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Acknowledgements:
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Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia 2020; 75(6): 613-25.

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Books and Other Monographs:
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Goodman NW, Edwards MB. 2014. Medical Writing: A Prescription for Clarity. 4 th Edition. Cambridge University Press.

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

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

Other Articles:
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The epidemiology of COVID-19 in ten Southeast Asian countries

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ABSTRACT

Introduction: Periodic benchmarking of the epidemiology of COVID-19 in the Association of Southeast Asian Nations (ASEAN) countries is critical for the continuous understanding of the transmission and control of COVID-19 in the region. The incidence, mortality, testing and vaccination rates within the ASEAN region from 1 January 2020 to 15 October 2021 is analysed in this paper.

Methods: COVID-19 data on cases, deaths, testing, and vaccinations were extracted from the Our World in Data (OWID) COVID-19 data repository for all the ten ASEAN countries. Comparative time-trends of the epidemiology of COVID-19 using the incidence rate, cumulative case fatality rate (CFR), delay-adjusted case fatality rate, cumulative mortality rate (MR), test positivity rate (TPR), cumulative testing rate (TR) and vaccination rate was carried out.

Results: Over the study period, a total of 12,720,661 cases and 271,475 deaths was reported within the ASEAN region. Trends of daily per capita cases were observed to peak between July and September 2021 for the ASEAN region. The cumulative case fatality rate (CFR) in Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam, was of 0.9% (N=68), 2.2% (N=2,610), 3.5% (N=142,889), 0.1% (N=36), 1.2% (N=27,700), 4.0% (N=18,297), 1.6% (N=40,424), 0.1% (N=215), 1.7% (N=18,123), and 2.6% (N=21,043), respectively. CFR was consistently highest between January-June 2020. The cumulative mortality rate (MR) was 9.5, 13.7, 51.4, 0.2, 80.3, 32.4, 34.5, 1.6, 23.9 and 19.7 per 100,000 population, respectively. The cumulative test positivity rate (TPR) was 8.4%, 16.9%, 4.6%, 7.5%, 11.1%, 12.9%, 0.5%, 11.7%, and 3.6%, with the cumulative testing rate (TR) at 25.0, 90.1, 27.4, 917.7, 75.8, 177.8, 3303.3, 195.2, and 224.9 tests per 1,000 population in Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam, respectively. The percentage of population that completed vaccinations (VR) was 44.5%, 65.3%, 18.5%, 28.2%, 61.8%, 6.8%, 19.2%, 76.8%, 22.7%, and 10% in Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam, respectively.

Conclusion: In 2020, most countries in ASEAN had higher case fatality rates but lower mortalities per population when compared to the third quarter of 2021 where higher mortalities per population were observed. Low testing rates have been one of the factors leading to high test positivity rates. Slow initiation of vaccination programs was found to be the key factor leading to high incidence and case fatality rate in most countries in ASEAN. Effective public health measures were able to interrupt the transmission of this novel virus to some extent. Increasing preparedness capacity within the ASEAN region is critical to ensure that any future similar outbreaks can be dealt with collectively.

KEYWORDS:
Epidemiology; Public health; SARS-CoV-2; Ten Southeast Asian Countries; Transmission; Global Health

INTRODUCTION

The SARS-CoV-2 virus has become the gravest threat that the global population has faced in the 21st century.[1]

It has caused an unprecedented health, socio-economic and political crisis in many countries globally. Even the high-income countries struggled on how to tackle the crisis in their respective countries. A total of 248.5 million cases and 5.03 million deaths have been reported globally as of 6 November 2021.[2] It is very important to understand that the dynamics of the epidemic were varied widely across time and space. Cumulative incidence globally over 22 months has ranged from 1 to 22,233 cases per 100,000 population, whilst mortality rates over the same period have ranged from 3.1 to 599.2 deaths per 100,000 population.[3,4] Case fatality rate (CFR) estimates similarly varied geographically from 0-25%.[4] Testing rates ranged from 8.6 to 15,552.2 tests per 1,000 population.[3] The numbers of populations that have completed their vaccinations ranged from 0.04-100%.[3]

Important indicators of COVID-19 transmission include the incidence rate, case fatality rate, mortality rate, test positivity rate and population testing rate.[5] The longitudinal trends of these indicators may be associated with the availability of resources, health systems capacity, social dynamics,

