BORNEO EPIDEMIOLOGY JOURNAL

VOL. 1. ISSUE 2, DECEMBER 2020

BEJ

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In affiliation with

MALAYSIAN
ASSOCIATION OF
EPIDEMIOLOGY

FACULTY OF MEDICINE AND HEALTH SCIENCES
UNIVERSITI MALAYSIA SABAH
Kota Kinabalu • Sabah • Malaysia
https://www.ums.edu.my
2020

BORNEO EPIDEMIOLOGY JOURNAL
VOL. 1. ISSUE 2, DECEMBER 2020
BEJ

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The Borneo Epidemiology Journal **(BEJ)** is a fully **open journal** for publishing rapidly growing **epidemiological studies**. This journal **publishes twice a year** under the Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah.

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BEJ, VOLUME. **1**, ISSUE **2**, DECEMBER **2020**

BORNEO EPIDEMIOLOGY JOURNAL

EDITORIAL **Open Access**

Public Health Response to Restore Polio Free Status in Malaysia

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Received: 11/12/2020
Accepted: 17/12/2020

Malaysia started the polio immunization programme since 1972 and achieved polio-free certification in 2000. After 27 years from the last reported polio case in 1992, on 8 December 2019, the Ministry of Health Malaysia announced the return of polio into the country when the first polio case detected in Sabah involving a 3-month-old male child (Abdullah, N.H., 2019). The child confirmed to be infected with vaccine-derived poliovirus type 1 (VDPV1) which later classified as a circulating vaccine-derived poliovirus type 1 (cVDPV1). Further test confirmed that the virus is genetically linked to poliovirus (PHL-NCR-2) circulating in the southern Philippines (Alleman, M.M. *et al.,* 2020). To date, a total of four polio cases were confirmed in Sabah of which due to vaccine-derived poliovirus type 1 (VDPV1). The vaccine-derived poliovirus type 2 (VDPV2) was also detected from environmental samples taken from various locations in Sabah.

In the neighboring countries, the Philippines and Indonesia also reported resurgence of polio after more than a decade free from the virus. Indonesia declared polio outbreak in February 2019 followed by the Philippines in September in the same year. Indonesia affected by the circulating vaccine-derived poliovirus type 1 and the Philippines affected by both circulating vaccine-derived poliovirus type 1 (cVDPV1) and circulating vaccine-derived poliovirus type 2 (cVDPV2) (Alleman, M.M. *et al.,* 2020). To date a total of 15 cases have been reported in the Philippines.

In response to the polio outbreak, Malaysia embarked on an aggressive immunization drive to prevent the virus from spreading further. Similar move was also carried out in Philippines and Indonesia. Malaysia received a good support from the World Health Organization (WHO) and United Nations Children’s Emergency Fund (UNICEF) in responding to this outbreak by ensuring all children under 13 years in Sabah receive the full doses of polio vaccine.

With the supply of 2.5 million doses of monovalent oral polio vaccine type 2 (mOPV2) received from WHO and additional allocation from the Government of Malaysia for bivalent oral polio vaccine type 1 and 3 (bOPV), aggressive immunization campaign was conducted since December 2019 to children aged 13 and below across Sabah.

It is a known fact that the only effective way to eradicate polio is by protecting the children from polio through vaccination. The occurrence of polio cases in Sabah indicates that the population is under-immunized. About one-third of Sabah population is immigrant and it is a well-known fact that large number of them is illegal thus has lower immunization coverage. Therefore, the priority is to stop the polio transmission by making sure that every child, regardless of their economic and nationality status to have access to polio immunization. All children aged 13 years old and below should receive two doses of mOPV2 and two doses of bOPV, even those who have received inactivated polio vaccine (IPV) according to the national immunization schedule. This immunization drive will only be considered successful if the immunization coverage achieves at least 95% on all children under the age of 13 years old for both mOPV2 and bOPV.

To ensure the smooth implementation of the immunization campaign, cooperation and collaboration between various agencies including the non-governmental organizations are crucial. During the campaign, the Ministry of Health Malaysia urges parents, childcare centers, kindergartens and school authorities to help ensure that the children receive both vaccines. The Sabah State Health Department together with various government agencies and non-governmental organizations had work hand in hand to ensure the success of the campaign. The vaccination campaigns were conducted by mobile teams and also at government clinics, community halls, business centers, religious sites, and more including drive-thru services in strategic locations.

In addition to aggressive immunization campaign, equally important in public health response to this outbreak are intensified polio case finding activities, conducting a comprehensive field investigation which include a thorough risk assessment in order to properly plan an effective outbreak response. The acute flaccid paralysis (AFP) surveillance need to be strengthened by conducting retrospective and active searches for additional AFP cases at all health facilities across districts in Sabah.

The immunization campaign started well in early part of year 2020 until the COVID-19 pandemic hit Malaysia. The first COVID-19 case was reported in Malaysia on 25 January 2020 and since then the cases continued to increase which prompt the Government of Malaysia to declare the movement control order (MCO) on 16 March 2020. The MCO interrupt badly the polio immunization drive. The campaign was only revived during the Recovery Movement Control Order (RMCO) that started in June 2020. With the COVID-19 cases recent surge in October 2020, the polio vaccination activities were halted again in many areas in Sabah. Despite all these obstacles, the immunization coverage as of 19 October 2020 was 95.6% children received two doses of bOPV and 80.6% for mOPV2 (Abdullah, N.H. 2020). As soon as the COVID-19 situation improve, vaccination activities for mOPV2 need to be continued until the target achieved for Malaysia to reclaims its polio-free status.

The vaccine policy change in Malaysia from oral polio vaccine (OPV) to inactivated polio vaccine (IPV) was approved in 2008. The policy change is aimed to minimise the risk of outbreaks of vaccine-derived polioviruses. However, whenever there is an outbreak of vaccine-derived polioviruses, oral polio vaccine (OPV) which contains Sabin strain types 1, 2 and 3 continue to be used in response to the outbreak. To maintain the global eradication of wild poliovirus as well as VDPV will not be achieved if we continue to use the Sabin strain OPV in outbreak response. Thus, new oral polio vaccines which are more stable genetically are needed. There are two novel OPV2 candidates currently under trial with promising result (Van, D.P. *et al.,* 2020). The world is looking forward for better oral polio vaccines that will not result in VDPV emergence.

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BEJ, VOLUME. **1**, ISSUE **2**, DECEMBER **2020**

BORNEO EPIDEMIOLOGY JOURNAL | BEJ

REVIEW ARTICLE **Open Access**

COVID-19 Pandemic - A Review and Assessing Higher Education Institution Undergraduate Student's Mental Health

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Abstract

Introduction: The current COVID-19 pandemic has sequelae reverberating around Malaysia, particularly in university students, as Malaysian university students are isolated in their university campuses in semi-quarantine status. This article seeks to review the existing literature on the specialized issue of university student-related psychological sequelae of COVID-19, and seeks to offer some recommendations through the process.

Methods: Existing literature demonstrates that COVID-19 has affected university students psychosocially, with the rate of anxiety and depression markedly increased. There have been significant alterations of lifestyle related to education, in accordance with the new normal, resulting in isolation and feelings of disengagement with education. Moreover, with the current uncertainties regarding their studies and possible financial depression post-pandemic, the future is deeply worrying and will adversely affect their mental health.

Results: Quantitatively, recent findings indicate 33.3% of the undergraduates in a higher education institution are noted to be in stress. Therefore, multiple interventions have been implemented; a customized ultra-brief psychological module, an online tele psychiatry hotline (COVID Cares) and tele-counselling, which have received universally positive feedback.

Conclusion: In conclusion, the review demonstrates that undergraduates' psychological health is an aspect that needs urgent attention as it is not merely limited to the fear of COVID-19, but also related to the social aspects of the pandemic. Multiple interventions have been seen to be efficacious in reducing the psychological sequelae.

Keywords: Undergraduate; Mental health; COVID-19; Education

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Received: 12/05/2020

Accepted: 25/11/2020

Introduction

Numerous articles have been written about the impact of the current COVID-19 pandemic on the mental health and wellbeing of the general population and front-line staff working in health care settings (Greenberg, N., *et. al.,* 2020; Kang, L., *et. al.,* 2020). However, little has been specifically focused on the impact of this crisis on undergraduate students trying to negotiate a whole new way of learning, the lack of social contact with peers and teachers, and managing to maintain their studies while potentially living in less than ideal situations. Hence, this is an especially vital aspect to explore, as the age of prevalence of mental health issues is predominantly in the early twenties, namely the same age as undergraduates.

While coronavirus disease 2019 (COVID-19) continues to spread around the world, many countries have decided to close educational institution as part of a policy to slow transmission and ease the burden on health systems (Van, L.W. *et. al.,* 2020). Up until 9th May 2020, The UN Educational, Scientific and Cultural Organization (UNESCO) estimates that 177 countries have closed schools and universities nationwide, and several other countries have implemented regional or local closures (UNESCO-IIEP, 2020). The situation in Malaysia is a peculiar one, in which many students are isolated in on campus accommodation and restricted to movements only within the university compound. This can cause a lot of behavioural consequences, including stigma, anxiety, and self-stigma (Koh, E.B.Y. *et. al.,* 2020).

Methodology

This paper was structured as a perspective from the authors, rather than aiming to be an overarching attempt to perform a systematic review of the existing literature. Papers that were related to the current situation and the impact on the mental health and wellbeing of undergraduate university students were reviewed and the various viewpoints synthesised in a perspective article. A literature search was performed in Google Scholar, Embase and PsychINFO to highlight papers that were focused on the effects of COVID-19 in undergraduate university students. The panel of authors then chose certain papers that were more relevant to the perspective of undergraduate students, be it from an aetiology, psychopathology, or intervention point of view. As this was not an original paper or a meta-analysis, statistical tests were not performed as part of the methodology of the paper, and there are no original results to report in this paper. Due to the paucity of literature focusing on undergraduate students in COVID-19 and the time pressures, the grey literature or postgraduate theses were unable to be searched, as the pandemic has only been present for an insufficient duration to allow a Master’s thesis to have been completed.

Results

Psychosocial Impact on Undergraduate Students

There is ongoing uncertainty about how long the coronavirus crisis will last and how it affects the short and long-term mental health of students and staff across the world's educational institutions. The psychological impact is markedly significant, with increasing anxiety and uncertainty, increased stress, and fear and sadness about the future. Current research strongly suggests that rates of anxiety and depression with increase dramatically, exacerbated by uncertainties and the intensive media focus on this pandemic above any other story (Zhai Y *et. al.,* 2020). The significant shortage of face masks and hand sanitizers does not help either (Ayittey, F.K. *et. al.,* 2020). There is likely to be ongoing negative physiological consequences of chronic and ongoing stress. For instance, loneliness, which has increased under the COVID-19 circumstances, appears to have a major negative impact on motivation and engagement with education and, as a result, increasing psychological distress and suffering in staff as well as students (Shoichet, C.E. 2020).

To put things in perspective, university students must confront a variety of unique and difficult challenges throughout and after this COVID-19 outbreak. The pandemic appears to be escalating and changing on a daily basis and so does the consequential challenge that it posed. Public health emergencies, such in this pandemic, generate fear and confusion and can lead to a wide range of psychological consequences, ranging from distress responses such as anxiety, depression, and substance abuse, to behavioural changes such as difficulty sleeping and stress over- or under-eating. (Zhai Y *et. al.,* 2020; Liu, N., 2020) Emotional regulations may also be impaired with increasing experiences of anger and rage for some people. Before this COVID-19 pandemic began, it had been reported that one in five university students worldwide had experienced one or more diagnosable mental disorders (Auerbach, R.P. *et. al.,* 2016). As we progress through these unprecedented times, the psychological impact of COVID-19 has the potential to dramatically increase this number and exacerbate mental health issues in students (Araújo, F.J.D.O. *et. al.,* 2020).

As the number of positive cases and deaths steadily increasing all around the globe, it is understandable that students are psychologically affected too. Questions and worries arose; whether there are positive cases around their vicinity, whether they are safe in their current location, and whether they or their family are exposed to risk of contracting the infection (Cao, W. *et. al.,* 2020). The dilemma is worse in those who have to be under quarantine, with the prospect of being infected being a very distressing thought for those involved. A study in 2004 of 129 Toronto residents who were under quarantine during the 2003 SARS epidemic found that 28.9% reported symptoms of post-traumatic stress disorder (PTSD) while 31.2% reported symptoms of depression (Robertson, E., *et. al.,* 2004). It has been noted that longer durations of quarantine is associated with an increased prevalence of PTSD symptoms. For many people who may live alone, or have had to return to the family home to stay with family, the isolation from friends and peers can be incredibly challenging.

Lifestyle Changes and the "New Normal"

As countries close educational institutions and restrict public movement, change in lifestyle is a certainty. The educational scene has changed too; with industrial training, clinical placements and rotations suspended for an unknown duration, students are left unsure of the future of their life and their studies (Mian, A. *et. al.,* 2020; Liang, Z.C. *et. al.,* 2020; Fuhat, N.S.A.M. *et. al.,* 2020). For some students, the following of a strict schedule with timelines and deadlines, is what gives them motivation, purpose and drive, enabling them to focus on the tasks that need to get done and having a schedule rather than spending time alone with their internal psychological struggles. The sudden disruption of the daily life routine may result in increase in anxiety (Tang, B. *et. al.,* 2020).

The distinct problem with social distancing and its correlation to mental health is the uncertain timeframe of when this might be all be over. Even if the university eventually opens, the 'new normal' would dictate smaller class gatherings, with social distancing applied on every circumstance. Lectures will be mostly online if possible, or face-to-face lectures or sessions are indicated, they will be done with minimal number of individuals and shorter durations. Large group discussions or numerous extra-curricular activities would not be encouraged. The graduation ceremony might even be less ceremonious, with likely less numbers of attendees allowed - or worst, postponed or cancelled (Lee, J. 2020; Abigail, J.H. 2020). Planning, or for some even thinking about, the future can cause higher experiences of fear and anxiety. The uncertainty of how the world will be post COVID-19 also adds to the sense of insecurity.

Graduation and Employment Issues

Looking to the future, the senior students of the university who are supposed to be graduating this year or next year would be worried that they would have to wait longer for their grand finale. This brings about cascades of implications, which may include economic stressors. Although an extension of the scholarship for eligible students may seems likely at sponsor's discretion, those who had to take study loans might not be so lucky. The loan made, mostly under Perbadanan Tabung Pendidikan Tabung Nasional (PTPTN) in Malaysian settings, would still have to be paid. With uncertainty clouding the future of their study, the delay in graduating will end up affecting their employment plans, which will eventually disrupt their capability to pay their dues. With this in mind, the Malaysian government has intervened and introduced a moratorium of PTPTN loans for 6 months (Kenneth, T. 2020). Nevertheless, the interest or the administrative charges of the loan will continue to pile up, making it harder for them to settle it, thus it is not all rosy for the students.

Having said that, the most unfortunate of all would be those who have had to rely on their parents for tuition fee and allowance? Because of the outbreak, some families would have lost their source of income, and the extension of the study would mean more money needed for the fees and the allowance.

Few universities have taken the liberty to waive the tuition fee or give discounts for the next semester, but the allowances would still be managed by the families. This will cause further distress to the students and their families (Cao, W. et. al., 2020; Peng, L., *et. al.,* 2020). From a wider perspective, the financial difficulties would affect the mental health, and subsequently poor mental health will exacerbate financial difficulty; a vicious cycle that needs attention from all stakeholders (Richardson, T. *et. al.,* 2020).

Additionally, another implication that might be overlooked is the effect of delayed study completion on mental health itself. Although deterioration of mental health is well known to contribute to educational setback, it appears that delays in study completion also adversely affect mental health, specifically anxiety and depressive symptoms (Melkevik, O. *et. al.,* 2020; Grøtan, K., *et. al.,* 2020). Many students as well as their families have tentative life plans like when to graduate, when to start work, when to go for further studies, and many more (Cao, W. *et. al.,* 2020). In view of this, disruption of these life plan, albeit unavoidable for the greater good in this case, may unfortunately precipitate anxiety or depression among those involved. On top of that, there will be severe disruptions of the prospect of employment in view of the impending global recession caused by the COVID-19 crisis. This will no doubt compound the anxiety and stress undergraduates are currently having (Sahu, P., 2020). In turn, this might lead to a ‘domino effect’, impairing academic performances or worse still, quitting studies altogether.

Interventions for Mental Health of Undergraduates

With all this recognized, it is imperative that the mental health of undergraduates at is be taken care of. This is in view of a study demonstrating 33.3% prevalence of stress in a similar undergraduate population in 2017, 3 years prior to the pandemic, and it would stand to reason that the levels of stress would have been elevated due to the additive effects of the pandemic (Musiun, A., *et. al.,* 2019). An ultra-brief psychological mindedness module, combining various therapeutic modalities like cognitive behavior threapy, mindfulness-based therapies, and motivational interviewing techniques, was designed and adapted for COVID-19 purposes to deal with undergraduate mental health (Pang, N.T.P. *et. al.,* 2020). An online system called COVIDCares was established in order to take referrals. This system incorporated peer support workers, using undergraduates to tend to each other’s mental health, as it was felt that peers would understand the unique psychosocial matrix of issues better than non-peers. Qualitative feedback suggests that both first responders and users of the system were generally satisfied by the network.

