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# MJM

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NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017; 389(10064): 37-55.

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Institute for Public Health. National Health and Morbidity Survey (NHMS) 2017: Adolescent Health Survey 2017. Malaysia: Institute for Public Health, Ministry of Health Malaysia; 2017.
5. Agency Publication  
National Care for Health Statistics. Acute conditions: incidence and associated disability, United States, July 1968 - June 1969. Rockville, Me: National Centre for Health Statistics, 1972. (Vital and health statistics). Series 10: data from the National Health Survey, No 69). (DHEW Publication No (HSM) 72 - 1036).

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Kaos J. 40°C threshold for 'heatwave emergency' Kuala Lumpur: The Star Malaysia; [updated 18 March 2016, cited March 2016]. Available from: <http://www.thestar.com.my/news/nation/2016/03/18/heatwave-emergency-threshold/>.

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# Malaysia's third COVID-19 wave – a paradigm shift required

Lekhraj Rampal, MBBS, DrPH<sup>1,2</sup>, Liew Boon Seng, M.D., M.S. Neurosurgery<sup>1,3</sup>

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## ABSTRACT

The first case of COVID-19 was reported in Malaysia on the 25 January 2020. By the 20 January 2021, the cumulative numbers reported confirmed cases of COVID-19 had reached 169,379 including 630 deaths. Malaysia has been hit by three waves of COVID-19. This article reports on the three waves, the current situation and some of the possible factors associated. It outlines the need to reassess the overall situation, re-strategize the approach in order to contain the spread. The first COVID-19 wave lasted from 25 January to 16 February 2020, the second wave occurred between the 27 February 2020 and the 30 June 2020. The current third wave began on 8th September 2020. The sudden surge of cases in the third wave was mainly due to the two largest contributors, namely the Benteng Lahad Datu cluster in Sabah state and Kedah's Tembok cluster. The current situation is critical. The daily confirmed cases of COVID-19 continue to soar. The challenges faced by healthcare workers and other front liners is tremendous. Non-communicable diseases such as cardiovascular diseases, diabetes and cancer are the leading cause of death in Malaysia. A paradigm shift in the approach is required to ensure the sustainability of the normal healthcare services provided by the government especially for the lower income groups. There is also a need to expedite the tabling of Tobacco Control Bill in coming parliament session which is long overdue. H.E. the King of Malaysia has called on all Malaysians to put aside political, racial and religious differences and show the spirit of loyalty, humanitarianism and steadfastness in fighting the COVID-19 pandemic.

## GLOBAL SITUATION UPDATE

By the 20 January 2021, the cumulative number of reported confirmed cases of COVID-19 globally had reached 96,624,404 including 2,065,672 deaths and 69,273,006 had recovered since the start of the pandemic.<sup>1</sup> The pandemic has caused high and far reaching social, economic and political impact on nearly all the countries in the world. With all the advancement in technology and tools over the years, scientists all over the world, are still grappling with a lack of detailed knowledge of the molecular mechanisms that generate the endless flow of mutations and adaptations that is making SARS-CoV-2 difficult or impossible to contend with. In addition to reducing the determinant/risk factors related to the disease, the most effective method of preventing infectious diseases is vaccination. Vaccine for COVID-19 is being developed and marketed globally at unprecedented scale and speed.<sup>2</sup> There are different COVID-19 vaccines.

There are currently more than 50 COVID-19 vaccine candidates in trials. The World Health Organization (WHO) on 31 December 2020 listed the Comirnaty COVID-19 mRNA vaccine for emergency use, making the Pfizer/BioNTech vaccine the first to receive emergency validation from WHO since the outbreak.<sup>3</sup> Comirnaty is a vaccine for preventing coronavirus disease 2019 (COVID-19) in people aged 16 years and older. Comirnaty contains a molecule called messenger RNA (mRNA) with instructions for producing a protein from SARS-CoV-2, the virus that causes COVID-19. However, there are COVID-19 vaccines for which certain national regulatory authorities have authorized for emergency use.

However, it is important to note that multiple COVID-19 variants are now circulating globally. In the United Kingdom (UK), a new variant called B.1.1.7 has emerged which has an unusually large number of mutations. This variant spreads more easily and quickly than other variants. Globally, scientists do not know how widely these new variants have spread, how the disease caused by these new variants differs from the disease caused by other variants that are currently circulating, how these variants affect the existing therapies and vaccines. Scientists are working to learn more about these variants and their implications.<sup>4</sup> More than 32 other countries have detected the new COVID-19 variant first seen in the UK.<sup>5</sup>

## COVID-19 STATUS IN MALAYSIA

The first case of COVID-19 in Malaysia was reported on the 25 January 2020, involving three China tourists who had entered Malaysia via Johor from Singapore on Jan 23.<sup>1</sup> Since then Malaysia was hit by three waves of COVID-19 before the end of 2020.<sup>2</sup> The first wave lasted from 25 January to 16 February 2020. The number of cases then rose to 22 by the 16 February 2020, representing a first wave of cases. The second wave started on the 27 February 2020 and lasted until the 30 June 2020. The biggest cluster was the Seri Petaling cluster, involving a religious gathering held at a mosque in Seri Petaling Kuala Lumpur. The handling of two waves were handled well.<sup>6-8</sup> Rampal in May 2020 reported that the number of new cases of COVID-19 confirmed per day showed a decline at that point in time. Although this may have indicated that the peak was over. It did not indicate that COVID-19 outbreak has ended. In a propagated source outbreak, we may experience many peaks, the successive waves may involve more and more people, until the pool of susceptible people is exhausted. It is important to remind that the flattening the curve does not mean eradication of the disease. COVID-19 infection will be around for a while.<sup>7</sup>

### ***The third wave***

The third wave began on 8 September 2020.<sup>6</sup> Malaysia is facing a much tougher task in curbing the COVID-19 pandemic in the third wave compared to the previous two waves. The COVID-19 pandemic is straining the health systems and the economy of the country. The Director General (DG) Health, Tan Sri Dato' Seri Dr Noor Hisham bin Abdullah, on 9 September 2020 stated that this sudden surge of cases was due to the two largest contributors, namely the Benteng LD cluster in Sabah and Kedah's Tembok cluster. The Institute of Medical Research (IMR) Malaysia had detected the D614G-type mutation in the virus samples. The D614G-type can be easily transmitted with a higher infection probability.<sup>9</sup> By the 20 January 2021, the cumulative number of reported confirmed cases of COVID-19 had reached 169,379 including 630 deaths and 127,662 had recovered. The daily number of confirmed cases continue to soar. The situation has become critical and the daily confirmed cases of COVID-19 reaching 2,000 to more than 4,000. Healthcare workers including doctors, nurses and other front-liners have been found to be positive for COVID-19. Politicians including Ministers have also been found to be positive for COVID-19. The increase in the number of COVID-19 cases and overburdened healthcare is taking a toll on the front-liners. The challengers faced by healthcare workers and other front-liners was tremendous. The COVID-19 designated hospitals and low-risk treatment centres were nearing their limits.

The DG of Health, Ministry of Health (MoH), Malaysia stated on 6 January 2021 that the Malaysian health system has been pressured and are at a breaking point because cases are increasing every day with almost full utilisation of the hospitals and low risk isolation centres. He has suggested for the implementation of targeted movement control order (MCO).<sup>10</sup> The MoH has issued several criteria to allow positive cases to be treated at home. These patients are instructed to remain home and be contactable at all times.

The Yang di-Pertuan Agong (King) has called on all Malaysians to put aside political, racial and religious differences and show the spirit of loyalty, humanitarianism and steadfastness in fighting the COVID-19 pandemic.<sup>11</sup>

### **Possible factors associated with the third wave**

The third wave can be attributed to multiple factors related to the agent, host and environment. The coronavirus disease 19 (COVID-19) is a highly transmissible and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Current evidence suggests that the main way the virus spreads is by respiratory droplets mainly when an infected person is in close contact with another person. The rapid human to human transfer has been noted widely.

### ***Politics and 16th Sabah election***

The Prime Minister of Malaysia, Tan Sri Dato' Haji Muhyiddin bin Haji Mohd Yassin, on the 18 November 2020 admitted that the Sabah state election in September was the cause of the latest wave of COVID-19 infections in the country. The number of cumulative cases in the state was 808

on nomination day on the 12 September 2020, increasing by 91.5% to 1,547 cases on polling day on the 26 September 2020. Four weeks later on the 24 October 2020, Sabah recorded 11,285 cumulative cases, becoming the first state in the country to record more than 10,000 cases.<sup>12</sup> By the 20 January 2021, 45,008 confirmed cases (out of which 44,602 had recovered) and 305 deaths have been reported.<sup>13</sup> It is to be noted that thousands of political campaigners along with Cabinet Ministers that returned to their home states after the state polls, caused a spike in coronavirus cases throughout Malaysia. A possible factor is that politicians were more interested in the polls rather than following standard operating procedures (SOPs) set by the Government. It is not possible at this stage to verify whether the politicians spread the disease from Sabah to Peninsular Malaysia or vice versa as no COVID-19 test was carried out before they went to Sabah. The Government of Malaysia and the MoH in particular has been constantly reminding the people regarding maintaining physical distancing, wearing facemask and regular hand washing. If this was followed strictly by the politicians, the third wave would not have been so serious. Another possible factor for the increase in confirmed cases is the rate of COVID-19 tests performed per 1,000 population in Malaysia and Sabah in particular before and after Sabah cluster.

The Tembok cluster from the Alor Setar prison in Kedah also contributed significantly to the third COVID-19 wave. This cluster was detected on the September 2020 following the death of a 46-year-old man who had worked in the prison. A COVID-19 test after his death found the man to have been infected with the virus. Subsequent tests discovered the infection within the cluster has spread among prison inmates. This cluster became one of the biggest and most active cluster in the country.

### **Other Factors**

#### ***COVID-19 testing rate***

Rampal et al, 2020 had reported that the rate of COVID-19 tests performed per 100 population in Malaysia was very much lower than in Singapore. The testing rate has subsequently been increased during the last few months. The increase in the COVID-19 testing rate and coverage of the population could partially explain the increase in confirmed cases. They may have been there and spreading to others but not tested.

#### ***Attitude of the politicians and the population***

The Government has been constantly providing risk communication on daily basis. While the healthcare workers and the other front-liners were taking risks because of COVID-19, what the public read in the papers daily, is efforts being made by politicians to destabilise the country and seek a change in the Government or clamour for general elections. All Malaysians need to put aside political, racial and religious differences and fight the COVID-19 pandemic. Pockets of the population have still not grappled with the seriousness of the current pandemic. This could be due to fact that their livelihood is affected badly, lack of knowledge,



internalisation of the knowledge leading to 'I won't be affected' attitude or due to the low mortality rate of SARS-CoV-2.

### **Third COVID-19 wave – a paradigm shift required** **Paradigm shift required**

As the country enters into this critical stage of the pandemic, we need to reassess the overall situation, re-strategise and move ahead. The questions we need to ask ourselves are: are we not putting too much resources such as money, materials, staff, and other assets in one disease that has low mortality? Are the other normal health care services for managing other diseases that cause more mortality being affected? Are we going to follow other countries where their health care structure is at the brink of collapse? We must sit back and realise that we are faced with the double burden of disease. Non-communicable diseases such as cardiovascular diseases, diabetes and cancer are the leading cause of death in Malaysia. Are they not being neglected and are we going to neglect our population especially those in the lower income group from these services provided by the Government?

### **Management of the outbreak**

The policy of Malaysia first need to be emphasised. All Malaysians should put aside political, racial and religious differences and show unity and steadfastness in fighting the COVID-19 pandemic. District Action Committee that already exist should be activated and become responsible for the containment of the outbreak in their own districts. It should be chaired by the District Officer and the Secretary should be the Medical Officer of Health. All heads of Government departments at the district must assist the MOH. All their staff should be roped in to assist the District Health Office to manage any COVID-19 outbreak. The Members of Parliaments and State assembly representatives members should play active part in ensuring the people understand their roles and abide by the SOPs set by the Government. The village and regional heads (*Ketua kampung* and *penghulu*) must play an active role. The District Officer and the Medical Officer of Health must be represented at the State Epidemic Committees. Meetings can be through an online platform in place of face-to-face ones and they should bring the most relevant people into the meeting. This will require broad and well-coordinated collaborative efforts to flatten the curve. In all the cities and towns similar committees to assist the health staff. There is no one-size-fits-all approach, hence all districts should be allowed to conduct their own level of preparedness, alert and response and reinforce community-led activities. The outbreak investigation and management teams need to be improved and better coordinated. Collaborative efforts and communication between District Health Office and hospitals need to be further enhanced and sustained.

The testing procedure may be speeded up. The time a patient's blood is sent for COVID-19 test to the time it is processed, and if diagnosed as positive; to the time the case is notified to the health authorities or authorities concerned with investigation; to the time action is taken need to be reduced. If the processing time for the test fails to achieve fast enough turnaround times (ideally, 1 to 2 days) to permit

effective contact-tracing efforts it will delay the action and contribute to the spread of the virus. Each of these steps are important and need to be monitored by the Medical Officer of Health.

Risk communication appears to be good, as the risk communication came from the top and have not caused panic among the public. However, it does not seem to have the impact it is expected to have. The population need to be constantly reminded on maintaining physical distancing, wear facemask, especially when distancing cannot be maintained, keeping rooms well ventilated, avoiding crowds and close contact, regularly washing their hands. A quick survey needs to be carried out to evaluate the impact of the risk communication and how to improve it.

### **Mobilisation of the communities, Non-governmental organisations (NGOs) and the private sector**

We need to further enhance the role of the general practitioners (GPs) in COVID-19 pandemic. They should be included to perform daily assessment on the health status of those that have been confined to home quarantine. COVID-19 patients who are asymptomatic or having mild symptoms (Clinical stage 1 and 2) with no comorbidity could be managed at home. The GPs could be included in the monitoring and assessment of this group of patients. The Government should formulate a payment mechanism to compensate the GPs for their contribution. Linkage between the public health sector and GPs as partners in prevention need to be enhanced. The standard of care among patients with non-communicable diseases should be maintained during this pandemic.

### **Meetings and Consultations with Experts in Public Health**

There are many public health experts who have sound practical experience in outbreak management and had served or are serving the Government. A committee/faculty can be formed to guide the Ministry of Health in flattening the curve.

### **End greed and corruption**

We have been constantly reminded in the newspapers of the extent of corruption in the country. We as Malaysians, need to end it. And we should all assist the nation out of this pandemic. We need to empathise not sympathise with those who have lost their loved ones, lost their jobs or businesses, lost their homes due to recent floods.

### **Smoking and COVID-19**

The current epidemiological finding suggests that active smoking is associated with an increased severity of disease and death in hospitalised COVID-19 patients. Smoking can upregulate the angiotensin-converting enzyme-2 (ACE-2) receptor utilized by SARS-CoV-2 to enter the host cell and activate a 'cytokine storm' which can lead to worsen outcomes in COVID-19 patients. This receptor can also act as a potential therapeutic target for COVID-19 and other infectious diseases.<sup>14</sup> There is a need to expedite the tabling of Tobacco Control Bill in coming parliament session which is long overdue. Rampal, 2020<sup>7</sup> has highlighted tobacco control measures that need to be taken during this pandemic without any more delay.

## CONCLUSION

The handling of this pandemic demands fast and difficult decisions within the health sector and beyond, i.e., leadership at the highest political level, and a 'whole of government' and 'whole of the society' approaches. It also requires the cooperation from all communities and private sectors. The whole Malaysian Government, Members of Parliament, community leaders and the people need to continue to work together to ensure the end of the COVID-19 crisis in Malaysia.<sup>7</sup> Volunteers should be trained to help in these efforts. Increase the capabilities of our public health service. Back-to-basics public health management should be our strategy. While we work towards rolling out a safe and effective vaccine, we must continue the essential public health actions to suppress transmission and reduce mortality. We should have the humility to listen, to learn, to change, to innovate and to grow.

## REFERENCES

1. Worldometer. 2021 COVID-19 CORONAVIRUS PANDEMIC Update <https://www.worldometers.info/coronavirus/> Accessed on 20/1/2021
2. United States Centers for Disease Control and Prevention (2011). A CDC framework for preventing infectious diseases.
3. World Health Organization. WHO issues its first emergency use validation for a COVID-19 vaccine and emphasizes need for equitable global access <https://www.who.int/news/item/31-12-2020-who-issues-its-first-emergency-use-validation-for-a-covid-19-vaccine-and-emphasizes-need-for-equitable-global-access>. Accessed on 20/1/2021
4. United States Centers for Disease Control. New COVID-19 Variants. <https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant.html>
5. New York Times. 32 More Countries Have Found the New Covid-19 Variant First Seen in Britain. <https://www.nytimes.com/live/2021/01/01/world/covid-19-coronavirus-updates>. Accessed on 20/1/2021
6. Rampal L, Liew BS. Coronavirus disease (COVID-19) pandemic. *Med J Malaysia* 2020; 75(2): 95-7.
7. Rampal L. COVID-19 Pandemic update. *Med J Malaysia* 2020; 75(3): 195-8.
8. Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. *Med J Malaysia* 2020; 75(6): 613-25.
9. New Straits Times. Covid-19: 3rd wave more challenging than last two, says Health DG. <https://www.nst.com.my/news/nation/2020/10/630993/covid-19-3rd-wave-more-challenging-last-two-says-health-dg> Accessed on 20/1/2021
10. Kenyataan Akhbar KPK 6 Januari 2021 – Situasi Semasa Jangkitan Penyakit Coronavirus 2019 (COVID-19) di Malaysia. [cited January 2021]. Available from: <https://kpkkesihatan.com/2021/01/06/kenyataan-akhbar-kpk-6-januari-2021-situasi-semasa-jangkitan-penyakit-coronavirus-2019-covid-19-di-malaysia/>
11. The STAR. The King calls on rakyat to unite in fight against virus. The STAR, Nation 20 January 2021 pp 5.
12. The Straits Times. Malaysia's PM Muhyiddin admits Sabah state polls in Sept caused current Covid-19 wave. <https://www.straitstimes.com/asia/se-asia/malaysias-pm-muhyiddin-admits-sabah-state-polls-in-sept-caused-current-covid-19-wave>
13. Sabahoutbreak COVID-19 Outbreak in Sabah. <https://www.sabahoutbreak.com> Accessed on 20/1/2021
14. Kashyap VK, Dhasmana A, Massey A, Kotnala S, Zafar N, Jaggi M, Yallapu MM, et al. Smoking and COVID-19: adding fuel to the flame. *Int J Mol Sci* 2020; 21(18): 6581.

# Reflections on the MMA CPD system

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The Malaysian Medical Association (MMA) is the body that represents registered medical practitioners in Malaysia. In 1994, it introduced a national Continuing Medical Education (CME) system on a voluntary basis for all doctors in the country. As a longstanding member of the MMA Continuing Professional Development (CPD) Committee, I wish to record some reflections on the MMA CPD System and document the history and the pioneering work of MMA in the area of CPD.

## History of the MMA CPD System

During the 33rd AGM of the MMA in Pulau Langkawi 1993, the following resolution was unanimously adopted by the House:

*“That this House resolves to direct the Incoming Council to ensure that the MMA will help implement, monitor and coordinate CME programmes for the MMA members, both specialists and non-specialists. Representatives from each group will be co-opted to form a committee and that the MMA will be the secretariat for the National CME Programme. Minimum attendance requirement for CME programmes will be monitored by the MMA through its branches and even at district levels. These returns will be conveyed to the MMC for their information towards eventual issuance of the Annual Practising Certificate.”*

Following this, the MMA Council formed the MMA CME committee to implement CME in a coordinated manner, the modus operandi for the MMA CME Programme was formulated and adopted by the MMA Council. The MMA CME Programme was launched in February, 1994.

## Collaboration between Malaysian Medical Council (MMC) and MMA

On 30th March 1994, the MMA was requested by the MMC “to undertake to conduct and co-ordinate CME credit activities for all medical practitioners (MMA members and Non-Members of the MMA). The MMA CME Committee and the MMC Standing Committee on CME met on 30th September 1994 and decided to adopt the MMC CME Grading system and the MMC, on 13th December 1994, officially appointed the MMA as the Secretariat for the MMC CME Grading System.

## MMC CME Grading System

This was launched on 11th January 1995 by the then President of the MMC, Tan Sri Dato’ Dr Abu Bakar bin Suleiman, with MMA as the Secretariat responsible for:

1. Registration of Providers
2. Accreditation of CME activities
3. Allocation of CME Points according to the MMC-CME Scoring Schedule

4. Collation of points accrued by registered participants, forwarding to MMC and preparation and issuance of certificates.

The name of the grading system was changed to MMC CPD Grading System in July 2006.

## MMC-CPD Grading System Scoring Schedule

The schedule for the MMC-CME Grading System initially had eight categories, 1A, 1B, 1C, 2, 3A, 3B, 4 and 5 (Appendix 1).

In 2014, the MMA worked with the MMC on a major revision of the MMC-CPD Grading System. The updated Scoring Schedule which had nine Categories, A1 to A9, was completed on 24th December 2014 and finalised on 31st January 2015 by the MMC CPD Committee. It was presented to the MMC on 17th March 2015 and confirmed during the MMC meeting on 21st April 2015. It was slightly edited on 5th May 2016 and further revised on 4th April 2018 (Appendix 2). The MMC CPD Grading System was later expanded and amended again in 2020 and the latest schedule with eight categories, A1 to A8, came into effect from 1st July 2020 (Appendix 3).

In the latest grading system, CPD points can be awarded not only for attendance at meetings and conferences but also for work-based learning and quality improvement activities. The scope of scholarly activities has been expanded for training and presentation during meetings as well as for involvement in research and publications as investigators, grant recipients, supervisors, authors, reviewers and journal editors. An additional category was added for professional development activities including leadership role in medical societies, self-development courses and community activities.

## MMA CPD Session

The first ten sessions (from 1994 until 2004) ran from 1st September until 31st August of the following year. Since it was anticipated that CPD points would eventually become a requirement for renewal of Annual Practising Certificate, the CPD Session was changed from the 11th session onwards (ending in 2005) to commence on 1st July of each year and to run until 30th June of the following year. This far-sightedness obviated the need to change the dates for the CPD session when it came to pass in 2017 that CPD points become a mandatory requirement for renewal of Annual Practising Certificate.

## Certificates for the CPD Programme

From the beginning, the process of verification of CPD points was stringent and required either validated certificates of attendance for overseas meetings or the submission by

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registered the CPD providers of attested attendance records with signatures against the names and identity card numbers of the participants. The MMA CPD Secretariat collated the CPD points according to the categories in the MMC-CME Grading System and sent verification statements to the MMC at the end of each CPD Session. Based on the verification statements, MMC issued a certificate of the credit points accrued by the Registered Medical Practitioners annually, beginning in 1996. The certificates with the number of CPD points accrued in all the categories were sent to all members shortly after the closure of each CPD Session.

### **The MMA CPD Committee**

From 1994, the MMA CME committee has overseen the accreditation of CPD points for all doctors, both primary care doctors and specialists, in the private and government sectors. This committee changed its name to MMA CPD Committee in 2005. MMA invested heavily in hardware, software and trained staff to administer this system which has been running smoothly for over two decades. The MMA CPD Committee has experienced members who have championed and nurtured the system for many years as well as more junior members who are no less enthusiastic. The committee members include both primary care doctors and specialists. In the early days, all the functions had to be carried out manually and resulted in much paperwork for registration of providers, accreditation of CPD activities, recording attendance for CPD activities and issuance of certificates.

After the MMA CPD System moved online in 2017, most of the work for accreditation of CPD activities was done on the MMA CPD Portal. Discussion on registration of new providers has been done via email circulation.

### **CPD Providers**

As of October 2020, 508 active CPD providers had re-registered with the MMA CPD System via the MMA CPD Portal. These providers are from the following categories:

- i. Government hospitals
- ii. Private hospitals and medical centres
- iii. Departments in the Ministry of Health
- iv. Specialist bodies and societies
- v. Universities, colleges and institutes

The largest number of Providers is from the category specialist bodies and societies, followed by Government and private hospitals, departments in the Ministry of Health and universities, colleges and institutes in Malaysia. The MMC has set out criteria for the providers in their Quality Standards and these criteria have to be fulfilled to assure that CPD activities have strong educational content and are relevant to the practitioners.

### **Activities to encourage participation in CPD**

Participation in CPD activities was voluntary from the commencement of the MMA CPD System in 1994 until 2017. Much work was done to encourage doctors to participate in CPD activities. Apart from the certificate provided by the MMC, MMA awarded an additional Certificate of Merit to those who attained 50 points and above on a yearly basis. In 2008–2009, Assoc. Prof. Dr. John George and I co-authored four articles for the MMA newsletter *Berita MMA* regarding the MMC-CPD Grading System. On 29th March 2009, a

MMA National CPD Symposium was organised by the MMA CPD Committee. Speakers from Singapore, Thailand and Indonesia shared their experiences regarding the CPD programme in their countries and there were also speakers from local stakeholder organisations including MMC, MMA, Ministry of Health, Academy of Medicine of Malaysia and Academy of Family Physicians of Malaysia.

### **Compulsory CPD for renewal of Annual Practising Certificate**

Internationally, formal CPD Systems have evolved apace in developed countries with stringent regulatory CPD requirements linked to recertification.<sup>1</sup> However, CPD has yet to evolve in many of the Southeast Asian countries.<sup>2</sup> Singapore had imposed compulsory Continuing Medical Education requirements on doctors for renewal of their practicing certificates from 2005.<sup>1</sup> There are also regulations on CPD in Indonesia<sup>2</sup> and the Philippines<sup>3</sup>, for doctors to renew their licenses, In Thailand and Myanmar, CPD is not a mandatory requirement for doctors to renew their license<sup>2</sup> and Vietnam, Cambodia and Lao PDR are currently in the process of instituting a licensing system.<sup>4,5</sup> An overview shows that CPD Systems have evolved at different rates with significant variations in organisational structure and regulatory mechanisms.

To facilitate the development of CPD and accord it legitimacy, Malaysia amended its Medical Act, 1971 to make CPD a mandatory requirement for fully registered medical practitioners and linked it to the renewal of annual practicing certificate (APC). Malaysia joined the ranks of nations that practise mandatory CPD for doctors when the Medical (Amendment) Act 2012, Medical Regulations 2017 came into force on 1st July 2017.

With regards to this, MMA was mandated as a CPD Administrator by the MMC. The other CPD administrators are the MyCPD System of the Ministry of Health and the Academy of Medicine of Malaysia Medical Specialist CPD System.

All Registered Medical Practitioners are encouraged to participate in the MMA CPD System. Members of MMA are automatically registered in the system. Non-members must register to participate in the MMA CPD System; they have to provide their MMC full registration number so that their status as a registered medical practitioner can be ascertained before registration is confirmed. As part of its Social and Corporate Responsibility, MMA has agreed to collate and tabulate the CPD points for non-MMA members without any applicable fees, so it can benefit all medical practitioners who are registered with the MMC.

### **MyCPD System of the Ministry of Health Malaysia**

The MyCPD system of the Ministry of Health had adopted the MMC-CPD Grading System in 2007 with additional categories included. From 2015, a project was undertaken by Ministry of Health to upgrade the MyCPD System to Version 2.0 and I attended many MyCPD Version 2.0 Project Management Meetings in 2016 and 2017 as representative of the MMA. This system is a web-based system and records CPD points for all Ministry of Health staff.

### MMA Mobile Application for CPD

A mobile application for CPD providers and doctors was launched in May 2017 during the 57th MMA Annual General Meeting in Penang. Via this application, points can be viewed in real time unlike the past where one had to wait for a whole year to receive the certificate. The aim was to automate the system so that registered participants can check accrued CPD points easily and in real time. Capabilities included the following:

1. Registration of non-members
2. Registration of CPD providers
3. Processing applications for accreditation of educational events by providers
4. Recording attendance instantaneously during educational activities (by swiping profile QR Code during physical events or swiping event QR code during online CPD events)
5. Issuance of certificates at the end of each CPD Session

This innovative solution based on information technology is part of MMA's effort to upgrade in order to cope in this era of expanding regulatory requirement for accurate recording of CPD activities. MMA also has equipped the mobile application with a Manual Submission section which will capture points for CPD activities other than accredited events organised by local CPD providers. Registered medical practitioners can apply for CPD points for these activities, including for international conferences and online events, attachments, audit and quality assurance activities, training, research, publications and professional development activities in the manual submission section of the MMA CPD mobile application. After clicking on the Manual Submission icon, the user has to upload details of the activity, programme and certificate; these details are then displayed in the MMA CPD Portal for approval by the MMA CPD Committee. Once approved, the CPD points will be shown in the user's MMA CPD mobile application.

The data recorded in the mobile application has been linked to the MyCPD System of the Ministry of Health and Malaysian Medical Council APC (MeRITS) website. This was made possible from the hard work of the Executive Committee and Information Technology (IT) Committee of the MMA.

### MMA CPD Online Modules

With the advent of the MMA mobile application, it has been possible to work with CPD providers of online CPD modules. The websites of these providers are linked to the MMA CPD Portal via application programming interface (API) and CPD points are accredited into the user's MMA CPD mobile application upon successful completion of each module. At present, the education websites with CPD online modules linked to the MMA CPD Portal include those of MIMS Education, Docquity, Medcomet, Prezcapture and the Malaysian Thoracic Society.

During the COVID-19 pandemic, the online CPD modules have become increasingly popular and there has been an increasing number of MMA CPD mobile app users claiming CPD points for completing CPD online modules apart from those listed above. These have to be submitted on the

Manual Submission section of the MMA CPD mobile application. Many conferences and meetings have had to be converted to virtual meetings and webinars, since face-to-face meetings have had to be curtailed from March 2020.

### Role of MMA State Branches

One of the strengths of MMA in CPD is the network of CPD Chairpersons and Coordinators at each State Branch; they were active in organising and accrediting CPD activities held under the auspices of their Branch and verified attendance records before sending to the MMA CPD Secretariat. Before the advent of the MMA mobile application, they also forwarded claims for CPD points by members for overseas meetings and publications to the MMA CPD Secretariat.

As an example, MMA Penang Branch organised many smaller meetings as well as a well-received conference for General Practitioners annually from 1998. The last conference held in September 2019 was the 23rd in the series. The Branch also organised theme conferences including Conferences on Pain Management (2004), Metabolic Syndrome (2006), Infectious Diseases (2007), Clinical Emergencies (2008, 2010 & 2014) and Childhood Diseases & Women's Health (2011), and the Penang Respiratory Conference (2019).

### CONCLUSION

The history and progress of the MMA CPD System has been documented from its inception in 1994 until the present day when it still plays an important role as CPD administrator for over 34,000 doctors in Malaysia. It is envisaged that the MMC will guide future developments as the regulatory authority overseeing the CPD mandatory requirement for renewal of Annual Practising Certificate for registered medical practitioners.

### ACKNOWLEDGEMENTS

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### REFERENCES

1. Murgatroyd GB. Continuing professional development, the international perspective. July 2011. General Medical Council. [cited November 2020] Available at: [https://www.gmc-uk.org/-/media/documents/cpd---the-international-perspective-jul-11\\_pdf-44810902.pdf](https://www.gmc-uk.org/-/media/documents/cpd---the-international-perspective-jul-11_pdf-44810902.pdf)
2. Jayarathne YG, Karunathilake IM, Marambe KN. Are South East Asian countries ready for revalidation process of physicians through mandatory continuing professional development (CPD) activities? *South-East Asian J Med Edu* 2016; 10(1): 1-2.
3. Calimag MMP. Empowering the Filipino physician through continuing professional development in the Philippines: Gearing towards ASEAN harmonization and globalization. *St Tomas J Med* 2018; 2(1): 121-32.
4. Sonoda M., Syhavong B., Vongsamphanh C, Phoutsavath P, Inthapanith P, Rotem A, Fujita N. The evolution of the national licensing system of health care professionals: a qualitative descriptive case study in Lao People's Democratic Republic. *Hum Resour Health* 2017;15(1): 51.
5. van der Velden T, Van HN, Vu Quoc HN, Van HN, Baron RB. Continuing medical education in Vietnam: New legislation and new roles for medical schools. *J Contin Educ Health Prof* 2010; 30(2): 144-8.

**Appendix 1**  
**MMC-CPD Grading System Scoring Schedule**  
**EFFECTIVE FROM: 01/01/1996**

Category	CPD Activity Description	Credit Points Attainable	Additional Criteria Required
1A	Medical Congress (Local/International)	20 points per congress	A congress should: a) Be conducted not less than 3 full days, a full day being 5-8 hours b) Involve speakers of international standing c) contain plenary lectures/symposia d) allow presentation of free communications/posters, etc.
1B	<b>Scientific meetings of Chapters of Academy/ Universities/Colleges/ Association/Public &amp; Private Medical Institutions</b> a) less than 2 hours b) 2-4 hours (1/2 day) c) 5-8 hours (full day) d) 4 or more full days	1 point 2 points 3 points 10 points	Between 1,2, or 3 days, points are awarded according to hours
1C	<b>Workshop/Courses</b> a) Full Day b) More than full day but less than two full days c) 3 or more full days	3 points 5 points 10 points	A full day is 5-8 hours
<b>For all activities in these categories, attendance lists or certificates of attendance for overseas meetings are to be submitted.</b>			
2A	<b>Ward rounds/Lectures/ Clinic Attendance</b>	1 point per hour	For ward rounds, credit points are awarded to participants from outside the hospital establishment, e.g. Private practitioners, verified by the CPD Chairman of that institution
3A	<b>Publication of Original Articles in Medical Journal/Chapters in Book</b> a) Indexed Journal (i) Principal author (ii) Others b) Non-indexed Journal (i) Principal author (ii) Others c) Chapter in book -each chapter (up to a maximum of 10 points)	10 points 7 points 5 points 3 points 5 points	An Indexed journal is one which has international standing and is listed in the Index Medicus or similar indexing system
3B	<b>Presentation at accredited meeting</b> a) Free paper/short paper/poster b) Plenary lecture/long paper c) Visiting Lecture	3 points 5 points 3 points	a) These credit points are in addition to full delegate attendance at Medical Congresses (1A), Scientific Meetings (1B), or Workshop (1C). Otherwise, only credit points for presentation are attainable. b) Attendees/audience should be medical practitioners.
4	<b>Self-Study/Group Study/ Distance Learning</b> a) Reading scientific Papers from indexed journals b) Audio-visual c) Organised group discussion under accredited co-ordinator	1 point 1 point 1 point	Documented evidence (with verification) needs to be produced.
5	<b>CPD Online (By Registered Accredited Provider)</b>	1 point	a) Participants will be allowed 2 weeks to read CPD Article and answer associated questions b) Each participants will only have one attempt at Answering allotted questions per article c) Participants must obtain a minimum of 65%, to be awarded 1 credit point

**Appendix 2**  
**MMC-CPD Grading System Scoring Schedule**  
**Updated 24.12.15, finalised on 30.1.15 (Edited on 5.5.16) (Reedited on 4.4.18)**

Category	CPD Activity Description	Credit Points	Additional Criteria Required
<b>A1</b>	<b>Medical Congress</b>		
	(Local/International)	Maximum points per Congress is 20 points	A congress should: a. Be conducted over full days, a full day being 5 – 8 hours. b. Involve speakers of international standing. c. Contain plenary lecturers/symposia. d. Allow presentation of free communication/poster, etc.
	a. 5-8 hours (full day)	8	
	b. 2 full days	16	
c. 3 or more full days	20		
<b>A2</b>	<b>Scientific Meetings</b>		
	Academy / Universities / Colleges / Association / Institutions	Maximum points per Meeting is 20 points	
	a. 1- 2 hours	2	
	b. 2-4 hours (1/2day)	4	
	c. 5-8 hours (full day)	8	
	d. 2 Full days	16	
e. 3 or more full days	20		
<b>A3</b>	<b>Workshops/Course/ study tour</b>		
	Includes hands-on & skills courses		For professional attachment, credit points are awarded to participants from outside the place of work, e.g. Tertiary Hospitals, University Hospitals.
	a. Half day (2-4 hours)	4	
	b. Full day (5-8 hours)	6	
	c. 2 Full days	10	
	d. 3 or more full days	15	
	e. Skills accredited courses by specific disciplines (e.g. ALS, PALS, NRP, MTLs)	20	
f. Study tour	5		
<b>A4</b>	<b>CME session/ other professional activities</b>		
	Topic seminar, Forum, Lectures, Formal Ward rounds (teaching rounds), Clinic attendance, Hospital clinical meeting, Video presentation, Medical video conferencing, Morbidity and mortality reviews, Epidemiological reviews		For ward rounds and clinic attendance credit points are awarded to participants from outside own hospital/ establishment, .e.g. Private practitioners, verified by the CPD Chairman.
	a. Organising Chairman for a Scientific meeting	5 pts/ meeting	
	b. Topic seminar	1 point/hr	
	c. Forum	1 point/hr	
	d. Lectures (postgraduate lectures are not eligible for CPD points)	1 point/hr	
	e. Ward rounds	1 point/hr	
	f. Clinic attendance	1 point/hr	
	g. Hospital clinical meeting	1 point/hr	
	h. Video presentation	1 point/hr	
	i. Medical video conferencing	1 point/hr	
	j. Morbidity and mortality reviews	1 point/hr	
	k. Epidemiological reviews	1 point/hr	
<b>A5</b>	<b>Presentation at meetings</b>		
	Plenary Lecture/long paper/ free paper/short paper/ poster/ Other lectures, Hospital Clinical meeting, CME sessions, Public Medical talks		These credit points are in addition to full delegate attendance at congresses, scientific meetings or workshops. Otherwise only credit points for presentation are attainable.
	a. Free paper/short paper/poster	10	
	b. Plenary lecture/long paper	10	
	c. Lecture presentation	5	
	d. Hospital clinical meeting	5	
	e. CME session	5	
f. Public medical talk	5		

Commentary

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<b>A6 Publications of original articles in journal/ chapters in book / reports &amp; Important role in journal</b>			
(i)	Publication of original articles in journal /chapters in books/ reports		An indexed journal is one which has international standing and is listed in the Index Medicus or similar indexing system. *Note: All whose name is in the paper will be given the points.
	a. Indexed/peer reviewed journal (authors)	20	
	b. Non-indexed journal (authors)	10	
	c. Chapters in book (authors)	10 per chapter	
	d. Reports e.g. Technical reports, working papers etc.	10	
(ii)	Editor, Member of Editorial Board, Referee/Reviewer		Pertaining to production of journals, special reports, bulletins, newsletters etc.
	a. Editor	10	
	b. Member of Editorial Board	5	
	c. Referee/reviewer (per article)	5	
<b>A7 Self-study/group study/distance learning</b>			
Reading scientific papers from indexed journals, organised group discussion under accredited co-coordinator	1 point per paper or session		Documented evidence (with verification) needs to be produced e.g. a. Self study - Self administered MCQ. b. Documented evidence in the form of synopsis / evidence table.
<b>A8 CME Online</b>			
	1 point per article or session		The CPD Board is ultimately responsible for accreditation of the providers.
<b>A9 Special interest training courses (Short training courses/Fellowship /Attachment)</b>			
			These should be a. Conducted by relevant recognised authorities - local or international. b. Verified by the CPD committee. c. Points are given only once, on completion of studies.
	a. >3 - 6 months	20	
	b. >6 months - 1 year	30	

For all activities, certificates of attendance, certified attendance lists or other evidence of verification are required.



**Appendix 3**  
**MMC-CPD Grading System**  
**Effective from 1st July 2020**

Category	CPD Activity Description	Credit Points
<b>A1</b>	<b>Scientific Meetings/Congress</b>	
	a. Half day (2-4 hours)	4 points
	b. Full day (5-8 hours)	8 points
	c. 2 full days	16 points
	d. 3 or more full days	20 points (max)
<b>A2</b>	<b>Workshops/Courses/Skill Courses including ATLS/CCrISP/CPR/ACLS/ALS/PALS/NRP/MTLS</b>	
	a. Half day (2-4 hours)	4 points
	b. Full day (5-8 hours)	8 points
	c. 2 full days	16 points
	d. 3 or more full days	20 points (max)
<b>A3</b>	<b>Work-based Learning</b>	
	a. Hospital/department CME	1 point/hr
	b. Small group discussion/case conference	1 point/hr
	c. Participation in inter-department clinical meeting / epidemiological review	1 point/hr
	d. Journal club meeting	1 point/hr
	e. Formal grand ward round	1 point/hr
	f. External CME lecture/ topic seminar	1 point/hr
	g. Short courses/attachment >1 – 3 months	10 points
	h. Short courses/attachment >3 - 6 months	20 points
	i. Short courses/attachment >6 months - 1 year	30 points
<b>A4</b>	<b>Quality Improvement Activities</b>	
	a. Morbidity and mortality reviews	1 point/hr
	b. Audit meetings	1 point/hr
	c. Participation in accreditation exercise	1 point/hr
	d. Participation in quality assurance (QA) activities	1 point/hr
<b>A5</b>	<b>Scholarly Activities/Training/Presentation</b>	
	a. Organising chairperson for a recognised Scientific meeting or workshop	5 points
	b. Examiner at final undergraduate/postgraduate examination	5 points
	c. Trainer/facilitator at a workshop	5 points
	d. Plenary /keynote lecture	5 points
	e. Presentation of lectures/oral/papers/posters at scientific meetings	5 points
	f. Presentation at hospital/departmental meetings and external lecture/topic seminar	5 points
<b>A6</b>	<b>Scholarly Activities/Research/Publication</b>	
	a. Principal/Co-Investigator in a clinical trial/research	5 points
	b. Obtained a research grant	5 points
	c. Author of an indexed/peer reviewed journal article	5 points
	d. Author of a non-indexed/non-peer reviewed journal article	5 points
	e. Author of a textbook/book chapter	5 points
	f. Chief Editor of a Journal Editorial Board	5 points
	g. Member of a Journal Editorial Board	5 points
	h. Reviewer of a peer reviewed journal article	5 points
	i. Reviewer of a textbook	5 points
	j. Supervisor for postgraduate research project	5 points
	k. Reviewer/examiner of research thesis	5 points
	l. Preparation of reports/member of reports committee e.g. technical reports, working papers, guidelines	5 points
m. Member of clinical guidelines/consensus guidelines (national/international)	5 points	
<b>A7</b>	<b>Self-directed Learning</b>	
	a. Online CME modules	1 point/module
	b. Self-study (Relevant books, publications, Journal articles, podcasts etc.)	1 point/module
	c. External lecture/ topic seminar	1 point/hr
<b>A8</b>	<b>Professional Development</b>	
	a. Leadership role in medical societies /NGOs	5 points
	b. Self-development courses e.g. IT courses, business management, administrative skills, leadership skills	5 points
	c. Risk management courses e.g. communications, ethics, medico-legal, patient safety	5 points
	d. Participation in community activities	5 points
	e. Participation in innovation projects	5 points
	f. Public lectures/talks, lectures/talks to NGO/radio/TV	5 points

# Clinical outcomes of acute stroke thrombolysis in neurologist and non-neurologist centres – A comparative study in Malaysia

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## ABSTRACT

**Background:** Thrombolytic therapy with intravenous alteplase is a well-established treatment for acute ischaemic stroke (AIS). However, in Malaysia, treatment prescription is often limited by the availability of neurologists. The objective was to compare the outcomes of acute stroke thrombolysis therapy prescribed by neurologists in the Seberang Jaya Hospital (SJH) and non-neurologists in the Taiping Hospital (TH).

**Methods:** In this cross-sectional study, all AIS patients who received thrombolytic therapy in SJH and TH between January 2012 and September 2019 were included. Clinical data was extracted from admission records. The outcomes assessed were the percentage of patients who achieved excellent functional outcome at 3 months (modified Rankin scale of 0 to 1), rates of symptomatic intracranial haemorrhage (SICH), and mortality.

**Results:** A total of 63 AIS patients who received thrombolytic therapy were included, of which 37 patients (58.7%) were treated in SJH. The median NIHSS on admission was 12 in SJH and 11.5 in TH. In all 21.6% of patients from SJH and 30.7% of patients from TH achieved favourable functional outcome at 3 months ( $p=0.412$ ). There were no significant differences between the two centres in terms of the rates of SICH (10.8% in SJH and 3.8% in TH,  $p=0.314$ ) and 3-month mortality (24.3% versus 12.5%,  $p=0.203$ ).

**Conclusion:** The 3-month functional outcomes and complication rates of stroke thrombolysis in hospitals with or without neurologists are not significantly different. Thus non-neurologist hospitals may be able to provide thrombolysis service to AIS patients safely and effectively.

## KEYWORDS:

*Acute ischaemic stroke, thrombolysis, functional outcome, non-neurologist*

## INTRODUCTION

Acute ischaemic stroke (AIS) is a devastating disease and one of the leading causes of disabilities worldwide. From 2010 to 2014, the incidence of stroke in Malaysia had increased from 65 to 187 per 100,000 population.<sup>1</sup> Thrombolytic therapy

with intravenous recombinant tissue plasminogen activator (rtPA) within 4.5 hours of symptom onset has been shown to be an effective treatment for AIS. Patients who receive thrombolysis are 30 percent more likely to achieve excellent functional outcome (modified Rankin scale of 0 to 1) at 3 months compared to placebo.<sup>2</sup>

Unfortunately, the delivery of stroke thrombolysis service in Malaysia is often limited by the availability of neurologists. To date, the ratio of neurologists capable of performing thrombolysis serving in public hospitals to the Malaysian population is 1:1.4 million.<sup>3</sup> To counteract this disparity and to cope with the increasing stroke burden in Malaysia, there has been an advocacy for greater involvement of non-neurologists, i.e., general and emergency physicians in performing of stroke thrombolysis.<sup>4</sup> Emerging data based on short term outcomes appear to support this notion.

Based on a 2015 single center study on 49 AIS patients in Australia, A. Lee et al., reported that there was no significant difference in door to needle time, rates of symptomatic intracranial bleeding (SICH), and mortality between patients thrombolysed by neurologists versus stroke physicians.<sup>5</sup> In 2016, a larger multicentre study in Thailand reported that patients thrombolysed in hospitals without neurologists had lower National Institute of Health Stroke Scale (NIHSS) scores at discharge and lower inpatient mortality rate compared to patients treated in neurologist hospitals.<sup>6</sup> Based on these short term outcomes, both studies suggest that non-neurologists are able to thrombolysed AIS patients safely and effectively. Data comparing long term functional outcomes in thrombolysis prescribed by neurologists and non-neurologists are still very limited.

The primary objective of this study was to evaluate and compare the 3-month functional outcomes of thrombolytic therapy between hospitals with and without on-site neurologists. The secondary objective was to assess the door-to-needle time and complication rates of thrombolysis service in both hospitals.

## METHODS

This study was conducted in Seberang Jaya Hospital (SJH) and Taiping Hospital (TH), two district hospitals in the

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northern region of peninsular Malaysia which are designated as Primary Stroke Centres (PSC). Both hospitals have similar bed capacity and numbers of medical staffs. They are equipped with emergency departments with streamline stroke activation protocols, 24/7 radiology services to provide rapid diagnostic imaging for stroke patients, intensive care support, and physicians trained in the administration of stroke thrombolysis.<sup>7</sup> In SJH, thrombolysis is prescribed by an in-house neurologist (referred herewith as the neurologist hospital) whilst in TH, as there is no on-site neurology support (referred as the non-neurologist hospital), stroke thrombolysis is led by a geriatrician. A comparison of both hospitals is shown in Table I.

In this cross-sectional study, we included all AIS patients who were admitted and given thrombolytic therapy in the SJH and the TH between 1st January 2012 and 1st September 2019. All AIS patients had urgent brain computed tomography (CT) scans on arrival and eligibility for thrombolysis and were assessed clinically. Patients who had onset of stroke within 4.5 hours with no exclusion criteria according to the protocol were given intravenous alteplase 0.9mg per kilogram. Patients with stroke of large vessel occlusion and received endovascular thrombectomy were specifically excluded from the study. All thrombolysed patients were transferred to the respective intensive care or acute stroke units for close monitoring. CT scans of the brain were repeated 24 hours post-thrombolysis and when required thereafter. All patients underwent in-patient rehabilitation during hospital stay and received antiplatelet (or anticoagulant if atrial fibrillation was detected) and statin therapy upon discharge. They were followed up later in clinics at three months.

The lists of AIS patients who received thrombolysis therapy were obtained from the National Stroke Registry of Malaysia. Relevant demographic and clinical data were extracted from admission records and patient charts. Stroke subtypes were classified according to clinical presentation using the Oxfordshire Community Stroke Project (OCSP) classification system, which had been shown to carry prognostic significance in stroke recovery.<sup>8</sup> The efficiency of thrombolysis service is determined by assessing the door to needle time.

The functional outcome measured was the modified Rankin scale (mRS) at three months. MRS was determined by trained personnel in the respective centers during clinic follow ups. For patients who were unable to return for clinic assessment, the mRS was ascertained by structured phone interviews using the validated revised version of simplified Modified Rankin Scale Questionnaire (smRSq).<sup>9</sup> Safety outcomes assessment included symptomatic intracranial haemorrhage (SICH), other major bleeding that required blood transfusion, minor bleeding, inpatient mortality and overall mortality at day 90. SICH followed the ECASS III definition of any extravascular blood in the brain within 36 hours that was associated with an increase of 4 points or more in NIHSS score or leading to death.<sup>2</sup>

The data were analysed using the SPSS version 22. When comparing between the two centers, independent student *t* test was used for analysis of continuous variables while Chi-square or Fisher's exact test (when appropriate) was used for categorical data. An alpha value of 0.05 was considered

statistically significant. To ascertain the effect of treating centres on the key clinical outcomes, logistic regression was performed using variables which carry univariate significance of  $p < 0.10$ .

Ethical approval for this study was obtained from the Malaysia Research Ethics Committee. (NMRR 08-16323189)

## RESULTS

Of the 63 AIS patients given thrombolytic therapy 37 patients (58.7%) were treated in the SJH whilst 26 patients (41.2%) were treated in the TH. There was no significant difference between the two patient cohorts in terms of demographic and baseline characteristics (Table II). Most of the stroke patients were relatively young, with the mean age of 58.2 and 54.0 years in SJH and TH respectively and 54.1% and 61.5% were men. Hypertension and diabetes were the two commonest risk factors associated with stroke in the study population. In all 13.5% and 7.7% of patients were found to have atrial fibrillation at presentation.

The median NIHSS scores on admission were 12 (interquartile range, IQR 9 to 18) in SJH and 10.5 (IQR 9 to 14) in TH. More than half of the AIS patients fell within the moderately severe stroke category (NIHSS 9 to 15). There were relatively more lacunar strokes and mild strokes (NIHSS of 1-8) in TH compared to SJH ( $p=0.640$ ). No patient with posterior circulation infarct was thrombolysed in both the cohorts. Majority of the stroke patients (60.3%) received thrombolysis therapy after 180 minutes from the onset of stroke symptoms. The door to needle time in the neurologist hospital was shorter compared to the non-neurologist hospital (112 minutes versus 130.6 minutes), the difference however, was not statistically significant ( $p=0.538$ ).

The median NIHSS scores on discharge were 10 (IQR 6-15) for SJH and 7.5 (3 -12) for TH, representing a mean reduction of NIHSS scores by 2 and 3 points respectively post thrombolysis. On average, the stroke patients in SJH spent 4 days in the hospital compared to 7 days for those in the TH. At 3 months follow up post thrombolysis, 21.6% of patients from SJH and 30.7% of patients from TH achieved excellent outcomes with mRS of 0 to 1. However, the difference was not statistically significant ( $p=0.412$ ). The overall distribution of mRS scores is shown in Figure 1 and the comparison of clinical outcomes is shown in Table III.

In terms of safety outcomes, the rate of symptomatic intracranial bleeding within 36 hours of thrombolysis was 10.8% in SJH and 7.7% in TH ( $p=0.678$ ). One patient from both the SJH and the TH required neurosurgical intervention for intracranial bleeding. There was no incidence of major extracranial bleeding in both the hospitals. Four patients from SJH suffered from minor bleeding complications, for instance cutaneous bruising that did not require blood transfusion. In all seven patients from the SJH and three patients from the TH passed away during index hospitalisation, mostly as a result of massive cerebral infarct and oedema. The overall mortality rate at three months was 24.3% in the SJH and 12.5% in the TH. Nonetheless, the difference was not statistically significant ( $p=0.546$ ).

Table I: Comparison of hospital characteristics

Hospital characteristics	Seberang Jaya Hospital	Taiping Hospital
Hospital level	District with specialist	District with specialist
Bed size	312	608
Catchment areas	Seberang Jaya, Bukit Mertajam	Larut Matang, Kerian, Kuala Kangsar, Ulu Perak
Population	452,720	634,146
Presence of neurologist	Yes	No
Number of medical specialists	14	14
Number of emergency physicians	5	5
Number of CT scanner	1	1

Table II: Demographic and baseline characteristics of the patients

Baseline characteristics	Seberang Jaya Hospital (N=37)	Taiping Hospital (N=26)	p value <sup>a</sup>
Age, year (mean $\pm$ SD)	58.2 $\pm$ 11.5	54.0 $\pm$ 13.4	0.127 <sup>b</sup>
Male sex, n (%)	20 (54.1)	16 (61.5)	0.552
Diabetes, n (%)	16 (43.2)	13 (50.0)	0.293
Hypertension, n (%)	26 (70.3)	19 (73.1)	0.808
Atrial fibrillation, n (%)	5 (13.5)	2 (7.7)	0.469
Smoker, n (%)	11 (29.7)	9 (34.6)	0.682
Recurrent stroke, n (%)	5 (13.5)	4 (15.4)	0.834
Prior use of antiplatelet, n (%)	8 (21.6)	10 (38.5)	0.145
NIHSS			
Median (IQR)	12 (9 -18)	10.5 (9 -14)	0.262 <sup>b</sup>
Minimum	7	6	
Maximum	25	22	
stroke subtype, n (%)			0.581
TACI	8 (21.6)	3 (11.5)	
PACI	18 (48.6)	14 (53.8)	
LACI	11 (29.7)	9 (34.6)	
stroke severity, n (%)			0.640
mild (NIHSS 1-8)	6 (16.2)	5 (19.2)	
moderate (NIHSS 9-15)	20 (54.1)	16 (61.5)	
severe (NIHSS 16-42)	11 (29.7)	5 (19.2)	
onset to treatment time (in minute)			
mean, SD	203.1 $\pm$ 53.9	201.2 $\pm$ 59.5	0.645 <sup>b</sup>
<180 min, n (%)	15 (40.5)	10 (38.5)	0.868
$\geq$ 180 min, n (%)	22 (59.5)	16 (61.5)	
Door to needle time (in minute)			
Mean, SD	112.1 $\pm$ 45.4	130.6 $\pm$ 52.6	0.538 <sup>b</sup>

<sup>a</sup>unless stated otherwise, p values were derived from Chi Square test for independence

<sup>b</sup>Independent samples t test

TACI, total anterior circulation infarct. PACI, partial anterior circulation infarct. LACI, lacunar infarct.

Table III: Clinical outcomes of stroke thrombolysis

Outcome measurements	SJH (N=37)	TH (N=26)	p value
NIHSS on discharge, median (IQR)	10 (6-15)	7.5 (3 -12)	0.132
Length of stay, mean $\pm$ SD	6.86 $\pm$ 9.67	9.15 $\pm$ 9.82	0.362
Patients with excellent recovery, mRS 0-1 at 3 months, n (%)	8 (21.6)	8 (30.7)	0.412
Patients with independent recovery, mRS of 0-2 at 3 months, n (%)	13 (35.1)	13 (53.3)	0.141
Symptomatic Intracranial haemorrhage, n (%)	4 (10.8)	2 (7.7)	0.678
Minor bleeding complications, n (%)	4 (10.8)	0 (0)	0.245
Inpatient mortality, n (%)	7 (18.9)	3 (11.5)	0.430
Mortality at 3 months, n (%)	9 (24.3)	3 (11.5)	0.203

<sup>a</sup>unless stated otherwise, p values were derived from Chi Square test

MRS modified Rankin scale

Table IV: Logistic regression analysis on factors associated with poor clinical outcomes and symptomatic intracranial haemorrhage

Clinical outcomes	Adjusted odds ratios for Non-neurologist centre (95% CI)	P value
Poor recovery, mRS 4-6	0.62 (0.21, 1.80)	0.375
Symptomatic Intracranial haemorrhage	0.72 (0.12, 4.30)	0.717

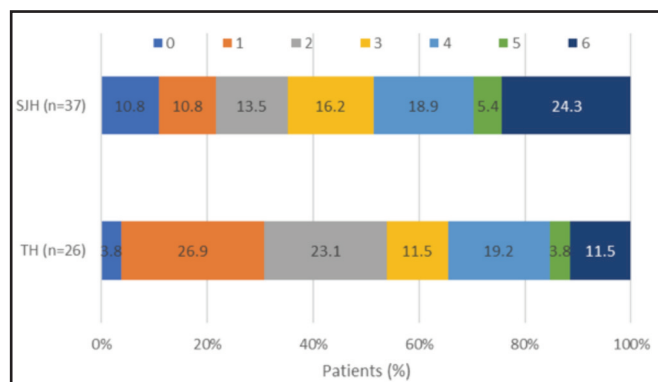


Fig. 1: Distribution of Scores on the Modified Rankin Scale.

In the univariate logistic regression analysis, NIHSS score on admission was the only independent predictors of poor functional outcome, defined as mRS 4 to 6. ( $p=0.095$ ). After adjusting for this, we demonstrated that thrombolysis treatment in non-neurologist centre is not a predictor of poor functional recovery (odds ratios [OR] 0.62, 95% confidence interval [95%CI] 0.21, 1.80), and also SICH (OR 0.72, 95% CI 0.12, 4.30). (Table IV)

## DISCUSSION

In the advent of endovascular thrombectomy treatment, with all its positive acclaim in treatment of acute stroke, intravenous thrombolysis with alteplase remains the mainstay of treatment, especially in developing countries like Malaysia. The existence of a clear selection protocol, in addition to the relative ease of administration without the need of highly skilled personnel or equipment, have led to a gradual uptake of thrombolysis service in more hospitals in Malaysia, including district hospitals without neurologists. Nonetheless, there is no data from Malaysia thus far to examine the safety and efficacy of thrombolysis service provided in non-neurologist centres.

To our knowledge this is the first study in Malaysia that directly compares the clinical outcomes of stroke thrombolysis between hospitals with and without neurologists. It is an important study as all thrombolysed patients were followed up for functional outcomes at three months post stroke. In this study, there were no significant differences in terms of door to needle time, NIHSS on discharge and the proportion of patients achieving favourable recovery between centres with neurologist and without. Most importantly, there were no excess in rates of SICH and inpatient mortality in the non-neurologist centre. These findings are consistent with previous studies comparing stroke outcomes post thrombolysis lead by neurologist versus non-neurologist.<sup>5</sup>

In order to explain these findings, we postulated that the overall system of thrombolysis service and post-thrombolysis care are more important factors than the specialties of the prescribers. In the past, AIS patients may be best managed by neurologists to ensure that an accurate diagnosis can be established. With increasing accessibility to comprehensive training in stroke assessment and thrombolysis via the

Angel's initiative, non-neurologists nowadays are better equipped to initiate the needed urgent intervention for stroke.<sup>10</sup> Admittedly, the confidence and duration of training of the treating physicians such as the number of stroke cases seen in a year and the overall experience in caring for stroke patients were not measured in this study. Equally important are the aspects of post-acute care in stroke units and quality of rehabilitation, which have been shown unequivocally important to reduce stroke morbidity and improve functional outcomes in stroke patients.<sup>11</sup> All these are pertinent confounders in determining the long-term functional outcomes of stroke patients. However, it was beyond the scope of this study to examine and compare all aspects of peri-thrombolysis care in both the hospitals.

The findings of the present study should be interpreted with caution due to some inherent limitations. Firstly, this was a retrospective, observational study. Randomisation was not possible as patients will always seek medical attention at the nearest stroke centre. However, the two district hospitals were comparable in terms of manpower and ancillary services available. The demographics of our patients and stroke severity in both centres were also not significantly different. Secondly, the sample size of 63 was small and may be underpowered to detect any significant differences in terms of functional outcomes and complication rates. Nonetheless, it did shed light on the trend of outcomes. With no signal of safety concern, the thrombolysis service will continue and more data will be prospectively collected to paint a clearer picture.

## CONCLUSION

Hospitals without in-house neurologists may be able to provide thrombolysis service to AIS patients safely and effectively. In this context, the absence of an on-site neurologist should not be a barrier to setting up thrombolysis service in district hospitals. In fact, the key to successful delivery of thrombolysis service lies with active participation of all parties including emergency physicians, general physicians and radiologists. A streamlined stroke activation pathway needs to be established, from pre-notification to ambulance transportation, rapid stroke assessment and priority imaging until the administration of thrombolysis. In addition, there should be proper post-acute care facilities to monitor patients post thrombolysis, together with a multidisciplinary team for stroke rehabilitation. Finally, as this study was essentially a single centre experience, more large-scale studies involving multiple centres are needed in order to verify this finding.

## DISCLOSURE

Financial support: None  
Conflict of Interest: None

## REFERENCES

1. Aziz ZA, Lee YYL, Ngah BA, Sidek NN, Looi I, Hanip MdR, et al. Acute Stroke Registry Malaysia, 2010-2014: Results from the National Neurology Registry. *J Stroke Cerebrovasc Dis* 2015; 24(12): 2701-9.
2. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008 25; 359(13): 1317-29.

3. Hiew FL. Stroke thrombolysis survey in Ministry of Health. Unpublished; 2019.
4. Donnan GA, Davis SM. Neurologist, Internist, or Strokologist? *Stroke* 2003; 34(11): 2765.
5. Lee A, Gaekwad A, Bronca M, Cheruvu L, Davies O, Whitehead C, et al. Stroke physician versus stroke neurologist: can anyone thrombolysed? *Intern Med J* 2015; 45(3): 305-9.
6. Kongbunkiat K, Kasemsap N, Tiamkao S, Chotmongkol V, Sawanyawisuth K, Mekawichi P, et al. Thrombolysis in ischaemic stroke in rural North East Thailand by neurologist and non-neurologists. *Neurol Asia* 2016; 21(4): 325-31.
7. Adams Harold P., del Zoppo Gregory, Alberts Mark J., Bhatt Deepak L., Brass Lawrence, Furlan Anthony, et al. Guidelines for the early management of adults with ischemic stroke. *Circulation* 2007 22; 115(20): e478-534.
8. Yang Y, Wang A, Zhao X, Wang C, Liu L, Zheng H, et al. The Oxfordshire Community Stroke Project classification system predicts clinical outcomes following intravenous thrombolysis: a prospective cohort study. *Ther Clin Risk Manag* 2016; 12: 1049-56.
9. Bruno A, Akinwuntan AE, Lin C, Close B, Davis K, Baute V, et al. Simplified modified rankin scale questionnaire: reproducibility over the telephone and validation with quality of life. *Stroke* 2011; 42(8): 2276-9.
10. Angels Initiative [Internet]. [cited Mar 2020]. Available from: <https://www.angels-initiative.com/>
11. Rudd AG, Hoffman A, Irwin P, Lowe D, Pearson MG. Stroke Unit Care and Outcome: Results from the 2001 National Sentinel Audit of Stroke (England, Wales, and Northern Ireland). *Stroke* 2005; 36(1): 103-6.

# Vasospasm and delayed cerebral ischaemia in patients with spontaneous subarachnoid haemorrhage (aneurysmal and pretruncal non-aneurysmal): a centre's perspective

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## ABSTRACT

**Background:** Spontaneous subarachnoid haemorrhage (SAH) is a significant cause of stroke and associated with high morbidity and mortality. One substantial complication of SAH is cerebral vasospasm (CV) and delayed cerebral ischemia (DCI). This study aimed to define the clinical profile in patients with SAH, CV and DCI secondary to spontaneous SAH (aneurysmal and pretruncal non-aneurysmal).

**Materials and Methods:** We analysed 122 consecutive patients with spontaneous SAH following intracranial aneurysmal and non-aneurysmal information (including patients' pattern characterisation and their possible risk factor association to pre-operative clinical decision and long-term clinical outcome) was documented and analysed.

**Results:** The main clinical presentations for spontaneous SAH following ruptured intracranial aneurysm and non-aneurysm were headache (77%) and nausea/vomiting (62.3%). The most common sites for SAH following ruptured intracranial aneurysm rupture were the anterior and posterior communicating arteries (57.5%). Hypertension was the most common cause for SAH at 64.8%. It was found 26.2% (n=32) out of the 122 patients developed CV and DCI. The mean day of vasospasm was  $6.0 \pm 2.8$  (range: 1-14 days). Age, length of stay, nausea/vomiting and visual field defect were significantly associated ( $p < 0.05$ ) with vasospasm. Mortality rate was also higher in the CV group compared to the group without CV in both at discharge and at 6 months; 281 versus 278 per 1000 and 312 vs 300 per 1000, respectively.

**Conclusion:** CV and DCI have a significant incidence among local patients with spontaneous SAH following an intracranial aneurysmal and non-aneurysmal rupture and it is associated with substantial morbidity. Prevention, effective monitoring, and early detection are keys to successful management. Regional investigation using a multicentre cohort to analyse mortality and survival rates may aid in improving national resource management of these patients.

## KEYWORDS:

*Cerebral Vasospasm, Delayed cerebral ischaemia, Malaysia, Outcome, Spontaneous subarachnoid haemorrhage*

## INTRODUCTION

Spontaneous subarachnoid haemorrhage (SAH) is a significant cause of stroke and may lead to severe neurological deficit or death. It is also associated with high morbidity and mortality for patients despite optimal medical and surgical treatment. Based on the World Health Organization the annual incidence of spontaneous SAH varies in different regions of the world between 2.0-22.5 per 100,000 populations with Finland and Japan having the highest incidence and South and Central America with lowest incidence.<sup>1</sup>

The secondary consequences of SAH – vasospasm (CV) and delayed cerebral ischaemia (DCI), by far one of the most notable complications of SAH carrying a 10-40% risk despite optimal medical treatment leading to permanent deficits in 20-40% of patients in this group.<sup>2</sup> Early recognition and rapid intervention in case of CV and DCI minimises morbidity and mortality in such patients.<sup>3</sup> Hence, identification of patients with spontaneous subarachnoid haemorrhage especially those spontaneous secondary to aneurysm rupture who develop CV is essential towards improving outcomes in patients with SAH.

Cerebral vasospasm (CV) can result in DCI. It was first documented angiographically by Ecker & Riemenschneider in 1951<sup>4</sup> and was associated with delayed focal neurological deficits.<sup>5</sup> Not all patients with CV, however, develop DCI. One third of the patients developed clinical manifestation of CV-DCI.<sup>6,7</sup> Vasospasm typically occurs between 3 to 21 days after the subarachnoid haemorrhage.<sup>3,8</sup> Although DCI is highly associated with CV, there may be other factors including microcirculatory constriction, micro-thrombosis, cortical spreading depression, and delayed cellular apoptosis.<sup>9</sup> Prevention, effective monitoring, and early detection of CV and DCI are the keys to successful management. Current practice involves administration of calcium channel blockers-

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nimodipine and hypertensive therapy<sup>10</sup> as per AHA guideline. There has been long standing controversy over the use of magnesium sulphate infusion in the management of spontaneous SAH to prevent vasospasm. Current studies in the literature do not suggest a role for magnesium sulphate in mortality reduction after SAH.<sup>11</sup> Also, intravenous Clazosentan (an endothelin receptor antagonist that effectively reduces CV), and cholesterol lowering agent statins have also been studied in randomised trials with negative results.<sup>12</sup>

The purpose of this hospital based retrospective study was to define the clinical profile in patients with spontaneous SAH (aneurysmal and non-aneurysmal) at University Malaya Medical Centre (UMMC). UMMC, an urban 1200-bed teaching hospital serving the Kuala Lumpur - Petaling Jaya area with the population of 2.3 million. It is also to provide a better insight into the causal and relationship of the natural history of disease and socioeconomic impact. This information would serve as a reference in socioeconomic loss / planning for management of patients suffering from haemorrhagic stroke in future.

## MATERIALS AND METHODS

### *Patients and data source*

This study was approved by the University of Malaya Medical Centre Human Research Ethics Committee and performed in accordance with institutional ethics committee guidelines (MRECID: 968.12). Data was collected retrospectively for the duration of 10 years (January 2003 and December 2012) and analysed. There was a total of 122 consecutive patients (43 males and 79 female) diagnosed to have spontaneous subarachnoid haemorrhage (aneurysmal and non-aneurysmal) between the stated time frame. Demographics, clinical indications and radiological and treatment-related information were noted as well. The spontaneous SAH was confirmed by computerised tomography (CT) scanning and aneurysm identified by CT angiography.

CV can be angiographic vasospasm and clinical (symptomatic) vasospasm.<sup>13</sup> Angiographic vasospasm was considered to be present when there was unequivocal narrowing of the lumen of the artery on angiograms. Not all patients with CV, however, develop symptomatic vasospasm-hence delayed ischaemia. DCI was defined as documented arterial vasospasm that was consistent with new neurological deterioration, either transient or permanent, between 4 and 21 days after the onset of spontaneous SAH, when all other potential causes such as surgery, hydrocephalus, intracranial re-bleeding, seizure, infection, cardiopulmonary dysfunction, electrolyte imbalance and metabolic disturbances have been excluded. Patients with traumatic and mycotic aneurysms were excluded. Associated risk factor of hypertension is defined as a history of treatment with antihypertensive medication and /or systolic and diastolic blood pressure levels of greater than 160mmHg and 90mmHg documented during previous out-patient reviews.

