuscitated at the intensive care unit and physiological derangements were restored. Intravenous heparin infusion was initiated with judicious fluid resuscitation. Reassessment of the remnant bowel was performed 48 hours later prior to the anastomosis and abdominal closure. Entero-colic side to side anastomosis was performed using linear cutter stapler and enterotomy closure using polyglactin suture 3/0.

Post-operatively, she was managed by a multidisciplinary team and recovered steadily. Parenteral nutrition was initiated with staged weaning after initiation of elemental enteral feeding. Individualised dietary treatment was offered, and she had remarkable intestinal adaptation without exhibiting symptoms of short bowel syndrome. She was discharged home two weeks later with Apixaban 5mg twice per day and advised to increase fluid intake to one litre from the pre-admission intake of 500ml.

She was readmitted three weeks later for acute pulmonary oedema secondary to fluid overload. Her fluid intake was restricted back to 500ml. She was on monthly follow-up, followed by three monthly surgical outpatient clinic visits with no short bowel syndrome complication. She had no weight loss, tolerated regular diet, and the Bristol stool chart

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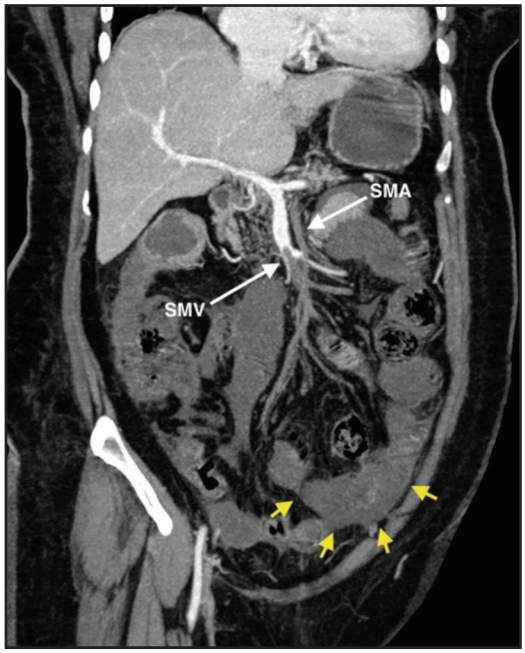

Fig. 1: Porto-venous phase computed tomographic angiography (Angio-CT) of abdomen and pelvis. Labelled image with long arrows shows filling defect within the SMA and SMV suggestive of emboli with non-enhancing bowel loop (short arrow).

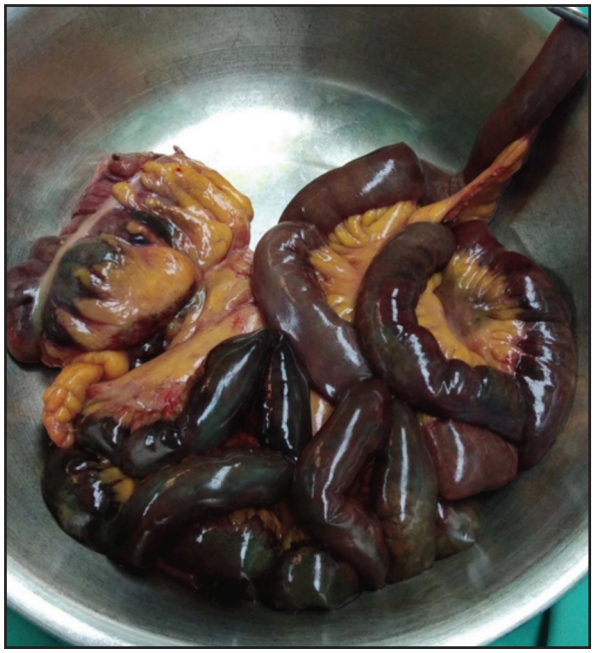

Fig. 2: Intraoperative finding of the extensive small bowel and ascending colon infarct.

was consistently Type 4 and 5. Her electrolytes were within the normal range. She, however, passed away one-year post-surgery due to cardiac-related complication.

DISCUSSION

AMI is an emergency that requires a high index of clinical suspicion. A mortality rate up to 54.1% to 77.4% was associated with acute mesenteric ischemia.[1,2] AMI can be further divided into occlusive and non-occlusive causes. Occlusive causes are mesenteric vein thrombosis, mesenteric artery embolism and thrombosis.[2,3] Urgent diagnostic investigation with Computed Tomography Angiography and therapeutic intervention should be performed.[2,3]

Early diagnosis and prompt intervention are necessary to improve outcome and survival.[3] Damage control surgery principle should be adopted in the management of critically ill patients with AMI.[2] Strategic planning by resecting the ischemic bowel, physiological optimization and planned reassessment of remnant bowel followed by the definitive procedure is ideal for managing this clinical entity.

Short bowel syndrome (SBS) in adulthood is common; it results from mesenteric ischemia, inflammatory bowel disease and malignancies. It is also associated with electrolytes imbalance, macro and micronutrient deficiency. Management of SBS is challenging and often dependent on parenteral nutrition. Affected patients tend to have a poor quality of life, and are burdened by socioeconomic and psychological impact.

Cardiac failure leads to multi-organ impairment, including the gastrointestinal tract. Gastrointestinal changes associated with cardiac failure is as a result of splanchnic hypoperfusion. Following which mucosal ischemia, bacterial translocation and alteration in intestinal barrier occur.[4] There was a component of both splanchnic hypoperfusion and venous congestion in our case of short bowel secondary to the superior mesenteric artery and vein emboli with underlying cardiac failure.

Fluid restriction is necessary for decompensated cardiac failure patients to achieve fluid homeostasis as a measure to avoid acute pulmonary oedema. Chronic cardiac failure patients tend to developed gastrointestinal changes. Enteral intake in short bowel should be tailored to gastrointestinal absorption of individual patient. In our patient, we anticipated a challenge to cope with increased intestinal permeability and the risk of malabsorption. Although the remaining small bowel length was 50 cm, the colonic adaptation should not be underestimated for the absorption of water, electrolytes and short-chain fatty acid.

Nutrient and non-nutrient factors are involved in complex intestinal adaptation following extensive bowel resection. There are promising studies with glutamine supplements, low dose short term growth hormone and glucagon-like peptide-2 to improve intestinal adaptation.[5] Fluid management needs to be balanced with consideration of total fluid intake and patient absorption capability. Once intestinal adaptation goals are achieved, the fluid restriction should be revised to pre-existing short bowel condition to avoid the risk of acute pulmonary oedema.

P-POSSUM scale in the context of AMI is a reliable tool for surgical risk assessment.[3] However, intraoperative evaluation and decision for withdrawal of treatment in diffused bowel

necrosis should be made a case to case basis. As our case highlights, urgent diagnosis, damage control surgery and post-operative multidisciplinary approach can improve patient outcome.

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Anterior tibial artery pseudoaneurysm

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SUMMARY

A pseudoaneurysm, or false aneurysm, is a haematoma that is formed secondary to a leaking hole in an artery. This haematoma is contained by surrounding fascia. In contrast, a true aneurysm contains all three layers of vessel wall, namely intima. Pseudoaneurysms are scarce and can arise consequential of numerous iatrogenic influences, including but not limited to, blunt or penetrating trauma, orthopedic procedures like tibial nailing or ankle arthroscopy, and sports injury.

A thorough history taking focusing on the recent history of trauma or instrumentation and clinical examination should raise the suspicion of a pseudoaneurysm. In doubtful cases, imaging modalities such as an ultrasound and doppler examination of the lower limb can be utilized to confirm the diagnosis.

Our case was a 37-year-old gentleman presented with progressive swelling in the anterior aspect of his left leg for the past two weeks. The patient had a atypical presentation, with absence of classic signs of a pseudoaneurysm such as a pulsatile mass, absence distal pulses or a thrill or bruit. However, these injuries albeit rare can be sinister and prompt diagnosis is critical, so that pertinent treatment can be delivered. Our case highlights the importance of sonographic approaches for suspected vascular injuries.

INTRODUCTION

A pseudoaneurysm arises when there is a break in the vessel wall, leading to leakage of blood through its wall. This leakage is occasionally contained by the adventitia or neighboring perivascular soft tissue. There is a direct connection of blood flow between the aneurysmal sac and vessel lumen through a gap in the vessel wall. The possibility of an aneurysmal rupture is greater than a true aneurysm of similar size due to low support. Therefore, a pseudoaneurysm typically needs treatment.

A pseudoaneurysm can arise from almost any vessel in our body. In the lower limb, the commonest vessel involved is the popliteal artery, followed by superficial femoral, then anterior tibial artery. The anterior tibial artery is the most commonly involved vessel in a pseudoaneurysm of the foot and ankle.[1] Vascular injuries ensuing trauma are unusual. The reported rate of pseudoaneurysm in access sites ranges from 0.88% to 8%.[2] In our case presentation we report a case involving the anterior tibial artery secondary to penetrating trauma.

CASE REPORT

A 37-year-old gentleman presented at Hospital Teluk Intan, Perak, Malaysia with progressive swelling in the anterior aspect of his left leg for the past two weeks. He had no significant past medical history. He suffered a penetrating injury 2 weeks earlier when he was pierced by a tree branch at the left distal lower limb while working. He did not seek medical attention.

On physical examination, there was a diffused swelling on the anterior and distal part of left lower leg. The swelling was firm. No obvious pulsation was noted. No overlying skin changes. There were no erythema or discolouration of the leg. The peripheral pulses of the foot were detectable and capillary filling of all toes were normal. No neurovascular deficit was detected. All vital signs and laboratory parameters were within the normal range.

On the second day of admission an urgent ultrasound doppler was requested. A few differential diagnosis was proposed by the orthopaedic team, which included a post traumatic haematoma, arteriovenous fistula or a soft tissue tumour. On ultrasound, B-mode imaging showed the pseudoaneurysm measuring approximately 2.2cm x 3.3cm (Fig. 1a). Colour Doppler scan in axial displayed the characteristic 'yin yang sign' (Fig. 1b), while longitudinal scan showed communication with the proximal normal calibre anterior tibial artery (Fig. 2). The imaging findings and ultrasound report were updated to the primary team. A CT angiography was offered but did not proceed as patient was already planned for surgical intervention. He was subsequently brought in for wound debridement, wound exploration, and ligation of the left anterior tibial artery. An incision was made over the anterolateral aspect of the lower leg.

The sloughy tibia and fibular periosteum were debrided. Noted was a 1 cm laceration of the left anterior tibial artery with a loss of 30% circumference. The pseudoaneurysm was noted and this followed the ligation of the left anterior tibial artery. Postoperatively the patient was able to ambulate and there was no recurrence of the swelling. He was then discharged and in his latest follow-up, he was ambulating normally with no active complaints.

DISCUSSION

The goal of this case presentation is to review the common causes and diagnostic imaging features of an anterior tibial artery pseudoaneurysm and briefly the available treatment options.