Also, a wide-ranging mental health network was set up through the system, with tele-counselling offered to university students via a wide network of counsellors, clinical psychologists, psychiatrists, and psychiatry medical officers. This network had been started even at the alert phase of the pandemic (Mukhsam, M.H., *et. al.,* 2020). This allowed the catchment area to be much wider than merely passive case referrals.

A large-scale Depression, Anxiety and Stress survey was also performed, with students being responded to where indicated, as there needs to be a high index of suspicion of possible psychopathology (Salvaraji, L. et. al., 2020). This was also correlated with the evidence available, as a preliminary validation of the Fear of COVID-19 scale into Bahasa Malaysia in the same university student population suggested that fear of COVID-19 was related to all three constructs - depression, anxiety and stress (Pang, N.T., et. al., 2020).

Conclusion

Undergraduates face a multitude of challenges both from a mental health symptoms point of view, and due to the many psychological and social factors that contribute to uncertainty. This includes current quarantine prospects, future employment uncertainties, and the effect on delayed study completion. New norms have been adopted in inpatient and outpatient psychiatric settings (Sze, C.L., 2020), and it is instrumental that we focus on implementing similarly efficacious new norms in university settings. Multiple interventions have been performed to ensure that there is a wide-ranging mental health network covering as many students as possible through active case finding rather than passive case referrals, which is essential as interventions increase psychological mindedness and consequently reduce depressive symptoms (Pang, N.T.P. *et. al.*, 2020). This hopefully will increase the levels of psychological wellness in vulnerable undergraduates.

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BEJ, VOLUME. **1**, ISSUE **2**, DECEMBER **2020**

BORNEO EPIDEMIOLOGY JOURNAL | BEJ

REVIEW ARTICLE **Open Access**

Host and Environmental Factors that Influence Plasmodium Knowlesi Malaria Infection in Humans: A Systematic Review

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Abstract

Introduction: *Plasmodium knowlesi* (*P.knowlesi*) is a zoonotic malaria parasite, transmitted between non-human primate hosts by the Anopheles (An.) mosquitos, and causing spill-over infections in humans where the parasite, vector, host, and human converge.

Methods: The search was done electronically to explore for appropriate papers *via* PubMed, and Science Direct for articles published up to March 2020, containing the words "factors associated" or "environmental factors" or "individual factors" or "ecological factors" and "*P.knowlesi*" and "human" including synonyms and Medical Subject Heading (MeSH) terms. A total of 27 articles from PubMed Databases and 18 articles from Science Direct were selected to be assessed for eligibility. Out of it, a total of 13 articles were selected to be analysed.

Results: Host factors such as sex and age, as well as occupation as individual factors, while environmental factors such as rainfall and geographic elevation have some association with *P.knowlesi* infection in humans. This zoonotic malaria poses unique challenges that will need to be addressed if all forms of malaria are to be eliminated based on the sustainable development goal (SDG).

Conclusion: This article highlights the importance of disease ecologies such as climate and landscape and human-environment interactions such as the land use patterns, such as agriculture or infrastructure activities) to reduce the further increase of cases and mortality globally due to *P.knowlesi* infection. This review focuses mainly on the host and environmental factors that influence *P.knowlesi* Malaria Infection in Humans.

Keywords: *Plasmodium knowlesi*, Zoonotic malaria, Malaria elimination, Human-environment interaction, Systematic review

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Received: 02/08/2020
Accepted: 25/11/2020

Introduction

World Health Organization (WHO) Malaria Report 2019 reports that 228 million cases of malaria occurred worldwide in 2018 compared with 251 million cases in 2010 and 231 million cases in 2017. The WHO African Region still bears the largest burden of malaria morbidity, with 213 million cases (93%) in 2018, followed by the WHO South-East Asia Region (3.4%) and the WHO Eastern Mediterranean Region (WHO, Malaria, 2020). Plasmodium knowlesi (*P.knowlesi*) is a zoonotic malaria parasite, transmitted between non-human primate hosts by the Anopheles (An.) mosquitos, and causing spill-over infections in humans where the parasite, vector, host and human converge (Abeyasinghe R. 2016). *P.knowlesi* was first isolated from a macaque imported into India from Singapore. *P.knowlesi* is now recognized as the fifth species of Plasmodium causing malaria in humans (Preis, J. *et. al.,* 2014).

P.knowlesi has a case fatality rate of around 1.7 per 1000 cases (6 deaths in total) (Rajahram, G.S. *et. al.,* 2019). *P.Knowlesi* has been reported to have at least 3-fold greater risk of severity than *P.falciparum* (Barber, B.E. *et. al.,* 2013). *P.knowlesi* acquisition risk factors related to behaviour or environment currently remain poorly defined (Grigg, M.J., *et. al.*, 2014). Therefore, it is important to understand the factors that contribute to the spillover of this zoonotic malaria to human to take the necessary measures to reduce the transmission among humans. Development of appropriate, practical and effective public health measures to control or prevent vector-borne diseases usually requires the assessment of all components and their interactions, and much remains to be elucidated, in particular the complex biological and ecological relationships that exist among pathogens, vectors, hosts and their environments (Carneiro, T.C., *et. al.*, 2017).

The vector that carried *P.knowlesi* is the *Anopheles spp*., such as the *An. leucosphyrus, An.latens,* An.*balabaensis* and *An.cracens* (Abeyasinghe R. 2016). The intermediate reservoir for *P.knowlesi* is the Long-tailed macaque (*M.fascicularis*), Pig-tailed macaque (*M.nemestrina*) and Banded leaf monkey (*P.melalophus*). Humans can be infected by *P.knowlesi* if they are fed upon by an infected mosquito (Preis, J. *et. al.,* 2014). A variety of factors intrinsic to the host, sometimes called risk factors, can influence an individual's exposure, susceptibility, or response to be infected by *P.knowlesi*. Susceptibility and response to the infection are influenced by individual factors such as genetic composition, nutritional and immunologic status, presence of medications, and psychological factors (CDC: USDHHS, Section 2, 2012). Environment refers to extrinsic factors that affect the agent and the opportunity for exposure. Environmental factors include physical factors such as geology and climate, biologic factors such as insects that transmit the agent, and socioeconomic factors like crowding, sanitation, and availability of health services (CDC: USDHHS, Section 8, 2012).

By systematically integrating these evidentiary sources, this article highlights the importance of disease ecology (e.g., climate & landscape) and human-environment interactions (e.g., land use patterns, such as agriculture or infrastructure activities) to reduce the further increase of cases and mortality globally due to *P.knowlesi* infection in accordance to the Sustainable Developmental Goal (SDG).

Goal 3 Target 3.3 of the SDG aims to "end the epidemics of AIDS, tuberculosis, malaria & neglected tropical diseases" by the year 2030 (WHO, 2019). This review focuses mainly on the host and environmental factors that influence *P.knowlesi* Malaria Infection in Humans. It is important to know these factors so that necessary prevention measures can be taken as well as in the education of the community on the risk factors of *P.Knowlesi* infection.

Methods

Various study designs were included but most of the study was expected to be observational designs. Papers that are published in all languages and dates from all over the globe were reviewed. Exclusion includes all non-primary literature, such as dissertations, theses, protocol studies and clinical guidelines. The search was done electronically to explore for appropriate papers *via* PubMed, and Science Direct for articles published any period of time up to March 2020, containing the words "factors associated" or "environmental factors" or "individual factors" or "ecological factors" and "*P.knowlesi*" and "human" including synonyms and Medical Subject Heading (MeSH) terms.

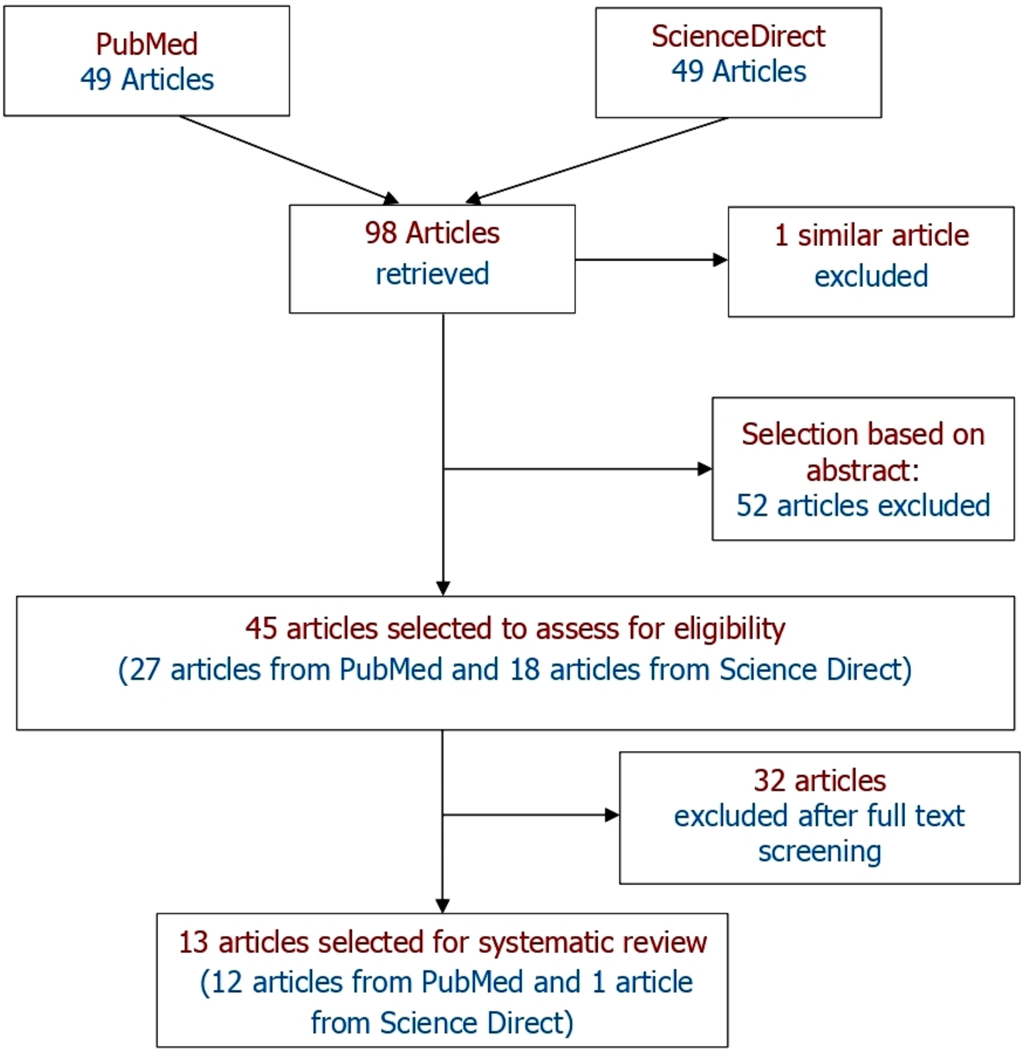

Figure 1: Summary of the article selection

Relevant references cited within these articles were also reviewed. Records that matched the inclusion criteria were selected and those that matched the exclusion criteria were excluded. The selected studies were screened by titles and abstracts by two reviewers. All data reviewed were presented in text and summary tables. Both databases gave 49 results upon the word search. Book chapters were excluded from the search. After removing the similar articles, 97 articles were screened through by reading the abstract. A total of 27 articles from PubMed Databases and 18 articles from Science Direct were selected to be analyzed but only 13 articles were finally selected for this review (**Figure 1 & Table 1**).

Results

Host factors

There are many individual factors that were found to be associated with *P.knowlesi* infection in humans. It can be divided into biological factors such as age and sex, medical history, genetic factors such as genetic diseases, occupation and behavioral factors. One of the articles found that age 15 years or older have 4 times higher odds to acquire *P.knowlesi* infection compared to the control (Grigg, M.J., *et. al.*, 2014). This is also supported by Herdiana et all, whereby *P.knowlesi* cases are reported more among the adults (Herdiana, H. *et. al.,* 2016). Even asymptomatic cases that were detected by serology test, showed that seroprevalence of *P.Knowlesi* positivity was higher among those 15 years old and above (Fornace, K.M. *et. al.,* 2018). Age also has been reported to be strongly correlated with the risk of severe *P.knowlesi* infection with 56% of those with severe *P.knowlesi* infection are those more than 60 years old (Barber *et al., 2*017). A retrospective review of malaria cases in Sabah showed that the overall median age of the patient with *P.knowlesi* was significantly higher than of patients infected with *P.vivax* and *P.falciparum* (William, T., *et al., 2*013). A seroprevalence study that was conducted in four districts in Sabah, Malaysia showed that every increase of years by 10 would increase the odds of getting *P.knowlesi* by 33 % (Fornace, K.M., *et al.,* 2019). Male has a higher risk to acquire *P.knowlesi* infection with around 80- 90% of the proportion in each of the study population (Herdiana, H. *et. al.,* 2016; Fornace, K.M. *et. al.,* 2018; Grigg, M.J., *et. al.,* 2017; Goh, X.T. *et. al.,* 2013).

Occupation of being plantation workers and farming also shows an increased risk of acquiring *P.knowlesi* (Grigg, M.J., *et. al.,* 2017). Those working forest related has a higher percentage of cases of P.knowlesi cases (55%) compared to other jobs (Herdiana, H. *et. al.,* 2016). A seroprevalence study showed that a farm or plantation worker was positively associated with *P. knowlesi* seropositivity (Fornace, K.M. *et. al.,* 2018). Behavioral or habits like sleeping outside is an independent risk factor in acquiring *P.knowlesi* infection (Grigg, M.J., *et. al.,* 2017). Having open eaves and gaps in the wall of the house is known to have two times higher odds of getting *P.Knowlesi* infection (Grigg, M.J., *et. al.,* 2017). History of interactions with monkeys can be a factor to get *P.Knowlesi* infection (Barber, B.E. *et. al.,* 2013; Grigg, M.J., *et. al.,* 2017). A study showed a visit to the forest a month before the infection for any reason has found out to be the potential risk factor in acquiring *P.knowlesi* (Herdiana, H. *et. al.,* 2016). The cases in Kudat, Sabah was found to be in two family clusters.

They have not travelled into forested areas but the family has reported seeing macaques close to their homes (Barber, B.E. *et. al.,* 2013). Travelers who have visited the forest in the endemic country has been reported to carry this disease to their country of origin (Cramer, J.P., 2015). There is less chance of human to human transmission occurring with *P.knowlesi*. A study in Sandakan, Sabah (Goh, X.T. *et. al.,* 2013). *P.knowlesi* cases in Kudat, Sabah from 2009-2011 also showed a wide range of distribution among all age group with the youngest being 8 months old (Barber, B.E. *et. al.,* 2013). The wide age distribution and family clustering could be because the *P.knowlesi* vector might be biting humans close to or inside their' houses or there may be a potential human-to human transmission (Barber, B.E. *et. al.,* 2013). *P.knowlesi* has found out to be the common cause of malaria in adults and children in Kudat, Sabah (Barber, B.E. *et. al.,* 2011).

Bridget et all study showed that among the cases of *P.knowlesi* in Sabah from 2010-2011, the cases had a higher percentage of the previous history of infection with Malaria (5) compared to other *Plasmodium spp* infection. The cases also have higher cases with chronic diseases (Barber, B.E. *et. al.,* 2013). Those with G6PD deficiency seemed to have protective against *P.knowlesi* infection (Grigg, M.J., *et. al.,* 2017). Those with Duffy Blood Group also has been said to have resistance again *P.knowlesi* infection (Mason, S.J. *et. al.,* 1977)**.**

Environmental factors

One of the driving factors of transmission of *P.knowlesi* to humans is due to ecological changes. Clearing vegetation has been shown to be associated with *P.knowlesi* infection (Fornace, K.M. *et. al.,* 2018; Grigg, M.J., *et. al.,* 2017). This suggests that ecological changes affect the human-vegetation interface. Land use and deforestation results in changes in ecological habitat affect the vector bionomics that favors increased blood feeding on humans (Grigg, M.J., *et. al.,* 2017). The higher historical forest was associated with a greater incidence of *P.knowlesi* infection (Fornace, K.M. *et. al.,* 2016). In another study conducted on seroprevalence in Sabah and Palawan showed that clearing areas within 500m of the house were associated with increased odds of *P.knowlesi* positivity (Fornace, K.M. *et. al.,* 2018).

P.knowlesi infection is seen in people living in rural forested and agricultural areas (Grigg, M.J., *et. al.,* 2017). Risk assessment has found as one who has a workplace near or in the forest has 7 times higher risk of infecting with malaria especially *P.knowlesi* (Herdiana, H. *et. al.,* 2016). A study on *P.knowlesi* risk map of cases using satellite imaging of Land-use and Land-cover (LULC) information showed a correlation (Sato, S. *et. al.,* 2019). The risk map showed that *P.knowlesi* cases in each village were affected by the LULC surrounding the village (Sato, S. *et. al.,* 2019). *P.knowlesi* seroprevalence was found to be higher in those living in low forest cover (Sato, S. *et. al.,* 2019). Besides that, seasonal variation has also shown as a significant factor for *P.knowlesi* infection, whereby maximum notification of cases occurs in June (William, T., *et al.,* 2013). The study in Kudat, Sabah showed that in 2009 the cases increased from March to July which in in 2009 it was from April to August. But in both years the number of reported cases peaked in May (Barber, B.E. *et. al.,* 2012). This same study showed that rainfall was strongly correlated with the number of *P.knowlesi* cases. The number of cases increased during the fifth month following the rainfall (Barber, B.E. *et. al.,* 2012).