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changing scientific landscape, and resilience of the respective economies and communities. The benchmarking of these indicators may support policymakers and public health officials in mitigating the spread of the virus, particularly in managing resources and implementing timely control measures.[6,7] Regional benchmarking of the above-stated indicators may be useful in estimating the risk of transmission from neighboring countries. However, there is a paucity of systematic analysis on the epidemiology of COVID-19 in Southeast Asian (ASEAN) countries, as accessed via the WHO Global COVID-19 literature database. Periodic benchmarking of these indicators between ASEAN countries is critical for the continuous understanding of the transmission and control of COVID-19 in the region. In this study, we analysed the data on the recent incidence, mortality, testing and vaccination rates within the ASEAN region.

METHODS

Data

This study extracted data on COVID-19 infection from the Our World in Data (OWID) COVID-19 data repository from 1 January 2020 to 15 October 2021. The extracted data included: i) daily new cases, ii) daily new deaths, iii) daily new tests, iv) daily vaccinations, and v) mid-year population.

Data were extracted for the following ten countries: i) Brunei, ii) Cambodia, iii) Indonesia, iv) Laos, v) Malaysia, vi) Myanmar, vii) Philippines, viii) Singapore, ix) Thailand, and x) Vietnam. A single open-source data repository ensured better transparency and consistency of data management, analysis and interpretation.

Data analysis

Daily cases counts were first extracted and visualised within epidemiologic curves. Daily cases per capita per 100,000 population were estimated based on the following function:

$$\text{Daily cases per capita} = \frac{\textit{Daily new cases (7-day moving average)}}{\textit{Mid-year population}} \times 100{,}000$$

Indicators such as the mortality rate (MR), test positivity rate (TPR), testing rate (TR) and vaccination rate (VR) were tabulated quarterly. These indicators were calculated using the following equations:

$$\text{Mortality Rate} = \frac{\textit{No. of reported mortalities (in time period)}}{\textit{Mid-year population}} \times 100{,}000$$

$$\text{Test Positivity Rate} = \frac{\textit{Reported cases (in time period)}}{\textit{No.of individuals tested (in time period)}}$$

$$\text{Testing Rate} = \frac{\textit{Average no of individuals tested per day (in time period)}}{\textit{Mid-year population}} \times 1{,}000$$

$$\text{Vaccination Rate} = \frac{\textit{Maximum cumulative number of completed vaccinations (in time period)}}{\textit{Mid-year population}} \times 100$$

A delay-adjusted case fatality rate (CFR) was then estimated to adjust the delay between reporting and death for mortalities.[8] A time-lagged delay distribution was estimated utilising an updated Malaysian dataset from GitHub that had complete information on dates of reporting and death. This time-lagged distribution of reporting to death was assumed to follow a Poisson distribution with a mean of 9.7 days (SD: 10.4 days). The time-lagged distribution was assumed to fit the delay profile of all the ten countries studied.

A back-projection method was carried out to estimate the unobserved death curve at the reported date. It utilised a time series of daily deaths and the empirically estimated time-lagged delay distribution from reporting to death. The counts of deaths (N_t) are assumed to follow a Poisson process and are independent within the linear Poisson model for observed counts (Y_t). A Poisson deconvolution projects the unobserved infection distribution by disaggregating the reported deaths backwards.

Poisson deconvolution:

$$\mu_t = \sum_{i=1}^{\iota} \lambda_i f_{t-1}, where$$

$\mu_t = E[Y_t\ ]$, $\lambda = E[N_i]$ *and,*

Y_t = *number of deaths diagnosed at time t,*

N_i = *number of deaths at time t,*

f_d = *probability that the duration of delay is d units of time long*

A non-parametric maximum likelihood estimation estimated the unobserved infection curve from reported data.[9-11] This estimation assumes that the deaths are independent and follows an identical Poisson distribution. Based on back-projection of deaths, an adjusted CFR is more accurate than crude CFR as it better estimates the risk set of incident deaths.[9,12] Visualisations and analyses utilised the "tidyverse", "epitools"," caret", ""tableOne", and "EpiEstim" packages in R 4.1.[13]

RESULTS

In the study period a total 10,251, 116,140, 4,233,014, 31,188, 2,377,033, 485,646, 2,705,792, 141,772, 1,762,186, and 857,639 cases were observed in Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam, respectively. A total 68, 2,610, 142,889, 36, 27,770, 18,297, 40,424, 215, 18,123, and 21,043 deaths were observed in Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam, respectively. (Figure 1)