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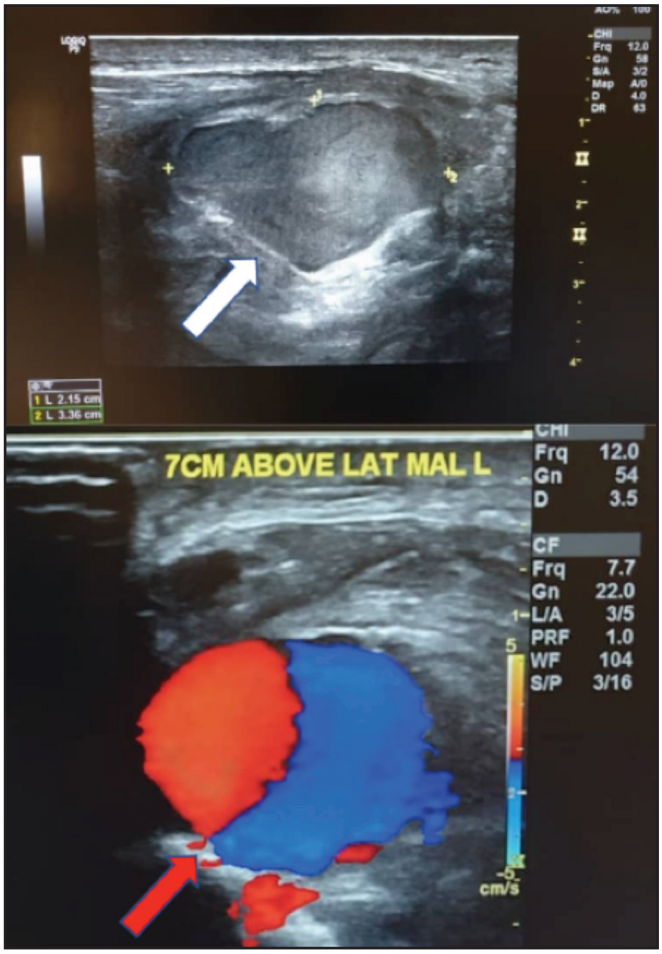

Fig. 1: White arrow shows the ultrasound image the pseudoaneurysm as an encapsulated, hypoechoic, irregular collection with internal echoes. Red arrow shows the ultrasound doppler (axial) image depicting the yin-yang sign secondary to turbulent flow within the aneurysmal sac.

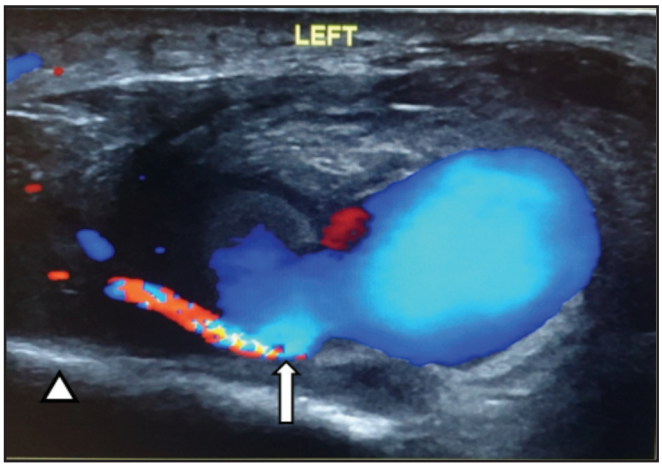

Fig. 2: Ultrasound doppler (longitudinal) image shows the pseudoaneurysm and its parent artery, the left anterior tibial artery. White arrow: communication between aneurysmal sac and its normal parent artery. White arrowhead: Tibia bone.

Traumatic aneurysms are frequently a consequence of penetrating vascular injuries. However, it may also follow a blunt injury. In our case, the patient developed a pseudoaneurysm following penetrating trauma to the lower limb. Traumatic aneurysm of an anterior tibial artery is a known but very rare complication of trauma to the vessels.[3]

A high degree of clinical suspicion is required to diagnose a vessel injury. Features that should raise suspicion include the presence of a growing pulsatile mass, unexplained swelling, and vascular insufficiency leading to absence of a palpable distal pulse. Uncommonly a systolic bruit or a thrill maybe present. In our case, an ultrasound and Doppler examination was performed on the day of admission, hence confirming the diagnosis and allowing for quick surgical intervention. Postponement in the diagnosis of these vascular injuries is the most frequent cause of complications. The consequent complications differ from severe pain, pulmonary embolism, rupture of the aneurysm, and hemorrhage to ulcer formation and potential amputation.[4]

Differential diagnoses of a pseudoaneurysm include deep vein thrombosis, haematoma, arteriovenous fistula, or a tumor of soft tissue or osseous origin. The role of imaging in these patients is to rule out other causes and confirm the diagnosis of a pseudoaneurysm.

Currently, ultrasound is the best imaging modality for initial assessment and diagnosis. This is because it is cost-efficient, widely, and easily available, and easy to learn. Ultrasound and doppler imaging both have high sensitivity and specificity in diagnosing a pseudoaneurysm. On ultrasound, an encapsulated, most commonly hypoechoic lesion is seen with internal echoes (Fig. 1) and shows communication with the proximal normal size artery. Colour doppler demonstrates a mosaic color signal pattern secondary to turbulent blood flow within the aneurysmal sac, displaying the characteristic 'yin yang sign'. Pulsed doppler shows a to and from wave pattern. Overall, sonography has a high sensitivity and specificity in diagnosing a pseudoaneurysm, ranging between 90-100% and 99-100% respectively.[5] A downfall to keep in mind is that the accuracy mentioned above is operator dependent, and ultrasound is limited in

certain anatomical regions such as the subclavian and iliac arteries. Ultrasound is also very useful to rule out other differential diagnoses. A haematoma is usually heterogeneous in appearance, with lesser internal vascularity compared to a pseudoaneurysm. A deep vein thrombosis usually shows an echogenic thrombus in the proximal deep vein with no color signal within. A soft tissue tumour can show a well or ill-defined margin depending on benignity, minimal vascularity, and occasionally infiltration into the underlying muscle.

Magnetic resonance imaging shows pseudoaneurysm as a heterogeneous low-intensity to iso-intensity signal on T2-weighted imaging and a high-intensity signal on T2*-weighted imaging. Transfemoral arteriogram has remained the gold standard investigation, as it allows treatment to be initiated.[4] To increase the probability of a successful outcome in these patients, prompt diagnosis and appropriate intervention and treatment are fundamental.

A computed tomography (CT) scan shows the aneurysm as a hypoattenuating (non-contrasted scan) or hyperattenuating (contrast-enhanced scan) sac, with this sac usually adjacent to an artery, usually with a communication to the parent vessel.

Internal appearance varies, depending on the degree of thrombosis. Partial rupture of the aneurysmal sac leads to complex multilobed composition, with multiple interconnected sacs. Complete rupture can show a more diffusely infiltrative haematoma. If an intermediate or high attenuation (haemorrhage) is visualized adjacent to the pseudoaneurysm, this could suggest a rupture, which differs in attenuation depending on it being chronic or acute. The pseudoaneurysm wall is usually smooth and well-defined except in a mycotic pseudoaneurysm, where the wall can be thickened, irregular, or ill-defined. While angiography is still the gold standard for evaluation of vascular injury, CT angiography has many advantages, such as being less invasive compared to catheter angiography, shorter examination time, lower rate of complication, with a high sensitivity and specificity, ranging from 98.7-100% and 90-95% respectively.[5]

Treatment options for a pseudoaneurysm of the anterior tibial artery include coil embolization, ultrasound-guided compression, percutaneous injection of thrombin, and open surgery. Percutaneous treatment using thrombin, although originally successful, does have associated risks, including distal embolization necrosis and, and when treatment is not successful, there is a potential delay in healing. Few distinct surgical or endovascular interventions are available such as artery ligation, direct primary repair with or without interposition grafting, coils or thrombin embolization, and covered stent graft. A multimodality treatment method using coil embolization, thrombin injection, and surgical approach is currently being described.

A special lesson that the authors would like to share from the case would be in presence of clinical diagnostic uncertainty, for example in our case where characteristic clinical symptoms were not present, imaging may be able to provide assistance in diagnosis and aid further management and intervention. Therefore, the authors would like to recommend ultrasound as a first line imaging modality in all suspected pseudoaneurysm cases, as it is widely available, cost effective and has a high sensitivity and specificity.

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CASE REPORT

Right ureteric reconstruction with vascularised interpositional appendix graft in retroperitoneal leiomyosarcoma

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SUMMARY

We present here a case of a 66-year-old lady who was diagnosed with right iliac fossa retroperitoneal leiomyosarcoma at Hospital Umum Sarawak. The challenge in this case was the extension of tumour with the involvement of her right ureter causing proximal hydroureter and hydronephrosis. After resection of tumour *en-block* with the involved segment of ureter, it was not possible to repair the ureteric defect directly. We used interpositional vascularized appendix graft to repair this large (7 cm) ureteric defect. We describe here this uncommon technique of ureter reconstruction.

INTRODUCTION

Retroperitoneal sarcomas (RS) are rare heterogeneous group of mesenchymal tumours comprising about 15% of soft tissue sarcomas.[1] Due to paucity of symptoms, delayed presentation, its large size, and involvement of important structures in the retroperitoneum, resection of these tumours is challenging. Depending on the site of the tumour, retroperitoneal sarcomas can invade the nearby vital tissues or organs. Surgical resection is the mainstay of curative treatment and it usually involves en-block resection of the involved structures.[1,2]

The ureter is one of the common structures which is involved by locally advanced abdominal, pelvic (colorectal cancers, cervix, uterine, ovarian cancers) and retroperitoneal tumours. The common methods of ureteric defect reconstruction are ileal interposition, psoas hitch and Boari flap.[2,3] We report here a case of right lower ureter reconstruction with interpositional appendix graft in order to repair the defect caused by resection of retroperitoneal leiomyosarcoma in an elderly lady.

CASE REPORT

A 66-year-old female presented at Hospital Umum Sarawak with a 3 months history of right lower quadrant abdominal discomfort, palpable abdominal mass and loss of weight. There was no history of change in bowel habit, fever or urinary symptoms. Systemic review was unremarkable. She was a known diabetic and hypertensive, on medication: tablet Amlodipine 10 mg once daily, Metformin 1 g twice daily, Perindopril 8 mg once daily, Simvastatin 10 mg once daily. There was no history of allergy and previous surgery.

On examination, she was alert, comfortable, and vital signs were stable (pulse rate 70/min, blood pressure 140/85mmHg, respiratory rate 14/min, temperature 36.5ºC. There was a non-tender, intra-abdominal, hard and fixed mass at right iliac fossa measuring about 7 x 8 cm. Otherwise there was no signs of metastases.