Table 1: Summary of the findings

S.No.	Author	Year	Location	Study Design	Sample Size	Population	Individual factor	Environmental factor	Protective factor
1.	Grigg et al.	2017	Sabah	Case control	229	Malaysians	Adult, male, farmer, and palm oil plantation worker, sleeping outside,	living in rural forested and agricultural areas, Having open eaves and gaps in the wall of the house, history of Clearing vegetation	G6PD Deficiency, presence of young sparse forest and rice paddy around the house
2.	Herdiana et al	2016	Indonesia	Cross sectional	20	Indonesians	Adult, male, forest related job, visit the forest, Overnight staying in a forest	living in the rural forested area	-
3.	Fornace et al	2016	Kudat, Kota Marudu	Ecological study	329	Malaysians	-	Deforestation	-
4.	Fornace et al	2018	Kudat, Pulau Banggi, Palawan	Cross sectional	4	Malaysians, Philippians	Adult, male, farm or plantation worker	Land clearing, deforestation	-
5.	Barber et al	2017	Sabah	Cross sectional	146	Malaysians	Older adult	-	-
6.	Cramer	2015	USA (2), Taiwan, Sweden, Finland, Spain, Netherlands (2), Australia, New Zealand, France, Japan, Scotland, Germany (2)	Ecological study	15	International travellers	Travelling to the forest in an endemic country	-	2-

Continued…

S.No.	Author	Year	Location	Study Design	Sample Size	Population	Individual factor	Environmental factor	Protective factor
7.	Barber et al	2013	Sabah	Cross sectional	130	Malaysians	Previous history of malaria infection, history of chronic disease, history of seeing a monkey	-	-
8.	Sato et al	2019	Kudat	Cross sectional	107	Malaysians	-	Land clearing	-
9.	Xiang et al	2013	Sandakan	Cross sectional	42	Malaysians	A wide distribution of P.knowlesi in all age group$	-	-
10.	William et al	2013	Sabah	Cross sectional	Positive cases of P.Malariae/ P.knowlesi in Sabah#	Malaysians	-	Seasonal variation (in June)	-
11.	Barber et al	2012	Kudat	Cross sectional	339	Malaysians	A wide distribution of P.knowlesi in all age group*	Seasonal variation and rainfall	-
12.	Steven et al	1977	USA	Case study	3	Blacks, 2 Cree Indians and a white Australian	-	-	Duffy blood group individual
13.	Fornace et al	2019	Kudat, Kota Marudu, Pitas, Ranau	Cross sectional-seropreval	515	Malaysians	Age, sex, travel to forest areas, contact with macaque	Low forest cover	living in higher geographical elevation

#: from1992-2011 and total cases not mentioned in the article; *: Human-human transmission; $: presence of gametocyte in microscopic findings.

Meanwhile, *P.knowlesi* infections were found to be lower among those individuals residing at higher geographical elevations and individuals residing in houses less than 1 m from the ground (Fornace, K.M. *et. al.,* 2019). The presence of young sparse forest and rice paddy around the house has been associated with a decreased risk of acquiring *P.knowlesi* (Grigg, M.J., *et. al.,* 2017).

Discussion

The systematic review of 14 studies identified factors that are associated with *P.knowlesi* infection, and these factors were divided into host factors and environmental factors. These studies show that among other factors identified in the smaller, individual studies, these studies collectively identify age, sex, and occupation is host factors in the transmission of *P.knowlesi*. The environmental factors identified from these studies include seasonal variations as well as rainfall, while protective factors include geographical elevation.

The review noted that males, and especially older males, tend to have higher rates of *P.knowlesi* infections which could be explained by the demographic characteristics of the persons who tend to be more exposed to Anopheles spp. They tend to be those consistent with forest or plantation occupation, since men, especially older men, tend to be those that were more likely to have direct exposure to *P.knowlesi* vector. Besides this occupation, forest hunters, logging camp workers, jungle trekkers, military personnel on jungle training and veterinarians involved in research/ other activity also have the risk to get *P.knowlesi* infection (Roughton, S.A. *et. al.,* 2012). *P.knowlesi* has a more severe effect on the older population, since the severity of infection is related to the level of parasitaemia, increased inflammation, endothelial activation and microvascular function due to age-related changes in the ability to respond to the *P.knowlesi* parasite (Barber, B.E. *et. al.,* 2017).

These men would also be the ones who would have greater forest-related occupations such as the timber industries or oil palm plantation workers and would be more likely to live near forests instead of women and children (Grigg, M.J., *et. al.,* 2017). In addition, these occupations would have longer hours of work outdoors, leading to greater exposure to *P.knowlesi* vectors and their known peak outdoor feeding times between 6pm and 7 pm (Goh, X.T. *et. al.,* 2013). This increased duration outdoors is also important since *P.knowlesi* vectors as members of the *Leucophyrus anopheline* mosquito group would rest and feed outdoors, especially after dark (Abeyasinghe R. 2016).

Although forest occupations are a significant factor in *P.knowlesi* infections, those involved in agricultural occupations, such as farmers and palm oil plantation workers, would also have increasing exposure to *P.knowlesi* vectors since these occupations would be entering the forest and involved in extensive deforestation in order to produce arable agricultural land (Goh, X.T. *et. al.,* 2013). These encroachments to clear forest areas for agricultural activities would blend the distinction between forest, clearing, and habitation by creating irregular and fragmented edges between forest areas and cleared areas, reducing the distinction as well as the distance between the areas as noted in the Land-Use and Land-Clearing maps in areas of Sabah, Malaysia especially oil palm plantations close to the dense forest (Sato, S. *et. al.,* 2019).

This ragged patchwork of clearings with forest areas may increase the interaction of human, mosquito, and macaque populations between the two areas, creating a greater risk for infection especially when the distances between the edges are reduced and the distinction between the areas blurred and clearings around human habitation within 5KM of forest are associated with increased *P.knowlesi* infection (Fornace, K.M. *et. al.,* 2018). The importance of the increased human movement into these partially cleared areas would also increase exposure to the *P.knowlesi* reservoir or macaques, since macaques can be found close to human habitation. Macaques have been found to be highly adaptive and can be found close to human habitation.

In addition, *An.balabacensis* is known to exhibit "learning behaviour" with regards to host preferability as well as "habitat loyalty", returning to previous feeding sites. This may even take place after deforestation since *An.balabacensis* is a highly efficient vector, maintaining high levels of malaria in low population areas, and is related to *An.dirus*, a Mekong vector that is capable of adapting to deforestation (Barber, B.E. *et. al.,* 2012). Despite the efficiency of the vector, there is still little evidence of human-to-human transmission even though the development of gametocytes in humans for *P.knowlesi* has been confirmed since 2009. However, since more gametocytes are noted in microscopy of *P.falciparum* and *P.vivax* compared to *P.knowlesi*, one may infer that humans are getting infected by mosquitos that fed on macaques instead of feeding on humans (Goh, X.T. *et. al.,* 2013).

Cases of *P.knowlesi* malaria increase periodically with peaks around July and June every year (Barber, B.E. *et. al.,* 2013). This corresponds with the start of the rainy season in may since that is that is the period when the new rice planting season begins. *An.balabacensis* is known to breed in ground pools and areas of stagnant water in areas of clearing, such as oil plantations, rubber plantations, and fruit orchards. Even animal footprints can become a breeding area for these mosquitoes (Abeyasinghe R. 2016). *Anopheline* mosquitos are known to depend on rainfall for breeding sites, and *An.balabacensis* is shown to increase in numbers during months of greatest rainfall (Barber, B.E. *et. al.,* 2012) with a corresponding increase in *P.knowlesi* cases sometime later. One factor that has a negative association with *P.knowlesi* infection is geographical elevation. This could be due to the cooler climate, which in turn may reduce the reproduction of the vector due to the cooler pools of water which may have a larvicidal effect, reducing reproduction.

Although *P.knowlesi* infection occurs in other countries, the vectors in other countries have variations in species of vector dominance among Anopheles mosquitoes. Even animal reservoirs for the parasite may also be different for example long-tailed macaque and pig-tailed macaque is available on Borneo Island, while the banded leaf monkey is a reservoir in Peninsular Malaysia and Northern pig-tailed macaque in Myanmar. Factors associated with *P.knowlesi* in this review were identified, but not explored further in the respective studies.

Limitations

The limitations of this systematic review are a geographical limitation since the studies were mainly those from Borneo. Although *P.knowlesi* infection occurs in other countries, the vectors in other countries are other species of Anopheles mosquitoes, which may have subtle but significant differences from the vectors in Malaysia, generally and in Sabah, specifically. In addition, the animal reservoirs for the parasite may also be different, since only the long-tailed macaque and pig-tailed macaque are available on Borneo Island, while the banded leaf monkey is a reservoir in Peninsular Malaysia and Northern pig-tailed macaque in Myanmar. Another limitation is the low strength of evidence for the included studies in the systematic review. Factors associated with *P.knowlesi* were identified, but not explored further in the respective studies. However, they are among the evidence available for the review to form current recommendations.

Conclusion

Host factors such as sex and age as well as occupation as individual factors and environmental factors such as rainfall and geographic elevation have shown to have some association with *P.knowlesi* infection. The interaction between human movement into the forest and cleared areas adjacent to these dense forest areas needs to be explored further. Although humans can acquire this infection from macaques, human-to-human transfer in nature has not been established. This zoonotic malaria poses unique challenges that will need to be addressed if all forms of malaria are to be eliminated based on the sustainable developmental goal (SDG).

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BEJ, VOLUME. **1**, ISSUE **2**, DECEMBER **2020**

BORNEO EPIDEMIOLOGY JOURNAL | **BEJ**

ORIGINAL ARTICLE **Open Access**

Polymorphisms of CYP1A1 Genes and Its Correlation with Clinical Variant of Pterygium

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Abstract

Background and Objective: CYP1A1 gene, which has role in carcinogenic metabolisms, is also detected in pterygium tissue. The aim of the study is to determine the polymorphisms of CYP1A1 m2 (rs1048943) and m4 (rs1799814) gene and its correlation with clinical variant of the pterygium.

Methods: DNA isolation was performed from blood sample of 80 pterygium patients consisting of 40 inflammatory and 40 non-inflammatory pterygium. Genotyping of rs1048943 SNP A→G (m2) in the CYP1A1 gene was performed using *Alel Specific Polymerase Chain reaction (AS-PCR)* and rs1048943) SNP Genotyping was performed using PCR. Polymorphism results are characterized as wild type (AA), mutant homozygote (GG), and mutant heterozygote (AG).

Results: CYP1A1 m2 and m4 gene polymorphism consist of wild type (AA), mutant homozygote (GG), and mutant heterozygote (AG). Both CYP1A1 m2 and m4 genes polymorphism of both groups of inflammatory and non-inflammatory pterygium was mostly consist of wild type polymorphism, followed by the mutant heterozygote polymorphism. The wild type polymorphism was found to be higher in inflammatory pterygium, meanwhile the mutant heterozygote was found to be higher in non-inflammatory pterygium.

Conclusion: There were differences in CYP1A1 m2 and m4 gene polymorphism in both pterygium group, but none has been shown to be statistically associated with the clinical variant of the pterygium.

Keywords: CYP1A1 gene polymorphism, inflammatory pterygium, non-inflammatory pterygium, Polymerase Chain Reaction, SNP, Genotyping

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Received: 11/09/2020

Accepted: 12/11/2020

Introduction

Pterygium has long been identified as fibrovascular tissue growth on the ocular surface, originating from the conjunctiva and proliferates toward the cornea (Bradley, J.C. *et. al.,* 2010). It is also considered a degenerative disorder of the conjunctiva. The abnormal tissue is thought to be associated with exposure to ultraviolet (UV)-B which primarily affect corneal stem cells in the limbus. Clinically, pterygium is associated with inflammation and neovascularization. Pterygium either primary or recurrent can cause changes in normal conditions such as astigmatism, and changes in ocular surface, which eventually can lead to visual dysfunction due to decreased visual acuity (Kaufman, S.C. *et. al.,* 2013; Hirst, L,W., 2009).

It has long been suggested that ultraviolet light exposure due to outdoor occupation is a major risk factor for the development of pterygium. Other factors associated with pterygium development are age, being male and having dry eyes (Bradley, J.C. *et. al.,* 2010; Kaufman, S.C. *et. al.,* 2013; Hirst, L,W., 2009). Genetic factors, tumour suppressor gene p53 and other genes may be involved in the pathogenesis of pterygium. Pterygium prevalence has found to be increased especially in countries closest to the equator line due to more sun exposure. The pathogenesis of pterygium is still not fully understood. According to the previous studies, there is a relationship between pterygium with the involvement of environmental factors such as viral infections or oxidative stress, anti-apoptotic mechanisms, mechanisms of immunology, cytokines, growth factors, extracellular matrix modulators, genetic factors, and possibly other factors (Bradley, J.C. *et. al.,* 2010; Detorakis, E.T. *et. al.,* 2010; Zhivov, A. *et. al.,* 2009).

Pterygium clinical symptoms may be mild and often with no complaints at all (asymptomatic). However, some patients may also have complaints such as red eye, inflammation or irritation, burning sensation, and foreign body sensation. Clinically, Donald Tan classified pterygium as atrophic, intermediate, and fleshy. In practice, complaints and symptoms of pterygium is composed of inflammatory and non-inflammatory (Bradley, J.C. *et. al.,* 2010; Hirst, L,W., 2009; Khakshoor, H. *et. al.,* 2010).

Environmental pollutants such as Polycyclic Aromatic Hydrocarbons (PAHs) compounds are the result of incomplete combustion of organic materials derived from environmental carcinogens and are metabolized by different xenobiotic-metabolizing enzymes, one of which cytochrome P450 (P450 or CYP). This enzyme is mainly instrumental in the change of PAHs into more polar metabolites and soluble in water, so the metabolites formed can be excreted from the body (Khakshoor, H. *et. al.,* 2010). However, during the metabolic process, various metabolites of PAHs unstable and reactive can be formed, and these metabolites to attack DNA, causing toxicity and cell transformation. The polymorphism of CYP1A1 was previously found in pterygium tissue. Thus, it is stated that carcinogenic process was also involved in the pathogenesis of pterygium (Balci, M. *et al.,* 2011; Shimada T., 2006).

CYP1A1 is a sub-family 1 CYP gene superfamily, one of the important genes that encode enzymes metabolizing carcinogens, and is involved in the metabolism of carcinogenic PAHs. This gene has an important role in catalyzing the oxidative reaction Benzo (a) pyrene, which is one of the most important classes of PAHs, into reactive metabolites carcinogen. CYP1 enzymes are responsible for the activation and detoxification of various metabolites of PAHs (Shimada T., 2006; Balaji L, *et al.,* 2012).

To our knowledge, the polymorphism of CYP1A1 gene and the relationship of CYP1A1 protein and genetic polymorphisms have not been widely discussed in pterygium. In general, several identified CYP1A1 gene polymorphism are m1, m2, m3, and m4. Peng et al evaluated the role of CYP1A1 allele variations in the pterygium tissue, *i.e.* m2/m2, m1/m2, and m1m1. The study found CYP1A1 gene expression associated with gene allele variations, where the m2/m2 allele group was found more in the pterygium tissue than the other two allele variations (Peng, M.L., *et al.,* 2012). Variations in pterygium mutations result in different patterns of expression of growth factors, and this may explain variations in growth seen clinically (Bradley, J.C. *et. al.,* 2010).

CYP1A1 m1 allele polymorphisms in both inflammatory and non-inflammatory pterygium have been evaluated in our previous study in 2017. We classified pterygium based on its clinical symptoms into inflammatory and non-inflammatory pterygium, and found that CYP1A1 m1 gene polymorphisms may occur in both pterygium groups especially in inflammatory pterygium although statistically the differences between the two pterygium groups were not significant (Hendriati, H. *et. al.,*2017). One year later, we also studied the correlation between CYP1A1 m1 gene polymorphism with CYP1A1 enzymes, p53 protein, and VEGF levels in pterygium. We found that CYP1A1 gene polymorphism did not affect the levels of CYP1A1 enzymes, p53 protein and VEGF in both pterygium groups (Hendriati, H. *et. al.,*2018). Therefore, in this study we aim to determine the polymorphism of CYP1A1 m2 (rs1048943) and m4 (rs1799814) gene and its correlation with clinical variant of the pterygium (inflammatory and non-inflammatory pterygium).

Materials and methods

This study was an observational study with cross sectional study comparative study design. We obtained 80 samples of pterygium tissues which consist of 40 inflammatory and 40 non-inflammatory pterygium from our previous study in 2017.

The study populations were all pterygium patients. The study sample is part of the population that meets the inclusion and exclusion criteria, both for inflammatory and non-inflammatory pterygium. The approximate size of the minimum sample is calculated based on the formula of hypothesis test of 2 different proportions. From that calculation, we obtained minimum samples number of 40 people for each group, thus the total sample was up to 80 patients.