Cambodia, Laos, Thailand and Vietnam were all observed to report similar trends with large increases of transmission beyond April 2021. Brunei was observed to report increasing trends beyond July 2021. Singapore and Myanmar were observed to have two distinct waves of transmission of COVID-19 while, Malaysia, Indonesia and the Philippines had three distinct waves of transmission. Trends of daily per capita cases were observed to peak between July and September 2021 for all countries within the ASEAN region. The highest daily per capita cases of 67 cases per 100,000 population was observed in Malaysia. (Figure 2)

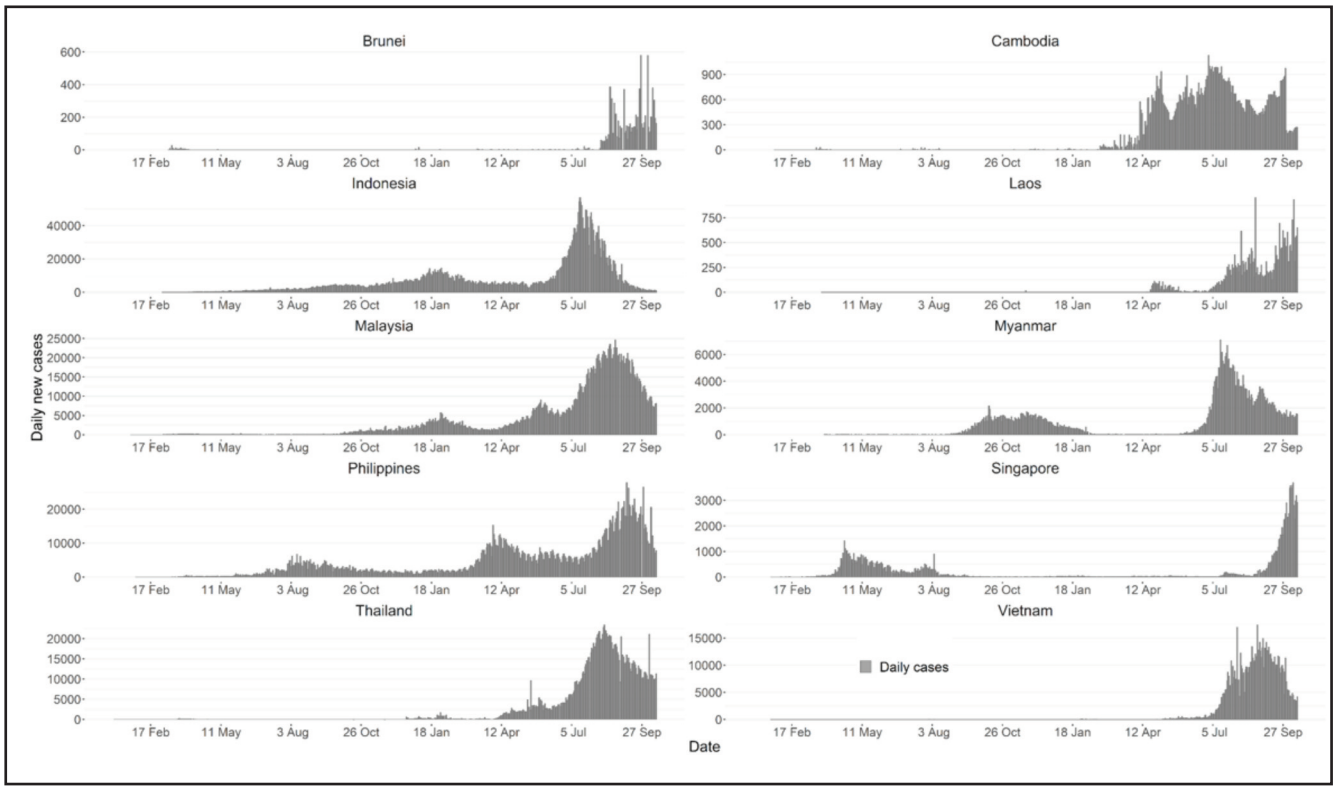

Fig. 1: Epidemiologic curves of cases in all ASEAN countries between 1st January 2020 to 15th October 2021.