Laboratory investigations results were normal except for leucocytosis (haemoglobin level = 12.9g/dl, total white cells count = 16.5 x 10^3/µL, platelets = 451x10^3/µL. Renal profile, liver function test and coagulation profile were normal. Tumour markers were not raised (CA 125 = 5.2 U/ml (Normal <35U/ml), CA19.9 = 9.3 U/ml (Normal <37U/ml), CEA = <0.5 ng/ml (Normal <0.5ng/ml).

Ultrasound of the abdomen and pelvis showed heterogeneous right iliac fossa mass with internal vascularity measuring 6 x 5.4 x 7.3 cm. Colonoscopy was normal. We proceeded with computerized tomography (CT) scan of thorax, abdomen and pelvis (Figure 1) which revealed lobulated heterogeneous mass at right iliac fossa. It measured 5.3 x 6.6 x 7cm with cystic and necrotic areas. There was loss of clear fat plane with right psoas muscle. However, the fat plane with right iliac vessels and overlying bowel loops was preserved. The right ureter was compressed at L5 and S1 levels with loss of clear fat plane with the mass causing mild proximal hydroureter and hydronephrosis. Tiny sub-centimetre enhancing mesenteric lymph nodes were seen in the right lower abdomen. The appendix was normal, and no bowel related mass or abnormal bowel dilatation found. The other surrounding organs were normal and showed no evidence of liver metastasis. Transvaginal ultrasound by gynaecologist showed normal uterus and both ovaries.

After discussion with our multidisciplinary teams, we proceeded with right ureter stenting and staging laparoscopy. The tumour was located behind the caecum, both ovaries, fallopian tubes and uterus looked normal. We converted to lower midline laparotomy (Figure 2). Right side of the colon was mobilised. Right ureter identified at both proximal and distal to the tumour. Tumour was retroperitoneal (8 x 9cm), appeared to be completely encasing the right ureter. Tumour

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was completely excised with *en-block* resection of about 7 cm of the ureter with clear margin.

The ureteric defect was reconstructed with vascularised appendix interpositional graft by our urologist. The appendix was normal about 8cm long. The base of appendix was divided and appendix stump ligated with vicryl (Polygalactin 910) 3/0 and invaginated. The tip of the appendix was divided, appendix mobilised maintaining the blood supply through appendicular vessels. Ends of the ureter and appendix were spatulated. Ureteric catheter was repositioned through the distal ureter into divided tip of appendix and into proximal ureter. Distal anastomosis between ureter and appendix completed with interrupted sutures of vicryl (Polygalactin 910) 4/0 followed by proximal anastomosis. A tube drain was inserted at right paracolic gutter and abdomen closed with loop nylon 1.

Post-operatively, the patient's recovery was uneventful. Abdominal drain was removed on post-operative day 3. Foley's catheter was removed on post-operative day 4 and the patient was able to urinate without any problems. She was discharged subsequently on post-operative day five. Patient was well at twelve months follow up and repeated CT scan did not show any recurrence.

Histopathological examination confirmed the diagnosis of retroperitoneal leiomyosarcoma. It showed a fairly circumscribed tumour with a pushing border composed of spindle and pleomorphic cells with eosinophilic cytoplasm forming interlacing but disorganized fascicles. Mitotic activity was high (21per 10 HPF). Coagulated necrosis characterized by an abrupt transition from viable to non-viable areas were seen in many areas (less than 50% of tumour area). There was a focus displaying infiltrative border, where tumour cells invaded into the adjacent adipose tissue. The tumour pushed the ureter without invading the stroma or epithelium. No apparent vascular or lymphatic permeation. Tumour cells were seen at the inked surgical margin. Tumour cells were positive for SMA, desmin and CD34(focal) and negative for S100. Final diagnosis was retroperitoneal leiomyosarcoma (FNCLCC Grade 3).

DISCUSSION

Retroperitoneal leiomyosarcoma is a rare cancer arising in the abdomen and pelvis. It is the second most common RS.[1] It mainly affects women in the six and seventh decade of life. The common presenting features are abdominal discomfort or pain, palpable abdominal mass and loss of weight,[2] which were also the main symptoms presented in our patient. However, most of these tumours are asymptomatic and may be discovered by imaging for some other reasons. Leiomyosarcomas are aggressive tumours and may infiltrate adjacent organs in the retroperitoneum like duodenum, colon, pancreas, great vessels, kidneys and ureter. Surgical excision is the mainstay of treatment due to lack of effective radiotherapy and chemotherapy for adult RS.[1,2] En-block resection of involved structures is necessary to get surgical free margin. After complete surgical resection (R0), local recurrence rate is about 50% and 5-year survival of 58%. Marginal and incomplete resections (R1, R2) has been reported in nearly 50% of cases undergoing surgery with curative intent.[1] Local recurrence of tumour is the main cause of treatment failure (40-80%) leading to death.[1,2] In our patient the tumour had encased the right lower ureter and thus requiring *en-block* resection. There are several techniques of ureteric reconstruction available including ileal interposition, Boari flap, Psoas Hitch, and buccal mucosal tubularized graft.[3,4] We used vascularised appendix graft to repair 7 cm ureteric defect after tumour resection. Although most of case reports described use of appendix for right ureter reconstruction because of its anatomical location near the right ureter, appendix graft can be used in left ureter reconstruction in selected cases.[5]

The appendix is a tubular structure consisting of all layers of bowel with irregular lumen. The mucosa is thrown into multiple longitudinal folds and is lined by simple columnar epithelium of colonic type. Its length varies between 7.5 and 10cm. Appendix is supplied by appendicular artery, a branch of ileocolic artery which runs in the free edge of mesoappendix. Appendix can be easily mobilized with its intact blood supply and retroperitonialised to repair the right ureteric defect. Appendix is the ideal structure for reconstruction of right ureter because of its ideal location and

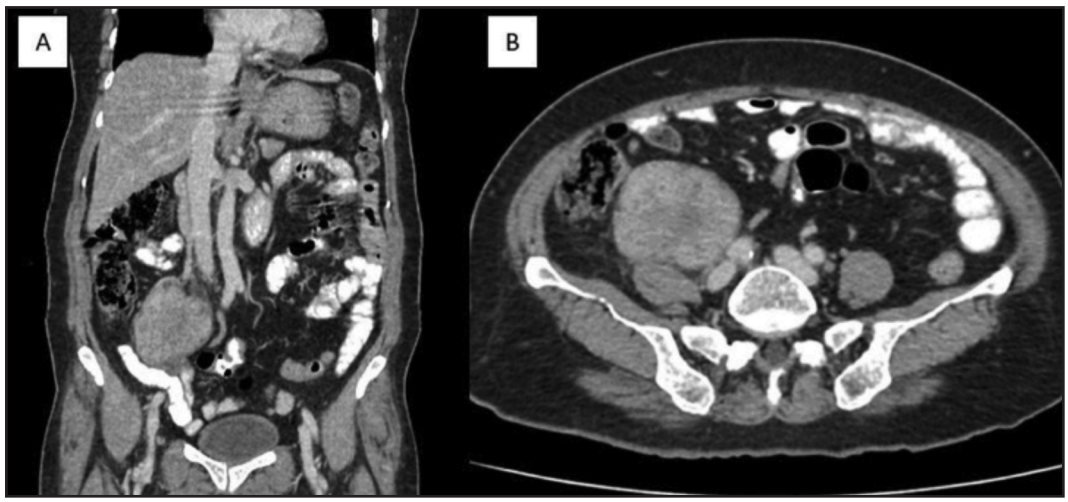

Fig. 1: CT scan of abdomen and pelvis. Coronal section (A) and transverse section(B) showed heterogeneous right iliac fossa mass with loss of clear fat plane with right psoas muscle but preserved fat plane with iliac vessels and overlying bowel loops. Mass compressing the right ureter causing mild hydroureter and hydronephrosis.