Patients were treated according to standard local protocol for the management of spontaneous subarachnoid haemorrhage. The patient's Glasgow Coma Scale (GCS) and World Federation of Neurosurgical Societies (WFNS) scale were recorded. The WFNS classification is a specialised

scoring system used to prognosticate patients with spontaneous subarachnoid haemorrhage. It uses Glasgow Coma Scale (GCS) and focal neurological deficits to gauge severity of symptoms. The WFNS scoring system<sup>14</sup> is used with the following categories, Grade 1 = GCS 15 with absent neurological deficit, Grade 2 = GCS 13-14 with absent neurological deficit, Grade 3 = GCS 13-14 with focal neurological deficit, Grade 4 = GCS 7-12 with or without focal neurological deficit and Grade 5 = GCS <7 with or without focal neurological deficit. Clinical (symptomatic) cerebral vasospasm was assessed clinically by the presence of acute onset of a focal neurologic deficit or a persistent (>1 hour) decline in the patient's Glasgow Coma Scale score by 2 or more points according to a recent consensus definition.<sup>15,16</sup> All suspected cases of cerebral vasospasm would then be confirmed by Transcranial Doppler (TCD). Transcranial Doppler vasospasm is defined as a mean blood flow velocity greater than 125cm/s in the anterior circulation or greater than 100cm/s in the posterior circulation in addition to a Lindegaard ratio (mean middle cerebral artery flow velocity/mean cervical internal carotid artery flow velocity) of greater than 3.<sup>17</sup> There was a standard protocol that all patients remain in follow up and TCD was consistently performed throughout the hospitalisation stay on day 1, day 3, day 5 and day 7 interval of admission.

The clinical status of each of the 122 surgical patients was documented at 6 months following surgery. A good outcome was defined as a modified Rankin Scale (MRS) score of 0 or 1; adverse outcomes were considered relevant if they produce a change in MRS of more than 1 as a result of intervention. The clinical condition assigned at last follow-up was used to determine the MRS. The MRS is the most widely used clinical measure for stroke clinical trials; measuring the degree of disability or dependence in the daily activities of people who have suffered stroke or other causes of neurological disability. The scale runs from 0-6; 0-No symptoms, 1-No significant disability, 2-Slight disability, 3-Moderate disability, 4-Moderately severe disability, 5-Severe disability and 6-Dead.<sup>18</sup>

### *Statistical Analysis*

The analyses were performed with IBM SPSS Statistics for Windows software (Version 20.0. Armonk, NY: IBM Corp). Descriptive statistics were utilized for participating demographic, risk factor, clinical sign/symptoms, lateralising sign and physical examination data. Continuous variables are expressed as mean  $\pm$  standard deviation and categorical variables as percentages.

Comparing outcome for numerical data between two groups was analysed using the independent t-test and Mann-Whitney test if the assumptions were not met. The Wilcoxon signed-rank test was used to compare two sets of modified Rankin scale (MRS) that come from the same participants. The Chi-square test was used to compare differences for categorical data among groups and Fisher's exact test was used as another alternative if the assumptions for chi-square test are not met. The McNemar test was used to test the difference between paired proportions. Two-tailed tests were used for all analyses, and the probability value of less than 0.05 (p-value<0.05) was considered as statistically significant.



## RESULTS

### Demographic and Clinical profile

#### Spontaneous subarachnoid haemorrhage

In the 10 years covered by this study, there were a total of 122 patients with spontaneous SAH treated at UMMC. Patients who were operated or initially received treatment in other centres were excluded as there was insufficient information on presenting symptoms. There were 43 men (35.2%) and 79 women (64.8%) with a male to female ratio of 1:2. The mean age was 56.6±14.17 years (range 27-83).

Patient's ethnicity was Chinese; 49.2% (n=60), Malay 32.0% (n=39), Indian 15.6% (n=19) and other ethnic; 3.3% (n=4). The most common clinical presentations for spontaneous SAH (aneurysmal rupture and non-aneurysmal) were headache (77%), nausea and vomiting (62.3%), loss of consciousness (52.5%) and seizures (12.3%). Other related presenting complaints were weakness (17.2%), visual disturbances (13.9%), speech disturbances (6.6%) and behavioural changes (2.5%).

There were multiple risk factors related to spontaneous SAH in this series. Hypertension was the most common associated risk factor for SAH which accounted for 79 patients (64.8%). However only 26.2% (n=32) were documented smokers.

The location of the aneurysm was determined following CT or invasive cerebral angiography. 106 patients (86.9%) were subjected to CT or Cerebral angiography. The remainder 16 patients were deemed unstable to undergo such a procedure. From the group of patients who underwent an angiography, an intracranial cerebral aneurysm was detected in 96 patients (90.6%). Most of the intracranial cerebral aneurysms were located at the anterior and posterior communicating arteries which account for more than half (57.5%) of the aneurysm locations. Other sites were middle cerebral artery 25.5% (n=27), internal carotid artery 5.7% (n=6), posterior inferior cerebral artery 1.9% (n=2), and one each for distal anterior cerebral artery, vertebral artery, anterior choroidal artery and basilar artery. Patients' presented with a poor WFNS grade (3, 4, 5) were marginally higher than a good WFNS grade, 54.9% (n=67) and 45.1% (n=55) respectively. However, there was no an association between WFNS grading and treatment (Table I).

*Cerebral vasospasm (CV) and delayed cerebral ischaemia (DCI)*  
Thirty-two (26.2%) out of 122 patients developed CV and DCI which was documented with cerebral angiography and TCD. The mean for days for patient with spontaneous subarachnoid haemorrhage developed CV and DCI was 6±

2.8 (range 1 -14 days). We found that younger age, length of stay, nausea/vomiting and visual field defect were common presenting symptoms and significant associated factors as a result from vasospasm. The mean age for the non-DCI group (59.6±11.7 years) was higher than the mean age for the DCI group (50.6±10.9 years). Meanwhile, the length of stay for DCI group (Median = 24.0, IQR = 17.0) was longer compared to non-DCI group (Median = 16.0, IQR = 19.0). In DCI group, the nausea/vomiting (87.5%) and visual field defect (25.0%) showed significantly higher prevalence than in the non-DCI group. Other variables such as mean arterial pressure (MAP), gender, race, hypertension, smoker, headache, level of consciousness (LOC), fits, speech disturbances, weakness, inappropriate behaviour and WFNS grade were not statistically significant (Table II). Based on the TCD study in patients with spontaneous SAH who developed CV and DCI, it is observed that the median for Lindegaard ratio was 3.5 while the mean for velocity of MCA was 111.8±38.1 m/s.

### Outcome

Thirty-four patients with spontaneous SAH following intracranial aneurysm and non-aneurysmal rupture died in hospital prior to discharge. The mortality rate was higher in the CV-DCI group compared to the group without the CV-DCI at discharge and 6 months, 28.1% vs. 27.8% and 31.2% vs. 30% respectively. The difference was not significant (Table III).

Patient's functional outcome was assessed with MRS and 75% (n=24) patients suffered a downgrade in function (MRS>1) as a result of CV-DCI based on noted in nine patients who died. There was no significant association between MRS upon discharge and 6 months with CV-DCI (Table III). Table IV and Table V showed WFNS grades, MRS at discharge and MRS at 6 months did not show any statistical significance to the outcome in patients who developed CV-DCI following spontaneous SAH (aneurysmal and non-aneurysmal rupture)

## DISCUSSION

### Demography

Spontaneous subarachnoid haemorrhage (SAH) is a dreadful cerebrovascular disease and contribute substantially to morbidity and mortality. Cerebral vasospasm is common sequelae that occurs in up to 70% of patients with spontaneous SAH.<sup>19,20</sup> In the 10 years covered by this study, a total of 122 patients were analysed. The mean age was 56.6 ±14.17 years (range, 27-83). There were total 43 male and 79 females. There is female preponderance and this is comparable to a study by Juvela which showed women,

Table I: Association between WFNS grade and treatment modality

Variables (n=122)	Treatment						p-value
	Interventional Coiling		Surgical Aneurysm Clipping		Conservative		
	n	(%)	n	(%)	n	(%)	
WFNS Grade							0.265 <sup>a</sup>
1 and 2	16	(50.0%)	26	(49.1%)	13	(35.1%)	
3, 4 and 5	16	(50.0%)	27	(50.9%)	24	(64.8%)	

<sup>a</sup>Pearson's chi-square test; WFNS = World Federation of Neurosurgical Societies

**Table II: Characteristics of 122 SAH patients according to variables and cerebral vasospasm (CV)-delayed cerebral ischaemia (DCI)**

Variables	No (n = 90)				Yes (n = 32)				p-value
	n	(%)	Mean	(SD)	n	(%)	Mean	(SD)	
Age, years			59.6	(11.74)			50.6	(10.90)	0.001 <sup>a</sup>
Length of Stay			16.0	(19.0)			24.0	(17.0)	0.035 <sup>b</sup>
Systolic Blood Pressure			162.9	(27.08)			157.5	(24.23)	0.328 <sup>a</sup>
MAP			107.8	(14.55)			110.2	(15.58)	0.461 <sup>a</sup>
Gender									0.458 <sup>c</sup>
Male	30	(33.3)			13	(40.6)			
Female	60	(66.7)			19	(59.4)			
Race									0.254 <sup>d</sup>
Malay	28	(31.1)			11	(34.4)			
Chinese	48	(53.3)			12	(37.5)			
Indian	12	(13.3)			7	(21.9)			
Others	2	(2.2)			2	(6.3)			
Hypertension									0.326 <sup>c</sup>
No	34	(37.8)			9	(28.1)			
Yes	56	(62.2)			23	(71.9)			
Smoker									0.514 <sup>c</sup>
No	65	(72.2)			25	(78.1)			
Yes	25	(27.8)			7	(21.9)			
Nausea/Vomiting									0.001 <sup>c</sup>
No	42	(46.7)			4	(12.5)			
Yes	48	(53.3)			28	(87.5)			
Headache									0.251 <sup>c</sup>
No	23	(25.6)			5	(15.6)			
Yes	67	(74.4)			27	(84.4)			
LOC									0.119 <sup>c</sup>
No	39	(43.3)			19	(59.4)			
Yes	51	(56.7)			13	(40.6)			
Fits									0.967 <sup>c</sup>
No	79	(87.8)			28	(87.5)			
Yes	11	(12.2)			4	(12.5)			
Speech Disturbances									0.453 <sup>c</sup>
No	85	(94.4)			29	(90.6)			
Yes	5	(5.6)			3	(9.4)			
Weakness									0.171 <sup>c</sup>
No	72	(80.0)			29	(90.6)			
Yes	18	(20.0)			3	(9.4)			
Visual Field Defect									0.035 <sup>c</sup>
No	81	(90.0)			24	(75.0)			
Yes	9	(10.0)			8	(25.0)			
Inappropriate Behaviour									0.566 <sup>d</sup>
No	87	(96.7)			32	(100.0)			
Yes	3	(3.3)			0	(0.0)			
WFNS Grade									0.860 <sup>c</sup>
1 and 2	41	(45.6)			14	(43.8)			
3, 4 and 5	49	(54.4)			18	(56.3)			

<sup>a</sup>Independent t-test; <sup>b</sup>Mann-Whitney test; <sup>c</sup>Pearson's chi-square test; <sup>d</sup>Fisher's exact test; <sup>e</sup>Presented as median (interquartile range); SD = standard deviation; MAP = mean arterial pressure; LOC = level of consciousness; WFNS = World Federation of Neurosurgical Society

**Table III: Mortality rate and cerebral vasospasm (CV) and delayed cerebral ischaemia (DCI)**

Variables	No (n = 90)		Yes (n = 32)		p-value
	n	%	n	%	
Mortality rate at discharge	278 per 1,000		281 per 1,000		0.970 <sup>a</sup>
No	65	72.2	23	71.9	
Yes	25	27.8	9	28.1	
Mortality rate at 6 months	300 per 1,000		312 per 1,000		0.895 <sup>a</sup>
No	63	70.0	22	68.8	
Yes	27	30.0	10	31.2	

<sup>a</sup>Pearson's chi-square test

Table IV: Association between MRS and cerebral vasospasm (CV) and delayed cerebral ischaemia (DCI)

Variables	No (n = 90)		Yes (n = 32)		p-value
	n	(%)	n	(%)	
<b>MRS at discharge</b>					0.325 <sup>a</sup>
0 and 1	31	(34.4)	8	(25.0)	
2 to 6	59	(65.6)	24	(75.0)	
<b>MRS at 6 months</b>					0.231 <sup>a</sup>
0 and 1	39	(43.3)	10	(31.2)	
2 to 6	51	(56.7)	22	(68.8)	

<sup>a</sup>Pearson's chi-square test; MRS = modified Rankin scale

Table V: Association between variables and outcome in cerebral vasospasm (CV) and delayed cerebral ischaemia (DCI)

Variables	Outcome								
	Lindegard Ratio			Velocity			Day of Vasospasm		
	Median	(IQR)	p-value <sup>b</sup>	Mean	(SD)	p-value <sup>a</sup>	Mean	(SD)	p-value
<b>Overall</b>	3.5	(0.8)		111.8	(38.05)		6.0	(2.82)	
<b>WFNS Grade</b>			0.711			0.806			0.711 <sup>b,c</sup>
1 and 2	3.4	(1.1)		109.8	(33.61)		6.5	(5.0)	
3, 4 and 5	3.5	(0.8)		113.3	(42.09)		6.0	(3.0)	
<b>MRS at discharge</b>			0.631			0.496			0.971 <sup>a</sup>
0 and 1	3.4	(0.8)		103.0	(26.65)		6.0	(2.52)	
2 to 6	3.5	(0.8)		114.5	(41.03)		6.1	(2.97)	
<b>MRS at 6 months</b>			0.114			0.203			0.917 <sup>a</sup>
0 and 1	3.2	(0.8)		98.1	(25.99)		6.1	(2.36)	
2 to 6	3.5	(0.8)		117.6	(41.34)		6.0	(3.03)	

<sup>a</sup>Independent t-test; <sup>b</sup>Mann-Whitney test; <sup>c</sup>Presented as median (interquartile range); SD = standard deviation; MRS = modified Rankin scale; WFNS = World Federation of Neurosurgical Societies

particularly those over the age 55, are more likely and have a higher risk of SAH from rupture brain aneurysm than men (3:2 ratio). In the study it was shown that female gender was the only significant independent risk factor ( $p < 0.05$ ) for *de novo* aneurysm formation for cerebral aneurysm growth.<sup>21</sup> It has been reported ethnicity of African-Americans and Hispanics are about twice as likely to have SAH from brain aneurysms compared to Caucasian.<sup>22</sup> In our study we found that the Chinese accounted for 49.2% of the study cohort. This does not reflect the national demographics of racial distribution in Malaysia which is predominantly of the Malay. This could be explained by the fact that this study was conducted in UMMC which is located in Petaling Jaya which has a higher density of Chinese population in Malaysia. However ethnic discrepancies can be a common affair for this disease based on previous data.<sup>23,24</sup>

It was also observed that more than half of intracranial cerebral aneurysms were located at the anterior and posterior communicating arteries (57.5%) in this cohort. Delgado Almandoz et al., in a previous study observed the size and location of ruptured intracranial aneurysms involving 588 patients with first-time acute SAH treated endovascularly at their centre noticed the similar pattern of aneurysm location over a 16-year time period. Ruptured brain aneurysm is fatal in about 50% of cases.<sup>25</sup> Of those who survived, about two third suffer some permanent neurological deficit.

### Monitoring

The extravasation of blood that accumulating in the subarachnoid and perivascular spaces could trigger CV. There are several predictors of CV, including the amount of blood on CT scan (Fisher CT scale), location of aneurysms, age, possible gender, smoking, hypertension and presence of intraventricular blood clot. Of all these factors, location and

high Fisher CT scale, are consistently reported as the most powerful predictors of CV.<sup>26</sup> Not all patients with CV, however, develop DCI. In current cohort, there was 26.2% of CV-DCI found in patients following spontaneous SAH which is comparable to other studies. The incidence of angiographic vasospasm reported at 43.3% and symptomatic vasospasm or delayed cerebral ischaemic (DCI) occurred in 32.5% based on a review conducted by Dorsch and King in an Australian population.<sup>27</sup>

Standard protocol is in placed including admitting patients to comprehensive stroke unit with continuous clinical and radiological assessment, as early detection of neurologic deterioration is the mainstay treatment of CV. Nimodipine (60mg every 4 hours) administration with baseline transcranial Doppler (TCD) ultrasound measurement on arrival is acquired and daily thereafter to guide blood pressure hypertensive therapy management. Haemodynamic optimisation (euvolemia plus hypertension) and early aggressive treatment within two hours of neurology deterioration is the best strategy to prevent DCI. We found that age was statistically significant factors with patients with CV-DCI. CV-DCI was seen to be more prevalent in the younger age group (50.6±10.90 versus 59.6±11.74). This result is consistent with a study by Kale and colleagues the risk of CV-DCI in aneurysmal SAH that a younger age group of patients developing CV-DCI (mean 48.51±11.23 years) compared to those did not develop CV-DCI (mean 59.67±13.30 years) with statistical significance of  $p < 0.001$ .<sup>28</sup> In addition, a stronger interventional radiology (IR) team support is crucial and should made available to patients with DCI from VS. The IR play an important role to make the treatment more robust and strongly conclusive of VS compared to only using TCD.<sup>29</sup>

The treatment of ruptured brain aneurysm is far more costly than the treatment of unruptured aneurysms. Patients who developed CV-DCI were found to have a significantly longer length of hospital stay compared to the group without CV, 24.0±17.0 days versus 16.0±19.0 days, respectively ( $p=0.035$ ). Yundt and colleagues some time ago had investigated hospital resource utilisation in the treatment of cerebral aneurysms deduced that the total cost per patient was highest in the group of patients who developed CV-DCI which is correlated with hospital stay.<sup>30</sup> Hence hospital resources can be used sparingly if patients with CV are identified early and rapid intervention is instituted. This would also improve patient outcome and length of patient hospital stay.

### Outcome

Approximately 15% of people with a spontaneous SAH from ruptured aneurysm die before reaching the hospital. Most of the deaths are due to rapid and massive haemorrhagic stroke. In the current series, more than half of the patients with spontaneous SAH (54.9%) presented to our centre were noted to have poor WFNS grades, i.e., 3, 4 and 5. This raises the question the level of health awareness among the community which leads to this late presentation for treatment once patients are at clinically deteriorated state. Nevertheless, in terms of patient care there was no statistical significance between the good and poor WFNS grade of the patient and the treatment provided, it was observed that both the WFNS groups were treated equally (Table V).

Identically a study conducted by Wostrack and colleagues<sup>31</sup> showed one hundred and three patients with WFNS grade V SAH received maximal treatment and retrospectively evaluated a favourable outcome at discharge 16% ( $n = 16$ ) of cases, whereas in the follow-up it rose to 26% ( $n = 27$ ). Their study concluded that a favourable outcome was achieved in 26% of aggressively treated patients, rendering the withdrawal of maximal therapy for WFNS grade V SAH patients unacceptable. Hence, patients with poor WFNS grade (grade V) should also be treated aggressively without any sense of bias as they have been proven to have a favourable outcome following aggressive treatment.<sup>31</sup>

This paper also described the functional outcome of patient with CV-DCI following spontaneous SAH in an urban Malaysian population. There have been numerous studies correlating functional outcome including Glasgow outcome scale (GOS) with in patients with CV-DCI following SAH.<sup>14,32,33</sup> The proportion of patients with a poorer MRS score, i.e., 2-6 was certainly higher in the group with CV-DCI in comparison to the group without CV-DCI at the 2-time point intervals which was at discharge and at 6 months. However, there is no difference between MRS upon discharge and 6 months with vasospasm. Further investigation would be promising.

### LIMITATIONS AND FUTURE DIRECTION

The main limitation in this study was sample size due to it being a single centre study. Nonetheless, this report looked at incidence of CV-DCI in a local Malaysian population. An establishment of a multicentre database of patients with spontaneous SAH (aneurysmal and non-aneurysmal) in

Malaysia would give a more accurate projection of incidence of CV-DCI, functional outcome and mortality for both treatment and non-treatment cohorts to reduce any potential biasness. In addition, another limiting factor due to insufficient numbers this work did not venture and investigate the well-known predictors and or risk factors of vasospasm or DCI hence worthwhile investigating in the near future with larger numbers of patients. Some of these known predictor or risk factors includes Fisher CT Grade, rebleeding, alcohol intake, leucocytosis, hyperglycaemia, and electrocardiographic QTc prolongation, left ventricular hypertrophy, and ST depression. Moreover, the effect of various treatment types and VS/DCI as well as the timing of these interventions should be investigated in future studies. A database collection with the aforesaid data provides valuable information on patient outcome and this may hopefully improve on patient management.

### CONCLUSION

Vasospasm and DCI has a significant incidence among local patients with spontaneous SAH (aneurysmal and non-aneurysmal) and it is associated with substantial morbidity. Prevention, close vigilant neurology and TCD monitoring with haemodynamic optimization (euolemia plus stepwise hypertensive therapy adjustment) are the keys to successful management. Further investigation using a multicentre cohort to analyse mortality and survival rates may aid in improving national resource management of these patients in Malaysia.

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### DISCLOSURES

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

### CONFLICT OF INTEREST

All the authors declared no conflict of interests.

### REFERENCES

1. Connolly ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2012; 43(6): 1711-37.
2. Garrett MC, McCullough-Hicks ME, Kim GH, Komotar RJ, Kellner CP, Hahn DK, et al. Plasma acrolein levels and their association with delayed ischemic neurological deficits following aneurysmal subarachnoid haemorrhage: a pilot study. *Br J Neurosurg* 2008; 22(4): 546-9.
3. Risselada R, Lingsma HF, Bauer-Mehren A, Friedrich CM, Molyneux AJ, Kerr RS, et al. Prediction of 60 day case-fatality after aneurysmal subarachnoid haemorrhage: results from the International Subarachnoid Aneurysm Trial (ISAT). *Eur J Epidemiol* 2010; 25(4): 261-6.
4. Ecker A, Riemenschneider PA. Arteriographic demonstration of spasm of the intracranial arteries, with special reference to saccular arterial aneurysms. *J Neurosurg* 1951; 8(6): 660-7.

5. Fisher CM, Roberson GH, Ojemann RG. Cerebral vasospasm with ruptured saccular aneurysm—the clinical manifestations. *Neurosurgery* 1977; 1(3): 245-8.
6. Dorsch NW. Cerebral arterial spasm—a clinical review. *Br J Neurosurg* 1995; 9(3): 403-12.
7. Petridis AK, Kamp MA, Cornelius JF, Beez T, Beseoglu K, Turowski B, et al. Aneurysmal Subarachnoid Hemorrhage. *Dtsch Arztebl Int* 2017; 114(13): 226-36.
8. Fluss R, Laarakker A, Nakhla J, Brook A, Altschul DJ. Prolonged delayed vasospasm in the setting of nonaneurysmal intraventricular hemorrhage. *Surg Neurol Int* 2019; 10: 29.
9. Macdonald RL. Delayed neurological deterioration after subarachnoid haemorrhage. *Nat Rev Neurol* 2014; 10(1): 44-58.
10. Siasios I, Kapsalaki EZ, Fountas KN. Cerebral vasospasm pharmacological treatment: an update. *Neurol Res Int* 2013; 2013: 571328.
11. Chen T, Carter BS. Role of magnesium sulfate in aneurysmal subarachnoid hemorrhage management: A meta-analysis of controlled clinical trials. *Asian J Neurosurg* 2011; 6(1): 26-31.
12. Psychogios K, Tsvigoulis G. Subarachnoid hemorrhage, vasospasm, and delayed cerebral ischemia. *Practical Neurology* 2019; 37-41, 9.
13. Rabinstein AA, Friedman JA, Weigand SD, McClelland RL, Fulgham JR, Manno EM, et al. Predictors of cerebral infarction in aneurysmal subarachnoid hemorrhage. *Stroke* 2004; 35(8): 1862-6.
14. Sano H, Satoh A, Murayama Y, Kato Y, Origasa H, Inamasu J, et al. Modified World Federation of Neurosurgical Societies Subarachnoid Hemorrhage Grading System. *World Neurosurg* 2015; 83(5): 801-7.
15. Etminan N, Vergouwen MD, Macdonald RL. Angiographic vasospasm versus cerebral infarction as outcome measures after aneurysmal subarachnoid hemorrhage. *Acta Neurochir Suppl* 2013; 115: 33-40.
16. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdevits EF, Muizelaar JP, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. *Stroke* 2010; 41(10): 2391-5.
17. Olkowski BF, Devine MA, Slotnick LE, Veznedaroglu E, Liebman KM, Arcaro ML, et al. Safety and feasibility of an early mobilization program for patients with aneurysmal subarachnoid hemorrhage. *Phys Ther* 2013; 93(2): 208-15.
18. Pegoli M, Mandrekar J, Rabinstein AA, Lanzino G. Predictors of excellent functional outcome in aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2015; 122(2): 414-8.
19. Carteron L, Bouzat P, Oddo M. Cerebral Microdialysis Monitoring to Improve Individualized Neurointensive Care Therapy: An Update of Recent Clinical Data. *Front Neurol* 2017; 8: 601.
20. Diringner MN, Bleck TP, Claude Hemphill J, 3rd, Menon D, Shutter L, Vespa P, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. *Neurocrit Care* 2011; 15(2): 211-40.
21. Juvela S. Natural history of unruptured intracranial aneurysms: risks for aneurysm formation, growth, and rupture. *Acta Neurochir Suppl* 2002; 82: 27-30.
22. Hobbs SD, Wilmsink AB, Bradbury AW. Ethnicity and peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2003; 25(6): 505-12.
23. Beydoun HA, Beydoun MA, Zonderman AB, Eid SM. Racial and Ethnic Disparities in Treatment Outcomes of Patients with Ruptured or Unruptured Intracranial Aneurysms. *J Racial Ethn Health Disparities* 2019; 6(2): 345-55.
24. Brinjikji W, Rabinstein AA, Lanzino G, Cloft HJ. Racial and ethnic disparities in the treatment of unruptured intracranial aneurysms: a study of the Nationwide Inpatient Sample 2001-2009. *Stroke* 2012; 43(12): 3200-6.
25. Delgado Almandoz JE, Crandall BM, Fease JL, Scholz JM, Anderson RE, Kadkhodayan Y, et al. Diagnostic yield of catheter angiography in patients with subarachnoid hemorrhage and negative initial noninvasive neurovascular examinations. *AJNR Am J Neuroradiol* 2013; 34(4): 833-9.
26. Brouwers PJ, Dippel DW, Vermeulen M, Lindsay KW, Hasan D, van Gijn J. Amount of blood on computed tomography as an independent predictor after aneurysm rupture. *Stroke* 1993; 24(6): 809-14.
27. Dorsch NW, King MT. A review of cerebral vasospasm in aneurysmal subarachnoid haemorrhage Part I: Incidence and effects. *J Clin Neurosci* 1994; 1(1): 19-26.
28. Kale SP, Edgell RC, Alsheklee A, Borhani Haghighi A, Sweeny J, Felton J, et al. Age-associated vasospasm in aneurysmal subarachnoid hemorrhage. *J Stroke Cerebrovasc Dis* 2013; 22(1): 22-7.
29. Samagh N, Bhagat H, Jangra K. Monitoring cerebral vasospasm: How much can we rely on transcranial Doppler. *J Anaesthesiol Clin Pharmacol* 2019; 35(1): 12-8.
30. Yundt KD, Dacey RG, Jr., Diringner MN. Hospital resource utilization in the treatment of cerebral aneurysms. *J Neurosurg* 1996; 85(3): 403-9.
31. Wostrack M, Sandow N, Vajkoczy P, Schatlo B, Bijlenga P, Schaller K, et al. Subarachnoid haemorrhage WFNS grade V: is maximal treatment worthwhile? *Acta Neurochirurgica* 2013; 155(4): 579-86.
32. Aiyagari V, Cross DT, 3rd, Deibert E, Dacey RG, Jr., Diringner MN. Safety of hemodynamic augmentation in patients treated with Guglielmi detachable coils after acute aneurysmal subarachnoid hemorrhage. *Stroke* 2001; 32(9): 1994-7.
33. Kapapa T, Tjahjadi M, Konig R, Wirtz CR, Woischneck D. Which clinical variable influences health-related quality of life the most after spontaneous subarachnoid hemorrhage? Hunt and Hess scale, Fisher score, World Federation of Neurosurgeons score, Brussels coma score, and Glasgow coma score compared. *World Neurosurg* 2013; 80(6): 853-8.

# A descriptive analysis of clinical characteristics of COVID-19 among healthcare workers in a district specialist hospital

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## ABSTRACT

**Introduction:** COVID-19 is a highly transmissible respiratory virus that has affected millions of people worldwide in the span of months. The burden of disease among healthcare workers (HCW) has not been well studied despite reports of infectivity and transmission around the world. Two HCW in Hospital Teluk Intan (HTI) contracted COVID-19 while attending a social event. They were in close proximity with colleagues upon returning to work, resulting in the spread of infection among other HCW in HTI.

**Objective:** The objectives of this paper are to gain a better understanding of the key presenting symptoms of COVID-19 in HCWs in a district specialist hospital, to establish the proportion of symptomatic COVID-19 cases among HCWs and its severity and to determine the time taken from onset of symptoms or perceived exposure to diagnostic testing.

**Methodology:** This is a retrospective descriptive analysis of clinical characteristics of subjects infected with COVID-19 among HCW in HTI. Their demography and clinical characteristics were recorded.

**Results:** There were 47 HCW in HTI who tested positive for COVID-19. The mean age of the patients was 37.5 years old. 7 patients (15.2%) had at least more than one comorbidity. Average duration of time from perceived close contact to onset of symptom was 4.5 days, while the mean duration of time from symptoms to first positive RT-PCR result was 3.4 days. Six patients (13.0%) were asymptomatic throughout, whereas 40 (87.0%) had at least one symptom prior to hospitalization. The most commonly reported symptoms were fever (65.2%), sore throat (39.1%) and cough (37.0%). In terms of severity of symptoms, the majority of patients experienced mild symptoms (Group 2, 52.2%). Two patients (4.3%) with multiple comorbidities had severe disease requiring ICU admission and mechanical ventilation. There were no mortalities, and the longest staying patient was hospitalized for 18 days. The high rates of infectivity among HCW in HTI can be attributed to working in close proximity while in the asymptomatic incubation phase, while no HCW directly involved in the care of COVID-19 positive patients were tested positive.

**Conclusion:** We report that HCW share similar clinical characteristics of COVID-19 infection as those of non HCW patients in earlier studies. The infection can spread rapidly within healthcare settings via close contacts among infected

HCWs. As such, we advocate distancing when working and usage of personal protective equipment when treating patients with respiratory illness to reduce transmission of COVID-19.

## KEYWORDS:

COVID-19, Healthcare workers, Personal Protective Equipment

## INTRODUCTION

In December 2019, healthcare professionals in Wuhan, China identified a severe manifestation of pneumonia appearing in clusters of patients who frequented a wet market in the region which sold exotic animals.<sup>1,2</sup> Local health authorities were alerted, and in subsequent days the number of patients presenting with viral pneumonia increased exponentially. By January 2020, the World Health Organization (WHO) issued a statement warning of a highly infectious novel coronavirus.<sup>3,5</sup> The pathogen was identified as a beta-coronavirus with phylogenetic similarity to the severe acute respiratory syndrome coronavirus (SARS-CoV), and eventually came to be known as the SARS-CoV2, and the disease caused as COVID-19.<sup>6-9</sup> Globally as of late March 2020, more than 750,000 people have contracted the disease with deaths over 36,000 consequent to the infection.<sup>10</sup>

COVID-19 is a highly transmissible viral illness with clinical manifestations primarily involving the respiratory system. Early epidemiological and descriptive studies by Chen et al., and Huang et al., described fever, cough and shortness of breath as the clinical manifestations most commonly presented in patients who tested positive for COVID-19.<sup>3,5</sup> Guan et al., reported human-to-human transmission among family members as the main source of transmission, attributing almost 73% of total human-to-human transmission in China.<sup>11</sup> Wu et al., reported that COVID-19 conferred an overall case-fatality rate (CFR) of 2.3%, with higher rates seen in patients above 70, with multiple underlying comorbidities and in the critically ill.<sup>12</sup>

The role of healthcare workers (HCW) in the COVID-19 pandemic has been paramount. Due to the rising number of COVID-19 cases and increased burden of care and screening, more cases of HCW infected with COVID-19 have been reported. In the United States of America, 9242 cases of COVID-19 infection were reported among HCW as of 9th April 2020.<sup>13</sup> In a summary report of 72,000 cases from the Chinese Center for Disease Control and Prevention, Wu et al.,

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reported a HCW infection rate of 3.8%, of which a large proportion were HCWs working in Wuhan.<sup>12</sup> There is also the increased risk of HCW infection and transmission among HCW in the non-clinical setting within the workplace. Despite this increased awareness, HCW remains to be a population that is understudied in relation to disease transmission.

On 25th January 2020, Malaysia reported the first case of COVID-19 from a traveler who returned from Wuhan.<sup>14-16</sup> Early efforts to contain and quarantine people with a travel history from China proved successful. The situation changed in early March 2020, when a large international religious gathering of more than 10,000 people took place in Selangor.<sup>16,17</sup> In the coming weeks, there was a sharp rise in the number of positive cases which were eventually traced to this event.<sup>18</sup> Several attendees of this gathering have already returned to other neighboring Southeast Asian countries including Brunei, Thailand and Indonesia. Globally as of late March, WHO reported more than 370,000 confirmed cases globally affecting 196 countries, with more than 16,000 deaths attributed to COVID-19.<sup>19</sup> As of 30th April 2020, Malaysia recorded 6002 cases who tested positive for COVID-19 with 102 deaths consequent to the infection.<sup>20</sup>

On 8 March 2020, 2 HCW in Hospital Teluk Intan (HTI) were diagnosed to be positive for COVID-19. Following this information, immediate action of assessment and investigation was done to verify and confirm the event. The primary objectives of this paper is to gain a better understanding of the key presenting symptoms of COVID-19 in HCWs in a district specialist hospital, to establish the proportion of symptomatic COVID-19 cases among HCW and its severity and to determine the time taken from the onset of symptoms or perceived exposure to diagnostic testing.

## MATERIALS AND METHODS

### Methods

This is a retrospective, single-centered study. We recruited HCW from HTI who tested positive for the COVID-19 genome via oropharyngeal or nasopharyngeal sampling and who came from the same epidemiological cluster between 15 March 2020 and 30 April 2020. The diagnosis of COVID-19 was confirmed by real-time polymerase chain reaction (RT-PCR) for SARS-CoV2 done on nasopharyngeal swab specimens. Specimens were obtained by a dedicated team of doctors trained in performing nasopharyngeal sampling and proper packing of laboratory specimens. Diagnostic testing was carried out in a designated laboratory in Ipoh. Only healthcare workers from HTI were included while those who did not consent to being interviewed were excluded from the study. Subjects were recruited from information made available by the COVID operation centre in HTI.

### Procedures

This study was conducted via phone interview as all of the subjects were either quarantined or admitted in isolation wards during the study period. Subjects were read a scripted patient information sheet over the phone by the investigator, and verbal consent was recorded by the investigator. They were then asked a series of questions prepared by the

investigators about their age, comorbidities, date of contact with confirmed case, date of onset of symptoms, symptoms manifested, dates when nasopharyngeal samples were taken and the results, and the management. Information was also cross-referenced with medical records of patients in the event that they were unable to recall any details.

### Statistical analysis

Descriptive analysis was used to characterise the study population by IBM SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Data were compiled and reported in frequency (percentages) and standard deviation.

### Ethical Consideration

The study was approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia. All subjects were read a scripted informed consent prior to interview and verbal consent was documented by the investigators. This is a retrospective study without any intervention on the part of the investigators and all efforts were taken to ensure confidentiality of those who agreed to participate.

## RESULTS

A total number of 1480 nasopharyngeal samples were taken. 54 samples (3.6%) were reported to have RT-PCR SARS-CoV2 genome detected, and diagnosed as COVID-19. Forty-seven (3.2%) were HCW from HTI. A total of 47 cases met the case definition, and 46 consented to be included in our study. They comprised of 24 doctors (52.2%), 14 nurses (30.4%), 5 medical assistants (10.9%) and 3 allied healthcare workers (6.5%) which included a counselor, a medical laboratory technician and a hospital safety officer.

The mean age of the patients was 37.5 years old (SD 8.9). There were 17 males (36.9%) and 29 females (63.1%). In all 27 patients were treated in Ipoh (58.7%) while the remaining 19 (41.3%) were treated in HTI. Of those who were treated in HTI, one patient had to be transferred to the state referral COVID-19 hospital in Ipoh due to clinical deterioration.

There were 7 patients (15.2%) with at least one comorbidity. The most common comorbidity among our cohort was hypertension (13.0%), followed by diabetes mellitus (6.5%), dyslipidemia (4.3%) and bronchial asthma (4.3%). Other comorbidities among our cohort were ischemic heart disease (2.2%), chronic kidney disease (2.2%), sleep apnoea (2.2%) and malignancy (2.2%). Three (6.5%) of them had multiple comorbidities. The majority of our patients were non-smokers, with only one smoker (2.2%) and three ex-smokers (6.5%). The mean BMI of the cohort was 26.4kg/m<sup>2</sup> (SD4.96). Thirteen (28.2%) of our patients were underweight with BMI of less than 23kg/m<sup>2</sup>, while 20 (43.6%) were considered obese with BMI of above 27kg/m<sup>2</sup> (according to the WHO Modified BMI categorisation for Asia Pacific population).

Six patients (13.0%) in our cohort were asymptomatic in the duration of time before and after hospitalization, whereas the remaining 40 patients (87.0%) experienced at least one symptom before or during the time of admission. Symptoms most commonly reported included fever (65.2%), sore throat (39.1%) and cough (37.0%). This was followed by myalgia

**Table I: Demographic of Healthcare Workers in Hospital Teluk Intan with COVID-19**

	Patients (n= 46)
<b>Age</b>	37.5 (8.9)*
<b>Gender</b>	
Male	17 (36.9%)
Female	29 (63.1%)
<b>Occupation</b>	
Doctor	24 (52.2%)
Nurse	14 (30.4%)
Medical Assistant	5 (10.9%)
Other allied healthcare professionals	3 (6.5%)
<b>*BMI</b>	26.4 (5.0)*
<23	13 (28.2%)
23-27	13 (28.2%)
>27	20 (43.6%)
<b>Comorbidities</b>	
Hypertension	6 (13.0%)
Diabetes mellitus	3 (6.5%)
Dyslipidemia	2 (4.3%)
Bronchial asthma	2 (4.3%)
Ischemic heart disease	1 (2.2%)
Chronic kidney disease	1 (2.2%)
Sleep apnoea	1 (2.2%)
Malignancy	1 (2.2%)
<b>Number of comorbidities</b>	
0	39 (84.8%)
1	4 (8.7%)
2 or more	3 (6.5%)
<b>Smoking status</b>	
Active	1 (2.2%)
Ex-smoker	3 (6.5%)
Non-smoker	42 (91.3%)

\*mean (SD)

n = frequency; % = percentage; BMI = body mass index.

BMI was based on WHO modified BMI for Asia Pacific region

**Table II: Presenting symptoms among Healthcare Workers in Hospital Teluk Intan with COVID-19**

	Patients (n= 46)
<b>Symptomatic</b>	40 (87.0%)
<b>First presenting symptoms</b>	
Fever	30 (65.2%)
Sore Throat	18 (39.1%)
Cough	17 (37.0%)
Myalgia	9 (19.6%)
Rhinorrhoea	6 (13.0%)
Lethargy	5 (10.9%)
Dyspnoea	4 (8.7%)
Diarrhea	3 (6.5%)
Nausea/ Vomiting	1 (2.2%)
<b>Other symptoms</b>	
Anosmia	4 (8.7%)
Headache	2 (4.3%)
Itch	1 (2.1%)
<b>Number of patients with more than 1 symptom on presentation</b>	27 (58.7%)
<b>Severity of Illness (Group)</b>	
1	12 (26.1%)
2	24 (52.2%)
3	7 (15.2%)
4	1 (2.2%)
5	2 (4.3%)
<b>Asymptomatic</b>	6 (13.0%)
<b>Number of days from close contact to symptoms (N=40)</b>	4.5 (3.8)*
<b>Number of days from close contact to first positive swab (N=46)</b>	8.0 (4.5)*
<b>Number of days from symptoms to first positive swab (N=39)</b>	3.4 (2.8)*
<b>Number of days from close contact to first sampling</b>	8.0 (4.2)*
<b>Number of HCWs with COVID-19 Genome detected on first swab</b>	35 (76.1%)
<b>Number of HCWs with COVID-19 Genome detected on second swab</b>	11 (23.9%)
<b>Duration of Hospitalisation</b>	12.0 (3.1)*

\*mean (SD)

n = frequency; % = percentage; HCW: healthcare workers

(19.6%), rhinorrhoea (13.0%), lethargy (10.9%), dyspnoea (8.7%), anosmia (8.7%), diarrhoea (6.5%) and nausea/vomiting (2.2%). 27 of them (58.7%) experienced two or more symptoms upon disease onset.

We further classified our HCW based on disease severity at the time of admission. These groupings were based on the national guidelines: Group 1: for asymptomatic patients, Group 2 are patients with non-pneumonia upper respiratory symptoms, Group 3 for patients with pneumonia not requiring oxygen, Group 4 refers to patients with pneumonia requiring oxygen supplementation, and Group 5 being patients with severe manifestation of COVID-19 requiring ventilator support or ICU admission.<sup>28</sup> During their entire duration of hospitalisation, their groupings of classification of symptoms changed in the event of new symptoms that development or any deterioration. In total, 12 (26.1%) patients were classified as Group 1, 24 (52.2%) as Group 2, 7 (15.2%) as Group 3, 1 (2.2%) as Group 4 and 2 (4.3%) patients as Group 5.

The two patients with Group 5 disease required admission to the intensive care unit (ICU). They had multiple comorbidities and were also obese. Both patients required

mechanical ventilation while one had to undergo haemodialysis as well. The patient who required haemodialysis had underlying chronic kidney disease secondary to diabetic nephropathy with a baseline creatinine of 159µmol/l. Both patients improved clinically and were discharged after 17 and 18 days of admission respectively. One patient had a healing pressure sore on discharge, whereas the creatinine of the other patient who required haemodialysis returned to baseline level during subsequent outpatient follow-up. There were no mortalities among our cohort of patients. No members of the public who were admitted during this period were tested positive for COVID-19.

The mean number of days from perceived close contact with a positive case to having the first diagnostic swab was 8.0 days (SD4.2). The mean number of days from perceived close contact to the onset of symptoms was 4.5 days (SD3.8). The time from perceived close contact to the first positive RT-PCR swab was 8 days (SD4.5). Among those who were symptomatic, the mean number of days from symptom onset to a first positive RT-PCR result was 3.4 days (SD 2.8). The mean duration of hospital stay was 12 days (SD 3.1), with the longest hospital stay being 18 days.



## DISCUSSION

On 8 March 2020, two HCW from HTI attended a wedding in Bandar Baru Bangi, Selangor. In this event, approximately 300 attendees were in contact with a person who were later confirmed to have COVID-19. Following this event, both HCW went back to work and continued their daily routine as they were asymptomatic. By mid-March 2020, these HCW developed symptoms of fever and cough. They underwent diagnostic RT-PCR nasopharyngeal swabs and were found to be positive for COVID-19.<sup>4-7,21</sup> Swift measures of containment, contact tracing and screening were performed among the HTI staff that had the closest contact to those HCW. These two patients were then transferred to the state's designated COVID-19 hospital for further management and care. Due to the repeated exposure between the two index cases with colleagues in their respective departments, COVID-19 continued to spread within the HTI. A total of 54 COVID-19 cases were identified from this cluster, of which 48 were HCW, whereas six others were family members of these HCW. All these patients were admitted and managed in HTI and the designated hospital.

Common presenting symptoms among our cohort namely fever and cough were consistent with global trends.<sup>3-5,22</sup> However, we also found that sore throat was reported more frequently compared to cough, and at a higher frequency when compared with other studies done in other centres.<sup>3-5, 22-26</sup> Our cohort also had substantially lower rates of deterioration reflected by ICU admissions, and reported no mortalities as compared with studies from Zhou et al., and Yang et al.<sup>22,23</sup> This was because our cohort consisted of a relatively younger population (65.2% were aged 40 years and below) and had no co-morbidities.<sup>22-24,27</sup>

Our patients were admitted in accordance with local COVID-19 guidelines, whereby positive cases were admitted into designated hospitals regardless of symptoms or severity.<sup>28,29</sup> Patients were only discharged when their nasopharyngeal swab 14 days from date of either symptom manifestation or first positive swab in those who were asymptomatic came back negative, and with no other clinical concerns. Due to this, the duration of hospitalisation may not be a true reflector of severity of disease. Prolonged hospitalisation adds to the burden of healthcare costs and resources of the public healthcare system, yet this measure to admit and actively isolate all positive cases regardless of severity may perhaps have played a pivotal role in reducing disease spread within the hospital community.

As of April 2020, HTI had the second highest number of COVID-19 infection among HCW in Malaysia. A number of key events led to this rapid spread. First was the increased number of meetings held in preparation for the management of COVID-19 patients. These included inter-department meetings between department heads and hospital management team. Secondly, regular teaching and training activities also contributed to the dissemination of the disease.

We observed a trend of infectivity relating to the number of occupants in a particular work area. Work areas that were enclosed and crowded were affected more: the busy and crowded Emergency and Trauma Department which had 20

healthcare staff per shift had the most number of cases at 22 (46.8%), followed by the Infection Control Unit (5 cases, 10.6%) which shared a small office, the Pathology Department (4 cases, 8.5%) and Radiology Department (2 cases, 4.3%). During this period of time, wearing of surgical 3-ply masks and social distancing were not strictly enforced as yet.

Another contributing factor was that 78.3% of affected staff had either no symptoms or mild symptoms and continued to work. Many staff tend to 'work-through' these mild symptoms as they perceive them to be the 'normal' flu or common cold. There is now an increasing awareness of the knowledge that COVID-19 is infective even in the asymptomatic incubation period.<sup>23,24,26</sup> A position statement from the National Centre for Infectious Diseases and the Chapter of Infectious Disease Physicians, Academy of Medicine, Singapore, state that the infectious period begins at around two days before symptom onset, while the mean incubation period of disease is around five days.<sup>30</sup>

Interestingly we noted that during this same period, apart from the six immediate family members of affected HCWs, only one other patient who spent the previous six months working aboard a cruise ship tested positive for COVID-19. No other patient from the community who was admitted for 'Severe Acute Respiratory Illness' (SARI) tested positive for COVID-19. Also of note is that there were no HCW who were directly caring for COVID-19 patients who tested positive for COVID-19 during this entire duration.

During the period between March and April 2020, a total number of 967 HCW were quarantined while awaiting for results from their confirmatory COVID-19 tests. At least five working days per HCW were lost from the quarantine time. Radiology, pathology and emergency medicine departments were reduced to 'skeleton services'. Elective procedures were postponed not only from the reduced workforce, but also in order to reduce COVID-19 contact risks by reducing patient flow in HTI. Also, added manpower was recruited from nearby hospitals during this period to provide adequate coverage of service during this period.

Following this outbreak, HTI enforced a strict 'health declaration' among HCW on a daily basis upon reporting to work. This involved HCW answering a questionnaire on their health condition (presence of fever, myalgia, cough or sore throat), recent travel out of the state, and close contact with COVID-19 positive patients. HCW who answered as yes to any of the above questions were subsequently assessed for risk of COVID-19 transmission. High risk HCW would then be quarantined and undergo a RT-PCR sampling. Strict hand hygiene, surgical 3-ply mask wearing, and social distancing rules was enforced and continuously reminded. Multiple training sessions involving prerecorded videos and online training of donning personal protective equipment (PPE) were conducted in all departments. Clinic and examination rooms which were previously shared were reduced to one-doctor, one-patient per room. Patients who presented to emergency department or as walk-in to the various clinics were screened with a similar health declaration questionnaire, and triaged to a special, isolated examination

area if deemed at risk of having SARI, influenza-like illness (ILI) or COVID-19.

To reduce risk of transmission among both patients and HCW in HTI, patients who were admitted for SARI or ILI awaiting RT-PCR results for COVID-19 were kept in isolation bays. Use of aerosol based nebulisers were significantly reduced. The pharmacy department innovated methods of delivering metered-dose inhalers via modified aerochambers with disposable plastic cups and disposable supplementary oxygen face masks. These innovations were required due to the costs and acute shortage of regular aerochambers during this period of time.

There were several limitations in this study. Due to travel restrictions during the study period, the investigators relied on phone interviews to obtain information pertaining to our patients. There were a few instances where our subjects could not recall certain information and we had to call them back later to clarify. There was also some delay in receiving test results during the early phase of the pandemic due to the sudden surge in sampling and testing. This improved as the testing capacity in Malaysia increased.

## CONCLUSION

The authors observed from this study that HCW share similar clinical characteristics of COVID-19 infection as those of non HCW patients in earlier studies. The infection can spread rapidly within healthcare settings via close contacts among infected HCW. As such, we recommend instilling the practice of masks wearing, distancing during clinical activities and hand hygiene in the daily work practice to reduce risks of disease transmission.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## REFERENCES

- World Health Organization. Press Release: Pneumonia of unknown cause – China [cited Jan 2020]. Available from <https://www.who.int/csr/don/05-january-2020-pneumonia-of-unknown-cause-china/en/>.
- British Society of Thoracic Imaging. Education material: Background COVID-19: First cases Wuhan City China [cited March 2020]. Available from [bsti.org.uk/media/resources/files/BSTI\\_COVID-19\\_Radiology\\_Guidance\\_version\\_2\\_16.03.20.pdf](https://bsti.org.uk/media/resources/files/BSTI_COVID-19_Radiology_Guidance_version_2_16.03.20.pdf).
- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395(10223): 507-13.
- Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health — The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 2020; 91: 264-6.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395(10223): 497-506.
- He F, Deng Y, Li W. Coronavirus disease 2019: What we know? *J Med Virol* 2020; 92(7): 719-25.
- National Institute for Health and Care Excellence. COVID-19 rapid guideline : critical care in adults [cited March 2020]. Available from: [www.nice.org.uk/guidance/ng159](https://www.nice.org.uk/guidance/ng159).
- Rahman S, Bahar T. COVID-19: The New Threat. *Int J Infect* 2020; 7(1): 1-6.
- Forster P, Forster L, Renfrew C, Forster M. Phylogenetic network analysis of SARS-CoV-2 genomes. *Proc Natl Acad Sci USA* 2020; 117(17): 9241-3.
- World Health Organization. Situation Report [cited Nov 2020]. Available from <https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200331-sitrep-71-covid-19.pdf>.
- Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; 382(18): 1708-20.
- Wu Z, McGoogamm JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. *JAMA* 2020; 323(13): 1239-42.
- Papoutsis E, Giannakoulis VG, Ntella V et al. Global burden of COVID-19 pandemic on healthcare workers. *ERJ Open Res* 2020; 6: 00195-2020 [cited Jun 2020]. Available from: <https://doi.org/10.1183/23120541.00195-2020>.
- Rampal L, Liew BS. Coronavirus disease (COVID-19) pandemic. *Med J Malaysia* 2020; 75(2): 95-7.
- Sipalan, Joseph; Holmes, Sam. Malaysia confirms first cases of coronavirus infection: Reuters [updated 18 Feb 2020, cited Feb 2020]. Available from: <https://www.reuters.com/article/china-health-malaysia/malaysia-confirms-first-cases-of-coronavirus-infection-idUSL4N29U03A>.
- Ministry of Health Malaysia. Press release: Situasi Semasa Pandemik COVID-19 Di Malaysia [updated 07 April 2020, cited April 2020]. Available from <http://covid-19.moh.gov.my/>.
- Ng K. Coronavirus: Malaysia cases rise by 190 after mosque event as imams urge online services: The Independent [updated 16 March 2020, cited March 2020]. Available from <https://www.independent.co.uk/news/world/asia/coronavirus-malaysia-cases-southeast-asia-mosque-islam-a9403816.html>.
- Coronavirus: Malaysia records eight deaths; 153 new cases bring total to 1,183. *The Straits Times* [updated 21 March 2020, cited March 2020]. Available from <https://www.straitstimes.com/asia/se-asia/malaysia-records-fourth-coronavirus-death>.
- World Health Organization. Press Release: WHO Director-Generals remarks for G20 trade ministers [cited March 2020]. Available from <https://www.who.int/dg/speeches/detail/who-director-generals-remarks-for-g20-trade-ministers>.
- Ministry of Health Malaysia, From the Desk of the Director-General of Health Malaysia. Press Release: Kenyataan Akhbar KPK 30 April 2020 – Situasi Semasa Jangkitan Penyakit Coronavirus 2019 (COVID-19) di Malaysia [cited April 2020]. Available from <https://kpksehatan.com/2020/04/30/kenyataan-akhbar-kpk-30-april-2020-situasi-semasa-jangkitan-penyakit-coronavirus-2019-covid-19-di-malaysia/>.
- Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DKW, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Eurosurveillance* 2020; 25(3): 1-8.
- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395(10229): 1054-62.
- Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8(5): 475-81.
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA - J Am Med Assoc* 2020; 323(11): 1061-9.
- Tingbo L. Handbook of COVID-19 Prevention and Treatment. *Handb Covid-19, Prev Treat* [cited 25 March 2020]. Available from: <https://covid-19.alibabacloud.com>.
- Gandhi M, Yokoe DS, Havlir D V. Asymptomatic transmission, the achilles' heel of current strategies to control Covid-19. *N Engl J Med* 2020; 382(22): 2158-60.
- Urner M, Ferreyro BL, Douflé G, Mehta S. Supportive care of patients on mechanical ventilation. *Respir Care* 2018; 63(12): 1567-74.
- Malaysian Ministry of Health. Clinical Management of Confirmed Case. Guidelines COVID-19 Management, Annex 2e, 5/2020 [updated 15 April 2020, cited April 2020]. Available from <http://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm>.
- Malaysian Ministry of Health. Management of PUI and Confirmed COVID-19 Case. Guidelines COVID-19 Management, Annex 2, 5/2020 [updated 22 March 2020, cited March 2020]. Available from <http://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm>.
- Academy of Medicine Singapore. Position statement: Period of Infectivity to Inform Strategies for De-isolation for COVID-19 Patients. [cited March 2020]. Available from <https://www.ams.edu.sg/view-pdf.aspx>.

# Laparoscopic cystectomy in treating women with endometrioma and pregnancy outcome – a case series

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## ABSTRACT

**Introduction:** The aim of this study was to determine the spontaneous pregnancy rate and safety of our surgical technique of performing laparoscopy cystectomy for endometrioma.

**Method:** This is a 5-year retrospective study, carried out at Mahkota Medical Centre, Melaka, Malaysia. 143 patients with endometrioma associated with moderate to severe endometriosis underwent laparoscopic cystectomy from 2015 to 2019. The surgery commenced with dissection and excision of all the endometriotic lesions followed by injection of diluted vasopressin into the space between the cyst wall and the normal ovarian cortex. Stripping of the cyst wall was performed until the ovarian hilum was reached. The cyst wall was then excised, leaving some of the cyst wall on the hilum area. Minimal bipolar electrocoagulation was done on this remaining cyst wall. The ovary was then reconstructed with suturing. During the surgery, the severity of the disease was staged, endometrioma diameter and intraoperative findings were recorded. Fertility outcomes were determined among patients who were keen to conceive via telephone questionnaire and further analysed based on different factors.

**Results:** Among the 143 patients, 33.6% had Stage III endometriosis while 66.4% had Stage IV endometriosis. Of the 76 infertile patients, 42.1% conceived spontaneously in the mean duration of 6.9 months. 62.5% patients successfully conceived via assisted reproductive treatment and 10% conceived with ovulation induction. 47.4% patients had an uneventful delivery while 2.6% patients miscarried. 6.6% patients conceived twice post-surgery.

**Conclusion:** The aim of performing laparoscopic cystectomy for endometrioma in an infertile patient is to achieve a spontaneous pregnancy. Our technique of performing laparoscopic cystectomy resulted in a spontaneous pregnancy rate of 42.1% in patients with moderate and severe endometriosis.

## KEYWORDS:

*Bipolar coagulation; cystectomy; endometrioma; fertility; gynaecological ultrasound; laparoscopic; vasopressin*

## INTRODUCTION

Endometriosis is a chronic disease caused by the presence of endometrial-like glands and stroma outside the uterine

cavity. Endometriotic lesions can be present on the side wall of the pelvis or on the surface of pelvic organs such as uterus, ovaries, fallopian tubes, bladder, bowels, ureter and appendix<sup>1</sup> Endometriosis has been reported among 6-10% of women during their reproductive age.<sup>2</sup> Its prevalence among infertile patients was reported to be as high as 30-50%.<sup>3</sup> The most common manifestation of endometriosis is endometrioma which is the presence of the ectopic endometrial tissues in the ovary. A total of 17-44% of women with endometriosis were found to have endometrioma.<sup>4</sup>

Endometrioma is usually associated with moderate to severe endometriosis.<sup>5</sup> It may cause dysmenorrhea, dyspareunia, pelvic pain and infertility. Medical management for endometrioma reduces its size and relieves the pain but does not improve fertility.<sup>6</sup> The gold standard treatment for endometrioma is laparoscopic cystectomy. While decreasing dysmenorrhea, dyspareunia and pelvic pain, cystectomy also reduces recurrence rate while increasing spontaneous pregnancy rate. Pregnancy rate reported following excision of endometrioma was 30-67%, at the mean of 50%.<sup>7</sup> However, studies have also shown that laparoscopic cystectomy will cause a significant negative impact on post-operative ovarian residual volume and reserve.<sup>8,9</sup> During cyst excision, the absence of a clear cleavage plane between the cyst wall and ovarian stroma causes unintentional removal of the healthy ovarian tissues and cortex, resulting in reduction of follicles. To preserve the ovarian function, other surgical techniques have been proposed such as drainage, sclerotherapy or ablation. Cystectomy involves removing the cyst wall while ablative surgery involves opening the endometrioma and destroying the inner lining of the cyst wall with carbon dioxide laser vaporisation, plasma energy vaporisation or electrosurgical coagulation. Although these techniques could prevent the risk of excising healthy ovarian parenchyma, the risk of recurrence was generally higher compared to cystectomy.<sup>7,10,11</sup>

Since different surgical techniques carry the risk of either impairment of the ovarian reserve or repeated surgery due to recurrence, some fertility specialist would prefer to proceed with *in-vitro* fertilisation (IVF) treatment first without surgery. However, the presence of endometrioma may theoretically interfere with ovarian responsiveness during ovarian stimulation as well as pose difficulties and risks during oocytes retrieval. Some difficulties that may be encountered are injury to the adjacent organs due to altered pelvic anatomy caused by adhesions, accidentally puncturing the

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endometrioma during oocyte retrieval causing infection and abscess formation as well as follicular fluid contamination with the endometrioma content.<sup>12,13</sup>

To obtain the most favourable post-surgical outcome, a combined excisional and ablative technique has been proposed. In this technique, the endometrioma is excised using the stripping technique until the hilum is reached. Then the endometriosis at the hilum area is ablated. A study has shown that this combined technique, whereby excision of the endometrioma leading to a lower recurrence rates as well as non-excision at the hilum for preservation of normal ovarian tissues has led to a 32% cumulative pregnancy rate and a 2% recurrence rate.<sup>14</sup>

In this study, we would like to propose a surgical technique of endometrioma excision that involves the combined technique described above and at the same time injecting diluted vasopressin into the space between the cyst wall and the normal ovarian cortex. We would like to determine the spontaneous pregnancy rate as well as the safety of the first author's technique of performing laparoscopy cystectomy for endometrioma.

## METHODS

A total of 143 women with endometrioma presenting with chronic pelvic pain and/or infertility who underwent laparoscopic cystectomy were recruited in this study. Also included were 78 patients from the previous study entitled 'Laparoscopic Transient Ovariopexy for Endometrioma and Fertility Outcome – a case series' based on the eligibility criteria. The surgeries were performed at Mahkota Medical Centre, Melaka, Malaysia from November 2015 to April 2019. Our institutional board approved this research and written informed consent were obtained pre-operatively from each woman for the surgery as well as to be involved in this retrospective study.

The pre-operative diagnosis of endometrioma was made by ultrasound scan (USS). In patients who were *virgo intacta* (VI), transabdominal ultrasound scan (TAUS) was performed and if the patient consented, transrectal ultrasound scan (TRUS) was done. For patients who were not VI, diagnosis was made by gynaecological examination and transvaginal ultrasound scan (TVUS). During the USS, the uterus and ovaries were carefully evaluated as well as the diameter of any ovarian cyst was measured and recorded. The severity of the disease was staged intra-operatively based on the revised American Society for Reproductive Medicine (rASRM) classification.

The duration of the surgery was calculated from the first incision for Verres needle insertion for pneumoperitoneum to completion of the last suture on the abdominal wall. All the surgeries were performed by the same surgeon.

### *Surgical technique*

The surgery was performed using a 3D laparoscope (Aesculap – BBraun Einstein Vision). Adhesiolysis was performed to mobilise the endometriotic cyst. The contents of the endometriotic cyst was aspirated. This was then followed by temporarily hitching of both ovaries up to the abdominal

wall using Prolene 2.0 (Ethicon Inc, Somerville, NJ) sutures. This is to allow a better view of the pelvic side walls and Pouch of Douglas (POD). Ureters were dissected out if thought necessary. Dissection in the POD was carried out to release all adhesions between the rectum and the uterus, cervix and uterosacral ligaments. Any endometriotic lesions present on the rectum, in the uterosacral ligament, cervix and uterus were excised. If the vagina was involved, part of the vagina was removed and defect was sutured. If the rectal wall was involved, the endometriosis was shaved with caution to prevent the risk of rectal perforation. The rectal wall integrity was tested by inserting a urinary catheter in the rectum. Saline was placed in the POD. The rectum distal to the area of dissection was compressed with bowel grasper. Air was then injected into the rectum via the urinary catheter. If there are no bubbles seen, this will indicate an intact rectal wall.

After dissecting all the endometriotic lesions, the suspended ovary was released and laparoscopic cystectomy was performed. Diluted vasopressin (One ampoule containing 20 units of vasopressin was diluted in 200ml of saline) is injected into the space between the cyst wall and the normal ovarian cortex. If the cyst was large, this injection was made at several points. The aim of this injection is to separate the cyst wall from the ovarian cortex by hydrodissection. This will allow stripping of the cyst wall to be done easily and the vasopressin will provide haemostasis. Stripping of the cyst is performed by gentle traction and counter traction on the edges of the cyst wall until the fluid between the layers is spilled. At the hilum area, the cyst wall is cut using cold scissors. The remaining part of the cyst wall at the hilar region was left in place. Light coagulation with bipolar forceps was performed on this remaining cyst wall. When there was bleeding on the ovarian parenchyma, light coagulation was performed. The exposed area of the ovary was sutured using absorbable polyglactin 2.0 sutures (Ethicon Inc, Somerville, NJ). This was to prevent adhesion formation between the raw areas of the ovary and other structures in the pelvis.

Before the end of the surgery, the surgeon performed extra surgical steps on certain patients. In some patients, (when the ovary is mobile enough and the patient has given consent) the repaired ovary was pulled towards the anterior abdominal wall and suspended temporary to the peritoneum of the lower anterolateral abdominal wall next to the ipsilateral round ligament of the uterus by using 2.0 absorbable suture (Vicryl, Ethicon Inc, Somerville, NJ). A 2-3cm gap was left between the abdominal peritoneum and the ovary. This temporary ovariopexy was done to avoid the repaired ovary from becoming adherent to the raw peritoneal surface that had resulted from the extensive dissection and excision of endometriosis that had been done in the pelvis. In some patients whom the surgeon felt that the uterus was retroverted and there is a risk of re-adhesion of the uterus to the rectum, the round ligament was plicated using polyglactin 1 suture (Vicryl, Ethicon Inc, Somerville, NJ).

### *Outcomes*

The primary outcome of this study is the fertility outcome in terms of clinical pregnancy rate. At the beginning of this study, all patients involved were contacted to complete a

telephone questionnaire. The questions included desire to conceive, success in conceiving, methods of conceiving, time taken to conceive and outcomes of the pregnancy. For patients who did not conceive spontaneously, a detailed information regarding the types of treatment they underwent either via ovulation, induction, insemination or assisted reproductive treatment (ART) was recorded. The last patient included in this study was at least 6 months post-operation.

The secondary outcomes of this study are the safety of this surgical technique. This was determined by the absence of any intra- and/or post-operative complications.

## RESULTS

A total of 143 patients with at least 1 endometrioma underwent laparoscopic cystectomy. The characteristics of the patients recruited in this study is shown in Table I. The mean age of patients in this study was 31.9. At the time of the surgery, 104 patients were married while 39 patients were single. Between the time of surgery and the beginning of the study, 7 single women got married. 99 (69.2%) of the patients were nulliparous while 44 (30.8%) had parity  $\geq 1$ . Thirteen patients had miscarriages and 76 (53.1%) patients were keen to conceive after the surgery.

During the clinical examination, 51.7% of the endometrioma was bilateral, 26.6% was on the left and 21.7% was on the right. The distribution of size of the cysts was as follows: 1-3cm (13.4%), 3-6cm (38.4%) and  $>6$ cm (48.1%). 20 (14%) patients had a previous history of cystectomy before visiting us.

Based on the intra-operative rASRM staging, 48 (33.6%) had Stage III endometriosis while 95 (66.4%) patients had Stage IV endometriosis. The mean rASRM score was 59.3. Most of the patients were found to have deep infiltrating endometriotic nodules and 65 (45.5%) of the patients had the POD completely obliterated. Concomitant adenomyosis was seen in 42 (29.4%) patients. During the surgery, the surgeon carried out additional procedures for some of the patients when necessary and this was believed to improve their chances of pregnancy. The mean duration of the surgery was 94.1 minutes.

### *Pregnancy outcomes*

Among these 143 patients, 76 of them wished to become pregnant. The post-operative pregnancy outcomes are shown in Table II. Out of the 76 patients, 53 were trying actively to conceive immediately after the surgery, 15 patients deferred attempt to conceive after a period of rest post-surgery and 8 patients were not married at the time of the surgery. Based on the conditions of the patients, infertility factor and preference, different mode of conception was practiced such as natural conception, in-vitro fertilization – intracytoplasmic semen injection (IVF-ICSI), intrauterine insemination (IUI) and ovulation induction via clomiphene citrate or letrozole.

A total of 32 (42.1%) of them conceived spontaneously at a mean duration of 6.9 months of actively trying to conceive, 30 (93.8%) patients had an uneventful delivery while 2

(6.3%) patients miscarried. Five (6.6%) patients conceived twice after the surgery.

Among the 76 patients, 8 patients underwent IVF-ICSI, 2 IUI and 10 patients underwent ovulation induction. As a result, 5 (62.5%) patients successfully conceived via IVF-ICSI and only 1 (10%) patient conceived with ovulation induction.

### *Factors affecting the spontaneous pregnancy outcomes*

We have analysed several factors which may affect the fertility outcomes such as the site of the endometrioma, severity of the disease, presence of adenomyosis, history of cystectomy and maternal age. Table III show the overall relationship between each factor and pregnancy outcomes. Among the 76 patients who were keen to conceive, 35 of them underwent unilateral cystectomy and 41 patients underwent bilateral cystectomy. After trying actively to conceive, 17 (48.6%) patients who underwent unilateral cystectomy and 16 (39%) patients who underwent bilateral cystectomy conceived spontaneously. In other words, patients who underwent bilateral cystectomy had lower pregnancy rate compared to unilateral cystectomy. The spontaneous pregnancy rate was also lower in patients with severe endometriosis as compared to moderate endometriosis, 34.6% vs 62.5% respectively.

Adenomyosis is also an important uterine factor that may affect embryo implantation. A total of 18 patients were found to have either focal or diffuse adenomyosis. Only 4 (22.2%) of them conceived spontaneously after the surgery. Besides, repeated cystectomy may also influence the chances of pregnancy. This was demonstrated in this study where 2 out of 13 (15.4%) patients with previous history of cystectomy conceived spontaneously. Lastly, the fertility outcome is also influenced by the reproductive age of the patients. The rate of spontaneous pregnancy decreases as the age increases (Table IV).

### *Safety of the procedure*

Among the 143 patients recruited in this study, 217 ovaries were excised. There were no intra-operative or post-operative complications such as excessive bleeding, infection, haematoma or bradycardia reported. The mean duration of hospital stay was 2.7 days. No changes in the ovarian function post-operatively as determined by any changes in the menstrual cycle were reported by any of the patients during the follow-up period.

## DISCUSSION

The effect of endometrioma on fertility has been given much attention. Endometrioma causes focal inflammation in the surrounding ovarian cortex, and subsequently reduces vascularization and increases oxidative stress, resulting in antral follicle count reduction, interstitial fibrosis and microvascular injury in the ovary. Superficial and deep infiltrative endometriosis are also commonly associated with pelvic adhesions. Pelvic adhesions may distort the anatomy of pelvic organs causing mechanical interference to oocyte pickup by the fallopian tubes and transportation of the oocytes in the tubes. All these factors may reduce fecundity rate.