The inclusion criteria were all patients diagnosed with primary pterygium both unilaterally and bilaterally, meeting the criteria of surgical indication, either clinical or cosmetic indications, not receiving anti-VEGF therapy or steroids in the last 2 weeks, and agreed to participate in this study. Exclusion criteria were patients suffering from anterior segment infection (conjunctivitis and keratitis) and patients suffering from other disorders in the conjunctiva, such as benign and malignant lesions of the conjunctiva.

Isolation of Genomic DNA

Genomic DNA was isolated from 300µL of blood sample using GF-1 Blood DNA Extraction Kit Vivantis. DNA isolation was performed in accordance with the kit procedure consisting mainly of the sample preparation stage, cell lysis stage, DNA binding stage, leaching stage, and the elution stage of DNA.

Genotyping rs1048943 (A→G) (*m2*)

Genotyping SNP rs1048943 (A→G) in the CYP1A1 gene was performed by AS-PCR using the specific primary alel P57(A) dan P58(G). Then, the PCR products were analyzed using electrophoresis on a gelose gel of 1.5% which had been dyed GelRed DNA, then observed with GelDoc. Individuals who have a wild type genotype (AA allele) will produce DNA bands of 972 bp. Individuals who have the heterozygous genotype (AG allele) will produce DNA bands from both A and G. Individuals who have genotype of mutant homozygotes (GG allele) will produce specific allele of G. As confirmation of PCR results, some samples of purified PCR products will be sent to Macrogen, South Korea for sequencing.

Genotyping rs1799814 (A→G) (*m4*)

Genotyping SNP rs1048943 (A→G) in the CYP1A1 gene was performed by PCR sequencing using the specific primary alel 142-F and 969-R **(Figure 1)**. Then, the PCR products were analyzed using electrophoresis on a gelose gel of 1.5% which had been dyed GelRed DNA, then observed with GelDoc.

The remaining PCR products were purified by the cold Na-acetate and Ethanol Absolute method. Furthermore, about 20 µl of pure PCR products were sent for sequencing to Macrogen, South Korea. The sequencing method used is the Sanger method. Sequencing data were analyzed with the help of Geneious bioinformatics software. The sequencing data for each sample from the forward primer is combined with the sequencing data from the reverse primer. Furthermore, the contig data is BLAST on the NCBI website.

Results

We obtained 80 pterygium tissues from 80 patients which consist of 40 inflammatory and 40 non-inflammatory pterygium. CYP1A1 m2 and m4 gene polymorphisms found in inflammatory and non-inflammatory pterygium were further divided into wild type, mutant homozygote and mutant heterozygote. Most of polymorphisms was found in all samples except the mutant homozygous polymorphism which is absent in both genes and in both group of pterygium. In both pterygium groups, wild type was found to be higher than the mutant heterozygous and homozygous polymorphism. **Table 1** shows the CYP1A1 m2 polymorphism in both pterygium groups.

Figure 1: The primary allele 142-F and 969-R

Table 1: CYP1A1 m2 polymorphism in both pterygium groups

Pterygium	Wild Type (AA)	Mutant Heterozygote (AG)	Mutant Homozygote (GG)	Total
Inflammatory	26	14	0	40
Non-inflammatory	22	16	2	40
Total	48	30	2	80

Based on table 1, wild type CYP1A1 m2 polymorphism was the most common polymorphism found in both groups followed by the mutant heterozygote. The wild type CYP1A1 m2 polymorphism was found higher in inflammatory group compared to non-inflammatory group. Meanwhile, the mutant heterozygote CYP1A1 m2 polymorphism was higher in non-inflammatory group. Mutant homozygote CYP1A1 m2 polymorphism was absent in inflammatory group. **Table 2** shows CYP1A1 m4 polymorphism in both pterygium groups.

Table 2: CYP1A1 m4 polymorphism in both pterygium groups

Pterygium	Wild Type (AA)	Mutant Heterozygote (AG)	Mutant Homozygote (GG)	Total
Inflammatory	27	13	0	40
Non-inflammatory	24	14	2	40
Total	51	27	2	80

Based on Table 2, wild type polymorphism was also the most common polymorphism found in m4 gen polymorphism followed by the mutant heterozygote. In similar pattern with the CYP1A1 m2 gene polymorphism, the wild type CYP1A1 m4 polymorphism was found higher in inflammatory group compared to non-inflammatory group. Meanwhile, the mutant heterozygote CYP1A1 m4 polymorphism was higher in non-inflammatory group. Mutant homozygote CYP1A1 m4 polymorphism was absent in inflammatory group.

Discussion

Cytochrome-P450 1A1 (CYP1A1) is included in the important superfamily of cytochrome P450 (CYPs) involved in the metabolism of many xenobiotic compounds and endogenous lipophilic substances, which can activate procarcinogen into DNA reactive metabolites (Shimada T., 2006; Tung, J.N. *et. al.,*2010; Shehadeh, M.R. *et. al.,*2011). The human CYP1A1 gene is located on chromosome 15q22-24, composed of seven exons responsible for procarcinogen activation of reactive metabolites and is involved in oxidation mediation, including polycyclic aromatic hydrocarbons and aromatic amino to mutagenic and carcinogenic metabolites. CYP1A1 genetic polymorphism may cause changes or loss of CYP1A1 enzyme activity, and result in cellular detoxification damage, which can lead to the absence of cell growth suppression mechanisms (Shehadeh, M.R. *et. al.,*2011; Jaworski, C.J. *et. al.,*2009; Young, C.H. *et. al.,*2010).

Tung et al (2010) studied the association of CYP1A1 allele variants and protein expression in primary culture epithelial cells. The association of CYP1A1 allele variants with CYP1A1 protein expression in the mutant homozygote m2/m2 group was significantly higher than the wild type m1/m1 and mutant heterozygote m1/m2 (p= 0.027). In the control group of normal conjunctive tissue there was no significant relationship (Tung, J.N. *et. al.,*2010).

In our previous study, we found that CYP1A1 m1 gene polymorphism was found in both pterygium groups. Mutant heterozygote polymorphism is a more common form of polymorphism in both groups compared to homozygote and wild type mutant forms. In both pterygium groups, each form of polymorphism was found to be almost similar in both inflammatory and non-inflammatory pterygium, so there was no significant difference between the two groups (Hendriati, H. *et. al.,*2017).

In this study, we also found CYP1A1 m2 and m4 gene polymorphism in form of wild type, mutant heterozygote and mutant homozygote polymorphism. In contrast to our previous study, wild type is the most common type of polymorphism found in both m2 and m4 genes compared to mutant heterozygote and mutant homozygote polymorphism. The wild type M2 and M4 gene polymorphism was found to be higher in inflammatory group compared to non-inflammatory group, meanwhile the mutant heterozygote was found to be higher in non-inflammatory group. On the other hand, mutant homozygote m2 and m4 polymorphism was found only in non-inflammatory pterygium.

Conclusion

The results of this study indicate the presence of polymorphisms in the CYP1A1 m2 and m4 gene either in the form of wild type (AA) mutant homozygote (GG), and mutant heterozygote (AC). This study showed that the polymorphisms in the CYP1A1 m2 and m4 genes that were most found in the inflammatory and non-inflammatory pterygium groups were wild type. This is different from our previous study which found more heterozygote mutant polymorphisms in the two groups of pterygium even though the differences found were not significant. Therefore, differences in variants of the CYP1A1 gene polymorphism found in the two groups of pterygium are thought to be related to the mechanism of pterygium formation and the clinical symptoms it creates.

Acknowledgement

This research is funded by *Penerimaan Negara Bukan Pajak* (PNPB) grant funds of 2018 and is a further research of our previous study of CYP1A1 m1 gene polymorphism published in 2017.

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BORNEO EPIDEMIOLOGY JOURNAL | BEJ

ORIGINAL ARTICLE Open Access

Indonesian Version of the Fear of COVID-19 Scale: Validity and Reliability

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Abstract

Background and Objective: The Fear of COVID-19 Scale (FCV-19S) is a seven-item uni-dimensional scale assessing the severity of COVID-19 concerns. A translation and validation of the FCV-19S in Bahasa Indonesia language was expedited in view of the worrying trends of COVID-19 in Indonesia as well as its psychological squeal.

Methods: Formal WHO forward and backward translation sequences were applied in translating the English FCV-19S into Bahasa Indonesia. Indonesian university participants were recruited *via* convenience sampling online using snowball methods. The reliability and validity of the Indonesian FCV-19S was psychometrically evaluated by applying confirmatory factor analysis and Rasch analysis in relation to sociodemographic variables and response to the depression, anxiety, and stress components of the Indonesian version of DASS-21. The sample consisted of 434 Indonesian participants.

Results: The Cronbach α value for the Indonesia FCV-19-I was 0.819 indicated very good internal reliability. The results of the confirmatory factor analysis showed that the uni-dimensional factor structure of the FCV19S fitted well with the data. The FCV-19-I was significantly correlated with anxiety ($r= 0.705$, $p< 0.001$) subscales of DASS-21. The FCV-19-I's properties tested using Rasch analysis were also satisfactory, although three items in FCV-19-I were not able to be tested.

Conclusion: Hence, the Indonesian FCV-19-I is valid and reliable, with robust psychometric properties from classical and modern psychometric methods. It can be a valuable and useful tool in identifying and responding to psychological distress caused by COVID-19.

Keywords: Indonesia, Fear of COVID-19, COVID-19, Rasch analysis, DASS-21

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Received: 19/10/2020
Accepted: 03/12/2020

Introduction

The Coronavirus Diseases 2019 (COVID-19) pandemic, first reported in China in December 2019, has resulted in high levels of displacement, worldwide psychological panic, and has had huge knock on effects on employment, people's livelihood, and the travel and aviation industry in general (Nicola, M. *et. al.*, 2020; Ho, C.S.H. *et. al.*, 2020). Despite South East Asia region reporting its first case back in January 2020, Indonesia as the largest country in the region only reported its first case on 2nd March 2020. Within a short space of time, COVID-19 spread to numerous provinces, with Jakarta as the epicenter. As of 8th June 2020, Indonesia recorded 32,033 total cases and 1,883 total deaths, translating to a mortality rate of 5.88%, ranking among the highest in the region. However, Indonesia also had one of the lowest coronavirus testing rates; only 36 in one million were tested as compared to Singapore which tested 6,666 people per million. Thus, the true number of cases in Indonesia has been underestimated. As part of its response, the Indonesian government implemented Pembatasan Sosial Berskala Besar (PSBB), a large-scale social distancing policy. However, the widespread infection and the social distancing policy are uncharted territory for most Indonesians, especially in quarantined situations e.g. university students (Mukhsam, M.H. *et. al.*, 2020; Salvaraji, L. *et. al.*, 2020). This appears to have resulted in numerous psychological consequences, including fear and stigma (Lin. C.Y. *et. al.*, 2020). The fear of contracting the infection has impacted many individuals as well as their families (Harper, C.A. *et. al.*, 2020).

It is crucial to forge methods of measuring distress that are quantitative in nature to allow more objective and focused assessment. This allows for better impact analysis, improving implementation of educational material or preventative management (Pakpour, A.H. *et. al.*, 2020). There are limited psychological scales available in Bahasa Indonesia, especially for fear of COVID-19 which is a new construct. A Persian and English Fear of COVID-19 scale (FCV-19) has been developed, which is a series of 7 questions scored on a 5-point Likert scale, proving to be a concise scale suitable for busy clinical settings (Ahorsu, D.K. *et. al.*, 2020). This scale has been translated and validated into multiple languages, including Arabic, Turkish, Russian, Bangladeshi, Italian and Malay (Alyami, M. *et. al.*, 2020; Satici, B. *et. al.*, 2020; Reznik, A. *et. al.*, 2020; Sakib, N. *et. al.*, 2020; Soraci, P. *et. al.*, 2020; Pang, N.T.P. *et. al.*, 2020). With high mortality and low detection rates in the Indonesian setting, it is imperative the FCV-19 be translated and validated into what is essentially the language of 200 million people, using rigorous statistical models.

Materials and methods

Ethical Approval

Ethical approval was obtained from the Universiti Malaysia Sabah Medical Research Ethics Committee & Universitas Nahdlatul Ulama Surabaya Medical Ethics Committee prior to commencement of this project. All participants were presented with participant information sheet in the first page of the Google Form and have the right to refuse to participate without penalty, shall they decline. All participants in this study provided informed consent.

Methodology

Standard WHO guidelines were employed for FCV-19 validation. First, two independent experts: one as a content expert who is familiar with COVID-19 and bilingual in English and Bahasa Indonesia; and one as a language expert who is more familiar with Bahasa Indonesia; forward translated the FCV-19 from English to Bahasa Indonesia. Then, two separate individuals serving as content and language experts respectively, who were blind to the original translation, translated the Bahasa Indonesia version back into English. The two versions were compared and analyzed for major inconsistencies, and a revised version was hence produced. The revision was pilot tested in 20 Bahasa Indonesia-speaking individuals. Once further inconsistencies and incongruence with the original English version were rectified, a final Bahasa Indonesia translation was then produced.

The validation study was performed in a few universities in Surabaya, Indonesia. Convenience sampling was employed, and snowball methods were used to recruit samples. Google Forms were used with incorporated consent forms, sociodemographic questionnaires and research instruments, due to the inherent limitations for face to face data collection caused by the Indonesian PSBB lockdown. Snowball recruitment was performed utilising student and staff mailing lists. A sample size of 400 was planned to be recruited to facilitate the use of factor analysis with classical test theory methods, as it was considered a fair sample size for the purpose of factor analysis (Voorhis C.R.W.V. *et. al.*, 2007). Each participant was given a questionnaire containing three sections to fill in as follows.

Sociodemographic Questionnaire:

This was a brief questionnaire requesting for age, gender, education level, current occupation, location where participant was staying during the pandemic and marital status.

Fear of COVID-19 scale

The English FCV-19 was administered concurrently with the fresh Bahasa Indonesia FCV-19-I. The English Fear of COVID-19 scale consists of seven items (e.g., “I cannot sleep because I am worried about getting coronavirus-19”), scored on a five-item Likert point response ranging from 1 (strongly disagree) to 5 (strongly agree). The possible scores range from 7 to 35. The higher the score, higher the level of fear of COVID-19 (Ahorsu, D.K. *et. al.*, 2020), the original English scale has good internal reliability (Cronbach alpha= 0.82) and test-retest reliability (ICC= 0.72), with satisfactory evaluations of other properties based on classical test theory and Rasch model analysis. The psychometric properties of the Bahasa Indonesia FCV-19-I are presented in the “Results” section.

DASS-21 scale

The DASS-21 (Lovibond, S.H. *et. al.*, 1995) is self-reported, assesses the level of emotional distress (depression, anxiety and stress). It consists of 21 items that capture information about three separate feels: depression (e.g., “I couldn’t seem to experience positive feeling”), anxiety (e.g., “I was aware of dryness of my mouth”) and stress (e.g., “I found it hard to wind down”).

The 21 items were rated on a four-point Likert scale ranging from 0 (*did not apply to me at all over the last week*) to 3 (*applied to me very much or most of the time over the past week*), with higher scores corresponding to greater severity. In the current study, the Indonesian version of Depression, Anxiety and Stress Scale 21 (DASS-21) was used.

Data Analysis

To assess the validity and reliability of FCV-19-I, classical test theory (CTT) (Novick, M.R., 1966) and Rasch measurement theory (RMT) (Hobart, J., 2009) were concurrently employed. Subsequently, validity and reliability tests were divided into two levels; which are scale level (the analyses were done at scale level) and item level (the analyses were done at item level). For the scale level, the CCT's methods employed were internal consistency measure using Cronbach's alpha, McDonald's omega, greatest lower bound, test-retest reliability using Pearson correlation test (Bahasa Indonesia version versus English version), average variance extracted (AVE), composite reliability, standard error of measurement, concurrent validity (fear of COVID-19 scale versus depression scale, anxiety scale, and stress scale), while the RMT's methods used were item and person separation reliability, and item and person separation index. On the other hand, for the item level, the CTT's methods employed were item-item correlation and item-total correlation, while the RMT's methods used were infit and outfit mean square (MnSq) and differential item functioning (DIF) to test the measurement invariance across gender. IBM SPSS 24.0 was used to run the CTT, while the RMT was run using jMetrik 4.1.1. The McDonald's omega and the greatest lower bound were calculated using JAPS. The original version (*i.e.* English version) (Ahorsu, D.K. *et. al.*, 2020) and the Bahasa Indonesia version of the fear of COVID-19 is as presented in **Table 1**.

Table 1: The Original English Version the Bahasa Indonesia Version of the FCV-19

Item	The original English version	The Bahasa Indonesia version
Item 1	I am most afraid of COVID-19	Saya sangat takut terhadap Virus Corona (COVID-19)
Item 2	It makes me uncomfortable to think about COVID-19	Saya merasa tidak nyaman apabila memikirkan tentang virus corona (COVID-19)
Item 3	My hands become clammy when I think about COVID-19	Tangan saya berkeringat ketika memikirkan tentang virus corona (COVID-19)
Item 4	I am afraid of losing my life because of COVID-19	Saya takut kehilangan hidup saya dikarenakan terpapar oleh virus corona (COVID-19)
Item 5	When watching news and stories about Corona Viruses-19 on social media, I become nervous or anxious	Saya merasa gugup dan khawatir apabila saya mendengar tentang virus corona (COVID-19) melalui siaran berita dan media sosial

Item 6	I cannot sleep because I am worrying about getting COVID-19	Saya tidak bisa tidur nyenyak karena khawatir terinfeksi virus corona (COVID-19)
Item 7	My heart races or palpitates when I think about getting COVID-19	Jantung saya berdebar debar memikirkan tentang virus corona (COVID-19)

Results

The sociodemographic of the respondents are displayed in **Table 2**. The majority of the participants were single, of female gender, students rather than employed, and the highest education being high school. Half of the participants resided in Surabaya during the pandemic, while another half was outside Surabaya. The mean age of the participants was 26 years old. Skewness and kurtosis for all 7 items on the Indonesian Fear of COVID-19 scale was acceptable as in the range of -0.883 to 2.608, and -1.056 to 6.383 respectively.