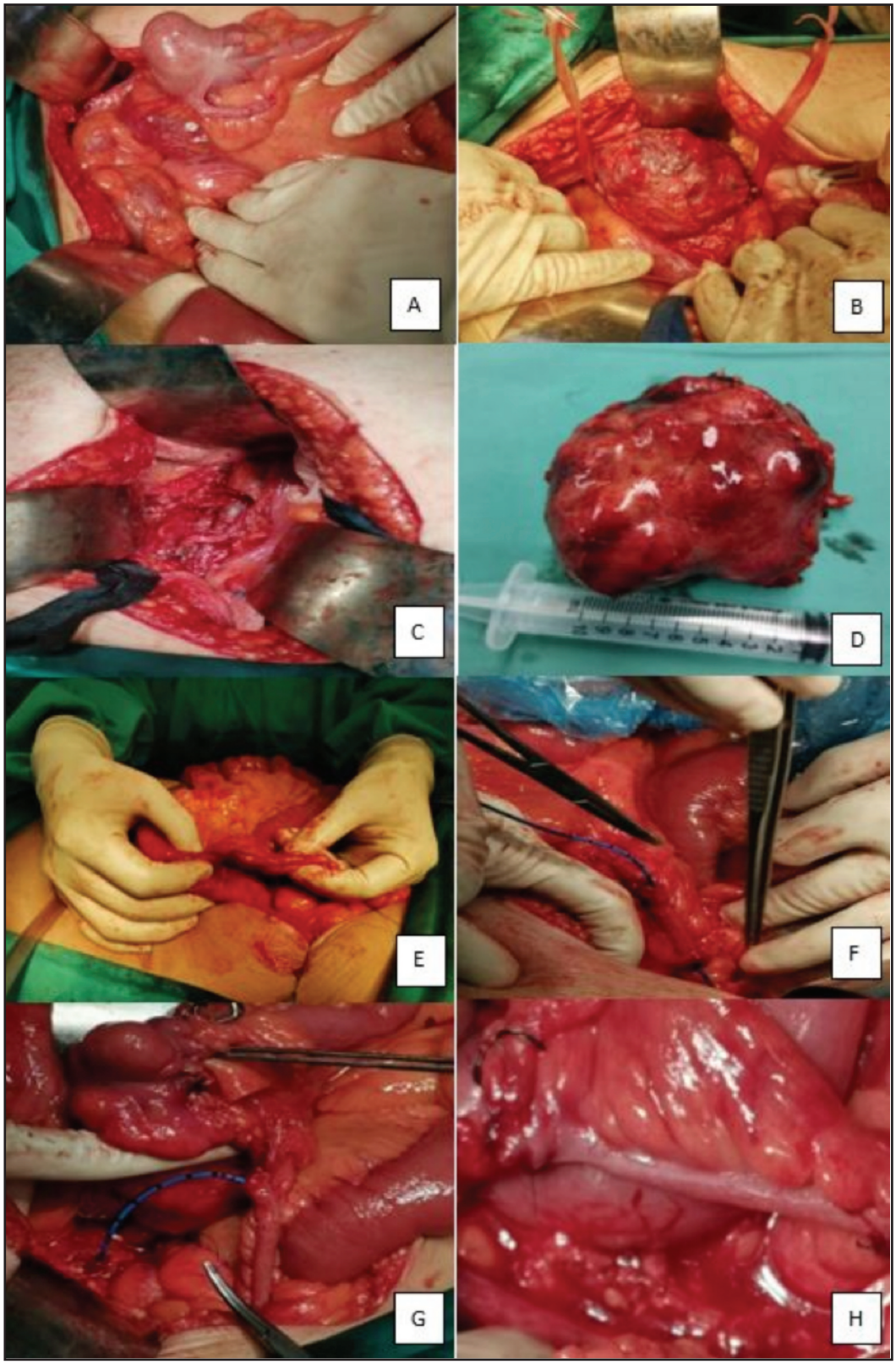

Fig. 2: Intraoperative photos. (A) Tumour at right iliac fossa behind the caecum and ascending colon. (B) Tumour delineated after mobilization of right colon. Retroperitoneal tumour encasing the right ureter with nylon tapes slinging the right ureter proximal and distal to tumour. (C) Tumour bed after resection, consisting of right psoas muscle, iliac vessels and inferior vena cava. (D) En-bloc excision of tumour with encased ureter. (E) Right ureter reconstruction with appendix graft: normal appendix mobilised with mesoappendix. Base of appendix ligated and divided. (F) Tip of appendix divided, ureteric stent traversing the lumen of appendix. (G) Distal anastomosis between appendix and distal ureter in progress followed by proximal anastomosis. (H) After completion of anastomosis.

structural similarity to the ureter. The diameter of the appendix is close to diameter of the ureter; it has peristalsis thus avoiding stasis of urine.[3] The lumen of appendix and surface area is small which avoid excessive absorption of urinary electrolytes. The common side effects of ileal interposition like metabolic acidosis due to excessive absorption of chloride, intestinal obstruction, anastomosis leak of bowel, recurrent UTI and stone formation in the ileal segment can be avoided.[4,5] The appendix cannot be used for ureter reconstruction if the length is too small to bridge the defect, or it has been removed earlier.

CONCLUSION

Appendiceal vascularised graft is a viable and effective technique for the reconstruction of large ureteric defect in number of clinical situations including surgical excision of retroperitoneal tumours. Since the appendix is an ideal organ for reconstruction of ureter, incidental appendectomy should be avoided.

CONSENT

Written informed consent was obtained from the patient for publication of this case report.

CONFLICT OF INTEREST

We declare no conflict of interest.

ACKNOWLEDGEMENT

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CASE REPORT

Immature ovarian teratoma with anti-NMDA-receptor encephalitis in a 13-year-old Japanese female patient

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SUMMARY

We report a 13-year-old Japanese female with ovarian teratoma due to anti-NMDAR encephalitis. The patient was admitted with psychiatric symptoms, including memory impairment, insomnia, binge eating and mouth and hand twisting, associated with constipation. Serum alpha-fetoprotein and neopterin levels were elevated 102 ng/mL and 19 pmol/mL, respectively. Electroencephalography showed epileptic spikes in frontal and temporal regions. Cerebrospinal fluid (CSF) examination exhibited a pleocytosis. Thereafter, her consciousness level immediately worsened. Brain magnetic resonance imaging (MRI) noted hyper intense lesions in bilateral hippocampi, she was diagnosed with limbic encephalitis. Abdominal echogram showed a solid right ovarian tumour. and also confirmed as a tumour by abdominal MRI. The next day, right ovariectomy was performed and she treated two courses of methyl-prednisolone steroid pulse with high-dose immunoglobulins. Later days, CSF analysis revealed anti-NMDAR antibodies. Pathological diagnosis of the tumour was immature round shaped grade 3 ovarian teratoma, measuring 11cm. Two years follow up after admission, she completely recovered and no neurological sequelae.

INTRODUCTION

Anti-N-methyl-D-Aspartate receptor (NMDAR) encephalitis is rare form of autoimmunological encephalitis. In addition, abdominal ovarian tumour complications have been reported. We read with interest the report by Mahendra et al.[1] of a 16-year-old female with ovarian teratoma associated with anti-N-methyl-D-Aspartate receptor (NMDAR) encephalitis diagnosed with rectal sonography and histological examination of the cystic mass. We also treated a similar case of a 13-year-old Japanese female patient with ovarian teratoma associated with anti-NMDAR encephalitis.

CASE REPORT

Two weeks after a bout of common cold, the above patient was hospitalized with psychiatric symptoms, including memory impairment, insomnia, binge eating and twisting of mouth and hand, and accompanied with constipation. Differential diagnosis included schizophrenia, epilepsy, depression and encephalitis. Blood and urine tests were normal. She was negative for antinuclear, anti-double-stranded DNA and anti SS-A antibodies. Alpha-fetoprotein and neopterin levels were 102 ng/mL and 19 pmol/mL,

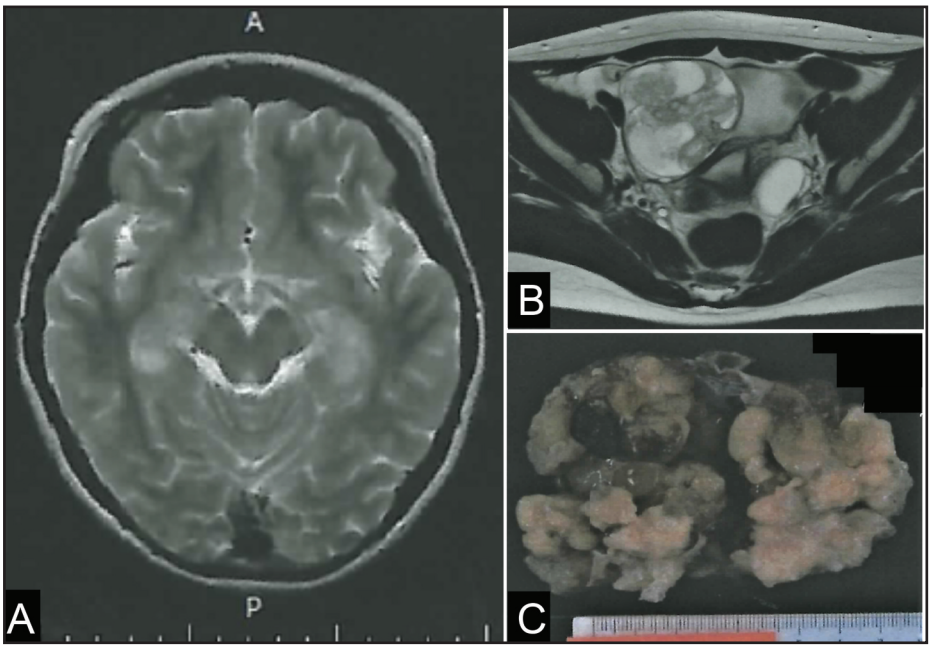

Fig. 1: (A) Magnetic resonance fluid-attenuated inversion-recovery image at admission showing hyper intense lesions in bilateral hippocampi. (B) Abdominal magnetic resonance image showing a round tumour, 11 cm in size, with a non-uniform signal. (C) The maximum diameter of the mass is 12.0 cm.

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respectively. Brain computed tomography findings were normal. Electroencephalography revealed sporadic spikes in frontal and temporal regions. Cerebrospinal fluid (CSF) analysis revealed a pleocytosis. The tentative diagnosis was viral encephalitis, and acyclovir and cefotaxime were initiated. However, her consciousness worsened immediately and her brain magnetic resonance imaging (MRI) revealed hyper intense lesions in bilateral hippocampi (Fig. 1A). She was diagnosed with limbic encephalitis, and abdominal ultrasonography revealed a solid right ovarian mass, which was diagnosed as a tumour by abdominal MRI (Fig. 1B). The updated diagnosis was anti-NMDA encephalitis due to an ovarian tumour, and right ovariectomy was performed the next day (Fig. 1C). After the operation, she received two courses of methyl-prednisolone steroid pulse (30 mg/kg, 3days) and high-dose immunoglobulins (400 mg/kg/5 days). One week after operation, she was apathetic during the day and apnoeic at night and had lost >10% body weight. She was administered valproic acid for repeated generalized seizures. Moreover, serum and CSF examination at admission revealed the presence of anti-NMDAR antibodies. She received another course of steroid pulse therapy, with subsequent, gradual improvements in mental state and memory. She was discharged two months after initial admission. The pathological diagnosis of the right ovarian tumour was immature grade 3 teratoma. Her IQ was 97 on evaluation two years after surgery, and antiepileptic drug treatment was discontinued at that time.

DISCUSSION

In a study of limbic encephalitis by Dalmau et al.,[2] 91 of the 100 patients were females; young female patients were predominant and 62% of the female patients had tumours, most of which were ovarian teratomas. Early tumour removal and immunotherapy are important for favourable outcomes in limbic encephalitis.[3] A microscopic teratoma was detected on autopsy in a case report. Therefore, exploratory laparotomy should be considered in severe refractory cases.[4] The prognosis was good following tumour excision in our case, similar to that reported by Mahendra et al.[1] Sudden appearance of psychiatric symptoms in young female patients should warrant prompt brain MRI and abdominal examination for potential ovarian teratoma associated with anti-NMDA-receptor encephalitis.

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CASE REPORT

Internal jugular vein thrombosis in a child

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SUMMARY

Venous thrombosis is a potentially life-threatening condition with varied aetiology. First described in 1912 as a complication of peritonsillar abscess, internal jugular vein (IJV) thrombosis is a rare entity in children with very few cases reported until now. Among the leading causes of this condition are prolonged use of IJV for venous access and central venous catheterisation, acute mastoiditis and Lemierre's syndrome.[1] IJV thrombosis can also occur as a complication of head and neck infections, but rarely appears as its first presentation. The clinical manifestations are often vague and ambiguous, thus requiring a high index of suspicion to diagnose IJV thrombosis. We describe here a case of internal jugular vein thrombosis (IJVT) and the management of this rare condition in an otherwise healthy 8-year-old boy. The patient was investigated thoroughly to rule out possible pathological causes of IJV thrombosis and managed holistically with a multidisciplinary team approach. Although the occurrence is rare, it should be recognised as a complication of deep neck infections in order to initiate prompt and accurate therapy.

CASE REPORT

A healthy 8-year-old boy was admitted with a 3-day history of enlarging, painful left sided neck swelling preceded by intermittent fever and cough for 2 weeks. There were no constitutional symptoms or weight lost, and his appetite was good. He had no significant history of contact with tuberculosis patients, prolonged central venous catheterisation or trauma. There were no known family history of haematological malignancies or pro-thrombotic disorders.