**Table I: The demographic of the study population**

Total number of patients recruited in this study = 143			
Mean age (years)	31.9		
Marital status	At the time of surgery	Married	104
		Single	39
	At the beginning of the study	Married	111
		Single	32
Obstetric history	Nulliparous	99 (69.2%)	
	Parous	44 (30.8%)	
	Miscarriage	13 (9.1%)	
Total number of patients who keen to conceive	76 (53.1%)		
Previous cystectomy surgery	20 (14%)		
TVUS / TRUS findings	Laterality of endometrioma	Left	38 (26.6%)
		Right	31 (21.7%)
		Bilateral	74 (51.7%)
	Mean diameter (cm)	Left	6.0
		Right	6.3

**Table II: Post-operative pregnancy outcome. (in-vitro fertilization – intracytoplasmic semen injection = IVF-ICSI)**

Total number of patients who were keen to conceive, n = 76		
Time planned to trying to conceive	Immediately after surgery	53
	Sometime after surgery	15
	After getting married	8
Mode of conception of all patients	Natural	56
	IVF-ICSI	8
	Intrauterine insemination	2
	Ovulation induction	10
Total number of patients who conceived successfully	38 (50%)	
Mode of successful conception	Spontaneous pregnancy	32 (42.1%)
	IVF-ICSI	5 (6.2.5%)
	Ovulation induction	1 (10%)
Number of patients who conceived more than once	5 (6.6%)	
Miscarriage	2	
Mean duration of trying to conceive (months)	6.9	

**Table III: shows the spontaneous pregnancy rate influenced by the infertility factors**

Factors which affect pregnancy outcomes	Number of patients who keen to conceive, n	Spontaneous pregnancy rate, n (%)
Unilateral cystectomy	35	17 (48.6)
Bilateral cystectomy	41	16 (39.0)
Moderate endometriosis	24	15 (62.5)
Severe endometriosis	52	18 (34.6)
Adenomyosis	18	4 (22.2)
History of cystectomy	13	2 (15.4)

**Table IV: The number of patients with successful spontaneous pregnancy according to the maternal age**

Age (years)	23 – 25	26 – 28	29 – 31	32 – 34	35 – 37	38 – 40	41 – 43	44 – 46
Number of patients who keen to conceive	10	16	15	22	7	4	1	1
Number of patients conceived spontaneously, n (%)	7 (70)	7 (43.8)	10 (66.7)	6 (27.3)	0	1 (25)	0	0

There is an ongoing debate regarding the most appropriate surgical technique to treat endometrioma at the same time enhancing fertility. Laparoscopic cystectomy is the gold standard in managing patients with endometrioma. However, the main worry is its potential deleterious effect on ovarian reserve. The absence of a clear cleavage plane between ovarian stroma and cyst wall may cause inadvertent removal of the healthy ovarian parenchyma along with the cyst wall which may lead to loss of follicular reserve. Besides, the excessive use of coagulation during the surgery will also

cause thermal destruction on the ovarian follicles, subsequently impair fertility.

In this retrospective study, we would like to propose the feasibility and safety of our surgical technique in which the ovarian pathology is removed with optimal preservation of ovarian function to give the best spontaneous pregnancy rates. During the surgery, we injected vasopressin into the space between the cyst wall and the normal ovarian cortex to provide a hydrodissection effect. When a certain amount of

**Table V: Review of other studies on surgical treatment of endometrioma and fertility outcomes**

		Diagnosis	Mean age of the participants	Surgical technique	Spontaneous pregnancy rate
1	Donnez et al (2010)	Endometrioma >3cm	29.2 + 3.7 years	Combined technique (stripping + CO2 laser vaporization)	12/52 (32%) at 6-month post-operatively 15/52 (41%) at 8.3-month post-operatively
2	Maggiore ULC et al (2017)	Rectovaginal endometriosis with endometrioma	33.3 + 3.8 years	Stripping technique	Crude pregnancy of 38/125 (30.4%) Cumulative pregnancy of 34.5%
3	Taniguchi et al (2016)	Endometrioma	31.7 + 5.4 years	Stripping technique	10/40 (25%)
4	Mircea et al (2016)	Endometrioma >3cm	28 + 3.8 years	Combined technique (excision + bipolar coagulation)	6/40 (15%)
5	Shervin et al (2016)	Deep infiltrative endometriosis with endometrioma	31.4 + 4.9 years	Global laparoscopic resection of endometriotic lesions and excisional cystectomy	26%
6	Current study (2020)	Endometrioma with endometriosis stage III and IV	31.9 years	Combined technique (stripping + excision and bipolar coagulation)	32/76 (42.1%)

saline diluted with vasopressin is injected into the correct space, the space between the cyst wall and the ovary will swell up, providing a clear boundary for excision, thus preventing the risk of accidental removal of normal ovarian tissue. Besides, vasopressin acts as vasoconstrictor. It helps to reduce the oozing from the ovarian cortex, thus reduce the frequency of electrocoagulation which may cause thermal damage to the ovarian follicles. Studies which have compared diluted vasopressin injection with control group showed that the frequency of electrocoagulation for haemostasis as well as the operation time is lesser in the vasopressin group.<sup>15,16</sup> In another similar study, Ren Qiong-zhen et al., reported that there was no significant difference in the thickness of the healthy ovarian tissue excised in both these groups.<sup>17</sup> Bradycardia is a known side effect of the usage of vasopressin. This was not seen in any of our patients in our study.

At the ovarian hilus region, the ovarian tissue is more functional and the plane of cleavage is less visible. One needs to be cautious when approaching this region. In 69% of cases of cystectomy where ovarian tissue at the hilar region was excised, primordial, primary and secondary follicles were seen in the excised specimen.<sup>18</sup> To reduce this loss of follicles at the hilum, carbon dioxide vaporisation or bipolar coagulation was used at the hilum instead of stripping of the cyst wall in this area.<sup>14,19,20</sup> In this study, we resected the cyst wall up to the hilum area and the cyst wall at the hilum was lightly coagulated using bipolar electrocoagulation. Reconstructing the ovary after endometrioma cystectomy is also not a commonly practiced procedure perhaps because it requires laparoscopic suturing skills and will increase the duration of the surgery. We believe that reconstruction of the ovary is necessary to ensure that the raw surface of the ovary after cystectomy will not become adherent to the peritoneal area in the pelvis caused by the extensive excision of endometriosis and endometriotic nodule. Coric et al., demonstrated that suturing the ovarian tissue and reconstructing the ovary at the end of cystectomy resulted in lesser adverse effect on ovarian reserve as compared to bipolar coagulation.<sup>21</sup>

In this retrospective study, 32 out of 76 (42.1%) patients who were keen to conceive, conceived spontaneously by the 7th month post-operatively. This is comparably higher compared to other studies.<sup>14,22</sup> Donnez et al., used a combined technique of excisional and ablative surgery and reported the cumulative pregnancy rate of 32% at 6-month and 41% at 8.2-month post-surgery.<sup>14</sup> Roberti et al., also reported the crude spontaneous pregnancy rate of 30.4% and cumulative spontaneous pregnancy rate of 34.5% post-surgery.<sup>22</sup> Our spontaneous pregnancy rate was much higher compared with results reported by Taniguchi et al., and Mircea et al., (42.1% vs 25% and 18.8% respectively).<sup>23,24</sup> Shervin et al., reported a total pregnancy rate of 35.6% and spontaneous pregnancy rate around 26% after a global laparoscopic resection of endometriotic nodules and laparoscopic excisional cystectomy for patients with deep infiltrative endometriosis and endometrioma.<sup>25</sup> Table V shows the comparison of the spontaneous pregnancy rate between the studies. The results of spontaneous pregnancy differ due to the different surgical techniques applied during the excision of endometrioma and no diluted vasopressin was injected during the surgery as compared to our study.

In the subgroup analysis, several factors affected the chances of spontaneous pregnancy. The presence of adenomyosis negatively affects pregnancy rates. Only 22.2% of patients with adenomyosis conceived. There are many factors that cause a decrease in fertility rate in patients with adenomyosis. This includes poorer implantation rate, which may be caused by dysfunction of the uterine junctional zone. Another poor prognostic factor for pregnancy is a history of previous ovarian cystectomy for endometrioma. Only 2 out of 13 patients (15.4%) of patients with a previous history of cystectomy conceived spontaneously. The impact of maternal age on fertility outcomes after cystectomy is clearly demonstrated in our study. Spontaneous pregnancy rate was only 7.7% in the age group after 34 years. This result is consistent with the other studies which reported that the fecundity rate significantly decreased after the age of 32 and more rapidly after 37.<sup>26,27</sup>

As in all other studies,<sup>14,22-25</sup> no complications were encountered during the surgery. Our surgical technique can be considered as a safe procedure to perform for patients with endometrioma.

The main limitation of this study is that it is a retrospective study. We performed the same technique for all patients. The sample size of patients who were keen to conceive was also small. There are several factors which may affect patient's ability to conceive such as male infertility factor and the tubal patency of the patients. We did not perform semen analysis for all the partners of our patients. Since some of the patients were VI at the time of the surgery, we did not check for tubal patency. Despite this, the spontaneous pregnancy rate in our study was fairly high.

## CONCLUSION

The primary outcome of this study is the fertility outcome in terms of clinical pregnancy rate after undergoing laparoscopic cystectomy for endometrioma. In this case series, we looked at a particular method of performing surgery on patients with endometrioma to see whether spontaneous pregnancy rates are within acceptable range. We found that the spontaneous pregnancy rate after surgery using our technique was 42.1% in women with moderate to severe endometriosis. This result appears superior to most other published reports on this subject. The secondary outcome of this study is the safety outcome. No postoperative complications were encountered in all the patients indicating that this is a safe technique.

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## ETHICAL APPROVAL

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The ethical approval has been exempted by our local institutional board.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

## REFERENCES

1. Abuzeid OM, Hebert J, Ashraf M, Mitwally M, Diamond MP, Abuzeid MI. Safety and efficacy of two techniques of temporary ovarian suspension to the anterior abdominal wall after operative laparoscopy. *Facts Views Vis Obgyn* 2018; 10: 71-9.
2. Giudice LC. Clinical practice. Endometriosis. *N Engl J Med* 2010; 362: 2389-98.
3. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. *Am J Epidemiol* 2004; 160: 784-96.
4. Alborzi S, Keramati P, Younesi M, Samsami A, Dadras N. The impact of laparoscopic cystectomy on ovarian reserve in patients with unilateral and bilateral endometriomas. *Fertil Steril* 2014; 101: 427-34.
5. Redwine DB. Ovarian endometriosis : a marker for more extensive pelvic and intestinal disease. *Fertil Steril* 1999; 72: 310-5.
6. Garcia-Velasco A, Somigliana E. Management of endometriomas in women requiring IVF : to touch or not to touch. *Hum Reprod* 2009; 24: 496-501.
7. Vercellini P, Somigliana E, Vigano P, Abbiati A, Barbara G, Crosignani PG. Surgery for endometriosis-associated infertility : a pragmatic approach. *Hum Reprod* 2009; 24: 254-69.
8. Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian reserve : a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2012; 97: 3146-54.
9. Exacoustos C, Zupi E, Amadio A, Szabolcs B, Vivo BD, Marconi D, et al. Laparoscopic removal of endometriomas : sonographic evaluation of residual functioning ovarian tissue. *AJOG* 2004; 191: 68-72.
10. Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometrioma. *Cochrane Database Syst Rev*. 16, 2008: CD004992.
11. Marana R, Caruana P, Muzil L, Catalano GF, Mancuso S. Operative laparoscopy for ovarian cysts. Excision vs aspiration. *J Reprod Med* 1996; 41: 435-8.
12. Benaglia L, Somigliana E, Lemmello R, Colpi E, Nicolosi AE, Ragni G. Endometrioma and oocyte retrieval-induced pelvic abscess: a clinical concern or an exceptional complication? *Fertil Steril* 2008; 89: 1263-6.
13. Jayaprakasan K, Becker C, Mittal M. On behalf of the Royal College of Obstetricians and Gynaecologist. The effect of surgery for endometriomas on fertility. *Scientific Impact Paper No 55. BJOG* 2017; 125: e19-e28.
14. Donnez J, Lousse JC, Jadoul P, Donnez O, Squifflet J. Laparoscopic management of endometriomas using a combined technique of excisional (cystectomy) and ablative surgery. *Fertil Steril* 2010; 94: 28-32.
15. Ghafarnejad M, Akrami M, Davari-Tanha F, Adabi K, Nekuie S. Vasopressin effect on operation time and frequency of electrocauterization during laparoscopic stripping of ovarian endometriomas : a randomized controlled clinical trial. *J Reprod Infertil* 2014; 15: 199-204.
16. Soeki A, Matsumoto T, Ikuma K, Tanase Y, Inaba F, Oku H, et al. The vasopressin injection technique for laparoscopic excision of ovarian endometrioma : a technique to reduce the use of coagulation. *J Minim Invasive Gynecol* 2010; 17: 176-9.
17. Qiong-zhen R, Ge Y, Deng Y, Qian ZH, Zhu WP. Effect of vasopressin injection technique in laparoscopic excision of bilateral ovarian endometriomas on ovarian reserve : prospective randomized study. *J Minim Invasive Gynecol* 2014; 21: 266-71.
18. Muzzi L, Bellati F, Bianchi A, Palaia I, Mancini N, Zullo MA, et al. Laparoscopic stripping of endometriomas : a randomized trial on different surgical techniques. Part II, Pathological results. *Hum Reprod* 2015; 20: 1987-92.
19. Seong SJ, Kim M-L. Surgical tips for the conservative surgical treatment of ovarian endometrioma : an overview with video presentation. *Clin Surg* 2018; 3: 2142.
20. Muzii L, Panicci PB. Combined technique of excision and ablation for surgical treatment of ovarian endometriomas : the way forward? *Reprod BioMed Online* 2010; 20: 300-2.
21. Coric M, Borisic D, Pavicic D, Karadzic M, Banovic M. Electrocoagulation versus suture after laparoscopic stripping of ovarian endometriomas assessed by antral follicle count : preliminary results of randomized clinical trial. *Arch Gynecol Obstet* 2011; 283: 373-8.
22. Maggiore ULR, Scala C, Tafi E, Racca A, Biscaldi E, Vellone VG, et al. Spontaneous fertility after expectant or surgical management of rectovaginal endometriosis in women with or without ovarian endometrioma : a retrospective analysis. *Fertil Steril* 2017; 107: 969-976.e5.
23. Taniguchi F, Sakamoto Y, Yabuta Y, Azuma Y, Hirakawa E, Nagira K, et al. Analysis of pregnancy outcome and decline of anti-Mullerian hormone after laparoscopic cystectomy for ovarian endometriomas. *J Obstet Gynaecol Res* 2016; 42: 1534-40.
24. Mircea O, Puscasiu L, Resch B, Lucas J, Collinet P, Theobald P, et al . Fertility outcomes after ablation using plasma energy versus cystectomy in infertile women with ovarian endometrioma : a multicentric comparative study. *J Minim Invasive Gynecol* 2016; 23: 1138-1145.
25. Shervin A, Mohazzab A, Aminlou M, Kamali K, Padmehr R, Shajoo K, et al. Fertility outcome after laparoscopic treatment of advanced endometriosis in two groups of infertile patients with and without ovarian endometrioma. *Eur J Obstet Gynecol Biol* 2016; 201: 46-50.
26. Fukuda M, Fukuda K, Andeersen CY, Byskov AG. 2001. Characteristics of human ovulation in natural cycles correlated with age an achievement of pregnancy. *Hum Reprod* 16: 2501-7.
27. American College of Obstetricians and Gynaecologist Committee on Gynaecologic Practice; Practice Committee of the American Society for Reproductive Medicine, 2014. Female age-related fertility decline. Committee Opinion No 589. *Obstet Gynecol* 123: 719-21.



# Comparison of cataract surgery refractive outcomes in a tertiary hospital and an outreach cataract service centre

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## ABSTRACT

**Objective:** The aim of this study was to compare the postoperative refractive outcome after cataract surgery between a hospital-based and an outreach-based cataract service centre.

**Methods:** This study was conducted at the Hospital Selayang (HS), Selangor, Malaysia, a tertiary referral centre and an outreach-based cataract service centre (Pusat Pembedahan Katarak MAIWP, PPKM). Data was sourced from the Cataract Surgery Registry (CSR) in the National Eye Database (NED).

**Results:** A total of 2318 surgeries were analysed. PPKM achieved postoperative refraction outcome within  $\pm 1.0D$  in 94.3% of cases compared with 88.4% in Selayang Hospital. Mean absolute prediction error was also better in PPKM ( $0.39 \pm 0.27D$  vs.  $0.33 \pm 0.24D$ ,  $p < 0.001$ ). Multivariate analysis showed that the tertiary hospital, persons of Chinese ethnicity, history of uveitis, previous history of ocular surgery and intraoperative complications as significant independent predictive factors for poor refractive outcomes.

**Conclusion:** The outreach-based cataract service centre, which incorporates streamlined process designs and workflows, achieved superior refractive outcomes within  $\pm 1$  dioptre after cataract surgery compared to a tertiary hospital.

## KEYWORDS:

*Refractive outcomes; cataract surgery; outreach; process design; workflow*

## INTRODUCTION

Malaysia is a developing country in the Southeast Asia region and adopts a universal healthcare system run by the Ministry of Health (MOH). MOH provides cataract surgery services via 42 healthcare facilities, including hospitals and cataract centres. Cataracts represent a significant burden of visual impairment and is the leading cause of bilateral reversible blindness in Malaysia (39.1%) with an estimate of 216000 people afflicted.<sup>1</sup> Based on the data from the 11th Report of the National Eye Database (Year 2017), a total number of 54242 cataract surgeries were performed in the MOH hospitals.<sup>3</sup> Phacoemulsification has become the

preferred surgical technique for cataract surgeries in Malaysia, accounting for more than three quarters of cataract surgeries performed.<sup>4</sup>

In view of the increased demand for cataract surgery especially in the urban communities, the MOH with the collaboration from the Federal Territories Islamic Religious Council founded the Cataract Surgical Centre (PPKM) in 2012. The PPKM is based on the Aravind Eye Care System model, which adheres to the principle of providing high volume and high-quality cataract surgery by adopting a set of process designs based on an efficient framework model into the cataract surgery pathway.<sup>5,6</sup> This streamlined process designs and workflows as interventions have shown improvement in error reduction and information flow in intensive medical units,<sup>7</sup> improved patient flow in the emergency department,<sup>8</sup> as well as improved Pap smear test quality and diagnostic accuracy.<sup>9</sup> Such process designs have also shown to improve quality in high-volume cataract pathways in terms of lead times, hospital visits and costs.<sup>10</sup> High volume and high-quality cataract surgery can be viewed from a system's approach, whereby demand and resources are considered as the input, systems and procedures as the process, and high volume, high quality cataract surgeries as the output.<sup>6</sup> PPKM aims to achieve this by optimising each of these components.

The rationale of this study is to determine and compare the outcomes of achieving postoperative spherical equivalent within  $\pm 1$  dioptre of target spherical equivalent after cataract surgery and intraocular lens implantation between a hospital-based and an outreach-based cataract centre. This study was also done to ascertain the main determinant factors for such outcomes. Analysis of such data providing evidence of potential improvement in postoperative refraction outcomes, and thus cataract surgery success would be an important supportive data in establishing more cataract centres structured on a similar model. Such intervention would be especially pertinent in reducing the significant cataract burden in the country.

## METHODS

A total of 2318 surgeries were included for this study by consecutive non-random sampling based on data sourced from the CSR. All patients who had undergone cataract

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surgery in the HS and PPKM from January 2017 to December 2017 who have fulfilled inclusion and exclusion criteria were considered. Patients who had undergone cataract surgeries on one or both eyes, as well as postoperative refractions done at or within 90 days were included. Patients with no documented preoperative vision or refraction, or no documented follow-up appointment within 90 days were excluded. The demographic variables (age, gender and ethnicity) and clinical variables were obtained through sourced data from CSR. Following our institutional protocol, all data reported were deidentified.

The data for refractive outcomes is derived from the values of absolute prediction error. Prediction error (PE) is the difference in dioptres between the actual and target refractive outcome in a patient and it is calculated in that the PE is negative for an outcome more myopic than intended and positive for a hyperopic outcome. The absolute value of this data is then used to calculate the mean absolute prediction error (MAPE), in which the mean of the absolute value of the PE is taken in a cohort.<sup>12</sup>

The descriptive statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) Version 24. Refractive error levels as dichotomous variables were used for simple logistic and multivariate logistic regression analysis. Multivariate logistic regression analysis was done to identify factors which may affect the probability of poor cataract outcomes, which in this case is measured as achieving mean absolute prediction error >1 dioptre. The variables which were analysed were age, gender, ethnicity, biometry, preoperative ocular comorbidities, intraoperative complications, surgeon experience and the type of cataract centre, which in this case constitutes a hospital-based cataract centre (Selayang Hospital) and an outreach-based cataract centre (PPKMS). For all analyses, a p value of less than 0.05 was considered statistically significant.

## RESULTS

A total of 571 cataract surgeries were performed on 549 patients in HS and 1747 cataract surgeries were performed on 1560 patients in PPKM. These represent 57.31% of the total surgeries in the HS and 56.28% of surgeries in PPKM respectively after taking into account inclusion and exclusion criteria. Of the 571 surgeries, 505 (88.4%) eyes achieved postoperative refraction within  $\pm 1.0$  dioptre of target refraction in HS compared to 1647 of the 1747 (94.3%) surgeries in PPKM.

Demographic data of the participants is presented in Table I. Patients in HS were significantly older, were more likely to be of Chinese ethnicity and had more systemic and ocular comorbidities. Table II compares the demographic and ocular characteristics of the subjects in the two centres. Significant differences were seen in patients with good refractive outcome (who fall within the <1D group) in terms of gender (more females in PPKM), ethnicity (more Malays in PPKM), some pre-operative co-morbidities (more glaucoma, diabetic retinopathy, age related macula degeneration and other ocular conditions in the HS) and postoperative complications (more in the HS). However, in patients with

poor refractive outcomes, there were no significant difference between the two centres apart from a higher number of extracapsular cataract extraction in the HS.

The PE, which is the difference between target and postoperative refraction, ranged from -3.55 to +4.60 D, with an average of  $-0.09 \pm 0.69$  D in the tertiary hospital; and from -3.48 to +4.25 D, with an average of  $-0.03 \pm 0.53$  D in the outreach-based cataract centre. The MAPE value in those who achieved  $\pm 1$  dioptre was significantly higher in the HS ( $0.39 \pm 0.27$ ) compared to PPKM ( $0.33 \pm 0.24$ ) ( $p < 0.001$ ). This difference may, however, not be clinically significant. It was interesting to note however that MAPE values were significantly higher in the HS group when stratified according to age groups, gender, biometry and surgeon expertise level.

Multivariable logistic regression was then done and showed there were five variables that were significantly associated with poor postoperative refractive outcomes (>1 dioptre) when other covariates were adjusted (Table III). Cataract surgeries performed at HS had 58.0% higher chance for poorer refractive outcome compared to those performed at PPKM when other factors were adjusted for ( $p = 0.016$ ). In other words, PPKM had a 36.7% lesser likelihood for poorer refractive outcomes compared with the HS. Patients of Chinese ethnicity were at 49% higher risk to experience poorer refractive outcome compared with Malay patients when other factors were adjusted ( $p = 0.039$ ). Surgery conducted on those patients who had history of uveitis had 4.42 times higher risk of poor refractive outcome compared to those without ( $p = 0.028$ ). Patients with history of previous ocular surgery tend to have 2.47 times higher risk to experience poorer refractive outcomes compared to those without ( $p < 0.001$ ). Cataract surgeries with intraoperative complications were at 6.35 times greater risk of poorer refractive outcome compared to without ( $p < 0.001$ ).

## DISCUSSION

In this study, the 88.4% of operations performed in the HS and 94.3% of operations performed in PPKM achieved postoperative refractive outcomes within  $\pm 1.0$  dioptres. Based on these results, the postoperative refractive outcomes of both these institutions have surpassed the benchmark adopted by the Royal College of Ophthalmologists, which is that at least 85% of cataract operations should have postoperative refraction outcomes within  $\pm 1.0$  dioptre of their planned refraction.<sup>13</sup> These outcomes were also better in comparison to other postoperative refractive outcomes studies without exclusion of pre-existing ocular diseases in other ophthalmology centres in Europe, the United States of America and Australia which range from 72-82%.<sup>14-17</sup> These results appear to surpass the results of studies measuring postoperative outcomes which excluded patients with pre-existing ocular disease and ocular surgeries like a study conducted in Parma University Hospital, Italy (77%),<sup>18</sup> and, in the case of PPKM, when compared to a study done in Queen Elizabeth Hospital, Australia (93%).<sup>19</sup>

The superior postoperative refractive outcomes could be accounted by the use of optical biometry as first-line biometry whenever possible. Optical biometry was performed on

Table I: Demographics (n=2109)

Characteristic	All population N = 2109		P-value
	Selayang Hospital N=549 (%)	PPKM-HS N=1560 (%)	
<b>Age (y),</b>			
Mean (standard deviation)	66.86(9.91)	65.21(8.86)	0.001 <sup>1</sup>
Range	20 – 89	20 – 89	
<b>Gender (%)</b>			
Male	269 (49.0)	682 (43.7)	0.032
Female	280 (51.0)	878 (56.3)	0.032
<b>Ethnicity (%)</b>			
Malay	180 (32.8)	674 (43.2)	<0.001
Chinese	273 (49.7)	595 (38.1)	<0.001
Indian	94 (17.1)	283 (18.1)	0.592
Others	2 (0.4)	8 (0.5)	>0.999 <sup>2</sup>
<b>Preoperative comorbidity (%)</b>			
Previous ocular surgery	59 (10.7)	114 (7.3)	0.012
Glaucoma	71 (12.9)	44 (2.8)	<0.001
Chronic uveitis	7 (1.3)	6 (0.4)	0.049 <sup>2</sup>
Diabetic retinopathy	87 (15.8)	90 (5.8)	<0.001
Age-related macular degeneration	19 (3.5)	21 (1.3)	0.002
Retinal detachment	9 (1.6)	5 (0.3)	0.003 <sup>2</sup>
Previous ocular trauma	2 (0.4)	1 (0.1)	0.168 <sup>2</sup>
Other ocular pathology	85 (15.5)	63 (4.0)	<0.001

PPKM=HS = Pusat Pembedahan Katarak MAIWP-Hospital Selayang or MAIWP Cataract Surgical Center

Pearson Chi-squared tests were applied

<sup>1</sup>Independent t-test with equal variance was not assumed; <sup>2</sup> Fisher's Exact tests were applied

Table II: Surgeries Population Characteristics (Number of Eyes; n=2318)

Characteristic	All population N=2318 eyes			Within 1 D N=2152 eyes			Outside 1D N=166 eyes		
	Hospital Selayang N=571 eyes	PPKM-HS N=1747 eyes	P-value	Hospital Selayang N=505 eyes	PPKM-HS N=1647 eyes	P-value	Hospital Selayang N=66 eyes	PPKM-HS N=100 eyes	P-value
<b>Age (y),</b>									
Mean (standard deviation)	66.88(9.79)	65.30(8.77)	0.001 <sup>1</sup>	66.98 (9.78)	65.29 (8.76)	<0.001 <sup>2</sup>	66.15(9.91)	65.53(9.00)	0.676 <sup>3</sup>
Range	20 – 89	20 – 89		20 – 89	20 – 89				
<b>Gender (%)</b>									
Male	280 (49.0)	753 (43.1)	0.013	251 (49.7)	703 (42.7)	0.005	29(43.9)	50 (50)	0.444
Female	291 (51.0)	994 (56.9)		254 (50.3)	944 (57.3)		37 (56.0)	50(50)	
<b>Ethnicity (%)</b>									
Malay	190 (33.3)	764 (43.7)	<0.01	173 (34.3)	727 (44.1)	<0.001	17 (25.8)	37(37)	0.130
Chinese	282 (49.4)	667(38.2)	<0.01	241 (47.7)	622 (37.8)	<0.001	41 (62.1)	45(45)	0.031
Indian	97 (17.0)	308 (17.6)	0.726	89 (17.6)	290 (17.6)	0.993	8 (12.1)	18 (18)	0.308
<b>Preoperative comorbidity (%)</b>									
Previous ocular surgery	59 (10.3)	129 (7.4)	0.025	45 (8.9)	114 (6.9)	0.135	14 (21.2)	15 (15)	0.302
Glaucoma	73 (12.8)	45 (2.6)	<0.001	66 (13.1)	41 (2.5)	<0.001	7 (10.6)	4 (4)	0.116 <sup>2</sup>
Chronic uveitis	7 (1.2)	6 (0.3)	0.014	4 (0.8)	5 (0.3)	0.137	3 (4.5)	1 (1)	0.302 <sup>2</sup>
Diabetic retinopathy	88 (15.4)	94 (5.4)	<0.001	78 (15.4)	86 (5.2)	<0.001	10 (15.2)	8 (8)	0.147
Age-related macular degeneration	19 (3.3)	21 (1.2)	0.001	18 (3.6)	20 (1.2)	<0.001	1(1.5)	1(1)	>0.999
Retinal detachment	9 (1.6)	6 (0.3)	0.004 <sup>2</sup>	5 (1.0)	5 (0.3)	0.061 <sup>2</sup>	4 (6.1)	1(1)	0.082
Previous ocular trauma	2 (0.4)	1 (0.1)	0.152 <sup>2</sup>	2 (0.4)	1 (0.1)	0.139 <sup>2</sup>	0	0	NA
Other ocular pathology	87 (15.2)	67 (3.8)	<0.001	75 (14.9)	58 (3.5)	<0.001	12 (18.2)	9 (9)	0.082
<b>Biometry</b>									
Optical	392 (68.7)	1319 (75.5)	0.001	353 (70.0)	1245 (75.6)	0.010	39 (59.1)	74 (74)	0.044
Ultrasound	179 (31.3)	428 (24.5)		152 (30.1)	402 (24.4)		27 (40.9)	26 (26)	
<b>Intraoperative complication (%)</b>									
Posterior Capsular Rupture	11 (1.9)	12 (0.7)	0.01	6 (1.2)	6 (0.4)	0.041 <sup>2</sup>	5 (7.6)	6 (6)	0.755 <sup>2</sup>
Vitreous Loss	6 (1.1)	7 (0.4)	0.1 <sup>2</sup>	2 (0.4)	4 (0.2)	0.63 <sup>2</sup>	4 (6.1)	3 (3)	0.438 <sup>2</sup>
Zonular Dialysis	9 (1.6)	10 (0.6)	0.03 <sup>2</sup>	4 (0.8)	8 (0.5)	0.492 <sup>2</sup>	5 (7.6)	2 (2)	0.116 <sup>2</sup>
Dropped Nucleus	1 (0.2)	1 (0.1)	0.432 <sup>2</sup>	0 (0)	0 (0)	1.0 <sup>2</sup>	1 (1.5)	1 (1)	1.0 <sup>2</sup>
Others	3 (0.5)	5 (0.3)	0.416 <sup>2</sup>	3 (0.6)	5 (0.3)	0.4 <sup>2</sup>	0 (0)	0(0)	1.0 <sup>2</sup>
<b>Surgery (%)</b>									
Phacoemulsification	552 (96.7)	1725 (98.7)	0.001	492 (97.4)	1628 (98.8)	0.021	60 (90.9)	97 (97)	0.158 <sup>2</sup>
ECCE	10 (1.8)	4 (0.2)	<0.001 <sup>2</sup>	6 (1.2)	4 (0.2)	0.014 <sup>2</sup>	4 (6.1)	0 (0)	0.024 <sup>2</sup>
Phaco convert ECCE	5 (0.9)	5 (0.3)	0.074 <sup>2</sup>	3 (0.6)	2 (0.1)	0.088 <sup>2</sup>	2 (3.0)	3 (3)	1.0 <sup>2</sup>
Lens aspiration	3 (0.5)	13 (0.7)	0.774 <sup>2</sup>	3 (0.6)	13 (0.8)	1.0 <sup>2</sup>	0 (0)	0 (0)	1.0 <sup>2</sup>
ICCE	1 (0.2)	0 (0)	0.246 <sup>2</sup>	1 (0.2)	0 (0)	0.235 <sup>2</sup>	0 (0)	0 (0)	1.0 <sup>2</sup>

PPKM=HS = Pusat Pembedahan Katarak MAIWP-Hospital Selayang or MAIWP Cataract Surgical Center

Pearson Chi-squared tests were applied

<sup>1</sup>Independent t-test with equal variance was not assumed; <sup>2</sup> Fisher's Exact tests were applied;

<sup>3</sup>Independent t-test with equal variance was assumed

\* Odd ratio <0.001; <sup>1</sup>Hosmer and Lemeshow test: X<sup>2</sup>(df) = 7.50(8); p=0.483, indicated the model was fit well. <sup>2</sup>Classification table showed 93.1% of outcome was correctly classified

Table III: Multivariate Logistic Regression Results for Main determinants of Postoperative Refractive Outcomes (n=2318)

Characteristic	Refractive Outcome		Simple Logistic Regression			Multivariate Logistic Regression		
	Within 1D n (%)	Outside 1D n (%)	Crude OR	95% CI	P-value	Adjusted OR	95% CI	P-value
<b>Cataract centre</b>								
Hospital Selayang	505(88.4)	66(11.6)	2.15	1.55-2.98	<0.001	1.58	1.09-2.28	<b>0.016</b>
PPKM-HS	1647(94.3)	100(0.06)	1			1		
<b>Age</b>								
20-29	10(0.5)	0(0)	0	NA	0.999	0	NA	0.999
30-39	21(1.0)	2(1.2)	0.90	0.18-4.40	0.892	0.64		0.616
40-49	48(2.2)	6(3.6)	1.18	0.40-3.43	0.768	1.12		0.841
50-59	367(17.1)	28(16.9)	0.71	0.34-1.53	0.389	0.80		0.577
60-69	998(46.4)	71(42.8)	0.67	0.33-1.34	0.256	0.76		0.460
70-79	614(28.5)	49(29.5)	0.75	0.37-1.53	0.430	0.78		0.518
80-89	94(4.4)	10(6.0)	1			1		
<b>Male Gender</b>	954(44.3)	79(47.6)	1.14	0.83-1.56	0.416	1.08	0.77-1.50	0.665
<b>Ethnicity</b>								
Malay	900(41.8)	54(32.5)	1			1		
Chinese	863(40.1)	86(51.8)	1.66		0.005	1.49	1.02-2.16	0.039
Indian	379(17.6)	26(15.7)	1.14	1.17-2.36	0.108	1.23	0.75-2.02	0.412
Others	10(0.5)	0(0)	*	0.71-1.85	0.999	*	NA	0.999
				NA				
<b>Preoperative ocular comorbidity</b>								
Glaucoma diagnosis	107(5.0)	11(6.6)	1.36	0.71-2.58	0.352	0.86	0.42-1.74	0.669
History of uveitis	9(0.4)	4(2.4)	5.88	1.79-19.30	0.003	4.42	1.17-16.68	<b>0.028</b>
Diabetic retinopathy	164(7.6)	18(10.8)	1.47	0.88-2.47	0.139	1.26	0.72-2.19	0.415
Age-related macular degeneration	38(1.8)	2(1.2)	0.68	0.16-2.84	0.595	0.48	0.11-2.10	0.325
Retinal detachment	10(0.5)	5(3.0)	6.65	2.28-19.70	0.001	2.45	0.71-8.47	0.157
Previous ocular surgery	159(7.4)	29(17.5)	2.65	1.72-4.09	<0.001	2.47	1.53-3.97	<0.001
Other ocular comorbidities	133(6.2)	21(12.7)	2.20	1.35-3.59	0.002	1.64	0.96-2.78	0.071
<b>Biometry</b>								
Optical	554(25.7)	53(31.9)	1			1		
Ultrasound	1598(74.3)	113(68.1)	1.35	0.96-1.90	0.082	1.26	0.88-1.80	0.217
<b>Surgeon Experience</b>								
Medical Officer	138(6.4)	22(13.3)	2.23	1.40-3.61	0.001	1.65	0.97-2.79	0.065
Specialist	2014 (93.6)	144(86.7)	1			1		
<b>Intraoperative complications</b>	32(1.5)	18(10.8)	8.06	4.42-14.70	<0.001	6.35	3.35-12.03	<0.001

PPKM=HS = Pusat Pembedahan Katarak MAIWP-Hospital Selayang or MAIWP Cataract Surgical Center

\* Odd ratio <0.001; 1 Hosmer and Lemeshow test:  $\chi^2(df) = 7.50(8)$ ;  $p=0.483$ , indicated the model was fit well. 2 Classification table showed 93.1% of outcome was correctly classified

68.7% and 75.5% respectively of patients in the HS and PPKM MAIWP in this study. The optical biometer known as IOLMaster (Carl Zeiss, Meditec AG, Jena, Germany) is currently used in both Selayang Hospital and PPKM. This optical biometer uses double-beam partial coherence interferometry (PCI) technology. Its use results in highly reproducible and operator-independent biometry measurements which are unaffected by the eye movement of the patients or any direct eye contact.<sup>21,21</sup> Studies achieving postoperative refractive outcomes within  $\pm 1.0$  dioptre using PCI technology has ranged from 92-96% (19, 22-24). Nevertheless, a meaningful comparison between these studies and ours would be difficult as many exclusion criteria including pre-existing ocular diseases or previous ocular surgeries have been used in these studies. However, it is interesting to note that, even when these exclusion criteria are employed, PPKM has achieved a higher postoperative refractive outcome as compared to a study in Aarhus University Hospital, Denmark (94.4% vs. 92.4%).<sup>22</sup>

Other factors leading to improved postoperative refractive outcomes for both these centres would include the standardisation of lens selection and implantation process. All selections of lenses are based in accordance to a standardised protocol such as the accurate lens formula for a

specific axial length or A-constant for a specific intraocular lens when a different biometry technique is used. These lens selections are then validated by another senior resident or surgeon to ensure minimisation of error. The practice of ensuring the availability of a sulcus lens and anterior chamber lens for all surgeries will promote the most optimal postoperative refraction in inadvertent complications or defective lenses during surgery.

Comparison between the mean absolute prediction error achieving  $\pm 1$  dioptre in the HS ( $0.39 \pm 0.27D$ ) and in PPKM ( $0.33 \pm 0.24D$ ) showed there was a statistically significant mean difference ( $p < 0.001$ ). Comparison of gender between the two centres also showed statistically significant difference between them with males achieving  $0.39 \pm 0.28D$  in the HS and  $0.32 \pm 0.24D$  in PPKM ( $p < 0.001$ ). Likewise, this was also seen in biometry comparison with statistical significant difference seen between them with optical biometry achieving  $0.38 \pm 0.27D$  in the HS and  $0.33 \pm 0.24D$  in PPKM ( $p < 0.001$ ); as well as in ultrasound biometry with  $0.40 \pm 0.27D$  in the HS and  $0.34 \pm 0.24D$  in PPKM ( $p = 0.013$ ).

Similar results were also seen concerning certain age groups showing statistical significant difference between these two centres, specifically, in the age groups of 40-49 with

0.53±0.25D and 0.35±0.20D ( $p=0.018$ ), 50-59 with 0.40±0.27D and 0.33±0.24D ( $p=0.027$ ), and 70-79 with 0.38±0.25D and 0.34±0.25D ( $p=0.044$ ) for the HS and the PPKM respectively. Apart from that, comparison of specialists performing cataract surgeries between the two centres showed statistically significant difference between them with 0.39±0.26D in the HS and 0.33±0.24D in the PPKM ( $p<0.001$ ).

These results highlight the fact that the PPKM, being a cataract centre with streamlined process designs and workflows, has produced significantly better postoperative refractive outcomes within those achieving  $\leq 1$  dioptre, in comparison to the HS. As a function of significant difference in regards to biometry of both ultrasound and optical techniques between these centres, they also demonstrate better quality of biometry service in the setting of streamlined process designs, as seen in the PPKM.

A multivariate logistic regression analysis was done to identify factors which may affect the postoperative refractive outcomes within these two centres; which in this case, poor cataract outcome is measured as achieving mean absolute prediction error  $>1$  dioptre. Based on the analysis, the type of cataract centre as a variable is identified as an independent predictor of postoperative refractive outcomes. In other words, a cataract centre with streamlined process designs and workflows such as the PPKM, is independently correlated with less poor cataract outcomes, in comparison to the HS. This analysis also revealed other independent variables as significant independent predictors of postoperative refractive outcomes. This includes Chinese ethnicity, history of uveitis, previous history of ocular surgery and patients with intraoperative complications. Age, gender and biometry technique were interestingly not identified as independent variables in predicting postoperative refractive outcomes.

Limitations in this study include the retrospective nature of the analysis; as well as the exclusion of patients who had missing data within the National Eye Registry. Some recommendations to intercept this problem may include methods of double validation of data entry by separate individuals, or automated software upgrades where missing patient data is highlighted and is not presented in the registry unless all essential or required data is entered. Also, a large number of patients were excluded from this study; with only 57.31% (571 of 937 surgeries) and 56.28% (1747 of 3104 surgeries) of surgeries analysed from The HS and MAIWP respectively. Patients who didn't have postoperative refractive assessment within 90 days, as well as those with missing data in the National Eye Registry were excluded. This included patients who may not have undergone post-op refraction in view of poor vision. Failure to capture these patients from the database and the possibility of poorer outcomes among these patients which may have skewed a more favorable result in our analysis. Nevertheless, this limitation is mitigated by the large population sample size. Other limitations include the lack of other cataract centres with streamlined process designs in Malaysia, and no comparable studies can be done and evaluated with the current study and its results.

## CONCLUSION

This study has shown that superior cataract surgery refractive outcomes are achieved in an outreach cataract service centre compared to a tertiary hospital. Patients of Chinese ethnicity, history of uveitis, history of ocular surgery and intraoperative complications were independent predictors of poorer refractive outcomes. This study also highlights the impact of cataract centres incorporating streamlined process designs and workflows in reducing the cataract waiting times in an urban setting.

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## REFERENCES

1. Chew FLM, Salowi MA, Mustari Z, Husni MA, Hussein E, Adnan TH, et al. Estimates of visual impairment and its causes from the National Eye Survey in Malaysia (NESII). *PLoS One* 2018; 13(6): e0198799.
2. Goh PP, Salowi, A., Adnan, T.H., Sa'at, N. The 8th Report of the National Eye Database 2014. Malaysia: National Eye Database (NED) Clinical Research Centre; 2016 June 2016.
3. Goh PP, Salowi, A., Adnan, T.H., Sa'at, N. 7th Report of the National Eye Database 2013. Malaysia: National Eye Database Clinical Research Centre; 2015.
4. Lee MY, Goh PP, Salowi MA, Adnan TH, Ismail M. The Malaysian Cataract Surgery Registry: Cataract surgery practice pattern. *Asia Pac J Ophthalmol (Phila)*. 2014; 3(6): 343-7.
5. Ravilla T, Ramasamy D. Efficient high-volume cataract services: the Aravind model. *Community Eye Health* 2014; 27(85): 7-8.
6. Thulasiraj R PR, Saravanan S. High volume, high quality cataract surgery. *Indian Journal of Community Health* 1997; 3(2): 26-9.
7. Jimmerson C, Weber D, Sobek DK, 2nd. Reducing waste and errors: piloting lean principles at Intermountain Healthcare. *Jt Comm J Qual Patient Saf* 2005; 31(5): 249-57.
8. King DL, Ben-Tovim DI, Bassham J. Redesigning emergency department patient flows: application of lean thinking to health care. *Emerg Med Australas* 2006; 18(4): 391-7.
9. Raab SS, Andrew-Jaja C, Grzybicki DM, Vrbin CM, Chesin CM, Fisch JM, et al. Dissemination of Lean methods to improve pap testing quality and patient safety. *J Low Genit Tract Dis* 2008; 12(2): 103-10.
10. Van Vliet EJ, Bredenhoff E, Sermeus W, Kop LM, Sol JC, Van Harten WH. Exploring the relation between process design and efficiency in high-volume cataract pathways from a lean thinking perspective. *Int J Qual Health Care* 2011; 23(1): 83-93.
11. Goh PP, Elias H, Norfariza N, Mariam I, National Eye Database Steering C. National Eye Database--a web based surveillance system. *Med J Malaysia* 2008;63 Suppl C: 20-3.
12. Sheard R. Optimising biometry for best outcomes in cataract surgery. *Eye* 2014; 28(2): 118-25.
13. Excellence NIoC. Cataracts in Adults:Management. Post-operative assessment. United Kingdom: NICE Guideline; 2017.
14. Zaidi FH, Corbett MC, Burton BJ, Bloom PA. Raising the benchmark for the 21st century--the 1000 cataract operations audit and survey: outcomes, consultant-supervised training and sourcing NHS choice. *Br J Ophthalmol* 2007; 91(6): 731-6.
15. Daniel C, Tuft S, Ionides A, Bunce C. Effect of visual acuity on biometry prediction error after cataract surgery. *J Cataract Refract Surg* 2003; 29(7): 1365-9.
16. Lum F, Schein O, Schachat AP, Abbott RL, Hoskins HD Jr., Steinberg EP. Initial two years of experience with the AAO National Eyecare Outcomes Network (NEON) cataract surgery database. *Ophthalmology* 2000; 107(4): 691-7.
17. Guzowski M, Rohtchina E, Wang JJ, Mitchell P. Refractive changes following cataract surgery: the Blue Mountains Eye Study. *Clin Exp Ophthalmol* 2002; 30(3): 159-62.
18. Nuzzi G, Cantu C, De Giovanni MA. Older age as risk factor for deviation from emmetropia in pseudophakia. *Eur J Ophthalmol* 2001; 11(2): 133-8.

19. Landers J, Goggin M. Comparison of refractive outcomes using immersion ultrasound biometry and IOLMaster biometry. *Clin Exp Ophthalmol* 2009; 37(6): 566-9.
20. Rose LT, Moshegov CN. Comparison of the Zeiss IOLMaster and applanation A-scan ultrasound: biometry for intraocular lens calculation. *Clin Exp Ophthalmol* 2003; 31(2): 121-4.
21. Drexler W, Findl O, Menapace R, Rainer G, Vass C, Hitzenberger CK, et al. Partial coherence interferometry: a novel approach to biometry in cataract surgery. *Am J Ophthalmol* 1998; 126(4): 524-34.
22. Olsen T. Improved accuracy of intraocular lens power calculation with the Zeiss IOLMaster. *Acta Ophthalmol Scand* 2007; 85(1): 84-7.
23. Madge SN, Khong CH, Lamont M, Bansal A, Antcliff RJ. Optimization of biometry for intraocular lens implantation using the Zeiss IOLMaster. *Acta Ophthalmol Scand* 2005;83(5):436-8.
24. Eleftheriadis H. IOLMaster biometry: refractive results of 100 consecutive cases. *Br J Ophthalmol* 2003; 87(8): 960-3.

# Markers of ineffective erythropoiesis in non-transfusion dependent $\beta$ -thalassaemia

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## ABSTRACT

Non-transfused  $\beta$ -thalassaemia patients develop complications related to unsuppressed ineffective erythropoiesis (IE). Serum markers of IE would be useful for risk stratification and monitoring treatment. We studied  $\beta$ -thalassaemia trait ( $\beta$ -TT) and non-transfusion-dependent  $\beta$ -thalassaemia ( $\beta$ -NTDT) patients. Serum erythropoietin (EPO) and soluble transferrin receptor (sTfR) were correlated against markers of clinical severity (haemoglobin, LDH, retics, bilirubin, spleen size) and iron overload (ferritin, hepcidin, and MRI-T2\* in NTDT patients).

Eleven  $\beta$ -NTDT and nine  $\beta$ -TT subjects were studied.  $\beta$ -NTDT patients had significantly higher markers of haemolysis and iron overload. In  $\beta$ -NTDT, liver iron ranged from mild to severe, but no cardiac loading was seen. EPO and sTfR were higher in patients with  $\beta$ -NTDT than  $\beta$ -TT, and correlated significantly with each other ( $\rho=0.630$ ,  $p=0.003$ ). Both markers were negatively correlated with haemoglobin (sTfR  $\rho=-0.540$ ,  $p=0.014$ ; EPO  $\rho=-0.807$ ,  $p<0.001$ , and positively correlated with spleen size (sTfR  $\rho=0.783$ ,  $p<0.001$ ; EPO  $\rho=0.654$ ,  $p=0.002$ ) and markers of iron overload. There was a strong correlation between ferritin and hepcidin ( $\rho=0.720$ ,  $p<0.001$ ), and a relatively lower increment of hepcidin for the degree of iron overload in  $\beta$ -NTDT compared to  $\beta$ -TT.

EPO and sTfR appear to be reliable markers of erythropoiesis in non-transfused  $\beta$ -thalassaemia and correlate well with markers of disease severity. Their role in managing patients, predicting complications, and monitoring response to treatments aimed at reducing IE should be explored.

## KEYWORDS:

*Non-transfusion-dependent thalassaemia,  $\beta$ -thalassaemia intermedia, ineffective erythropoiesis*

## INTRODUCTION

$\beta$ -thalassaemia is due to mutations in the  $\beta$ -globin gene which cause a reduction or absence of the synthesis of the  $\beta$ -globin chains. There is a wide range of clinical presentation within the  $\beta$ -thalassaemia syndromes. Those with anaemia too severe to be considered as minor, but who may be transfused occasionally are termed non-transfusion-dependent  $\beta$ -thalassaemia, ( $\beta$ -NTDT).<sup>1</sup> The imbalance in  $\alpha/\beta$ -globin chain synthesis leads to excess free  $\alpha$ -globin

chains which form toxic aggregates.<sup>2,3</sup> This leads to early destruction of erythroid precursors in the marrow and defective mature erythrocytes, which is termed 'ineffective erythropoiesis' (IE).<sup>4,5</sup>

The three important pathogenetic features of IE are: accelerated erythroid differentiation; maturation blockade or arrest; and early death of erythroid precursors.<sup>2,6</sup> These result in reduced production of mature, functioning erythrocytes. In response to the chronic anaemia, there is a dramatic rise in erythropoietin (EPO) production.<sup>2</sup> Unfortunately, the marrow can only respond to this EPO signal by increasing the ineffective expansion of the erythroid compartment in the marrow, which in turn leads to bone deformities, osteoporosis and extramedullary erythropoiesis.<sup>6</sup>

Erythropoiesis is closely linked to iron metabolism, especially to its absorption from the gut. Normally, serum hepcidin values rise in iron sufficiency/overload and this down-regulates gut iron absorption.<sup>7</sup> However, in a mouse model of  $\beta$ -thalassaemia, bone marrow factors such as erythroferrone and GDF-11 increase in erythroid hyperplastic states, and inappropriately suppress hepcidin production,<sup>7,8</sup> facilitating iron absorption even in states of plentiful body iron. Hence, slowly-progressive iron overload, may occur in  $\beta$ -NTDT patients, albeit at an older age compared to thalassaemia major patients who are regularly transfused.<sup>3</sup>

The serum level of soluble transferrin receptor (sTfR) has been investigated as a marker of IE. The rate of synthesis of this receptor is related to cellular iron demands.<sup>9</sup> Kohgo et al., showed that sTfR levels paralleled peripheral reticulocyte counts, reflecting turnover of transferrin receptors in marrow erythrocyte precursor cells.<sup>9</sup> In  $\beta$ -NTDT, sTfR levels are elevated, whilst in  $\beta$ -thalassaemia major patients who are well transfused the levels are near-normal indicating effective suppression of marrow erythropoiesis.<sup>10,11</sup>

As  $\beta$ -NTDTs are not transfusion dependent, they were relatively neglected until recent clinical studies revealed that there is a spectrum within this group.<sup>12</sup> Those at the severe end of the spectrum overlap with thalassaemia major patients, and some of the  $\beta$ -NTDT patients eventually go on to regular transfusion because of the effects of chronic anaemia. Even those  $\beta$ -NTDT patients of intermediate severity may develop serious clinical complications due to IE and iron overload, so they require regular monitoring and careful management.<sup>12</sup>

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Although there have been many reviews and laboratory studies on IE,<sup>2,13</sup> clinical studies correlating biomarkers of IE with clinical severity parameters are few. It would be useful to have markers of IE by which to assess severity, predict complications, and monitor new approaches to therapy, in  $\beta$ -NTDT.

## MATERIALS AND METHODS

### Subjects

This cross-sectional study was conducted between June and December 2017. A search for suitable patients was made from the University Malaya hospital electronic patient record system and a personal database, and by identifying haemoglobin electrophoresis results in the Haematology Unit laboratory that fulfilled our inclusion criteria. Patients who were included in the study were aged 12 years and above, with either  $\beta$ -thalassaemia trait (TT), or  $\beta$ -NTDT confirmed by standard laboratory criteria, i.e. high performance liquid chromatography and gel electrophoresis demonstrating  $\beta$ -thalassaemia intermedia by having abnormalities of both  $\beta$ -globin genes (E/ $\beta$ O, E/ $\beta$ + or  $\beta$ +/ $\beta$ +) or mild to moderate HbE/ $\beta$ -thalassaemia as defined by the Mahidol score for HbE/ $\beta$ -thalassaemia severity.<sup>14</sup> The  $\beta$ -NTDT cases had to have received less than three units of transfused red blood cells in the previous 12 months, with the last transfusion (if any) occurring more than three months prior to recruitment. Exclusion criteria included: other forms of thalassaemia (e.g.  $\alpha$ -thalassaemias such as HbH disease, HbH with Constant Spring); sickle cell disease; concurrent iron deficiency; use of iron chelators; splenectomy; the presence of other haematological conditions such as immune thrombocytopenic purpura or autoimmune haemolytic anaemia. All subjects gave written informed consent to take part in this study.

### Parameters measured

Haemoglobin (Hb), haemolytic markers (i.e. lactate dehydrogenase (LDH), bilirubin, reticulocytes), serum erythropoietin (EPO), soluble transferrin receptor (sTfR) and ferritin, were measured. Venous blood samples for sTfR and hepcidin were obtained and collected in 2 separate plain plastic tubes without additives. The tubes were kept at room temperature for 2 hours to allow the blood to clot, after which they were centrifuged, and the serum was then separated and kept frozen at -20°C until the time of assay. The Hpcidin 25 (bioactive) HS ELISA (DRG Diagnostics, USA) and the N Latex sTfR assay (Siemens Healthcare Diagnostics Products, Germany) kits were used for the study.

The maximum diameter of both the liver and the spleen were measured either by ultrasound (in  $\beta$ -TT) or MRI (in  $\beta$ -NTDT). Liver and cardiac iron content were estimated by standard MRI T2\* analysis, but only in patients with  $\beta$ -NTDT.

### Statistical methods

Baseline demographics and patient characteristics were analysed using descriptive statistics. Correlations were assessed using Spearman's correlation coefficients ( $\rho$ ) and scatter plots: strong, fair and weak correlations were defined as  $\rho > 0.60$ ,  $0.30$ - $0.60$  and  $< 0.30$  respectively. The p-values were considered significant when  $< 0.05$ . All statistical

analyses were performed using SPSS for windows (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Approval was obtained from the Research Ethics Committee of the University Malaya Medical Centre prior to commencement of the study.

## RESULTS

### Baseline demographics and patient characteristics

Twenty-three patients were initially recruited. Three patients were excluded from the study (one for iron deficiency; one for autoimmune haemolysis; and one for concomitant  $\alpha$ -thalassaemia trait). Results of 20 patients were analysed. Eleven patients had  $\beta$ -NTDT (five with  $\beta$ -thalassaemia intermedia and six with HbE/ $\beta$ -thalassaemia) and nine had  $\beta$ -TT. Age, gender and transfusion requirements were similar between these two groups (Table I).

Table II shows the results for the markers of haemolysis, iron overload and erythropoiesis. As expected, Hb was lower, and HbF was higher, in the  $\beta$ -NTDT group. Markers of iron overload (ferritin and hepcidin) and erythropoiesis (EPO and sTfR) were markedly higher in  $\beta$ -NTDT than in  $\beta$ -TT. Nine  $\beta$ -NTDT patients underwent T2\* MRI (two refused): in terms of liver iron loading, five showed mild ( $T2^* > 7.2$  msec,  $< 5$  mg Fe/g), two moderate (3.3-7.2 msec, 5-10 mg Fe/g), and two severe (2.2-3.3 msec, 10-15 mg Fe/g). No iron loading of the heart was seen in any of these patients. Median liver and spleen sizes were bigger in  $\beta$ -NTDT patients.

### Relationships between anaemia and erythropoietic markers

Looking at the whole study population (i.e. both groups) together, as a spectrum of IE, there was a strong negative correlation between EPO and Hb levels ( $\rho = -0.807$ ,  $p < 0.001$ ). sTfR and Hb showed a weak but significant negative correlation ( $\rho = -0.540$ ,  $p = 0.014$ ). sTfR and EPO showed a strong positive correlation with each other ( $\rho = 0.630$ ,  $p = 0.003$ ) (Figure 1).

### Relationships between clinical signs and erythropoietic markers

Strong, significant associations were noted between both markers of erythropoiesis, EPO and sTfR, and spleen size ( $\rho = 0.654$ ,  $p = 0.002$ ; and  $\rho = 0.783$ ,  $p < 0.001$ , respectively). Moderate-to-strong correlations were also noted between liver size and both EPO and sTfR ( $\rho = 0.574$ ,  $p = 0.008$ ; and  $\rho = 0.809$ ,  $p < 0.001$ , respectively).

### Relationships between iron overload and erythropoietic markers

There was a significant positive correlation between hepcidin and ferritin ( $\rho = 0.720$ ,  $p < 0.001$ ). Although our data showed an increase in hepcidin with increasing ferritin, this is less pronounced in the NTDTs compared to the traits, as shown in Figure 2. EPO and sTfR strongly correlated with ferritin (EPO vs ferritin  $\rho = 0.632$ ,  $p = 0.003$ ; sTfR vs ferritin  $\rho = 0.642$ ,  $p = 0.002$ ). However the correlations of the two markers with hepcidin were weak and non-significant (EPO vs hepcidin  $\rho = 0.167$ ,  $p = 0.482$ ; sTfR vs hepcidin  $\rho = 0.370$ ,  $p = 0.108$ ).

## DISCUSSION

### Anaemia and markers of erythropoiesis

This is the first study comparing markers of erythropoiesis in



**Table I: Patient demographics and characteristics**

Characteristic	All (n=20)	$\beta$ -TT (n=9)	$\beta$ -NTDT (n=11)	p-value
<b>Age, years.</b>				
Median (range)	31.5 (14-66)	37 (14-66)	29 (16-62)	0.710
<b>Ethnicity</b>				
Malay	14 (70%)	4 (44.4%)	10 (90.9%)	0.024
Chinese	6 (30%)	5 (55.6%)	1 (9.1%)	
<b>Gender</b>				
Male	4 (20%)	1 (11.1%)	3 (27.3%)	0.369
Female	16 (80%)	8 (88.9%)	8 (72.7%)	
<b>Ever Transfused?</b>				
Yes	10 (50%)	3 (33.3%)*	7 (63.6%)	0.178
No	10 (50%)	6 (66.7%)	4 (36.4%)	

$\beta$ TT:  $\beta$ -thalassaemia trait.

$\beta$ -NTDT: non-transfusion-dependent  $\beta$ -thalassaemia.

\*Isolated episodes of transfusion in  $\beta$ -TT: 2 during pregnancies and 1 during intercurrent illness.

**Table II: Haemoglobin, and markers of haemolysis, erythropoiesis and iron overload**

Parameter	All subjects (n=20)	$\beta$ -TT (n=9)	$\beta$ -NTDT (n=11)	p-value ( $\beta$ -TT vs $\beta$ -NTDT)
<b>Median (range)</b>				
Hb (g/L)	91.0 (62.0-140.0)	104.0 (91.0-140.0)	80.0 (62.0-131.0)	0.004
RBC ( $\times 10^{12}/L$ )	5.1 (3.8-7.3)	5.2 (4.3-6.6)	4.5 (3.8-7.3)	0.295
MCV (fL)	61.5 (52.0-71.0)	65.0 (61.0-71.0)	65.0 (52.0-69.0)	0.002
MCH (pg)	19.3 (15.5-22.2)	20.4 (19.1-22.2)	17.9 (15.5-20.2)	0.001
MCHC (g/L)	312.5 (290.0-327.0)	315.0 (305.0-327.0)	308.0 (290-326)	0.230
HbF (%)	4.7 (0.4-43.7)	1.6 (0.4-12.3)	7.0 (1.8-43.7)	0.007
Reticulocyte count ( $\times 10^9/L$ )	132.1 (59.3-239.0)	95.9 (78.3-173.0)	163.0 (59.3-239.0)	0.031
LDH (U/L)	177 (121-564)	163 (128-207)	219 (121-564)	0.041
Total Bilirubin ( $\mu$ mol/L)	26 (8-65)	13 (8-49)	40 (18-65)	0.007
Hepcidin (ng/mL)	21.9 (4.9-76.1)	15.5 (4.9-38.1)	22.4 (12.2-76.1)	0.112
Ferritin ( $\mu$ g/L)	383.2 (25-4218)	101.7 (25.0-445.0)	495.5 (160-4218.0)	0.001
Erythropoietin (mg/L)	34.4 (5.0-97.7)	13.9 (5.0-45.0)	45.9 (14.5-97.7)	0.007
sTfR (mg/L)	3.7 (0.1-13.1)	1.8 (0.1-3.4)	5.8 (3.1-13.1)	<0.001
MRI T2*liver (msec)#	9.5 (0.8-15.9)	Not performed	9.5 (0.8-15.9)	
Liver size (cm)	16.1 (11.0-23.5)	14.4 (11.0-16.0)	19.6 (15.4-23.5)	<0.001
Spleen size (cm)	11.6 (7.9-21.2)	10.0 (7.9-12.8)	16.2 (10.0-21.2)	0.001

( $\beta$ -TT  $\beta$ -thalassaemia trait,  $\beta$ -NTDT  $\beta$ -non-transfusion-dependent thalassaemia,

Hb haemoglobin, RBC red blood cell count, MCV mean cell volume, MCH Mean corpuscular haemoglobin. MCHC mean corpuscular haemoglobin concentration,

HbF fetal haemoglobin, LDH lactate dehydrogenase, sTfR soluble transferrin receptor.)

# MRI T2\* hepatic loading (n=9, as 2 patients refused to undergo MRI).

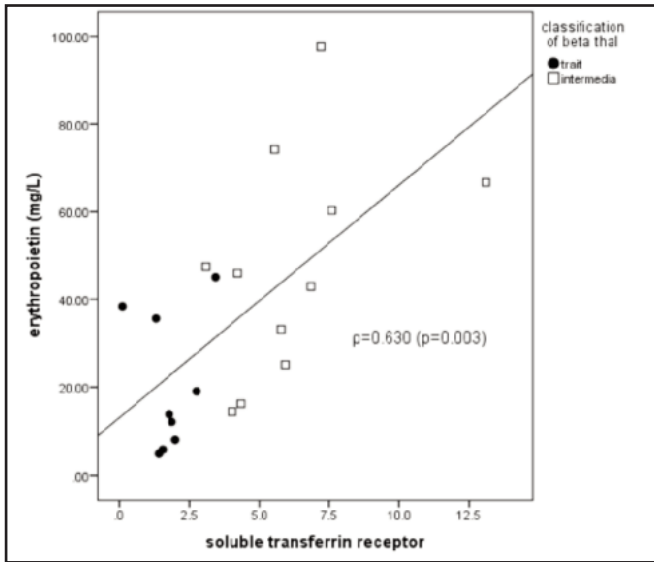


Fig. 1: Correlation between EPO and sTfR.

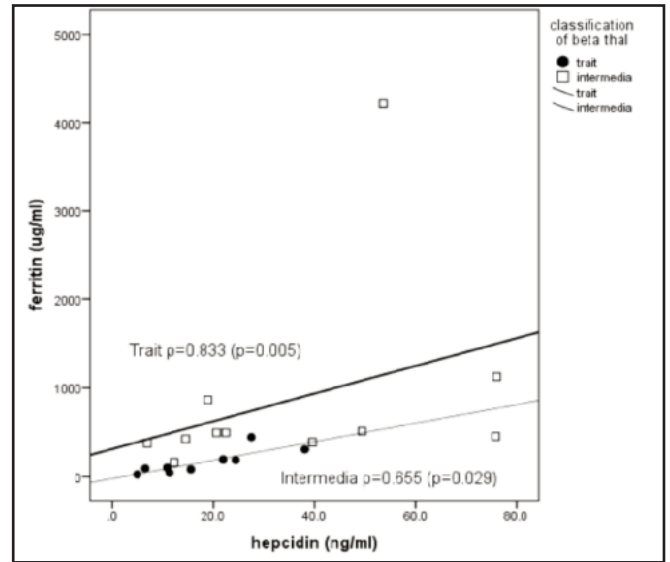


Fig. 2: Correlation between hepcidin and ferritin (for  $\beta$ TT and  $\beta$ -NTDT separately).

$\beta$ -NTDT and  $\beta$ -TT patients. There have been studies performed on ineffective erythropoiesis in NTDs, but generally with a mixture of  $\beta$  and  $\alpha$  thalassaemia patients.<sup>13</sup> We made co-existing  $\alpha$ -thalassaemia an exclusion criterion as the reduction of  $\alpha$  chains might ameliorate the degree of ineffective erythropoiesis. Patients involved in our study had not had a blood transfusion during the preceding three months, and were not on iron chelators, eliminating the confounding effects these might have on erythropoiesis and markers of iron overload.

Anaemia was more pronounced in the NTDs, but with some overlap in range with the traits. HbF levels were higher in the intermedias, as expected.<sup>6</sup> Markers of haemolysis (lactate dehydrogenase, reticulocyte count and total bilirubin) were higher in NTDs reflecting the high red cell turnover.

Patients with  $\beta$ -NTDT had higher sTfR and EPO levels, reflecting the increased rate of (ineffective) erythropoiesis (Table II). Thalassaemic marrow may have five-to-six times the number of erythroid precursors compared to healthy marrow, but with a 15-fold increase in apoptotic rate.<sup>15</sup> Two major cytokines control erythropoiesis, stem cell factor (SCF) and erythropoietin (EPO).<sup>2</sup> EPO not only controls the rate of erythroid precursor proliferation, it prevents apoptosis. The negative correlation between EPO and haemoglobin in our study is consistent with EPO production responding to anaemia but failing to produce adequate red cell production (i.e., IE). The significant negative correlation between sTfR and Hb in our study is consistent with ineffective erythroid hyperplasia being proportional to the degree of anaemia, as found in previous studies.<sup>13</sup>

The response of thalassaemic marrow to EPO is insufficient, resulting in erythroid hyperplasia and expansion of the bone marrow without an adequate increase in production and release of mature erythrocytes into the peripheral blood.<sup>4</sup> Direct measurement of bone marrow expansion in thalassaemia (e.g., by radiological means) has not yet been

explored. However, it has been shown that sTfR strongly correlates with bone marrow expansion in  $\beta$ -thalassaemia intermedia.<sup>16</sup> Further evidence for this relationship is shown by the positive correlation between spleen and liver size with sTfR levels in our study.

*Iron overload and erythropoiesis*

Despite not having regular transfusions, NTD patients are often found to have significant iron overload, especially in the liver.<sup>6,12</sup> Hepcidin is the main regulator of iron absorption and its level is usually increased in iron overload, downregulating iron absorption.<sup>2</sup> However, hepcidin is partially suppressed by ineffective erythropoiesis, allowing intestinal iron absorption and increased release of recycled iron from the reticuloendothelial system, causing clinical iron overload.<sup>6,12</sup>

In this study, we chose hepcidin and ferritin as biochemical markers for iron overload. A significant positive correlation was seen between the two markers, with a lesser degree of increase in hepcidin was seen in NTD compared to TT (Figure 2). This is consistent with relative hepcidin suppression in NTD which could contribute to an inappropriate failure to suppress iron absorption and hence, higher ferritin levels in NTDs compared to traits.

Although EPO and sTfR correlated well with ferritin, the same degree of correlation was not found with hepcidin. Hepcidin levels respond to competing stimuli: they are increased in response to iron overload but reduced by mediators related to erythropoiesis such as erythroferrone and GDF-15.<sup>18</sup> The lower degree of correlation is likely due to hepcidin being an indirect marker of iron overload. Hepcidin has been shown to be better as a marker of iron deficiency rather than that of iron overload.<sup>17</sup>

It is important to note that iron overload is strongly influenced by transfusion history. It would be best if there had been a complete, lifelong transfusion record for our

patients. Unfortunately this was not available as these patients were transfused only intermittently and some had had transfusions at other hospitals.

The relationship between ineffective erythropoiesis and iron overload is further demonstrated by the positive correlation between both EPO and sTfR with iron loading as measured by serum ferritin. It is interesting to note that even in NTDs there is a wide spectrum of severity of iron overload in the liver, ranging from mild to very severe. This lends further support to the heterogeneity of NTD and the need to stratify them further, into different classes of severity.

#### *Clinical signs and biomarkers of erythropoiesis*

Expansion of erythropoiesis in the bone marrow is associated with localised bone deformities and osteoporosis, but it also causes extramedullary haematopoiesis, e.g. proliferation and homing of these precursors to the spleen and liver causing hepatosplenomegaly.<sup>6</sup> Haematopoietic tissue can expand further into other areas causing debilitating clinical consequences, for example paraplegia if this occurs in the spinal canal. Our study has shown that there is a correlation between both sTfR and EPO with both spleen and liver size. The stronger correlation with sTfR suggests it is the most reliable, currently available, marker of bone marrow expansion and extramedullary haematopoiesis. Further studies are ongoing to examine the relationship between these markers of erythropoiesis and clinical complications such as osteoporosis.

#### **CONCLUSION**

In conclusion, our study demonstrates a clear correlation of the markers of erythropoiesis, sTfR and EPO, with extramedullary haematopoiesis (as shown by hepatosplenomegaly), and with iron overload. There is potential to use these two markers in the clinical setting to identify  $\beta$ -NTDT patients at higher risk of complications. These findings merit further assessment in a larger prospective study to establish whether they could be used to risk stratify patients with  $\beta$ -NTDT. Such markers could also be used to monitor the effectiveness of different forms of treatment, especially those specifically targeted at reducing IE, such as the TGF- $\beta$  ligand scavengers luspatercept and sotatercept.<sup>18</sup>

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#### **DISCLOSURE OF INTEREST**

The authors declare no conflicts of interest.