Table 2: The respondents' background information (n= 434)

Background	Category	N	%	Mean
Age				26 years old
Age category	25 years and below	291	67.10%	
	More than 25 years old	143	32.90%	
Gender	Male	108	24.90%	
	Female	326	75.10%	
Education level	High school	275	63.40%	
	Diploma	20	4.60%	
	Bachelor degree	44	10.10%	
	Master degree	82	18.90%	
	Doctoral Degree	13	3.00%	
Job	Staff	26	6.00%	
	Educational Staff	13	3.00%	
	Lecturer	94	21.70%	
	Librarian/ Laboratory Assistant	11	2.50%	
	Student	290	66.80%	
City	Surabaya	217	50.00%	
	Others	217	50.00%	
Marital status	Single	321	74.00%	
	Married	113	26.00%	

From **Table 3**, it is noted that none of the participants selected 'strongly agree' option in item 3, 6 & 7. Otherwise, the results of the Pearson correlation coefficient show that almost all the inter-item correlation coefficients were higher than 0.3 (**Table 4**). This implies that the instrument has an acceptable validity (Cohen, J., 1992). Furthermore, there was only one corrected item-total correlation coefficient with a value of less than 0.5 (**Table 5**). This concurs with recommendations that in an empirical approach, as a rule of thumb, if the score of the item-to-total correlations is more than 0.50 and the inter-item correlations exceed 0.30, the construct validity is satisfied (John, P.R. *et. al.*, 1991).

Table 3: The respondent's choices

Item	Strongly disagree		Disagree		Neutral		Agree		Strongly agree	
	Count	%	Count	%	Count	%	Count	%	Count	%
Item 1	22	5.10%	39	9.00%	106	24.40%	224	51.60%	43	9.90%
Item 2	110	25.30%	132	30.40%	99	22.80%	72	16.60%	21	4.80%
Item 3	281	64.70%	91	21.00%	59	13.60%	3	0.70%	0	0.00%
Item 4	53	12.20%	44	10.10%	89	20.50%	219	50.50%	29	6.70%
Item 5	206	47.50%	74	17.10%	113	26.00%	40	9.20%	1	0.20%
Item 6	199	45.90%	132	30.40%	90	20.70%	13	3.00%	0	0.00%
Item 7	366	84.30%	49	11.30%	18	4.10%	1	0.20%	0	0.00%

Table 4: The item-item correlation matrix (n= 434)

Item	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6
Item 2	0.440**					
Item 3	0.286**	0.501**				
Item 4	0.618**	0.321**	0.319**			
Item 5	0.381**	0.546**	0.452**	0.444**		
Item 6	0.404**	0.489**	0.346**	0.430**	0.399**	
Item 7	0.122*	0.523**	0.536**	0.206**	0.398**	0.376**

Table 5: The corrected item-total correlation (n= 434)

Item	Corrected Item-Total Correlation	Item exclusion or retention
Item 1	0.565	Retained
Item 2	0.650	Retained
Item 3	0.550	Retained
Item 4	0.559	Retained
Item 5	0.622	Retained
Item 6	0.575	Retained
Item 7	0.489	Retained

All the psychometric measures' results as shown in **Table 6** have confirmed the validity and reliability of FCV-19-I as all the values have passed the suggested cut-off except for AVE. Additionally, at the item level, all the factor loadings were higher than 0.3 which means that the items are important (Pituch, K.A. *et. al.*, 2015) as presented in **Table 7**. All the communalities were also closer 1 except for Item 6 suggesting that extracted factor explains more of the variance of an individual item. The FCV-19-I's properties tested using Rasch analysis were also satisfactory where infit MnSq values were between 0.85 and 1.07, outfit MnSq values were between 0.85 and 1.12. These item fit statistics show that each item meets the unidimensional requirement of a Rasch model as all the values within 0.5-1.5 range (Wright, B.D. *et. al.*, 1994). The most difficult item was Item 5 (*i.e.* the highest value) and the easier item was Item 1 (*i.e.* the lowest value). There was also no substantial DIF found across gender since all the DIF contrast values were less than 0.5 (Shih, C.L., et. al., 2009).

Table 6: Psychometric properties for the Indonesia version of the fear of COVID-19 scale at the scale level (n= 434)

Psychometric method	**Psychometric measure**	**Result**	**Suggested cut-off**
CTT	Internal consistency measure using Cronbach's alpha	0.819	> 0.7
	Internal consistency measure using McDonald's omega	0.829	> 0.7
	Internal consistency measure using Greatest lower bound	0.882	> 0.7
	Test-retest reliability	0.997**	See Note
	Average variance extracted (AVE)	0.420	> 0.5
	Composite reliability	0.820	> 0.7
	Concurrent validity (Fear of COVID-19 scale versus Depression scale)	0.554**	See Note
	Concurrent validity (Fear of COVID-19 scale versus Anxiety scale)	0.705**	See Note
	Concurrent validity (Fear of COVID-19 scale versus Stress scale)	0.530**	See Note
RMT	Item separation reliability	0.997	> 0.7
	Item separation index	19.261	> 2
	Person separation reliability	0.811	> 0.7
	Person separation index	2.072	> 2

*Correlation is significant at the 0.05 level (two-tailed test);

** Correlation is significant at the 0.01 level (two-tailed test);

Note: Correlation coefficients of < 0.25 were considered as small; 0.25-0.50 as moderate; 0.50-0.75 as good; and > 0.75 as excellent

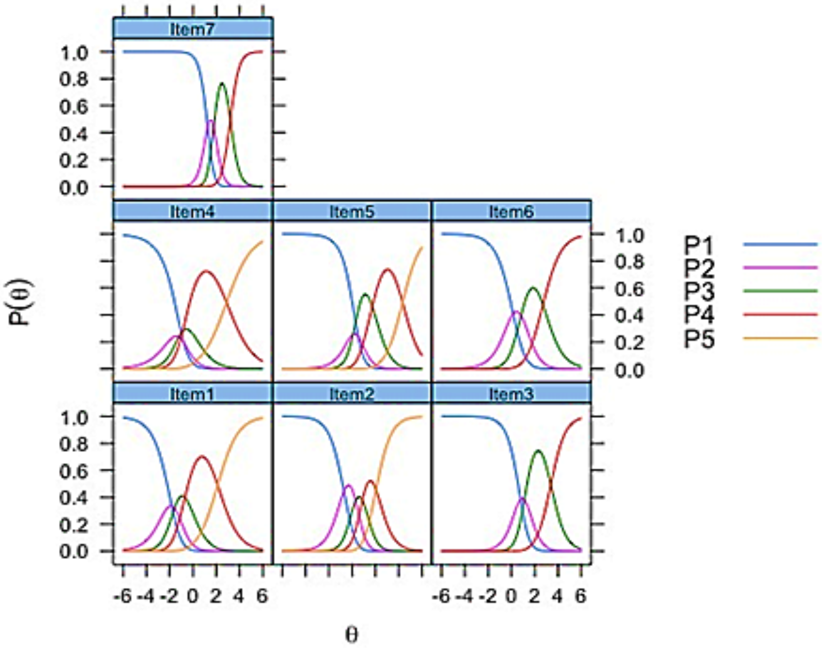

Figure 1: Item traces lines

Confirmatory factor analysis result also showed acceptable fit, with GFI= 0.870, NFI= 0.791, CFI= 0.800, and SRMR= 0.088. GFI more than 0.85 indicates good fit (Anderson, J.C. *et. al.*, 1984), while NFI of 0.7-0.9 is considered as acceptable fit, with the ideal value is more than 0.9 (Fattah, S.M.A.E., 2010). CFI of 0.8-0.9 indicates acceptable fit, while CFI value of > 0.90 is accepted as good fit (Browne, M.W. *et. al.*, 1993). On the other hand, SRMR< 0.90 is considered as acceptable fit, with the value of < 0.80 considered as ideal fit (Hu, L.T. *et. al.*, 1999). In ultimate the correlation diagram for Item 1 to 7 have shown in **Figure 1** above.

Table 7: Psychometric properties of Indonesia version of the fear of COVID-19 scale at the item level (n= 434)

Item	Factor loading*	Communalities	Infit MnSq	Outfit MnSq	Difficulty	DIF contrast across gender^{a,b}
Item 1	0.300	0.776	0.85	0.97	-1.65	-0.06
Item 2	0.789	0.663	1.07	1.12	0.44	-0.02
Item 3	0.789	0.622	-----------------------------Dropped-------------------------			
Item 4	0.336	0.742	1.00	1.08	-0.89	0.20
Item 5	0.673	0.558	0.91	0.85	2.10	0.05
Item 6	0.577	0.499	-----------------------------Dropped-------------------------			
Item 7	0.841	0.753	-----------------------------Dropped-------------------------			

Item 3, 6 & 7 dropped due to unobserved categories mainly ‘Strongly agree’ as per Table 3; MnSq is mean square error, DIF is differential item functioning;

*Extraction method: Oblimin rotation with Kaiser Normalization;

[a] DIF contrast> 0.5 indicates substantial DIF;

[b] DIF contrast across gender = difficulty for males (reference group) - difficulty for females (focal group).

Positive values indicate items that are differentially easier for the focal group than the reference group.

Negative values indicate items that are differentially harder for the focal group than the reference group.

Discussion

This study applied Rasch analysis in order to evaluate the psychometric characteristic of Fear of COVID-19 Scale (FCV-19) Indonesian version. However, as item 3, item 6 and item 7 had no 'strongly agree' response, Rasch analysis for the respective items were not able to be done. Nevertheless, the FCV-19-I demonstrates acceptable psychometric properties which render it valuable for use in assessing the brand new construct of COVID-19 related concerns and fears. With such psychometric properties, it can be used on a larger national scale in Indonesia to capture associations between fear and other related psychological process variables as part of larger studies exploring the psychological sequelae of COVID-19 on the Indonesian population.

The correlations with associated constructs in validated scales of similar language are noticeable in Anxiety subscale of the DASS, with correlations of .705. This suggests that more research needs to be performed to explore this finding further, as it is crucial to investigate how similar anxiety as encoded in the existing DSM-5 is to the construct of fear of COVID-19, as there are ultra-brief psychological interventions that can assist so (Pang, N.T.P. *et. al.*, 2020). The findings of these study mirror the Malay version of the Fear of COVID-19 Scale, which showed strong correlations with anxiety (Pang, N.T.P. *et. al.*, 2020); this means that relationships between behavioral explanations and anxiety are largely viable (Eugene K.B.Y. *et. al.*, 2020).

The main limitations are that this study used predominantly university staff and students in Surabaya. This is an unavoidable limitation as PSBB significantly restricts face to face collection of data for all psychometrics research, which has significantly constrained research work. Secondly, the sample size of 434 may not be sufficiently representative, due to difficulties in recruiting larger samples amid the restrictions; hence a sufficient number to perform factor analysis was recruited. Besides that, the content of item 3, item 6 and item 7 in the Bahasa Indonesia language may not yield polarized or strong answers in the language, as the translated version did not yield any 'strongly agree' responses. Apart from that, this study is also limited by difficulty in performing concurrent validity with other scales measuring anxiety, as there is no equivalent of a phobia scale validated into Indonesian. Lastly, there is also possibility of cross-language correlation which might affect the way participants answer the scales in both Bahasa Indonesia and English language. As this study was done at the height of COVID-19, there was urgent need to expedite the process to translate and validate the scale, so it can be further utilized in the bigger population.

Across multiple measures, it retains reasonable internal consistency, with Cronbach's alpha of 0.819, McDonald's omega of 0.829, and greatest lower bound of .882; acceptable construct validity based on the accepted score of the item-to-total correlations > 0.50 and the inter-item correlations > 0.30; good test-retest and composite reliability; good item separation reliability and item separation index based on Rasch analysis; reasonable concurrent validity based on reasonable correlations with the depression, anxiety, and stress components of the DASS-21; and Rasch analyses at the item level were deemed acceptable. When comparing with the existing validated instruments that are currently available, the single factor structure and good factor loadings for all items showed that the items are generally relevant.

Conclusion

In conclusion, this study proved that FCV-19-I is a psychometrically sound instrument, validated by classical and modern statistical approach. As Indonesia facing ongoing battle against COVID-19, it is hoped that this scale able to provide useful insight to psychological distress suffered by Indonesians; an aspect that might be overlooked in this testing times, and perhaps provide an impetus for a proper intervention much needed in the community. Further validation study in a more representative sample is recommended.

Conflict of Interest

All authors declared no conflict of interest. No funding received.

Ethical Approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

Consent

Informed consent was obtained from all participants for being included in the study.

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BEJ, VOLUME. **1**, ISSUE **2**, DECEMBER **2020**

BORNEO EPIDEMIOLOGY JOURNAL | BEJ

ORIGINAL ARTICLE **Open Access**

Correlation between Serum Magnesium Levels and HbA1C in Type 2 Diabetes Mellitus

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Abstract

Background and Objective: Type 2 Diabetes Mellitus is a chronic disease resulting from a complex inheritance, environmental interaction along with risk factors such as obesity and sedentary life style. Magnesium has been stated to have potential role in improving insulin sensitivity and preventing diabetes related complications. Hypomagnesaemia is proposed as one of the factor in the pathogenesis of diabetic complications. The aim of our study is to estimate the correlation between serum Magnesium levels and the level of Glycemic control (HbA1c) in patients with Type 2 Diabetes Mellitus.

Methods: This is an observational study conducted in SVRRGGH and SVMC, Tirupati, Andhra Pradesh which included 94 patients with type 2 Diabetes mellitus of more than 5 years duration. These patients were divided into 2 groups based on level of Diabetic control. Group A included 30 patients with HbA1c below 7.0mg/dL (good glycemic control) and Group B included 64 patients with HbA1c above 7.0mg/dL (poor glycemic control). In both the groups Serum Magnesium levels were estimated.

Results: Mean Serum Magnesium levels in Group A was 2.280±0.3955mg/dL while in Group B it was 2.087±0.5834 mg/dL with a p-value 0.0379 (<0.05) which is statistically significant. In our study though the mean values of serum Magnesium are within normal reference range, mean values of serum Magnesium levels in patients with poor glycemic control(HbA1c>7.0) are statistically low as compared to patients with good glycemic control (HbA1c <7.0).

Discussion: It has been reported that Serum Magnesium levels are lower in uncontrolled diabetics when compared to controlled diabetics and also serum magnesium levels vary with treatment for diabetes. In our study, although the mean values of serum magnesium in both groups are within Normal reference range (1.7-2.2mg/dL), they are statistically low in group with poor glycemic control (HbA1c >7.0mg/dL) when to group with good glycemic control (HbA1c< 7.0mg/dL).Thus this gives an insight into the association of hypomagnesaemia and level of diabetic control.

Conclusion: This effective comparative study of deals with varying Magnesium levels in specific diabetic therapies and analysed the effect of urinary magnesium detected in Hypermagnesuria with Magnesium supplementation.

Keywords: Diabetes, HbA1c, Hypomagnesaemia, Serum Magnesium

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Received: 02/09/2020
Accepted: 13/12/2020

Introduction

Diabetes mellitus is one of the most common metabolic disorder and leading cause of death and disability in the world. The incidence of diabetes is increasing globally and in India as well. WHO has declared India as the global capital of diabetes. In 1997 WHO estimate of the prevalence of the diabetes in adults showed an expected rise of >120% from 135 million in 1995 to 300 million in 2025. It has been estimated that 57.2 millions of Indians will be affected by diabetes by the year 2025 (King, H. *et al.*, 1998).

Magnesium (Mg^{2+}) has several functions in the human body. It acts as a cofactor for more than 300 enzymes, regulating a number of fundamental functions such as muscle contraction, neuromuscular conduction, glycemic control, myocardial contraction, and blood pressure (Bertinato, J. *et al.*, 2015; Grober, U. *et al.*, 2015). Cellular magnesium is a crucial cofactor for various enzymes involved in glucose transport, glucose oxidation, insulin release, and is a cofactor for ATPase and adenylate cyclase enzymes (Hans, C.P. *et al.*, 2002). It plays the role of a second messenger for insulin action; on the other hand, insulin itself is an important regulatory factor of intracellular magnesium accumulation (Paolisso, G.*et al.*, 1990). Intracellular Mg plays a key role in regulating insulin action, insulin-mediated-glucose-uptake and vascular tone. Reduced intracellular Mg concentrations result in a defective tyrosine kinase activity, postreceptorial impairment in insulin action and worsening of insulin resistance in diabetic patients. A low Mg intake and an increased Mg urinary loss appear the most important mechanisms that may favor Mg depletion in patients with type 2 diabetes (Takaya, J. *et al.*, 2004).