Clinically he was stable with no signs of tachypnoea or respiratory distress. He was febrile with temperature of 39°C and neck examination revealed a tender, firm, diffuse swelling over the left anterior triangle, measuring approximately 3cm x 5cm. There were multiple small cervical lymph nodes palpable bilaterally but there were no axillary or inguinal lymphadenopathy. BCG scar was present and he had moderate congestion of his throat. Respiratory examination revealed clear lung fields bilaterally on auscultation and examination of other systems were unremarkable. Following his clinical presentation, differential diagnoses of lymphadenitis and deep neck infections were sought and worked up.

Initial laboratory test revealed white blood cell count of 22.5 x 10^9/L predominantly neutrophils 89% with an elevated C-reactive protein of 70.9 mg/L and erythrocyte sedimentation rate (ESR) of 78 mm/hr. Platelet count and liver enzymes were within normal ranges apart from serum albumin of 25g/L. Tuberculosis (TB) workup which included Mantoux test, gastric lavage for acid fast bacilli (AFB) smear and culture were negative. Chest radiograph performed was normal with no evidence of consolidation or widened mediastinum. Serial bacterial cultures in the blood and nasopharyngeal aspirates, as well as polymerase chain reaction (PCR) tests for common viruses yielded no growth. Titres were negative for *Burkholderia pseudomallei* and *Bartonella henselae*. Urgent ultrasound of the neck demonstrated a deep heterogenous collection over the left sternocleidomastoid (SCM) extending into the left thyroid lobe and isthmus, with thrombosis of the left internal jugular vein. Following the findings of venous thrombosis on the ultrasound report, thrombophilia and autoimmune screening were initiated. Blood tests were sent for protein C and S, antithrombin III, antiphospholipid antibody, antinuclear antibody, rheumatoid factor as well as complement levels, and results were within normal limits. Screening for primary and secondary immunodeficiency were unremarkable. Chest radiograph did not show any consolidation or widened mediastinum.

Following that, antimicrobial therapy comprising of intravenous ceftriaxone and cloxacillin was initiated to provide appropriate antimicrobial coverage. Further radiological evaluation with computed tomography (CT) scan and echocardiography reported similar findings of left IJV thrombosis and soft tissue inflammation, with the involvement of the oropharynx, thyroid lobe and sternomastoid muscle. Referral to surgical and cardiology team was sought. Intravenous heparin infusion was initiated and subsequently converted to subcutaneous enoxaparin after one week. The patient improved clinically while on treatment, did not required surgical drainage and was ultimately discharged with a total of 8 weeks subcutaneous enoxaparin and two weeks of antibiotics (consisting of intravenous ceftriaxone and cloxacillin for one week, followed by oral cefuroxime and coxacillin). Repeated doppler ultrasonography after 2 months showed resolution of the neck abscess and IJV recanalization with residual short segment thrombosis. Anticoagulant treatment was discontinued at this junction as he was asymptomatic and well. Unfortunately, his clinical course was later complicated with recurrent abscess formation. He was readmitted 4 months after his initial hospitalisation with similar presentation of neck swelling associated with pain and compressive symptoms. Ultrasonographic examination demonstrated the presence of a left neck collection with persistent unilateral short segment IJV devoid of colour signal, in keeping with chronic thrombosed IJV. A contrast

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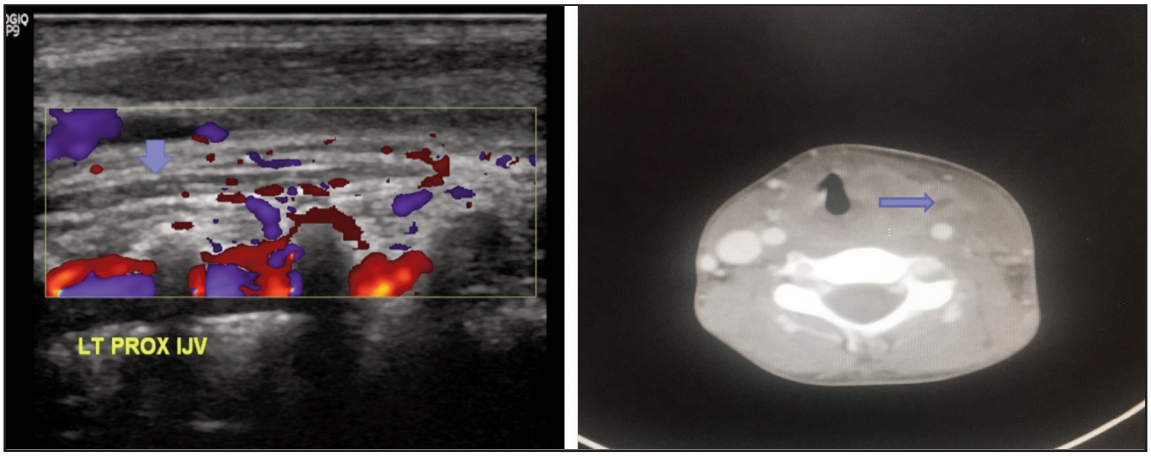

Fig. 1: (a), (b): Short segment IJV thrombosis (blue arrow) noted on the ultrasound doppler of neck. CT scan of neck (axial view) demonstrating a partially occlusive thrombus in the left internal jugular vein (blue arrow) with diffuse soft tissue thickening.

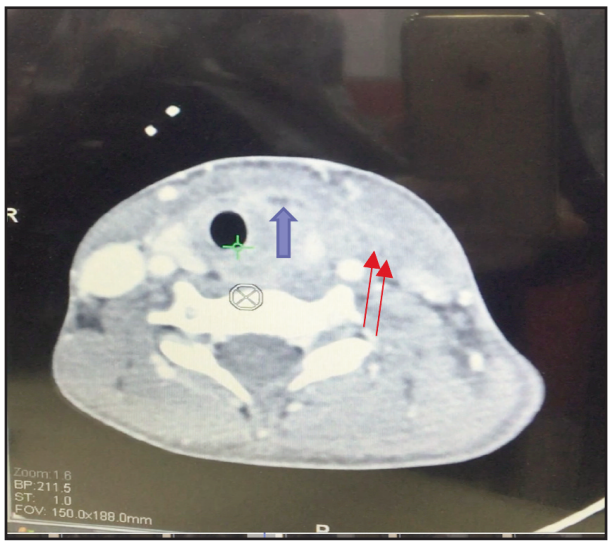

Fig. 2: A repeated CT scan of the neck showing compressed thrombus in the left internal jugular vein (blue arrow) with multi-loculated abscess measuring 2.1 x 1.9 x 2.5 cm (red arrow). Trachea is displaced to the right.

enhanced CT of the neck showed the presence of multi-loculated left neck abscesses causing mass effect to the trachea, thyroid gland and left IJV. Otherwise, there was no reported transverse sinus thrombosis or mediastinal extension involvement. He subsequently underwent incision and drainage of the abscess, with total of 30mls pus drained. Intraoperative samples sent for bacterial and TB culture, TB PCR and cytology were negative. In addition to intravenous ceftriaxone and cloxacillin, oral clarithromycin was initiated as his serum titre of *Mycoplasma pneumoniae* antibody was 1:320. There was rapid resolution of fever and he was discharged 2 weeks later upon completion of intravenous antibiotics. Oral clarithromycin and cloxacillin was continued for a total four weeks respectively. The patient eventually made gradual recovery with complete resolution of his abscesses and remained well 12 months later during his routine follow-up.

DISCUSSION

Internal jugular vein thrombosis is commonly seen in adult patients and very few cases are reported in children. The pathophysiology behind the inherited and acquired causes of venous thrombosis is the impaired local or systemic blood flow based on the Virchow triad of stasis, hypercoagulable state and vascular injury.[2] In our case, all three factors may be in operation and contributed to the development of IJV thrombosis. The unresolved neck abscess with the surrounding matted lymph nodes in this patient led to venous stasis and vascular obstruction. The ongoing infection and inflammation are risk factors for hypercoagulable state, attributed by an increased rate of fibrinogen production and platelet activity which developed secondary to an acute phase response. Venous thrombosis also occurs as a result of infection induced vascular damage when the vein is affected by an adjacent septic focus. The adventitia, which is the

initial site of involvement usually becomes congested and infiltrated by inflammatory cells. Thrombus formation occurs when the inflammation reaches the intima and involves all the layers of the vein where the adherence of fibrin, blood cells and platelet take place.

Despite the increasing awareness of *M. pneumoniae* infection, IJV thrombosis is an extremely rare extrapulmonary manifestation described in the literature. Our patient's IJV thrombosis occurred at the same time he had a serologically proven *M. pneumoniae* infection. The question remains if the Mycoplasma infection happens to be a casual or causal relationship to the development of venous thrombosis in this patient. Although there were reports detailing the thrombotic manifestations associated with *M. pneumoniae* infections, the exact mechanism of the venous thrombosis remained obscure.[3] Hypothetical mechanisms postulated are the direct invasion by the organism causing toxin production, autoantibody with immune complex formation, microthrombosis and impaired immunity. *In vitro* experimental studies have previously suggested the production of lipoglycans from *M. pneumoniae* infection can induce procoagulant activity and potentially trigger the mechanism of intravascular coagulation.[4]

In most cases, venous thrombosis occurs in patients with generalized hypercoagulable state which may be inherited or acquired. However, retrospective history and extensive laboratory screening for antithrombin III deficiency, deficiency of protein C or S, and antiphospholipid syndrome in our patient did not revealed any significant contributors to the pathogenic mechanisms. General guidelines for the treatment of thromboembolic events in children include intravenous heparin or subcutaneous low molecular weight heparin for several days and subsequent overlapping with anticoagulants until the target therapeutic value of prothrombin time is achieved. Anticoagulant therapy is stopped after three to six months when risk factors for thrombotic events are eliminated. Despite the presence of residual short segment thrombosis, anticoagulants were discontinued after 2 months as there was documented evidence of jugular vein recanalization and the patient was asymptomatic. When a second recurrence of thromboembolic event is present, indefinite oral anticoagulant therapy should be considered though some investigators dispute the usefulness of anticoagulants that are thought to carry significant potential risks. Intravenous antibiotic treatment against targeted infective organisms should be started and tailored accordingly to the culture results. Should a favourable resolution be observed after approximately 2 weeks of intravenous antibiotics, oral administration can be started and continued for a total duration of four to six weeks.[5] Surgical drainage is indicated for non-resolving, loculated abscesses or other adverse sequelae, which occurs as a result of poor response to medical therapy.

CONCLUSION

We propose that the present case demonstrates the importance of identifying IJV thrombosis as an important differential diagnosis in children who present with painful neck swelling, especially in the course of any oropharyngeal or deep seated neck infections. Successful management rests on the awareness of the condition, a high index of suspicion and prompt intervention with a multidisciplinary team approach. Antibiotic treatment for four to six weeks associated with anticoagulant treatment can be considered as safe and effective. Surgical intervention should be performed to eliminate the source of infection if there is failure to respond to appropriate and adequate duration of antimicrobial therapy.