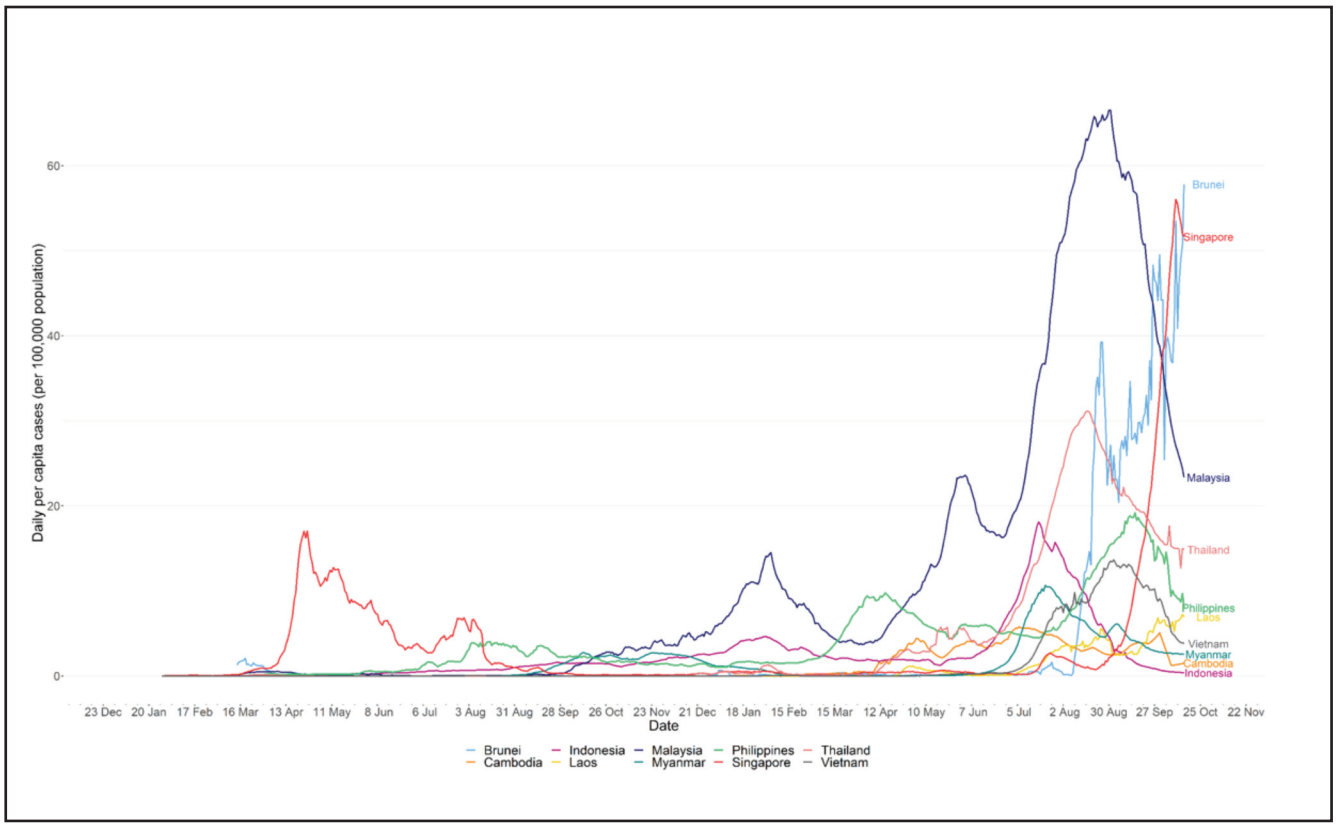

Fig. 2: Daily per capita cases (7-day moving average per 100,000 population) of ASEAN countries between 1st January 2021 to 15th October 2021.