Type 2 diabetes is frequently associated with both extracellular and intracellular magnesium deficits. A chronic latent Mg deficit or an overt clinical hypomagnesemia is common in patients with type 2 diabetes, especially in those with poorly controlled glycemic profiles (Barbagallo, M. *et al.*, 2015). Glycosylated Hemoglobin (HbA1 c) results from post translational changes in the hemoglobin molecule, and their levels correlate well with glycemic levels over the previous six to ten weeks. Glycosylation of hemoglobin takes place under physiological conditions by a reaction between glucose and N-terminal valine of Beta chain of Hb molecules (Kareem, I. *et al.*, 2004). The American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD) and the International Diabetes Association (IDF) recommend the use of HbA1c assay in the diagnosis of T1DM and T2DM (Nathan, D.M. *et al.*, 2009). Measurement of glycosylated hemoglobin shows a promising approach to monitor diabetic patient and also provides a conceptual frame work for the pathogenesis of secondary sequelae of DM (Gabby, K.H. *et al.*, 1977).

Diabetes management involves strictly maintaining a person's blood glucose level close to the normal range. There is a strong relationship between an elevated blood glucose level and the risk of complications and mortality in people with diabetes (Alsulaiman, T.A. *et al.*, 2016). Poor glycemic control is defined as a glycated hemoglobin (HbA1c) equal to or above 7% or a fasting plasma sugar (FPS) above 7.2 mmol/L for adults who are not pregnant (Kaabi, J.A. *et al.*, 2008).

Type 2 Diabetes Mellitus (DM) is a chronic disease resulting from a Complex Inheritance, Environmental ethnicity along with risk factors such as Obesity and Sedentary life style (Wu. Y, *et al.*, 2014). It has been projected that global prevalence of diabetes would be 4.4% by 2030 with a total number of people suffering to rise to 366 million by 2030 (Sarah W *et al.*, 2004). India has around 69 million cases of diabetes in 2015, second highest in the world after China *i.e.*, IDF Diabetes atlas 7E.

Magnesium (Mg) is the 2nd most abundant cation in ICF and 4th abundant in body (Avinash S. S. *et al.*, 2013). It serves as cofactor for all enzymatic reactions that require ATP. Hypomagnesaemia can be both a cause and a consequence of diabetic complications (Ahmed, F., 2019). Magnesium has been stated to have potential role in improving insulin sensitivity and preventing incidence of diabetes mellitus, reducing blood glucose levels and related Microvascular and Macrovascular complications mainly retinopathy (Mendía, L.E.S. *et al.*, 2016). Magnesium is involved in insulin secretion, binding and activity (Paolisso, G. *et al.*, 1990). Hypomagnesaemia alters the activity of Na+ K+ ATPase which is required for insulin dependent glucose transport, postreceptorial .insulin action and worsening of insulin resistance. Magnesium deficiency may be due to increased urinary loss, less dietary intake or impaired absorption of magnesium Compared to Healthy Adults (Walt MK *et al.*, 2003). It was found that poor glycemic control, insulin resistance and low Mg level were strongly associated with increased the prevalence of microalbuminuria (Xu, B. *et al.*, 2013).

The aim of our present study is to estimate the correlation between Serum Magnesium Levels and Glycemic Control (HbA1c) in patients with Type 2 Diabetes Mellitus. Although the assessment of serum magnesium level has been reported in many studies from various countries, the comparative studies within the diabetic population based on glycemic control are limited.

Materials and methods

This is a observational comparative study conducted in the Department of Biochemistry and Multidisciplinary research unit, Sri Venkateswara Medical College, Tirupati, India among the patients who attended the medical OPD for diabetic consultation. A simple random sampling was done and included the patients with Type-2 Diabetes Mellitus of more than 5 years duration without any other co-morbidities are included in this study. The exclusion criteria are patients with Chronic Renal Failure, Epilepsy, and Acute Myocardial Infarction in Past 6 months, Malabsorption syndrome, and Alcohol abuse, those receiving Diuretics or Magnesium Supplements. The study included 94 patients with Type 2 Diabetes Mellitus of more than 5 years duration out of which 75% were on Oral hypoglycemics (OHA-two drugs), 20% on OHA and Insulin and 5% were on only Insulin. Patients were divided into 2 groups based on the level of Glycemic Control. Group A included 30 patients with HbA1c $<$ 7.0(Good glycemic control) and Group B included 64 patients with HbA1 $>$ 7.0 (Poor glycemic control).

After getting approval from the institutional ethical committee fasting blood samples were collected, serum separated and stored at 2-8˚C and analyzed on weekly basis. Serum HbA1c is estimated by Boronate Affinity immune turbido metric method using Nycocardwhile Serum Magnesium is estimated by Xylidyl Blue method using Biosystems A25 auto analyzer. Data was analyzed statistically using descriptive statistics, contingency coefficient analysis, and student t-test. $P < 0.05$ was considered as statistically significant.

Results

Table 1 shows that the mean serum Magnesium levels in Group A with good glycemic control (HbA1c <7.0) is 2.280±0.3955 mg/dL while in Group B with poor glycemic control (HbA1c>7.0), it was 2.087±0.5834 mg/dL with a p-value 0.0379(<0.05) which is statistically significant which has also represented in **Figure 1**.

Table 1: Statistical evaluation of Serum Magnesium levels in Group A & Group B samples

Study Groups	Mean	Standard Deviation	P-value
Group A [HbA1c (< 7.0 mg/dL)]	2.280	0.3955	0.0379 (<0.05)
Group B [HbA1c (> 7.0 mg/dL)]	2.087	0.5834	Statistically Significant

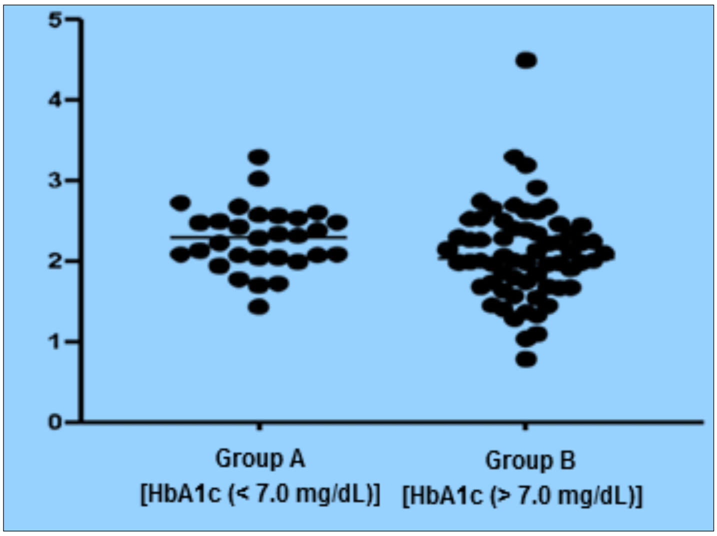

Figure 1: Statistical evaluation of Serum Magnesium levels in Group A & Group B samples

Discussion

Magnesium depletion has a negative impact on glucose homeostasis and insulin sensitivity in type 2 diabetic patients (Wälti, M.K. *et al.*, 2003). It has been suggested that hypomagnesemia may induce altered cellular glucose transport by altering Na-KATP gradients5, reduce pancreatic insulin secretion, defective post receptor insulin signaling, and altered insulin–insulin receptor interactions .Low levels of magnesium have shown to damage tyrosine kinase activity and receptors involved in signaling (Sales, C.H. *et al.*, 2004).

Magnesium deficiency may be a common factor associated with insulin resistance (Nadler, J.L. *et al.*, 1993). The lower the basal Mg, the greater the amount of insulin required to metabolize the same glucose load, indicating decreased insulin sensitivity (Chi, T.P.P. *et al.*, 2007). Insulin has been suggested to enhance intracellular Mg uptake via tyrosine kinase. It also stimulates the production of cAMP and potentiate Mg uptake via other cAMP-dependent hormones. Active intestinal Mg absorption is presumed to involve transient receptor potential channel melastatin 6 (TRPM6), which is expressed along the brush border membrane of the small intestine. Mutations of TRPM6 have been reported to be associated with hypomagnesemia (Chi, T.P.P. *et al.*, 2007).

By this we can establish that diabetes itself can induce hypomagnesemia and hypomagnesemia in turn can induce onset of diabetes mellitus. Insulin has been implicated to play a role at loop of henle by increasing the favorable transepithelial potential difference for Mg reabsorption. Paracellular Mg reabsorption at loop of heme is facilitated by claudin 6 (paracellin 1) which is a tight junction protein whose mutation is associated with severe hypomagnesemia (Chi, T.P.P. *et al.*, 2007). Both hyperglycemia and hypoinsulinemia may increase urinary Mg excretion and decreases Mg tubular reabsorption (Nair, P.M. *et al.*, 1982) Saris NE et al and Weglicki WB *et al* opined a link between Mg deficiency and reduced insulin sensitivity in the presence of oxidative stress and increased free radicals in DM2 (Saris, N.E. *et al.*, 2000; Weglicki, W.B., 2012). Low magnesium has been associated with oxidative stress, thrombogenesis via increased platelet aggregation, vascular calcifications and endothelial dysfunction (Chi, T.P.P. *et al.*, 2007; Wolf, F.I. *et al.*, 2008).

Magnesium deficiency also opens N-methyl-D-aspartate calcium channels and activates nuclear factor-kappa B as primary mechanism of inflammation.28 Mg deficiency associates with the onset of proinflammatory and profibrogenic response leading to increased circulating levels of cytokines, which trigger an oxidative response in endothelial cells. Mg deficiency also interferes with normal cell growth and regulation of apoptosis as it is crucial in DNA synthesis and repair (Chi, T.P.P. *et al.*, 2007; Wolf, F.I. *et al.*, 2008). Mg deficiency can result in enhancement of coronary vascular tone, potentiation of coronary vasoconstrictors, as well as microcirculatory ischaemia. Mg deficiency inhibits the ability of coronary arteries to relax in response to acetylcholine which can cause vasospasm (Altura, B.T. *et al.*, 987). Low circulating magnesium levels have been related to elevated blood pressure, dyslipidemia, increased inflammatory burden, oxidative stress, carotid wall thickness, and coronary heart disease (Ma, J. *et al.*, 1995; Romero, F.G. *et al.*, 2006). Coronary Artery Risk Development in Young Adults (CARDIA), a longitudinal study of American adult population found an inverse association between magnesium intake and diabetes risk (Kim, D.J. *et al.*, 2010).

It has been reported that Serum Magnesium levels are lower in uncontrolled diabetics compared to controlled diabetics and also serum magnesium levels vary with treatment for diabetes (Ahmed, F., 2019) In another study, stated that Serum Magnesium Concentrations of 37.6% of the Diabetics were below the reference range (Walti, M.K. *et al.*, 2003).

While few studies reported that no significant difference exists in serum Magnesium level of diabetics when compared with Control Subjects (Masood *et al.*, 2009; Walter *et al.*,

1991) stated that hypermagnesuria is evident in diabetics. We have included only those patients with more than 5 years duration of DM in our study as the onset of complications of DM usually seen after 5years of duration. Many studies were inconsistent with the target Hba1c being 7.7 and above. So we set a near normal HbA1c of 7.0 as target to divide the groups.

In our study, although the mean values of serum magnesium in both groups are within Normal reference range (1.7-2.2 mg/dL), they are statistically low in group with poor glycemic control (HbA1c>7.0) when to group with good glycemic control (HbA1c<7.0).

Conclusion

This is only a comparative study with smaller sample size. It would have been more effective if there were trials with Magnesium supplementation, any variation of Magnesium levels with various types of diabetic therapies and estimation of urinary magnesium to detect Hypermagnesuria were included.

Limitations

Hypomagnesaemia is one of the factors along with duration of DM in the pathogenesis of Diabetes related Microvascular and Macrovascular complications. Hence it is worthy to measure Serum Magnesium levels in patients with Type 2 Diabetes mellitus periodically along with HbA1c, calcium, Na, K, Creatinine, uric acid.to detect and prevent complications of DM like Retinopathy and Nephropathy.

Acknowledgements

The authors would like to acknowledge the staff of Multi-disciplinary Research Unit, Sri Venkateswara Medical College, Tirupati for their co-operation and support in making this study a success. We convey our heartfelt gratitude to 'Institutional Scientific and Ethics Committee' for the study approval.

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BEJ, VOLUME. **1**, ISSUE **2**, DECEMBER **2020**

BORNEO EPIDEMIOLOGY JOURNAL | BEJ

MINI REVIEW **Open Access**

Mitigation Measures during Elections and It's Impacts on COVID-19 Pandemic: Sabah State (Malaysia), New Zealand and the United States

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Abstract

Background and Objective: Countries all over the world respect the election process as one of the fundamental steps in forming a government. However, the exponential spread of COVID-19 has been deeply alarming, with a high number of positive cases and total deaths, forcing World Health Organization to declare it as a pandemic on 11th March 2020. During these unprecedented events, governments have had a tough decision to balance between the constitutional obligation to hold an election and the safety of the people. As such, electoral commissions have implemented numerous approaches to allow election to proceed in a safe and controlled setting during the pandemic.

Methods: The preventative measures and standard operating procedures in the Sabah state of Malaysia, New Zealand and the United States elections are discussed, as well as COVID-19 post-election situation in respective countries. Innovative approaches and election flexibilities shall be considered to allow voting in the safest way possible, following the new normal.

Discussion: Nevertheless, countries need to evaluate its strength of public health response when deciding to hold elections due to potential devastating outbreaks following elections despite measures taken.

Conclusion: The election is a fundamental process in a democracy. Countries are required to be flexible and innovative in their approach to hold a safe election. Nevertheless, it may be prudent for countries with fewer resources and poor pandemic control to postpone election as a rise in cases will be catastrophic, putting many lives at risk.

Keywords: Election, COVID-19, voting, Sabah, New Zealand, United States

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Received: 28/11/2020
Accepted: 13/12/2020

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is the virus strain that causes COVID-19 pandemic that has grappled the world since March 2020. It is transmitted via respiratory droplets, highly infectious in closed spaces and prolonged exposures (Cevik, M. *et al.*, 2020). Many countries have had some form of government instituted "Lockdown" as a part of public health measures to curb the spread, much to the detriment of the economy and social mobility. Malaysia went through its Movement Control Order (MCO), heavily regulated with multi enforcement agency involvement and has seen success at flattening the second wave that started in late February of 2020 with only 277 cases recorded. (MHM; 04 June, 2020).

Malaysia operates a few level of lockdown, Enhanced MCO (EMCO) is a more stringent order for specific locations where a high number of cases from clusters were found, Conditional MCO (CMCO) have more relaxed regulations that aim to reopen the economy safely. The Recovery MCO (RMCO) allows for interstate travel and lifting of most restrictions, it was introduced on the 10th of June after successful 'flattening of the curve' (reduction of projected number of cases with public health intervention). Although the borders were closed, Malaysians were free to travel within the country with constant iterations to adopt the new normal of physical distancing and compulsory mask-wearing in public places (MHM; 01 August, 2020). However, the country's pandemic response was tested when the third most populous state (3.2million) situated in its Bornean Island, Sabah went through a state election. Other countries such as the United States, New Zealand, South Korea, and Singapore have also held their general elections, while 67 countries have seen its election postponed (IFES; 17 November, 2020).

Hence, International Foundation for Electoral Systems (IFES), an international and non-profit organization that provides technical support and engages in critical issues in regards of democracy and election, has published useful guidelines and recommendations on conducting election during the pandemic (IFES; 21 October, 2020). IFES has engaged and actively observing elections in many countries such as Libya, Tajikistan, Czech Republic, Moldova and Myanmar. IFES recommendations have been an important reference to electoral commissions all over the world in effort to build sustainable democracy.

This article will discuss the situation and protective measures taken during the election period, as well as COVID-19 trend post-election in Sabah (Malaysia), New Zealand and the United States between September and November 2020.

Methods

Sabah, Malaysia

The state election was held on the 26th of September after the dissolution of the State Legislative Assembly on the 30th of July 2020. A standard operating procedure (SOP) was released by the Election Commissions of Malaysia which covered campaigning as well as voting guidelines. Campaigning involved public rallies, home visits, and inter-state travel between east and west Malaysia (MEC; 20 September, 2020).

Public gatherings were limited to 250 people, subject to venue capacity with physical distancing of 1meter. Home visits were allowed limited to 3 persons, with no physical contact. The electoral commission opened postal votes for election workers, absent voters abroad, and authorized health and security personnel. Other than the aforementioned groups, no postal voting was allowed (MEC; 22 September, 2020). This includes Sabahans residing in Sarawak or peninsula Malaysia, which was estimated at 250,000 people, including the elderly, who were more susceptible to complications of COVID-19 infection (Boo, S., 24 August 2020). Early voting was allowed for policemen and military personnel on the 22nd of September for 16,877 eligible voters (MEC; 22 September, 2020). COVID-19 patients were not allowed to vote, and individuals under quarantine order were allowed to vote after health clearance with the district health officer (ECM; 27 September 2020).