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DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the authorship and/or publication to this article.

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Severe central airway stenosis and tracheomalacia in hunter syndrome

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SUMMARY

Hunter Syndrome is a genetic disease characterized by deficiency of Iduronate-2-Sulfatase enzyme activity, resulting in accumulation of glycoaminoglycans in various organs including the central airways. We report a case of severe tracheomalacia and airway stenosis at Hospital Sultanah Aminah, Johor Bahru, Malaysia requiring mechanical ventilation in a middle aged gentleman who was previously undiagnosed of mucopolysaccharidosis. The patient underwent emergency tracheostomy for failed intubation, when he presented with shortness of breath and acute respiratory failure. A contrast-enhanced computed tomography of the neck and thorax revealed that the trachea distal to the tracheostomy tube had collapsed with narrowed right and left main bronchus. These findings were confirmed via direct visualization of the airway through a flexible bronchoscopy. Eventually, a tracheal stenting were performed to maintain the airway patency and assist in weaning off from mechanical ventilation. Further investigations to identify the aetiology of the central airway stenosis revealed elevated urinary glycoaminoglycans and the absence of iduronate-2-Sulfatase activity tested on dried blood spots, thus confirming the diagnosis of Hunter Syndrome. Managing mucopolysacharidosis with central airway obstruction requires multidisciplinary team effort in handling the difficult airway, anaesthesiology risk, potential comorbidities and providing genetic counselling.

INTRODUCTION

Mucopolysaccharidoses (MPS) are a group of rare genetic diseases caused by the deficiency of any of the lysosomal enzymes that are involved in the glycoaminoglycans (GAGs) catabolism.[1] The estimated cumulative incidence is approximately 1 in 25,000 newborns. Most cases are diagnosed in the paediatric age group due to the early manifestation of the symptoms. The median age of diagnosis of Hunter syndrome (HS) were 3.5 years, with the age of onset of symptoms at the age of 1.5 years.

In patients with MPS, the accumulation of GAG in various organs and tissues results in a multisystemic clinical picture. Seven distinct clinical types of MPS are known: type I, II, III, IV, VI, VII, and IX. HS or MPS II is caused by deficiency of the lysosomal enzyme iduronate-2-sulfatase. Clinical features and severity of symptoms are widely variable ranging from severe infantile onset disease to an attenuated form, which generally has a later onset with a milder clinical presentation. Symptoms may include coarse facies, short stature, cardiac valvular disease, recurrent respiratory infections, obstructive sleep apnoea, joint stiffness, hepatosplenomegaly, umbilical and inguinal hernias, hearing loss, gingival hypertrophy and developmental delay and regression.[1] Tracheomalacia and tracheal stenosis may present as a result of deposition of storage material in the airways. The attenuated forms of MPS II are more difficult to diagnose since the disease progresses silently over decades and early symptoms are subtle and may be overlooked by physicians who are not familiar with the disease.

CASE REPORT

A 51-year-old Malay gentleman, who is a chronic active smoker, was diagnosed to have chronic obstructive pulmonary disease (COPD) five years ago and treated with metered-dose inhaler ipratropium bromide/fenoterol 40mcg/100mcg tds, budesonide 400mcg bid and salbutamol 200mcg PRN. His COPD was controlled and only had one episode of acute exacerbation that required hospital admission. He presented at the Hospital Sultanah Aminah, Johor Bahru, Malaysia with fever and cough for two days associated with worsening shortness of breath for the past three months. He also had loud snoring with daytime somnolence and his past medical history include hypertension and herniorrhaphy for umbilical hernia.

Upon arrival in emergency department, he was tachypnoeic with oxygen saturation of 97% under room air, blood pressure 145/86mmHg, pulse rate 97 beats/min, and febrile with temperature of 38.7°C. General examination showed that he has short stature with a thick neck (figure 1a), while lung examination revealed generalized ronchi bilaterally. Besides, he also had a palpable liver of 3 finger breadth below subcostal margin. He was initially treated as acute exacerbation of COPD. Despite being given intravenous hydrocortisone and nebulized bronchodilator, he developed worsening of type I respiratory failure with oxygen saturation of 80% and dropped in conscious level. Multiple attempts for

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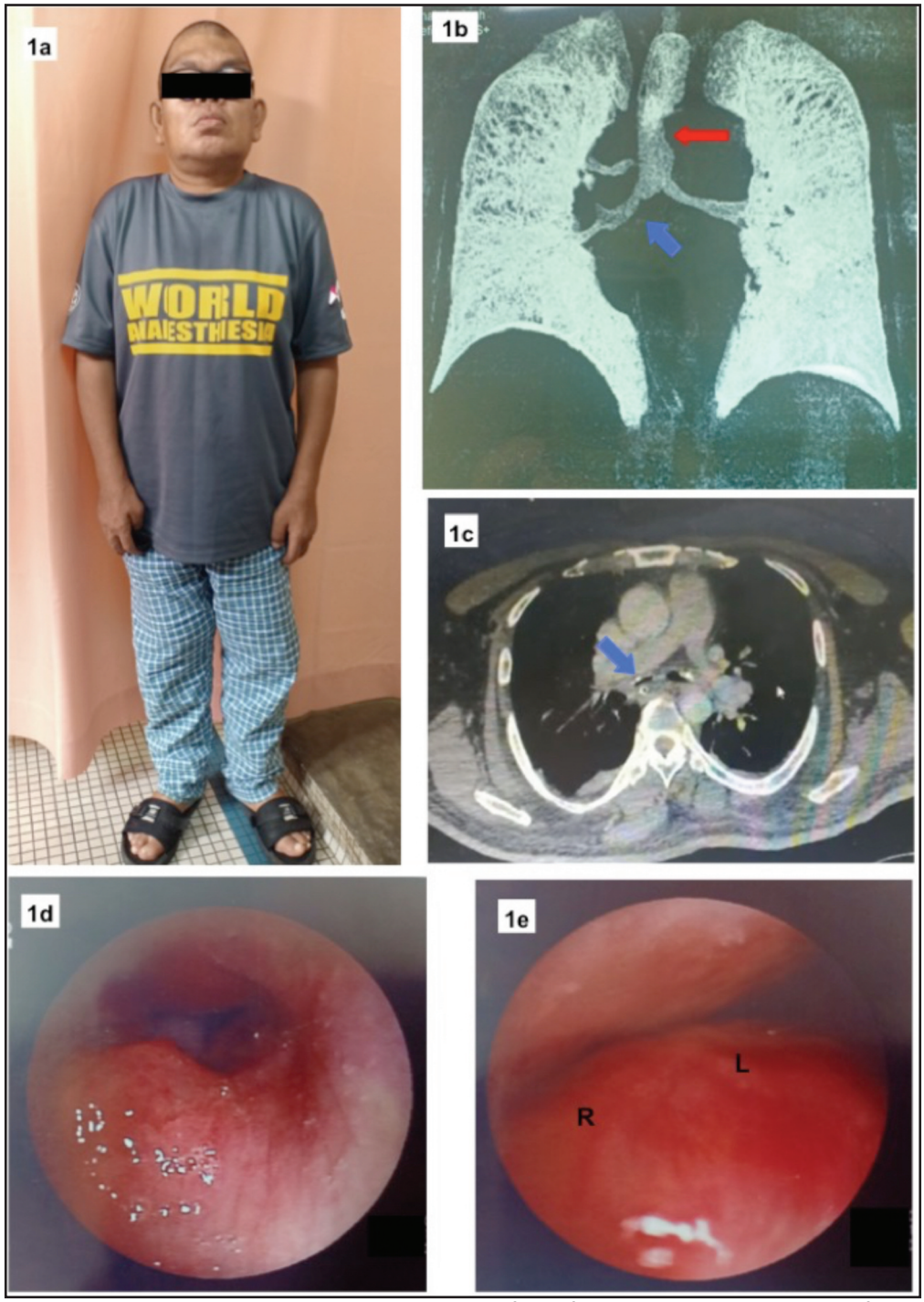

Fig. 1: a) The patient's height is 155cm. He has thick neck and course facial features, which is suggestive of mucopolysaccharide syndrome. Publication of the patient's photo was permitted and consented by the patient b,c) CECT Thorax and reconstruction CT revealed a collapsed trachea (red arrow) inferior to the tracheostomy tube with anterior-posterior diameter of 0.7cm. Both main bronchi are also stenotic, more severe on the right (blue arrow). d) Bronchoscopy through the nasal cavity showed oedematous nasopharynx and the trachea proximal to the trachestomy tube was narrowed with presence of granulation tissue e) Lower third of the trachea and bilateral main bronchi were stenotic. As seen during bronchoscopy, right main bronchus (R) was narrower compared to left main bronchus (L).

intubation failed resulting in an emergency tracheostomy to secure the airway.

A contrast-enhanced CT neck and thorax revealed that the trachea distal to the tracheostomy tube had collapsed with anterior-posterior diameter of 0.7cm (Figure 1b,1c). Both bronchi were also narrowed with the right and left main bronchus measured 0.4cm and 0.5cm respectively. There were bilateral consolidations at the perihilar extending to both lower lobes suggestive of lung infection. Bronchoscopy