#### **REFERENCES**

1. Taher AT, Musallam KM, Cappellini MD, Weatherall DJ. Optimal management of beta thalassaemia intermedia. *Br J Haematol* 2011; 152(5): 512-23.
2. Ribeil JA, Arlet JB, Dussiot M, Moura IC, Courtois G, Hermine O. Ineffective erythropoiesis in beta-thalassemia. *ScientificWorldJournal* 2013; 2013: 394295.
3. Gardenghi S, Grady RW, Rivella S. Anemia, ineffective erythropoiesis, and hepcidin: interacting factors in abnormal iron metabolism leading to iron overload in beta-thalassemia. *Hematology/Oncology clinics of North America* 2010; 24(6): 1089-107.
4. Rivella S. The role of ineffective erythropoiesis in non-transfusion-dependent thalassemia. *Blood Rev* 2012; 26 Suppl 1: S12-5.
5. Taher AT, Radwan A, Viprakasit V. When to consider transfusion therapy for patients with non-transfusion-dependent thalassaemia. *Vox Sang* 2015; 108(1): 1-10.
6. Musallam KM, Rivella S, Vichinsky E, Rachmilewitz EA. Non-transfusion-dependent thalassaemias. *Haematologica* 2013; 98(6): 833-44.
7. Kautz L, Jung G, Du X, Gabayan V, Chapman J, Nasoff M, et al. Erythroferone contributes to hepcidin suppression and iron overload in a mouse model of  $\beta$ -thalassaemia. *Blood* 2015; 126(17): 2031-7.
8. Dussiot M, Maciel TT, Fricot A, Chartier C, Negre O, Veiga J, et al. An activin receptor IIA ligand trap corrects ineffective erythropoiesis in  $\beta$ -thalassaemia. *Nat Med* 2014; 20(4): 398-407.
9. Kohgo Y, Niitsu Y, Kondo H, Kato J, Tsushima N, Sasaki K, et al. Serum transferrin receptor as a new index of erythropoiesis. *Blood* 1987; 70(6): 1955-8.
10. Tancabelic J, Sheth S, Paik M, Piomelli S. Serum transferrin receptor as a marker of erythropoiesis suppression in patients on chronic transfusion. *Am J Hematol* 1999; 60(2): 121-5.
11. Guimaraes JS, Corninal JG, Silva-Pinto AC, Olbina G, Ginzburg YZ, Nandi V, et al. Altered erythropoiesis and iron metabolism in carriers of thalassaemia. *Eur J Haematol* 2015; 94(6): 511-8.
12. Taher A, Vichinsky E, Musallam K, Cappellini MD, Viprakasit V. Guidelines for the management of Non Transfusion Dependent Thalassaemia (NTDT). *Thalassaemia International Federation, Nicosia, Cyprus* 2013.
13. Porter JB, Cappellini MD, Kattamis A, Viprakasit V, Musallam KM, Zhu Z, et al. Iron overload across the spectrum of non-transfusion-dependent thalassaemias: role of erythropoiesis, splenectomy and transfusions. *Br J Haematol* 2017; 176(2): 288-99.
14. Sripichai O, Makarasara W, Munkongdee T, Kumkhaek C, Nuchprayoon I, Chuansumrit A, et al. A scoring system for the classification of beta-thalassaemia/Hb E disease severity. *Am J Hematol* 2008; 83(6): 482-4.
15. Centis F, Tabellini L, Lucarelli G, Buffi O, Tonucci P, Persini B, et al. The importance of erythroid expansion in determining the extent of apoptosis in erythroid precursors in patients with beta-thalassaemia major. *Blood* 2000; 96(10): 3624-9.
16. Ricchi P, Ammirabile M, Costantini S, Di Matola T, Verna R, Diano A, et al. A useful relationship between the presence of extramedullary erythropoiesis and the level of the soluble form of the transferrin receptor in a large cohort of adult patients with thalassaemia intermedia: a prospective study. *Annals of Hematology* 2012; 91(6): 905-9.
17. Hare DJ. Hepcidin: a real-time biomarker of iron need. *Metallomics* 2017; 9(6): 606-18.
18. Piga A, Perrotta S, Gamberini MR, Voskaridou E, Melpignano A, Filosa A, et al. Luspatercept improves hemoglobin levels and blood transfusion requirements in a study of patients with  $\beta$ -thalassaemia. *Blood* 2019; 133(12): 1279-89.

# Haemophilia care and outcome in a major haemophilia treatment centre in Malaysia

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## ABSTRACT

**Introduction/Objective:** The management of potential treatment-related complications and bleeding events in haemophilia is challenging in developing countries. Providing optimal care among these patients improve their quality of life (QOL) and life expectancy. This study explores the demographic characteristics and treatment outcome in a major haemophilia treatment centre in Malaysia.

**Materials and Methods:** A total of 260 patients were recruited in this retrospective cross-sectional analysis. Clinical data, including treatment regimens and outcome, were collected and analysed.

**Results:** A total of 211 patients were diagnosed with haemophilia A (HA) (severe disease, 72.5%) and 49 patients had haemophilia B (HB) (severe disease, 65.3%). The median age was 31 (IQR;2-84) years. Majority of the patients had at least one episode of musculoskeletal bleeding since diagnosis. The mean annual bleeding event (ABE) was 4.91 (SD±6.07) in 2018. Target joints were identified in 80.4% of the patients. Chronic arthropathy and synovitis collectively accounted for more than half of the musculoskeletal complications. 30.1% of the patients had contracted hepatitis C with less than half received treatment. Thirty-one patients (16.8%) with severe haemophilia developed inhibitor and 12 patients successfully underwent immune tolerance induction. More than three-quarters of the severe haemophilia patients were treated with factor concentrate prophylaxis. The mean prophylaxis dose for HA and HB were 41.3 (SD±19.1) and 48.6 (SD±21.5) IU/kg/week, respectively. In patients with severe disease, prophylaxis significantly reduced the ABE (5.45,9.03;p=0.005).

**Conclusion:** The importance of utilising a low to moderate dose regimen as prophylaxis in haemophilic patients is highlighted in our study. Future studies should include QOL assessment will further improve the management in haemophilia.

## KEYWORDS:

*Haemophilia, Malaysia, bleeding disorder, prophylaxis*

## INTRODUCTION

Haemophilia is a group of X-linked recessive disorders, affecting the coagulation factors responsible for the clotting

mechanism. The two most common forms of haemophilia are haemophilia A (HA) and haemophilia B (HB). The management of potential treatment-related complications and bleeding events in haemophilia is challenging in developing countries. Providing optimal care among these patients improve their quality of life (QOL) and life expectancy. With a total population of 31.5 million in Malaysia, the estimated total number of patients of all types of haemophilia was 1,075 in 2018, making the prevalence of 3.4 per 100,000 population.<sup>1</sup>

The use of recombinant factors and plasma-derived factors has significantly improved the overall clinical outcomes and survival among patients with haemophilia (PWH). However, exposure to the factor replacement may lead to the production of alloantibody (inhibitor) against the factor protein and the management for this group of patients is challenging, requiring the use of expensive bypassing agents such as factor VIII inhibitor bypassing agent (FEIBA) and activated factor VII. The incidence of transfusion-transmitted infection, such as hepatitis B, hepatitis C, and human immunodeficiency virus (HIV), is now significantly reduced but is not negligible. Complications involving the musculoskeletal system which are observed frequently in haemophilia include acute intraarticular haemorrhage, intramuscular haemorrhage, recurrent intraarticular bleeding, chronic synovitis, and chronic arthropathy. All these complications will have a significant impact on their quality of life, besides creating an enormous economic burden on the national health care system.

Clinical data about haemophilia is scarce in Malaysia. This study aimed to determine the demographic characteristics, treatment characteristics, and its effectiveness in preventing complications among patients diagnosed with haemophilia in a major haemophilia treatment centre in Malaysia. To the best of our knowledge, this is the first published study on the epidemiological profile of haemophilia in Malaysia. The outcome of this study will serve to improve the overall future management of haemophilia.

## MATERIALS AND METHODS

### *Study design and population*

This is a retrospective cross-sectional study conducted in a Malaysian tertiary hospital, Hospital Ampang, Ministry of Health Malaysia, Selangor treating PWH. All patients

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diagnosed with HA and HB treated and followed up from January till December 2018, were recruited. Patients from the central region in Peninsular Malaysia were followed up in our haemophilia treatment centre (HTC). Patients with other congenital clotting deficiency, acquired haemophilia, and of uncertain diagnosis were excluded. Socio-demographic data, clinical characteristics, complications, treatment regimens, and outcomes were collected from the medical records using a standardised data collection forms. This study was registered with the National Medical Research Register, Malaysia, and the ethical approval for this study was obtained from the Medical Research and Ethical Committee (MREC), Ministry of Health Malaysia (NMRR-19-2979-51363).

A patient with haemophilia was defined as any patient who was diagnosed with HA or HB in the presence of bleeding tendency and confirmed by laboratory evidence of low coagulation factor activity level. Patient with HA was any patient with factor VIII deficiency since birth and patient with HB was any patient with factor IX deficiency since birth. The severity of haemophilia was divided into mild, moderate, and severe based on the activity level and this applies for both HA and HB.

Mild haemophilia is defined as factor activity between 5 to 40% of normal factor activity; moderate haemophilia include factor activity between 1 to 5% of normal factor activity, and severe haemophilia is defined as factor activity less than 1% in the bloodstream. Target joint is defined as the joint with recurrent bleeding, as diagnosed by the physician and recorded in the medical record. This includes joint with at least 3 or more bleeding events occurring within 3 to 6 months period. Annual bleeding event is defined as the total bleeding events documented for each patient for one year.

#### Statistical Analysis

The statistical software Statistical package for Social Science (SPSS) version 22 (SPSS Inc., Chicago, IL, USA) was used to analyse all the data collected and extracted. Categorical data were expressed as frequencies and percentages and continuous data was expressed as mean  $\pm$  standard deviation. Independent student's t-tests were used to compare group means of continuous dependent variables while the Kolmogorov-Smirnov Test of Normality was used to test the distribution of a sample. All p values are 2-sided and p values  $<0.05$  were considered statistically significant.

## RESULTS

### Socio-demographic data and clinical features

260 patients were recruited with a median age of 31 (range, 2-84) years old. The median age of diagnosis was 2 (range 1 – 73) and 6 years old (range 1 – 39) for HA and HB, respectively. Majority of the site of the first bleed was unknown due to missing documentation. All patients were males, and 52.7% were Malays followed by Chinese (34.6%), and Indians (10%). A total of 211 patients were diagnosed with HA with 72.5% of them had severe disease, while 49 patients had HB (severe disease, 65.3%). About two-third had a significant family history. Details of clinical characteristics are illustrated in Table I.

The overall mean annual bleeding event in 2018 was 4.91 (SD6.07). Chronic arthropathy and synovitis collectively accounted for more than half of the musculoskeletal complications with only 39% of them undergoing intervention such as radioisotope synovectomy and arthroplasty. Target joints were identified in 81.5% of patients with HA and 83.7% of patients with HB. Other complications included intracranial bleeding (15.6%), surgical bleeding (8.1%), and gastrointestinal bleeding (7.6%) in HA. Conversely, surgical bleeding (16.3%) was the second commonest complication in HB followed by intracranial bleeding (10.2%), and gastrointestinal bleeding (8.2%) (Table II).

Seventy-eight patients with HA and HB contracted hepatitis C. Among these patients, three had co-infection with hepatitis B and two had co-infection with human immunodeficiency virus (table II). Only 32 patients were treated for their underlying hepatitis C, while treatment was exempted for eight patients due to spontaneous seroconversion. Patients contracted with hepatitis B and HIV were all treated accordingly with appropriate antiviral therapy.

Thirty-one patients with HA and two patients with HB developed inhibitors. Among these, 16 patients with HA underwent immune tolerance induction (ITI) with 12 of them (75%) successfully achieved ITI and resumed on regular prophylaxis. Fifteen patients with inhibitor were treated with on-demand/prophylaxis bypassing agents. Treatment with clotting factor concentrate (CFC) is illustrated in Table III. Prophylaxis with factor concentrate was started on 80.4% of the patients with severe HA and 78.1% of the patients with severe HB, respectively. Plasma-derived factor concentrate remained the main treatment option in our centre. The mean prophylaxis dose calculated for HA was 41.3 ( $\pm$ 19.1) IU/kg/week and HB was 48.6 ( $\pm$ 21.5) IU/kg/week in 2018. In patients with severe haemophilia A and B, prophylaxis significantly reduced the annual bleeding event (5.45, 9.03;  $p=0.005$ ). Five patients were treated with emicizumab and two patients were recruited in fitusiran clinical trial.

## DISCUSSION

Haemophilia results in lifelong bleeding disorder with factor replacement being the key to achieving a better quality of life in these patients. With the advent of factor prophylaxis in moderate to severe haemophilia, this has significantly reduced the incidence of bleeding, especially joint haemorrhage, and hence, improved the joint function and enabled PWH to lead a healthy and active lifestyle. Haemophilia Joint Health Score (HJHS) is a validated tool in assessing joint function with higher score indicates poorer joint health.<sup>2</sup> A study from Singapore reported a median score of 5.5 and 4 in their cohort of younger children ( $<10$  years old) and older children (11-20 years old), who were mostly on prophylactic therapy and these findings were consistent with most developed countries.<sup>3</sup> Unfortunately, HJHS assessment is not routinely carried out in our centre, and thus a comparison cannot be made. Nonetheless, reduction in bleeding events among patients using prophylaxis may indirectly translate into better joint health as majority of our patients had at least one episode of

Table I: Socio-demographic data and clinical characteristic of patients with haemophilia

	Mild n (%)	Moderate n (%)	Severe n (%)	Missing n (%)	Total, N (%)
<b>Haemophilia A</b>					
Severity	28 (13.3)	28 (13.3)	153 (72.5)	2 (0.9)	211 (100)
<b>Age distribution</b>					
0-10	1	1	4	0	6 (2.8)
11-20	4	4	30	1	39 (18.5)
21-30	9	8	39	1	57 (27)
31-40	3	3	45	0	51 (24.2)
41-50	3	8	22	0	33 (15.6)
Above 50	8	4	13	0	25 (11.8)
<b>Ethnicity</b>					
Malay	10	12	85	1	108 (51.2)
Chinese	12	12	54	1	79 (37.4)
Indian	6	2	10	0	18 (8.5)
Others	0	2	2	0	4 (1.9)
<b>Inhibitors</b>					
Yes	0	1	29	1	31 (14.7)
No	28	26	124	1	179 (84.8)
Missing	0	1	0	0	1 (0.5)
<b>Haemophilia B</b>					
Severity	7 (14.3)	10 (20.4)	32 (65.3)	0	49 (100)
<b>Age distribution</b>					
0-10	0	0	2	0	2 (4)
11-20	1	1	6	0	8 (16.3)
21-30	1	5	5	0	11 (22.4)
31-40	2	2	10	0	14 (28.6)
41-50	2	1	9	0	12 (24.5)
Above 50	1	1	0	0	2 (4)
<b>Ethnicity</b>					
Malay	4	6	19	0	29 (59.2)
Chinese	2	1	8	0	11 (22.4)
Indian	1	3	4	0	8 (16.3)
Others	0	0	1	0	1 (2)
<b>Inhibitors</b>					
Yes	0	0	2	0	2 (4.1)
No	5	10	30	0	45 (91.8)
Missing	2	0	0	0	2 (4.1)

Table II: Bleeding events and treatment complications among patients with haemophilia

Types of bleeding	Haemophilia A N = 211 n (%)	Haemophilia B N = 49 n (%)
Musculoskeletal (At least one episode)	187 (88.6)	41 (83.7)
Presence of target joints	172 (81.5)	35 (71.4)
Number of target joints		
1	50	14
2	63	8
3	32	8
>3	24	5
Psoas bleeding	36 (17.1)	5 (10.2)
Intracranial bleeding	33 (15.6)	5 (10.2)
Surgical bleeding	17 (8.1)	8 (16.3)
Gastrointestinal bleeding	16 (7.6)	4 (8.2)
Annual bleeding event (mean±SD)	4.91 (±6.07)	
<b>Treatment complications</b>		
Hepatitis C	66 (31.3)	12 (24.5)
Hepatitis B	3 (1.4)	1 (2)
HIV	2 (0.9)	0 (0)

SD: Standard deviation; HIV: human immunodeficiency virus

Table III: Treatment characteristics for patients with haemophilia

Characteristics	Mild n=28 (%)	Moderate n=28 (%)	Severe n=153 (%)
<b>Haemophilia A</b>			
• On-demand CFC	27 (96.4)	18 (64.3)	29 (19.6)
• Prophylaxis CFC	1 (3.6)	10 (35.7)	123 (80.4)
<b>Treatment for target joints</b>			
Radiofrequency ablation	0	2	31
Arthroplasty	0	2	5
Dysarticulation	0	0	1
Others	0	0	5
Missing	0	0	1
	Mild n=7 (%)	Moderate n=10 (%)	Severe n=32 (%)
<b>Haemophilia B</b>			
• On-demand CFC	7 (100.0)	6 (60.0)	7 (21.9)
• Prophylaxis CFC	0 (0)	4 (40.0)	25 (78.1)
<b>Treatment of target joints</b>			
Radiofrequency ablation	0	1	5
Arthroplasty	0	0	2
Dysarticulation	0	0	0
Others	0	0	1
Missing	0	0	0
<b>Mean CFC in prophylaxis</b>		<b>Dose (iu/kg/week)</b>	
• PwH A		41.3 (± 19.1)	
• PwH B		48.6 (± 21.5)	

CFC: clotting factor concentrate; PwH: patients with haemophilia

musculoskeletal bleeding and more than 70% of them had target joints. This will require validation from future studies.

British Society of Haematology (BSH) and World Federation of Haemophilia (WFH) have recently updated their guidelines in the management of haemophilia, with recommendations including the approach, timing, and dosing for patients requiring prophylaxis.<sup>4,5</sup> All severe and moderate haemophilia patients with factor level of <3% should be considered for prophylaxis.<sup>4</sup> Low, intermediate, and high dose prophylaxis were explored to achieve “zero” bleeding. The used of plasma-derived and recombinant factors has been the mainstay of factor replacement for many years, and in Malaysia, providing coagulation factor concentrates (CFC) as prophylaxis remains a huge financial burden with limited access to novel agents. As our public health system consists of tax and government-run primary health care centres and hospitals with support mainly through general revenue and taxation collected by the federal government,<sup>6</sup> the economic burden remains a challenge in managing these patients. This is in addition to the common challenges faced including catheter-related infections, development of factor inhibitors, and viral infections from plasma-derived replacement factors.

A variety of regimens are used by different countries for the initiation of prophylaxis therapy of which there is long term data.<sup>7</sup> The Canadian protocol,<sup>8,9</sup> Malmo (high dose) protocol<sup>10</sup> or Utrecht (intermediate dose) protocol<sup>10</sup> had been practised widely in prophylaxis therapy. With financial limitation, utilisation of a low dose prophylaxis regimen is common to meet the demands of severe haemophilia patients.<sup>11-13</sup> The approach in our centre is by initiating patients on 10-15IU/kg of body weight two to three times per week in low dose regimen and escalate them according to the breakthrough bleeds. This has shown good results with a significant reduction in the annual bleeding events in those with the

severe phenotype in which prophylaxis significantly reduced the ABE from 9.03 to 5.45 (p=0.005) compared to those who were on-demand factor replacement. This benefit was observed despite a low to moderate dose replacement schedule with a mean CFC dose 41.3 (±19.1) IU/kg/week in HA and 48.6 (±21.5) IU/kg/week in HB. A similar trend of reduction in bleeding rates was observed in the other studies utilising the low dose approach.<sup>11-13</sup> However, a direct comparison to our study is not feasible due to the different protocols in the delivery of factor replacement and assessment of bleeding. Unfortunately, although the vast majority of our patients with severe disease were treated with regular prophylaxis, one-fifth of them still opted for on-demand replacement due to various reasons, including logistics and reluctance by our patients. Patient education and compliance is important to further reduce the bleeding events in our haemophilia population.

The acquisition of inhibitors is common among those on plasma-derived factors with the highest risk in the first 20 exposure days. Among severe HA, the cumulative incidence of all inhibitors was 26.8% with the plasma-derived factors and 44.5% with the recombinant factors. Out of this, 18.6% and 28.4% had high titres (>5 Bethesda units) respectively.<sup>14</sup> In HB, inhibitor development is less frequent (1.5-3%) but associated with significant morbidity especially an increased bleeding risk.<sup>15</sup> The current management strategies in patients with inhibitors include the provision of a bypassing agent, non-factor replacement (e.g. emicizumab, fitusiran, and concizumab) commonly through enrolment into clinical trials, and ITI. To date, ITI is the only proven method of which eradication of inhibitors are possible.<sup>16</sup> Various ITI protocols with high dose infusions of factors had resulted in 60-90% success rates in HA<sup>17,18</sup> and 30% in HB.<sup>19</sup> In our cohort of patients, 31 HA and 2 HB patients developed inhibitors, a 12.7% cumulative incidence which is comparable to another study.<sup>20</sup> Herein 16 patients (HA) were subjected to ITI with

75% of them were successful in eliminating the inhibitor. Therefore, ITI is generally feasible and should be practised in this group of patients.

Another complication surrounding plasma-derived factor replacement is the presence of blood product-related infections. Improvements seen in haemophilia treatment over time will see these patients having a longer life span, and thus, have an increased risk of infections with repeated exposure of plasma-derived factors.<sup>21</sup> The availability of commercial plasma-derived factor, which is highly purified and undergone strict processing method, significantly reduces the risk of contracting transfusion-transmitted infections and has almost eradicated it. Despite that, it remains a risk not to be neglected. WFH in their recent annual global survey reported HIV and hepatitis C infection continues to be a challenge even in developed countries, such as Japan and France based on the prevalence of infective cases reported with regards to PWH.<sup>22</sup> In our cohort of patients, a proportion of patients who contracted hepatitis C, received cryoprecipitate and fresh frozen plasma during the early 1990s when screening was not widely available. Only half of the patients received treatment for hepatitis C and this might be related to the course of treatment, which was previously prolonged and patient needs to be committed before treatment initiation. With the availability of oral antiviral agents, the proportion of patients receiving treatment likely will increase significantly. The rates of other viral infections were fortunately low.

#### STUDY LIMITATIONS AND CONCLUSION

This study is limited by its retrospective nature and unavailability of quality of life assessment of the patients. Despite being the major HTC covering almost one-quarter of the haemophilia population in Malaysia, a comprehensive study for the whole of Malaysia would be beneficial.

Nonetheless, our study has provided an insight into the demographics of the haemophilia population and highlighted the importance of prophylaxis in patients with moderate to severe haemophilia albeit the use of low to moderate dose regimen. We should anticipate increasing age-related health issues as more older patients, e.g., those with cardiovascular morbidity and renal impairment)among them. Understanding our current haemophilia landscape will eventually improve future care of haemophilia patients.

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#### REFERENCES

1. Boo YL, Liam CCK, Yong KY, Fann RJ, Lee GWC, Wilferd G, et al. Haemophilia in Malaysia [abstract]. In: Proceedings of the World Federation of Hemophilia Virtual Summit; 2020 June 14-19. Abstract nr 375.
2. Hilliard P, Funk S, Zourikian N, Bergstrom BM, Bradley CS, McLimont M, et al. Hemophilia joint health score reliability study. *Haemophilia* 2006; 12(5): 518-25.
3. Ng HJ, Lam J, Koh PL, Ho L, Lim CY, Akhbar Ali M, et al. A comprehensive study of current haemophilia care and outcomes in Singapore. *Haemophilia* 2015; 21(5): e428-31.
4. Rayment R, Chalmers E, Forsyth K, Gooding R, Kelly AM, Shapiro S, et al. Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. *Br J Haematol* 2020; 190: 684-95.
5. Srivastava A, Santagostino E, Dougall A, Steven K, Megan S, Steven WP, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia* 2020; 26(suppl 6): 1-158.
6. World Health Organization. Malaysia health system review. 2012.
7. Jiménez-Yuste V, Auerswald G, Benson G, Lambert T, Morfini M, Remor E, et al. Achieving and maintaining an optimal trough level for prophylaxis in haemophilia: the past, the present and the future. *Blood Transfusion* 2014; 12(3): 314.
8. Blanchette VS, Rivard GE, Pai MK, Israels SJ, McLimont M, Feldman BM. 10 year musculoskeletal outcomes with tailored primary prophylaxis: The Canadian Hemophilia Prophylaxis Study. *Blood* 2007; 110(11): 84.
9. Hilliard P, Zourikian N, Blanchette V, Chan A, Elliott B, Israels SJ, et al. Musculoskeletal health of subjects with hemophilia A treated with tailored prophylaxis: Canadian Hemophilia Primary Prophylaxis (CHPS) Study. *J Thromb Haemost* 2013; 11(3): 460-6.
10. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Guidelines for the management of hemophilia. *Haemophilia* 2013; 19(1): e1-47.
11. Wu R, Luke KH, Poon MC, Wu X, Zhang N, Zhao L, et al. Low dose secondary prophylaxis reduces joint bleeding in severe and moderate haemophilic children: a pilot study in China. *Haemophilia* 2011; 17(1): 70-4.
12. Eshghi P, Sadeghi E, Tara SZ, Habibpanah B, Hantooshzadeh R. Iranian low-dose escalating prophylaxis regimen in children with severe hemophilia A and B. *Clin Appl Thromb Hemost* 2018; 24(3): 513-8.
13. Verma SP, Dutta TK, Mahadevan S, Nalini P, Basu D, Biswal N, et al. A randomized study of very low-dose factor VIII prophylaxis in severe haemophilia-A success story from a resource limited country. *Haemophilia* 2016; 22(3): 342-8.
14. Peyvandi F, Mannucci PM, Garagiola I, El-Beshlawy A, Elalfy M, Ramanan V, et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. *N Engl J Med* 2016; 374(21): 2054-64.
15. Santoro C, Quintavalle G, Castaman G, Baldacci E, Ferretti A, Riccardi F, et al. Inhibitors in hemophilia B. *Semin Thromb Hemost* 2018; 44(06): 578-89.
16. Witmer C, Young G. Factor VIII inhibitors in hemophilia A: rationale and latest evidence. *Therapeutic advances in hematology* 2013; 4(1): 59-72.
17. Brackmann HH, White GC, Berntorp E, Andersen T, Escuriola-Ettingshausen C. Immune tolerance induction: What have we learned over time?. *Haemophilia* 2018; 24: 3-14.
18. Nakar C, Manco-Johnson MJ, Lail A, Donfield S, Maahs J, Chong Y, et al. Prompt immune tolerance induction at inhibitor diagnosis regardless of titre may increase overall success in haemophilia A complicated by inhibitors: experience of two US centres. *Haemophilia* 2015; 21(3): 365-73.
19. Lenk H. The German Registry of immune tolerance treatment in hemophilia--1999 update. *Haematologica* 2000; 85(10 Suppl): 45-7.
20. Plug I, van der Bom JG, Peters M, Mauser-Bunschoten EP, de Goede-Bolder A, Heijnen L, et al. Thirty years of hemophilia treatment in the Netherlands, 1972-2001. *Blood* 2004; 104(12): 3494-500.
21. Di Minno G, Canaro M, Ironside JW, Navarro D, Perno CF, Tiede A, et al. Pathogen safety of long-term treatments for bleeding disorders: still relevant to current practice. *Haematologica* 2013; 98(10): 1495-8.
22. Stonebraker JS, Bolton-Maggs PH, Brooker M, Evatt B, Iorio A, Makris M, et al. The World Federation of Hemophilia Annual Global Survey 1999-2018. *Haemophilia* 2020; 26: 591-600.



# Demographics and outcome of patients with congenital haemophilia in Sarawak, Malaysia

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## ABSTRACT

**Introduction:** Sarawak has a population that is geographically and characteristically widely varied. This study aimed to determine the demographic profile of patients in Sarawak, Malaysia.

**Materials and Methods –** A cross-sectional study was conducted in 2019 at four major haemophilia treatment centres in Kuching, Sibul, Bintulu and Miri Hospitals, Sarawak. Demographic and clinical data were collected with consents from patients.

**Results and Discussion:** Ninety-six haemophilia patients were identified - 79(82.3%) haemophilia A(HA) and 17(17.7%) haemophilia B(HB). Severe haemophilia patients were noted in 45.6% (36/79) of HA and 64.7% (11/17) of HB. In all 44.3% of the HA and 52.9% of the HB population had no identifiable family history of haemophilia. Two-thirds of the patients with severe HA were on prophylaxis [24/36 (66.7%)] and only one-third [4/11 (36.4%)] in severe HB. Inhibitors developed in 9/79 (11.4%) of the HA population [3/79 (3.8%) high responders]. The median inhibitor titre was not significantly different between the different treatment groups – on demand versus prophylaxis (1.0BU versus 2.0BU; z statistic -1.043, p-value 0.297, Mann-Whitney test). None of the patients developed inhibitory alloantibodies to factor IX. Four HA patients (5.1%) underwent immune tolerance induction where one case had a successful outcome. Three severe HA patients received emicizumab prophylaxis and showed remarkable reduction in bleeding events with no thromboembolic events being reported. One female moderate HA patient received PEGylated recombinant anti-haemophilic factor. Eleven patients underwent radiosynovectomy. One mild HB patient succumbed to traumatic intracranial bleeding. Our data reported a prevalence (per 100,000 males) of 5.40 cases for all severities of HA, 2.46 cases for severe HA; 1.16 cases for all severities of HB, and 0.75 cases for severe HB. The overall incidence of HA and HB was 1 in 11,500 and 1 in 46,000, respectively.

**Conclusion:** This study outlines the Sarawakian haemophilia landscape and offers objective standards for forward planning. Shared responsibilities among all parties are of utmost importance to improve the care of our haemophilia population.

## KEYWORDS:

*Demographics; Haemophilia; Sarawak*

## INTRODUCTION

Haemophilia, an X-linked congenital bleeding disorder, may be inherited or arise from spontaneous mutation. Haemophilia A (HA) and haemophilia B (HB) are caused by deficiencies of factor VIII (FVIII) and factor IX (FIX), respectively. Overall, the global prevalence (per 100,000 males) reported by a recent meta-analysis was 17.1 cases for all severities of HA, 6.0 cases for severe HA; 3.8 cases for all severities of HB, and 1.1 cases for severe HB.<sup>1</sup> A total of 173,711 and 34,289 patients with HA and HB were identified by the World Federation of Haemophilia annual survey in 2018.<sup>2</sup> The expected number of males with haemophilia worldwide was 1,125,000, the majority of whom were undiagnosed, including an estimated 418,000 males with severe haemophilia.<sup>1</sup> A national study in Singapore conducted in 2015 reported that the local prevalence of HA to be 10.31 per 100,000 males and HB to be 2.11 per 100,000 males.<sup>3</sup> The only study on congenital haemophilia in Malaysia was reported by Duraisamy in 1998, where HA made up 72% and HB 12% of all congenital bleeding disorders.<sup>4</sup>

Sarawak, the largest state in Malaysia, has a very diverse population where 2.8 million people from 26 ethnic groups living on the island of Borneo, with the Dayaks making up 40%, Malays 24%, Chinese 24% and the others by the other minority groups.<sup>5,6</sup> There is currently no published study reporting the epidemiological data and outcome of haemophilia in Sarawak. We hope this study will help to show the demographic profile of patients in Sarawak and study their outcome in order to gauge the performance of our management model and allow forward planning.

## MATERIALS AND METHODS

This cross-sectional study was conducted in 2019 at four haemophilia treatment centres in Sarawak: Sarawak General Hospital (SGH), Sibul Hospital, Bintulu Hospital and Miri Hospital. SGH houses a Comprehensive Haemophilia Treatment Centre (CHTC) and maintains the State Haemophilia Registry with data collected from the 4 regional

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hospitals stated above. The registry provides the baseline demographic information on our haemophiliacs as well as their clinical status. Consents were obtained from patients prior to any data entry into the registry.

Data were collected in English using a standardised form (available online and on paper), quality checked and reviewed. Demographic data collected included age at study, gender, ethnicity and which part of the state they came from. Clinical data pertaining to haemophilia comprised the types and severity of haemophilia, treatment options and outcome. Disease severity was defined by: (a) Severe – clotting factor level less than 1% of normal or below 1IU/dL; (b) Moderate – clotting factors 1-5% of normal or 1-5 IU/dL; and (c) Mild – clotting factor 5 to 40% of normal or 5-40 IU/dL. The most recent inhibitor titre in Bethesda Unit (BU) was recorded and used in statistical analysis.

Ordinal or categorical data was expressed as frequency and percentage. The relationship between inhibitor titres and treatment groups was analysed using Mann-Whitney test. The prevalence of inhibitor between on-demand (OD) and prophylaxis groups was analyzed using Fisher's Exact test. Statistical significance was determined as *p*-value less than 0.05.

## RESULTS

In the population of 2.8 million in Sarawak, a total of 107 patients with congenital bleeding disorders were identified – 79 (73.8%) HA and 17 (15.9%) HB. The others being non-haemophilia bleeding disorders, totaling 11 patients were Von Willebrand disease (4), Factor VII (3), FX (3) and FXI (1). Demographic and clinical characteristics of these individuals are shown in Table I and II. Their ages ranged from 6-month-old to 66-year-old. All except one were males. Severe haemophilia patients were noted in 45.6% (36/79) of HA and 64.7% (11/17) of HB. Almost half (44.3%) of our HA and 52.9% of our HB population had no identifiable family history of haemophilia. All patients included in our registry were Malaysians. The incidence of HA and HB in Sarawak was shown in Table III.

Two-thirds of our patients with severe HA were on prophylaxis [24/36 (66.7%)] and only one-third [4/11 (36.4%)] in severe HB. Out of all moderate HA patients, four (15.4%) were on prophylaxis due to bleeding events and target joints. The clinical profile of the latter subset is shown in Table IV. The one female with moderate HA presented with scalp and multiple intramuscular haematoma. She required 144 vials of Factor VIII concentrate (each vial 250IU) the year before she was switched to prophylaxis and subsequently enrolled into a clinical trial in 2015. Post study, she was provided free access to PEGylated recombinant anti-haemophilic factor (ADYNOVI). None of the moderate HB patients received prophylaxis.

Inhibitors developed in 9/79 (11.4%) of our HA population [3/79 (3.8%) high responders]. The median inhibitor titre was not significantly different between different treatment groups – OD versus prophylaxis (1.0BU versus 2.0BU; *z* statistic - 1.043, *p*-value 0.297, Mann-Whitney test). The prevalence of

HA patients with inhibitors in OD and prophylaxis treatment groups were 5.9% (3/51) and 21.4% (6/28), respectively. This was statistically not significant (*p*-value 0.061, Fisher's Exact test). None of our patients had inhibitory alloantibodies to FIX.

Immune tolerance induction (ITI) was initiated in three Sarawakian HA paediatric patients with inhibitors using a dose regimen of 100 IU/kg/day at Ampang Hospital – national haematology centre in Malaysia. The pre-ITI inhibitor titre levels were 6.2, 9.0 and 54.5 BU, respectively. Inhibitors were successfully removed in one patient who had pre-ITI inhibitor level of 9.0BU after 2.5 years of ITI treatment with absence of inhibitors to date. However, ITI treatment failed in two others and was stopped as they continued to have frequent bleeds (about 2 bleeds per month) and required OD bypassing agents. ITI treatment was tried in one adult HA patient but was unsuccessful in eradication of the inhibitor hence ITI never took off in Sarawak due to the high cost of treatment and reluctance of patients to comply with the protocol. The other five non-ITI patients with inhibitors were non-bleeders with pre-ITI inhibitor titre levels being 0.55BU, 0.6BU, 2.0BU, 2.2BU and 48.0BU, respectively.

Out of the nine patients who developed inhibitory alloantibodies to FVIII, three (including two patients who failed ITI earlier) fulfilled the criteria for compassionate use of emicizumab prophylaxis (3mg/kg every 2 weeks). All three had severe HA with a median latest inhibitor titre of 3.0BU, ranging from 1.6 to 20.0BU. Two had achieved 100% reduction in bleeding events after receiving emicizumab. One, who failed ITI earlier, had an episode of minor spontaneous bleed one day prior to the scheduled dose, which fully resolved after emicizumab administration without any bypassing agents. Two patients who required walking aids prior to commencement of emicizumab were able to ambulate independently post treatment. One of them failed ITI earlier. None had any adverse events. No thromboembolic events were identified.

Four and three HA patients were hepatitis B and C carriers, respectively. One patient with severe HB was a hepatitis B carrier. There was one case of human immunodeficiency virus (HIV) infection in a patient with HA. All except one received plasma-derived factor concentrate. Eleven patients (11.6%) who had recurrent target joint pain underwent radiosynovectomy. One mild HB patient, who was diagnosed at 5-month-old succumbed to traumatic intracranial bleeding at the age of 27 months.

## DISCUSSION/ CONCLUSION

CHTC registry which was started in January 2019 reported a prevalence (per 100,000 males) of 5.40 cases for all severities of HA, 2.46 cases for severe HA; 1.16 cases for all severities of HB, and 0.75 cases for severe HB. This data was based on the latest 2020 male population estimates reported by the Department of Statistics, Malaysia.<sup>5</sup> This figure was likely under-reported in contrast to the prevalence reported by a recent meta-analysis and Singapore data.<sup>1,3</sup> According to the Annual Global Survey 2016, a total of 1360 HA and 235 HB patients were reported in Malaysia, respectively.<sup>8</sup> This gives

Table I: Demographic data and inhibitor status of haemophilia A patients in Sarawak, Malaysia

	Mild (%)	Moderate (%)	Severe (%)	Total (%)		
Severity	17 (21.5)	26 (32.9)	36 (45.6)	79 (100)		
Age distribution						
< 10	3	3	8	14 (17.7)		
10-19	3	14	9	26 (32.9)		
20-29	7	3	9	19 (24.1)		
30-39	1	4	7	12 (15.2)		
40-49	0	2	2	4 (5.1)		
50-59	1	0	1	2 (2.5)		
≥ 60	2	0	0	2 (2.5)		
Ethnicity						
Chinese	4	7	6	17 (21.5)		
Malay	6	5	11	22 (27.9)		
Sarawak native	7	14	19	40 (50.6)		
Division					Male population 2019 ('000)	Prevalence (100,000males)
Kuching (HTC)	9	17	10	36 (45.6)	409.8	8.8
- Kuching	9	14(1female)	10	33 (41.8)	357.5	9.0
- Lundu	0	2	0	2 (2.5)	20.4	9.8
- Bau	0	1	0	1 (1.3)	31.9	3.1
Serian	0	0	3	3 (3.8)	53.5	5.6
Samarahan	1	3	1	5 (6.3)	50.5	9.9
Sri Aman	0	0	0	0 (0.0)	39.4	0.0
Betong	1	1	0	2 (2.5)	63.5	3.1
Sarikei	0	0	0	0 (0.0)	33.8	0.0
Mukah	0	0	0	0 (0.0)	28.8	0.0
Sibu (HTC)	0	3	9	12 (15.2)	164.5	7.3
Kapit	0	0	0	0 (0.0)	32.2	0.0
Bintulu (HTC)	2	0	9	11 (13.9)	145.1	7.6
Miri (HTC)	4	2	4	10 (12.7)	230.7	4.3
- Miri	4	2	1	7 (8.9)	190.6	3.7
- Marudi	0	0	3	3 (3.8)	40.1	7.5
Limbang	0	0	0	0 (0.0)	52.7	0.0
- Limbang	0	0	0	0 (0.0)	28.7	0.0
- Lawas	0	0	0	0 (0.0)	24.0	0.0
Inhibitors <sup>^</sup>						
High responders	0	0	3*	3 (3.8)		
Low responders	0	1	5	6 (7.6)		

<sup>^</sup> High responders - inhibitor above 5BU; low responders – inhibitor levels less than 5BU which did not increase with exposure to additional factor

\* Pre-ITI inhibitor titre was used

HTC: Haemophilia treatment centre

rise to a prevalence (per 100,000 males) of 8.34 cases for all severities of HA and 1.44 cases for all severities of HB in Malaysia. The proportions of our HA and HB in Sarawak were consistent with the finding reported by Duraisamy.<sup>4</sup>

From our data, the overall incidence of HA and HB was 1 in 11,500 and 1 in 46,000, respectively. This is considerably lower than the data reported by a study in which the incidence of HA and HB was reported to be approximately 1 in 5,000 and 1 in 30,000, respectively.<sup>9</sup> This might be attributed to the fact that patients with mild haemophilia who were non-bleeders and those who refused to come forward for medical diagnosis are not captured in this study. This is the first study representative of the whole Sarawak looking at the demographics of haemophilia. Having the knowledge of the prevalence of haemophilia patients in each population is important for us to deliver haemophilia care closer to the community. Based on this study, we think that haemophilia may be undiagnosed in isolated parts of Sarawak; hence more effort needs to be done to increase awareness and improve the diagnosis of haemophilia among the health care workers.

Several studies reported that about one-third of cases arise from a spontaneous mutation with no family history of haemophilia.<sup>3,10,11</sup> However, our data found 45.8% with absence of family history. We are uncertain whether it is because parents and patients are not forthcoming with a good 3-generation family history and testing or we have a higher frequency of spontaneous mutation which necessitates genetic mutation studies which are not readily available in Malaysia.

Our study shows that haemophilia A gene is present among the Sarawak indigenous groups which constitute almost half of the state population.<sup>5,6</sup> Haemophilia B gene although present in all the ethnic groups, seems to be disproportionately higher amongst the Malays. This might be due to the fact that about half [5/9 (55.6%)] of the Malay HB patients are blood-related. The issues confronting our haemophilia population and their caregivers are varied and complex. The key factors resulting in no treatment in two-fifth of the severe haemophilia patients include: (a) from patients or resistance of parents to intravenous injection; (b) cost and accessibility to factor replacement; and (c) logistic

Table II: Demographic data and inhibitor status of haemophilia B patients in Sarawak, Malaysia

	Mild (%)	Moderate (%)	Severe (%)	Total (%)		
Severity	3 (17.6)	3 (17.6)	11 (64.7)	17 (100)		
Age distribution						
< 10	1	1	4	6 (35.3)		
10-19	0	0	3	3 (17.6)		
20-29	1	0	1	2 (11.8)		
30-39	1	1	3	5 (29.4)		
40-49	0	1	0	1 (5.9)		
50-59	0	0	0	0 (0.0)		
≥ 60	0	0	0	0 (0.0)		
Ethnicity						
Chinese	0	0	1	1 (5.9)		
Malay	1	1	7	9 (52.9)		
Sarawak native	2	2	3	7 (41.2)		
					Male population 2019 ('000)	Prevalence (100,000males)
Division						
Kuching (HTC)	2	0	3	5 (29.4)	409.8	1.2
- Kuching	1	0	3	4 (23.5)	357.5	1.1
- Lundu	1	0	0	1 (5.9)	20.4	4.9
- Bau	0	0	0	0 (0.0)	31.9	0.0
Serian	0	0	1	1 (5.9)	53.5	1.9
Samarahan	0	1	2	3 (17.6)	50.5	5.9
Sri Aman	0	0	0	0 (0.0)	39.4	0.0
Betong	0	0	1	1 (5.9)	63.5	1.6
Sarikei	0	1	1	2 (11.8)	33.8	5.9
Mukah	0	0	0	0 (0.0)	28.8	0.0
Sibu (HTC)	1	1	3	5 (29.4)	164.5	3.0
Kapit	0	0	0	0 (0.0)	32.2	0.0
Bintulu (HTC)	0	0	0	0 (0.0)	145.1	0.0
Miri (HTC)	0	0	0	0 (0.0)	230.7	0.0
- Miri	0	0	0	0 (0.0)	190.6	0.0
- Marudi	0	0	0	0 (0.0)	40.1	0.0
Limbang	0	0	0	0 (0.0)	52.7	0.0
- Limbang	0	0	0	0 (0.0)	28.7	0.0
- Lawas	0	0	0	0 (0.0)	24.0	0.0
Inhibitors	0	0	0	0 (0.0)		

HTC: Haemophilia treatment centre

Table III: Incidence of haemophilia A and B in Sarawak, Malaysia from 2011 to 2019

Year	Live birth (male) in Sarawak <sup>6,7</sup>	Haemophilia A birth	Incidence	Haemophilia B birth	Incidence
2011	22,318	4	1 in 5578	0	0
2012	22,517	1	1 in 22,517	0	0
2013	20,415	3	1 in 6,805	0	0
2014	21,243	1	1 in 21,243	1	1 in 21,243
2015	20,551	2	1 in 10,276	0	0
2016	19,652	1	1 in 19,652	1	1 in 19,652
2017	19,547	1	1 in 19,547	1	1 in 19,547
2018	18,876	1	1 in 18,876	1	1 in 18,876
2019	18,876*	2	1 in 9,438	0	0
Total	183,995	16	1 in 11,500	4	1 in 46,000

\*Data on total number of male live birth in Sarawak in 2019 was unpublished at the time of manuscript writing, thus the data in 2018 was used.

Table IV: Clinical profile of moderate haemophilia A patients receiving prophylaxis in Sarawak, Malaysia

No.	Gender	Ethnicity	Age of first bleed	Type of bleed	Type of FVIII concentrate	Target joint(s)	Inhibitor status and level
1	Male	Native	At birth	Sub-aponeurotic haemorrhage	Plasma	Absent	Absent
2	Female	Malay	11 months old	Left parietal, scalp and intramuscular haematoma	Recombinant, PEGylated (ADYNOVI)	Absent	Absent
3 <sup>^</sup>	Male	Native	3 years old	Left ankle haemarthrosis and iliopsoas haematoma	Plasma	Left elbow, left knee	Absent
4	Male	Native	10 years old	Iliopsoas haematoma	Plasma	Absent	Absent

<sup>^</sup> This patient underwent left knee radiosynovectomy

difficulties owing to widely varied geographical characteristics. Therefore, treatment regimens in Sarawak is tailored to the Sarawakian haemophilia population where we try to provide haemophilia care accessibility to all district hospitals. Patient and family-centered haemophilia courses are organized to promote a holistic care, which may be facilitated through shared decision making (SDM), an intervention in which the patient and healthcare professionals collaborate in making healthcare decisions based on the best interest of patients. As Sarawak has limited transportation accessibility and this poses significant challenges to many patients, we try to encourage, engage and train parents and patients to self-administer the factor concentrates at home.

The inhibitor development rate for our HA population (11.4%) is slightly higher than the reported norms of 5 to 7%.<sup>12</sup> Due to the considerable cost, prophylaxis therapy with bypassing agents or bispecific antibody is not widely practised in Sarawak. Therefore, only three HA patients with inhibitors and significant bleeding events/ restricted mobility were treated with emicizumab. The relationship between inhibitor titres and treatment groups in our study was found to be statistically not significant, which might be attributable to the small sample size of our population who developed alloantibodies.

Genetic testing for HA and HB is available in Malaysia, adopting long range polymerase chain reaction (PCR) and DNA sequencing methods to detect genetic mutations in haemophilia. However, the take-up rate is not high due to cultural reasons by the local community. Awareness of haemophilia disease in Sarawak community needs to be ramped up in the future.

Limitations of this study include a small sample size and the results were generally descriptive. The data of haemophilia patients who deceased prior to the registry commencement date might be incomplete. Additional studies focusing on the quality-of-life of patients, socio-economic status, bleeding manifestations, complications and genetic mutations are warranted. It is also of utmost importance to study per capita usage of factor concentrate in addition to the related cost-utility and cost-effectiveness analysis.

In conclusion, this study outlines haemophilia landscape in Sarawak and thus can offer objective standards for planning ahead. Shared responsibility among haemophiliacs, families, care providers, public agencies, non-government organizations (NGOs) and insurance policy makers should be heightened so as to improve the care of our haemophilia population. An economic evaluation should be conducted to determine the best model of treatment for haemophilia patients in Sarawak.

#### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia with registered ID NMRR-19-2722-50668.

#### COMPETING INTERESTS

The authors declare that they have no competing interest.

#### FUNDING

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#### AUTHORS' CONTRIBUTIONS

ASOT was responsible for the study design, data collection, data analysis and manuscript writing. QYW, YYT, CHC and CTK participated in data collection and contributed to data analysis. GBO and LPC were involved in the study design and manuscript editing. All authors read and approved the final manuscript.

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#### REFERENCES

- Iorio A, Stonebraker JS, Chambost H, Makris M, Coffin D, Herr C, et al. Establishing the prevalence and prevalence at birth of hemophilia in males: a meta-analytic approach using national registries. *Ann Intern Med* 2019; 171: 540-6.
- Stonebraker JS, Bolton-Maggs PHB, Brooker M, Evatt B, Iorio A, Makris M, et al. The World Federation of Hemophilia Annual Global Survey 1999-2018. *Haemophilia* 2020; 00: 1-10.
- Ng HJ, Lam J, Koh PL, Ho L, Lim CY, Akhbar Ali M, et al. A comprehensive study of current haemophilia care and outcomes in Singapore. *Haemophilia* 2015; 21: 428-31.
- Duraisamy G. Congenital coagulation disorders in Malaysia. *Malaysian J Child Health* 1998; 10(1): 62-71.
- Pocket Stats Negeri Sarawak ST2 2020. Department of Statistics Malaysia [cited Sept 2020]. Available from: [https://www.dosm.gov.my/v1/index.php?r=column/cone&menu\\_id=MWtRSXZUNIV2ZzZVNhMMHB5M2N5QT09](https://www.dosm.gov.my/v1/index.php?r=column/cone&menu_id=MWtRSXZUNIV2ZzZVNhMMHB5M2N5QT09)
- Minority Rights Group International, World Directory of Minorities and Indigenous Peoples - Malaysia: Indigenous peoples and ethnic minorities in Sarawak. January 2018 [cited Aug 2020]. Available from: <https://www.refworld.org/docid/49749ce83a.html>
- Vital statistics Malaysia 2019, Department of Statistics, Malaysia. October 2019 [cited Sept 2020]. Available from: <https://newss.statistics.gov.my/newss-portalx/ep/epFreeDownloadContentSearch.seam?cid=104329>
- Report on the Annual Global Survey 2016. World Federation of Hemophilia. 2017 [cited Sept 2020]. Available from: <https://www1.wfn.org/publications/files/pdf-1690.pdf>
- Rodriguez V, Warad D. Pediatric coagulation disorders. *Pediatr Rev* 2016; 37: 279-91.
- Goodeve AC, Peake IR. The molecular basis of hemophilia A: genotype-phenotype relationships and inhibitor development. *Semin Thromb Hemost* 2003; 29(1): 23-30.
- Oldenburg J, Ananyeva NM, Saenko EL. Molecular basis of haemophilia A. *Haemophilia* 2004; 10(4): 133-9.
- Wight J, Parsley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia* 2003; 9: 418-35.

# Quality of life of leprosy patients in Sabah

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## ABSTRACT

**Objective:** To determine the Dermatology Life Quality Index (DLQI) among the subtypes of leprosy and to examine correlation with deformity and lepra reactions.

**Methods:** This was a cross-sectional study done at Dermatology Outpatient Clinic, Queen Elizabeth Hospital and two health clinics in Kota Kinabalu between 1st April 2019 and 30th November 2019. A standardised case report form was formulated to collect the demographic data and disease profile of the leprosy patients. The quality of life (QoL) was assessed using Dermatology Life Quality Index (DLQI) questionnaire.

**Results:** A total of 54 patients were included with a male to female ratio of 2.4:1 (38 males and 16 females). The mean DLQI score was 8.31±6.15. The difference between the mean DLQI scores among the leprosy subtypes was not significant. The most affected domain was symptoms and feeling followed by daily activities and leisure. Twenty-one patients (38.9%) had facial deformity and they were found to have significantly higher DLQI score. WHO grade 1 and 2 disability were observed in 37 patients (68.5%) with higher DLQI score compared to those without any disability. More than half of patients with MB leprosy (52.2%) developed lepra reactions but the difference of mean DLQI scores were not significant.

**Conclusions:** Leprosy-related disabilities may predispose patients to develop psychosocial problems which may have negative impact on QoL. Thus, periodic assessment of QoL should be incorporated into the management of leprosy patients

## INTRODUCTION

Leprosy, also known as Hansen's disease, is a chronic granulomatous infectious disease caused by Mycobacterium leprae. It can affect the skin, peripheral nerves, nasal mucosa and eyes. Leprosy, if left untreated, may lead to permanent skin and nerve damage, limb deformity and functional disability.<sup>1</sup> In Malaysia, although leprosy has been eliminated as a public health problem since 1994, new cases are still being reported annually, mainly in Sabah and Selangor.<sup>2</sup> Sabah is the second largest state in Malaysia with an area of 73,904 km<sup>2</sup> and a population of 3.9 million.<sup>3</sup> Among the 214 new cases detected in 2017, Sabah reported 72 cases (33.6%), followed by Selangor 34 cases (15.9%); 2.8% had WHO grade 2 disability at the time of diagnosis.<sup>4</sup> The number of leprosy cases was more frequent in suburban and rural areas with substantial numbers of vulnerable migrant patients.

The implementation of multidrug therapy throughout the world has been effective against leprosy and it shows good prospects for the management. Early case detection and adherence to therapy are both equally important. However, if the treatment is delayed, patients with leprosy may progress to develop nerve damage and disability. The leprosy-related disabilities may affect the physical and emotional wellbeing of patients eventually leading to psychosocial and economic burden with negative impact on the quality of life (QoL).

There is insufficient information on the QoL among leprosy patients in South East Asia. Hence this study is aimed to assess the QoL of different subtypes of leprosy and its correlation with deformity and lepra reactions.

## MATERIALS AND METHODS

This was a cross-sectional study done at Dermatology Outpatient Clinic of the Queen Elizabeth Hospital (QEH) and two health clinics in Kota Kinabalu (Menggatal and Putatan Health Clinic) between 1st April 2019 and 30th November 2019. All patients with leprosy were requested to participate in this study. The QEH is the referral centre for the management of leprosy with complications for Sabah and Labuan.

The inclusion criteria were patients with leprosy age 12 years and above who had given consent. Diagnosis was made based on clinical examination and slit skin smear, as well as histopathological examination in selected cases. The exclusion criteria were patients with the aged below 12 years and those with other active dermatoses.

A standardised case report form was formulated to collect the demographic data and disease profile of the participants. The presence of lepra reaction, the World Health Organization (WHO) disability grading and facial deformity were recorded. WHO grade 1 disability (G1D) includes the presence of anesthesia of the hands and feet or presence of eye problems due to leprosy, but not severely affected with visual acuity of at least 6/60 or able to count fingers at 6 metres. WHO grade 2 disability (G2D) is defined as visible deformity at the hands and feet or severe visual impairment.<sup>5</sup> Facial deformity includes saddle nose, external ear deformity, madarosis and eye deformity such as lagophthalmos.

The QoL was assessed using Dermatology Life Quality Index (DLQI) questionnaire which was created by Professor Finlay and permission to use it was granted.<sup>6</sup> DLQI questionnaire is a user-friendly and validated tool commonly used which demonstrated satisfactory validity and reliability in assessing the QoL of patients. It is designed for use in children and

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adults comprising of 10 multiple choice questions which is usually completed in one to two minutes. The domains assessed by the DLQI questionnaire are physical symptoms and feelings (question 1 and 2), daily activities (question 3 and 4), leisure (question 5 and 6), school or work (question 7), interpersonal relationship (question 8 and 9) and treatment (question 10). The DLQI score is calculated by summing the score of each question resulting in a maximum score of 30 and a minimum of 0. The higher the score, the more impaired the QoL. The interpretation of DLQI score is: 0-1=no effect on patient's life, 2-5=small effect on the life of patients, 6-10=moderate, 11-20=very large and 21-30=extremely large.

Data collected were analysed using Statistical Package for the Social Sciences (SPSS) version 24. Categorical data were analysed using Chi-square test or Fischer Exact test and presented as number (percentage). Continuous data were analysed using t-test and Mann-Whitney test. For more than 3 groups of continuous data, the data were analysed using One-Way ANOVA or Kruskal Wallis test. The analysed data were presented as mean  $\pm$  standard deviation or median and interquartile range. Level of significance was set at  $p < 0.05$ .

## RESULTS

A total of 54 patients participated in this study with 38 (70.4%) males and 16 (29.6%) females. There were 37 (68.5%) Malaysians and 17 (31.5%) foreigners. Ten patients were recruited from the health clinics. The mean age at presentation was  $37.96 \pm 16.05$  years. A total of 18 patients (33.3%) had history of contact in the family. The mean bacteriological index (BI) and morphological index (MI) at presentation were  $2.78 \pm 1.66$  and  $1.51 \pm 2.31$  respectively. Table I shows the demographic characteristics of leprosy patients. Of the 54 patients, 46 (85.2%) had multibacillary (MB) leprosy and 8 (14.8%) had paucibacillary (PB) leprosy. Half of the MB leprosy (50%) were borderline lepromatous and 7 out of 8 PB leprosy (87.5%) were borderline tuberculoid. Table II shows the clinical characteristics of leprosy patients.

The mean time interval between symptoms onset and diagnosis of leprosy was  $20.62 \pm 22.57$  months. The mean DLQI score was  $8.31 \pm 6.15$ , ranging between 0 and 23. There was no significant difference between the mean DLQI scores of MB and PB leprosy patients ( $8.57 \pm 6.27$  vs.  $6.88 \pm 5.51$ ,  $p = 0.478$ ). The difference between the mean DLQI scores among leprosy subtypes was also not statistically significant. Four out of 8 patients (50%) with PB had moderate to extremely large impairment in QoL. Among patients with MB leprosy, the QoL of as many as 30 patients (65.2%) was moderate to extremely largely impaired. The most affected domain was symptoms & feelings followed by daily activities and leisure in both groups. Table III shows the association between DLQI scores and the types of leprosy.

Twenty-one patients (38.9%) had facial deformity. Two-third of them were diagnosed with lepromatous leprosy while the others having borderline lepromatous leprosy. Those with facial deformity were found to have significantly higher DLQI score compared to those without facial deformity

( $10.57 \pm 6.01$  vs  $6.88 \pm 5.87$ ,  $p = 0.030$ ). WHO grade 1 and 2 disability were observed in 37 patients (68.5%). They had higher DLQI scores compared to those without any disability [median (IQR) 9.0 (10) vs. 3.0 (9),  $p = 0.007$ ]. Table IV shows the association between DLQI score and facial deformity & WHO disability grading respectively. Significantly more patients with WHO disability (both grade 1 and 2) reported their QoL to be moderate to extremely largely affected [75.6% (28 of 37 patients vs 35.3% (6 of 17 patients),  $p = 0.013$ ].

More than half of the patients with MB leprosy (24 out of 46, 52.2%) developed lepra reactions, with 7 patients (15.2%) and 17 patients (37.0%) having type 1 and type 2 reaction respectively. Patients with type 2 lepra reaction were found to have significantly higher BI compared to patients with type 1 lepra reaction and patients without any reaction [median (IQR) 4.20 (2.09) vs. 2.55 (1.64) vs. 2.50 (3.83),  $p = 0.030$ ]. However, the difference between the mean DLQI scores among patients with and without lepra reaction was not statistically significant.

## DISCUSSION

Leprosy, particularly multibacillary leprosy, may be associated with facial deformity, neuropathic pain and physical disability.<sup>7</sup> Facial deformity can have significant psychosocial implications, including altered body image, poor self-esteem and social avoidance, resulting in impaired social interaction and negative self-perception. Leprosy causes damage that goes beyond the discomfort related to physical impairment; eventually these patients will suffer from social stigma, discrimination and low QoL.<sup>8</sup>

The QoL among patients with leprosy is moderately impaired as evidenced by the mean DLQI score of  $8.31 \pm 6.15$ . Our scores are similar to a study in India where the reported mean score was  $8.48 \pm 5.48$ .<sup>9</sup> However our mean score is slightly lower than that of the leprosy patients in Egypt (11.58) and Brazil (10.23).<sup>10</sup> Interestingly our lepromatous leprosy (LL) patients had much lower DLQI score compared to the LL patients in China (18.78).<sup>11</sup> This may be due to the lower proportion of WHO grade 2 disability among the LL patients in our cohort. Majority of the patients with PB leprosy did not have QoL impairment in Brazil,<sup>12</sup> in contrast to our study where half of PB leprosy patients had moderate to extremely large impairment in QoL. This could be due to the presence of nerve damage and lepra reactions among our PB patients.

The new case detection rate of leprosy in Malaysia was 0.57 per 100,000 however it was 1.6 per 100,000 in Sabah which was higher than the national indicator ( $< 1$  per 100,000).<sup>13</sup> The higher burden of leprosy in Sabah compared to other states in Malaysia might be due to unique socioeconomical situation of Sabah and its less developed topography. Nearly a third of the population in Sabah comprises of non-Malaysians.<sup>13</sup> The geographical location of Sabah in South East Asia with its extensive and porous borders makes it accessible from neighbouring countries thus resulting in higher burden of leprosy.<sup>14</sup> In addition, Sabah has the highest poverty rate among all the states in Malaysia.<sup>15</sup> Late recognition of leprosy is often associated with inadequate knowledge about the disease and lack of awareness not only

Table I: Demographic characteristics of leprosy patients, n= 54

Variables	n (%)
<b>Gender</b>	
Male	38 (70.4)
Female	16 (29.6)
<b>Marital status</b>	
Married	32 (59.3)
Single	19 (35.2)
Divorced	3 (5.6)
<b>Nationality</b>	
Malaysian	37 (68.5)
Non-Malaysian	17 (31.5)
<b>Family History</b>	
Present	18 (33.3)
Absent	36 (66.7)

Table II: Clinical characteristics of 54 leprosy patients

Variables	n (%)
<b>WHO Classification</b>	
Multibacillary (MB)	46 (85.2)
Paucibacillary (PB)	8 (14.8)
<b>Ridley-Jopling Classification</b>	
Lepromatous (LL)	20 (37.0)
Borderline Lepromatous (BL)	23 (42.6)
Midborderline (BB)	3 (5.6)
Borderline Tuberculoid (BT)	7 (13.0)
Tuberculoid (TT)	1 (1.9)
<b>Facial deformity</b>	
Present	21 (38.9)
Absent	33 (61.1)
<b>WHO Disability Grading</b>	
Grade 0	17 (31.5)
Grade 1	17 (31.5)
Grade 2	20 (37.0)
<b>Lepra reactions</b>	
No reaction	29 (53.7)
Type 1 reaction	8 (14.8)
Type 2 reaction	17 (31.5)

Table III : Association between types &amp; subtypes of leprosy and DLQI score

WHO Classification	DLQI score Mean (SD)
Multibacillary (MB)	8.57 (6.27)
Paucibacillary (PB)	6.88 (5.51)
Ridley-Jopling Classification	DLQI score Median (IQR)
Lepromatous (LL)	6.5 (10.0)
Borderline Lepromatous (BL)	8.0 (10.0)
Midborderline (BB)	13.0 (-)
Borderline Tuberculoid (BT)	5.0 (11.0)
Tuberculoid (TT)	-

Table IV : Association between DLQI score and facial deformity &amp; WHO disability grading

Facial Deformity	DLQI score Mean (SD)
Present	10.57 (6.01)
Absent	6.88 (5.87)
WHO Disability Grading	DLQI score Median (IQR)
Grade 1 & 2	9.0 (10)
Grade 0	3.0 (9)



among patients but also health-care workers and community members. This lack of knowledge on leprosy and persistence of leprosy-related stigma may reflect a lack of dissemination of correct information in the community.<sup>16</sup> G2D were observed in 20 (37%) patients and this is much higher than previously reported, 8.6% in India, 17.1 % in Brazil and 20.66% in Egypt.<sup>17-19</sup> This could be due to the lack of education and delay in diagnosis and treatment, as shown by the prolonged time interval between the onset of symptoms and diagnosis in our study. Misdiagnosis of leprosy as other similar cutaneous diseases by primary care personnel could be another contributing factor to the delay in diagnosis leading to G2D. This may be due to the limited experience and poor confidence level among the primary care doctors.<sup>20</sup> A study done in a tertiary referral centre in Kuala Lumpur, the capital of Malaysia reported misdiagnosis in 44.4% of the cases in primary care setting.<sup>21</sup> G2D can also develop after patients was diagnosed, while on or after completion of treatment due to reactions.<sup>22</sup>

Patients with MB leprosy experienced more impairment in QoL compared to patients with chronic skin diseases, such as acne vulgaris (mean DLQI 4.1), chronic urticaria (mean DLQI 4.8), vitiligo (mean DLQI 5.2), psoriasis (mean DLQI 5.8) and atopic dermatitis (mean DLQI 6.1).<sup>23-26</sup> The QoL impairment was significantly larger among leprosy patients with facial deformity and grade 1 & 2 disabilities. Govindharaj, P et al from India using WHO Quality of Life questionnaire (WHOQOL-BREF) reported significant differences in all the domains (physical health, psychosocial health, social relationship and environment) among leprosy patients with or without disability.<sup>27</sup>

A study conducted by Santos et al. in Brazil also using the WHOQOL-BREF questionnaire showed that leprosy patients with functional activity limitations (FALs) were associated with low QoL. They tend to have more severe impairment in the physical and environmental domains. The FALs which was determined by Screening of Activity Limitation and Safety Awareness Scale (SALSA) were found to be associated with the presence of disability. The SALSA score was higher in MB leprosy indicating lower QoL.<sup>28</sup> However we found no significant difference in the DLQI score among our MB patients compared to PB patients probably due to the small number of patients.

Leprosy patients had moderate impairment in their QoL, with larger effect among patients with lepra reactions, especially type 2 reaction, also known as erythema nodosum leprosum (ENL). A previous study done in Malaysia found MB leprosy patients with ENL had a mean DLQI score of 9.1 vs. 6.2 in those who did not suffer from ENL.<sup>29</sup> Lepra reactions are immunological mediated inflammation that may occur before, during or after the completion of multidrug therapy (MDT). Type 2 reactions or ENL is a serious debilitating immunological complication of lepromatous leprosy (LL) and borderline lepromatous (BL) leprosy. It may manifest as tender erythematous subcutaneous nodules with the presence of systemic illness. These reactions are accountable for most of the neuropathy and permanent disability.<sup>30</sup> This leads to decrease in daily activities and work & school as reported in our study. Absenteeism may lead to decreased work efficiency

and financial loss as a result of low productivity, which in turn negatively impact the performance of the company and eventually leading to job insecurity.<sup>31</sup> Apart from that, patients with ENL often experience problems in body image, social isolation and also have feelings of stigma and embarrassment regarding their appearance. As a result of these problems, patients with leprosy are associated with QoL impairment and higher risk of psychiatric disorders such as depression and anxiety disorder. Majority suffered from moderate to severe depression and even had suicidal ideation after developing deformity.<sup>32,33</sup>

QoL measurement has been regarded as an important outcome in clinical management and patient care especially in patients with skin diseases.<sup>34</sup> Early recognition of skin diseases and appropriate treatment will reduce complications and physical disabilities or deformities, eventually minimize the impairment of QoL. Serial measurement of DLQI score would be able to detect small but meaningful changes over time; this may elucidate disease progression and determine therapeutic options.<sup>34</sup>

#### LIMITATIONS OF STUDY

The study was limited because of its cross-sectional design. It would be beneficial to do a prospective study to assess the QoL upon the diagnosis, changes over the course of the treatment or after undergoing rehabilitation programme. We did not include leonine facies and pigmentation symptoms related to MDT as part of the criteria for facial deformity. Majority of the patients (85%) recruited from our Dermatology Outpatient Clinic were referred from primary care clinics for complications related to leprosy.

#### CONCLUSION

The QoL of the leprosy patients in Sabah was moderately impaired. There were significantly more patients with WHO grade 1 and 2 disability or facial deformity experiencing moderate to severe impairment in the QoL. The impairment in QoL was worse than other chronic skin diseases, such as acne, chronic urticaria, vitiligo, psoriasis and atopic dermatitis. Leprosy-related disabilities may predispose patients to develop psychosocial problems which may have negative impact on QoL. Thus, the management of leprosy patients should incorporate periodic assessment of quality of life in order to provide guidance to rehabilitation programme to achieve well-being.