On polling day, voters were required to adhere to time slots as stated in their voter's cards to avoid congestion. Temperatures were taken; voters with symptoms were taken aside to vote in a separate area and received immediate medical attention from healthcare workers (MEC; 20 September, 2020). The electoral commission reported 749,083 voters or a 66.61% voter turnout, including postal and early voters (ECM; 27 September 2020).

Sabah saw a rise in cases before polling day with the first case identified at a detention centre in Lahad Datu on the 1st September 2020. Transmission from residents to workers at the centre caused a community outbreak. This cluster is the largest in Sabah with a total of 1146 cases (MHM; 28 August, 2020). Cases in Tawau, and Lahad Datu started increasing prior to voting day, whilst other regions saw an increasing trend after the Election Day. Interior division of Sabah which rarely records cases was also affected. The porous borders also attributed to the cases on the East Coast (**Figure 1**).

Enhanced MCO was enforced in Tawau prison from 11th of September, and Tawau division was subsequently under Conditional MCO on the 29th of September after polling day. The West Coast followed with reinstatement of CMCO on the 7th of October 2020, and eventually a state-wide directive for CMCO was implemented on 12th of October 2020 due to a rise in community spread. Schools were closed, inter-district travels were restricted, and only essential services were allowed to operate (Ibrahim, M.I., 11 October, 2020).

During the campaign and voting period, inter-state travel was permitted which have caused some spread to the Peninsular Malaysia. As of 21st of November 2020, 31 new clusters were identified across 9 states in West Malaysia linked to Sabah returnees contributing to a total of 528 cases (**Figure 2 & 3**). Before the rise of cases, a mandatory quarantine of 14 days was not imposed on returnees, however, quarantine and testing were then made mandatory with the increasing trend of cases linked to Sabah. Selangor and the Federal State of Kuala Lumpur and Putrajaya had the most cases with 15 clusters seen (Abdullah. N.H., 20 November 2020).

Although the election was constitutionally mandatory and held under a seemingly safe and controlled setting, it ultimately led Malaysia into the third wave of the pandemic. Due to the logistical and resource issues in Sabah, in addition to movement control order and test, trace and isolate strategy, the Ministry of Health Malaysia had to mobilise the workforce from the Peninsular Malaysia. This has successfully reduced the R_0 from 2.2 to 1.06 in 6 weeks (Abdullah. N.H., 01 November, 2020). However, the economic and social burden of this strategy is immense.

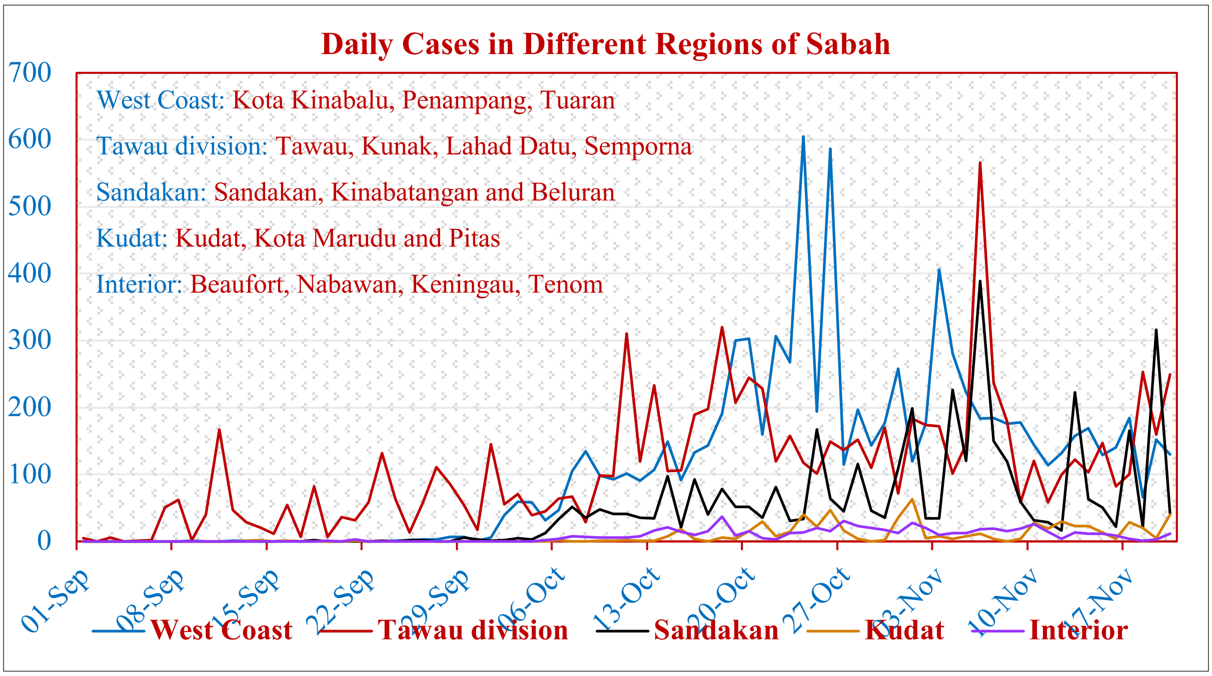

Figure 1: Trend of weekly COVID-19 cases according to divisions

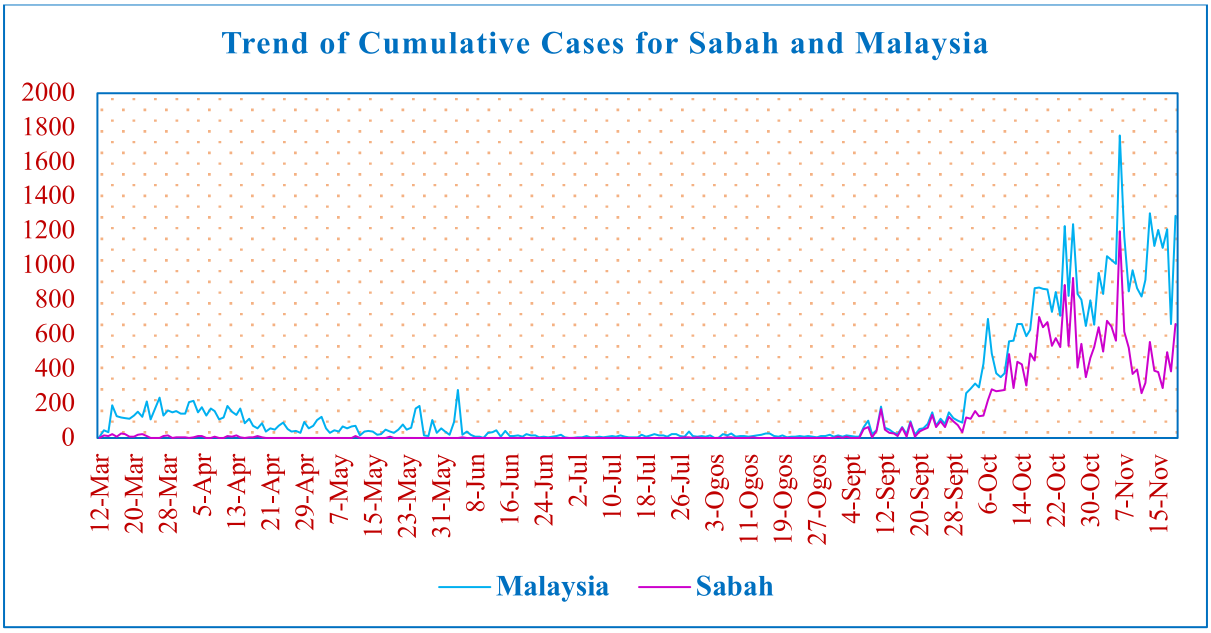

Figure 2: COVID-19 Case Trends in Malaysia and Sabah

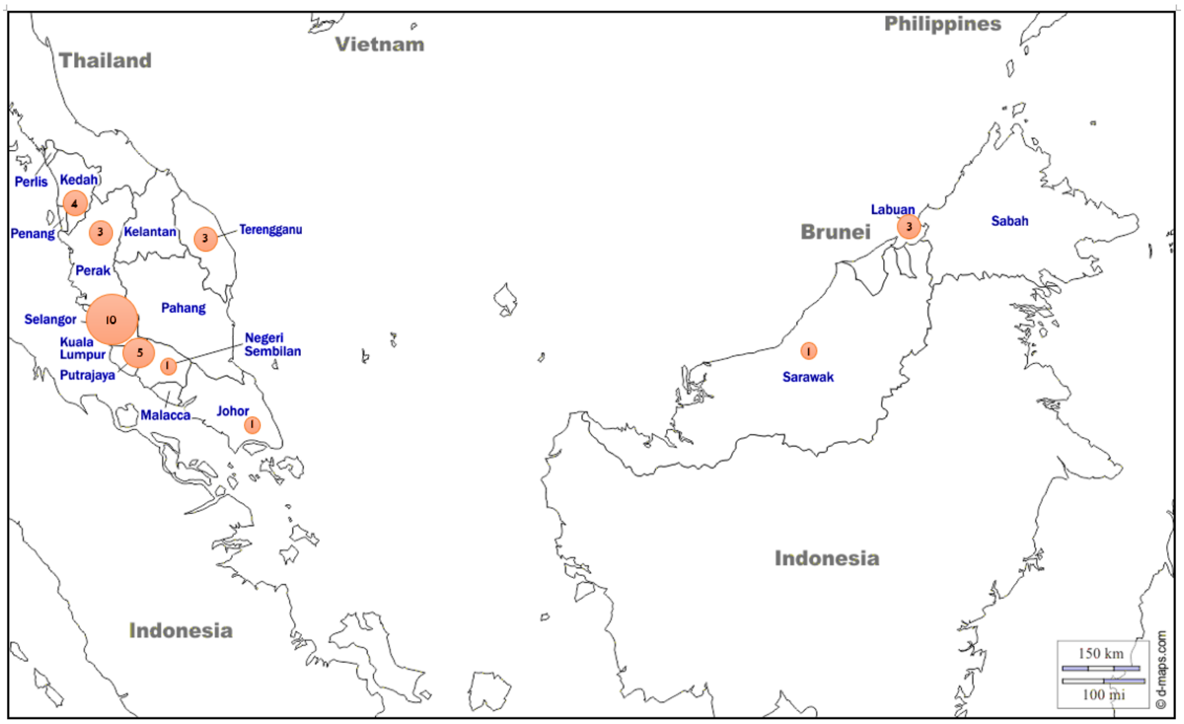

Figure 3: Number of clusters linked to Sabah returnees across Malaysia

New Zealand

An islandic country in Oceania region with an estimated population of 5,101,400 as of 20th September 2020 (Stats, 30 September, 2020), New Zealand has been among the better countries in dealing with COVID-19. It was contributed by the swift and decisive action taken by the government, implemented a stringent nationwide lockdown on 26th March 2020 which lasted for 7 weeks, as well as strong border control, which was easier for remote island states, as compared to other countries (Baker, M.G et. al., 2020; Cousins, S. 2020). Subsequently, the number of positive cases drastically reduced and New Zealand was among the earliest to flatten the curve.

As a democratic country, New Zealand held its election every three years, which recently took place on 17th October 2020. Prior to the election, New Zealand had 46 active cases, all of which were imported cases, with a total cumulative number of 1,524 as of 16th October 2020 (MHNZ; 16 October, 2020). In fact, New Zealand was on 3-weeks streaks of no community COVID-19 case, which was last detected on 25th September 2020 (MHNZ; 25 September, 2020). With these reassuring figures, the New Zealanders went on to vote as planned on 17th October 2020.

The Electoral Commission of New Zealand introduced several measures to accommodate the voting process during this pandemic. One of the measures was to allow advance voting starting from two weeks before the election date, to reduce queues and crowds in the voting centers (Ensor, J., 13 October, 2020). These voting centers also adopted preventive measures by increasing the size and number of voting places, promoting contact tracing phone application, abundant hand sanitizers, encouraging voters to bring their pen, as well as observing social distancing rules (ECNZ; 03 October, 2020).

Apart from that, the category of voters allowed for postal vote also widened, allowing citizens in rest homes, prisons, overseas, and hospitals to cast their vote. Even registered voters in isolation or quarantine facilities also can exercise their rights to vote by telephone dictation service, to minimize the risk of COVID-19 transmission (ECNZ; 03 October, 2020).

With these proactive initiatives, New Zealand was able to conduct the election in a controlled setting. Despite recording of one positive COVID-19 community case on the next day *i.e.*, on 18th October 2020 (Roy. E.A., 18 October, 2020), the pandemic still appeared under control, with the cases for the next two weeks post-election varied from zero to 25 cases daily, and the majority of the positive cases were imported cases constituting around 95% of the daily cases. As of 18th November 2020, approximately one month after the election, the cumulative confirmed cases were 1652 cases (MHNZ., 18 November, 2020), an increase of 128 cases compared to pre-election, with the community cases approximately 15 to 20 percent of the increase. Meanwhile, the total deaths were 25 cases, and thus, death rate of 0.015 percent, significantly lower than most countries (**Figure 4**). New Zealand has proven that an election certainly could be held during the pandemic, with the help of strict preventive measures and a relaxed voting process, while ensuring the integrity and voices of its citizens will always remain respected.

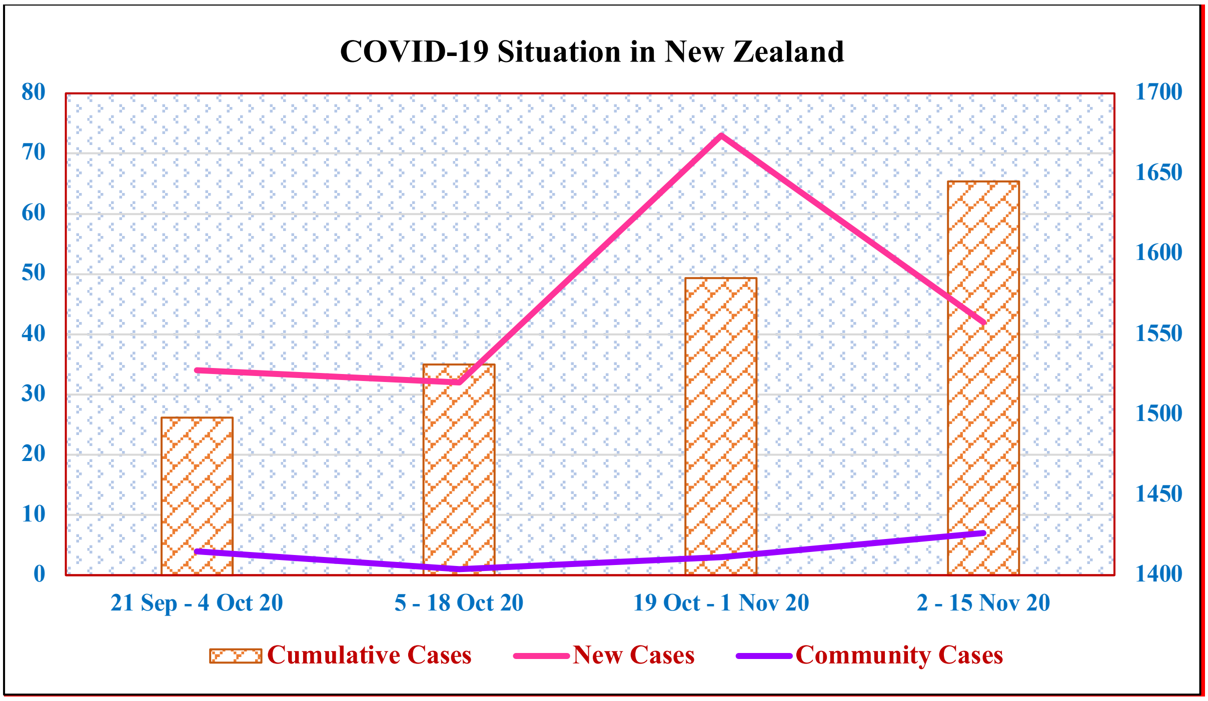

Figure 4: COVID-19 Situation One Month Prior and After Election on 17th October 2020

United States

The United States of America, or commonly known as United States (US), is a country in the North American continent, between Canada and Mexico. The US consists of 50 states and an estimated population of 328,239,523 as of 1st July 2019, making it the third-most populous country in the world (USCB, 19 November, 2020).

As COVID-19 swept across countries all over the world, US was not spared, having recorded its first case on 20th January 2020 (Holshue, M.L. *et. al.*, 2020). Since then, positive cases and death rates have exponentially increased, surpassing China, India, and Italy, becoming the leading country in terms of the highest number of COVID-19 positive cases and highest total deaths (Miller, I.F. *et. al.*, 2020). Despite its technological advancement, the healthcare professionals were alarmed by the possibility of an overburdened and overwhelmed healthcare system if the infection trend does not show any signs of improvement soon (Perc, M., *et. al.*, 2020).

The worry turned into a major concern with the looming general election in early November. The US held its election every 4 years, and the highly anticipated US election between President Trump (Republican) and Joe Biden (Democrats) on 3rd November 2020, was bound to cause increased movement intra- and interstate as well as mass gathering, hence increasing the risk of COVID-19 transmission (James, T.S., *et. al.*, 2020). In view of this, Centres for Disease Control and Prevention (CDC) and US Election Assistance Commission (EAC) have proposed numerous recommendations to minimize the risk during the election period. Among the recommendations were observing social distancing, frequent cleaning and disinfection of the polling place, handwashing, as well as offering masks and gloves (USEAC; 19 November, 2020). Physical barriers like plexiglass shields were also used between workers and voters and between voting stations. Postal votes also showed a significant increase, with more than 65 million postal votes sent in (BBCN; 06 November, 2020).