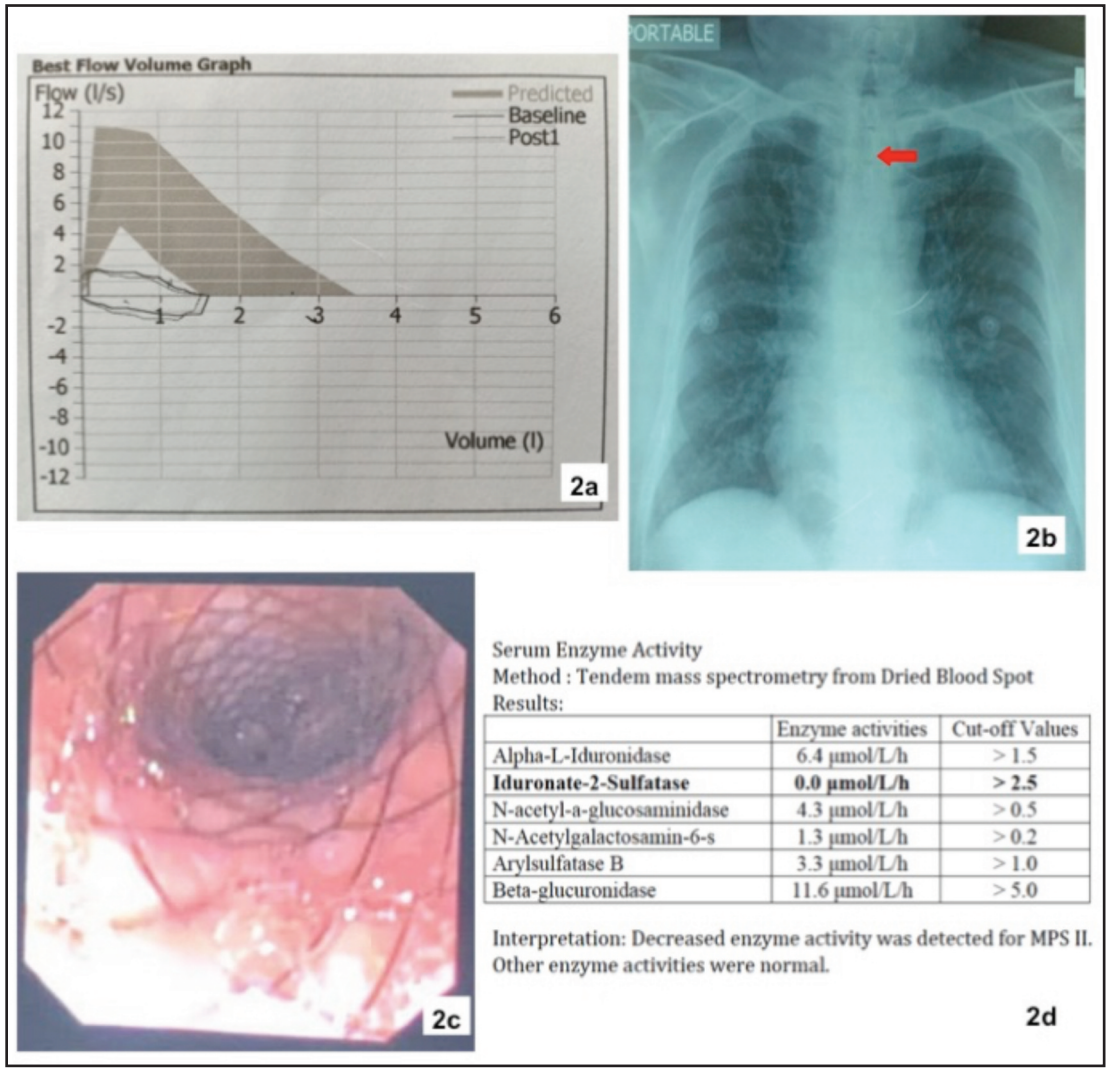

Fig. 2: a) Plateau in both inspiratory and expiratory portion of the flow-volume loop indicates fixed airway obstruction. b) Chest x-ray post tracheal stenting shows stent in-situ (red arrow) with patent trachea. c) Post airway stenting with metallic stent revealed a patent trachea. d) Elevated urine GAG and absence of serum Iduronate-2-Sulfatase activity confirm the diagnosis of Hunter Syndrome. Other enzyme activities are normal.

revealed a stenotic trachea with oedematous mucosa and presence of tracheomalacia. Both main bronchus and all segmental bronchi were narrowed (Figure 1d,1e). Bronchial washing from the right lower lobe were negative for acid-fast bacilli direct smear and the GeneXpert test for tuberculosis. Endobronchial biopsy over the right bronchus intermedius was negative for malignancy or granulomatous lesion. His previous spirometry during clinic visit was reviewed and showed fixed upper airway obstruction with post bronchodilator forced expiratory volume in one second (FEV1) 1.10 litre (44% of predicted), forced vital capacity (FVC) 1.43 litre (51% of predicted) and FEV1/FVC ratio of 0.77 (Figure 2a).

The trachea and bronchial stenosis as well as recurrent lung infection had led to prolonged ventilation. He was treated for influenza pneumonia and later hospital acquired pneumonia secondary to Klebsiella pneumoniae and Stenotrophomonas maltophilia. Besides, he was given one week of intravenous dexamethasone 8mg tds in view of oedematous oropharynx, trachea and bronchi. After a prolonged stay of 34 days in the intensive care unit, he was finally weaned off from ventilator.

Subsequently, he underwent tracheal stenting under totally intravenous anaesthesia and spontaneous ventilation. Flexible bronchoscopy findings revealed tracheomalacia and tracheal stenosis 3cm below the vocal cord and 6 cm in length. The distal end of the stenosis situated at 1 cm above the carina. Balloon dilatation was performed over both the bronchi and post dilatation a 5.2mm bronchoscope could easily pass through the bronchus. A fully covered metallic stent (Hanarostent trachea) with a diameter of 16mm and a length of 6cm was deployed into the tracheal stenotic segment (Figure 2b, 2c) through the tracheostomy opening using flexible bronchoscope as guidance. The oxygenation was maintained via a nasal cannula and spontaneous ventilation. After stent adjustments, the tracheostomy tube was removed. The stent could not be inserted through the vocal cord due to severely narrowed larynx. Although he

required re-intubation one week later due to excessive secretion causing airway compromise, he was finally discharged home well with Modified Medical Research Council (mMRC) dyspnoea scale I.

Since discharge, the patient had recovered gradually and was scheduled for regular chest physiotherapy. He was taught about effective cough technique to expectorate the airway secretion. He is able to perform the activity of daily living and four months later, he resumed his duty in his workplace.

The unusual trachea and bilateral bronchial stenosis has prompted an effort to identify the underlying aetiology. He did not have past history of intubation, airway trauma, recurrent chest infection or symptoms of autoimmune disease. Pulmonary tuberculosis was ruled out based on the bronchial washing result and absence of typical symptoms. The central airway stenosis together with the presence of short stature, short neck, umbilical hernia and hepatomegaly raise the suspicion of MPS, which was later confirmed to be HS with the elevated urine GAGs of 35.5g/mol creatinine and absence of serum Iduronate-2-Sulfatase activity in dried blood spots (Figure 2d). Other sulfatase enzymes were normal, thus excluding the diagnosis of multiple sulfatase deficiency.

DISCUSSION

Tracheobronchial stenosis can result from malignant and benign causes. Prolonged intubations or tracheostomy is the commonest cause of non-neoplastic stenosis of proximal airways. Besides, granulomatous infection such as tuberculosis, and aspergillosis need to be ruled out in patients with tracheobronchial stenosis. Other causes include systemic diseases such as relapsing polychondritis, amyloidosis, sarcoidosis and inflammatory bowel disease. Due to the rarity of the disease, diagnosis of MPS with proximal airway stenosis requires high index of suspicion in a patient with facial dysmorphism and skeletal dysfunction, followed by laboratory confirmation.

Airway obstructions particularly in patients with MPS types I, II, and VI may lead to fatal complications in emergency cases, during surgical procedures or during intubation.[2] Large amount of storage material deposition may lead to upper airway obstruction as well as bronchial and tracheal stenosis. Besides, tracheomalacia and bronchomalacia are commonly seen, resulting in complete major airway collapse. These airways stenoses occurred around adolescence and are progressive, leading to almost complete obstruction of a bronchus or the trachea.

There is no standard management guidelines available regarding the treatment of upper airway obstructions in patients with MPS. Many MPS patients with upper airway obstruction are treated with tracheostomy. However, in patients who underwent tracheostomy, when the auto-positive end-expiratory pressure (PEEP) function of the glottis is reduced, airway collapse caused by the malacia will become apparent.[2] Jeong et al reported that infrastomal tracheal stenosis (85.7%) and stomal narrowing(71.4%) are frequent in patients with MPS type II post tracheostomy, resulting in difficult cannula care and need for revision.[3]

There are few case reports on performing airway stenting in patients with MPS complicated with airway stenosis and tracheomalacia. Davitt et al. reported a case of a 22 year-old male with HS who had drastic improvement in his symptoms and functional status after insertion of plastic and metallic stents for major airway obstruction. Another two patients with mucopolysaccharide storage disorders (Maroteaux–Lamy syndrome and HS) with tracheal stenosis and tracheomalacia were reported to be weaned off from prolonged ventilation after stenting of the trachea. During the subsequent 2-year follow up period, no further requirement for mechanical ventilation was reported.2 However, Karl et al. concluded that the short-term benefit of airway stenting needs to be weighed against the possible long-term stent-related complications and morbidity in patients with MPS and airway stenosis.[4]

Enzyme replacement therapy and bone marrow transplantation are two treatment options for MPS type II. Idursulfase are enzymes produced by recombinant deoxyribonucleic acid (DNA) technology for treating patients with MPS type II via catabolism of accumulated GAGs. In a double-blind, placebo-controlled trial involving 96 MPS II patients, those who were given weekly idursurface reported a 37-m increase in the 6-minute-walk distance and 160mL increase in absolute FVC compared to placebo group. Besides, patients on ERT have decreased urinary GAGs level, improved elbow mobility, reduced hepatomegaly and better quality of life.[5] However, to date, no evidence of ERT benefit on airway stenosis or tracheomalacia has been reported. Data on the effect of bone marrow transplantation in HS is limited. Reported benefits include stabilization of cardiovascular abnormalities, resolution of hepatosplenomegaly as well as improvement in joint stiffness and hearing defect.[5]

As seen in our patient, central airway obstruction can be misdiagnosed as COPD. Both conditions presented with shortness of breath and may have cough and chest tightness. The initial presenting signs and symptoms of shortness of breath, ronchi on auscultation and no audible stridor in a chronic smoker resulted in the diagnosis of COPD. Eventually, the unusual tracheal and bronchial stenosis with facial dysmophism, elevated urinary GAGs and absence of iduronate-2-sulfatase revealed the true pathology behind the symptoms. A careful evaluation of the flow volume loop from spirometry would guide us in differentiating between COPD and fixed airway obstruction. The former shows concave-shaped maximal expiratory flow-volume curve, whereas flattening of both the inspiratory and expiratory flow-volume loop is seen in the latter.

Most of the cases of HS are diagnosed during childhood. We report here a case of MPS type II diagnosed at middled age man after he presented with severe tracheal and bilateral bronchial stenosis requiring mechanical ventilation. The basis of tracheal stenting is on the intention to treat, since he was difficult to be weaned off from ventilator and tracheostomy initially. Managing MPS patients with central

airway stenosis can be challenging as it involves multidisciplinary team in handling the difficult airway, anaesthesiology risk, potential comorbidities such as obstructive sleep apnoea, cardiac valvulopathy, skeletal dysfunction and the need for genetic counselling.

CONCLUSION

This is an unusual case of severe tracheobronchial stenosis and tracheomalacia leading to the diagnosis of HS in adulthood. In addition to genetic counseling, ERT and bone marrow transplantation, tracheal stenting and tracheostomy remain the important strategies in maintaining airway patency in this rare genetic disease.