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## REFERENCES

1. Alemu BW, Naafs B. Position statement: Leprosy: Diagnosis, treatment and follow-up. *J Eur Acad Dermatol Venereol* 2019; 33: 1205-13
2. Yap FB. Pediatric leprosy in Sarawak, Malaysia. *Pediatr Infect Dis J* 2009; 41: 933-4
3. Department of Statistic Malaysia Official Portal. [cited February 14th 2020]. Available from: <https://www.dosm.gov.my/v1/index.php>
4. Perutusan Menteri Kesihatan Malaysia Sempena Hari Kusta Sedunia Tahun 2018. [cited February 14th 2020]. Available from: <http://www.moh.gov.my/index.php>
5. Brandsma JW, Van Brakel WH. WHO disability grading: operational definitions. *Lepr Rev* 2003; 74: 366-73
6. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; 19: 210-6.
7. Santos VS, Santana JCV, Castro FDN, Oliveira LS, Santan JCV, Feitosa VLC, et al. Pain and quality of life in leprosy patients in an endemic area of Northeast Brazil: a cross-sectional study. *Infectious Diseases of Poverty* 2016; 5: 18.
8. Savassi LC, Bogutchi TR, Lima AC, Modena CM. Quality of life of leprosy sequelae patients living in a former leprosarium under home care: univariate analysis. *Qual Life Res* 2014; 23: 1345-51.
9. Das NK, De A, Naskar B, Sil A, Das S, Sarda A, et al. A quality of life study of patients with leprosy attending the Dermatology OPD of a tertiary care center of Eastern India. *Indian J Dermatol* 2020; 65: 42-6.
10. Budel AR, Raymundo AR, Costa CF, Gerhardt C, Pedri LE. Profile of patients affected by Hansen's disease seen at Outpatient Clinic of Dermatology at Hospital Evangélico de Curitiba. *An Bras Dermatol* 2011; 86: 942-6.
11. An JG, Ma JH, Xiao SX, Xiao SB, Yang F. Quality of life in patients with lepromatous leprosy in China. *J Eur Acad Dermatol Venereol* 2010; 24: 827-32.
12. Bottene IM, Reis VM. Quality of life of patients with paucibacillary leprosy. *An Bras Dermatol* 2012; 87: 408-11.
13. Department of Statistics Malaysia. [cited October 24, 2020]. Available from <https://newss.statistics.gov.my/newssportalx/ep/>
14. Rahman SA, Abdullah K. The securitization of Sabah's Threat Challenges. *Int J of Arts Humanities and Social Sciences* 2019; 4(2): 28-38
15. Sabah ranks Malaysia's poorest state, again. [cited October 24, 2020]. Available from <https://www.nst.com.my/news/nation/2020/09/625711/sabah-ranks-malaysias-poorest-state-again>
16. van't Noordende AT, Korfage IJ, Lisam S, Arif MA, Kumar A, van Brakel WH. The role of perceptions and knowledge of leprosy in the elimination of leprosy: A baseline study in Fatehpur district, northern India. *PLoS Negl Trop Dis* 2019; 13: e0007302.
17. Sarkar J, Dasgupta A, Dutt D. Disability among new leprosy patients, an issue of concern: An institution based study in endemic district for leprosy in the state of West Bengal, India. *Indian J Dermatol Venereol Leprol* 2012; 78: 328-34.
18. Raposo MT, Reis MC, Caminha AVdQ, Heukelbach J, Parker LA, Pastor-Valero M, et al. Grade 2 disabilities in leprosy patients from Brazil: Need for follow-up after completion of multidrug therapy. *PLoS Negl Trop Dis* 2018; 12: e0006645.
19. El-Refeal AMA, Daifalla AEM, Kasem SM, Bayomy HE. Health related quality of life in Egyptian leprosy patients using DLQI and WHOQOL-BREF questionnaires. *J Clin Exp Dermatol Res* 2018; 9: 475.
20. Yap FB, Kiung ST. Knowledge and confidence in the diagnosis and management of leprosy among Family Medicine Specialists in Malaysia. *Journal of Dermatology & Dermatologic Surgery* 2016; 20: 46-50.
21. Kwan ZL, Pailoor J, Tan LL, Robinsin S, Wong SM, Ismail R. Leprosy – An imported disease. *Lepr Rev* 2014; 85: 170-6.
22. Rathod SP, Sagati A, Chowdhary P. Disabilities in leprosy: an open, retrospective analyses of institutional records. *An Bras Dermatol* 2020; 95: 52-6
23. Yap FB. The impact of acne vulgaris on the quality of life in Sarawak, Malaysia. *J Saudi Soc Dermatol Surg* 2012; 16: 57-60.
24. Itakura A, Tani Y, Kaneko N, Hide M. Impact of chronic urticaria on quality of life and work in Japan: Results of a real world study. *J Dermatol* 2018; 45: 963-70.
25. Morales-Sanchez MA, Vargas-Salinas M, Peralta-Pedrero ML, Olguin-Garcia MG, Jurado-Santa Cruz F. Impact of vitiligo on quality of life. *Actas Dermosifiliogr* 2017; 108:637-42.
26. Yap FB. Psoriasis among Sarawakian natives in a tertiary skin centre in Sarawak. *Australas J Dermatol* 2010; 51: 210-1.
27. Govindharaj P, Srinivasan S, Darlong J. Quality of life of person affected by leprosy in an endemic district, West Bengal, India. *Indian J Dermatol* 2018; 63: 459-64.
28. Santos VS, Oliveira LS, Castro FDN, Gois-Santos VT, Lemos LMD, Ribeiro MCO et al. Functional activity limitation and quality of life of leprosy cases in an endemic area in northeastern Brazil. *PLoS Negl Trop Dis* 2015; 9: e0003900.
29. Yap FB, Kiung ST, Yap JB. Quality of life in patients with erythema nodosum leprosum in Kuala Lumpur, Malaysia. *Indian Dermatol Online J* 2016; 7: 255-8.
30. Pandhi D, Chhabra N. New insights in the pathogenesis of type 1 and type 2 lepra reaction. *Indian J Dermatol Venereol Leprol* 2013; 79: 739-49.
31. Wee LH, Yeap LLL, Chan CMH, Wong JE, Jamil NA, Nantha YS, et al. Antecedent factors predicting absenteeism and presenteeism in urban area in Malaysia. *BMC Public Health* 2019; 19: 540.
32. Tsutsumi A, Izutsu T, Islam AM, Maksuda AN, Kato H, Wakai S. The quality of life, mental health, and perceived stigma of leprosy patients in Bangladesh. *Soc Sci Med* 2007; 64: 2443-53.
33. Gurvider PS. Psychosocial aspects of Hansen's disease (leprosy). *Indian Dermatol Online J* 2012; 3: 166-70.
34. Mazzotti E, Picardi A, Sampogna F, Sera F, Pasquini P, Abeni D. Sensitivity of the Dermatology Life Quality Index to clinical change in patients with psoriasis. *Br J Dermatol* 2003; 149: 318-22.

# Intention to seek professional help for depression and its associated factors among elderly patients in Tenkera Health Clinic, Melaka, Malaysia

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## ABSTRACT

**Background:** Prevalence of mental disorders such as depression in the elderly is rising with the ageing population. This study is aimed to determine the prevalence of depression, their intention to seek help and the factors associated to seek professional help among elderly patients in a primary care clinic.

**Methods:** This was a cross-sectional with systematic sampling conducted from June to December 2019 in Tengker Health Clinic (THC). Patient Health Questionnaire-9 (PHQ-9), socioeconomic data and a dichotomous yes-no response for intention to seek help was collected from 273 elderly patients attending the outpatient clinic.

**Results:** The prevalence of elderly depression at THC was 10.3% and the prevalence of intention to seek professional help for depression among elderly patients at Tengker Health Clinic was 27.5%. Factors that were associated with intention to seek professional help for depression were prior experience of seeking professional help, adjusted OR 3.45[95%CI (1.41-8.48)] and education level of the respondents- secondary education, adjusted OR 3.10 [95%CI (1.01-9.53)] comparing with no formal education; tertiary education, adjusted OR 4.66 [95%CI (1.08-20.04)] comparing with no formal education.

**Conclusion:** The prevalence of elderly depression was high while the prevalence of intention to seek professional help for depression in the sample population was low. Primary care physicians play a vital role in identifying elderly patients with low education level for screening and treatment as well as promoting awareness and breaking down barriers and stigma towards mental illness.

## KEYWORDS:

*Intention, help-seeking, depression, elderly, Malaysia*

## INTRODUCTION

Elderly population as defined by World Health Organization (WHO) and in Malaysia is 60 years old and above.<sup>1</sup> The Malaysia population is rapidly ageing in tandem with most of the developed nations, at 5% of the elderly population in 2010 and projected to reach 14.5% (6 million) in 2040.<sup>2</sup> In 2018, the total population of elderly in Malaysia was 6.2% at 2.3 million, and the life expectancy was at 74.7 years old.<sup>2</sup>

According to National Health and Morbidity Survey (NHMS) 2018, 5.3% elderly screened had depression, while 8% tested had dementia.<sup>3</sup> Various similar prevalence study in Malaysia previously described elderly depression between 7.8% to 18%.<sup>4</sup> Prevalence of elderly depression in other Asian countries based on Geriatric Depression Scale-15 (GDS-15) ranged from 17.2% in Vietnam to 33.8% in Indonesia.<sup>5</sup> Globally, depression disorders are ranked as the single most significant contributor to non-fatal health loss at 7.5% of all Years Lived with Disability (YLD).<sup>6</sup> In Malaysia, depression is more prevalent among females, those who are unmarried, those with no formal education, those with family income less than RM 300 per month, and those living urban areas.<sup>7</sup>

Despite the high prevalence, the rate of help-seeking for patients with depression is often low. Various studies showed rate of seeking help for depression ranged from 17.4% to 30.6%.<sup>8-11</sup> Help-seeking is a dynamic process, based on health belief model by Becker et al., the perceived susceptibility and seriousness of depression, demographics variables, perceived threats, perceived benefits, and barriers all contributes to the final decision to seek treatment.<sup>12</sup> Known factors associated with intention to seek professional help were higher education, socioeconomic status, engagement in valued activities, religion or spiritual engagement and good emotional regulation.<sup>13</sup> Elderly patients were significantly associated with negative attitudes towards seeking help.<sup>14</sup>

Stigma associated with seeking psychological help, the lack of trust in helping professionals, their services and lack of knowledge about the availability of services also further discourage elderly patients with depression to approach health care providers.<sup>14</sup> Most of the studies done in Malaysia for depression addressed the prevalence and causal effects of depression. Here the data on the rate of intention to seek help is scarce and thus a study is needed.

This study is aimed to determine the prevalence of depression, their intention to seek help and the associated factors associated with intention to seek professional help for depression among elderly patients in a primary care clinic.

## MATERIALS AND METHODS

This is a cross-sectional study conducted from 1st June 2019 to 31st December 2019 in a government health clinic, Tengker Health Clinic (THC) in the district of Melaka

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Tengah in Melaka state in Malaysia. The clinic is located in the semi-urban area of the district and had about 10,000 to 12,000 patient visits per month, and almost 50% of the visits were patients over 60 years old.

A questionnaire was used to determine the prevalence of depression and their intention to seek help. This was divided into three sections. The first section was the sociodemographic data, the second was Patient Health Questionnaire-9 (PHQ-9) questionnaire and the third section being help seeking behaviour. Ethical approval was obtained from relevant regulatory bodies highlighted in the ethical approval section. Depression was measured using the PHQ-9 and was prepared in three languages (English, Malay, and Mandarin). The cut-off value for the diagnosis of depression was  $\geq 10$ . PHQ-9 is a self-report measure, consisting of nine questions based on the nine DSM-IV criteria for major depression. Its validity as a brief depression severity measure was first published in 2001.<sup>15</sup> The Malay version of PHQ-9 was found to be a valid and reliable case-finding instrument for depression in Malaysian primary care clinic.<sup>16</sup> The sensitivity of the PHQ-9 at the cut-off value of 10 and above was 87%, and the specificity was 82%.<sup>16</sup>

The second and third section of the questionnaire used was in two languages, namely English and translated to Malay by the authors. Sociodemographic data were also measured with twelve questions including age, gender, race, education level, marital status, working status, income levels, living arrangements, co-morbid medical illness, co-morbid psychiatric illness and physical limitations were collected. The items were adapted from previously used health services research survey on elderly population in Malaysia.<sup>3</sup>

The last section measured the help seeking of the participants. Three items were used in the section, which were adapted from a large population study by Chin et al. Question 1 explored the prior experience of professional help-seeking among respondents. Respondents were asked: "Do you have any prior experience in discussing your mental health or emotional problem with any of the following?" Response options included: friends and family; religious organisation, traditional medicine practitioner; religious healer; counsellor; general practitioner; psychiatrist; psychologist; social worker; telephone hotline and 'no help-seeking'. Respondents could choose more than one option. Past professional help-seeking was defined as a respondent's self-report of having received consultation from a member of a professional mental healthcare worker in the past and was identified by a checked response to general practitioner, psychiatrist, psychologist or counsellor options. Question 2 explored their intention to seek professional help for depression. Respondents were asked: "If you were to be depressed in the next six months' time, which of the following would you prefer to seek help from?" Response options included: friends and family, religious organisation, traditional medicine practitioner, religious healer, counsellor, general practitioner, psychiatrist, psychologist, social worker, telephone hotline and 'no help-seeking'. Respondents could choose more than one option. Intention to seek professional help for depression was defined as the participant's self-reported intention to consult a healthcare professional, which were general practitioner, psychiatrist, psychologist or counsellor, in the next six months if he or she were depressed.

Question 3 explored the preferred point of first contact of mental health care among the participants. Respondents were asked: "Given a choice, which healthcare professional would you approach initially for your depressed symptoms?" Response options included general practitioner, psychiatrist, psychologist, counsellor or social worker. Respondents were asked to choose only one option. Respondents who do not wish to seek professional help can opt to abstain from answering the final question.

Face validity and content validity of the questionnaire were carried out before the actual data collection. A senior consultant in Family Medicine and a senior consultant psychiatrist reviewed the lists of items asked in the questionnaire, and their expert recommendations were obtained and incorporated. Ten sets of questionnaires were distributed to elderly patients randomly, and their understanding of the questionnaire was assessed. Seven out of ten elderly patients were unable to answer the questionnaire due to poor literacy and needed to be fully assisted by the field researcher.

During the study period, patients aged 60 and above were recruited, using systematic sampling. Every third patient registered at the counter who was more than 60 years was selected for the study. Sampling of patients was done every Thursday during the duration of the study. Those patients who visited the emergency units, had severe mental disorder, severe cognitive impairment, and mental retardation or refused to participate were excluded. The cognitive impairment (dementia) and mental health pre-morbid of patients were obtained from the outpatient card and through direct questioning of the respondents by the field researcher at the registration counter. Respondents who were on treatment for depression were excluded from the study.

The questionnaires were given to participants once written consents were obtained according to the approval by relevant regulatory bodies and administered face to face by the field researcher at a designated room while waiting for the doctor's consultation. Chinese patients requiring assistance with questionnaire were helped by field researcher using standard verbal translations of the second and third sections of the questionnaire. After completion of the questionnaire, participants with a PHQ-9 score of 10 or more were referred to the family medicine specialist for further confirmation of the diagnosis of depression and management. Cases with moderate to severe depression with or without suicidal ideation were referred to the psychiatrist at Melaka General Hospital through both written and oral referral for expert care.

The sample size was calculated based on Kish L formula.<sup>17</sup> We estimated a sample size of 273 patients considering an estimated prevalence of elderly depression of 13.9%<sup>4</sup> and rate of intention to seek professional help for depression, 24.3%.<sup>8</sup> We set an absolute precision of 5% and a confidence interval of 95%. We did not account for non-responders because recruitment would continue until the desired sample size was reached.

Data collected was analysed using the Statistical Package for Social Sciences (SPSS), version 22. For descriptive analysis, the mean was used to describe the age of the participants.

**Table I: Social Demographic characteristics (N=273)**

Variables		N	(%)
Age (mean, SD)		(69.9, 6.9)	
Gender	Male	130	47.6
	Female	143	52.6
Ethnicity	Malay	86	31.5
	Chinese	174	63.7
	Indian	11	4.0
Marital status	Married	188	68.9
	Single/Divorced	85	31.1
Education level	No formal education	38	13.9
	Primary	104	38.1
	Secondary	110	40.3
	Tertiary	21	7.7
Employment	Employed	60	22.0
	Retired/Non employed	213	78.0
Income (RM)	Less than 1000	141	51.6
	1000- 4000	117	42.9
	Above 4000	15	5.5
Living arrangement	Staying alone	31	11.4
	With family	242	88.6

**Table II: Participants' help seeking preferences (N=273)**

Help seeking option †	Past help seeking preferences		Help seeking preferences if depressed in the next six months	
	Frequency	%	Frequency	%
Friends and family	152	55.7	192	70.3
Religious organization	129	47.3	126	46.2
General practitioner	22	8.1	72	26.4
'No help-seeking'	63	23.1	44	16.1
Counsellor	1	0.4	11	4.0
Psychiatrist	1	0.4	11	4.0
Social worker	3	1.1	5	1.8
Religious healer	11	4.0	3	1.1
Traditional medicine practitioner	7	2.6	2	0.7
Psychologist	0	0.0	1	0.4
Telephone hotline	0	0.0	1	0.4

†Participants could choose more than one option during the survey.

**Table III: Participants' preferred first point of contact with health care worker (N=273)**

Help-seeking option	%, (n)
General practitioner	49 (134)
Psychiatrist	21 (58)
Counsellor	17 (45)
Social worker	9 (25)
Psychologist	4 (11)

Percentages and proportions were used to describe participants' demographic data, the prevalence of depression among the respondents and the prevalence of intention to seek professional help for depression among the respondents. Simple logistic regression was performed for bivariate analysis, and subsequently, the independent factor associated with the intention to seek professional help for depression among the elderly was identified with multiple logistic regression. The independent variables are depression, prior experience of seeking professional help, education level, living arrangement, gender, marital status, employment status, income level, psychiatric premorbid, medical illness and physical limitation. The cut-off value of p to be included in multiple regression was 0.25. Significant p was set at <0.05. Model fit was tested with Hosmer and Lemeshow

statistics, using the criteria of a non-significant  $\chi^2$  goodness of fit at  $p>0.05$  to indicate an adequate model fit.

**RESULTS**

The mean age of patients was 70 years (SD of 6.9) (Table I). Majority of the respondents were Chinese (63.7%) followed by Malays (31.5%) and most were married and with living partners. Majority of the participants had low education level: defined as having no formal education (13.9%) and primary education (38.1%). Socio-economically 78.0% of them were not employed, and most of them had a monthly income of less than RM1000, whereas, 11.4% of the participants were staying alone. More than 90% of the participants had co-morbid medical/surgical problems, with

**Table IV: The association between intention to seek professional help for depression with participants' sociodemographic, premorbid conditions and depression status (N=273)**

Variable	Intention to seek help n (%)	No intention to seek help n (%)	Crude OR (95% CI)	P value
<b>Depression</b>				
Yes	9 (32.1)	19 (67.9)	1.29(0.55-2.98)	0.56
No	66 (26.9)	179 (73.1)	1	
<b>Prior experience of seeking professional help</b>				
Yes	14 (56.0)	11 (44.0)	3.90(1.68-9.05) †	0.01
No	61 (24.6)	187 (75.4)	1	
<b>Education</b>				
No formal education	5 (13.2)	33 (86.8)	1	
Primary education	22 (21.2)	82 (78.8)	1.77(0.62-5.07)	0.29
Secondary education	39 (35.5)	71 (64.5)	3.63(1.31-10.04) †	0.01
Tertiary education	9 (42.9)	12 (57.1)	4.95(1.38-17.76) †	0.01
<b>Living arrangement</b>				
Alone	11 (35.5)	20 (64.5)	1	0.29
Family	64 (26.4)	178 (73.6)	0.65(0.30-1.44)	
<b>Gender</b>				
Female	35 (24.5)	108 (75.5)	1	0.25
Male	40 (30.8)	90 (69.2)	1.37(0.81-2.34)	
<b>Marital status</b>				
Married	58 (30.9)	130 (69.1)	1	0.06
Single/divorced	17 (20.0)	68 (80.0)	1.79(0.97-3.30)	
<b>Ethnicity</b>				
Malay	22 (25.6)	64 (74.4)	1	
Chinese	49 (28.2)	125 (71.8)	1.14(0.63-2.05)	0.55
Indian	3 (27.3)	8 (72.7)	1.09(0.27-4.48)	0.51
Others	1 (50.0)	1 (50.0)	2.91(0.17-48.50)	0.50
<b>Employment</b>				
Employed	14 (23.3)	46 (76.7)	1	0.42
Retired/unemployed	61 (28.6)	152 (71.4)	0.76(0.39-1.48)	
<b>Income level</b>				
Less than RM1000	32 (22.7)	109 (77.3)	1	
RM1000-4000	39 (33.3)	78 (66.7)	1.70(0.98-2.95)	0.06
More than RM4000	4 (26.7)	11 (73.3)	1.24(0.37-4.15)	0.73
<b>Psychiatry premorbid</b>				
No	72 (26.9)	196 (73.1)	1	0.13
Yes	3 (60.0)	2 (40.0)	0.25(0.04-1.50)	
<b>Physical limitation</b>				
No	72 (27.7)	188 (72.3)	1	0.72
Yes	3 (23.1)	10 (76.9)	1.28(0.34-4.77)	
<b>Medical premorbid</b>				
No	7 (41.2)	10 (58.8)	1	0.20
Yes	68 (26.6)	188 (73.4)	1.94(0.71-5.29)	

(1)Reference group, †Statistically significant at p&lt;0.05

80.2% (n=219) having hypertension and 40.7% (n=111) having Diabetes Mellitus; while thirteen participants have had stroke and nine participants had been diagnosed with cancer. Only five participants had underlying psychiatric diagnoses such as anxiety, while thirteen participants had physical limitations.

The prevalence of depression among elderly patients in THC was 10.3% (n=28). The prevalence of intention to seek professional help for depression among elderly patients was 27.5% (n=75).

#### Past help seeking behaviours

Among all the respondents, 76.9% (n=210) of them reported having sought help from others in handling their emotional problems from either friends and family; religious organisation; traditional medicine practitioner; religious healer; counsellor; general practitioner; psychiatrist;

psychologist or social worker. Friends and family were the most sought help, followed by religious organisation. (Table II) Only 8.8% (n=24) had sought help from professional.

#### Intention to seek professional help for depression and help-seeking preferences

Majority of the participants were keen to seek help from either friends and family members and religious organisations. Their help-seeking preferences are listed in Table II. Among those respondents who were identified as depressed based on PHQ-9 (n=28), only 32.1% or 9 respondents had intention to seek professional help for their depression.

As for the preferred first point of contact with health care workers among participants for their depressed symptoms listed in Table III, 49.6% of the participants chose general practitioner followed by psychiatrist 21.0%.

**Table V: Multivariate analysis of independent factors associated with intention to seek professional help for depression (N=273)**

Variable	Adjusted OR	95% C.I.		P value
		Lower	Upper	
<b>Gender</b> (Female)				
Male	1.08	0.60	1.95	0.73
<b>Marital status</b> (Married)				
Single/Divorced	0.74	0.38	1.45	0.61
<b>Education</b> (No formal education)				
Primary education	1.63	0.54	4.97	0.39
Secondary education	3.10†	1.01	9.53	0.01
Tertiary education	4.66†	1.08	20.04	0.01
<b>Income level</b> (less than RM1000)				
Income RM1000-4000	1.17	0.63	2.19	0.23
Income >RM4000	0.51	0.12	2.09	0.27
<b>Medical premorbid</b> (No) Yes	0.46	0.16	1.31	0.20
<b>Psychiatry premorbid</b> (No)Yes	2.32	0.31	17.68	0.39
<b>Prior experience of seeking professional help</b> (No) Yes	3.45†	1.41	8.48	0.01

Brackets indicate reference categories, †statistically significant at p<0.05  
 Hosmer and Lemeshow test suggested an adequate model fit. Chi square=7.394, P=0.495  
 Nagelkerke's R<sup>2</sup>=15.3

*Factors associated with intention to seek professional help for depression*

Prior experience of seeking professional help and education level were significant factors associated with the intention to seek professional help among the respondents. Having a prior experience has an adjusted odds of 3.45[95%CI (1.41-8.48)] compared to without prior experience to seek professional help. Having higher education was also associated with higher odds of seeking professional help compared to no formal education as shown in Table IV and Table V. Table IV showed that having diagnosed with depression was not associated with intention to seek professional help.

**DISCUSSION**

The prevalence of intention to seek professional help for depression among elderly patients in THC Clinic was 27.5% and the prevalence of depression among elderly patients was 10.3%. Factors or variables that were significantly associated with the intention to seek professional help for depression were level of education and prior experience in consulting mental health professionals. From this study the intention to seek professional help for depression was not associated with the status of depression.

Latest NHMS 2018 findings from elderly health survey showed that 1 in 10 elderly are depressed and have low education level.<sup>3</sup> There seems to be much agreement between our study with the data presented in the national survey. Previous local studies on elderly depression showed prevalence in Malaysia to be between 7.6% to 19.2%.<sup>3,4,18,19</sup> The prevalence studies done showed that the elderly depression was significant in Malaysia as the population is ageing and the elderly population is facing ever increasing physical, mental, financial, and social challenges.

From various studies done worldwide, the intention to seek help for depressive symptoms were low. Chin et al. showed suboptimal utilisation of mental health facilities at 24.3%. A Korean study noted that only 17.4% of the participants (all

age groups) had a consultation to mental health professional,<sup>9</sup> research in Japan stated that 18.7% of participants sought help.<sup>10</sup> Help-seeking study done in Turkey showed 23.6% to 30.6% utilisation of health care services.<sup>11</sup>

Female elderly patients, patients who were not married and patients with higher education were more likely to seek professional psychology consultation.<sup>14</sup> The education level of the participants in our study was an essential factor influencing their intention to seek help as compared to studies done in Canada and the US.<sup>13</sup> Our study showed that majority of the participants sought help from family members and friends and religious organisation and higher education level resulted in higher intention to seek professional help for depression.

A study done in Singapore showed that people with higher religion affiliation showed less frequent treatment by mental health professionals.<sup>20</sup> Systematic review and meta-analysis showed that personal attitudes toward mental illness such as own negative attitudes towards mental health help-seeking and their stigmatising attitudes towards people with a mental illness were associated with less active help-seeking.<sup>21</sup>

In Malaysia, previous studies showed mixed responses as to which pathway the patients sought help, with the majority willing to seek help from religious and traditional healers.<sup>22</sup> The consulting of traditional or religious healers in our sample population was low. Khan et al., reported that 65.5% were willing to seek help from psychiatrists, while 58.22% preferred to consult general practitioners.<sup>22</sup> Most participants in our study (49.6%) preferred to consult general practitioners or primary care physicians for their symptoms of depression. Almost half of our subjects preferred to consult general practitioners with their emotional problems which may indicate that the participants trusted the general practitioners and were comfortable and confident with the general practitioners to managing their depression.

Help-seeking is a complex behaviour that is thoroughly investigated by numerous studies. According to Theory of

Planned Behaviour,<sup>23</sup> intentions to perform behaviours of different kinds can be predicted with high accuracy from attitudes toward the behaviour (positive or negative evaluation of behaviour), subjective norms (perception of social support to engage in the behaviour), and perceived behaviour control (the extent to which a behaviour is regarded as able to be done).<sup>23</sup> An Intention to seek help does not necessarily translate to actual help-seeking that is observed as an endpoint. It merely predicts a higher possible tendency of the studied population to perform the desired behaviour.

From this study it was interesting to note that 67.86% (n=19) of the depressed participants did not intend to be treated for depression by professional mental health providers in the forthcoming six months. This low rate of help seeking can be explained by the low motivation, unclear treatment process, internalised stigma and public stigma. Primary care physician needs to break down the barriers of seeking help by addressing the above problems.

#### *Strength and limitations of the study*

The strength of this paper was the usage of PHQ-9 for the study of depression among elderly patients in THC. PHQ-9 has acceptable diagnostic properties such as high specificity and sensitivity to diagnose depression, as mentioned in our paper. The straightforward and simple language used in this instrument based on DSM-IV criterion makes it easy to administer. However, the use of checklist screening to diagnose depression has its limitation as the instrument lack the ability to differentiate dementia from depression in elderly population and unable to identify life events and chronic stresses endured by the elderly patients.

The sample population was unable to represent the elderly population of Malaysia as our subjects were from one government health clinic in Malaysia, and the respondents were predominantly Chinese from a semi-urban community with low to middle income and were generally healthy, not hospitalised and not institutionalised. The intention to seek professional help for depression among the elderly was not further investigated with a follow-up interview in a longitudinal study to ascertain the actual behaviour to seek professional help when depressed. The actual consultation with a professional mental health care worker was not determined in this study. However, the result from this study may be used by primary care practitioners in this discipline to engage the elderly population to increase their awareness regarding the availability of treatment options for mental health in primary care clinic.

The intention to seek professional help in this study was based on dichotomous yes-no intention, which was derived from the respondents choosing professional help as defined in the methodology. This method of identifying the intention to seek help was relatively simple, but it did not allow the respondents to indicate degrees of intentionality and did not provide additional information on the degrees of preference in the chosen help options.

Factors that would influence the help-seeking behaviour were explored in this study, but the attitudes, perceptions and stigma of mental health help-seeking were not addressed. It

would be challenging to administer complicated questionnaire involving the attitudes, perceptions and stigma with the elderly population in the study area as most of the elderly patients had lower education level, and it would be difficult for them to understand the questionnaires.

Most of the participants required assistance while answering the questionnaire, and some participants needed translation and further clarification with the questions. Due to the low level of education of the participants, the single field researcher required more time to administer the questionnaire and may result in observer bias when interpreting the responses of the participants.

#### **CONCLUSION**

The prevalence of intention to seek professional help for depression in this study was 27.5%. This study showed that primary care clinicians can play an essential role in mental health services in the community. Also this study revealed that past experience of professional help-seeking and the level of education of the elderly patients are important factors affecting the intention to seek professional help for depression. Future study on help-seeking behaviour in the elderly population in Malaysia should investigate the attitudes, perceptions and stigma influencing the intention to seek help for elderly depression by using qualitative approach or using instruments such as ATSPPH-SF (Attitudes toward seeking professional psychological help- Short Form) or other similar instruments.

#### **ETHICAL APPROVAL**

Approval was obtained from the Research & Ethics Committee of UKM (UKM-JEP-2018-043), National Medical Research Registry (NMRR-17-3332138911(IIR)) and the Medical Research and Ethics committee (MREC). All respondents gave their informed consent prior to their participation in this study.

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#### **CONFLICT OF INTEREST**

The authors of this study declare that there is no conflict of interest.

#### **REFERENCES**

1. World Health Organization (WHO). Proposed working definition of an older person in Africa for the MDS project 2002. [cited Jan 2020] Available from: <https://www.who.int/healthinfo/survey/ageingdefnolder/en/>.
2. Department of Statistics Malaysia, Official Portal, [cited Jan 2020] Available from: <https://www.dosm.gov.my/v1/index.php>
3. NHMS (National Health & Morbidity Survey 2018) key findings from the elderly health survey. [cited Jan 2020] Available from: <http://iku.moh.gov.my/images/IKU/Document/REPORT/NHMS2018/NHMS2018ElderlyHealthVolume1.pdf>



4. Imran A, Azidah AK, Asrenee AR, Rosediani M. Prevalence of depression and its associated factors among elderly patients in outpatient clinic of Universiti Sains Malaysia Hospital. *The Med J Malaysia* 2009; 64(2): 134-9.
5. Samy AL, Khalaf ZF, Low WY. Mental Health in the Asia-Pacific Region: An Overview. *International Journal of Behavioral Science* 2015; 10(2).
6. World Health Organization (WHO). 20 leading Causes of DALY globally, 2015 and 2000. [cited Jan 2020] Available from: [https://www.who.int/healthinfo/global\\_burden\\_disease/GlobalDALYmeth ods\\_2000\\_2015.pdf](https://www.who.int/healthinfo/global_burden_disease/GlobalDALYmeth ods_2000_2015.pdf)
7. Mohd Sidik S, Mohd Zulkefli NA, Shah SA. Factors associated with depression among elderly patients in a primary health care clinic in Malaysia. *Asia Pacific Family Medicine* 2003; 2(3): 148-52.
8. Chin WY, Chan KT, Lam CL, Lam TP, Wan EY. Help-seeking intentions and subsequent 12-month mental health service use in Chinese primary care patients with depressive symptoms. *BMJ Open* 2015; 5(1): e006730.
9. Kim JL, Cho J, Park S, Park EC. Depression symptom and professional mental health service use. *BMC Psychiatry* 2015; 15(1): 261.
10. Suka M, Yamauchi T, Sugimori H. Help-seeking intentions for early signs of mental illness and their associated factors: comparison across four kinds of health problems. *BMC Public Health* 2016; 16(1): 301.
11. Topuzoğlu A, Binbay I, Ulaş H, Elbi H, Tanık FA, Zağlı N, et al. The epidemiology of major depressive disorder and subthreshold depression in Izmir, Turkey: Prevalence, socioeconomic differences, impairment and help-seeking. *J Affect Disord* 2015; 181: 78-86.
12. Janz NK, Becker MH. The Health Belief Model: a decade later. *Health Educ Q* 1984; 11(1): 1-47.
13. Maggaard JL, Seeralan T, Schulz H, Brütt AL. Factors associated with help-seeking behaviour among individuals with major depression: A systematic review. *PloS one* 2017; 12(5).
14. Picco L, Abdin E, Chong SA, Pang S, Shafie S, Chua BY, et al. Attitudes toward seeking professional psychological help: factor structure and socio-demographic predictors. *Front Psychol* 2016; 7: 547.
15. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; 16(9): 606-13.
16. Sherina MS, Arroll B, Goodyear-Smith F. Criterion validity of the PHQ-9 (Malay version) in a primary care clinic in Malaysia. *Med J Malaysia* 2012; 67(3): 309-15.
17. Kish I. Sampling organizations and groups of unequal sizes. *Am Sociol Rev* 1965; 30: 564-72.
18. Rashid A, Tahir I. The prevalence and predictors of severe depression among the elderly in Malaysia. *J Cross Cult Gerontol* 2015; 30(1): 69-85.
19. Sherina MS, Rampal L, Mustaqim A. The prevalence of depression among the elderly in Sepang, Selangor. *Med J Malaysia* 2004; 59(1): 45-9.
20. Ng TP, Nyunt MS, Chiam PC, Kua EH. Religion, health beliefs and the use of mental health services by the elderly. *Aging Ment Health* 2011; 15(2): 143-9.
21. Schnyder N, Panczak R, Groth N, Schultze-Lutter F. Association between mental health-related stigma and active help-seeking: systematic review and meta-analysis. *Br J Psychiatry* 2017; 210(4): 261-8.
22. Khan TM, Sulaiman SA, Hassali MA, Anwar M, Wasif G, Khan AH. Community knowledge, attitudes, and beliefs towards depression in the state of Penang, Malaysia. *Community Mental Health Journal* 2010; 46(1): 87-92.
23. Ajzen I. The theory of planned behaviour: reactions and reflections. *Psychol Health* 2011; 26(9): 1113-27.

# The role of acute internal medicine service in handling burden of medical access block in a tertiary hospital, Hospital Melaka experience

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## ABSTRACT

**Introduction:** Access block is a major problem faced by most hospitals. It has led to congestions in emergency departments (ED) leading to sub-optimal or delayed treatment. Inevitably the spotlight falls on medical department, being accountable for the highest proportion of access block in ED.

**Materials and Methods:** This is a retrospective study looking at data collected during office hours on 79 working days, excluding weekends and public holidays in Hospital Melaka, Malaysia. Details on all medical access block cases that were reviewed were recorded including their locations, diagnosis, disposition decisions and if they received specialist input at the time of their initial assessment by the medical team in ED. The aim is to revolutionise patient admission flow by offering early specialist care with rapid assessment, investigation and treatment. Hence, improving the overall treatment efficiency and reduce medical access block.

**Results:** There were 1321 admissions. A total of 82% of the patients were admitted to the medical wards while 13% of them were given acute treatment in ED and discharged home with appropriate follow ups. We managed to resolve 18% of medical access block by re-triaging our cases and offering timely acute medical treatment. Nearly 90% of patients received first hand medical specialist input during the initial assessment by the Acute Internal Medicine (AIM) team in ED.

**Conclusion:** The significant resolution in medical access block with active screening, re-triaging and management of patients by the AIM team allows a more optimal hospital bed management. Patients also receive timely access to medical intervention with specialist care and stable patients can benefit from early supported discharge.

## KEYWORDS:

*Access block, Emergency Department congestion, Acute Internal Medicine (AIM), Acute Medical Unit (AMU), AIM physician*

## INTRODUCTION

Access block for emergency patients to inpatient beds is becoming an increasing problem globally. The Royal College of Emergency Medicine defined 'access block' as the situation

where patients who have been assessed in the emergency department (ED) are unable to leave the department due to a lack of capacity in the downstream system.<sup>1</sup> The causes for this congestion vary in different regions ranging from shortage of acute medical inpatient beds, financial restrictions on service provision to the availability of staff.<sup>2</sup> Effects on patient care include delays in being assessed and receiving the required care, reduced patient satisfaction, increased complaints, increased inpatient length of stay, increased cost of treatment and poorer outcomes.<sup>3,4</sup> Delays are also associated with waiting for the relevant medical team to assess an acute medical patient in ED.

In 2017, there were a total of 39,378 admissions through ED in Hospital Melaka (HM) and 48% were medical patients. The Department of Internal Medicine has the largest number of inpatient beds with 338 beds; which comprised of 31% from total of 1091 beds in HM. The average number of medical admissions per day were 55 patients with average medical wards Bed Occupancy Rate (BOR) of 85% and Average Length of Stay (ALOS) of 5.28 days. Nearly half of medical patients had experienced access block upon admission and 37% of them had access block for more than 4 hours (Table I). This data were obtained from Bed Management Annual Report 2017 by Quality Unit, Hospital Melaka.

In the past, all acute medical admissions were managed by internal medicine specialists and consultants including subspecialty teams in Internal Medicine. However, as the pressures of the acute medical take increased and the need for earlier specialist input was recognised, it was realised that the systems of acute care needed to be changed. It was recognised that care for acutely admitted patients should ideally be concentrated in acute medical units (AMUs), however due to our limited resources the Acute Internal Medicine (AIM) service was developed in the ED as an alternative with an AIM specialist at the head. It should be stressed that AIM is not the same as emergency medicine, although the two specialties work together closely.

A physician's role in the management of acute medical problems is that he or she can assess and treat these patients in the most appropriate fashion within the first 24 hours of presentation to the ED, aiming either for an early discharge with appropriate outpatient follow-up or transfer to medical ward. Severely ill patients who need close observation but do

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not require intensive care will be treated by a dedicated physician leading the high dependency ward.

## MATERIALS AND METHODS

AIM is a relatively new subspecialty in Malaysia. A career in acute medicine has been possible since 2005 via training on a previous General Internal Medicine (GIM) curriculum. However, since 2009, physicians have been able to be trained in AIM and in 2012, we had our first AIM Physician in Malaysia. The AIM curriculum was revised with defined competencies in 2018.

Our AIM team in ED in HM consist of one AIM specialist or internal medicine physician, one medical officer (MO) and two house officers (HOs). Office hours are from 8am to 5pm. The role of AIM team is to actively screen, review and manage all medical patients in ED who are stranded due to access block. The aim of this service is to reorganise patient admission flow by offering early specialist care with rapid assessment, investigation and treatment. Hence, improving overall treatment efficiency and reduce medical access block.

**Primary objective:** To determine the impact of AIM service in resolution of medical access block in ED, HM

### Secondary objectives:

1. To determine the proportion of office hour medical admissions reviewed by AIM team in ED
2. To determine the proportion of cases with first hand medical specialist input.
3. To determine the proportion of cases with early discharge and appropriate outpatient follow-up

## METHODOLOGY

This was a retrospective study looking at data collected from 13th August 2018 to 14th December 2018 during daily office hour reviews in ED excluding weekends and public holidays. Study was carried out for a total of 79 working days (n=79). All cases reviewed by the AIM team was recorded together with location of the patients to where they were triaged to; either red, yellow, green or if they were lodged in observation bay due to access block. We also recorded if they were reviewed by a specialist at the time of their initial assessment by the medical team and their disposition decision; either for admission to the medical wards, transferred to other centres, discharged home or referred for admission to other departments. The total number of medical admissions during office hours was retrospectively calculated from the admission census book in ED. All data collected were analysed according to objectives (Figure 1).

## RESULTS

We reviewed 72% of medical cases out of a total 1321 medical patients who were admitted during office hours throughout the study period. Nearly 87% of patients received first hand medical specialist input during initial assessment by the AIM team in ED. Forty percent of the cases were in the red zone followed by 33% and 27% from observation bay and yellow zones, respectively. A very small percentage (<1%) were green zone cases (Table II).

A total of 82% of the patients were admitted to the medical wards while 13% of them were given acute treatment in ED and discharged home with appropriate follow ups. Four percent of the cases were identified as non-medical case and hence referred and admitted to the respective department wards. A small percentage (1%) of patients were transferred to other centres for services not available in HM (eg: emergency cardiac intervention or emergency neurosurgeries). In summary, we managed to resolve 18% of medical access block by re-triaging our cases and offering timely acute medical treatment (Table II).

## DISCUSSION

The main impact of AIM team service in ED was the resolution of 18% of medical access block cases. These had allowed avoidance of inappropriate admissions and hence providing more optimal medical bed management.

Approximately 13% of the patients were given treatment in ED and discharged home with referrals to nearest primary care clinics, daycare service or an early AIM clinic appointment. (Table III). Further analysis was done on this group of patients and they were classified according to their main systemic diagnosis at presentation. The top two most common diagnoses were of cardiovascular and respiratory in nature. Cardiovascular cases include stable angina, stable heart failure, uncontrolled hypertension and patients that had resolved supraventricular tachyarrhythmia following acute treatment in ED. Respiratory cases included upper respiratory tract infection and pneumonia, where a quarter of the patients having concomitant mild exacerbation of asthma or chronic obstructive pulmonary disease. The third commonest diagnosis is viral fever including dengue fever cases without warning signs and deemed stable for home treatment with close primary care clinic follow up. Asymptomatic patients who came for semi-emergency procedures such as the reinsertion of a dislodged dialysis catheter, peritoneal tapping or blood transfusion were given immediate or early daycare appointment. The outcome of this study highlighted the importance of AIM service at ED level to screen and select cases eligible for early discharge. They were equipped with knowledge in internal medicine and outpatient clinic or daycare follow-up facility. This strategy also helped to reserve hospital beds for those who truly need advanced tertiary care.<sup>5</sup>

Early assessment by medical team with medical specialist input allows more efficient treatment and management of medical patients in ED. This possibly reduced complications related to delay of treatment and prevent misdiagnosis.<sup>6</sup> In this study, 87% of the patients received specialist cares during their first assessment by our AIM team in ED. Cases given priority for review were red zone cases and medical access block in observation bay hence the reason why a higher percentage of cases are from these two zones.

Critically ill medical patients attending an average ED has outnumbered critical trauma emergencies by at least 5:1.<sup>7</sup> Patients in red zone whom were generally more ill and required immediate attention were being co-managed both by ED and AIM teams. Improved relationship and co-management between both teams allowed delivery of

**Table I: Data of admissions through Emergency Department, Hospital Melaka and medical access block for year 2017.**  
 [Source: Bed Management Annual Report 2017, Quality Unit, Hospital Melaka]

Admissions to Hospital Melaka, Year 2017	Total (n = 365)	Percentage (%)
Admissions through ED	39,378	100
Medical admissions through ED	18,750	48
All access block cases in ED	12,851	33
Medical access block in ED	8598	46
Medical access block > 4 hours	4751	37
Proportion of medical cases among all access block	8598/12,851	67

**Table II: Data collected throughout study period during office hours and analysed**

	Total (n = 79)	Percentage (%)
Office hours medical admissions	1321	100
Medical access block reviewed by AIM Team	956	72
Cases receiving first hand medical specialist input	836	87
<b>Distribution of cases by zones:</b>		
Red Zone	380	40
Yellow Zone	257	27
Observation bay	313	33
Green Zone	6	< 1
<b>Decisions after AIM team assessment:</b>		
Admit to medical wards	782	82
Discharge home with appropriate follow up	126	13
Refer to other specialty for non medical cases	39	4
Transfer to other specialised centres	9	1
Cases re-triaged and not admitted to medical wards	174	18

**Table III: Classification of diagnosis by system for patients who were discharged home**

Diagnosis	Total (n = 126)	Percentage (%)
<b>Cardiovascular</b> (stable angina, heart failure, supraventricular arrhythmias, uncontrolled blood pressure etc.)	34	27.0
<b>Respiratory</b> (respiratory infections, chronic lung diseases etc.)	25	19.8
<b>Viral fever</b> (Including dengue fever)	15	11.9
<b>Gastroenterology &amp; Hepatology</b> (acute gastritis or gastroenteritis, ascites)	12	9.5
<b>Neurology</b> (transient ischaemic attack, seizure, vasovagal attack)	11	8.7
<b>Allergic reaction or symptoms from side effects of medications</b>	11	8.7
<b>Musculoskeletal</b> (cellulitis, costochondritis etc.)	9	7.1
<b>Haematology</b> (anaemia)	5	4.0
<b>Genitourinary</b> (urinary tract infection)	2	1.6
<b>Miscellaneous</b>	2	1.6

optimum care for critically ill medical patients. These patients were given priority for admission to medical wards including our physician lead high dependency ward and intensive care units. Perhaps we may see the formation of multidisciplinary emergency medical team with emergency physicians, acute medicine physicians and intensivists in providing care for critically ill medical patient in the future. Communication between our AIM team members with other medical colleagues in the general medical wards to assist admissions helped to hasten the admission process of our medical access block cases.

Four percent of the cases reviewed were diagnosed with a non-medical diagnosis and referred to the respective primary team for further assessment and admission. Nearly three

quarter (74%) of them were surgical cases (e.g. upper gastrointestinal bleeding, acute abdomen, obstructive jaundice etc.), followed by 12% of orthopaedic cases and seven percent each for both psychiatry and gynaecology cases. The introduction of AIM had helped in preventing inappropriate non-medical case admissions, delays in management as well as preventing potential complications. In the long run, this could be one of the effective solutions to reduce the proportion of medical access block in hospitals in Malaysia.

Our AIM service is currently limited to working during office hours due to limitation of manpower. We believe that our initiative may bring bigger impacts to the system if we

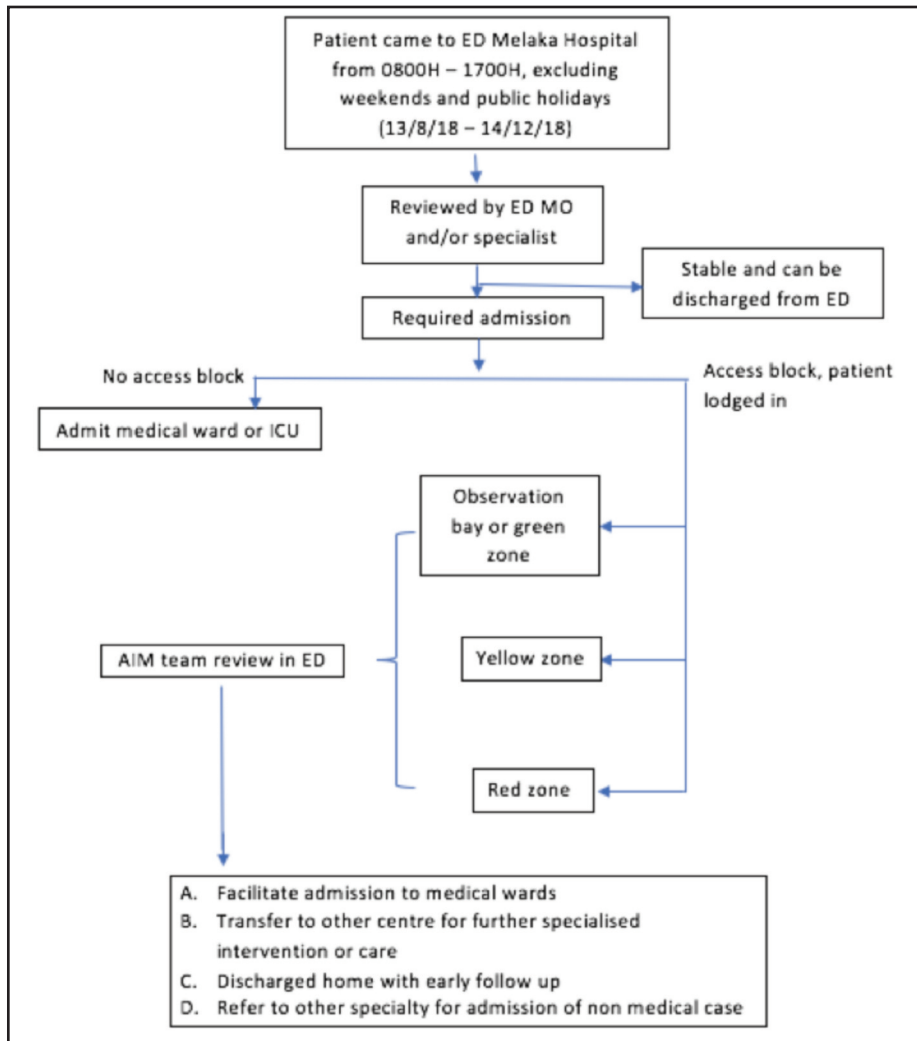


Fig. 1: Flow chart on admission pathway of medical patients.

manage to extend our service up to 24 hours and 7 days a week. We hope that HM may extend our AIM service into developing an AMU in which focused internist lead teams are stationed on site to rapidly assess and re-triage patients. This team may provide more holistic, patient centric care with better ownership, improved efficiency and less fragmentation in management.

#### LIMITATIONS AND CHALLENGES

This study has some limitations. First, this is a single centre study so the results may not be applicable to other hospital settings or healthcare facilities in Malaysia. The HM is currently using manual medical record system for most of our daily work. Hence, to obtain the total number of medical admissions during office hours, we had to calculate retrospectively the sum of admissions from the admission census book in ED. This manual calculation may not be accurate and we may have missed out cases and certain important data that might not be captured in the source document.

There was no data collected on follow ups of outcomes of patients after being discharged from ED. As a paper-based hospital, we faced difficulties to trace medical record of patients in a timely manner and we had no proper tagging system to identify any cases that were readmitted within a period of time. Hence, there were limitations to capture data of any readmission with similar symptoms within 28 days from the time they were discharged from ED. It would be interesting to study on this aspect to further evaluate the effectiveness of the AIM service provided.

#### CONCLUSIONS

The significant resolution in medical access block with active screening, re-triaging and management of patients by AIM team allows a more optimal hospital bed management and provide solutions for medical access block in ED HM. Early specialist care with rapid assessment, investigations and treatment offered within the first few hours of admission to ED may lead to better patient outcomes. Patients also received timely access to medical interventions and stable patients may benefit from early supported discharge.

#### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia with registered under National Medical Research Register (NMRR ID: 19A3634A50937) dated 2nd January 2020.

#### COMPETING INTERESTS

The authors declare that they have no competing interest.

#### FUNDING

The authors declare no financial disclosure.

#### AUTHORS' CONTRIBUTIONS

NUHA was responsible for the study design, data collection, data analysis and manuscript writing. CLG was involved in the design of the study, data collection, data analysis and manuscript editing. Both authors read and approved the final manuscript.

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#### REFERENCES

1. Royal College of Emergency Medicine: ED crowding overview and toolkit, December 2015, [cited Dec 2019]. Available from: <https://www.rcem.ac.uk/docs/CollegeGuidelines/>
2. Hardern RD. Acute medicine: the physician's role. A working party report of the Federation of Royal Colleges of Physicians of the United Kingdom. London & Royal Colleges of Physicians of the United Kingdom. *J Accid Emerg Med* 2000; 17(6): 391.
3. Peter AC, Anthony PJ and Sally MC. Access block can be managed. *Med J Aust* 2009; 190(7): 364A368.
4. Roberto F, Sally MC, Ken H. Access block and emergency department overcrowding. *Crit Care*. 22 Mar 2011; 15(2): 216.
5. Campbell D, Cameron P, Scown P. Managing access block. *Australian Health Review*, Vol. 25, No. 4, 200; 59A68. [cited Dec 2019]. Available from: <https://citeseerx.ist.psu.edu/>
6. Dr Michael T. So you want to be an Acute Physician. *Ulster Med J*. 2017 Jan; 86(1): 74–75. [cited Dec 2019]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5324194/>.
7. Andrew A, Paul P, Alan D, Brian HR, Howard JO. Emergency department overcrowding and access block. *Canadian Journal of Emergency Medicine* 2013; 5(6): 359A70.
8. Goh WP, Han HF, Uma CS, Geraldine B, Aisha L. Acute medical unit: experience from a tertiary healthcare institution in Singapore. *Singapore Med J* 2018; 59(10): 510–13. DOI:10.11622/smedj.2018124.
9. Royal College of Physicians. Acute Medical Care: the right person in the right setting, first time. Report of the acute medicine task force. London: RCP; 2007.
10. Qing H, Amardeep T, Jonathan FD, Gregory SZ. The impact of delays to admission from the emergency department on inpatient outcomes. *BMC Emerg Med* 2010; 10: 16.
11. Chris R. Acute medicine and general practice: a key interface in managing emergency care pressures. *Br J Gen Pract* 2014; 64(620): 122–23.
12. RCPE UK Consensus Statement on 'Acute Medicine: Improving quality of care through effective patient flow – it's everyone's business!'. [cited Dec 2019]. Available from: [http://www.rcpe.ac.uk/sites/default/files/files/final\\_statement\\_patient\\_flow\\_.pdf](http://www.rcpe.ac.uk/sites/default/files/files/final_statement_patient_flow_.pdf).

# Perception of nurses on the practice environment: Experience from Malaysia

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## ABSTRACT

**Introduction:** Positive professional practice environments are crucial to safeguard a healthy and safe working conditions for health workforce, including nurses; so as to ensure provision of quality healthcare and safety of patient.

**Methods:** This was a cross-sectional study to assess nurses' perceptions towards nursing practice environment and factors associated with their perceptions. A validated Practice Environment Scale of the Nursing Work Index (PES-NWI) questionnaire was administered to nurses working in two Ministry of Health hospitals. The questionnaire comprises of five subscales: Participation, Foundation, Managers Support, Workforce Adequacy and Physician/Nurse Relations. Mean scores of >2.50 were considered as favourable, and ≤2.50 were considered as unfavourable. Simple linear and multiple linear regression analysis were employed to identify factors associated with their perceptions. Analysis was carried out using STATA version 14.0.

**Results:** A total of 366 respondents took part in the study, with a response rate of 98.4%. Majority were working shift (89.6%) and working extended hours (62.3%). In general, the nursing practice environments were rated as favourable. Overall mean score was 2.90±0.03 and four out of five subscales' mean scores were >2.50. Foundation for quality nursing care was perceived as the most favourable subscale, while workforce adequacy was perceived as the least favourable. There were statistically significant association between working extended hours, doing double shift and working during day off with perceived unfavourable workforce adequacy.

**Conclusion:** Nursing practice environment was perceived as favourable in the studied hospitals. Policy makers, service providers, and hospital managers could explore further on human resource planning and management of nursing personnel to tackle the issue of nurse staffing in the country.

## KEYWORDS:

*Nursing, hospitals, practice, working, environment*

## INTRODUCTION

Positive practice environments (PPEs) for healthcare professionals have gained growing attention globally.<sup>1,2</sup> PPEs are defined by the World Health Organization<sup>1</sup> and Baumann<sup>3</sup> as “settings that ensure the health, safety and personal well-being of health professionals, improve motivation, productivity and performance of individuals and organization, and thus, support the provision of quality patient care”.

In Malaysia, the employers are responsible in provision and maintenance of work settings that are functional, safe, risk-free and sufficient pertaining to the amenities for their well-being at workplace. The purpose is to encourage a working condition for workers that conform to their needs.<sup>4,5</sup> Malaysia has a dual healthcare system where both the private and public healthcare services co-exist.<sup>6</sup> The main provider of public healthcare services is the Ministry of Health Malaysia, together with the Ministry of Higher Education and Ministry of Defence. On the other hand, private healthcare services are delivered in autonomous clinics or hospitals.

Nurses form the biggest healthcare professionals in Malaysia. There were 102,564 nurses in both private and public sectors in 2016<sup>7</sup> constituting almost 50% of healthcare professionals. Seven in ten of nurses were practicing in the public sector. Many issues related to nursing such as insufficient staff in workplace, inadequate skill mix, excessive nurse migration, low job satisfaction, stressful experience, poor retention and high turnover were reported not being noticed or voiced out.<sup>8,9</sup> These issues were thought to be related to Nursing Practice Environment (NPE) factors.<sup>10</sup> NPE refers to the institutional characteristics of a work environment that encourages or restricts professional nursing practice from providing quality care to patients.<sup>11</sup> A good environment for nurses to practice at workplace (such as job aid, management style and relationship, growth opportunities, mentoring-coaching, and physical work environment) play an important role towards the retention and job satisfaction of nurse. Nursing practice environment, along with nursing knowledge, skills and competencies, are important factors in ensuring provision of quality healthcare and patient safety.<sup>3,12,13</sup>

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There are several instruments used to measure nursing practice environment such as Nursing Work Index, Revised Nursing Work Index (NWI-R), Job Characteristics Survey Inventory (JCI), Ward Organization Features Scale (WOFS), Work Quality Index (WQI) and Assessment of Work Environment Schedule (AWES).<sup>14</sup> However, recent empirical evidence published suggest that the Practice Environment Scale of the Nursing Work Index (PES-NWI) is considered to be the most applicable and suggested for future research.<sup>14,15</sup> The PES-NWI had also been adopted by a local study to measure NPE in public university hospitals<sup>16</sup> and private hospitals in Malaysia.<sup>17</sup>

Studies showed that nursing practice environment was unfavourable in university hospitals,<sup>16</sup> whereas it was favourable in private hospitals in Malaysia.<sup>17</sup> There is a paucity of research assessing nursing practice environment in public hospitals. Given this, the present study was conducted with the objective to assess Nursing Practice Environment among nurses in selected public (Ministry of Health) hospitals in Malaysia using a validated tool. This study provides information valuable for introducing changes in practice that are likely to create positive practice environments.

## MATERIALS AND METHODS

### *Study design*

A cross-sectional study using a validated questionnaire was carried out among nurses working in two MOH hospitals, namely Hospital Putrajaya and Hospital Ampang situated in the central region of Peninsular Malaysia. Data collection were conducted from September to October 2017. By using the sample size formula for frequency in a population study, a minimum sample size of 290 (from a total estimation of 1,176 eligible nurses in both hospitals) was calculated using OpenEpi online sample size calculator Version 3.0,<sup>18</sup> using 50% response distribution, 95% confidence interval and 5% level of precision. In order to adjust for potential non-response (20%), the minimum sample size needed was 363. A convenience sampling method was used. All nurses who worked in the clinical setting were recruited in the study, whereas nurses who were on long leave were excluded. Overall, 372 questionnaires were distributed.

### *Study instrument*

The questionnaire used was divided into two parts. The first part consisted of seven items that assessed the socio-demographic and work-related characteristics of respondents such as age, sex, marital status and education level (certificate, diploma and higher), while items related to their work included working experience, department, and working patterns (normal work shift, working extended hours, doing double shifts, working during day off). A continuous age and working experiences variables were re-coded into categorical variables for ease of interpretation.

The second part of the questionnaire contained 31 items of PES-NWI, which were grouped into five subscales: (1) "Nurse participation in hospital affairs" (Participation); (2) "Nursing Foundations for Quality of Care" (Foundation); (3) "Nurse Manager Ability, Leadership and Support of Nurses"

(Managers Support); (4) "Staffing and Resource Adequacy" (Workforce Adequacy); and (5) "Collegial Nurse - Physician Relations" (Physician/Nurse relations). A four-point Likert scale format (1 = "strongly agree", 2 = "agree", 3 = "disagree", and 4 = "strongly disagree") was used to assess the responses for the PES-NWI. The scoring was reversed for each item, thus greater agreement reflected by higher scores.

Initially, the English version of the original questionnaire was forward translated to the Malay language, and then translated back to English, by two independence translators. The questionnaires were then compared and discussed by the two translators to resolve any existing ambiguities and discrepancies. The bilingual versions of the questionnaires were then tested for validity and reliability. Content validity was conducted by seven experts in the field of nursing. The experts rated each item of the questionnaire on a four-point scale (from 1 = not relevant to 4 = very relevant) to validate the appropriateness of the construct studied. An overall percentage of agreement between the experts was calculated to get Scale-Content Validity Index/Average (S-CVI/Ave) for each subscale and the entire questionnaire. Of the five subscales, all had adequate S-CVI/Ave at the subscale level except the Subscale 1 (S-CVI/Ave = 0.84) which was just slightly below the desired S-CVI/Ave of 0.90.<sup>19</sup> The S-CVI/Ave for the entire questionnaire was 0.91 and considered acceptable (Table II).<sup>19</sup> Comments from the experts were used to improve the terminology and structure of the items in the questionnaire. The revised questionnaire was then pre-tested with cognitive debriefing among 20 nurses to determine the clarity of the terms used. The words were made appropriate to suit their current work environment. The bilingual version of the questionnaire was then pilot tested for internal consistency using Cronbach's alpha. The Cronbach's alpha value for the subscales were ranged from 0.68 to 0.85. All the subscales showed sufficient internal consistency except for Subscale 5, which was just slightly below moderate ( $\alpha < 0.7$ ).<sup>11</sup> The reliability for the overall PES-NWI was considered high ( $\alpha = 0.92$ ) (Table II).<sup>11</sup>

### *Operational definitions*

A normal work shift is considered to be a work period of seven consecutive hours each day on weekdays. In this study the term working extended hours was defined as working extra hours which was more than the normal work shift and doing double shifts was defined as working two normal work shifts. Working during day off was defined as working on weekends.

### *Data Collection*

Questionnaires were distributed to eligible nurses with a Respondent Information Sheet explaining the survey during a training session. Their anonymity and confidentiality were reassured. The completed questionnaires were collected at the end of the session.

### *Data analysis*

Data was analysed using STATA version 14.0. Nurses' socio-demographic characteristics and perceptions of NPE was analysed using descriptive statistics. Analysis of NPE was done in terms of subscale and overall scores, and the mean score was calculated for each subscale. The mean summary scores were then calculated for each subscale and overall,



**Table I: Socio-demographic and work-related characteristics of respondents (N=366)**

Items	n	%
<b>Age (years)</b>		
21-30	206	56.3
31-40	134	36.6
More than 40	26	7.1
<b>Sex</b>		
Male	13	3.6
Female	353	96.4
<b>Marital status</b>		
Single	100	27.3
Married	266	72.7
<b>Highest education level</b>		
Certificate	33	9.0
Diploma and higher	333	91.0
<b>Working experience (years)</b>		
Less than 3	67	18.3
3-10	221	60.4
11-20	71	19.4
More than 20	7	1.9
<b>Working normal shift</b>		
Yes	328	89.6
No	38	10.4
<b>Working extended hours</b>		
Yes	228	62.3
No	138	37.7
<b>Doing double shifts</b>		
Yes	200	54.6
No	166	45.4
<b>Working during day off</b>		
Yes	136	37.2
No	230	62.8

**Table II: Practice Environment Scale – Nursing Work Index (PES-NWI): Content Validity Index, Internal Consistency, and Descriptive Statistics (N=366)**

Scale	S-CVI/Ave	α	Mean	SD	Min	Max	Skewness	Kurtosis
Overall PES-NWI scale	0.91	0.92	2.90	0.314	1.90	4.00	0.003	0.003
Subscale 1: Participation	0.84	0.85	2.85	0.402	1.44	4.00	0.116	0.011
Subscale 2: Foundation	0.93	0.77	3.12	0.274	2.40	4.00	<0.001	<0.001
Subscale 3: Managers Support	0.91	0.74	2.85	0.449	1.20	4.00	<0.001	<0.001
Subscale 4: Workforce Adequacy	0.96	0.74	2.44	0.550	1.25	4.00	0.166	0.446
Subscale 5: Physician/Nurse Relations	0.95	0.68	3.00	0.391	1.33	4.00	0.002	<0.001

S-CVI/Ave = Scale-Content Validity Index/Average; α = Cronbach’s alpha; SD = standard deviation; min = minimum; max = maximum

based on the number of items in the subscale and total number of items in the scale, respectively.

Neutral midpoint (2.50) for a four-point response set was used to categorise the score.<sup>20</sup> Mean scores of >2.50 were considered favourable, and mean scores of ≤2.50 and below were considered unfavourable.<sup>11,16</sup> The setting was then classified into either favourable, mixed and unfavourable, based on the composite subscale scores. For setting with four or five subscales with scores of >2.50, it will be classified as favourable. Mixed was classified for setting with two or three subscales with scores of >2.50, while unfavourable was classified for setting with none or one subscale with score of >2.50.<sup>20</sup>

For the bivariate analysis, values on the PES-NWI (considered as dependent variables) were assessed in relation to the independent variables (age, sex, marital status, education level, working experience, and working patterns that is normal work shift, working extended hours, doing double

shifts, working during day off) using simple linear regression as statistical hypothesis tests. Finally, multivariate analysis was performed through multiple linear regression. Independent variables obtaining statistical significance ≤0.20 at bivariate level were considered as predictive variables and included in the final analysis. 95% Confidence intervals were calculated (95%CI). All analyses were conducted with a significance level of ≤0.05.

**RESULTS**

*General characteristics*

Out of 372 questionnaires distributed, a total of 366 valid questionnaires were included in the final analysis (response rate 98.4%). More than half of the respondents (56.3%) were aged between 21 and 30 years and majority of them were female (96.4%). Majority of the respondents were married (72.7%) and had diploma and higher (88%) as their highest educational level. Majority were working normal shift (89.6%) and working extended hours (62.3%). Table I shows

**Table III: Summary scores of the subscales and overall PES-NWI by age, gender, marital status, education level, years of experience, and working patterns**

Variable	Participation (maximum value: 36) Mean (95% CI)	Foundation (maximum value: 40) Mean (95% CI)	Managers Support (maximum value: 20) Mean (95% CI)	Workforce Adequacy (maximum value: 16) Mean (95% CI)	Physician/Nurse Relations (maximum value: 12) Mean (95% CI)	Overall (maximum value: 124) Mean (95% CI)
<b>Age (years)</b>						
21-30	25.56 (25.04-26.08)	31.27 (30.87-31.68)	14.11 (13.80-14.41)	9.82 (9.52-10.13)	9.01 (8.84-9.18)	89.78 (88.37-91.18)
31-40	25.51 (24.95-26.06)	30.96 (30.56-31.35)	14.17 (13.78-14.56)	9.56 (9.18-9.94)	8.96 (8.76-9.16)	89.16 (87.66-90.66)
More than 40	27.31 (25.78-28.83)	32.19 (31.06-33.32)	15.31 (14.47-16.15)	10.35 (9.57-11.12)	8.96 (8.72-9.20)	94.12 (90.39-97.84)
p value	0.140	0.651	0.060	0.903	0.698	0.274
<b>Sex</b>						
Male	23.53 (20.41-26.67)	30.23 (28.37-32.10)	13.15 (11.43-14.88)	8.62 (7.03-10.21)	8.69 (7.63-9.75)	84.23 (76.12-92.35)
Female	25.75 (25.37-26.12)	31.26 (30.97-31.54)	14.25 (14.02-14.49)	9.80 (9.58-10.03)	9.00 (8.88-9.12)	90.07 (89.07-91.06)
p value	0.031	0.184	0.084	0.056	0.350	0.033
<b>Marital status</b>						
Single	25.83 (25.15-26.51)	31.27 (30.70-31.84)	14.23 (13.83-14.63)	9.78 (9.32-10.24)	9.00 (8.74-9.26)	90.11 (88.12-92.10)
Married	25.61 (25.16-26.05)	31.20 (30.88-31.53)	14.21 (13.93-14.49)	9.76 (9.50-10.02)	8.99 (8.85-9.12)	89.76 (88.60-90.92)
p value	0.597	0.835	0.941	0.925	0.935	0.761
<b>Highest education level</b>						
Certificate	27.21 (25.93-28.49)	32.48 (31.33-33.64)	15.09 (14.33-15.86)	10.67 (9.97-11.36)	9.42 (8.86-9.99)	94.88 (91.11-98.64)
Diploma and higher	25.51 (25.13-25.90)	31.10 (30.81-31.38)	14.13 (13.89-14.37)	9.67 (9.43-9.91)	8.95 (8.83-9.07)	89.36 (88.34-90.38)
p value	0.019	0.005	0.019	0.013	0.026	0.002
<b>Working experience (years)</b>						
Less than 3	26.25 (25.34-27.16)	31.69 (30.89-32.48)	14.34 (13.75-14.94)	10.45 (9.92-10.98)	9.03 (8.72-9.34)	91.76 (89.24-94.28)
3-10	25.18 (24.70-25.66)	31.04 (30.69-31.38)	13.91 (13.61-14.20)	9.40 (9.10-9.68)	8.97 (8.80-9.14)	88.49 (87.21-89.77)
11-20	26.31 (25.53-27.09)	31.20 (30.58-31.81)	14.82 (14.34-15.29)	10.21 (9.72-10.71)	9.01 (8.82-9.20)	91.55 (89.47-93.62)
More than 20	28.86 (27.05-30.66)	32.86 (30.69-35.02)	16.57 (15.39-17.75)	10.29 (8.90-11.67)	9.14 (8.79-9.49)	97.71 (92.41-103.02)
p value	0.274	0.777	0.020	0.813	0.939	0.412
<b>Working normal shift</b>						
Yes	25.48 (25.10-25.87)	31.15 (30.86-31.44)	14.13 (14.19-15.71)	9.66 (9.42-9.90)	8.98 (8.85-9.10)	89.41 (88.38-90.43)
No	27.24 (26.00-28.47)	31.84 (30.83-32.85)	14.95 (14.19-15.71)	10.63 (9.93-11.33)	9.11 (8.68-9.53)	93.76 (90.13-97.40)
p value	0.005	0.140	0.035	0.010	0.530	0.009
<b>Working extended hours</b>						
Yes	25.27 (24.81-25.72)	31.04 (30.69-31.38)	14.01 (13.72-14.31)	9.41 (9.13-9.69)	8.95 (8.80-9.10)	88.67 (87.49-89.85)
No	26.33 (25.69-26.96)	31.53 (31.04-32.02)	14.55 (14.18-14.92)	10.35 (9.98-10.72)	9.07 (8.86-9.27)	91.82 (90.07-93.57)
p value	0.007	0.094	0.027	<0.001	0.353	0.003
<b>Doing double shifts</b>						
Yes	25.29 (24.80-25.77)	31.00 (30.63-31.37)	13.86 (13.54-14.18)	9.50 (9.20-9.79)	8.87 (8.71-9.02)	88.51 (87.22-89.79)
No	26.13 (25.55-26.70)	31.49 (31.06-31.92)	14.64 (14.32-14.97)	10.08 (9.73-10.43)	9.14 (8.96-9.33)	91.49 (89.95-93.02)
p value	0.027	0.089	0.001	0.011	0.023	0.003
<b>Working during day off</b>						
Yes	25.10 (24.47-25.73)	31.06 (30.55-31.56)	13.70 (13.28-14.12)	9.07 (8.73-9.42)	8.74 (8.54-8.94)	87.68 (86.01-89.34)
No	26.00 (25.54-26.46)	31.32 (30.98-31.65)	14.52 (14.25-14.79)	10.17 (9.88-10.45)	9.14 (8.99-9.29)	91.15 (89.92-92.37)
p value	0.022	0.383	0.001	<0.001	0.002	0.001

the socio-demographic and work-related characteristics of respondents.