Table I: Covid-19 burden of mortality in ASEAN between January 2020 and September 2021

Location	Cumulative	Period						
		Jan-March 2020	Apr-Jun 2020	Jul-Sep 2020	Oct-Dec 2020	Jan-Mar 2021	Jan-Mar 2021	Jan-Mar 2021
Case fatality rates*								
Brunei	0.9	0.8	17.1	0.0	0.0	0.0	0.0	0.9
Cambodia	2.2	0.0	0.0	0.0	0.0	1.3	1.8	2.6
Indonesia	3.5	18.7	6.0	3.7	2.8	2.5	3.5	3.9
Laos	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.1
Malaysia	1.2	2.6	0.9	1.5	0.4	0.3	1.2	1.5
Myanmar	4.0	12.0	1.1	4.6	2.1	2.1	3.4	4.8
Philippines	1.6	10.4	3.2	1.8	2.0	2.0	1.7	1.2
Singapore	0.1	0.7	0.0	0.0	0.2	0.1	0.3	0.3
Thailand	1.7	4.4	3.4	9.7	11.1	3.6	2.1	1.6
Vietnam	2.6	0.0	0.0	4.9	0.0	0.0	0.5	2.7
Mortality rates**								
Brunei	9.5	0.2	0.5	0.0	0.0	0.0	0.0	8.8
Cambodia	13.7	0.0	0.0	0.0	0.0	0.1	3.5	10.1
Indonesia	51.4	0.0	1.0	2.8	4.1	6.8	6.4	30.2
Laos	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.2
Malaysia	80.3	0.1	0.2	0.0	1.0	2.4	11.9	64.6
Myanmar	32.4	0.0	0.0	0.6	4.3	1.0	0.2	26.3
Philippines	34.5	0.1	1.1	3.8	3.4	3.6	10.2	12.3
Singapore	1.6	0.1	0.4	0.0	0.0	0.0	0.1	1.0
Thailand	23.9	0.0	0.1	0.0	0.0	0.0	2.8	21.0
Vietnam	19.7	0.0	0.0	0.0	0.0	0.0	0.0	19.6

* Case fatality rates, %, was delay adjusted to reflect a more valid population at risk of the case fatality

** Mortality rates (per 100,000 population)

Table II: Covid-19 testing indicators in ASEAN between January 2020 and September 2021

Location	Cumulative	Period						
		Jan-March 2020	Apr-Jun 2020	Jul-Sep 2020	Oct-Dec 2020	Jan-Mar 2021	Apr-June 2021	Jul-Sep 2021
Test positivity ratios (%)								
Brunei	NA	NA	NA	NA	NA	NA	NA	NA
Cambodia	8.4	NA	NA	NA	NA	NA	10.2	6.1
Indonesia	16.9	28.4	12.4	15.7	15.9	21.4	14.2	17.1
Laos	4.6	NA	NA	NA	NA	NA	0.4	6.4
Malaysia	7.5	4.0	0.7	0.4	3.9	3.9	5.4	11.5
Myanmar	11.1	NA	0.4	7.3	7.4	2.4	11.8	19.8
Philippines	12.9	NA	5.3	9.8	5.6	8.5	14.4	20.3
Singapore	0.5	NA	6.3	0.7	0.0	0.1	0.0	0.6
Thailand	11.7	3.0	0.3	0.1	0.7	1.3	4.5	25.4
Vietnam	3.6	0.5	0.0	0.1	0.1	NA	0.5	4.3
Cumulative testing rates (per 1,000 population)								
Brunei	NA	NA	NA	NA	NA	NA	NA	NA
Cambodia	25.0	NA	NA	NA	NA	NA	13.9	11.1
ndonesia	90.1	0.0	1.6	5.3	10.4	13.0	16.9	42.9
Laos	27.4	NA	NA	NA	NA	NA	8.3	19.1
Malaysia	917.7	2.1	26.0	19.7	80.1	180.4	227.7	228.6
Myanmar	75.8	NA	1.3	3.3	27.6	13.2	2.2	28.3
Philippines	177.8	NA	5.6	25.3	25.9	29.0	41.5	50.3
Singapore	3303.3	NA	111.1	359.5	435.7	564.7	816.9	1015.3
Thailand	195.2	0.8	8.3	5.8	7.7	23.7	73.3	67.8
Vietnam	224.9	0.4	1.7	8.4	0.4	NA	29.0	185.0

Testing data is available up to 12 July 2021 for Cambodia, 26 September 2021 for Indonesia, and 18 September for Thailand. Testing data for Laos is missing between 7 July 2021 and 31 August 2021.