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CASE REPORT

Coinfection between SARS-CoV-2 and HIV with a low CD4+ T-cells count

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SUMMARY

Coronavirus Disease 2019 (COVID-19) is an acute respiratory infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection that started in Wuhan, China in December 2019 and has spread rapidly worldwide. It's critical to take extra precautions if a person has chronic illnesses (comorbidities), such as human immunodeficiency (HIV) infection. Concerns about people living with HIV (PLHIV) having a higher risk of serious COVID-19 disease may be based on the assumption that PLHIV are more likely to be immunocompromised. On the other hand, limited information is available in such people about the characteristics of co-infection between SARS-CoV-2 and Human Immunodeficiency Virus (HIV) who are at greater risk than the general population. Our findings, is of a 32 year old patient who came to Emergency Unit of Wangaya Hospital, Medical Faculty, Udayana University in Denpasar, Bali with complaint of fever, dry cough, and shortness of breath since prior 3 days and had also the past history prolonged fever, weight loss more than 10% 4 weeks. Diagnosis of COVID-19 was confirmed by nasopharyngeal swab sample was used for RT-PCR assay and PITC to confirm HIV infection. He had prolonged hospitalized and discharge after 18 days.

INTRODUCTION

WHO has declared that COVID-19 as a global pandemic and it became an of international concern.[1] Increasing age, hypertension, diabetes are risk factors causing worse COVID-19 outcomes. It is unclear that co-infection SARS-CoV-2 and HIV is at greater risk than in the general population.[2] COVID-19 is an acute infectious respiratory disease that is caused by a novel coronavirus. COVID-19 has a 2 to 14 day incubation period, and the principal pathways of transmission are respiratory droplets and close person-to-person contact (within 1 meter). Transmission can also happen if a person comes in contact with an infected surface or object, such as a pets.3 Fever, cough, shortness of breath, pneumonia, and other respiratory tract abnormalities are the most common symptoms. COVID-19 is diagnosed using a reverse-transcription polymerase chain reaction (RT-PCR) test from pharyngeal swabs and a chest X-ray to identify lesions.[1,2]

The concern about PLHIV having a higher risk of severe COVID-19 disease stems from the assumption that PLHIV are more likely to be immunocompromised. HIV infection causes abnormal humoral and T-cell-mediated immune responses, increasing susceptibility to a variety of opportunistic infections.[3]

PLHIV have a low CD4 cell count, advanced illness, a high viral load, or who are not on antiretroviral therapy (ART) should exercise extra caution. Many PLHIV may develop chronic conditions associated with severe COVID-19 disease as they live longer with ART.[4]

CASE REPORT

We present the case of a 32 year old male patient with COVID-19 and HIV co-infection, with longer hospitalization. He was living in Denpasar, Bali, Indonesia, came to Emergency Unit of Wangaya Hospital, Medical Faculty, Udayana University in Denpasar, Bali on November 3rd, 2020 (day 1) with complaint of fever, dry cough, and shortness of breath since prior 3 days. He had contact with a COVID-19 patient. He was fully alert, Chest X-Ray (CXR) showed bilateral infiltrates in the lungs (Figure 1). On the nasopharyngeal swab sample, RT-PCR assay was confirmed of COVID-19.

He also had a past history with prolonged fever (fever more than a month), weight loss more than 10% in 4 weeks (62 kg to 52 kg). Based on the clinical manifestation and his condition the provider initiative testing and counseling (PITC) was performed. Finally the patient was confirmed with HIV infection.

The diagnosis was SARS-CoV-2 pneumonia (COVID-19), HIV co-infection and hypoalbuminemia. The therapy was antiviral favipiravir loading dose 1,600 mg BID on day 1, followed by 600 mg BID, for 5 days (1 to 5 day) and 750 mg levofloxacin drip once daily, azithromycin 500 mg once /day orally, ascorbic acid 600 mg BID 4 and high calorie protein diet. The patient progress note is shown in Table I.

On 18-day, November 20th, 2020 (>2 weeks hospitalization), he was discharged and carried out isolation for 14 days from his community.

DISCUSSION

This patient was hospitalized with complaints of fever, dry cough, and shortness of breath for 3 days. He had contact with a COVID-19 patient. He was fully alert, Chest X-Ray (CXR) showed bilateral infiltrates in the lungs (Figure 1). On

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Table I: The progress note

Date	11. 3	11. 4	11. 9	11. 12	11. 16	11. 20
Day of admission	1	2	7	10	14	18
Fever (°C)	38.40C	38.20C	36.70C	37.30C	36.60C	36.40C
Shortness of breath	+	+	±	±	±	-
Respiratory rate (times/minute)	30	28	26	24	22	20
Blood pressure (mmHg)	110/70	110/70	110/70	110/70	115/70	115/70
Pulse rate(times/minute)	96	96	92	92	92	88
SPO2 (%)	93%	94%	94%	95%	96%	98%
WBC (10^3 /µL)	2.61			5.02	4.84	-
Neutrophil (10^3 /µL)	7.88			6.94	6.80	
Lymphocyte (10^3 /µL)	0.81			1.22	1.39	
NLR	9.73			5.68	4.89	
ALT (U/L)	29					
AST (U/L)	35					
Albumin (g/dL)	2.9				3.5	
Urea (mg/dL)	32					
Creatinine serum (mg/dL)	1.0					
Blood sugar (mg/dL)	134					
Sodium (mmol/L)	135					
Potassium (mmol/L)	4.1					
Chlorida (mmol/L)	110					
D-Dimer (ng/mL)	491.0					
CXR	Bilateral infiltrates (Pneumonia)			The alleviation of pulmonary infiltrates		
SARS-CoV-2 IgM Rapid test	Non Reactive					
SARS-CoV-2 IgG Rapid test	Non Reactive					
(Serology anti HIV)	Reactive					
RT-PCR	Positive			Positive	Negative	
CD4 T-Cell count (Cells/µL)	28					

SPO_2, Oxygen saturation; WBC, White Blood Cell; NLR, Neutrophil Lymphocyte Ratio

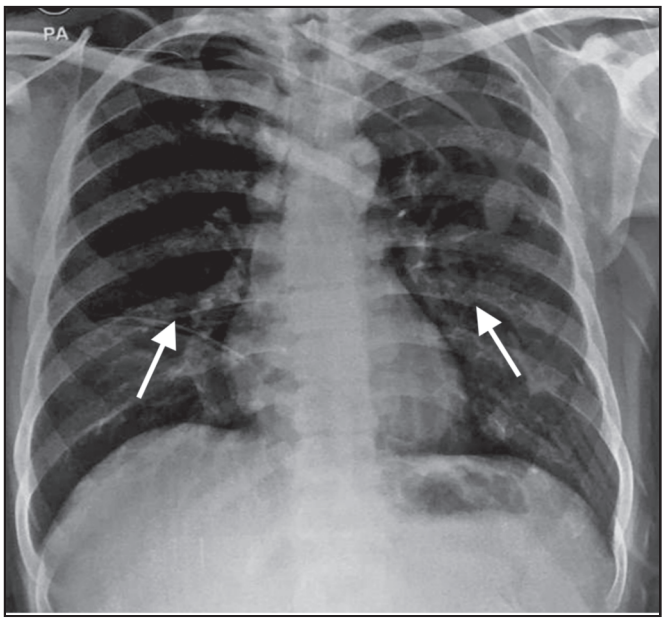

Fig. 1: Chest X-ray showed bilateral infiltrates.

the nasopharyngeal swab sample, RT-PCR assay was confirmed of COVID-19. He had the past history with prolonged fever (fever more than a month), weight loss more than 10% in 4 weeks (62 kg to 52 kg). Based on this condition the provider initiative testing and counseling (PITC) was performed. Finally the patient was confirmed with HIV infection.

COVID-19 clinical characteristic are fever, shortness of breath, dry cough, myalgia, normal / decreased leukocyte counts, radiographic evidence of pneumonia. Clinical course of COVID-19 among HIV infected patients are still unclear. An increased of COVID-19 risk, due to HIV related immunosuppression.[5,6]

In this patient, SARS-CoV-2 IgM and SARS-CoV-2 IgG were non-reactive, HIV antibody was reactive. IgM is widely known to provide the first line of defense during viral infection prior to IgG and it has been documented after SARS-CoV-2 infection. IgM antibodies can be identified in the blood after 3-6 days and IgG after 8 days.[7,8] A significant explanation for the non-reactive IgM and IgG outcomes is the disparity in individual immune responses to antibody production.[2] Co-infection Covid-19 and HIV, which HIV had destroyed the immune system and the specific antibody reactions were compromised. In patients with COVID-19, total number of NK-cells, T-cells and B-cells, significantly decreased. The SARS-CoV-2 can damage T-lymphocytes in particular, and the immune system is compromised. On the chronic phase of untreated HIV (HIV ARV naïve), immune activation and reduction of CD4 lymphocyte or low CD4 cells count occurs. The neutrophil to lymphocyte ratio (NLR) calculated by dividing absolute neutrophil count and absolute lymphocyte count, having an important value in

detecting the inflammatory status of COVID-19 patients.[6] Lymphopenia on admission in patients with COVID-19 is associated with poor outcome. A low serum albumin level can potentially lead to early recognition of severe disease.[7]

We found in this patient that the laboratory results were leukocyte (in lower levels) 2.61 x 10^3 /µL, neutrophilia (increased of neutrophil levels) 7.88 x 10^3 /µL, lymphopenia (decreased of lymphocyte levels) 0.81 x 103 /µL, increased of neutrophil to lymphocyte ratio (NLR was 9.73), and high level of blood sugar 134 mg/dL. There were no abnormalities of renal, liver function test, and electrolyte (Urea was 32 mg/dL, creatinine serum was 1.0 mg/dL, ALT was 29 U/L, AST was 35 U/L, Sodium was 135 mmol/L, Potassium was 4.1 mmol/L, Chlorida was 110 mmol/L). D-Dimer was 491.0 ng/mL. Decreased of albumin serum (hypoalbuminemia / a low albumin serum level) was 2.9 g/dL. Oxygen saturation (SpO2) was 93%. Anti SARS-CoV-2 (SARS-CoV-2 IgG was non-reactive, SARS-CoV-2 IgM was non-reactive), HIV antibody was reactive. Chest X-Ray showed bilateral infiltrates in the lungs and heart in the normal limits.

Finally, the working diagnosis was pneumonia caused by SARS-CoV-2 infection, HIV infection ARV naïve and hypoalbuminemia.

Symptomatic and antiviral medications are the primary empirical therapies immediately at the onset of symptoms, including antibiotic, nutrient supplements, and oxygen therapy.[9,10] Therapy given for this patient were for symptoms, antibiotic and antiviral drugs. Hypoalbuminemia were given albumin 20% (100 cc) 7 drops/min once daily until albumin serum was ≥ 3.5g/dl and high calorie protein diet.

CONCLUSION

Detail and chronologically clinical history exploration may be essential to be aware in the case of COVID-19 and HIV co-infection and it may relate to the prolonged hospitalization. Symptomatic, antiviral and other supportive are the primary empirical therapies should be given immediately at the symptoms onset.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

COMPETING INTERESTS

No conflict of interest.

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