*Nurses’ perception towards practice environment*

Table II illustrates the descriptive statistics for overall scale and each subscale of the PES-NWI. Mean values for each subscale were as follows: 2.85 (95%CI: 2.81-2.89) for the subscale Participation; 3.12 (95%CI: 3.09-3.15) for the subscale Foundation; 2.85 (95%CI: 2.80-2.89) for the subscale Managers Support; 2.44 (95%CI: 2.38-2.50) for the subscale Workforce Adequacy; and 3.00 (95%CI: 2.96-3.04) for the subscale Physician/Nurse relations. Overall NPE was rated as being favourable with mean score of 2.90 (95%CI: 2.87-2.93). The study also revealed that four out of five subscales’ mean scores were more than 2.50 which indicated the favourable setting. Workforce Adequacy was perceived as the least favourable which was concordance with two items with high percentage of minimum agreement, 69.7% and 61.4%, for “Enough nurses to provide quality patient” (mean score = 2.15), and “Enough staff to get the work done” (mean score = 2.16), respectively.

The skewness and kurtosis values of the overall PES-NWI and each subscale were within the normal distribution range which was -1.96 to +1.96. Thus, the data was distributed normally and appropriate for further inferential parametric statistics analysis.

*Associations between nurses’ socio-demographic and work-related characteristics on perception towards practice environment*

Table III shows the summary scores of the subscales and overall PES-NWI by age, sex, marital status, education level, years of experience, and working patterns. Statistically significant differences were showed for overall PES-NWI scores between nurses with different sex, educational level, working patterns such as working in shift, working extended hours, doing double shifts and working during day off. Nurses aged 31-40 years, married, with 3-10 years working experience scored lower for overall PES-NWI; however, the differences were not significant compared to their counterparts. There were no statistically significant differences in scores of all subscales with respect to their age groups and marital status. Between male and female

**Table IV: Associated factors for perception towards PES-NWI**

Variables	Simple linear regression		Multiple linear regression		
	Unadjusted $\beta$ (95% CI)	Sig.	Adjusted $\beta$ (95% CI)	t	Sig.
Age: 31-40 years <sup>a</sup>	-0.620 (-2.727, 1.487)	0.563	-1.647 (-4.003, 0.709)	-1.37	0.170
Age: More than 40 years <sup>a</sup>	4.339 (0.387, 8.290)	0.031	1.191 (-3.903, 6.285)	0.46	0.646
Sex (ref: male)	5.834 (0.471, 11.197)	0.033	6.393 (1.234, 11.552)	2.44	0.015
Marital status	-0.347 (-2.588, 1.894)	0.761	-	-	-
Highest education level (ref: certificate)	-5.518 (-8.959, -2.078)	0.002	-4.763 (-8.142, -1.383)	-2.77	0.006
Working experience: Less than 3 years <sup>b</sup>	-3.273 (-5.894, -0.651)	0.015	3.835 (1.247, 6.424)	2.91	0.004
Working experience: 11-20 years <sup>b</sup>	-0.212 (-3.414, 2.990)	0.897	2.641 (-0.420, 5.701)	1.70	0.091
Working experience: More than 20 years <sup>b</sup>	5.953 (-1.514, 13.420)	0.118	6.632 (-1.880, 15.145)	1.53	0.126
Working normal shift (ref: yes)	4.358 (1.114, 7.601)	0.009	2.461 (-1.015, 5.937)	1.39	0.165
Working extended hours (ref: yes)	3.148 (1.113, 5.183)	0.003	1.986 (-0.077, 4.048)	1.89	0.059
Doing double shifts (ref: yes)	2.983 (1.000, 4.966)	0.003	1.399 (-0.750, 3.548)	1.28	0.201
Working during day off (ref: yes)	3.471 (1.436, 5.507)	0.001	2.702 (0.612, 4.793)	2.54	0.011

Models' parameter: R<sup>2</sup>: 0.1396; Adjusted R<sup>2</sup>: 0.1128; F (11: 354) = 5.22; p = <0.001.

<sup>a</sup>Reference category: Age less than 30 years.

<sup>b</sup>Reference category: Working experience of 3-10 years.

respondents, there were no significant differences for scores of all subscales, except for subscale Participation. Those working extended hours, doing double shifts and working during day off scored lower for all subscales. All differences were statistically significant except for subscale Foundation as well as for subscale Physician/Nurse Relations for working in shifts and extended hours.

The variables that remained significant in the multiple linear regression model (dependent variable: overall score in PES-NWI), adjusted by age, working normal shift, working extended hours, and doing double shifts, with p<0.05, were sex (coefficient  $\beta$  = 6.393, for female; category of reference: male), highest education level (coefficient  $\beta$  = -4.763, for diploma and higher; category of reference: certificate), working experience (coefficient  $\beta$  = 3.835, for less than 3 years; category of reference: 3-10 years), and working during day off (coefficient  $\beta$  = 2.702, for no; category of reference: yes) (Table IV). In the adjusted model, female nurses, nurses with certificate, less than three years of experience, and not working during day off were more likely to have more positive perception towards the practice environment.

**DISCUSSION**

Assessment of nurses' perception on their practice environment enables us to explore and comprehend areas that need changes to make better environment for nursing care to be delivered to the patients. To the best of our knowledge, this paper is the first study that analysed the perception of nurses towards their practice environment in MOH hospitals. Overall, our findings indicated that nursing

practice environment was favourable. All subscales were rated as favourable except Workforce Adequacy. Our finding was similar to another study conducted among nurses at private hospitals in Malaysia, where overall, the nurses had high agreement for the availability of positive environment in their local setting.<sup>17</sup>

The most favourable aspect was subscale Foundation; the finding was similar to Malaysian and international studies.<sup>21</sup> Of the nine items in this subscale, active human resource management or continual learning plan for nurses scored highest reflecting the presence of continuing education opportunities for nurses. This positive finding could be due to both private and MOH hospitals provide strong foundation to the nurses that empower nurses to perform their responsibilities. This was also consistent with the MOH's policy to provide the MOH's staff at least seven days of in-service training annually.<sup>22</sup> In addition, renewal of Annual Practicing Certificate for nurses required a minimum number of Continuing Professional Development (CPD) points.<sup>23</sup>

In this study, the subscale Workforce Adequacy was scored relatively low compared to others. This finding was similar to previous published studies.<sup>15,17,24</sup> Respondents scored lowest for items "enough nurses to provide quality patient" and "enough staff to get the work done". This is corresponding with the findings that majority of the respondents had experienced working extended hours, more than half had experienced doing double shift and about one-third experienced working during day off. Adequate staff is one of the elements contributing to positive clinical work environment.<sup>3</sup> Several studies showed that sufficient staff were associated with the quality of nursing care, satisfaction

of patients, patient care outcomes, nurses' job satisfaction, and nurse retention.<sup>16,24,25</sup> In recent years, adequacy of nurse staffing in Malaysia and neighbouring country have been highlighted and debated.<sup>26</sup> In 2017, it was reported that the ratio of nurses per 1,000 population was 3.5,<sup>27</sup> far below the Organisation for Economic Cooperation and Development (OECD) member countries ratio of nurses per 1,000 population of 8.8.<sup>28</sup> Although the ratio has increased remarkably over years, from 1.7 nurses per 1000 population in 2000,<sup>27</sup> but it was still considered low.

Staffing and rostering are a complicated and critical area to deal with. It involves effective planning and management of working schedule for staff to meet the demand for services without risking staff burnout. The present study showed lowest agreement level on statements for "enough nurses to provide quality patient" and "enough staff to get the work done". This warrant attention from the management of MOH hospitals since nursing care is crucial in ensuring patient safety and quality of care.<sup>29</sup>

The strength of the present study included the fact that we explored NPE among nurses in MOH hospitals, as published studies conducted locally found were only reported NPE in private and non-MOH hospitals. In addition, the present study also reported predictors for perception towards NPE. In the adjusted model, female nurses, nurses with certificate, less than three years of experience, and not working during day off were more likely to have more positive perception towards the practice environment.

#### LIMITATIONS

We acknowledge that this study has a few limitations. As this was a self-administered questionnaire survey, the accuracy of the results was heavily dependent upon information given by respondents and open to recall bias. Apart from this, selection bias may occur due to convenience sampling as we only distributed the paper-based questionnaire among nurses at two public hospitals. Another limitation is that the study was conducted at computerised and less crowded hospitals. Thus, the findings may not be appropriate to generalise to the whole of hospitals in Malaysia. In addition, our study did not measure outcomes related to nursing practice environment. The distribution of respondents between male and female nurses (13 versus 353) and educational level (33 versus 333) also were not balanced in this study. However, both characteristics were included in the model as it reflects the real scenario of population of nurses in Malaysia.

#### CONCLUSION

The findings showed that nurses from the two public hospitals studied here reported favourable practice environments, except for the staffing and resource adequacy. Unfavourable nursing staff adequacy was associated with working extended hours, doing double shift and working during day off; which indicates shortage of nurses. Optimal staffing and scheduling of nurses in hospital are essential to address the unfavourable perception of nurses on nursing staff adequacy. Policy makers, service providers, and hospital managers should perhaps explore further on human resource planning and management of nursing personnel to tackle

long standing issue on nursing staff shortage. Further research is needed to study whether quality of nursing care and outcome of patients were affected by staffing and resource adequacy, and to explore the effects of other compounding variables (e.g., being nurse leader/manager or salary satisfaction), towards their perception on the practice environment.

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#### REFERENCES

1. World Health Organization & Joan Burton. WHO Healthy Workplace Framework and Model. Switzerland; 2010 (cited July 2020). Available from: [https://www.who.int/occupational\\_health/healthy\\_workplace\\_framework.pdf](https://www.who.int/occupational_health/healthy_workplace_framework.pdf).
2. World Health Organization. Positive Practice Environments Campaign. 2018 (cited July 2020). Available from: <http://www.who.int/workforcealliance/about/initiatives/pppe/en/>.
3. Baumann A. Positive Practice Environments: Quality Workplaces = Quality Patient Care. Information and Action Tool Kit. International Council of Nurses. Geneva; 2007. 1-69.
4. Department of Occupational Safety and Health, Ministry of Human Resources Malaysia. Guidelines on Occupational Safety and Health Act 1994 (Act 514). Malaysia; 2006 (cited October 2020). Available from: <https://www.dosh.gov.my/index.php/legislation/guidelines/general/598-05-guidelines-on-occupational-safety-and-health-act-1994-act-514-2006/file>.
5. Laws of Malaysia. Act 514 Occupational Safety and Health Act 1994. Malaysia; 1994 (cited October 2020). Available from: <https://www.dosh.gov.my/index.php/legislation/acts-legislation/23-02-occupational-safety-and-health-act-1994-act-514/file>.
6. Rannan-Eliya RP, Anuranga C, Manual A, Sararaks S, Jailani AS, Hamid AJ, et al. Improving health care coverage, equity, and financial protection through a hybrid system: Malaysia's Experience. *Health Aff* 2016 May 1; 35(5): 838-46.
7. Ministry of Health. Health Facts 2016. Malaysia; 2016 (cited July 2020). Available from: [http://www.moh.gov.my/images/gallery/publications/KKM\\_HEALTH\\_FACTS\\_2016.pdf](http://www.moh.gov.my/images/gallery/publications/KKM_HEALTH_FACTS_2016.pdf).
8. Alam MM, Mohammad JF. Level of job satisfaction and intent to leave among Malaysian nurses. *Bus Intell J* 2009; 3(1):123-37.
9. Atefi N, Abdullah KL, Wong LP. Job satisfaction of Malaysian registered nurses: A qualitative study. *Nurs Crit Care* 2016; 21(1): 1-10.
10. Rokiah M. Stress prevalence and causes of occupational stress among staff nurses in Kuala Lumpur Hospital. (Master's thesis). The National University of Malaysia, Selangor, Malaysia; 1994.
11. Lake ET. Development of the Practice Environment Scale of the Nursing Work Index. *Res Nurs Health* 2002; 25: 176-88.
12. Aiken LH, Clarke SP, Sloane DM, Cheney T. Effects of hospital care environment on patient mortality and nurse outcomes. *J Nurs Adm* 2008; 38(5): 223-9.
13. Xu X. Identification of nursing-sensitive indicators for nursing quality monitoring and reporting in an Australian context. (Master's thesis). Victoria University; 2015.
14. Lake ET. The Nursing Practice Environment: Measurement and evidence. *Med Care Res Rev* 2007; 64: 104S-122S.
15. Swiger PA, Patrician PA, Miltner RSS, Raju D, Breckenridge-Sproat S, Loan LA. The Practice Environment Scale of the Nursing Work Index: An updated review and recommendations for use. *Int J Nurs Stud* 2017; 74: 76-84.

16. Maziah A, Wichaikhum O, Nantsupawat R. Nursing Practice Environment and patient outcomes in university hospitals in Malaysia. *Heal Environ J* 2012; 3(1): 16-26.
17. Tang WM, Idris AR. Nursing Practice Environment as perceived by the Malaysian private hospital nurses. *Int eJournal Sci Med Educ* 2016; 10(2): 11-20.
18. Open Source Epidemiologic Statistics for Public Health. 2013 (cited October 2020). Available from: <http://www.openepi.com/SampleSize/SSPropor.htm>.
19. Polit DF, Beck T, Owen S V. Focus on research methods: Is the CVI an acceptable indicator of content validity? Appraisal and Recommendations. *Res Nurs Health* 2007; 30: 459-67.
20. Lake ET, Friese CR. Variations in Nursing Practice Environments. *Nurs Res* 2006; 55(1): 1-9.
21. Warshawsky NE, Havens DS, Sullivan D. Global Use of the Practice Environment Scale of the Nursing Work Index. *Nurs Res* 2012; 60(1): 17-31.
22. Public Service Department of Malaysia. Training Policy for Human Resource in Public Sector. 2005.
23. Ministry of Health. Guidelines: Continuing Professional Development (CPD) for Nurses. 2016.
24. Parro-Moreno A, Serrano-Gallardo P, Díaz-Holgado A, Aréjula-Torres JL, Abraira V, Santiago-Pérez IM, et al. Impact of primary care nursing workforce characteristics on the control of high-blood pressure: a multilevel analysis. *BMJ Open* 2015; 5(12): e009126.
25. Anzai E, Douglas C, Bonner A. Nursing practice environment, quality of care, and morale of hospital nurses in Japan. *Nurs Health Sci* 2014; 16: 171-8.
26. Seah R. Overworked nurses pose health risks to patients: But why can't nurses catch a break? [Internet]. 2016 (cited July 2020). Available from: <https://today.mims.com/overworked-nurses-pose-health-risks-to-patients--but-why-can-t-nurses-catch-a-break->.
27. World Health Organization. Global Health Observatory (GHO) data repository - Density of nursing and midwifery personnel. 2020 (updated June 2020; cited July 2020). Available from: <https://apps.who.int/gho/data/view.main.UHCHRHv>.
28. OECD. Health at a Glance 2019: OECD Indicators. Paris; 2019 (cited July 2020). Available from: <http://www.oecd.org/health/health-at-a-glance.htm>.
29. Trinkoff AM, Johantgen M, Storr CL, Gurses AP, Liang Y, Han K. Nurses' work schedule characteristics, nurse staffing, and patient mortality. *Nurs Res*. 2011; 60(1): 1-8.

# Antidiabetic potential and high synergistic antibacterial activity of silver nanoparticles synthesised with *Musa Paradisiaca* tepal extract

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## ABSTRACT

This work investigates the *Musa Paradisiaca* plant and its tepal extracts. The research findings show that the tepal extracts of *M. Paradisiaca* contain high phytochemical activity. Hence we can conclude that these plants have a number of beneficial properties. Phytochemical analysis concludes that the plant is rich in flavonoids, phenolic compounds, tannins, terpenoids, and phytosterol. In the current work, silver nanoparticles (AgNPs) have revealed the antioxidant properties of *M. Paradisiaca*. The results show that the methanolic extracts of these tepals exhibit antioxidant potential and are also sources of natural antioxidant compounds, though comparatively, AgNPs have shown the best antioxidant activity. This work investigates the link between the ethnopharmacological statements and the bioactive constituents found in *M. Paradisiaca* toward all probable markers for cervical cancer via in vivo studies and molecular docking, to form a pharmacophore setting for the active target. However, most of the mechanisms of action of herbal medicines are not in total agreement, and the information collected from their traditional remedies over the years must not be neglected. Hence, it is sensible to investigate the options available in herbal medicine for cancer progression. Biosynthesised AgNPs are principally spherical and nanosized. It was also found that tepal-mediated AgNPs exhibit excellent antimicrobial efficacy against tested human pathogens. This green method can be used as a better alternative source than the chemical fabrication of nanomaterials and the biosynthesised nanoparticles can be used in antibacterial medicines. The methanolic tepal extract of *M. Paradisiaca* with AgNPs displayed proficient antidiabetic properties in the diabetes rat model and so could have a possible development for medical use in the future.

## KEYWORDS:

*Musa Paradisiaca*, diabetes, antioxidant, silver nanoparticles, flavonoids

## INTRODUCTION

Nanotechnology is a rapidly growing field owing to its application in science and technology for engineering new

materials at the nanoscale level. The term “nano” specifies one billionth of a meter ( $10^{-9}$ ) and particles of size less than 100 nm are stated as nanoparticles (NPs).<sup>1,2</sup> Currently, nanotechnology is one of the key compelling research areas in material science with the discovery of different plants for the use of NP synthesis. Nanotechnology can be administered in various fields including agriculture, medicine, healthcare, transport, textiles, water treatment, and cosmetics, which enhances the value of products. It is a characterisation, design, production, and application system by monitoring the shape and size on a certain nanometer scale.<sup>3</sup>

Diabetes mellitus (DM) is an endocrine metabolic disorder and it is quickly cumulating worldwide. People with DM are not able to secrete sufficient insulin, hence they have abnormal levels of blood glucose in their body. If this is not treated, it may lead to severe disease. The most common form of the disease is differentiated into two main types: Type-1 and Type-2 DM. Type-1 is responsible for at least 5%–10% of the total cases while Type-2 comprises more than 90%–95% of all cases. The risk factors of DM are undefined, however both genetic and environmental factors including obesity and lack of physical activity seem to play an important role.<sup>5</sup>

DM-associated complications include diabetic retinopathy, diabetic nephropathy, and arteriosclerosis, which are the principal causes of morbidity and mortality among diabetic patients. These complications are caused by low levels of cellular antioxidant enzymes which lead to oxidative stress. The World Health Organization (WHO) reports that patients with diabetes are predicted to grow to 300 million or even more by the year 2025.<sup>6</sup> Studies of diabetes has grown recently and its treatment options are therapies including use of insulin, medicinal plants, and numerous other oral antidiabetic drugs such as sulfonylureas, biguanides, alpha-glucosidase inhibitors, and glinides. It has been seen that entirely oral antidiabetic agents have adverse effects.

In the literature, there are 400 plant species mentioned that have hypoglycemic properties. However, the search for new antidiabetic agents from medicinal plants continues to be in demand because they contain novel substances that reveal safe and cost-effective impacts on DM. Most natural plants

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have secondary metabolites such as flavonoids, alkaloids, glycosides, terpenoids, and carotenoids that are commonly associated with antidiabetic activity.<sup>7</sup> Ethnobotanical evidence recommends that about 800 plants may contain antidiabetic potential, and among them, *Momordica charantia*, *Pterocarpus marsupium*, and *Trigonella foenum graecum* seem to be most valuable for the treatment of Type 2 diabetes.<sup>8</sup>

Medicinal plants have an optimistic future as there are still half a million undiscovered plants in the world.<sup>9</sup> However, the application of the whole plant for research or treatment has many disadvantages, such as variations in the plant bioactive components based on the climate.<sup>10</sup> The different plant parts are the root, fruit, skin, leaf, seeds, and flowers. The bioactive materials in almost all medicinal plants have treatment properties that can serve as therapeutic agents.<sup>11</sup> There are over one-tenth of plant extracts (more than 50,000 species) that are incorporated into cosmetic and pharmaceutical products.<sup>12,13</sup> Plants with antioxidant properties have been reported to be valuable for atherosclerosis and cardiovascular disease prevention by halting lipids peroxidation.<sup>14</sup> Natural products have various mechanisms to cope with this issue, using antioxidant enzymes.<sup>15</sup>

NPs from plants are much stable and the synthesis is more rapid than NPs from microorganisms. The benefits of using medicinal plant and plant based compounds for the synthesis of metal NPs have been attentive to explore the mechanisms of metal ions uptake and bioreduction by the plants, and the likely mechanisms of metal NPs production in plants. The plant extracts may function as reducing and capping agents in NPs synthesis.<sup>16</sup> NPs can be used to monitor the oxidative status of tissues *in vivo* using conjugated biosensor.<sup>17</sup> NPs are reported to have antimicrobial activity.<sup>18</sup> They are used for cell tagging and drug delivery.<sup>19</sup> and can also be applied as a conjugated biosensor for reaction oxygen species in diabetes. Nanotechnology is concerned with the synthesis of NPs of various sizes and shapes and their potential applications.<sup>17</sup>

The use of medicinal remedies for the prevention and treatment for the disease is of increasing because the advantage and efficiency phytoconstituents activity in the herbs. Medicinal plants have a number of medicinal. One of such plant is *M. paradisiaca*. It has been reported to have biological activities such as antioxidant, antilithiatic, antimicrobial, antidiabetic, antidiarrheal, antiulcer, hepatoprotective, hypocholesterolaemic, anti-snake venom, wound healing and anti menorrhagic.<sup>20</sup> Banana is the commonly used term used for genus *Musa*, herbaceous plants for the fruit they produce. It is one of the oldest cultivated plants. All the parts in banana tree have medicinal uses: the flowers are used in dysentery and bronchitis and ulcers. Cooked flowers used in patients with diabetes. The astringent plant is used for patients such as hysteria, leprosy, fevers, epilepsy, haemorrhages, acute dysentery and diarrhea and also for hemorrhoids, insect bites, and stings.<sup>21</sup> In this study *M. paradisiaca* flowers (tepals) the edible part will be used for anti diabetic activity with the help of NPs. In previous studies antidiabetic drugs were discovered from different plant

materials which will be used on human kind. The key objective of the study is to determine the ethno pharmacological knowledge of *M. paradisiaca* using green Technology.

## MATERIALS AND METHODS

### Collection of specimens

The *M. paradisiaca* flowers were collected from vegetable market of Koyambedu, Chennai. The plants were washed properly with tap water and air-dried. The drying of plant is necessary to eliminate the water remaining from the plants before storing. The air dried plants were powdered using conventional blender for future use.

### Preparation of methanolic crude extract

Compound with limited solubility in solvent must be subjected to soxhlet extraction. This method uses only single batch of solvent instead of several portions of solvent being exposed to the compound. However, this method cannot be used for thermo labile compound as extended exposure to heating can lead to degradation of compounds.<sup>22</sup>

### Qualitative analysis of phytochemicals

Phytochemical analysis was performed for the following components such as alkaloids, amino acids, carbohydrates, phenolic compounds, saponins, phytosterols, flavanoids, and terpenoids.

### Synthesis of silver nanoparticles

An amount of 1 mM silver nitrate ( $\text{AgNO}_3$ ) in aqueous solution was prepared in 250 mL. For reduction into  $\text{Ag}^+$  ions, tepal extract was added. The mixture was microwaved at 300 W for 4 min for complete bioreduction to avoid pressure increase. While the colour changed from light to yellowish brown and then to reddish brown and to colloidal brown, the variation was observed at room temperature for at least 30 min by UV-visible spectrophotometry (in dark to avoid photoactivation of  $\text{AgNO}_3$ ). Experimental controls were sustained for the entire period.  $\text{AgNO}_3$  was completely reduced to  $\text{Ag}^+$  ions, established by the presence of colloidal brown colour changes. The solution was then cooled and left for about 24 h for comprehensive bioreduction. after which the mixture was stored in an airtight container for further analysis. The silver nanoparticle (AgNP) formation was confirmed by spectrophotometric analysis.<sup>23</sup>

### Characterization of AgNPs

Analysis using scanning electron microscopy (SEM) was performed by fabrication of suspension onto clean electric stubs and permitting water for complete evaporation. For voltage acceleration to 15 kW, JEOL-5800-LV16 SEM was used with a sample current of 41  $\mu\text{A}$ .

### Antioxidant assay (DPPH Assay)

The crude extracts and AgNP antioxidant effects were evaluated by DPPH assay according to the method described previously.<sup>24</sup> The free radical DPPH (2,2-diphenyl-2-picryl hydrazyl) changes to diphenyl-picryl hydrazine which is noticed by color changes from deep violet to light yellow when acted upon by an antioxidant. The changes can be measured using a spectrophotometer at 518 nm to determine

Table I: Phytochemical screening of *Musa paradisiaca*

S. No	Constituent	Test	Inference
1.	Alkaloids	Mayer's test	++
2.	Amino acid	Ninhydrin test	+
3.	Carbohydrate	Molish's test	+
4.	Phenolic Compounds	Ferric Chloride test	+
5.	Protein	Biuret test	+
6.	Saponin	Foam test	+
7.	Phytosterol	Liebermann–Burchard's test	–
8.	Flavonoid	Alkaline reagent test++	
9.	Triterpenes	Terpenoid test	++

the DPPH scavenging activity of the antioxidant sample. Extracts measuring 25 µm and 0.48 ml of methanol were added to 0.5 ml of methanolic solution of DPPH. The mixed solution was allowed for reaction to take place at room temperature for at least 30 min. Methanol was used as blank and AgNPs served as the positive control. After incubation, the purple colored discolorisation was measured at 518 nm.

#### Antibacterial activity by disc diffusion method

Antibacterial activities of crude extracts and AgNPs were carried out using disc diffusion technique following the Kirby–Bauer technique.<sup>25,26</sup> The bacterial strain was culture in nutrient agar (NA). Pure culture was inoculated from the Petri plate to the MHA plate for subculture at 37°C for 24 h. The aseptically prepared inoculum was prepared by inoculating the fresh culture into 2 ml of sterile 0.145 mol/L saline tube and the cell density (1.5×10<sup>8</sup> cfu/ml) was adjusted according to 0.5 McFarland turbidity standard. Then the inoculum was plated evenly on an MHA plate to yield a lawn culture. Sterile Whatman No. 1 filter paper discs 5 mm in diameter were placed and impregnated with plant extracts (100 µg/disc) on the inoculated MHA plates. The plates were allowed to incubate for 24 h at 4°C and incubated at 37°C. The following day, the plates were monitored for a clear zone around the disc, indicating inhibition of bacterial growth. The inhibition zone was measure in millimeters. A clear zone indicates no activity.<sup>27</sup> Experiments were done in triplicate and expressed as resistant (<7 mm), intermediate (8–10 mm), and sensitive (>11 mm).<sup>28</sup>

#### Antidiabetic activity

##### Chemicals and reagents

The following chemicals were purchased from invitrogen Sigma–Aldrich

MTT(3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide), acridine orange amphotericin B, and all other solvent chemicals, respectively.

##### Cell lines and culture

3T3 cells were purchased from the National Centre For Cell Science (NCCS, Pune), sustained in Rose well Park Memorial Institute medium (RPMI), supplemented with 10% fetal bovine serum, and penicillin/streptomycin (250 U/mL) at 37°C in a humidified atmosphere of 5% CO<sub>2</sub>. Cells grown to log phase were used for analysis.

##### Cell viability assay

The cytotoxicity and cell viability were assessed by colorimetric assay (MTT). Cells were cultured (1X10<sup>5</sup>

cells/mL) in culture plates (96 well) and pretreatment was done according to the assay requirements. In all, 10 µm of MTT (5 mg/mL) was supplemented to the cell containing well and subjected to incubation for another 4 h. The solution was decanted and the tetrazolium product was dissolved with 100 µL of DMSO per well. The absorbance reading was obtained (570 nm) using a spectrophotometer and the cell viability values were calculated.<sup>29</sup>

## RESULTS

### Methanolic crude extract of *M. Paradisiaca*

The methanolic crude extract was prepared from the powdered flowers of *M. paradisiaca* using soxhlet apparatus at 1.4 mg after yield. The extract was concentrated by vacuum and dried in a dessicator.

### Phytochemical screening of methanolic extract of *M. paradisiaca*

Qualitative analysis of the *M. paradisiaca* methanolic extract revealed the existence of flavonoids, alkaloids, glycosides, polyphenols, tannins, proteins, saponins, sterols, and triterpenes in the tepal extract (Table I).

### Synthesis of AgNPs

Noble metals are recognized to display exclusive optical activity as they have the property of surface plasmon resonance. The AgNPs formation was supervised with change of color. The color of the reaction mixture changed to yellowish brown in 10 min and to reddish brown after 1 h, signifying the production of AgNPs, because silver metal ions Ag<sup>+</sup> reduced to AgNPs Ag through the active molecules.

### Characterisation of crude extract and AgNPs by SEM analysis

SEM images of the crude extract and AgNPs are shown in Figure 1. It is observed that different shapes of AgNPs were taken from different tepal extracts and used as reducing and capping agents. *M. paradisiaca* tepal extracts produced are spherical, triangular, and cuboidal AgNPs. This might be affected by the different quantity and nature of capping agents in the different tepal extracts.

The morphology of the produced AgNPs using SEM magnified at 9400X and 10,000X are shown in Figure 2 for both the control and treated samples. The monodispersed spherical AgNPs were shaped on the surface of methanolic crude extract derived biological materials. The picture acquired from FESEM also presented spherical NPs, approving the result achieved by SEM.



### Antioxidant activity

#### DPPH assay

The percentage inhibition of free radical generation by methanolic extracts was found to increase in a concentration-dependent manner, showing an IC<sub>50</sub> value of 152.6 µg/ml (53.4% inhibition) and 118.2 µg/ml (59.36% inhibition), respectively, compared with the standard, ascorbic acid IC<sub>50</sub> value (112.7 µg/ml). With regard to peroxide radical activity, MFF extract exhibited high inhibition (58.63% with IC<sub>50</sub> value of 130.3 µg/ml) compared to TTF (53.26% inhibition with IC<sub>50</sub> value of 190.4 µg/ml) when taking into account the IC<sub>50</sub> value of standard, ascorbic acid (111.7 µg/ml) (Figure 2).

#### Disc diffusion method

The methanolic extract antibacterial activity against human pathogenic organisms by disc diffusion technique demonstrated a full zone of inhibition. The antibacterial activity of AgNPs was examined on *Bacillus*, *Pseudomonas*, *Staphylococcus*, and *E. coli* colonies in NA plates impregnated with AgNPs. The zones of inhibition show the maximum activity toward the test sample. In addition, crude extracts showed better inhibition when associated with AgNO<sub>3</sub> and AgNPs. The data obtained from previous work showed similar results, which support the antibacterial activity of AgNPs. Less inhibition zone was seen in the controls (Figure 3).

#### Antimicrobial activity

In the present study, cytotoxicity of the methanolic crude extract *in vitro* and AgNPs was evaluated against 3T3 diabetic cell line at different concentrations. The samples indicated prominent cytotoxicity activity against the 3T3 cells. The data displayed that cell proliferation of 3T3 was inhibited significantly by methanolic crude extract: AgNPs with an IC<sub>50</sub> value of 41.55 (µg/ml) of the crude extract and 47.19 (µg/ml) of the NPs. The percentage of toxicity increases with the concentration of AgNPs, proposing that synthesised AgNPs are important in medicine as antidiabetic agents. The percentage viability of the diabetic cells reduced with increased concentration of the samples, while cytotoxicity against 3T3 cell lines increased with the increased concentration of the samples (Figure 4). MTT assay of methanolic crude extract and AgNPs was performed. Of these, AgNPs showed better cytotoxicity results (Figure 5).

#### Antidiabetic activity

##### MTT Assay (3T3 cell line)

##### Comparative study of AgNPs and methanolic crude extract

## DISCUSSION

Traditional medicine worldwide is redefined by research activities on various plants and their therapeutic values. Currently an epidemic expansion of DM has been reported worldwide. There are several therapeutic benefits of the different parts of the *M. paradisiaca*. However, most of the pharmacological properties of *M. paradisiaca* are based on anecdotal data and hence the present study was made to scientifically evaluate the antidiabetic property of *M. paradisiaca* tepal extract. Preliminary research showed the nontoxicity of the tepal extract on 3T3 cell lines.

The medicinal properties of the plant depend on the bioactive compounds that produce a certain physiological reaction on the human physiological process. Recently, some work has been done on phytochemistry, specifically on the banana flower of the *Musa species*. Preliminary screening phytochemical analysis of the air dried leaves and fruit peels from *M. paradisiaca* exposed the existence of glycosides, anthocyanin, tannins, flavonoids, and carbohydrate.<sup>30</sup> A quantitative study on saponin and flavonoid was reported by Boshia,<sup>31</sup> and later, the phenolic content by Mazumder.<sup>32</sup> The bark of *M. paradisiaca* was testified to comprise anthocyanins such as delphinidin, pelargonidin, peonidin, and malvidin.<sup>33,34</sup> The total phenolic content in bracts was reported to be the lowest compared with that in other plant parts such as the rhizome and fruit peels. Some bracts are almost bioactive compounds whose structure is identical to insulin and function as 'insulin-like elements,' aiding in the treatment of type I and type II diabetes.

Almost all plants with antidiabetic activity showed to have secondary metabolites like glycosides, alkaloids and flavonoids.<sup>35</sup> It has also been reported that numerous plants display effective antioxidant activity due to their phenolic compounds. Flavonoids and tannins are the phenolic compounds and plant phenolics are the main category of compounds that are primary antioxidant-free radical scavengers.<sup>36</sup> Various *in-vitro* studies have shown that certain flavonoids are potent inhibitors of the oxidative modification of LDL by macrophages.<sup>37</sup>

Flavonoids play a crucial part in the treatment of diabetes<sup>38</sup> as they can protect against hyperglycemic and alloxan-induced oxidative stress in experimental *in vivo* models.<sup>39</sup> Plant alkaloids have the tendency to release insulin from pancreatic beta cells and also have the possibility to protect it from alloxan-induced pancreatic damage in experimental animals.<sup>40</sup> Terpenoids as vitamins act as metabolism regulators and are protective antioxidants.<sup>41</sup> The results of the present study indicate that the tepal extract contains biologically active ingredients of known pharmacological actions.

Nanotechnology includes research and technology development at the atomic, molecular or macromolecular levels. The methanolic extract was used to synthesise silver nanoparticles and showed that the silver nanoparticles was successfully synthesised and identified by the colour change of the extract. The characterised silver nanoparticles were analysed by the displayed SEM images. So far many studies have investigated the antioxidant and antibacterial features of *M. paradisiaca*.<sup>42</sup> A comparative study was also done between the methanolic crude extract and nanoparticles. The results also showed that the Silver nanoparticles have more stable and better zone of inhibition against bacteria. Therefore the silver nanoparticles have many applications such antibactericidal, antioxidant properties. Antidiabetic activity of *M. Paradisiaca* against 3T3 cell line was confirmed against methanolic crude extract and silver nanoparticles. From the results it showed that the percentage of cell viability decreases and for cytotoxicity it increases. Hence it proves that *M. Paradisiaca* AgNps has better antidiabetic activity.

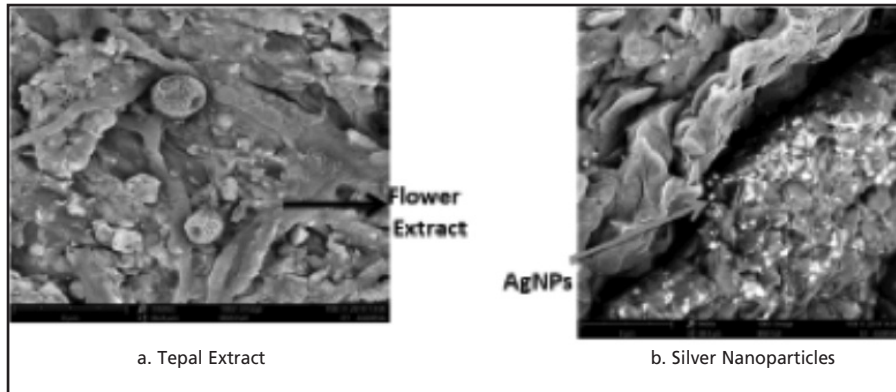


Fig. 1: Comparative SEM image of Tepal Extract and Silver Nanoparticles at 10,000X.

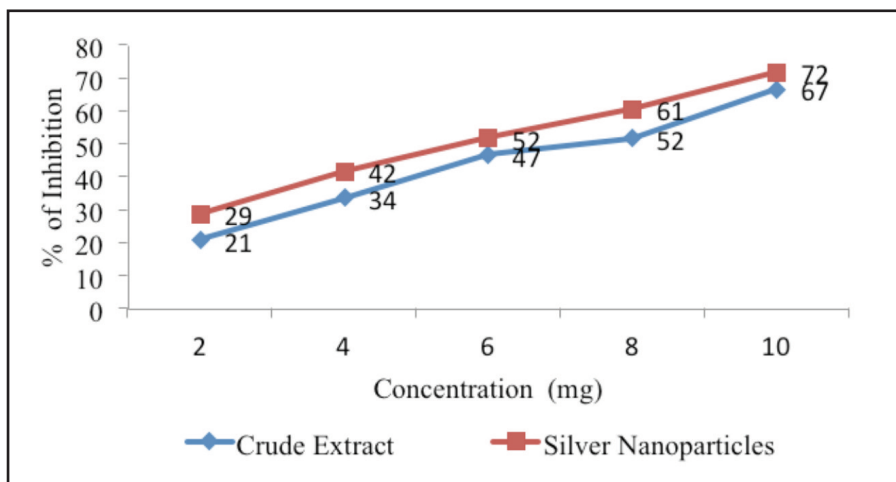


Fig. 2: Antioxidant activity in different concentrations.

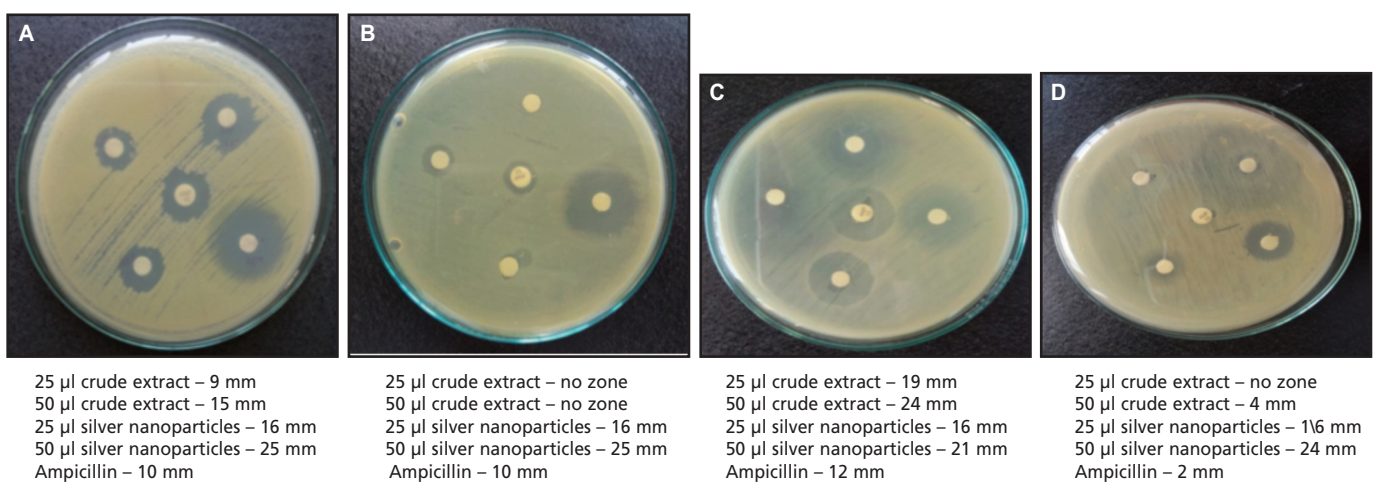


Fig. 3: Antimicrobial activity of crude extract and Silver nanoparticles against A) *Escherichia coli*, B) *Pseudomonas aeruginosa*, C) *Staphylococcus aureus* and D) *Candida albicans*.

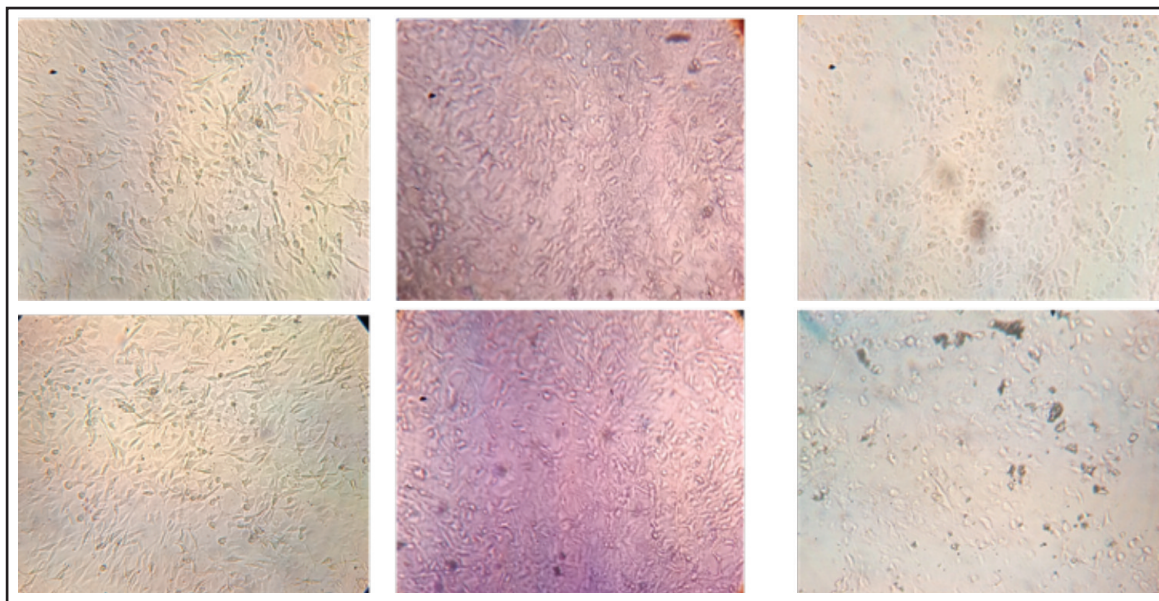


Fig. 4: Antidiabetic activity of Silver nanoparticles and crude extract against 3T3 cell line.

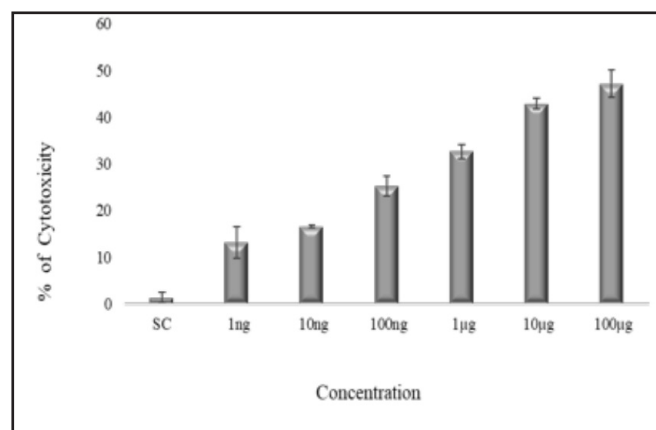
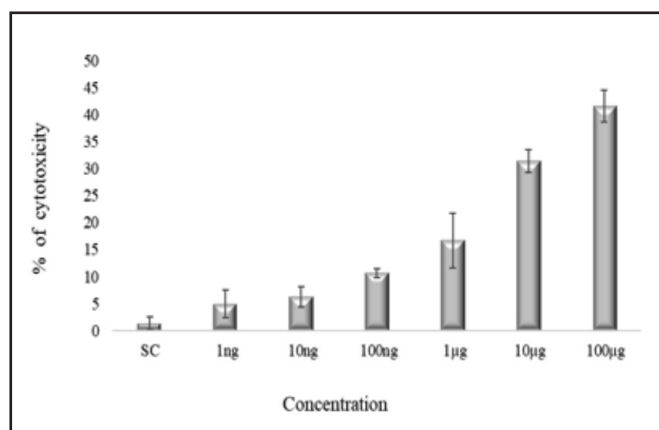


Fig. 5: MTT assay of methanolic crude extract and silver nanoparticles.

**CONCLUSION**

*M. paradisiaca* has been studied and the results of the present research findings show that the tepal extract was found to contain high phytochemical activity. Hence we can conclude that these plants are highly nutritious in nature. Phytochemical analysis concludes that it is rich in flavonoids, phenolic compounds, tannins, terpenoids, and phytosterol. In the present study, AgNPs showed the antioxidant activity of *M. paradisiaca*. The results showed that the methanolic extracts of these tepals also exhibit antioxidant potential and they are sources of natural antioxidant compounds. Comparatively, AgNPs showed the best antioxidant activity. This study aimed to find the link between ethnopharmacological claims and bioactive components in *M. paradisiaca* against all possible targets for cervical cancer through in vivo studies and molecular docking to develop a pharmacophore model for the active target. The biosynthesized AgNPs are predominantly spherical and nanosized. It is also found that tepal-mediated AgNPs exhibit excellent antimicrobial efficacy against tested human

pathogens. This green method can be used as a better alternative source than chemical fabrication of nanomaterials and the biosynthesized NPs can be used in antibacterial medicines. The methanolic tepal extract of *M. paradisiaca* of AgNPs exhibited efficient antidiabetic activity in the diabetic rat model, so they may have potential for developing medical use.

**REFERENCES**

1. Deepa K, Panda T. Synthesis of gold nanoparticles from different cellular fractions of *Fusarium oxysporum*. *J Nanosci Nanotechnol* 2014; 14: 3455.
2. Shi C, Zhu N, Cao Y, Wu P. Biosynthesis of gold nanoparticles assisted by the intracellular protein extract of *Pycnoporus sanguine* and its catalysis in degradation of 4-nitroaniline. *Nanoscale Res Lett* 2015; 10: 147.
3. Tidke PR, Gupta I, Gade AK, Rai M. Fungus-mediated synthesis of gold Nanoparticles and standardization of parameters for its biosynthesis. *IEEE Trans Nanobioscience* 2014; 13: 397.
4. Tina N, Tapan KD. Photocatalytic activity of *Aspergillus foetidus* mediated biosynthesized CdS Nanoparticles on methylene blue dye. *Ind J Biochemistry & Biophysics* 2016; 53: 44-50.
5. Ramachandran V, Baojun X. Antidiabetic properties of dietary flavonoids: a cellular mechanism review. *Nutr Metabol* 2015; 12: 60.

6. Onakpa MM, Asuzu IU. Histological changes and antidiabetic activities of *Icacina trichantha* tuber extract in beta cells of alloxan-induced diabetic rats. *Asian J Trop Biomed* 2015; 3: 628.
7. Erbas O, Pala HG, Pala EE, Artunc U, Akman L, Akman T, et al. Therapeutic effect of sunitinib on diabetes mellitus related ovarian injury: an experimental rat model study. *Gynecol Endocrinol* 2015; 31: 388.
8. Ponnusamy S, Ravindran R, Zinjarde S, Bhargava S, Kumar AR. Evaluation of traditional Indian antidiabetic medicinal plants for human pancreatic amylase inhibitory effect in vitro. *Evid Based Complement. Alternat Med* 2011; 515.
9. Singh R. Medicinal plants: A review. *J Plant Sci* 2015; 3: 50.
10. Zhang H. Bioactive Natural products: detection, isolation, and structural determination. *Phytomedicine* 2011; 18: 902.
11. Negahdari S, Galehdari H, Kesmati M, Rezaie A, Shariati G. Wound healing activity of extracts and formulations of Aloe vera, Henna, *Adiantum capillus-veneris*, and Myrrh on mouse dermal fibroblast cells. *Int J Prev Med* 2017; 8: 18.
12. Huang H. Plant diversity and conservation in China: planning a strategic bioresource for a sustainable future. *Bot J Linn Soc* 2011; 166: 282.
13. Rafieian-Kopaei M. Medicinal plants and the human needs. *J Herb Med Pharmacol* 2012; 1: 2.
14. Estampador AC, Franks PW. Precision Medicine in Obesity and Type 2 Diabetes: The Relevance of Early-Life Exposures. *Clin Chem* 2018; 64: 130.
15. Jasmine R, Ganesh Kumar A, Rajaram R. Probing the mechanism of the anti-diabetic of a terpenoid from *Elephantopus scaber* L., an Indian ethnomedicinal plant in STZ diabetic rats- In vivo and in silico analysis. *Ind J Biochemistry & Biophysics* 2018; 55: 384-88.
16. Iravani, S. Green synthesis of metal nanoparticles using plants. *Green Chem* 2011; 13: 2638.
17. Kirthika P, Deeba B, Sivakumar R, Sheikh A. *Int. J. Pharm & Pharmaceutical Science* 2014; 6: 304.
18. Meena K, Muthu K, Meenatchi V, Rajasekar M, Bhagavannarayana G, Meenakshisundaram SP. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 2014; 124: 663-669.
19. Akgul A, Senol SG, Yildirim H, Secmen O, Dogan Y. An ethnobotanical study in Midyat (Turkey), a city on the silk road where cultures meet. *J Ethnobiol Ethnomed* 2018; 14: 1.
20. Nuri Y, Semir K, Alkim GSY, Cagdas S, Gurkan Y, Altug Y, et al. Silymarin ameliorates and ovarian damage in streptozotocin induced diabetic rat model. *Ind J Biochemistry & Biophysics* 2018; 55: 137.
21. Kumar KS, Bhowmik D, Duravel S, Umadevi M. Traditional and medicinal uses of banana. *Journal of Pharmacognosy and Phytochemistry* 2012; 1: 1.
22. Nikhal SB, Dambe PA, Ghongade DB, Goupale DC. Hydroalcoholic extraction of *Mangifera indica* (leaves) by Soxhletion. *International Journal of Pharmaceutical Sciences* 2010; 2: 30.
23. Priya B, Leaf Extract Mediated Green Synthesis of Silver Nanoparticles from widely available Indian plants: synthesis, characterization, antimicrobial property and toxicity analysis. *Bioresources and Bioprocessing* 2014; 1: 3.
24. Kumar MP, Suba V, Reddy BR. Wound healing activity of *Celtis morensis* Span. (Cannabaceae) leaf extract in wistar albino rats. *Indian J Exp Biol* 2017; 55: 688.
25. Aili SR, Touchard A, Escoubas P, Padula MP, Orivel J, Dejean A, et al. Diversity of peptide toxins from stinging ant venoms. *Toxicon* 2014; 92: 166.
26. Konrad M, Vyleta ML, Theis FJ, Stock M, Tragust S, Klatt M, et al. Social transfer of pathogenic fungus promotes active immunisation in ant colonies. *PLoS Biol* 2012; 10: 1001.
27. Torres AFC, Quinet YP, Havt A, Radis-Baptista G, Martins AMC. Molecular pharmacology and toxicology of venom from ants (Chapter 8), in integrated view of the molecular recognition and toxicology. *Analytical procedures to biomedical applications* 2013; 10: 5772.
28. Shukla RK, Painuly D, Shukla A, Kumar V, Singh J, Porval A, et al. Physical evaluation, proximate analysis and antimicrobial activity of *Morus nigra* seeds original article. *Int J Pharm Pharm Sci* 2015; 7: 191.
29. Tofighi Z, Moradi-Afrapoli F, Ebrahimi SN, Goodarzi S, Hadjiakhoondi A, Neuburger M et al. Securigenin glycosides as hypoglycaemic principles of *Sescurigera securidaca* seeds. *J Nat Med* 2016; 71: 272.
30. Kasali FM, Wendo FM, Muysia SK, Kadima JN, Comparative hypoglycemic activities of flavonoids and tannins fractions of *Stachytar phetaindica* (L) Vahl leaves extracts in guinea pigs and rabbits, *Int J Pharm Pharm Res* 2016; 5: 48.
31. Boshia A, Anoga AO, Asuzu IU. Bioassay-guided isolation and structural elucidation of anti-diabetic principle of methanol leaf extract of *Newbouldia laevis* (P. Beauv), *J Pharm Pharmacol* 2015; 3: 516.
32. Mazumder M, Ponnann P, Das U, Gourinath S, Khan HA, Yang J, et al. Investigations on binding pattern of kinase inhibitors with PPAR $\gamma$ : molecular docking, molecular dynamic simulations, and free energy calculation studies. *PPAR Research* 2017; 1.
33. Aba PE, Asuzu IU. H-Proton NMR spectra of antihyperglycemic terpenoid isolated from *Cussonia arborea*. *J Nat Prod* 2016; 9: 1.
34. Al-Numair KS, Chandramohan G, Veeramani C, Alsoif MA, Ameliorative effect of kaempferol, a flavonoid, on oxidative stress in streptozotocin-induced diabetic rats, *Redox Rep* 2015; 20: 198.
35. Patrick EA, Issac UA. Mechanisms of actions of some bioactive anti-diabetic principles from phytochemicals of medicinal plants: A review, *Indian J Nat Prod and Res* 2018; 9: 85.
36. Abd El-Ghffar EA. Ameliorative effect of glabridin, a main component of *Glycyrrhiza glabra* L. roots in streptozotocin induced Type 1 diabetes in male albino rats, *Indian J Tradit Knowle* 2016; 15: 570.
37. El-Kashak WA, Hamed AR, El-Raey M, Elshamy AI, Abd-Ellatef GEF. Antiproliferative, antioxidant and antimicrobial activities of phenolic compounds from *Acrocarpus fraxinifolius*. *J Chem Pharmaceut Res* 2016; 8: 520.
38. Abd El-Ghffar EA, El-Nashar HAS, Eldahshan OA, Singab ANB. GC-MS analysis and hepatoprotective activity of the n-hexane extract of *Acrocarpus fraxinifolius* leaves against paracetamol-induced hepatotoxicity in male albino rats. *Pharmaceut Biol* 2016; 55: 441.
39. Alofi MT, Zaki AA, Abdel-Rahman HA, El Tigani EA. Antioxidant and anti-stress biomarkers of some nutraceuticals in alloxan-induced diabetic rats. *Int J Basic Appl Med Sci* 2016; 6: 68.
40. Eman Ali AEG, Safia MS. Antioxidant and anti-inflammatory effects of *Acrocarpus fraxinifolius* on hyperglycemia, hyperlipidemia and liver/kidney dysfunctions against alloxan induced Type 1 diabetes in rats, *Ind J Trad Knowle* 2018; 17: 223.
41. Ibrahim AA, Madkour NK. Insulin augmentation and glucagon inhibition in cinnamon treated diabetic rats. *Int J Adv Res* 2016; 4: 1227.
42. Kumas M, Esrefoglu M, Guler EM. Protective effects of silymarin against isotretinoin induced liver and kidney injury in mice. *Indian J Exp Biol* 2018; 56: 158.

# Upregulation of Megalin, Cubilin, NGAL mRNA expression in kidney may represent tubular injury and apoptosis in chronic condition of rat diabetic model

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## ABSTRACT

**Introduction:** Diabetes mellitus (DM) leads to microvascular injury development and produces diabetes nephropathy (DN) with proteinuria, tubular injury, apoptosis and autophagy with upregulation of Bax, BASP and mTORC-1. Megalin, Cubilin and Neutrophil Gelatinase Associated Lipocalin (NGAL) play role in acute pathological condition of kidney injury, however its expression in chronic and slowly progressive kidney injury such as DN has not been elucidated yet. This study focuses upregulation of Megalin, Cubilin and NGAL in association with tubular injury and apoptosis in DN condition.

**Materials and methods:** Diabetic condition was performed with intraperitoneal injection of Streptozotocin 60 mg/kg body weight (BW) in Sprague Dawley rats (2 months old, n=24), and were kept for 1, 2, and 4 months (DM1, DM2, and DM4, respectively). Control group was injected with NaCl 0.9%. Serum glucose level and proteinuria score were assessed, furthermore tubular injury score was quantified based on Periodic-Acid Schiff (PAS) staining. Reverse Transcriptase-PCR (RT-PCR) was carried out for NGAL, Megalin, Cubilin, m-TOR, Bax, and BASP-1 mRNA expression. Data were analyzed using SPSS 22 software.

**Results:** DM led to kidney injury in this model with significant higher glucose level, proteinuria and tubular injury, especially in DM4 group which represented chronic phase of DN and CKD. These findings associated with upregulation of Megalin, Cubilin and NGAL mRNA expression in DM groups, especially in DM4 group. DM4 group also revealed higher expression of Bax, BASP and mTOR mRNA expression which demonstrated apoptosis.

**Conclusion:** Megalin, Cubilin and NGAL upregulation may represent tubular injury and apoptosis as progression of DN.

## KEYWORDS:

*diabetes mellitus, tubular injury, Megalin/Cubilin, NGAL, apoptosis*

## INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disease which lead to micro-vessels (microvascular) and macro-vessels (macrovascular) complications.<sup>1</sup> One of the microvascular complications of DM is diabetic nephropathy (DN) which becomes the high risk of End-Stage Renal Disease (ESRD).<sup>1,2</sup> DN is often characterized by macroalbuminuria or microalbuminuria, with targeted renal small vessel injury leading to inefficient renal function and tubular injury.<sup>3</sup> Detection of DN is an essential step in minimalising further complication. Elucidating signalling which represents renal injury and tubular injury severity may provide better understanding for DN mechanism.<sup>4</sup>

Tubular injury represents the complication of DN, furthermore upregulation of signaling from injured tubule may give early detection of DN. Neutrophil Gelatinase Associated Lipocalin (NGAL) is a transmembrane glycoprotein exclusively expressed in injured kidney and undetected in normal kidney<sup>4</sup>, which associates with ATP depletion.<sup>5</sup> NGAL is also upregulated in neutrophil activation resulted from inflammation process.<sup>4,6</sup> Tubular injury is caused by increase reabsorption of protein in the glomerular filtrate due to filtration disruption in DN. Megalin and Cubilin are glycoproteins that may be found in various organ, including kidney, related to the endocytosis process of various protein reabsorption on epithelium.<sup>7</sup> Megalin plays a part in reabsorption of plasma protein leaking from glomerular filtration, meanwhile Cubilin is endocytosis receptor with molecular weight of 460 kDa that will form a ligand-receptor complex with Megalin.<sup>8</sup>

Apoptosis and autophagy signaling activation play role in podocyte injury, glomerulosclerosis and tubular injury.<sup>9</sup> Bax and Brain Acid Soluble Protein 1 (BASP1) play role in apoptosis along with p53 in intrinsic pathway,<sup>9</sup> and it has a direct role on renal parenchymal cell apoptosis.<sup>10</sup> Bax contributes directly in intrinsic pathway of apoptosis and p53 gene activation, then lead to apoptosis.<sup>11</sup> Other signalling such as mammalian Target of Rapamycin Complex-1 (mTORC-1) also plays an important role for autophagy and

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roles on integration process of metabolic, energy, hormonal, and nutrition stimulation to regulate cell metabolism, growth, and survival.<sup>9,12</sup> Physiologically, activated mTORC-1 contributes to a balanced homeostasis of  $\beta$  cell, adaptation, insulin secretion and cell development.<sup>13-15</sup> On the other hand, mTORC-1 upregulation may be caused by  $\beta$ -cell apoptosis.<sup>12</sup>

This study revealed association between upregulation of Megalin, Cubilin and NGAL with tubular injury and apoptosis in kidney of diabetic rat model, for detecting the progression of DN. Elucidating the signaling in slowly and chronic progressive kidney injury such as DN may provide underlying mechanism for biomarker of DN progression to CKD in association with renal dysfunction, apoptosis and tubular injury.

**MATERIALS AND METHODS**

*Animal model of diabetes mellitus*

This research had obtained a permission from the Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada with the ethical expedience number KE/FK0098/EC/2020. The DM model was performed with single intraperitoneal injection of Streptozotocin (Nacalai, 32238-91) 60mg/Kg Body Weight<sup>16</sup> in male Sprague Dawley rats (age 3-4 months, 150 – 200 grams, n=24). Rats were placed in cages with a light-dark cycle of 12 hours. Blood glucose level was quantified in day 5 after injection to examine the success of the model. DM was defined if the blood glucose level was higher than 200 mg/dL. Rats were divided based on the time of sacrificed, 1 month (DM1 group, n=6), 2 months (DM2 groups, n=6), 4 months (DM4 group, n=6) since we aimed to assess the progressivity of diabetes mellitus. Control group was injected with NaCl 0.9% for single dose, then sacrificed after 4 months.

For termination and sacrifice, rats were anesthetized using ketamine at a dose of 60-100mg/kg BW intramuscularly (i.m.). The blood was withdrawn from retro-orbital sinus for glucose level examination. Then, the abdomen and thorax were opened after deep anesthetized, left ventricle was perfused with NaCl 0.9%. Kidneys were harvested kept in Normal Buffer Formalin for paraffin making and RNA preservation solution for RNA extraction.

*Proteinuria score assessment*

Before termination of the rats, proteinuria score was measured with a dipstick (3 GPH strip; Uriscan®) into the urine. The score was assessed based on the positive levels in the dipstick.

*Tubular injury score assessment*

Periodic-Acid Schiff (PAS) staining was performed to examine renal histology and tubular injury score quantification. The tubular injury scores were determined through a semiquantitative scoring system. Fifteen random fields with 400x magnification were examined for each kidney, and the lesions were graded from 0 to 4 (0, no change; 1, changes affecting <25% of the section; 2, changes affecting 25 to 50% of the section; and 3, changes affecting 50 to 75%; and 4, changes affecting more than 75%), according to the area with tubulointerstitial lesions (tubular atrophy, tubular dilatation, loss of brush-border intraluminal casts, interstitial inflammation and fibrosis). The score index of each rat was expressed as a mean value of all scores obtained.

*RNA extraction, cDNA making and Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)*

The RNA from fat tissues were extracted using Genezol solution (GENEzol™, Cat No. GZR100) based on the manufacturer's protocol. RNA concentrations were quantified using a nanodrop. The synthesis of RNA to cDNA was done using ReverTra Ace® (Toyobo, Cat. No. TRT-101), deoxyribonucleotide triphosphate (dNTP) (Takara, Cat. No. 4030), and primary random (TAKARA, Cat No. 3801). Reverse Transcriptase-PCR (RT-PCR) was performed for these following gene:

For RT-PCR, we used Taq Master Mix (GoTaq®Green Master Mix, Cat No. M7122). PCR products were analyzed on 2% agarose gel with DNA ladder (Bioron, Germany, Cat No. 306009). Gene expression was quantified with densitometric analysis using ImageJ software and  $\beta$ -actin used to normalize expression.

**RESULTS**

*DM associated with proteinuria and tubular injury*

We demonstrated that 60mg/kg BW of STZ-injection enhanced glucose levels in DM groups. The glucose level in DM1, DM2, and DM4 was significantly higher compared to the control group ( $p<0.001$ ). Moreover, the glucose level showed significant differences among DM groups ( $p<0.01$ ). The DM groups demonstrated disruption of renal function as shown by significantly higher proteinuria scores in DM groups compared to the control group ( $p<0.001$ ). DM 4 group had the highest proteinuria score; however, we did not find any significant difference among DM groups. It seemed DM induced filtration disruption from the first month of induction.

**Table: The list of primers which were used in the study.**

Gene	Forward primer (5' → 3')	Reverse primer (5' → 3')
Megalin	ACTGGGCAGCAGGAAATCTT	CGGGGCATATCCACTGAGAC
Cubilin	CTGTCCAAGGCCGTTACTGT	GATGAAAACGCCAACAGGGG
NGAL	CCGACTACTGACTACGACCAG	CATTGGTCGGTGGGAACAGA
Bax	GTGAGCGGCTGCTTGCT	GGTCCCGAAGTAGGAGAGGA
BASP-1	CAAAGCCGAACTCCAAGATGGG	CGCCTTCAGCCTTCTTGCTT
mTOR	CACCCATCCAACCTGATGCT	ATCGAGACCGGTAACCTCCA
$\beta$ -actin	GCAGATGTGGATCAGCAAGC	GGTGATAAACGCAGCTCAGTAA

Histological observation showed tubular injury as which was characterized by tubular epithelial effacement, brush border loss, tubular lumen dilatation, tubular atrophy, and inflammatory cell invasion in DM groups. Tubular injury score quantification also revealed renal injury with significant differences among groups ( $p < 0.001$ ). The tubular injury score was higher in DM groups ( $p < 0.001$ ) compared to the control group. These results also revealed significant progression of kidney injury from the first to fourth month (from DM1 to DM4,  $p < 0.001$ ).

#### *DM associated with activation of Megalin-Cubilin and upregulation of NGAL*

RT-PCR analysis demonstrated DM2 and DM4 groups had significantly higher Megalin mRNA expression compared to control and DM1 groups ( $p < 0.01$ ). The upregulation of the Megalin mRNA expression was markedly observed in DM4, and there was a significant difference between DM4 and DM2 groups ( $p < 0.01$ ). Furthermore, the mRNA expression of Cubilin is clearly observed at the chronic diabetes mellitus stage. We demonstrated that DM4 represented higher Cubilin mRNA expression compared to control ( $p = 0.007$ ) and DM1 ( $p = 0.049$ ) groups. In addition, the DM4 group showed a significant upregulation of the NGAL mRNA expression ( $p = 0.003$ ) compared to the control group. We assumed that the activation of Megalin-Cubilin might associate with the progression of DM and NGAL expression.

#### *DM associated with upregulation of proapoptotic and autophagy pathways*

The upregulation of the BASP-1 mRNA expression was observed in DM2 and DM4 groups, not in the DM1 group. There was no significant difference in BASP-1 mRNA expression between DM1 and the control group. We demonstrated that DM2 had significance elevation compared to the control ( $p = 0.011$ ) group, and DM4 exhibited the highest mRNA expression of BASP-1 compared to the control ( $p < 0.001$ ), DM1 ( $p < 0.001$ ), and DM2 ( $p = 0.001$ ) groups.

On the other hand, the proapoptotic mRNA expression, Bax, tremendously increased in DM groups compared to the control group ( $p < 0.001$ ). We found that long-term hyperglycemia (DM4) enhanced the mRNA expression of Bax compared to the DM1 ( $p = 0.026$ ) and control ( $p < 0.001$ ). Besides, the mRNA expression of m-TORC1 upregulated in DM2 ( $p = 0.006$ ) and DM4 ( $p = 0.037$ ) groups compared to the control group. We found that there was no significant difference between DM2 and DM4 in the mRNA expression of m-TORC1.