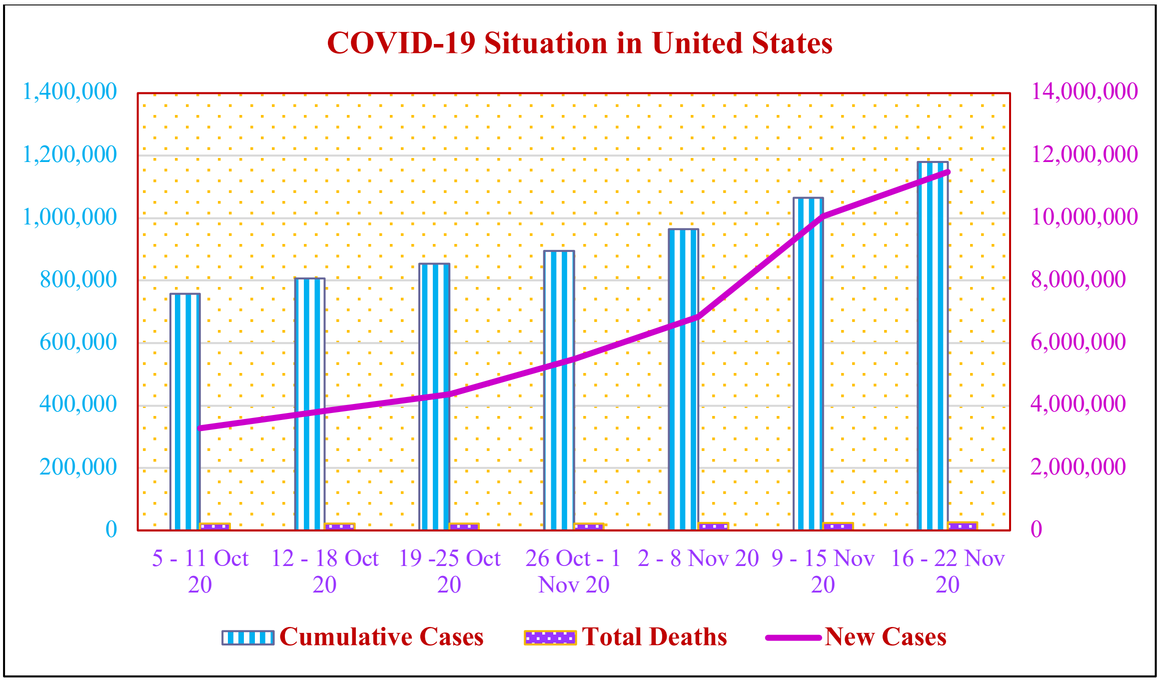

Figure 5: COVID-19 Situation Prior and After Election 3rd Nov 2020

Despite the encouraging actions, wearing a face mask was not made mandatory nationwide, as this falls under the jurisdiction of state governors. States such as Oklahoma, Nebraska, Missouri, and Mississippi encouraged the use of face mask but rejected the calls for state mandate (Markowitz, A., 17 November 2020).

Hence, voters were able to go to polling stations without wearing a face mask, which increased the risk of COVID-19 transmission (Waldmeir, P.; 29 October 2020). To make things worse, large-scale political rallies were held at various venues all over the countries (AJ; 31 October 2020), with little practice of wearing masks and physical distancing.

A month before the election, there were 7,645,156 positive cases and 214,690 total deaths in the US. As of 18th November 2020 (approximately two weeks post-election), there were 11,300,635 cumulative COVID-19 positive cases and 247,834 total deaths recorded in the US (CDC; 18 November, 2020). A significant increase of 3,655,479 positive cases was seen in just 6 weeks, and total deaths also increase by 33,144, which equates to a death rate of 0.022% (**Figure 5**). The most worrying thing is this data is only illustrating the COVID-19 situation two weeks post-election and based on the earlier Sabah state election in Malaysia scenario, the US may show a similar increasing infection trend. The updated forecasts based on these alarming surge of cases offered grim outlook, and with Thanksgiving and Christmas on the horizon, the worst is perhaps yet to come (CDC; 11 December, 2020).

Discussion

There is no doubt that election is an integral part of democracy. As such, to uphold the constitution status as the supreme law of the country, countries must abide by and hold elections accordingly. There are only a few exceptions that can result in the postponement of an election such as a state of emergency, but never to cancel the election altogether (James, T.S. et. al., 2020). Article 21(3) of the Universal Declaration of Human Rights notes that states must have regular, periodic elections (35). Article 4 of the International Covenant on Civil and Political Rights, meanwhile, states that “in time of public emergency which threatens the life of the nation and the existence of which is officially proclaimed, the States Parties may take measures derogating from their obligations under the present Covenant to the extent strictly required by the exigencies of the situation” (UNGA; 1966).

In Malaysia, Yang di-Pertuan Agong is the constitutional monarch and the head of state of Malaysia. His Majesty was elected by the Conference of Rulers, which comprised of the nine rulers of the Malay states. His Majesty has the absolute power to prorogue or dissolve the parliament and call for an election, as well as the power to declare a state of emergency. Likewise, in New Zealand and the US, the power to dissolve the parliament or postpone the election is in the hands of the Governor-General and US Congress, respectively. The commitment to call for election is certainly not a decision made lightly and done after careful deliberation and extensive due diligence.

As shown by New Zealand, a truly democratic process can be continued amid pandemic, with the proviso that the necessary precautionary measures are complied with and adopted, as well as encouraging innovative approach to enable citizens to fulfil their responsibilities and choosing the government (Gunia, A., 12 October, 2020). On the other hand, Malaysia, for its part, had initial relative success in flattening the curve.

The decisive actions by the government to implement Movement Control Order (MCO) back in March 2020 were instrumental in Malaysia's effort to reduce the R_0 to less than one. In the run up to Election Day in Sabah and the US, large-scale political gatherings and campaigns held by the political parties resulted in a surge of new cases, ultimately leading Malaysia into the third wave of the pandemic (TST; 18 November 2020). Although the Electoral Commission of Malaysia has enforced a strict standard operating procedure (SOP) for the election to control the risk of COVID-19, it certainly had room for further improvement.

In these unprecedented times, embracing the new normal is a matter of survival. With vaccine development still in progress, this pandemic is far from ending (Jabbari, P., 2020). Many sectors, such as education and business have evolved and transitioned to the virtual environment, following the new normal. Admittedly, a similar shift in operational methods is difficult to achieve in an election. It is a monumental process in which the possibility of error or manipulation cannot be tolerated, but the pandemic has challenged the traditional approach and calls for the election process to be reviewed. Perhaps, election flexibility as shown by New Zealand could be the perfect example of how to conduct a safe election.

Conclusion

The election is a fundamental process in a democracy. Countries are required to be flexible and innovative in their approach to hold a safe election. Nevertheless, it may be prudent for countries with fewer resources and poor pandemic control to postpone election as a rise in cases will be catastrophic, putting many lives at risk.

Conflict of Interest

The authors wish to declare that there is no conflict of interest. No funding was received.

Authors Contribution

All authors contributed equally to this work.

Acknowledgements

The authors would like to thank COVID-19 Preparedness and Action Centre University Malaysia Sabah for data on COVID-19 trends in Sabah and Malaysia.

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BEJ, VOLUME. **1**, ISSUE **2**, DECEMBER **2020**

BORNEO EPIDEMIOLOGY JOURNAL | BEJ

PERSPECTIVE **Open Access**

Teaching Epidemiology and Biostatistics: A Peer-Led Teaching Module for Postgraduate Psychiatry Student

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Abstract

Background and Objective:

Biostatistics and epidemiology have been integral subjects in any postgraduate courses, including medical specialties Master programs. Both are widely accepted as among the difficult and confusing subjects, which worsen by lack of adequate exposure and often, time constraints. Hence, peer-led learning approach was proposed as a viable option to the traditional lecturer-driven learning style.

Method:

The peer-led approach intends to promote targeted learning and conceptual understanding, instead of widely sweeping learning, which is rather directionless and could cause information overload.

Discussion:

Students were divided into two groups, namely humanities-inclined group and science-inclined group. Different pedagogical methods to address the different groups were discussed.

Conclusion:

This approach helps to make the learning more palatable, boosting knowledge retention and fostering camaraderie spirit among colleagues.

Keywords: Biostatistics, postgraduate students, teaching tip, peer-led pedagogical approach

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Received: 19/10/2020
Accepted: 15/12/2020

Introduction

Biostatistics and epidemiology is a core part of any postgraduate curriculum with any research component. Uniquely in Malaysia, it is an especially integral part of the clinical specialist training pathway (Sidi, H. *et. al.*, 2008). This is because in Malaysia the training pathway is structured as a four-year part time Master's degree, while providing clinical service at the same time in either university or Health Ministry hospitals, culminating with an in-course dissertation in the final year (Ahmad, Z. et. al., 1999). Unlike pure research or part research Masters Programmes, however, the clinical specialist Masters programme is especially academically taxing, as it merely has one six month in-campus training section. This is not pure classroom-driven, but rather structured as clinical service with protected teaching time (Salim, H. *et. al.*, 2018). Due to these constraints, provision of research methodology education differs from university to university. Each university in theory will have at least ten hours of research methods training in the first year and a week-long research methodology course in the third year. However, as this can be blended into clinical work, it is difficult to have complete focus, and hence the realistic outcomes of this teaching method can be of varying quality, from complete understanding and application, to mere surface level understanding sufficient for passing written examinations only and not retained in any form subsequently (Baharudin, A. *et. al.*, 2009). Hence, to facilitate the learning process for these difficult subjects, a peer-led driven pedagogical approach was adopted and the feedbacks were encouraging. The peer-led styles are discussed further in this article.

Methods

Teaching Tip

One way of overcoming these issues is to get "peer support" to provide education to subsequent batches. This support would be given by fellow Masters Students from senior batches that have undergone the same Masters programme and passed the examinations previously. This would be more efficacious as the knowledge would be provided by peer educators who would be more aware what aspects of research methodology were more relevant for clinical practice or dissertation preparation. The idea of peer educators is not new and has been used in various international settings (Yu, T.C. *et. al.*, 2011). However it is more novel in a Malaysian system, perhaps due to a lecturer-driven learner style, which is reflective of "large power distance, collectivism, and high uncertainty avoidance" (Yong, F.L., 2010). However this attitude has changed in recent years in view of parallel moves towards both student-centred education and self-directed learning approaches (Spencer, J.A. *et. al.*, 1999). Peer education and support has been increasingly viewed as a valuable and untapped teaching resource of learners assisting other learners (Cate, O.T. *et. al.*, 2007).

Over three years, two Masters Trainees in Psychiatry gave peer-driven education about biostatistics and epidemiology to juniors in the same programme. This would be tailored to two specific requirements - exam requirements, and also topics of relevance to both actual critical appraisals in clinical practise and also towards research related requirements.

This served the purpose of preventing directionless, overly widely sweeping learning that did not serve any practical requirements and caused information overload. Instead, learners were encouraged to do targeted learning with some assessment, clinical or research utility. This ensured information was encoded longer for potential use.

A few unique pedagogical methods were employed. One was stratification of peers into "science-inclined" and "humanities-inclined" learners, which essentially determined by method of their learning and judgement, either by primarily technical judgement or humane judgement, as well as preference to think in algorithms or the abstract aspects. This was because one of the main barriers noted in learning biostatistics and epidemiology was that a one-size-fits-all method of teaching was applied to all learners for a topic that many trainees had previously little or no exposure to. As psychiatry training programmes generally attract a large proportion of humanities-inclined doctors, traditional approach would result in poor understanding amongst them. The two groups were taught using subtly different methods, but both methods were blended during the class, and trainees could pick and choose the aspects of each method that suited them best.

For the science-inclined trainees, a method was devised where they were taught to recognise patterns and focus on core understanding of first principles of biostatistics. For instance, they were taught to derive odds ratios and relative risks from scratch rather than blindly memorising formulae. For the humanities-inclined group, overall principles were taught in a "storyline" method, categorizing study designs and associated statistical tests in order from "weak" to "strong". Any new information was always linked back to the same overarching "evolutional" model of biostatistics. This helped them see the bigger picture and form a narrative about the biostatistics they were about to learn. The shock and humour factor were also used to great effect. As biostatistics is traditionally seen as dry and difficult to remember, where possible, memorable bordering on improbable examples were used to illustrate statistical principles. Both methods were blended and mixed during each session.

For instance, instead of blindly educating about "Type I and Type II errors" - traditionally one of the most difficult subjects to master - we began with use of humorous examples. "Television is associated with lung cancer" was taught as an example of Type I error, which essentially a simple analogy to describe false positive and rejection of true null hypothesis, as television is not associated with lung cancer. Meanwhile, "Clozapine is not able to treat schizophrenia - however the study is done in 3 people" was used as an example of Type II error, which would be considered as false negative and non-rejection of false null hypothesis, as Clozapine is well known to be one of the better medicine to treat schizophrenia. Expanding on that, we then diverted into the "science-inclined" method where the method of deriving alpha and beta values was explained step by step rather than through blind formula memorisation. Subsequently, trainees from both groups were asked to provide peer-led education, by teaching what they had just learnt to each other. The science-inclined group thus helped the humanities-inclined group with the understanding of basic principles, while the humanities-inclined group helped the science-inclined group to see the bigger picture better. It was felt that trainee-driven peer teaching meant better empathy as they could identify better with each other's' weaknesses, as compared to teachers or seniors with mastery.

This method was refined over three years with three consecutive batches of trainees, who ranged from batches between six months to two and a half years junior in relation to the authors. The authors sought continual feedback over the years in order to modify and improve the pedagogical methods to be of better relevance. Also, over the years, the modules were shortened significantly but made more frequent, as it was found that it was almost impossible to spend more than 45 minutes to an hour learning about postgraduate level statistics due to primary and recency effect. A further addition was also implemented, where during subsequent sessions a five-minute refresher of the past week's lessons would be done, also by one of the trainees. Each session would then also end with a five-minute peer-led assessment, summarization and reflection.

Discussion

Over the years, the feedback was that a peer-driven teaching model was a valuable addition to the existing biostatistics curriculum. It does not supplant, but rather, enhances existing lecturer-driven education. This was because peers from earlier batches were more in touch with the practical and assessment requirements of learning statistics. Students were more likely to pick up information if they were informed that it would assist in passing an exam, and they were more likely to pick up tips about passing exams when they came from fellow students who had already passed.

Through the peer-driven approach, it was found that most of the students agreed that there were remarkable changes and they were able to comprehend these difficult subjects much better, learning from someone who have "been there, done that". This is consistent with models of adult learning where adult learners are more motivated to learn when it is perceived as relevant and builds on their previous experiences (Spencer, J.A. *et. al.*, 1999). Also peer-driven programmes were helpful as less jargon was used. This is elaborated by Lockspeiser et al as due to increased "cognitive congruence" between near-peer educators and teachers (Cate, O.T. *et. al.*, 2007), as they share a similar knowledge base, and hence can pitch teaching to trainees' similar standards (Lockspeiser, T.M. *et. al.*, 2008).

This is fairly consistent with existing literature that shows that peer-driven learning is helpful in selected contexts (Yu, T.C. *et. al.*, 2011). The General Medical Council in the UK in fact explicitly states that "medical graduates must function as educators" (GMS *et. al.*, 2010), and medical schools in the UK are already adopting pilot projects to that effect (Jackson, T.A. *et. al.*, 2012). In the long run, this is important as doctors will have to hold teaching roles (Dandavino, M. *et. al.*, 2007). Specifically, psychiatry trainees will become psychiatrists who will be expected to be able to educate both their patient through psychoeducation within clinical consultations, and the general public through awareness talks. Hence peer-led education is a good start in developing those skills in the long run. Moreover, there is of course consensus that peer-driven teaching also refines the knowledge of the teacher through reflective learning (Tang, T.S. *et. al.*, 2004).

This concurs better with international efforts to move towards student-centred and problem-based learning, and encourages students to take charge of their own education rather than wait to be spoon-fed by lecturers. This also indirectly helps boost their retention, as peer-driven models by definition involve newly educated peers repeating their newfound information back to other peers, thus reinforcing the registration pathways due to repeated use (Cate, O.T. *et. al.*, 2007). Through this process also, peers learn the valuable lesson of working together as a team to surmount obstacles of understanding and application (Evans, D.J.R. *et. al.*, 2009). This is a lesson that doctors today will need to carry forward to their careers, as patient care is always best optimized when a multidisciplinary rather than solitary approach is practiced.

Conclusion

As conclusion, we would like to suggest peer-driven teaching of postgraduate clinical specialist trainees who are simultaneously serving in hospitals during training and are unable to devote full-time attention to learning biostatistics and epidemiology. Future research to develop systematic peer-led pedagogical approach should be considered to advance medical education delivery. Comparison between the peer-driven and lecturer-driven educational style, similar to the comparison between module-based and subject-based medical education, would also be of great interest in defining future academic syllabus and producing better medical graduates.

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ACKNOWLEDGEMENTS

Acknowledgements to the funders, supporting organizations to be mentioned in the manuscripts.

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