## DISCUSSION

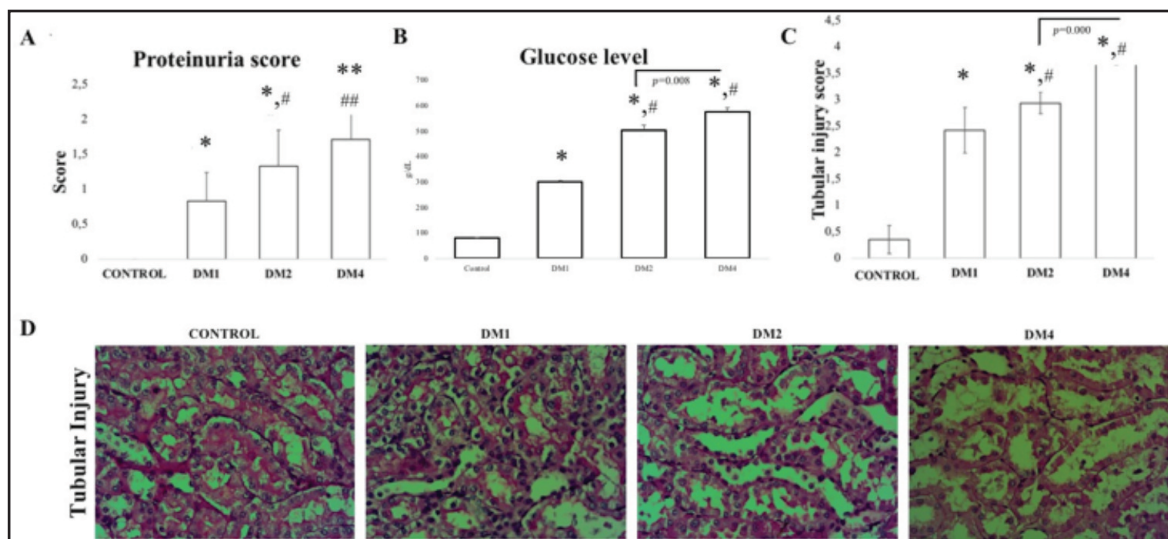
Based on the finding on this research, hyperglycemia induced renal dysfunction, apoptosis and tubular injury in association with upregulation of Megalin, Cubilin, and NGAL mRNA expression. Renal function deterioration also occurred in this study as shown by proteinuria with tubular injury. Advanced Glycation End (AGE) product in DN has broad effects on cell, tissue, chemical, and metabolic changes,<sup>17</sup> especially in the proximal tubules cells.<sup>18</sup> These cells need a high level of energy to support its role in reabsorbing a variety of molecules passing glomerular

filtration and rely on aerobic metabolism in fulfilling high energy metabolic demand.<sup>18</sup>

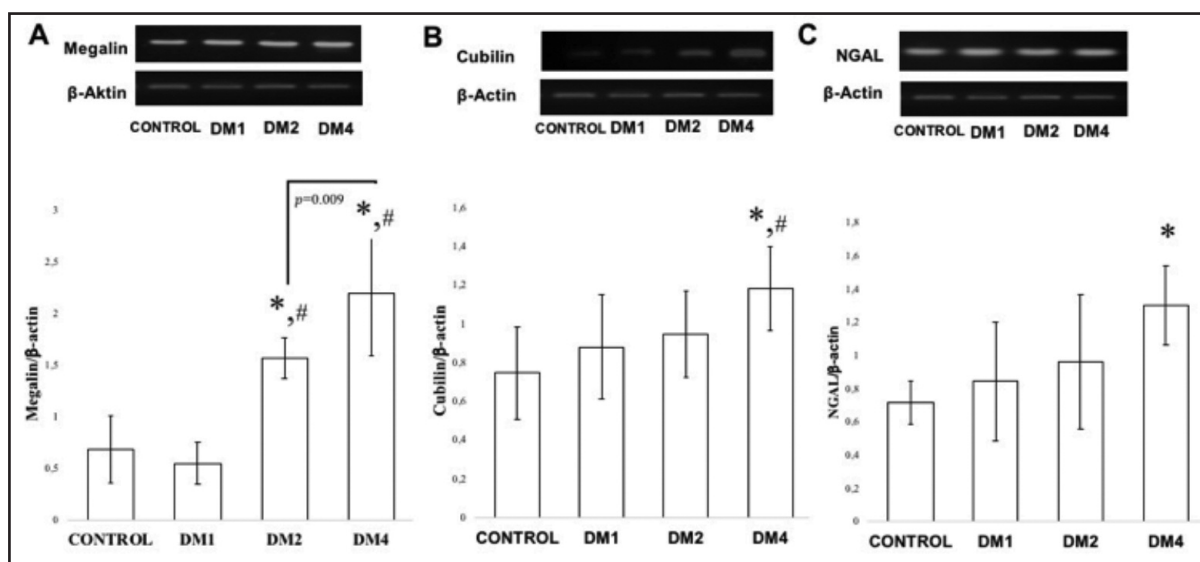
Our study also revealed Megalin/Cubilin complex and NGAL mRNA upregulation might represent DM-induced tubular injury. Megalin-Cubilin-Amnion less complex in proximal convoluted tubules reabsorbs AGE in diabetic condition,<sup>19</sup> then stimulates AGE intoxication and the transcription factor Nuclear Factor- $\kappa$ B (NF $\kappa$ B) and Reactive Oxygen Species (ROS) activation.<sup>17</sup> Our study also revealed proteinuria occurred from first month of diabetic condition, however upregulation of Megalin and Cubilin occurred in 4 month of DM. Previous studies stated that Megalin expression will be increased in diabetic nephropathy, however a decreased in Megalin expression can also be found in acute condition. Proteinuria with albuminuria occurred in the first month of DM caused albumin overload which has similar effect with Megalin knockdown.<sup>20</sup> Megalin hyperexcretion relates with progression of DN and proximal tubules cells dysregulation in early phase of DM.<sup>21</sup> Cubilin functions for internalising albumin to proximal tubular epithelial cells in the normal condition. Megalin play roles in albumin reabsorption for internalising Cubilin-Albumin complex for further lysosomal degradation.<sup>22</sup>

Megalin/Cubilin deficiency might protect against inflammation and fibrosis.<sup>23</sup> Inhibition of Cubilin expression using antisense RNA delivery protects against glomerulosclerosis and tubulointerstitial injury in adriamycin treated mice.<sup>24</sup> Megalin positive cells upregulates inflammatory and fibrotic markers in model with anti-glomerular basement membrane antibodies injection<sup>25</sup> and podocyte dysfunction induction.<sup>26</sup> Megalin inhibition using siRNA in invitro study showed that Megalin played role in albumin-induced activation of proximal tubule synthesis of components of the renin-angiotensin system.<sup>27</sup> Other studies revealed upregulation of Megalin in acute kidney injury (AKI) condition. Inhibition of Megalin function has been demonstrated to ameliorate nephrotoxic acute kidney injury (AKI).<sup>28</sup> Megalin mediates the endogenous substances uptake, such as NGAL<sup>29</sup> and survivin<sup>30</sup> which involves in modulation and recovery from AKI.<sup>31-33</sup>

Upregulation of NGAL also occurs especially in the acute kidney injury (AKI) condition. Urine NGAL increased in 2 hours after injury in *Acute Kidney Injury* (AKI) condition, then reach the highest level at 6 hours, then decreased after 5 days.<sup>34</sup> NGAL expression which is specific in tubular epithelial cells, beside sepsis condition,<sup>5</sup> might provide beneficial condition as biomarker of tubular injury in chronic condition, such as DN without appearance of sepsis. Further research is needed about the relationship between Megalin expression and NGAL excreted in the urine on broader spectrum of time to ensure whether it is possible for NGAL to become a biomarker for renal injury in the future.<sup>5</sup> NGAL upregulation occurred primarily in acute renal pathology, furthermore it needs to study in chronic and slowly progressive CKD model with proteinuria.<sup>23</sup> Our study revealed Megalin, Cubilin and NGAL mRNA upregulation in chronic phase of DN as represented CKD model with proteinuria and slowly progressive mechanism. Quantification of the mRNA level is the limitation of our study, further protein level



**Fig. 1:** Proteinuria and tubular injury occurred in DM groups. A. Proteinuria score quantification showed filtration disruption occurred in DM groups. B. Tubular injury score quantification showed higher tubular injury score in DM groups. C. PAS staining showed tubular injury with effacement of tubular epithelial cells and loss of brush border in tubules of DM group. \* $p < 0.05$  VS control, \*\* $p < 0.01$  VS control, # $p < 0.05$  VS DM1, ## $p < 0.01$  VS DM1.



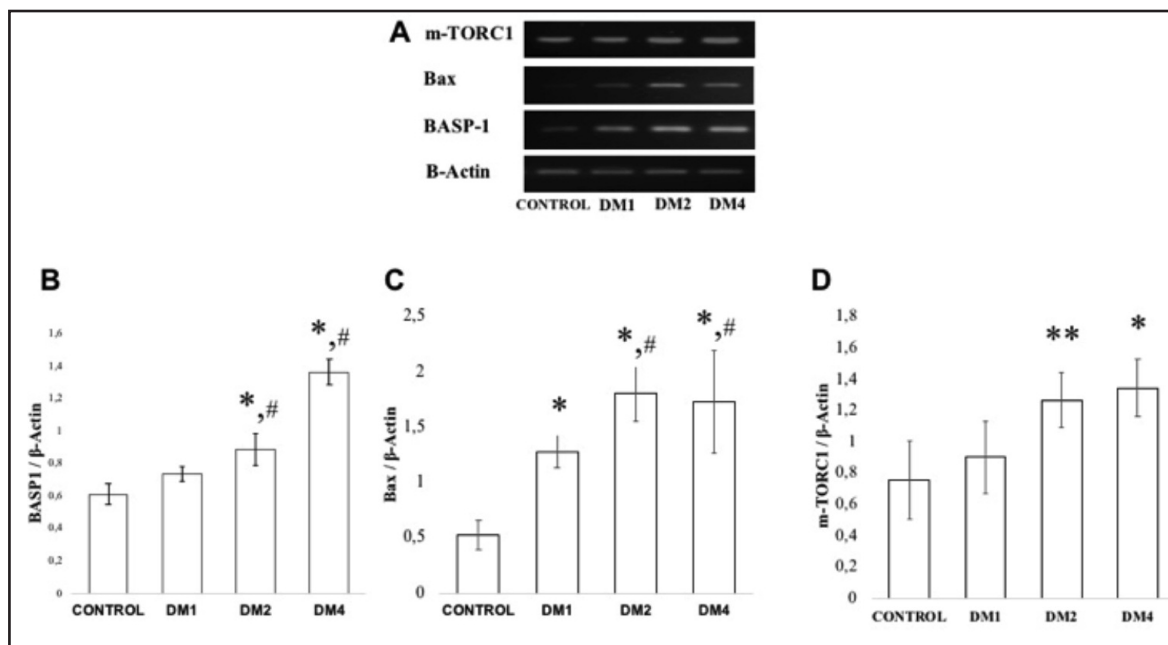
**Fig. 2:** Upregulation of Megalin, cubilin and NGAL in DM groups. A. Representative picture and densitometry analysis of Megalin mRNA expression. DM4 group demonstrated the highest Megalin mRNA expression. B. Representative picture and densitometry analysis of cubilin mRNA expression. DM4 group demonstrated the highest cubilin mRNA expression. C. Representative picture and densitometry analysis of NGAL mRNA expression. DM4 group demonstrated the highest NGAL mRNA expression. \* $p < 0.05$  VS control, \*\* $p < 0.01$  VS control, # $p < 0.05$  VS DM1.

analysis of Megalin/Cubilin in tissue and urine may provide better understanding for elucidating early and chronic phase of DN, especially in association with tubular injury.

This study also demonstrated upregulation of apoptotic signaling in diabetic condition. BASP-1 is expressed by tubular cells and relates to apoptosis in DN, which leads to tubulointerstitial damage and apoptosis of tubular cells.<sup>35</sup> Other study also demonstrated an association between hyperglycemic state of diabetes mellitus and pro-apoptosis

Bax gene expression in qualitative data in patients with type 2 diabetes mellitus.<sup>36</sup> In vitro study also demonstrated hyperglycemia induced apoptotic intrinsic pathway on MS-1 cell, upregulation of proapoptotic protein Bax and downregulation of antiapoptotic protein Bcl-2. It was found that treatment hyperglycemia increased Bax protein expression without changing the expression of Bcl-2.<sup>37</sup> Increased Bax/Bcl-2 expression ratio was obtained in diabetic nephropathy which associated with apoptosis and glomerulus size changing.<sup>38</sup> High glucose also induced





**Fig. 3:** Upregulation of BASP-1, Bax and m-TORC1 in DM groups. A. Representative picture and densitometry analysis of BASP-1 mRNA expression. DM4 group demonstrated the highest BASP-1 mRNA expression. B. Representative picture and densitometry analysis of Bax mRNA expression. DM4 group demonstrated the highest Bax mRNA expression. C. Representative picture and densitometry analysis of m-TORC1 mRNA expression. DM4 group demonstrated the highest m-TORC1 mRNA expression. \* $p < 0.05$  VS control, \*\* $p < 0.01$  VS control, # $p < 0.05$  VS DM1.

apoptosis with increased on Bax/Bcl-2 expression ratio in *human embryonic kidney* (HEK) culture.<sup>39</sup>

Based on the research, statistically significant increased on mTORC-1, an autophagy regulator was obtained. mTORC-1 that has an anti-autophagy feature affecting impaired regeneration process in type 1 diabetes mellitus hyperglycemic model.<sup>39</sup> Autophagy is a cell self-degrading catabolic process needed for  $\beta$  cell viability, insulin secretion to stabilized blood glucose level and glucose homeostasis.<sup>40</sup> Activation of mTORC-1 relates to autophagy inhibition mechanism in diabetic cases. Moreover, hypertrophy of podocyte can be a predictor of renal lesion progression in patient with diabetes and mTORC-1 excessive activation in hyperglycemia condition may mediate continuous hypertrophy stimuli that can cause podocyte degeneration, glomerulosclerosis and proteinuria.<sup>9</sup> Elucidating protein localization of the Megalin, Cubilin and NGAL in association with apoptosis and autophagy pathway in the chronic kidney injury model, such as DN may provide better understanding for continuing this study.

## CONCLUSION

In summary, upregulation of Megalin, Cubilin and NGAL mRNA expression may represent tubular injury and apoptosis as characteristic of DN. Elucidating protein level in kidney and urine may provide better understanding about the potency of these signaling as biomarker of DN, especially in association with tubular injury and apoptosis.

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## REFERENCES

1. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia.; 2007 [cited March 2020]. Available from: [https://www.who.int/diabetes/publications/diagnosis\\_diabetes2006/en/](https://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/)
2. Hovind P, Tarnow L, Rossing K, Rossing P, Eising S, Larsen N, et al. Decreasing incidence of severe diabetic microangiopathy in type 1 diabetes. *Diabetes Care* 2003; 26(4): 1258-64.
3. Amico G D', Bazzi C. Pathophysiology of proteinuria. *Kidney Int* 2003; 63: 809-25.
4. Luo Q, Chen M, Chen Z, Huang C, Cheng A, Fang J, et al. Evaluation of KIM-1 and NGAL as early indicators for assessment of gentamycin-induced nephrotoxicity in vivo and in vitro. *Kidney Blood Press Res* 2016; 41(211): 911-8.
5. Alge JL, Arthur JM. Biomarkers of AKI : a review of mechanistic relevance and potential therapeutic implications. *Clin J Am Soc Nephrol* 2014; 1-9.
6. Si Nga H, Medeiros P, Menezes P, Bridi R, Balbi A, Ponce D. Sepsis and AKI in clinical emergency room patients: the role of urinary NGAL. *Biomed Res Int* 2015; 413751.
7. Christensen EI, Birn H. Megalin and cubilin: multifunctional endocytic receptors. *Nat Rev Mol Cell Biol* 2002; 3(4): 258-68.
8. Christensen EI, Birn H, Storm T, Weyer K, Nielsen R. Endocytic receptors in the renal proximal tubule. *Physiol* 2012; 27: 223-36.
9. Yamahara K, Yasuda M, Kume S, Koya D, Maegawa H, Uzu T. The role of autophagy in the pathogenesis of diabetic nephropathy. *J Diabetes Res* 2013; 2013: 1-9.

10. Perez-gomez M V, Poveda J, Sanz AB. Albumin-induced apoptosis of tubular cells is modulated by BASP1. *Nat Publ Gr* 2015; 2015(6): 1-11.
11. Westphal D, Dewson G, Czabotar PE, Kluck RM. Molecular biology of Bax and Bak activation and action. *Biochim Biophys Acta* 2011; 1813(4): 521-31.
12. Laplante A, Sabatini DM. mTOR signaling in growth control and disease. *Cell* 2013; 149(2): 274-93.
13. Blandino-rosano M, Chen AY, Scheys JO, et al. mTORC1 signaling and regulation of pancreatic  $\beta$ -cell mass. *Cell Cycle* 2012; 11(10): 1892-902.
14. Kulkarni RN, Mizrahi E, Ocana AG, Stewart AF. Human B-cell proliferation and intracellular signaling driving in the dark without a road map. *Diabetes* 2012; 61(September): 2205-13.
15. Yoon M. The role of mammalian target of rapamycin (mTOR) in insulin signaling. *Nutrients* 2017; 9: 1-17.
16. Kumar S, Kumar V, Prakash OM. Antidiabetic and hypolipidemic activities of *Kigelia pinnata* flowers extract in streptozotocin induced diabetic rats. *Asian Pac J Trop Biomed* 2012; 2(7): 543-6.
17. Forbes JM. Role of advanced glycation end products in diabetic nephropathy. *J Am Soc Nephrol* 2003; 14(90003): 254S-258.
18. Gilbert RE. Proximal tubulopathy : prime mover and key therapeutic target in diabetic kidney disease. *Diabetes* 2017; 66(April): 791-800.
19. Saito A, Sato H, Iino N, Takeda T. Molecular mechanisms of receptor-mediated endocytosis in the renal proximal tubular epithelium. *J Biomed Biotechnol* 2010; 2010: 403272.
20. Peruchetti DB, Cheng J, Caruso-Neves C, Guggino WB. Mis-regulation of mammalian target of rapamycin (mTOR) complexes induced by albuminuria in proximal tubules. *J Biol Chem* 2014; 289(24): 16790-801.
21. Figueira MF, Castiglione RC, Barbosa CMDL, Ornellas FM, Feltran GDA, Morales MM, et al. Diabetic rats present higher urinary loss of proteins and lower renal expression of megalin, cubilin, CLC-5 , and CFTR. *Physiol Rep* 2017; 5(13): 1-13.
22. Liu D, Wen Y, Tang TT, Lv L, Tang R, Liu H, et al. Megalin/cubulin-lysosome-mediated albumin reabsorption is involved in the tubular cell activation of NLRP3 inflammasome and tubulointerstitial inflammation. *J Biol Chem* 2015; 290(29): 18018-28.
23. Nielsen R, Christensen EI, Birn H. Megalin and cubilin in proximal tubule protein reabsorption: From experimental models to human disease. *Kidney Int* 2016; 89(1): 58-67.
24. Liu J, Li K, He Y, Jianguo Z, Wang H, Yang J, et al. Anticubilin antisense RNA ameliorates adriamycin-induced tubulointerstitial injury in experimental rats. *Am J Med Sci* 2011; 342(6): 494-502.
25. Theilig F, Kriz W, Jerichow T, Schrade P, Hahnel B, Willnow T, et al. Abrogation of protein uptake through megalin-deficient proximal tubules does not safeguard against tubulointerstitial injury. *J Am Soc Nephrol* 2007; 18(6): 1824-34.
26. Motoyoshi Y, Matsusaka T, Saito A, Pastan I, Willnow TE, Mizutani S, et al. Megalin Participates in the early injury of proximal tubule cells in glomerular disease with non-selective proteinuria. *Kidney Int* 2009; 74(10): 1262-69.
27. Cao W, Zhou QG, Nie J, Wang GB, Liu Y, Zhou ZM, et al. Albumin overload activates intrarenal renin-angiotensin system through protein kinase C and NADPH oxidase-dependent pathway. *J Hypertens*. 2011; 29(7): 1411-21.
28. Mahadevappa R, Nielsen R, Christensen EI, Birn H. Megalin in acute kidney injury: Foe and friend. *Am J Physiol* 2014; 306(2):F147-54.
29. Hvidberg V, Jacobsen C, Strong RK, Cowland JB, Moestrup SK, Borregaard N. The endocytic receptor megalin binds the iron transporting neutrophil-gelatinase-associated lipocalin with high affinity and mediates its cellular uptake. *FEBS Lett* 2005; 579(3): 773-7.
30. Jobst-Schwan T, Knaup KX, Nielsen R, Hackenbeck T, Buettner-Herold M, Lechler P, et al. Renal uptake of the antiapoptotic protein survivin is mediated by megalin at the apical membrane of the proximal tubule. *Am J Physiol* 2013; 305(5): 734-44.
31. Chen J, Chen JK, Conway EM, Harris RC. Survivin mediates renal proximal tubule recovery from AKI. *J Am Soc Nephrol* 2013; 24(12): 2023-33.
32. Mishra J, Mori K, Ma Q, Kelly C, Yang J, Mitsnefes M, et al. Amelioration of ischemic acute renal injury by neutrophil gelatinase-associated lipocalin. *J Am Soc Nephrol* 2004; 15(12): 3073-82.
33. Mori K, Lee HT, Rapoport D, Drexler IR, Foster K, Yang J, et al. Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. *J Clin Invest* 2005; 115(3): 610-21.
34. Corbacioglu SK, Cevik Y, Akinci E, Uzunozmanoglu H, Dagar S, Safak T, et al. Value of plasma neutrophil gelatinase-associated lipocalin (NGAL) in distinguishing between acute kidney injury (AKI) and chronic kidney disease (CKD). *Turkish J Emerg Med* 2017; 17(3): 85-8.
35. Sanchez-nin MD, Sanz AB, Lorz C, Gnirke A, Rastaldi MP, Nair V, et al. BASP1 promotes apoptosis in diabetic nephropathy. *J Am Soc Nephrol* 2010; 21: 610-21.
36. Gokalp-ozkorkmaz E, Kirman G, Pekkoly Z, Asir F, Devci E. Expression of apoptotic proteins Bax and Bcl-2 in blood cells of type 2 diabetic patients. *Proc MDPI* 2018; 1563(2): 2-5.
37. Gong L, Liu F, Wang J, Wang X, Hou X, Sun Y, et al. Hyperglycemia induces apoptosis of pancreatic islet endothelial cells via reactive nitrogen species-mediated Jun N-terminal kinase activation. *Biochim Biophys Acta* 2011; 1813(6): 1211-9.
38. Jung D, Lee SH, Kwak S, Li JJ, Kim DH, Nam BY, et al. Apoptosis occurs differentially according to glomerular size in diabetic kidney disease. *Nephrol Dial Transpl* 2012; 27(1): 259-66.
39. Eslami H, Sharifi AM, Abbas B, Abbas B. Role of Bax protein and Caspase-3 at high glucose-induced apoptosis in human embryonic kidney (HEK) 293 cells. *Zahedan J Res Med Sci* 2013; 15(5): 25-9.
40. Ardestani A, Lupse B, Kido Y, Leibowitz G, Maedler K. A double-edged sword in diabetic B-cells. *Cell Metab* 2017; 27(2): 314-31.

# A review of the literature on the health benefits of *Salat* (Islamic prayer)

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## ABSTRACT

**Introduction:** Recent studies explored the association between health and religious practice/spirituality. Several studies revealed that religious commitment and spirituality are generally associated with better health outcomes. Throughout the world, millions of Muslims perform *salat* (prayer) regularly five times a day. *Salat* is not only a physical activity but involves recitations of various Quranic verses and performance of certain postural positions. Several studies showed that *salat* does have positive effects on health status. This review aims to investigate the effects of Islamic *salat* on general health.

**Methods:** A series of searches were conducted of Medline databases published in English between 1966 and October 2020 with the following keywords: Prayer, *salat*, health, and Islam. **Results:** Several positive effects of *salat* on health were identified. These include: psychological, neurological, cardiovascular, and musculoskeletal effects.

**Conclusion:** *Salat* is a non-pharmacological intervention and resource, and may be included in the holistic care and rehabilitation program aimed at the well-being of patients.

## KEYWORDS:

*Prayer, Salat, Islam, Health benefits*

## INTRODUCTION

Over the last three decades there has been increasing medical interest in mind and body medicine.<sup>1</sup> Religion at large has always lent a useful guide to approach both the physiological illnesses and psychological maladies. Researchers at the Mayo Clinic reviewed 350 studies examining the influence of religion on the physical health of patients and 850 studies investigating the impact of religion on mental health. Most studies have shown that religious involvement and spirituality are associated with better health outcomes, including greater longevity, coping skills, and health-related quality of life (even during terminal illness) and less anxiety, depression, and suicide. They concluded that religion promotes illness prevention, coping with illnesses, and recovery.<sup>2</sup>

High levels of spirituality and religiosity are correlated with lower morbidity and mortality, enhanced quality of life and well-being, and lower levels of depression and psychological stress.<sup>3</sup> Possible mechanisms by which spirituality and

religiosity may affect health outcomes include healthier lifestyles (e.g., healthy diets, less smoking and alcoholism, lower rates of stress and depression, optimism and hope, enhancement of social ties, lower rates of suicide and a more favorable immune profile.<sup>4,6</sup>

Recent studies endeavored to explore the health effects of prayer from a scientific standpoint. In a survey of 4404 Muslim individuals, the investigators found that the participants who prayed regularly achieved better health, exhibited more favorable health-related behaviors and use of preventive services, and reported greater satisfaction with care.<sup>7</sup> However, *salat* (Islamic prayer) is different from the personal prayer or invocation associated with the Christian faith. In Islam, that is called the "Du'a", or supplication, formal and informal.

Islamic prayer, commonly represented by the Arabic term *salat* is the second pillar of Islam. As an obligatory requirement of ritual worship, *salat* combines the essential tenets of Islam; worship of one God, remembrance of Allah, submission to the Allah's will, supplication, as well as, a symbol of unity of the Muslim community.<sup>1,8</sup> *Salat* is performed at five appointed times during a day as commanded in the Quran, the Holy Book "Verily, *Salah* is an obligation on the believers to be observed at its appointed time" (Qur'an 4:10).

It is preceded by the ritual ablution (*wudu*) and it includes various postures (*raq'aas*) which involves standing, raising and lowering of arms, bowing, sitting on shins, prostration and head rotation. Voluntary prayers in addition to the above are highly encouraged and are recommended as a means of turning to divine help, especially at times of personal grief and distress.<sup>9</sup>

Regular prayer is emphasized more strongly in Islam than in Christianity and Judaism. While prayer is very important to devout Christians, it is usually carried out less than the five times per day as is required in Islam.<sup>10</sup> The five times are dawn prayer (*Fajr*), noon (*Duhaar*), early evening (*Asr*), after sun set (*Magrib*) and night prayer (*Isha*). The form of prayer is also different between the two faiths, whereas Muslims become involved with their entire bodies by standing toward Makkah, reciting verses from the Quran, kneeling and bowing (*Rokoo*), bowing down to the ground and touching it with their foreheads (*prostration, Sujood*).

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The Orthodox Jews also stand during their prayers and face towards Jerusalem, then they bow and finally stand up swaying their head forward and backward frequently and quickly. They don't prostrate to the ground, although it is mentioned in the Book of Daniel that Daniel prostrated down to the ground during his prayers. The orthodox Jews pray three times a day: early morning, afternoon and at night.

Several studies showed that *salat* has positive effects on the health status. The objective of this review is to investigate the current evidence of health benefits of *salat*, and discuss what is known regarding these effects.

### Health benefits of Salat:

#### Psychological

Many patients encounter psychological and emotional distress in the face of illness and possible death. High levels of anxiety may worsen their physical condition. Several reports on the application of prayers in psychotherapy illustrate the positive outcome in an individual exhibiting pathological symptoms such as tension, anxiety, depression and anti-social tendencies.<sup>11</sup> Yucel<sup>12</sup> conducted a study, at Brigham and Women's Hospital, exploring the effects of *salat* and *Dua* (supplicative prayer), on sixty adult Muslims aged between 18–85 years. He found that *salat* reduced stress and depression while providing comfort and hope. Findings were consistent with prior studies on prayer-health relationship. The study also revealed that 75% of the participants indicated that Islam was an important factor in their lives. The mind and body relationship in *salat* may provide a basis for overcoming life's exigencies, decreasing anxiety and depression while relying on Divine assistance and guidance.<sup>12</sup>

In a study of 30 healthy Muslim men, Doufesh<sup>13</sup> investigated the effect of Muslim prayer (*salat*) on the relative power (RPa) of electroencephalography (EEG) and autonomic nervous activity. During *salat*, a significant increase ( $p < 0.05$ ) in the mean RPa in the occipital and parietal regions of the brain and a normalized unit of high-frequency (nuHF) power of HRV (as a parasympathetic index) were observed. Meanwhile, the normalized unit of low-frequency (nuLF) power and LF/HF of HRV (as sympathetic indices) decreased. The increased Electroencephalogram (EEG) occipital and parietal RPa during *salat* suggest that prayer produces positive changes in brain function and human well-being. These changes are associated with an increase in the parasympathetic component and a decrease in the sympathetic component in the autonomic nervous system (ANS). Therefore, regular *salat* practices may help promote relaxation, minimize anxiety, and might reduce cardiovascular risk.<sup>13</sup>

#### Meditation

Meditation is a practice where a person uses a technique, such as focusing the mind on a particular object, thought or activity to train awareness and achieve a mentally clear and emotionally calm state. Numerous studies have reported the benefits of meditation. Meditation may be a potentially attractive cost-effective adjunct to more traditional medical therapies.<sup>14</sup> Almost all religions incorporate some form of meditation and the Muslim prayer is the meditation of Islam.

From the Islamic point of view, the prayer is not the goal itself. The real goal is the remembrance of God and the training of attention during prayer to focus on God ("... and keep up prayer for my remembrance") (Quran 20:14).

Studies have shown that *salat* results in the activation of parasympathetic nervous system, and a decrease in sympathetic activity.<sup>13</sup> This may explain why *salat* is often considered as a form of meditation as it decreases anxiety and promote relaxation. The majority of studies on meditation reveals alpha rhythm slowing, and increased alpha rhythm coherence on the EEG. Doufesh et al.,<sup>15</sup> investigated the concept of relaxation attained when performing the Muslim prayers by measuring the alpha activity in the brain. Nine Muslim subjects were asked to perform the four required cycles of movements of "*Dhuha*" prayer, and the EEG was subsequently recorded. Findings were similar to other studies revealing increased alpha amplitude in the parietal and occipital regions of the brain during meditation and mental concentration. The incidence of increased alpha amplitude suggested parasympathetic activation, thus suggesting a state of relaxation. More studies are needed to delineate the role of mental concentration, and eye focus, on alpha wave amplitude while performing acts of worship.<sup>15</sup>

Doufesh et al.,<sup>16</sup> also investigated the difference of mean gamma EEG power between actual and mimic *salat* practices in 20 healthy Muslim subjects. In the actual practice of *salat*, the participants were requested to recite and perform the regular steps of *salat*; whereas participants mimicking *salat* practice were instructed to perform only the physical steps without Quran recitation. The gamma power during actual *salat* was statistically higher than during the mimic *salat* in the frontal and parietal regions in all stages. Increased gamma power during the actual *salat*, probably related to an increase in the cognitive processing, in keeping with the concept of *salat* as a focus attention meditation.<sup>16</sup> Future research focusing on the medical benefits of *salat* should be conducted with an aim of educating Muslim physicians on *salat* as a form of mind and body medicine.

Meditation may be considered as an adjunctive to the guideline-directed cardiovascular risk reduction by lifestyle modification. Neurophysiological studies reveal that meditation may have long-standing effects on the brain.<sup>14</sup>

Achour et al.,<sup>17</sup> examined how *salat* moderates the relationship between job stress and life satisfaction among 335 Muslim nursing staff in Kuala Lumpur, Malaysia. They found that job stress was associated negatively with life satisfaction. There was a strong positive correlation between *salat* and life satisfaction and *salat* helped in reducing the stress and might have improved the life satisfaction of these Muslim nurses.<sup>17</sup> Physicians should consider incorporating more mind and body techniques in view of the dramatic increase in chronic stress-related disorders throughout the world.<sup>1</sup>

#### Neurological

Beside the spiritual and religious aspects of prayer, *salat* is a repetitive and/or mentally enhancing activity. It involves both cognitive and motor components. Prostration (*Sujoud*) is

the only position in which the head is in a position lower than the heart and therefore, receives increased blood supply, which consequently, may have a positive effect on memory, concentration, psyche and cognitive function (the mental processes that allow us to carry out any task). There is only one study that examined the relationship between religiosity and cognitive function in Muslims. Inzelberge et al.,<sup>18</sup> conducted a door-to-door survey of 935 Arabs in Palestine, men and women over the age of 65 years, examining the relationship between the number of praying hours per month during midlife and cognitive function. Of the 935 individuals who were approached, 778 [normal controls (n=448), Alzheimer's disease (n=92) and mild cognitive impairment (MCI) (n=238)] were evaluated. The results showed that 87% of cognitively normal persons practiced prayers at midlife, compared to 71% of those with mild cognitive impairment and 69% of those with Alzheimer's disease (AD) ( $p < 0.0001$ ). The study found that prayer during midlife significantly reduced the likelihood of mild cognitive impairment over the age 65 in Arabic women in Palestine.<sup>18</sup>

Alabdulwahab et al.,<sup>19</sup> compared the dynamic balance of 60 healthy male subjects who performed *salat* regularly with non-practising individuals using a Balance Master. They found that individuals who performed *salat* regularly had a significantly superior dynamic balance ( $p < 0.05$ ) in terms of reaction time, movement velocity, end-point excursion, and directional control than the non-practising healthy subjects.<sup>19</sup>

### Cardiovascular

Religious involvement is associated with less cardiovascular disease.<sup>2</sup> Islamic prayer is performed at least five times a day and consists of a series of movements entailing standing, prostrating and sitting. *Salat* maneuvers were equivalent to light exercise in terms of their physical exercise value. When performing prayer, the Qur'an discourages lazily performing prayer as performed by the Hypocrites; thus, a lethargic and careless approach to prayer neither obtains any spiritual nor physical benefit to the state of health. The physical movements during prayer with repetitive standing-sitting actions throughout the day may also help in preventing deep vein thrombi.<sup>20</sup>

Doufesh et al.,<sup>21</sup> reported the effects of the *salat*, on heart rate (HR) and blood pressure (BP) while performing and miming the actions of *salat*: standing, bowing, prostrating and sitting. Thirty Muslim subjects were asked to perform the actual and mimicking *salat*. HR was measured during actual and mimicked *salat*. However, BP was measured immediately before and 5 minutes after performance of both actual and mimed *salat*. There was a significant difference in the HR of the subjects performing and miming *salat*. The standing and prostration positions of *salat* produced the highest and the lowest HR, respectively. The systolic BP decreased slightly after performance ( $118.0 \pm 5.6$  vs.  $115.0 \pm 4.7$ ,  $p < 0.05$ ) and mime of *salat* ( $119.3 \pm 4.9$  vs.  $117.1$ ).<sup>21</sup>

Religious involvement was associated with lower blood pressure. *Salat* is a type of meditation exercise and evidence shows meditation results in a decrease in both systolic and diastolic blood pressure, and thus might be of benefit to mildly hypertensive individuals.<sup>21,22</sup>

Al-Kandari<sup>22</sup> tested the blood pressure of 223 Kuwaitis and compared the blood pressure of those who pray to those who do not. He concluded that those who pray were generally found to have lower blood pressure. Al-Kandari noted that involvement in religious activities seemed to be a factor in lowering blood pressure as it provided a social support network.<sup>22</sup>

Byrne and Price<sup>23</sup> pointed out that two of the most important functions of religion for human health are providing a sense of security and a source of strength extracted from an individual's social support network and from his/her religious community.<sup>23</sup> Steffen et al.,<sup>24</sup> also found that African Americans who engage in prayers and religious activities had lower blood pressure. Among African Americans with higher levels of religious commitment were associated with lower awake ( $p < 0.05$ ) and sleep ( $p < 0.01$ ) ambulatory blood pressure. Lower 24-hour BP load may be a pathway through which religious practice and cardiovascular health are related.<sup>24</sup> Further studies to explore the benefits of *salat* maneuvers for patients with cardiovascular diseases are warranted.

### Musculoskeletal

Most of the muscles and joints of the body are usually involved in the performance of *salat*. This kind of activity will be convenient for most patients, including the elderly. Prayer may be considered as a type of stretching exercise. The physical activities performed during *salat* are simple and gentle exercises that are suitable for all ages and different conditions. During *salat*, the gentle muscle contraction and relaxation are done with harmony, resulting in flexibility of the muscles without over-exhaustion. A small study of seven adult subjects investigated the electrical activity of two muscles located at the dorsal surface (the erector spinae and trapezius muscles) during *salat* and showed that both muscles maintain a balance in terms of contraction and relaxation during bowing and prostration position.<sup>25</sup>

*Salat* consists of at least two "*rakaats*", and each rakaat involves a series of seven postures. In the prayer performed before sunrise, 2 rakaats or 14 consecutive postures must be performed. Therefore, each Muslim is obliged to perform at least 119 postures every day, that is 3570 postures monthly, and 42,840 postures every year. *Salat* is considered obligatory at the puberty, and if someone lives up to an average of 60 years, a Muslim would have performed over 1,927,800 compulsory postures during *salat* in his lifetime.<sup>26</sup>

The therapeutic aspects of *salat* in promoting psycho-physical well-being have been discussed by several authors and focused on the musculoskeletal benefits of *salat* which include maintenance of postural equilibrium, providing muscle tone, improving circulation, and may have protective role in reducing osteoarthritis (OA) of the weight bearing joints.<sup>27-29</sup>

The role of this repetitive action on knee and hip osteoarthritis and osteoporosis was explored. Forty-six patients who performed prayers for at least 10 years, and 40 patients who had not performed the prayer, were included in this prospective study. The authors concluded that the prayer had no negative effect on knee and hip osteoarthritis.<sup>30</sup>

Chokkhanchitchai<sup>31</sup> studied the effect of *salat* on both the prevalence and severity of knee osteoarthritis (OA) in a Thai elderly population with the same ethnicity but different religions. The study involved 153 Buddhists and 150 Muslims aged over 50 years. The prevalence of knee pain was significantly higher among Buddhists than in Muslims (67.1 vs. 55.8,  $p = 0.02$ ). The prevalence of OA was lower in Muslims than in Buddhists. It is postulated that the Muslim way of praying since childhood, forcing the knees into deep flexion, may stretch the soft tissue surrounding the knees and decrease the stiffness of the articular cartilage.<sup>31</sup>

### Rehabilitation

It is well known that even moderate intensity activities, when performed daily, can have some long-term health benefits. During different positions and transitions of *salat*, movement occurs at almost all joints of the body. *Salat*, with its various postures and movements, can play a role in increasing psychological well-being including the self-esteem, improving musculoskeletal fitness and cerebral blood flow that may be beneficial in the rehabilitation program of geriatric and disabled patients.<sup>27</sup>

The practice of *salat* may help in the rehabilitation process in patients with neurological or musculoskeletal impairments as it involves minimum effort and promotes mental and physical health. Different postures of *salat* (standing, bowing, prostration and sitting) may play a role against the adaptive postures which the affected patients may adopt after suffering a neurological insult.<sup>32</sup>

*Salat* is concluded by looking over one's right and left shoulder, during which, neck rotational movements take place. This might further contribute to neuromuscular fitness. These possible therapeutic effects of *salat* may suggest incorporating it in rehabilitation as a gentle exercise. More studies are needed to determine the full beneficial effects of the *salat* prayer on the rehabilitative process of disabled persons.

### Benefits in specific conditions:

#### Cervical Spondylosis

Cervical spondylosis is a common, age-related condition that affects the joints and discs in the cervical spine, in the neck. The practice of *salat* may improve the strength of neck muscles. *Sala'm*, turning the head towards both shoulders at the end of *salat*, might be a limited gentle neck exercise. A small pilot study examined the muscle activity of the neck extensors (NE), sternocleidomastoids (SCM) and biceps brachii muscles was performed in 14 healthy subjects during *salat* and specified exercises using surface electromyography (EMG). No significant difference between *salat* and exercise for NE ( $p = 0.482$ ) and SCM ( $p=0.161$ ) was shown and *salat* might be considered a useful tool in the warming up exercises or in the rehabilitation programs.<sup>33</sup>

*Salat* may also be beneficial in improving the wellbeing of patients with cervical spondylosis. In a recent study, 200 participants were divided into two groups, group A: Muslim males between the age group 40-60 years who performed *salat* four times a day or more, and group B: Muslim males between the age group 40-60 years who performed *salat* infrequently (<3/wk). They were followed up for a period of

one and half years. Out of the 118 males who performed regular *salat*, only 17 had cervical spondylosis, while among the 82 males who performed irregular *salat*, 30 had cervical spondylosis ( $p<0.05$ ). They postulated that performing regular *salat* might assist in the prevention of cervical spondylosis.<sup>34</sup>

### Erectile Dysfunction

The leading cause of erectile dysfunction (ED) or impotence is arterial dysfunction, with cardiovascular disease as the most common comorbidity. Physical activity has proved to be a protective factor against erectile problems, and it has been shown to improve erectile function for men affected by vascular ED.<sup>35</sup> Physical exercise therapy, particularly involving pelvic floor muscles, has been shown to provide beneficial effects on ED, boosting blood circulation and reducing ED symptoms. *Salat* movements may be a beneficial form of pelvic floor exercise. A small pilot study including 10 volunteers were divided into two groups. Subjects who were Muslims (Group I) were asked to perform their daily *salat* and a new intervention of an additional 12 movement cycles of *salat* three sessions a week for a duration of 4 months. Non-Muslim subjects (Group II) were taught to mimic *salat* movements, and were asked to perform a total of 12 movement cycles without reading the recitation for three sessions a week. A nocturnal electrobioimpedance volume assessment (NEVA) device was used to measure the nocturnal penile tumescence (NPT) parameters. All measured parameters improved significantly, with the largest change observed in the maximum percent volumetric change over the baseline (from 138 to 222%). This preliminary study suggests that *salat* and mimicking *salat* movements, may have beneficial effects for ED patients.<sup>35</sup> A larger study, however, is required in the future to validate these findings, particularly in their utility as an adjunct to PDE5 inhibitors.

### CONCLUSION

*Salat* is a spiritual and physical activity during which, nearly all muscles of the human body become more active than any kind of exercise without muscle fatigue. It induces serenity on the body and soul. The interaction between the central nervous system and autonomic nervous system during *salat* promotes relaxation and minimizes anxiety for individuals who regularly practice *salat*. *Salat* involves both cognitive and motor components. However, only one study is available in the literature addressing the relationship between religiosity and cognitive function. Performing *salat* may slightly reduce systolic and diastolic blood pressure but the studies available are very preliminary and more constructive studies on the effects of *salat* on cardiovascular system are warranted. Mind and body medicine as offered in the practice of *salat* may assist in the prevention of chronic illnesses such as degenerative musculoskeletal ailments and alleviate the symptoms of chronic disease. The physical activities involved in the performance of *salat* helps in the rehabilitation process in disabled geriatric patients by improving blood flow and increasing musculoskeletal fitness. As noted in this review, many studies conducted on *salat* involve small number of patients. More quantitative and qualitative research is needed to further examine the medical aspects of *salat*. Long-term studies that enroll a larger population should provide more accurate data.

## LIMITATIONS OF THE REVIEW

There are several limitations in this review. There is paucity of research on this subject and hence there are very few studies investigating the clinical effects of *salat*. The majority of the studies included in this review enrolled a small number of patients. There is certainly lack of longitudinal long-term follow up of the studied subjects, and the majority of the studies were observational and not randomised. No specific attention was made to the confounding factors such as age or gender in the majority of the studies reviewed. No comparative studies were performed on the Islamic prayer and prayers in other religions. More work needs to be carried out to explore the biomechanics of *salat* and the way *salat* influences the overall health and wellbeing. For example, current literature shows that there is some activation of different muscle groups during *salat*, but the extent of activation is inconsistent in the literature and additional studies need to be carried out.<sup>29</sup> More studies enrolling larger numbers of participants are necessary to further elucidate the health effects of *salat*.

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## CONFLICT OF INTEREST

No conflict of interest.

## ETHICAL APPROVAL

This review article does not contain any studies with human participants or animals performed by any of the authors.

## REFERENCES

- Saniotis A. Understanding mind/body medicine from muslim religious practices of salat and dhikr. *J Relig Health* 2018; 57(3): 849-57.
- Mueller PS, Plevak DJ, Rummans TA. Religious involvement, spirituality, and medicine: implications for clinical practice. *Mayo Clin Proc* 2001; 76(12): 1225-35.
- Levin JS. How religion influences morbidity and health: reflections on natural history, salutogenesis and host resistance. *Soc Sci Med* 1996; 43: 849-64.
- Strawbridge WJ, Cohen RD, Shema SJ, Kaplan GA. Frequent attendance at religious services and mortality over 28 years. *Am J Public Health* 1997; 87: 957-61.
- Koenig HG, Cohen HJ, George LK, Hays JC, Larson DB, Blazer DG. Attendance at religious services, interleukin-6, and other biological parameters of immune function in older adults. *Int J Psychiatry Med* 1997; 27: 233-50.
- Rasic D, Robinson JA, Bolton J, Bienvenu OJ, Sareen J. Longitudinal relationships of Religious worship attendance and spirituality with major depression, anxiety disorders, and suicidal ideation and attempts: findings from the Baltimore epidemiologic catchment area study. *J Psychiatr Res* 2011; 45: 848-54.
- O'Connor PJ, Pronk NP, Tan A, Whitebird RR. Characteristics of adults who use prayer as an alternative therapy. *Am J Health Promot* 2005; 19(5): 369-75.
- Al-Bar, M. A, & Chamsi-Pasha, H. Contemporary bioethics: Islamic perspective. Springer (Open access), 2015. Accessed from <http://link.springer.com/book/10.1007/978-3-319-18428-9>.
- Sayed SA, Prakash A. The Islamic prayer (Salah/Namaaz) and yoga togetherness in mental health. *Indian J Psychiatry* 2013; 55: 224-30.
- Koenig HG, Al Shohaib S. Health and Well-Being in Islamic Societies: Background, Research, and Applications. Springer International Publishing, Switzerland ISBN 978-3-319-05873-3. 2014.
- Majeed A. Salat offset the negative health effect of stress. *Inter J Adv Res* 2016; 4(2): 339-43
- Yucel S. The effects of prayer on Muslim patients' well-being. Boston University School of Theology. 2007. [cited October 2020] Accessed from <https://hdl.handle.net/2144/40>
- Doufesh H, Ibrahim F, Ismail NA, Wan Ahmad WA. Effect of Muslim prayer (salat) on  $\alpha$  electroencephalography and its relationship with autonomic nervous system activity. *J Altern Complement Med* 2014; 20(7): 558-62.
- Levine GN, Lange RA, Bairey-Merz CN, Davidson RJ, Jamerson K, Mehta PK et al. American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and Council on Hypertension. Meditation and Cardiovascular Risk Reduction: A Scientific Statement from the American Heart Association. *J Am Heart Assoc* 2017; 6(10): e002218.
- Doufesh H, Faisal T, Lim KS, Ibrahim F. EEG spectral analysis on Muslim prayers. *Appl. Psychophysiol Biofeedback* 2012; 37(1): 11-8.
- Doufesh H, Ibrahim F, Safari M. Effects of Muslims praying (salat) on EEG gamma activity. *Complement Ther Clin Pract* 2016; 24: 6-10.
- Achour M, Muhamad A, Syihab AH, Mohd Nor MR, Mohd Yusoff MYZ. Prayer moderating job stress among muslim nursing staff at the University of Malaya Medical Centre (UMMC). *J Relig Health* 2019; 10.1007/s10943-19-00834-6. doi:10.1007/s10943-019-00834-6
- Inzelberg R, Afigin AE, Massarwa M, Schechtman E, Israeli-Korn SD, Strugatsky R et al. Prayer at midlife is associated with reduced risk of cognitive decline in Arabic women. *Curr Alzheimer Res* 2013; 10(3): 340-6.
- Alabdulwahab SS, Kachanathu SJ, Oluseye K. Physical activity associated with prayer regimes improves standing dynamic balance of healthy people. *J Phys Ther Sci* 2013; 25(12): 1565-8.
- Chamsi-Pasha, H. Islam and the cardiovascular patient – pragmatism in practice. *Br J Cardiol* 2013; 20(3): 1-2.
- Doufesh H, Ibrahim F, Ismail NA, Wan Ahmad WA. Assessment of heart rates and blood pressure in different salat positions. *J Phys Ther Sci* 2013, 25: 211-4.
- Al-Kandari YY. Religiosity and its relation to blood pressure among selected Kuwaitis. *J Biosoc Sci* 2003; 35(3): 463-72.
- Byrne JT, Price JH. In sickness and in health: the effects of religion. *Health Education* 1979; 10(1): 6-10.
- Steffen PR, Hinderliter AL, Blumenthal JA, Sherwood A. Religious coping, ethnicity, and ambulatory blood pressure. *Psychosom Med* 2001; 63(4): 523-30.
- Rabbi MF, Ghazali KH, Mohd II, Alqahtani M, Altwijri O, Ahamed NU. Investigation of the EMG activity of erector spinae and trapezius muscles during Islamic prayer (Salat). *J Back Musculoskelet Rehabil* 2018; 31(6): 1097-104.
- Imamoglu O. Benefits of prayer as a physical activity. *International Journal of Science Culture and Sport (IntJSCS)* 2016; (SI 1): 306-18.
- Reza MF, Urakami Y, Mano Y. Evaluation of a new physical exercise taken from salat (prayer) as a short-duration and frequent physical activity in the rehabilitation of geriatric and disabled patients. *Ann Saudi Med* 2002; 22(3-4): 177-80.
- Al-Barzinjy N, Rasool MT, & Al-Dabbagh TQ. Islamic praying and osteoarthritis changes of weight bearing joints. *Duhok Medical* 2009; 3(1): 33-44.
- Osama M, Malik RJ. Salat (Muslim prayer) as a therapeutic exercise. *J Pak Med Assoc* 2019; 69(3): 399-404.
- Yilmaz S, Kart-Köseoglu H, Guler O, Yucel E. Effect of prayer on osteoarthritis and osteoporosis. *Rheumatol Int* 2008; 28(5): 429-3.
- Chokkhanhitchai S, Tangarunsanti T, Jaovisidha S, Nantiruj K, Janwityanujit S. The effect of religious practice on the prevalence of knee osteoarthritis. *Clin Rheumatol* 2010; 29(1): 39-44.
- Ghous M, Malik AN. Health benefits of salat (prayer); neurological rehabilitation. *Professional Med J* 2016; 23(8): 887-8.
- Safee M KM, Wan Abas WAB, Ibrahim F, Abu Osman NA. Electromyographic activity of the upper limb muscle during specific salat's position and exercise. *Inter J Appl Phys & Math* 2012; 2(6): 433-5.
- Pandey A, Singh AK, Kumar S, Chaturvedi M, Verma S, Agarwal P et al. The prevalence of cervical spondylosis in Muslim community with special reference to Namaz in Agra. *Internet Journal of Rheumatology and Clinical Immunology (IJRCI)* 2017; 5(1): 1-5
- Silva AB, Sousa N, Azevedo LF, Martins C. Physical activity to improve erectile function: a systematic review of intervention studies. *Sex Med* 2018; 6(2): 75-89.
- Ibrahim F, Sian TC, Shanggar K, Razack AH. Muslim prayer movements as an alternative therapy in the treatment of erectile dysfunction: a preliminary study. *J Phys Ther Sci* 2013; 25(9): 1087-91.

# The handling of safety concerns among anaesthetists when restarting full surgical lists during the COVID-19 pandemic

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## SUMMARY

Around June 2020, many institutions restarted full operating schedules to clear the backlog of postponed surgeries because of the first wave in the COVID-19 pandemic. In an online survey distributed among anaesthetists in Asian countries at that time, most of them described their safety concerns and recommendations related to the supply of personal protective equipment and its usage. The second concern was related to pre-operative screening for all elective surgical cases and its related issues. The new norm in practice was found to be non-standardized and involved untested devices or workflow that have since been phased out with growing evidence. Subsequent months after reinstating full elective surgeries tested the ability of many hospitals in handling the workload of non-COVID surgical cases together with rising COVID-19 positive cases in the second and third waves when stay-at-home orders eased.

## KEY WORDS:

COVID-19, pandemic, anaesthetic practice, aerosol box, elective surgery, Personal Protective Equipment (PPE), N95 respirator

## INTRODUCTION

The pandemic had changed the delivery of medical care in many ways. When the focus was mainly on the management of COVID-19 cases during the first wave, many institutions suspended elective surgeries to conserve resources and manpower.<sup>1</sup> But when the outbreak slowed down, full surgical lists restarted to clear the backlog of postponed cases and allowed operating theatre (OT) schedules to return to their previous pace. As anaesthetists resumed duties in OT, their roles interchanged from being front-liners, intensivists and anaesthesia providers. The inherent risk of contracting COVID-19 remained, although personal risk was accepted as part of the responsibility in patients' best interest. In most hospitals, although perioperative guidelines prioritising patient and health care workers' (HCW) safety were in place, many techniques and equipment were newly implemented and improvised. Some were practiced with limited evidence as the new 'norm', leading to difficulty in standardising the best practice.

## METHODS

A brief anonymous online survey was sent to anaesthetists in the Asian region in May 2020 to determine their views on

three domains (Table I) – own safety when restarting full OT services, the new anaesthetic practice and personal experience with COVID-19. Responses received from practicing colleagues in Malaysia, Singapore, Thailand, China, Korea, Philippines and Vietnam are presented in Table II.

## RESULTS

### Personal Protective Equipment

We ascertained that there was anxiety about their safety in restarting full OT services. Two main themes identified repeatedly were related to either personal protective equipment (PPE) or pre-operative screening of surgical cases. "PPE supply is not constant" and "Staff does not have full PPE!" were examples describing the shortage of PPE as it had become a tightly monitored commodity under the control of non-anaesthetic departments in some centers. PPE shortage posed a tremendous challenge to healthcare systems around the world because of the sudden surge capacity and institutions chose to conserve the use in the coming load of surgical procedures unless required. Among all PPE, the most commonly mentioned was unsurprisingly the N95 respirator as it controls exposures to airborne infections when fitted and used properly. Strategies to overcome the unbalanced supply-demand matching included recognising the institutional capacity as being conventional, contingency or critical to precisely calculate the PPE 'Burn Rate' and estimate the added volume.<sup>2</sup> In some centers, KN95 respirators replaced N95's and subsequently 3-ply masks were used. Regular steps to adjust the level of protection based on epidemiological risks will overcome unnecessary wastage. Added concerns about the cost especially with PPE's escalating price was also noted as a reason for its limitation in practice. Furthermore, issues with incorrect use and non-compliance among colleagues were also raised and these required constant education, training and reassessment of the current epidemiological risks.

### Viral screening

Pre-operative screening was another dilemma with most anaesthetists preferring to test even asymptomatic patients. Many were aware that the initially available screening test with real-time polymerase chain reaction (PCR) identification of viral RNA had its share of setbacks with a false negative rate of 30%, delayed results and limited test capacity.<sup>3</sup> Thus, recommending the surveillance for every case remained



**Table I: Outline of the questions in the anonymous survey from May 26th to 7th June 2020**

No	Question	Answer
1.	Do you feel safe in the current anaesthetic practice? a) If no, what is the reason? b) What is the improvement needed?	Yes/ No
2.	Describe the current anaesthetic practice in your institution regarding - a) Pre-operative COVID-19 screening b) Types of PPE worn c) The use of an aerosol box and intermission time after AGP	Free text
3.	Have you had personal experience for the following: a) Screened for COVID-19 b) Colleagues who are COVID-19 positive and their point of contact, if positive	Yes/ No

(PPE - personal protective equipment, AGP - aerosol generating procedures, PAPR - powered air-purifying respirator, OT - operating theatres, CO<sub>2</sub> – carbon dioxide, RT-PCR – rapid polymerase chain reaction)

difficult, especially in urgent procedures. This was frightening when the volume of surgical cases escalated together with the uncertain supply of PPE. Potential risks of exposure while anaesthetising cases with unknown status was real and felt by the respondents. So, a consultant wrote “screening should be included as a standard of care similar to performing ECG and other routine blood tests.” For serologic screening to be meaningful, the timing of the test was crucial and both false or positive results must be utilised in conjunction with clinical presentations, patient history and epidemiological information. In the end, the necessity to screen with rapid tests relied mainly on international and local guidelines according to individual disciplines and institutions, patient risk category and results from screening questionnaires.

#### Workflow

As predicted, peri-operative workflow was not standardised even within the same healthcare system. During the peak of the pandemic, several untested and unproven devices were invented, which initially took the medical community by storm as a pragmatic approach to meet the dual challenge of caring for infectious patients and protecting HCW.<sup>4</sup> One of them was the aerosol box, used by half of the respondents but shunned by the other knowing that the evidence to support it was lacking. With more reports of its cumbersome use and problems, fewer anaesthetists used it eventually. Similarly, techniques were modified with respondents giving examples of “clamping the tracheal tube just after intubation till reconnection to the breathing circuit”, “using plastic sheet as it is more accommodating for all intubation/ extubation, suctioning and naso-gastric tube insertion”, “wipe down all surfaces after intubation” and “recovery in OT itself”. Some practiced interval time for clearance of aerosols after aerosolising generating procedures (AGP) in OT by prohibiting entry of personnel without filtering respirators but none could mention a suitable timing for this. Therefore, the new ‘norm’ in OT started with a lot of uncertainties but with time, eased to a better workflow with increased knowledge of the virus and its virology.

#### Personal experience

At the end of the survey, we identified personal experience of anaesthetists themselves who had to undergo COVID-19 screening. The point of contact for positive colleagues was also reported from both work-related and community acquired. An anaesthetist suggested “health care workers must be tested regularly” because non-compliance to PPE was an issue with constant exposure to high risk AGP. In a recent report, 34% of HCW who tested positive for COVID-19 can be

asymptomatic while, 59% symptomatic HCW had negative results when tested.<sup>5</sup> The potential benefit of universal staff screening should be considered when the target number of tests per day could be achieved to prevent nosocomial transmission to susceptible patients, staff and the community.

#### CONCLUSION

The following months tested the ability to completely alleviate COVID-19 in many countries especially when the pandemic continued with second and third waves. As evidence grew, uncertainties in perioperative care ironed out and personal risk while managing patients returned to minimal when anaesthetists performed their clinical duties.

#### CONFLICT OF INTEREST

None

#### ACKNOWLEDGEMENTS

We thank the Malaysian Society of Anaesthesiologists MSA for their support in disseminating the questionnaire of this study to MSA members in Malaysia and their counterparts in other Asian countries.

We also thank all the participating anaesthetists from other countries (Singapore, Thailand, China, Korea, Philippines and Vietnam) for taking part in this survey.

#### REFERENCES

1. ACS, ASA, AORN, AHA. Joint Statement: Roadmap for resuming elective surgery after COVID-19 pandemic. [cited June 2020] Accessed from <https://www.asahq.org/about-asa/newsroom/news-releases/2020/04/joint-statement-on-elective-surgery-after-covid-19-pandemic>.
2. Centers for Disease Control and Prevention. Strategies to optimize supply of PPE and equipment. Coronavirus Disease 2019 (COVID-19). [cited June 2020] Accessed from <https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/index.html>.
3. Rezaie S. COVID-19 Update: aerosol box, awake proning, prediction scores, & doing the basics right. REBEL EM - Emergency Medicine Blog. 2020. [cited June 2020] Accessed from <https://rebelem.com/covid-19-update-aerosol-box-awake-proning-prediction-scores-doing-the-basics-right/>.
4. Woloshin S, Patel N, Kesselheim A. False negative tests for SARS-CoV-2 infection — challenges and implications. N Engl J Med 2020 ;383(6):e38.
5. Khalil A, Hill R, Ladhani S, Pattison K, O'Brien P. COVID-19 screening of health-care workers in a London maternity hospital. Lancet Infect Dis 2020; 21(1): 23-4.

**Table II: Results and representative quotes extracted from survey responses among anaesthetic trainees, specialists and consultants in Malaysia, Singapore, Thailand, China, Korea, Philippines and Vietnam (n=77)**

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### SAFETY

19.5% respondents did not feel safe in their current anaesthetic practice. Representative quotes for their reasons were divided into the following major themes and their respective suggestions for improvement:-

#### Shortage of PPE:

- "PPE supply is not constant. We reuse our PPE whenever possible."
- "Staff does not have full PPE!"
- "Limited proper PPE and N95 masks to use daily. The Medical Department controls usage."

#### Suggestions for improvement:

- "Insurance companies refuse to pay for the use of PPE hence in private practice, it is a constant challenge to educate patients why it is important to protect medical staff and have them fund the cost of PPE."
- "PAPR for all AGP. We hope to have more PAPRs especially for long procedures and aerosolizing procedures."

#### Issues with wearing PPE:

- "Face shields tend to fog, making handling of sharps a challenge."
- "Due to use of hoods and half face respirators, communication is a challenge."
- "Long surgeries are a challenge due to the higher heat and humidity in the negative pressure OT and CO2 retention among team members using the N95 respirator mask."

#### Suggestions for improvement:

- "Better quality face shields with good anti-fogging property and less distortion of vision."
- "We hope to have negative pressure OTs and adequate air exchange. Not all of our machines have active scavenging, so we also have to modify anaesthetic techniques as needed."
- "If there are not enough isolation rooms in the ward, all ward staff should at least wear N95 respirator masks when stepping into that ward with strict and clear guidelines to lower risks of exposure."

#### Non-compliance with PPE among colleagues:

- "Many surgeons are hampered by face shields and tend to remove them intraoperatively."
- "This situation creates anxiety among the nursing staff, who have to work with the surgeons day in and day out in close contact with them."
- "Staff nurses are sitting at nursing counter without putting their masks on."

#### Suggestions for improvement:

- "Health care workers must be tested regularly for COVID-19."
- "Clear top-down directives, good inter-departmental or inter-discipline communication."

#### Pre-operative COVID-19 screening:

- "Untested cases."
- "Worried about asymptomatic COVID-19 positive patients as RT-PCR test may not be positive initially."
- "Screening time is too long in my setting."
- "I hope that the testing can be done quicker and is easily performed in the paediatric age group."
- "I think all patients coming for surgery should be screened. Currently only symptomatic patients are screened."

#### Suggestions for improvement:

- "Screening for all patients coming for surgery regardless of symptoms."
  - "A sensitive point-of-care test for COVID-19 would be better, with less time required awaiting results."
  - "Pre-operative testing of COVID-19 should be included as standard of care similar to performing ECG and other routine blood tests."
- 

### NEW ANESTHETIC PRACTICE

Towards the end of the first wave in the pandemic, 81.8% respondents performed pre-operative screening in their institutions for all cases. For those who didn't, 61.5% answered that COVID-19 screening was not necessary after questionnaire screening and 15.4% did not have enough tests.

The most common items worn were full PPE such as N95 respirator (81.8%), face shield (88.3%) and water-resistant gown (74.0%) during AGP at intubation and extubation. Most respondents doffed within OT (57.1%) and performed a wipe down of surfaces after each AGP (66.2%). In addition, 58.4% and 57.1% did not practice interval time after intubation and extubation with reasons given as no evidence to do so, no time to wait and unsure (33.3% each)

57.1% utilized the aerosol box during intubation but less used it during extubation (46.8%). The majority who did not use the aerosol box said they either did not have it (38.4%) or claimed lack of evidence to support its usage (30.8%).

#### Representative quotes for their practice were:

- "Intubation is by modified rapid sequence induction, therefore, aerosol box is not necessary."
  - "The aerosol box is not conducive for difficult intubation and obese patients."
  - "Can use as a trial but not compulsory."
  - "No intermission time during intubation because tracheal tube is immediately connected to the circuit."
  - "Our OT is neither truly positive nor negative pressured. We just have a presumed constant air exchange for 16x per hour."
  - "We are clamping the tracheal tube just after intubation till reconnection to circuit, is it necessary?"
  - "At the moment, our management of non COVID-19 cases are very similar to COVID-19 cases."
  - "I do not like the aerosol box as it is cumbersome and difficult to manipulate the videolaryngoscope, tracheal tube and suction plus difficult for the assistant as well. We find the plastic sheet more accommodating and use that for all intubation and extubation, suctioning and Ryles tube insertion."
  - "Patients recover in OT. Once they are stable, they are transferred straight to the ward."
- 

### PERSONAL EXPERIENCE WITH COVID-19

In terms of personal experience with COVID-19 screening, 28.6% had taken the screening. Out of these 22 respondents, 62.6% had repeated the swabs twice but fortunately all turned out to be negative. 15.6% knew of a colleague who was COVID-19 positive and their point-of contact were often work-related (50.0%), non-work related (41.7%) or unsure.

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# Diagnosis of neonatal meningitis: Is it time to use polymerase chain reaction?

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## SUMMARY

**Group B Streptococcus (GBS) is a predominant causative pathogen of neonatal meningitis that is associated with a high rate of mortality and morbidity. The establishment of antenatal screening and intrapartum chemoprophylaxis has led to a significant reduction in the incidence rate of invasive GBS disease in developed countries. However, these strategies are not routinely practiced in most developing countries. To ensure good recovery of infants affected with GBS, a prompt diagnostic strategy and appropriate therapy are essential. We highlight here the case of a preterm male infant diagnosed with early-onset of GBS meningitis diagnosed by using polymerase chain reaction (PCR) method on the cerebrospinal fluid (CSF) of the infant. Initially the pathogen was not isolated in both blood and CSF cultures as sampling was performed after the administration of antibiotics. Hence, PCR was a crucial diagnostic test in facilitating the detection of the pathogen in CSF. We believe that PCR is a potentially fast and precise diagnostic method for infection in a newborn.**

## INTRODUCTION

*Streptococcus agalactiae*, or group B Streptococcus (GBS) is a common causative pathogen of neonatal meningitis. GBS meningitis has been associated with high rates of mortality and morbidity.<sup>1</sup> A timely diagnosis and prompt treatment with the appropriate antibiotic is essential to ensure optimal outcome. Unfortunately, the commonly used diagnostic method to isolate GBS from the cerebrospinal fluid (CSF) sample lacks sensitivity despite high specificity.<sup>2</sup> In this case report, we illustrate a case of GBS neonatal meningitis that failed to grow in the routine CSF culture but was instead detected via PCR.

## CASE REPORT

A preterm male infant was admitted to the neonatal intensive care unit (NICU) of Hospital Serdang at 6 hours of life for recurrent episodes of symptomatic hypoglycaemia. He was born at 36 weeks of gestation via an emergency caesarean section for unprovoked foetal heart rate deceleration. His birth weight was 3100gm and the Apgar score was normal. The mother presented with late-onset pregnancy-induced hypertension on the day of delivery with no history of fever or premature rupture of chorioamniotic membrane. No GBS screening was performed throughout the

course of her pregnancy. On examination, the baby had jitteriness and a weak cry. His body temperature was 36.3°C, pulse rate was 144 beats/minute with immediate capillary refilling time and blood pressure was 62/49mmHg. His anterior fontanelle was normotensive on palpation and he was actively moving all four limbs with normal tone and reflexes.

On further examination, blood sugar profile ranged between 1.6-2.4mmol/L, thus requiring multiple doses of Dextrose 10% bolus and intravenous glucose infusion at the rate of 15mg/kg/min. His condition deteriorated a day later despite the normalisation of blood glucose level. He developed respiratory distress requiring non-invasive respiratory support. Haematological indices were within the normal limits (haemoglobin 14.7g/dL, total white cell count 19,100/ $\mu$ L with 60% neutrophils, 22% lymphocytes and platelet 150,000/mm<sup>3</sup>). Blood culture was sterile for bacterial growth, even though the C-reactive protein was elevated (19mg/dL).

In view of that, he was treated as presumed sepsis and commenced on intravenous c. penicillin and gentamycin. However, no clinical improvement was observed after 48 hours. A repeated haematological test revealed a reduced platelet count (haemoglobin 12.9g/dL, total white cell counts 15,200/ $\mu$ L and platelet 92,000/mm<sup>3</sup>). In addition, CSF microscopy showed pleocytosis (60 polymorphonuclear cells/mm<sup>3</sup>) with a ratio of CSF glucose to serum glucose of 0.79 and CSF protein of 862mg/dL. However, the microbiological study of both blood and CSF did not yield any microorganism. CSF sample was also sent for polymerase chain reaction (PCR) test to amplify the 16S rRNA gene and it turned out to be positive. The primer sequences used were: primer U1 (F): 5'-CCAGCAGCCGCGGTAATACG-3' and primer U2(R): 5'ATCGGYTACCTTGTTACGACTTC-3'. Following that, the PCR product was sent for sequencing and the species was identified as *S.agalactiae*. A high vaginal swab sample was taken from the mother subsequently and a similar pathogen was isolated in the culture.

Following the diagnosis, the antibiotic treatment was escalated to a high dose intravenous c. penicillin and cefotaxime for 21 days. Upon completion of the antibiotics, his symptoms resolved and he was discharged home on day 25 of life. He continued to do well on follow-up.

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## DISCUSSION

GBS meningitis is a devastating infection associated with significant mortality and morbidity in the neonatal population. It is associated with a 30% mortality rate and the survivors are predisposed to a high risk of neurological sequelae.<sup>3</sup> Even though the overall incidence and mortality of GBS meningitis have declined in recent decades, its morbidity remains virtually unchanged.<sup>1</sup> Therefore, prompt diagnostic strategies with appropriate therapies is crucial to ensure better outcome for the affected infants.

Nevertheless, accurate diagnosis of early-onset GBS meningitis is often difficult due to the non-specific clinical symptoms manifested by infants. Thus, the definitive diagnosis is highly dependent on the positive identification of infecting microorganisms isolated in the CSF culture. Unfortunately, the conventional microbiological diagnostic method is associated with low sensitivity and high false-negative culture results, especially if the CSF sampling is done after intrapartum or postnatal exposure to antibiotics.<sup>2</sup> In our experience, the diagnosis of neonatal meningitis is often presumptive based on a combination of clinical suspicion and clues from the CSF microscopy. However, the CSF indexes vary according to age and normal values of CSF in infancy are poorly defined.<sup>4</sup> A study evaluating the use of  $>20/\text{mm}^3$  CSF leucocyte count as a cut-off value for the diagnosis of neonatal meningitis subsequently showed that 13% of confirmed meningitis cases had normal CSF parameters. In addition, CSF protein and glucose are also considered as poor predictors of meningitis due to possible overlapping of values between infants with or without meningitis. This is further compounded by the rapid sterilisation once antibiotics have been initiated.<sup>2,3</sup> In other words, it is difficult to predict the diagnosis of neonatal meningitis solely based on CSF parameters. Thus, the identification of the offending microorganism is still paramount in the optimisation of antibiotic therapy and in order to minimise the risk of severe neurological sequelae.

To date, several PCR-based methods have been explored as a diagnostic tool for bacterial meningitis. Apart from having a significantly higher sensitivity and specificity for direct detection of bacteria from CSF, the PCR method has also been proven to be able to produce the result within a day, thus

representing a shorter turn-around time than the conventional methods.<sup>5,6</sup> Moreover, PCR yields higher sensitivity and specificity in detecting the pathogen in CSF among individuals who have been on antibiotic treatment because it is not affected by the viability of microorganisms.<sup>5,6</sup> Therefore, even though the cost of PCR is higher, it can lead to faster and more accurate detection of pathogens in the CSF. As a result, it enables the appropriate chemotherapy to be initiated early prior to CSF collection and subsequently contributes to a better prognosis in patients with GBS meningitis.

## CONCLUSION

Microbiological studies remain the gold standard for the diagnosis of neonatal meningitis. However, its low sensitivity often results in false-negative results. Therefore, PCR is more promising and helpful method in investigating infants who are clinically suspected of meningitis, especially those who have been treated with antibiotics prior to CSF sampling.

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## REFERENCES

1. Heath PT, Okike IO, Oeser C. Neonatal meningitis: can we do better? *Adv Exp Med Biol* 2011; 719: 11-24.
2. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. *Pediatrics* 2001; 108 (5): 1169-74.
3. Libster R, Edwards KM, Levent F, Edwards MS, Rensch MA, Castagnini LA et al. Long-term outcomes of group B streptococcal meningitis. *Pediatrics* 2012; 130 (1): e8-15.
4. Schrag SJ, Zell ER, Lynfield R, Roome A, Arnold KE, Craig AS et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. *N Engl J Med* 2002; 347(4): 233-9.
5. Sarookhani MR, Ayazi P, Alizadeh S, Foroughi F, Sahmani A, Adineh M. Comparison of 16S rDNA-PCR Amplification and culture of cerebrospinal fluid for diagnosis of bacterial meningitis. *Iran J Pediatr* 2010; 20(4): 471-5.
6. Zeng YF, Chen CM, Li XY, Chen JJ, Wang YG, Ouyang S, et al. Development of a droplet digital PCR method for detection of *Streptococcus agalactiae*. *BMC Microbiol* 2020; 20(1): 179.

# First case of pulmonary hydatid cyst in a pregnant Syrian refugee woman in Malaysia

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## SUMMARY

**Pulmonary hydatid cyst (PHC) in pregnancy is a very rare pathology. We report here a case of ruptured PHC during pregnancy in a 26-year old Syrian (refugee) woman who presented with complaints of productive cough with metallic taste and dyspnoea. PHC was suspected due to her clinical and radiological findings. Interestingly, the sputum examination confirmed the diagnosis as numerous protoscolecocytes were present. Serology for *Echinococcus* infection revealed positive at high titre. Early diagnosis and prompt treatment by providing care improves the patient outcome. Parasitological examination of the respiratory specimen in suspected ruptured PHC is desirable as a valuable detection tool.**

## INTRODUCTION

Echinococcosis (hydatidosis or hydatid disease) is a zoonotic infection that is acquired by the ingestion of eggs from the tapeworm *Echinococcus* spp. There are several species that cause echinococcosis such as *Echinococcus granulosus* in most cases while others such as *Echinococcus multilocularis*, *Echinococcus vogeli* and *Echinococcus oligarthrus* also infect humans. Echinococcosis is rarely reported in Malaysia but is one of a major public health concerns throughout the Mediterranean region, northern Africa, and Asia region, where domesticated animals are commonly raised. In these countries, the incidence rate is about 50 per 10,000 person-years, whilst about 1 in 20,000 to 30,000 cases are reported in pregnancy.<sup>1</sup> There are only few reports of pulmonary hydatid cyst, especially in pregnant women. Thus, insufficient data is available to have guidelines based on the clinical presentations, diagnosis, and management of echinococcosis infection especially in non-endemic countries such as Malaysia. There are only two reported cases of echinococcosis from Malaysia, both involving the liver. This is the first case report of a ruptured pulmonary hydatid cyst (PHC) in a pregnant refugee lady from Syria residing in Malaysia.

## CASE REPORT

A 26-year-old Syrian lady, primigravida at 32 weeks of pregnancy; presented to the emergency department of the Selayang Hospital, Selangor, Malaysia with chief complaints of productive cough and shortness of breath for two months. She complained of experiencing oral metallic taste especially whilst coughing. There was no fever, abdominal pain,

nausea, vomiting, haemoptysis, night sweat, loss of weight or loss of appetite. She had no other previous medical illness. Social history included arrival in Malaysia two years prior to the appearance of the symptoms. She denied previous contact or travel history associated with animal hosts particularly sheep, dogs, or cattle. However, she had a twin sister who had presented with similar symptoms and was diagnosed to have large bilateral lung cysts; who was treated with anti-parasitic medication and the cysts removed surgically. On physical examination of our patient, her vital signs were stable with 95% oxygen saturation under room air. Her lungs were clear on auscultation but there was reduced breath sound on the left middle and lower zone. Other systemic examinations were unremarkable and foetal condition was stable.

During admission, her full blood count showed leukocytosis ( $13.5 \times 10^9/L$ ) with neutrophil predominant (93%). There was no anaemia, thrombocytopenia or eosinophilia. On the fourth day of admission, her eosinophilic count rose from 0.2% to 1.21%. Her chest radiograph (Figure 1A) revealed a large cavitation with thick wall on the left lung involving the mid and lower zones. There was also consolidation of bilateral lung lower zone with pleural effusion. Computed tomography pulmonary angiography (CTPA) (Figure 1B-1D) was performed which showed a large solitary cavitating lesion in the left lower lobe measuring  $9.7 \times 7.7 \times 12.3$ cm. A communication of the large cyst with lower lobe bronchiole of the left lung was observed but there was no evidence of pulmonary embolism.

The sputum test for acid-fast bacilli was negative. Parasitological microscopic examination of her sputum confirmed *Echinococcus* infection with protoscolecocytes of hydatid sand present in the wet mount (Figure 2A, 2B) and with Giemsa stain (Figure 2C-2F). There were also fragments of the laminated membrane of the cyst (Figure 2E, 2F). Further diagnostic test was performed with enzyme-linked immunosorbent assay (ELISA). Serology sample for *Echinococcus* IgG antibody showed positive at a very high titre of 49.35 DU.

Thus, a diagnosis of pulmonary hydatid cyst (PHC) was made. She was started on oral albendazole and referred to a tertiary hospital with a cardiothoracic unit. She underwent induction of labour at 35 weeks. She delivered a healthy baby via forceps assisted vaginal delivery and with a plan of

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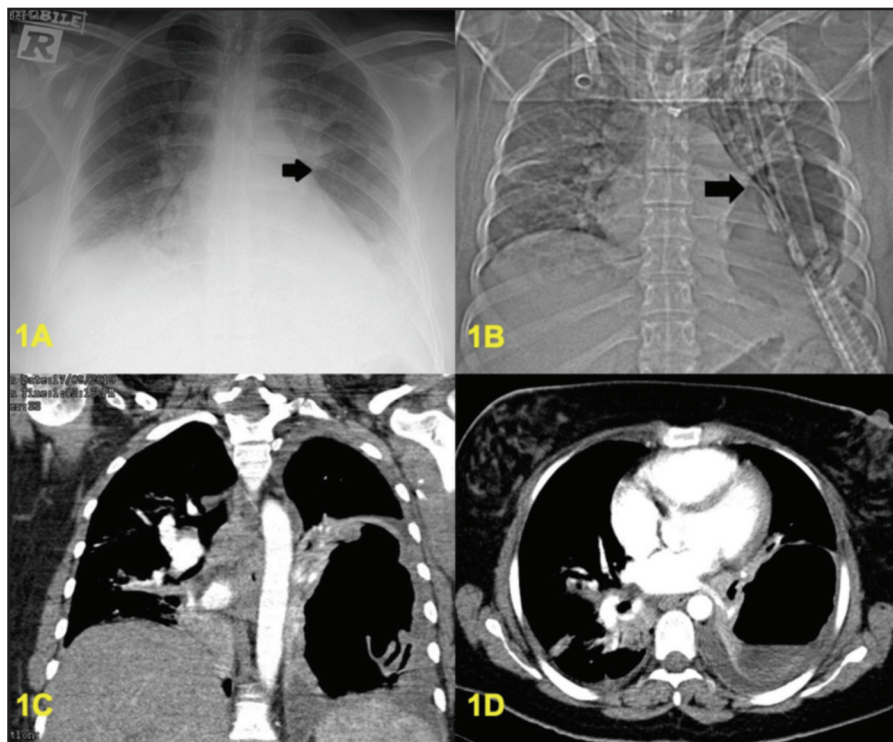


Fig. 1: A). Chest radiograph showing the large *Echinococcus* cyst in the left lung (black arrow). B,C,D). CTPA scan showing the complicated large cavitation with onion peel sign.

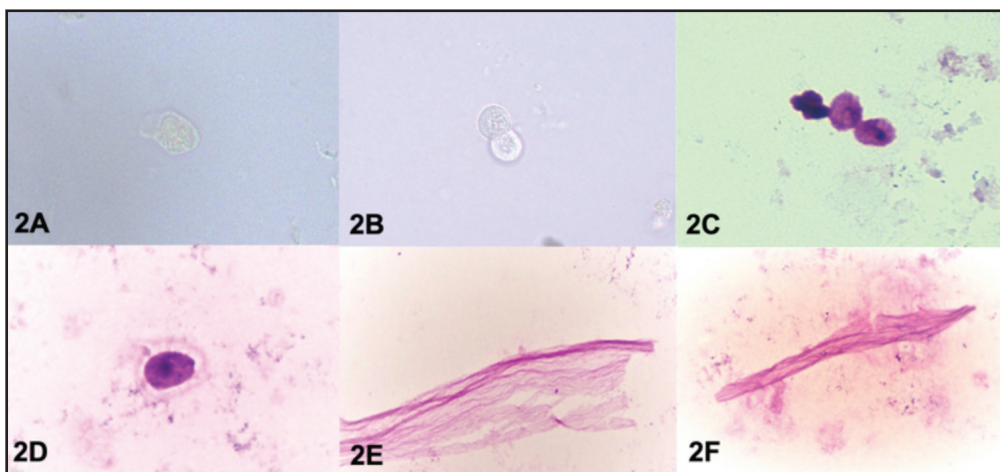


Fig. 1: A,B). Direct smear of sputum in saline showing invaginated protoscolex/protoscoleces with refractile row of hooklets/rostellum in the centre (30–45µm x 25–35µm), under x40 magnification. C,D) Giemsa stain of sputum revealed protoscolex/protoscoleces from hydatid cyst were oval measuring about 42–45µm x 30–32µm, had rostellum/hooklets in the centre, under x1000 magnification. E,F) Giemsa stain of sputum seen fragments of outer, acellular laminated membrane, remnant of the cyst wall, under x1000 and x40 magnification respectively.

surgical removal of cyst postpartum. Albendazole was administered 400mg twice daily for 28 days. Successful surgical resection of the cyst was done six months postpartum.

**DISCUSSION**

Hydatid cysts (HC) are commonly seen in the liver.<sup>2</sup> Compared to the dense liver tissue, pulmonary HC can grow swiftly and expand due to less physical resistance in the lung

tissue. Some reports state that during pregnancy, suppression of cellular immunity may cause rapid increase in parasite growth and steroids secreted from the placenta causing the cysts to enlarge.<sup>3</sup> Thus, those factors may explain the reason why the *Echinococcus* cysts grew larger and produced symptoms suddenly in our patient.

Commonly, HC is reported to enlarge steadily to approximately 1 to 5cm per year and fully mature in about 20 years or more. Most cysts do not cause any symptoms

initially in the infected person and usually takes several years to reach the size to cause clinically symptoms. In our patient, the infection perhaps had been present for decades earlier, possibly during her childhood, in the same environment as her twin sister.

The diagnosis of PHC is usually made by taking full medical history involving social background, travel history, radiographical findings of the patient and subsequently confirmed by laboratory tests. Our patient a Syrian refugee, has a twin sister with a past history of PHC. She experienced oral metallic taste, which may perhaps be a salty or peppery taste just as experienced by other patients of ruptured HC cases. Hydatidosis is defined as vomiting out of hydatid fluid through the mouth. Complication of HC such as ruptured cyst was reported seen in 27.6% of cases, but relatively rare in pregnant women. Rupture of HC may occur during pregnancy due to enlarging uterus that compresses the cyst, trauma or secondary infection. This may also be due to decreased cell mediated immunity in the patient that facilitate rapid parasitic growth of the organism.<sup>4</sup> PHC tends to rupture into the bronchus and trigger expectoration of cyst fluid, causing cough, chest pain and abdominal pain. Serious pleural complications may occur, although rare, which may become life-threatening due to anaphylactic shock.

Hydatid fluid is highly toxic and antigenic which contains acidic fluid with pH 6.7, salt, protein and colourless. Thus, spillage of the hydatid fluid into the circulation of the infected person may give rise to eosinophilia and expose the patient to risk of anaphylaxis. Fortunately, our patient did not have eosinophilia or anaphylaxis reaction when she presented to the emergency and remained stable through her pregnancy. Her initial full blood count investigation did not show any specific results. Studies showed less than 15% of HC cases present with eosinophilia and this generally occur when the cysts have ruptured. While other studies report that only 2% of cases had anaphylactic reaction,<sup>5</sup> and patients rarely had anaphylactic reaction during pregnancy. The eosinophil count of our patient rose only on the fourth day of admission which could have been due to the cysts rupturing during her admission. This complication was anticipated by the clinician as the patient was given medication to prevent anaphylactic prophylaxis and anthelmintic. Such prompt and efficient patient management does improve PHC patient prognosis.

To this date, the diagnosis of echinococcosis mainly relies on radiological findings and further supported by serological confirmation. Serological test is very helpful and is available in the form of direct haemagglutination test, immunoblot and enzyme-linked immunosorbent assay (ELISA). Only ELISA for the detection of IgG against *Echinococcus* is available in Malaysia. The antigen used in the serological test is mainly derived from protoscoleces of *E. granulosus* or *E. multilocularis*. The sensitivity is highest for infection in multiple organs (90-100%) followed by liver (85-95%) and lowest for pulmonary (50-60%). Even though so, detection of high titre in our pulmonary case was most likely due to ruptured HC.

Examination of ova and parasite in the stool of the infected patients is not diagnostic as parasite eggs are not shed by humans, since humans are the accidental dead-end host. Confirmation of *Echinococcus* via microscopy respiratory sample is not widely done. In this case study, we would like to address an interesting aspect of the diagnosis *Echinococcus* i.e. the presence of protoscoleces during microscopic examination. Diagnostic aspiration of hydatid sand from patients is seldom indicated in view of the invasiveness of the procedure and the possible risk of seeding of the hydatid. But in our case, the patient coughed out protoscoleces and we were able to diagnose by basic parasitological examination and subsequently confirmed by the serological test. Microscopic examination of the respiratory specimen in cases of ruptured HC and hydatidosis is important because the procedure is practical, non-invasive, cheap, and also diagnostic of infection. A wet unstained mount procedure is simple to perform and often adequate for confirmatory diagnosis especially if protoscoleces are seen with or without hooklets.

Furthermore, our case was more complex as the patient was pregnant at 32 weeks and thus the management was risky. Surgical treatment remains the main choice of HC disease. However, medical treatment is just as important. In our case, a combination of anthelmintic and anaphylactic medication was given. Albendazole remains the anthelmintic of choice for this disease. It can penetrate the complex cyst wall and prevents the eggs from hatching. Thus, administration of albendazole is recommended preoperatively in order to sterilise the cyst, to decrease the tension in the cyst so that there are less chances of seeding from the spillage and subsequently preventing anaphylaxis reaction. It needs to be noted that albendazole is teratogenic and not recommended to be used in the first trimester. Postoperative medical treatment for up to 30 days is recommended to reduce the high recurrence rates and hydatidosis considerably. Treatment with albendazole results in 30% resolved response rate and generally, the prognosis with anthelmintic remains varies. Some studies recommend that HC during pregnancy should be managed conservatively with courses of albendazole after the first trimester of pregnancy. Some other cases which had great prognosis and outcome treated with anthelmintic postnatally without antenatal anthelmintic course.

Surgical removal is also controversial, especially in pregnant women. When there is a potential risk and complication of the HC interfering with normal labour, delivery should be by caesarean section and, whenever possible the cysts removed later when safe. As in this case, prophylaxis against anaphylaxis during labour should be anticipated and shortening the second stage of labour can reduce the risk of rupture of HC.

## CONCLUSION

Our case highlights the non-specific and mild clinical presentation of a ruptured PHC in a pregnant lady. Timely diagnosis and management of ruptured hydatid cysts in pregnant women will improve the prognosis. In symptomatic and cases of suspected ruptured PHC, microscopic

examination of respiratory specimen is a faster and cheaper diagnostic method to confirm the infection, especially in non-endemic countries. We recommend anthelmintic therapy during antenatal (second and third trimester) and postnatally in managing pregnant women with ruptured PHC.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest to disclose.

#### REFERENCES

1. Junghanss T, Da Silva AM, Horton J, Chiodini PL, Brunetti E. Clinical management of cystic echinococcosis: State of the art, problems, and perspectives. *Am J Trop Med Hyg* 2008; 79(3): 301-11.
2. Hayati MPS, Eugene CBT, Jin BJ, Rose IM. Chronic hydatid cyst in Malaysia: A rare occurrence. *Malaysian J Med Sci* 2015; 22(1): 79-83.
3. Kain KC, Keystone JS. Recurrent hydatid disease during pregnancy. *Am J Obstet Gynecol* 1988; 159(5): 1216-7.
4. Ekim H, Ekim M. Echinococcal tension pneumothorax in a pregnant woman. *Pakistan J Med Sci* 2009; 25(1): 159-61.
5. Ye J, Zhang Q, Xuan Y, Chen S, Ma L, Zhang Y, et al. Factors associated with echinococcosis-induced perioperative anaphylactic shock. *Korean J Parasitol* 2016; 54(6): 769-75.



# Fatal subarachnoid haemorrhage in a patient with severe dengue

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## SUMMARY

Dengue fever is one of the commonest tropical disease in the tropics. It can present with mild acute febrile illness to severe organ failure. Reported neurological complications of dengue include dengue encephalopathy, encephalitis, transverse myelitis and intracranial haemorrhage. Intracranial haemorrhage in dengue can present as subdural haematoma, extradural haematoma, intracerebral haemorrhage and subarachnoid haemorrhage. We report here a case of subarachnoid haemorrhage in a patient with severe dengue. Our patient was a 30-year-old man who presented with acute febrile illness. He subsequently developed plasma leakage and upper gastrointestinal bleeding. He then had reduced conscious level. Computed tomography of his brain showed subarachnoid haemorrhage. He eventually succumbed to his illness.

## INTRODUCTION

Dengue fever is an important public health problem in the tropics. The incidence has increased dramatically over the past three decades.<sup>1</sup> The World Health Organization estimated that 390 million dengue infections occur annually with 96 million cases manifested clinically. Neurological complications occur in 1% to 5% of the dengue patients. Reported neurological manifestations of dengue include dengue encephalopathy, encephalitis, stroke, Guillain-Barre Syndrome, encephalomyelitis and intracranial hemorrhage. We report here a case of subarachnoid haemorrhage in a patient with severe dengue.

## CASE PRESENTATION

A previously healthy 30-year-old man presented with fever for 4 days associated with arthralgia, myalgia and vomiting. He denied diarrhoea, abdominal pain or bleeding tendencies. On arrival at the Hospital Lahad Datu, Sabah, Malaysia, he was alert and conscious. His blood pressure was 129/88mmHg, pulse rate was 78bpm, temperature was 36.7C. Respiratory examination showed reduced breath sounds over right hemithorax. Cardiovascular and abdominal examination were unremarkable.

His admission full blood count showed haemoglobin of 17.8g/dl, total white cell count of  $5.4 \times 10^9/L$  and platelet of

$19 \times 10^9/L$ . Renal profile showed acute kidney injury with urea 6.2mmol/L, creatinine 259 $\mu$ mol/L. His liver enzymes were deranged with alanine aminotransferase (ALT) of 4159U/L and aspartate aminotransferase (AST) of 22590U/L (Table I). His dengue NS-1 (SD Bioline NS-1) was negative and serology was positive for dengue IgM and IgG (SD Bioline Dengue Duo). Chest radiograph showed right pleural effusion. He was treated as severe dengue with plasma leakage, acute kidney injury and liver injury and admitted to intensive care unit.

10 hours into admission, he developed haematemesis. Full blood count showed haemoglobin of 12.9g/dl and platelet of  $9.4 \times 10^9/L$ . He was started on infusion of intravenous pantoprazole. Emergency oesophagogastroduodenoscopy showed Forrest IIb prepyloric ulcer. He received blood product with 6units packed cell, 12units fresh frozen plasma and 10units platelet were given. He was intubated soon after for worsening respiratory distress. Over the next 2 days, his condition stabilised and entered into the recovery phase uneventfully.

On day 4 of admission, he was noted to have unequal pupils. An urgent computed tomography (CT) of the brain showed subarachnoid haemorrhage with generalized cerebral oedema (Figure 1). However, no CT angiogram (CTA) of the brain was done due to renal impairment and haemodynamic instability. Electroencephalography performed showed severe background suppression with no discernable cerebral activities. He eventually succumbed to his illness on day 6 of admission from subarachnoid haemorrhage.

## DISCUSSION

Dengue fever is endemic in South East Asian region and continue to be a public health challenge. The clinical presentation of dengue fever can vary from mild acute febrile illness to severe organ failures and death. Neurological manifestation of dengue is rare with intracranial haemorrhage (ICH) reported as an uncommon complication. DENV-2 and DENV-3 are more commonly associated with neurological complications of dengue fever.

The pathogenesis of ICH in dengue is multifactorial.<sup>1</sup> The postulated pathogenesis involves a complex interaction

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Table I : Relevant Result of the Patient

Parameters	Results 14/12	15/12	16/12	17/12	18/12	19/12	Unit	Normal Range
Hemoglobin	17.8	9	8.8	11.5	10.4	10.4	g/dL	13 – 18
Total White Blood Cell	5.18	5.4	8	7.7	7.2	22	109/L	4 – 10
Platelet	14.7	11.6	29.8	52	43	98	109/L	150 – 400
Hematocrit	51	26.1	25.8	35.7	30.8	30		40 – 54
Sodium	120.7	128.6	135	139	142	139	mmol/L	135 – 145
Potassium	6.2	5.9	4.8	4.3	4	5	mmol/L	3.5 – 5
Urea	20.4	23.1	27.4	24	32.3	17	mmol/L	2.8 – 7.8
Creatinine	259	342	432.2	425	505.5	331	µmol/L	90 – 110
Total bilirubin	49	45	60.9	89.9		135	µmol/L	0 – 17.1
ALT	4159	1716	1227	867		875	U/L	<40
AST	22590	7831	-	4448		-	U/L	1 – 38
Alb	34	30	32	34		36	g/L	34 – 48
Glo	23	20	21	32		32	g/L	20 – 35
ALP	169	115	94	134		176	U/L	40 – 129
PT	13.5	16.2	15.1	15.3	16.6	25	seconds	10.7 – 13.8
APTT	55.4	59.4	33.5	47.7	31.9	>180	seconds	24.6 – 37.5
INR	1.14	1.40	1.49	1.48	1.63	2.43		1 – 1.5
pH	7.36	7.31		7.53		7.1		7.35 – 7.45
PCO2	37.2	42.7		27		45	mmHg	33 – 48
PO2	43.7	40.6		88		129	mmHg	80 – 100
HCO3	20.6	21		26		12.8	mmol/L	22 – 28
Lactate			3.4	10.9			mmol/L	0 – 2
Blood culture	No growth							
Serum dengue PCR	DEN-3							



**Fig. 1:** Computed tomography of brain of the patient showing hyperdensity along the circle of Willis (arrowed) suggestive of subarachnoid hemorrhage. Basal cistern is effaced with associated cerebral edema.

between coagulopathy, thrombocytopenia, plasma leakage, vasculopathy and platelet dysfunction.<sup>2</sup> Besides that, host, virus factors and cytokines are also thought to play a role.<sup>3</sup> The presence of dengue virus in the brain together with the cytokines such as TNF alpha further enhance the immunopathological mechanism of plasma leakage and

haemorrhage in dengue. Apart from that, NS-1 antigen released from dengue infected cells can have immunomodulatory effects on complement system. Activation of complement system can enhance cytokines production, which ultimately leads to bleeding and shock in dengue.<sup>3</sup>

Our patient was diagnosed to have severe dengue with plasma leakage and GI bleeding. He subsequently developed subarachnoid hemorrhage (SAH) in his recovery phase. We believe that his SAH could have developed earlier but was unable to detect early changes of increased intracranial pressure as he was intubated. Early symptoms and signs of SAH can be very subtle. The pathophysiology of SAH in this patient is likely to be multifactorial. Thrombocytopenia, plasma leakage, vasculopathy and disseminated intravascular coagulation could probably all have contributed to his SAH.

The diagnosis of ICH is often difficult as the symptoms of ICH can mimic the symptoms of dengue. CT brain should be done in any patient with suspicion of ICH especially in high risk groups. Previous study suggests that patients with secondary dengue with positive NS-1 antigen and IgG are at higher risk of ICH.<sup>1</sup> In patients presenting with severe headache and vomiting in the presence of thrombocytopenia, we should have lower threshold for brain imaging to exclude ICH. Presence of seizures, focal neurological deficits and reduced conscious level also warrant evaluation with brain imaging.

Management of ICH in dengue fever is often difficult. Surgical options have to be carefully considered as often patient have thrombocytopenia, platelet dysfunction and plasma leakage which can lead to uncontrollable bleeding and potentially harm the patient. It remains unclear if

medical or surgical management of dengue ICH is optimal, as the data to make definite recommendations remains limited currently.<sup>4</sup> There is also no evidence that prophylactic platelet transfusion improves outcome and there is no correlation between platelet count and bleeding in dengue patients.<sup>5</sup>

### CONCLUSION

In conclusion, ICH is a potentially fatal complication of dengue fever. It can present as subdural haematoma, intracerebral haemorrhage and subarachnoid haemorrhage. Clinicians should have low threshold to perform brain imaging to exclude ICH in high risk patients with consistent clinical symptoms and signs. At present, there is insufficient evidence to address optimal care and it remains a consideration on case-by-case basis.

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### REFERENCES

1. Singh A, Balasubramanian V, Gupta N. Spontaneous intracranial hemorrhage associated with dengue fever: An emerging concern for general physicians. *J Family Med Prim Care* 2018; 7(3): 618-28.
2. Sam JE, Gee TS, Nasser AW. Deadly intracranial bleed in patients with dengue fever: A series of nine patients and review of literature. *J Neurosci Rural Pract* 2016; 7(3): 423-34.
3. Guzman MG, Harris E. Dengue. *Lancet* 2015; 385(9966): 453-65.
4. Kumar R, Prakash O, Sharma BS. Intracranial hemorrhage in dengue fever: Management and outcome: A series of 5 cases and review of literature. *Surg Neurol* 2009; 72: 429-33.
5. Lee T-H, Wong JGX, Leo Y-S, Thein T-L, Ng E-L, Lee LK, et al. Potential Harm of Prophylactic Platelet Transfusion in Adult Dengue Patients. *PLoS Negl Trop Dis* 2016;10(3): e0004576.

# Mature ovarian teratoma associated with anti-N-Methyl-D-aspartate receptor encephalitis: A case report

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### SUMMARY

**Encephalitis associated with anti-N-Methyl-D-aspartate (NMDA) receptor is a rare form of autoimmune encephalitis. We report the first case of anti-NMDAR encephalitis in an unmarried 16-years old female who was admitted to the Neurology Emergency Unit Faculty of Medicine, Udayana University, Sanglah General Hospital Bali, Indonesia due to decreased consciousness, repetitive talking, headache, involuntary movements in the mouth and feet, and seizures. She was initially diagnosed with viral encephalitis and symptomatic epilepsy. After four weeks of treatment, she was referred to the Gynecology Department. Rectal ultrasound revealed a cystic lesion with a solid component measuring 3.6x2.64x3.18 cm from the left ovary. Laparotomy cystectomy was performed, and the histopathological examination revealed glial cells and mesoderm components in the form of cartilage tissue. Serum and cerebrospinal fluid were positive for anti-NMDA receptor antibodies. She was treated with human intravenous immunoglobulin and rituximab. Her condition was improved gradually. She recovered fully after almost six weeks of hospitalisation.**

### INTRODUCTION

The ovarian mature cystic teratoma, which leads to anti-N-methyl-D-Aspartate Receptor encephalitis (NMDAR) is a rare case and often undiagnosed.<sup>1</sup> The first case of NMDAR encephalitis was detected in 1997 and was formally defined in 2007 by Dalmau et al.<sup>2</sup> Based on the systematic review by Acien et al. showed 157 cases of NMDAR throughout the world for the period 2007-2013.<sup>3</sup> Although rare, it is the second most common cause of immune-mediated encephalitis secondary to antibodies to the N-methyl D-aspartate receptor. It may be the cause of encephalitis in up to 4% of patients.<sup>1</sup>

NMDAR encephalitis is a disease that can cause severe symptoms that can lead to death. This disease causes psychiatric symptoms, seizures, memory deficits, and reduced awareness which often requires ventilator support.<sup>2</sup> Three risk factors that are associated are: adolescent female, the presence of ovarian teratomas, and detection of antibodies NMDAR in the serum. Since 2007, there has been a progressive increase in the number of articles and case reports. Thus, it appears that the incidence of this condition is higher than previously estimated and will continue to increase with improvements in health care, knowledge of the disease and improved socioeconomic development.<sup>3</sup>

Up to 77% of NMDAR encephalitis patients are initially seen by psychiatrists and misdiagnosed with new-onset schizophrenia or bipolar disorder.<sup>3</sup> Given approximately 60% of cases in women are caused by an ovarian teratoma, it is essential to rule out an ovarian mass when anti-NMDA encephalitis is the differential diagnoses.<sup>1</sup> There are differences of opinion amongst gynaecologists about the best surgical approach to manage ovarian mature cystic teratoma. There is a lack of well-designed comparative clinical trials to define the criteria to select a particular technique, and consequently, there are variations in surgical practices.<sup>4</sup> If untreated, the disease can lead to lethal hypoventilation, autonomic instability, and catatonia.<sup>4</sup>

Here we report a case of mature ovarian teratoma associated with probable anti-N-Methyl-D-aspartate receptor encephalitis. The case was successfully managed through a comprehensive multidisciplinary collaboration involving a gynaecologist, neurologist, rheumatologist, and intensive care specialist.

### CASE DESCRIPTION

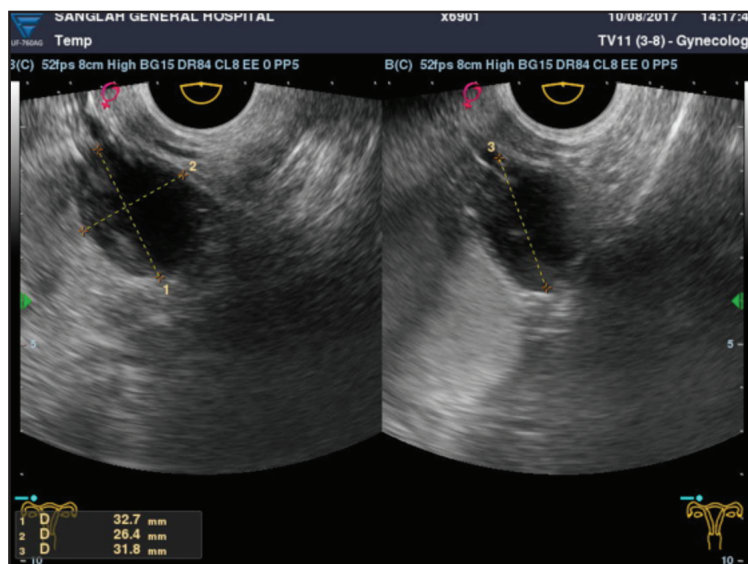
A 16 years old female patient was admitted to the intensive care unit (ICU) of the Sanglah Hospital, Denpasar, Bali, Indonesia, in July 2017 due to a decreased consciousness, repetitive talking, headache, involuntary movements on mouth and feet, and seizures. Physical examination upon admission revealed a decreased Glasgow Coma Scale (eye response: 2; verbal response: could not be measured; movement response: 2), blood pressure was 144/61mmHg, pulse was 84 times per minute, respiratory rate was 18 times per minute, and body temperature was 38.3°C. The neurological examination concluded cranial nerves paralysis of the 7th and 12th with complex partial seizures. CT scan and lumbar puncture showed no abnormalities. EEG performed on 1st and 7th day after seizures. The result was a deflection on left temporal and extent to other brain regions, respectively. Initial diagnosis included viral encephalitis, with differential diagnosis of autoimmune encephalitis. She was initially treated with anticonvulsants (oxcarbazepine, phenytoin), neuroprotector, vitamin B, and intravenous immunoglobulin.

After almost four weeks of treatment, as seizures persisted, a prompt diagnosis was not establish as yet. Multidisciplinary team meeting (Neurologist, Internist, Intensivist, Anesthesiologist) suspected encephalitis associated with anti-

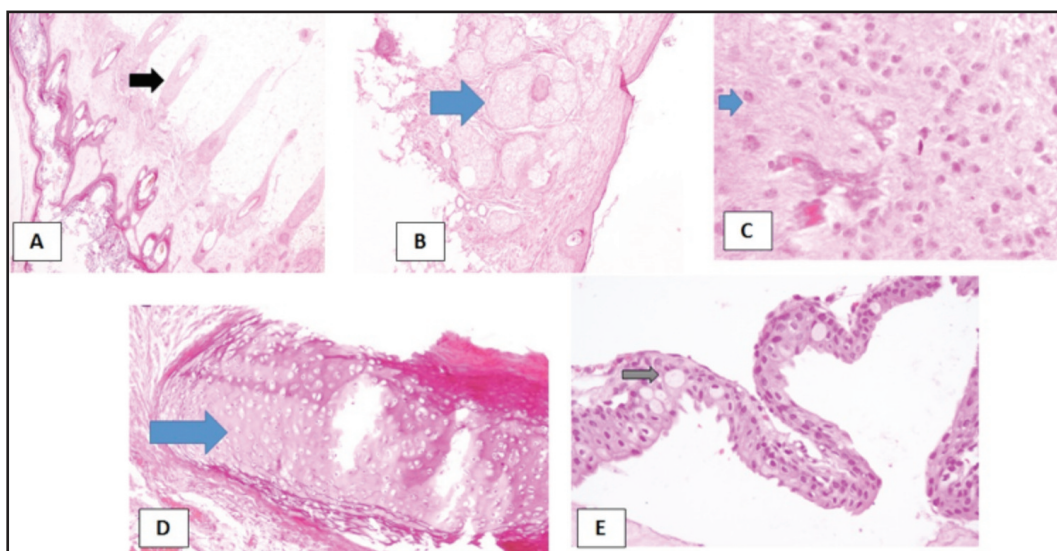
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**Fig. 1:** The picture from rectal sonography reveals a cystic lesion from the left adnexa with 3.2x2.64 cm dimensions on the longitudinal plane (left) and 3.18 cm dimension on the transversal plane (right). US performed using GE Logiq V5.



**Fig. 2:** A panel of histological examination from the cystic mass showing hallmarks of ectoderm: hair follicle (A), sebaceous gland (B), a glial component of the tumour (C); mesoderm layer: cartilage (D); and endoderm layer: cuboid epithelial with goblet cell (E). (Hematoxylin Eosin staining, magnification 100x, light microscopy).

NMDA receptor and suggested an abdominal ultrasound to rule out abnormality in the abdominal cavity. The abdominal ultrasound (US) revealed a cystic mass with solid component in left adnexa size 3x3 cm. Then, the patient consulted with the Gynecology Department. In the abdominal ultrasound, a left adnexal cystic lesion with solid components in size of 3.6x3.2 cm was found. Rectal ultrasound revealed ovarian cysts of 3.2 x 2.64 x 3.18 cm dimension. The diagnosis was a functional cyst, while the differential diagnosis was a dermoid cyst. The picture of rectal sonography image is presented in Figure 1. Laparotomy left cystectomy was performed and found a 4x2x2 cm cysts.

Histopathology examination observed under a light microscope after haematoxylin and eosin staining revealed

cyst walls containing ovarian connective tissue, corpus albicans and follicular cysts. The cyst tissue contains ectoderm components, i.e., squamous epithelium and their adnexa (sebaceous glands, hair follicles), glial cells and mesoderm components in the form of cartilage tissue. It was concluded that the histomorphology appearance was indicative of mature cystic teratomas (Figure 2).

Testing for NMDAR antibodies was unavailable at Sanglah Hospital Bali. We sent the blood, and cerebrospinal fluid of the patient for the NMDAR antibodies to be tested in Clinical Pathology Clinic Cipto Mangunkusumo Hospital/Faculty of Medicine Universitas Indonesia, Jakarta. The results of anti-NMDAR antibodies in both the serum and CSF of patients was positive.

After the surgery, first-line medical therapy included steroid, intravenous immunoglobulin (IVIG), plasmapheresis and rituximab. The steroid used as antiinflammation and immunosuppressive to prevent CNS damage. The rationale used of IVIG to decrease T-cell proliferation and cytokine level and depresses B-cell differentiation. The benefit of plasmapheresis was removed antibodies and inflammation mediator, such as serum cytokine. Rituximab function, in this case, diminished the CNS antibodies, including B-cell. After the complete treatment, condition of the patient improved. She was sent home from the hospital with good consciousness. However, her speech was slurred; continued using a urine hose and walked with an ataxic gait. Speech and physical walking physiotherapy were continued regularly for six months. At the end of the treatment, the patient could speak fluently and resumed school again.

## DISCUSSION

Mature cystic teratomas are ovarian neoplasm which contain mature tissue components originating from two or three germinal layers.<sup>4</sup> These tumours are more often cystic, rarely solid. Macroscopically this can be a unilocular cyst that contains sebaceous material and hair, and sometimes there are teeth. Microscopically, the ectoderm component can be squamous epithelial cells, the structure of adnexa, and brain tissue (glia, ependymal tubule, and cerebellum). The mesoderm component can be bone, cartilage, smooth muscle, and adipose tissue. The endoderm components can be gastrointestinal, respiratory or bronchial epithelium, thyroid, and salivary gland.<sup>5,6</sup>

The ovarian cystic mature teratoma can lead to anti-N-methyl-D-Aspartate Receptor encephalitis (NMDAR). It is hypothesised that the glial cells present within the teratoma produce antibodies to NMDAR, which in turn cause severe encephalitis. The cause of that antibody production is still unknown. The targets are NR 1 and NR 2 subunits at NMDA receptors, which cause reduced synaptic plasticity. This change reduces NMDAR activity, which affects cognitive and behavioural deficits leading to schizophrenia and psychosis. With the removal of this teratoma, it will stop the production of the antibody.<sup>7</sup>

Anti-NMDAR encephalitis caused by mature cystic ovary teratoma is a difficult disease to diagnose. Histological and antibodies examination is needed to confirm the diagnosis. In our case, the histology of cystic teratomas was observed. The management of the case requires interdisciplinary collaboration, (gynaecology, neurology, rheumatology, and intensive care) in order to establish careful management including early diagnosis, standard operative procedures, selection of therapies, follow-up, suppressive immunotherapy and evaluation of recurrence.<sup>5,8</sup> The prognosis depends on the early diagnosis and appropriate treatment given. Our case is interesting because the incidence of this disease is infrequent, and there is no consensus on strategy and management.

Tumour removal and immuno-therapy (immunoglobulin, corticosteroids, plasmapheresis and rituximab) were performed in this case. Both procedures must be done to get the right and fast recovery. Before the tumour was removed,

the psychomotor and hemodynamic condition of the patient must be stable. If the tumour is not remove early, it can result in death.<sup>1</sup> Intravenous immunoglobulin and plasmapheresis are very useful, but the treatment often fails if there is the involvement of the central nervous system. A positive response to plasmapheresis supports the argument that this disease is due to increased antibodies.<sup>9</sup> Seizures associated with anti-NMDAR encephalitis are often challenging to treat with antiepileptic drugs. Abnormal EEGs are usually found despite antiepileptic therapy at maximum doses. Immunotherapy such as IVIG is useful in dealing with seizures that do not respond to antiepilepsy.<sup>9</sup>

Prognosis varies considerably based on the time of diagnosis, neurological diagnosis, identification and removal of the tumour.<sup>7,10</sup> However, we are still investigating about the prognosis of our case. This case is rare and difficult to treat. We need clear protocols for the management of the disease. Until now, no report has stated that the prognosis is good. This case was the first case of encephalitis associated with anti NMDAR caused by ovarian cystic mature teratoma in Sanglah General Hospital, Bali, Indonesia.

Our experience in managing this case has resulted in the following producing some recommendations, regarding possibility misdiagnosis as psychiatric disease or other types of encephalitis. We emphasise the importance of multidisciplinary collaboration to make a diagnosis as soon as possible in this particular disease. Treatment strategy in case of the ovarian tumour as suspected aetiology, surgery followed by immunotherapy will result in maximal outcome for the patient. A comprehensive approach, continuing monitoring must be performed every 3-6 months for the first five years after completing the therapy. All these strategies will avoid permanent damage and disability to the patient.

## CONCLUSION

Ovarian mature cystic teratoma, which leads to anti-N-methyl-D-Aspartate Receptor encephalitis (NMDAR) is a sporadic case and often challenging to diagnose. In the present case, the small size of the tumour made diagnosis difficult, causing a delay in the final diagnosis. However, there has been a substantial improvement six months after the surgery. Management of the case required experts in gynaecology, neurology, rheumatology, and intensive care to establish careful management that included early diagnosis, standard operative procedures, selection of therapies, follow-up, suppressive immunotherapy, and evaluation of recurrence. This positive response to surgery and immunosuppressant therapy underlines the fact that early diagnosis is of paramount importance, as it may result in almost complete recovery. There is a need for further multicenter studies to investigate the prognosis of anti NMDAR encephalitis.

## REFERENCES

1. Gnade CM, Williams HR, Stockdale CK. A case of hysteria: anti-N-methyl-D-aspartate receptor encephalitis resulting from a mature ovarian teratoma. *Proceedings in Obstetrics and Gynecology* 2016; 6(1): 1-6.
2. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008; 7(12): 1091-8.

3. Ación P, Ación M, Ruiz-Maciá E, Martín-Estefanía C. Ovarian teratoma-associated anti-NMDAR encephalitis: a systematic review of reported cases. *Orphanet Journal of Rare Diseases* 2014; 9: 157.
4. Sinha A, Ewies AAA. Ovarian mature cystic teratoma: challenges of surgical management. *Obstetrics and Gynecology International* 2016; 2390178: 1-7.
5. Rosenfeld MR, Titulaer MJ, Dalmau J. Paraneoplastic syndromes and autoimmune encephalitis. *Neurology Clinical Practice* 2012; 215-23.
6. Scheer S, John RM. Anti-N-Methyl-D-Aspartate Receptor Encephalitis in Children and Adolescents. *J Pediatr Health Care* 2016; 30(4): 347-58.
7. Day GS, Laiq S, Tang-Wai DF, Munoz DG. Abnormal neurons in teratomas in NMDAR encephalitis. *JAMA Neurol* 2014; 71(6): 717-24.
8. Cree IA, White VA, Indave BI, Lokuhetty D. Revising the WHO classification: female genital tract tumours. *Histopathology* 2020; 76(1): 151-6.
9. Rosenfeld MR, Dalmau J. Diagnosis and management of paraneoplastic neurologic disorders. *Curr Treat Options Oncol* 2013; 14(4): 528-38.
10. Dulcey I, Cespedes MU, Ballesteros JL, Preda O, Aneiros-Fernandez J, Clavero PA, et al. Necrotic mature ovarian teratoma associated with anti-N-methyl-D-aspartate receptor encephalitis. *Pathol Res Pract* 2012; 208(8): 497-500.

# A case of xanthogranulomatous appendicitis in the female pelvis

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### SUMMARY

**Xanthogranulomatous inflammation is an uncommon form of chronic inflammatory process. Only a few isolated case reports of xanthogranulomatous appendicitis (XA) have been published. XA has nonspecific imaging findings and cannot be reliably differentiated on imaging from locally advanced malignancy. XA however follows a benign course and can potentially be treated with surgical resection.**

### INTRODUCTION

Xanthogranulomatous inflammation (XI) is an uncommon form of chronic inflammation. It can involve multiple organs and the most reported presentations include cholecystitis and pyelonephritis. Histologically, it is characterized by lipid-laden macrophages or histiocytes admixed with lymphocytes and plasma cells.

Xanthogranulomatous appendicitis (XA) has nonspecific imaging findings and may mimic a locally advanced or remnant malignancy as it cannot be reliably differentiated on imaging. XA however follows a benign course and can potentially be treated with surgical resection.

### CASE REPORT

A 41-year-old Chinese female with no significant past medical history presented to the Tan Tock Seng Hospital, Singapore with a 2-week history of right iliac fossa pain associated with low grade fever. Subsequent pelvic ultrasound revealed a right pelvic mass. Because of the size, it was difficult to establish if this mass was of ovarian or uterine origin. As such, further evaluation with magnetic resonance imaging (MRI) of the pelvis was performed. This showed the mass to be a thick-walled, lobulated rim-enhancing cystic lesion. Thick, enhancing septations were also seen within the lesion. The fluid contents of the lesion demonstrated T2 hyperintensity and restricted diffusion. No discrete solid component was noted. The lesion was inseparable from the caecum.

Based on the findings of the MRI, the primary considerations were that of a neoplasm or inflammatory process arising from either the appendix or gynaecological organs. Computer tomography (CT) of the thorax, abdomen and pelvis was thus performed to exclude distant metastases. The CT scan also showed a complex cystic structure in the right

iliac fossa, inseparable from the caecum and terminal ileum. No distant metastases were seen. Of note, the appendix and right ovary could not be identified on both CT and MRI. There was no inflammatory fat stranding surrounding the lesion. The differential diagnoses based on the imaging studies thus far remained as either an appendiceal or ovarian pathology, of which a neoplastic or inflammatory process was a possible cause.

The patient underwent a colonoscopy which did not reveal any colonic masses. However, the mucosa overlying the appendiceal orifice was noted to be abnormal. Diagnostic laparoscopy was thus performed which showed a mass posterior to the caecum. This mass was noted to involve the caecum and terminal ileum. The appendix could not be identified. The right ovary and fallopian tube were attached to the mass. The working diagnosis after the diagnostic laparoscopy was either an appendiceal abscess or neoplasm. Right hemicolectomy with en bloc right salpingo-oophorectomy was subsequently performed, one week after the initial pelvic ultrasound, in view of the inability to rule out an underlying neoplasm.

The appendix showed mucosal ulceration, and suppurative and xanthogranulomatous inflammation. The inflammation extended into the periappendiceal fat and into the right ovary and fallopian tube. No acid fast bacilli or fungal organisms were identified on special stains.

### DISCUSSION

Xanthogranulomatous inflammation is a rare pathological finding that was first described in the kidney by Osterlind in 1944. It has also been reported in the gallbladder, kidneys, endometrium and female genital tract including the fallopian tube.<sup>1</sup> It usually presents as pyelonephritis and cholecystitis. Only a few isolated case reports of XA have been published so far.<sup>2</sup>

The pathophysiology of XI is not well understood. The proposed mechanisms include lymphatic obstruction, defective lipid transport as well as a immune response specific to *Escherichia* and *Proteus*.<sup>3</sup> On histology, XI is characterised by the development of foamy macrophages.

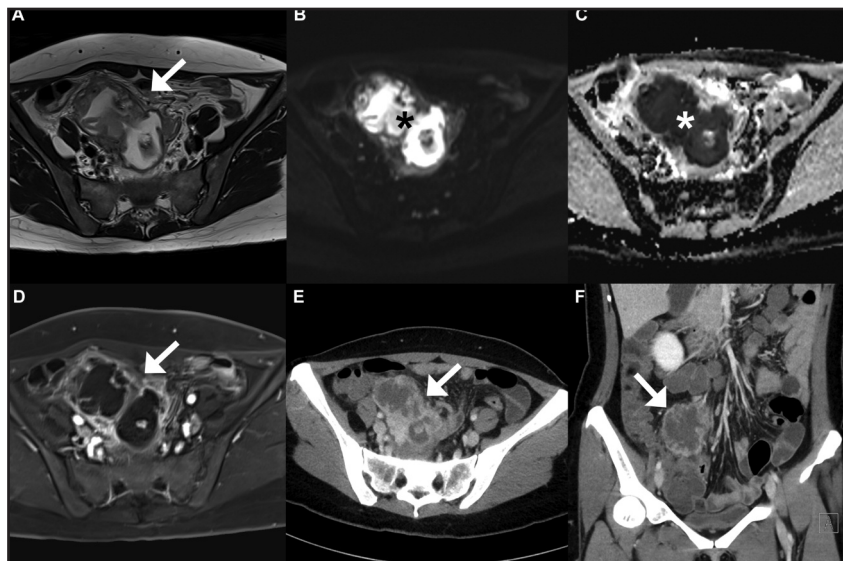
XA has variable imaging features. It can present as a heterogeneously enhancing mass or inflammatory process in

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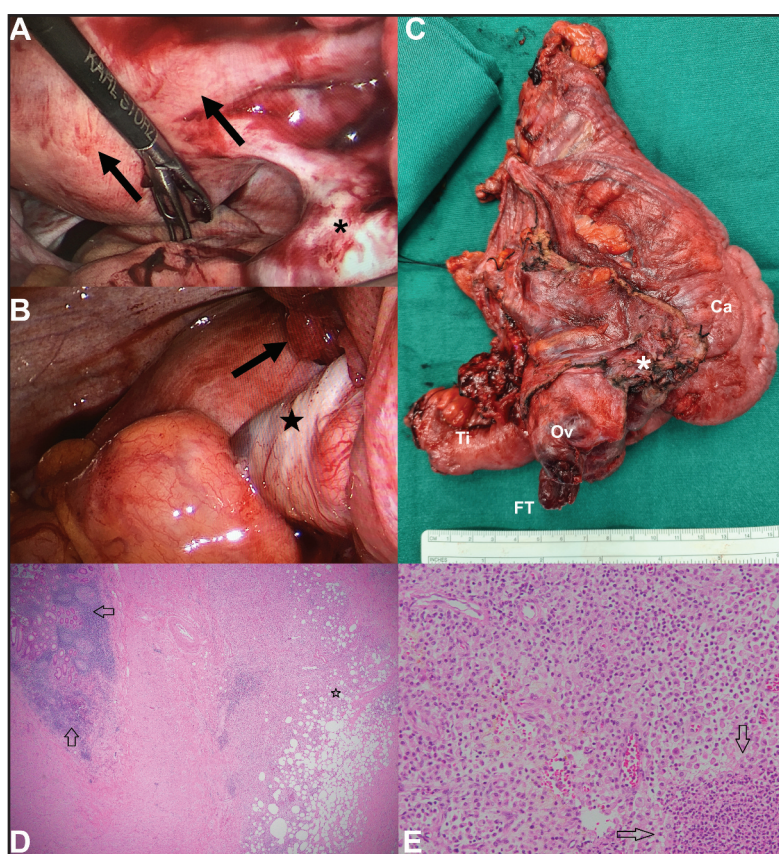
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**Fig. 1:** MRI of the pelvis. (A) T2-weighted image reveals a heterogeneous solid cystic lesion in the right hemipelvis. (B-C) Diffusion weighted image demonstrates hyperintensity (black asterisk) in the contents of the lesion corresponding to T2 hyperintense areas. Abnormally low values on the apparent diffusion coefficient map (white asterisk) in the contents of the lesion confirm the presence of abnormal restricted diffusion. (D) Post-gadolinium T1-weighted image shows rim-enhancement of the complex cystic lesion. Of note, the appendix and right ovary could not be seen. Contrast-enhanced CT of the abdomen and pelvis in (E) axial and (F) coronal planes reveals a corresponding rim-enhancing complex cystic lesion (arrow). There is minimal surrounding inflammatory stranding. Of note, the appendix and right ovary could not be seen.



**Fig. 2:** Diagnostic laparoscopy showed an (A) inflammatory mass (black asterisk) posterior to the caecum (black arrows) which is being lifted. (B) The mass also involves the right fallopian tube (black arrow) and right ovary (black star). (C) Posterior surface of resection specimen demonstrates the appendiceal mass (white asterisk) densely adhered to the caecum (Ca), terminal ileum (Ti), right ovary (Ov) and fallopian tube (FT). (D) Low power view (H&E x20) shows the tip of the appendix on the left, with an area of xanthogranulomatous inflammation extending into the periappendiceal fat on the right. The open arrows show the appendiceal mucosa and the star marks the area of inflammation in the periappendiceal fat. (E) High power view (H&E x200) shows the xanthogranulomatous inflammation with sheets of foamy macrophages admixed with small lymphocytes and plasma cells. On the bottom right marked with open arrows is an area of suppurative inflammation, consisting of abundant neutrophils.

the right iliac fossa, as in our case. A few reports have also described XI being detected in patients who undergo a delayed, interval appendicectomy after an acute episode of appendicitis.<sup>4</sup> The described clinical course is similar to our case as the patient underwent definitive surgery approximately three weeks after onset of symptoms and one week after first presentation to the hospital.

Although this is a known entity, it is difficult to differentiate it from a locally advanced malignancy on imaging since the inflammatory process often extends to the surrounding structures or soft tissues, giving an appearance of an invasive malignancy.<sup>5</sup> Our case profoundly shows this difficulty in the female pelvis, where the main differential diagnoses encompass entities such as tubo-ovarian abscesses, perforated appendicitis, mucinous tumours of the appendix and ovary. These entities can potentially resemble one another on imaging.

#### *Tubo-ovarian abscess*

Tubo-ovarian abscess is a late complication of pelvic inflammatory disease (PID) which is most commonly seen in sexually active women. This can occur unilaterally or bilaterally as a result of inadequately treated PID. On imaging, tubo-ovarian abscesses appear as a complex, rim-enhancing fluid collection with surrounding inflammatory changes. The involved ovary is often obscured by the abscess and inflammation. Internal gas bubbles are specific sign of an abscess on imaging but are not common in tubo-ovarian abscesses.<sup>6</sup> A loss of definition of the uterine border and anterior displacement of thickened broad ligament may also help to distinguish a tubo-ovarian abscess from other causes of pelvic abscess.<sup>7</sup>

#### *Perforated acute appendicitis*

Perforated appendicitis can present in a variety of ways on imaging. A few features such as extra-luminal appendicolith, abscess formation, and discrete enhancement defect in the wall of the appendix are often described as specific features of perforated appendicitis.<sup>8</sup> However, perforated appendicitis can manifest as a complex-looking abscess in the right lower quadrant. At times, these processes can also obscure the adjacent right ovary which would make differentiation from ovarian pathologies difficult.

#### *Mucinous tumours of the ovary and appendix*

Mucinous tumours of the appendix and ovary often present clinically with vague, non-specific symptoms. The imaging features can vary depending on the stage of disease. Mucinous cystadenomas of the appendix can appear as an appendiceal mucocele with no solid component and can mimic the appearance of appendicitis.<sup>9</sup> Conversely, mucinous cystadenocarcinomas may present as a complex solid-cystic mass with enhancing solid components and septa. Mucinous cystadenocarcinomas have a higher chance of perforation resulting in diffuse ascites, peritoneal nodules and pseudomyxoma peritonei.<sup>10</sup>

Mucinous epithelial lesions of the ovary also present as a multiloculated, complex cystic lesion with thickened enhancing septa. The presence of solid components increases the suspicion of malignancy.<sup>11</sup> Given the similarity in

imaging features between appendiceal cystadenocarcinomas and ovarian mucinous tumours, differentiating between the two entities can be difficult.

MRI is helpful to distinguish between abscesses and mucinous tumours. On MRI, the contents of abscesses typically show restricted diffusion due to the highly cellular and complex nature of purulent fluid. In contrast, the fluid contents of mucinous tumours demonstrate T2 hyperintensity, DWI hyperintensity and high ADC values (T2-shine through).<sup>12</sup>

The contents of the lesion in our case showed restricted diffusion which would allude to presence of an abscess. However, as there can be overlap in the imaging findings between an abscess and a necrotic or mucinous malignancy, diagnosis and curative treatment would still depend on surgical resection.<sup>13</sup>

Identification of a normal appendix or ovary on imaging is very important in narrowing down the differential diagnoses of solid-cystic lesions in the female pelvis. Unfortunately, solid-cystic lesions involving these organs can be large and extensive in the pelvis. As such, these structures may not be readily identified. In such scenarios, the definitive diagnosis can only be established intra-operatively or on histological analysis.

## CONCLUSION

Xanthogranulomatous appendicitis is a rare disease that is difficult to diagnose on imaging alone. The imaging features of XA can resemble other inflammatory and malignant processes of the pelvis and is difficult to diagnose prospectively on imaging. Nonetheless, the condition should be considered in the differential diagnosis during the evaluation of pelvic masses and pathologies. The definitive diagnosis relies on surgical resection and histopathological examination of the mass.

## REFERENCES

- Bourm KS, Menias CO, Ali K, Alhalabi K, Elsayes KM. Spectrum of xanthogranulomatous processes in the abdomen and pelvis: a pictorial review of infectious, inflammatory, and proliferative responses. *AJR Am J Roentgenol* 2017; 208(3): 475-84.
- Kochhar G, Saha S, Andley M, Kumar A, Kumar A. Xanthogranulomatous appendicitis with a fulminant course: report of a case. *J Clin Diagn Res* 2014; 8: ND01-ND02
- Chuang YF, Cheng TI, Soong TC, Tsou MH. Xanthogranulomatous appendicitis. *J Formos Med Assoc* 2005; 104(10): 752-4.
- Guo G, Greenson JK. Histopathology of interval (delayed) appendectomy specimens: strong association with granulomatous and xanthogranulomatous appendicitis. *Am J Surg Pathol* 2003;27(8): 1147-51.
- Nam S, Kang J, Choi SE, Kim YR, Baik SH, Sohn SK. Xanthogranulomatous appendicitis mimicking residual Burkitt's Lymphoma after chemotherapy. *Ann Coloproctol* 2016; 32(2): 83-6.
- Wilbur AC, Aizenstein RI, Napp TE. CT findings in tuboovarian abscess. *AJR Am J Roentgenol* 1992; 158: 575-9.
- Bennett GL, Slywotzky CM, Giovanniello G. Gynecologic causes of acute pelvic pain: spectrum of CT findings. *Radiographics* 2002; 22 (4): 785-801.
- Kim HY, Park JH, Lee YJ, Lee SS, Jeon JJ, Lee KH. Systematic review and meta-analysis of CT features for differentiating complicated and uncomplicated appendicitis. *Radiology* 2018; 287(1): 104-15.
- Demetrasvili Z, Chkhaidze M, Khutsishvili K, Topchishvili G, Javakhishvili T, Pipia I, et al. Mucocele of the appendix: case report and review of literature. *Int Surg* 2012; 97(3): 266-9.
- Lim HK, Lee WJ, Kim SH, Kim B, Cho JM, Byun JY. Primary mucinous cystadenocarcinoma of the appendix: CT findings. *AJR Am J Roentgenol* 1999; 173(4): 1071-4.

11. Ledermann JA, Luvero D, Shafer A, O'Connor D, Mangili G, Friedlander M, et al. Gynecologic Cancer InterGroup (GCIg) consensus review for mucinous ovarian carcinoma. *Int J Gynecol Cancer* 2014; 24(9 Suppl 3): S14-S19.
12. Galea N, Cantisani V, Taouli B. Liver lesion detection and characterization: role of diffusion-weighted imaging. *J Magn Reson Imaging* 2013; 37(6): 1260-76.
13. Holzapfel K, Rummeny E, Gaa J. Diffusion-weighted MR imaging of hepatic abscesses: possibility of different apparent diffusion coefficient (ADC)-values in early and mature abscess formation. *Abdom Imaging* 2007; 32(4): 538-9.

# Primary splenic hodgkin lymphoma masquerading as splenic abscess

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### SUMMARY

**Hodgkin lymphoma is a form of malignant lymphoid neoplasm. It can have various clinical presentations such as prolonged fever, night sweats, weight loss and asymptomatic lymphadenopathy. It has a distinct fever pattern known as Pel Ebstein fever. However, in some instances, its clinical presentation can mimic some tropical infections. Here, we present a case of primary splenic lymphoma masquerading as splenic abscess in a 53-year-old man with underlying dyslipidemia.**

### INTRODUCTION

Hodgkin lymphoma (HL) is a malignant lymphoid neoplasm that can involve nodal and extra-nodal sites. Spleen is one of the extra-nodal organs that can be involved initially in 30% of the cases. Broadly, HL can be divided into two categories, namely classical HL and nodular lymphocyte predominant HL. Clinically, HL can be of various presentations. In some instances, HL may mimic infections especially in patients who present with B-symptoms in the absence of lymphadenopathy. Here, we reported a case of primary splenic Hodgkin lymphoma masquerading as splenic abscess.

### CASE PRESENTATION

A 53-year-old man with underlying dyslipidemia presented to the Hospital Queen Elizabeth, Sabah, Malaysia complaining of fever for 2 weeks associated with anorexia and weight loss of 10 kg for the past one year. He denied respiratory or gastrointestinal symptoms. He has no night sweats. On examination, he was pale with splenomegaly 5cm below left costal margin. There was no hepatomegaly or peripheral lymphadenopathy. Other systemic examinations were unremarkable.

His initial blood investigations revealed bicytopenia with hemoglobin of 8.2 g/dl and total white cell of 3.88x10<sup>9</sup>/L and raised inflammatory makers with C-reactive protein 115 mg/L and erythrocyte sedimentation rate 68 mm/Hour. His serum lactate dehydrogenase was 313 IU/ml with negative human immunodeficiency virus serology (Table I). Peripheral blood film reported no leucoerythroblastic picture and no circulating blast cells. A contrast-enhanced computed tomography (CT) abdomen revealed splenomegaly with

multiple ill-defined splenic collections largest measuring 3.3x3.9x4.6 cm with no lymphadenopathy (Figure 1). He was empirically treated as melioidosis with splenic abscess as melioidosis is endemic in Sabah. Blood cultures were negative for bacteria, fungal and tuberculous infection.

Despite being 8-weeks on intravenous antibiotics, there was no clinical improvement with persistent fever, bicytopenia and non-resolving splenic collections on repeated imaging. In view of persistent bicytopenia and fever, a bone marrow aspirate and trephine biopsy was done. Bone marrow aspirate showed no abnormality but his trephine biopsy showed numerous interstitial infiltrate of small to medium sized lymphoid cells forming no aggregate or nodule, admixed with pale histiocytic cells. Sprinkles of large atypical cells were also observed and these cells were CD30+ with heterogenous PAX5- to dim PAX5+ (Figure 2). Hence, the findings confirmed the diagnosis of classical Hodgkin lymphoma with bone marrow infiltration. Patient was then started on chemotherapy consisting of Adriamycin, Bleomycin, Vinblastine and Dacarbazine (ABVD). He responded clinically with resolution of fever and improvement of blood parameters. Interval CT scan showed almost complete resolution of splenic lesions after 3 cycles of chemotherapy. He subsequently completed 6 cycles of chemotherapy and under follow up of hematology unit since then.

### DISCUSSION

HL accounts for approximately 10% of all known lymphomas. Clinically, most patients present with asymptomatic lymphadenopathy. Some patients may present with fever of unknown origin. Fever in HL exhibits with a distinctive pattern known as Pel-Ebstein fever. Pel-Ebstein fever typically occur at 7 days interval. On the other hand, bone marrow infiltration of HL at diagnosis represents stage IV disease and it is uncommon, ranging between 2% and 32% with average incidence of 10%.<sup>1</sup> In fact, HL with bone marrow involvement is often associated with extensive disease and significant lymphadenopathy.

B-symptoms of Hodgkin lymphoma can masquerade as infectious process and have previously been described as initial presentation in clinically unsuspected HL.<sup>2</sup> The presentation of fever, weight loss can mimic any infectious

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Table I: Investigation chart of the patient

Parameters	Results 31/03	03/04	10/04	15/04	29/04	06/05	Unit	Normal Range
Hemoglobin	8.2	7.2	8.5	8.5	7.6	8.9	g/dL	13 – 18
Total White Blood Cell	3.88	3.03	3.78	3.37	3.43	2.69	109/L	4 – 10
Platelet	198	200	240	264	178	233	109/L	150 – 400
Hematocrit	27.5	21.8	30	26.6	25.6	28.8		40 - 54
Sodium	133	136	135	133	127	136	mmol/L	135 – 145
Potassium	3.7	4.1	4.2	4.1	4.1	4.6	mmol/L	3.5 – 5
Urea	3.3	3.1	3.1	3.5	3.1	3	mmol/L	2.8 – 7.8
Creatinine	62.5	59.6	61.3	65.7	52.7	56.4	µmol/L	90 – 110
Total bilirubin	7.1	10.5		8.1	12.1	9.9	µmol/L	0 – 17.1
ALT	15	19		36	10	21	U/L	<40
Alb	30	26		29	25	29	g/L	34 – 48
Glo	38	32		46	37	39	g/L	20 – 35
ALP	94	98		170	112	133	U/L	40 - 129
ESR	68				100		mm/h	<10
CRP	115		85	137	96		mg/L	<10
LDH	313						iU/L	70-250
Lactate	1.6						mmol/L	0 – 2
Blood culture	No Growth (NG)		NG	NG	NG			
Blood Fungal Culture	No Growth (29/04)							
Blood M. Tuberculosis culture				NG				
HIV Serology	Non-reactive							
Blood Smear Malaria Parasite	Negative x3 (31/4, 1/4, 2/4)							

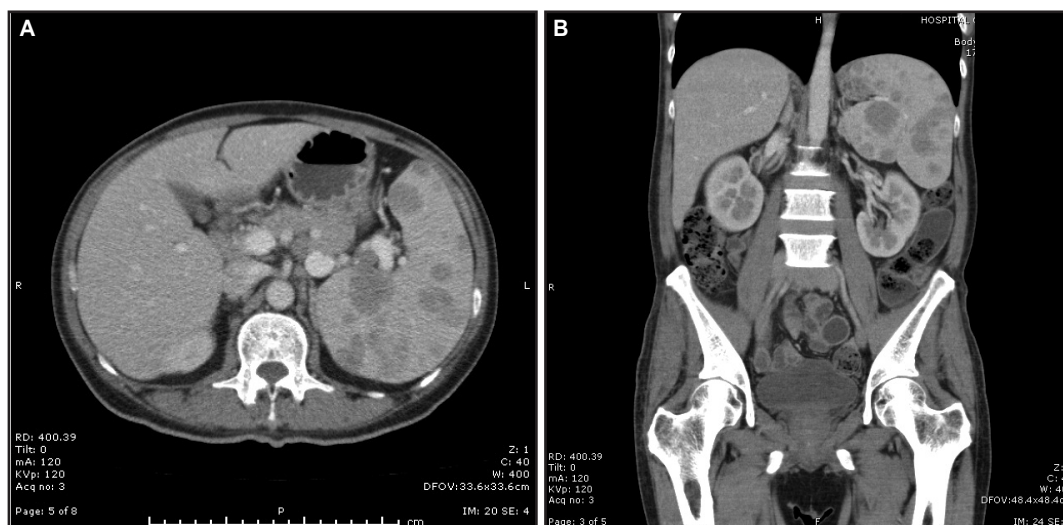
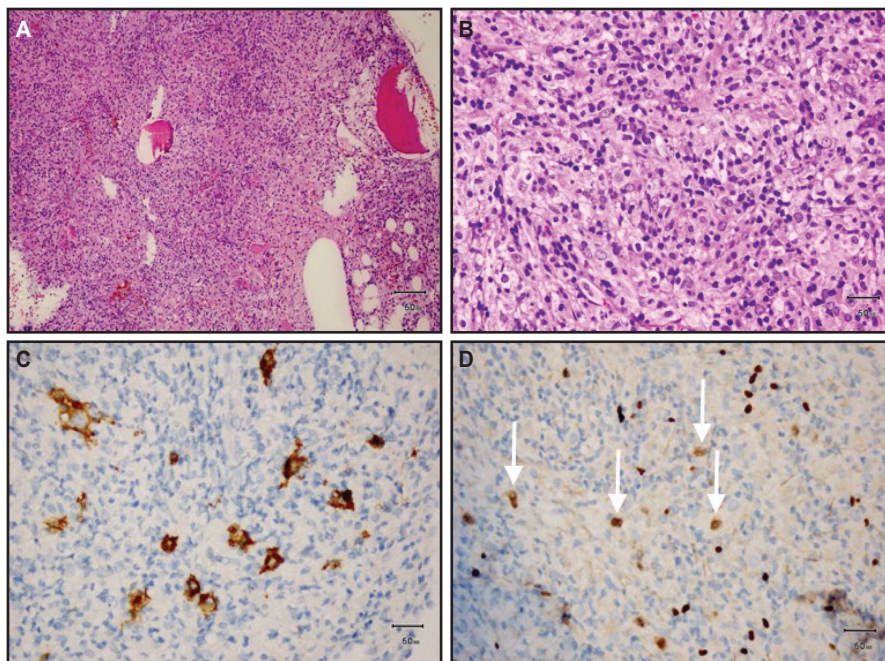


Fig. 1: (A&B) Multiple ill-defined hypodense lesions throughout the enlarged spleen.



**Fig. 2:** (A): Trephine biopsy showing hypercellular marrow for age with presence of fibrosis. Original magnification: x100. (B): The abnormal large lymphoid cell. Original magnification: x400. (C): Hodgkin's cell showing positive CD30 immunohistochemical staining. Original magnification: x400. (D): Hodgkin's cell that show weak PAX5 immunohistochemical staining; white arrow. Original magnification: x200 Note: The abnormal lymphoma cell will show weak or dim PAX5. The normal lymphoid or mature B cells will show strong staining.

process. In addition, the differential diagnosis of splenomegaly can vary from benign to malignant process. The diagnosis of HL often require a histopathological examination. Excisional biopsy of lymph node is often recommended because lymph node architecture is important for histological classification. Classically, Reed-Sternberg cells can be seen on histological examination. Bone marrow biopsy is sometimes needed especially in patients with pyrexia of unknown origin. There has been a case series reported wherein clinically unsuspected Hodgkin diseases were primarily diagnosed from bone marrow trephine biopsy as part of PUO workup.<sup>3</sup>

Prolonged fever is a common and intriguing clinical problem that we face in our daily practice. It can be caused by various aetiologies such as neoplasia, infection, autoimmune, drug and etc. The diagnosis of the cause will need complete diagnostic evaluation. In our case, the diagnosis of HL was particularly difficult due to uncommon presentation of fever, constitutional symptoms and the absence of significant lymphadenopathy. This was further confounded by multiple splenic collections which in turn resembled tropical infections such as melioidosis or tuberculosis. Both tuberculosis and melioidosis can manifest as splenic abscess.<sup>4</sup> Furthermore, cytopenia is common in infection and CT imaging cannot reliably differentiate splenic lesion as either abscess or lymphoma.<sup>5</sup> Hence, a high index of suspicion is vital for disease like lymphoma when a patient fails to respond to antimicrobial therapy.

## CONCLUSION

In conclusion, our case highlights the importance of diagnostic evaluation in patients with prolonged fever. Prolonged fever can be caused by infection, malignancy or autoimmune disease. In the presence of cytopenia with splenic abscess-like lesion with no microbiology evidence of sepsis, lymphoma should be considered as a differential diagnosis. Bone marrow examination should be done in such cases.

## Conflict of Interests

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## REFERENCES

1. Subramanian R, Basu D, Badhe B, Dutta TK. Role of Bone marrow trephine biopsy in the diagnosis of marrow involvement in Hodgkin's disease. *Indian J Pathol Microbiol*. 2007; 50(3): 640-3.
2. Jain A, Gupta HL. Primary Hodgkin's disease of bone marrow. *JACM* 2002; 3: 395-6.
3. Kar R, Dutta S, Tyagi S. Clinically unsuspected Hodgkin's lymphoma diagnosed primarily from bone marrow trephine biopsy: Report of six cases. *Indian J Pathol Microbiol* 2008; 51: 186-9.
4. Cheng AC, Currie BJ. Melioidosis: epidemiology, pathophysiology, and management. *Clin Microbiol Rev* 2005; 18(2): 383-416. pmid:15831829
5. Karlo CA, Stolzmann P, Do RK, Alkadhi H. Computed tomography of the spleen: how to interpret the hypodense lesion. *Insights Imaging* 2013; 4(1): 65-76. doi:10.1007/s13244-012-0202-z

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