NA: Data not available

Table III: Proportion of total population completed vaccinations in ASEAN between January 2021-September 2021

Location	Period		
	Jan-Mar 2021	Apr-June 2021	Jul-Sep 2021
Brunei	0.0	3.3	44.5
Cambodia	1.4	18.0	65.3
Indonesia	1.3	4.9	18.5
Laos	0.0	7.2	28.2
Malaysia	0.7	7.1	61.8
Myanmar	0.1	2.8	6.8
Philippines	0.0	2.4	19.2
Singapore	6.4	35.5	76.8
Thailand	0.0	4.0	22.7
Vietnam	0.0	0.2	10.0

Vaccination data is available till 25 September 2021 for Myanmar and 22 September 2021 for Thailand.

The cumulative CFR rate was 0.9%, 2.2%, 3.5%, 0.1%, 1.2%, 4.0%, 1.6%, 0.1%, 1.7%, and 2.6%, in Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam, respectively. The delay-adjusted CFR was consistently highest between January-June 2020. Peak delay-adjusted CFR of 18.7% was observed in Indonesia between January-March 2020, followed by peaks of 17.1% and 12.0% between April-June 2020 in Brunei and January-March 2021 in the Philippines. MR trend trajectories within the region is 'U' shaped with a peak in early 2020 followed by another smaller peak in mid-2021. (Table I)

The cumulative mortality rate (MR) was 9.5, 13.7, 51.4, 0.2, 80.3, 32.4, 34.5, 1.6, 23.9 and 19.7 per 100,000 population in Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam, respectively. MR was consistently highest between July-September 2021. Peak MR of 64.6 deaths per 100,000 population was observed in Malaysia between July-September 2021, followed by peaks of 30.2 and 26.3 deaths per 100,000 population between July-September 2021 in Indonesia and Myanmar, respectively. CFR trend trajectories within the region were upgoing with a sharp rise of deaths in September 2021. (Table I)

The cumulative test positivity rate (TPR) was 8.4%, 16.9%, 4.6%, 7.5%, 11.1%, 12.9%, 0.5%, 11.7%, and 3.6% in Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam, respectively. The majority of countries within the region reported peak TPRs between July-September 2021. A peak TPR of 25.4% was observed in Indonesia between January-March 2020, followed by peaks of 25.4% and 20.3% between July-September 2021 in Thailand and the Philippines, respectively. Six of the ten highest TPRs were observed in Indonesia. The TPR trend trajectories within the majority of the region was 'U' shaped with peaks between January-March 2020 and July-September 2021. (Table II)

The cumulative testing rate (TR) was 25.0, 90.1, 27.4, 917.7, 75.8, 177.8, 3303.3, 195.2, and 224.9 tests per 1,000 population in Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam, respectively. TR was consistently highest between April-September 2021. Peak TR of 1,015.3 tests per 1,000 population was observed in Singapore between July-September 2021. Six of the ten peak TR were observed in Singapore. This was followed by a peak TR of 228.6 and 185.0 tests per 1,000 population in Malaysia and Vietnam, respectively. TR trend trajectories within the region were upgoing with a sharp rise in tests between July-September 2021. (Table II)

The percentage of completed vaccinations (VR) was 44.5%, 65.3%, 18.5%, 28.2%, 61.8%, 6.8%, 19.2%, 76.8%, 22.7%, 10% in Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam, respectively. Peak VR of 76.8% was observed in Singapore between July-September 2021, followed by 65.3% in Cambodia and 61.8% in Malaysia. VR trend trajectories within the region were upgoing with a sharp rise in vaccination between July-September 2021. The sharpest increase in vaccinations was observed in Malaysia between April-September 2021. (Table III)

The following are brief accounts from the respective ASEAN nations.

Brunei

A large Malaysia-based religious event led to a large cluster of cases in Brunei in early March 2020.[14] In response to this incident, Brunei implemented strong non-pharmaceutical interventions such as prohibitions of social gatherings and movement restrictions as early as 10 March 2020.[15,16] This led to a rapid decrease in transmission before the staged reopening of almost all sectors by July 2020. Effective public health and social measures led to the eradication of local transmission within Brunei lasting for more than one year. Local transmission emerged again on 7 August 2021.[17] Despite the tightening of measures, transmission had increased within the country. As of 30 September, Brunei reported the highest daily per capita cases within the region. Brunei does not share data on testing statistics which is an important mediator of effective disease control.[18]

Cambodia

Despite the reported lack of intense non-pharmaceutical interventions in Cambodia, only 83 cases of local transmission were reported between 27 January 2020 and 15 February 2021.[19-21] However, from 20 February 2021, a total of 112,651 cases and 2,319 deaths were reported. In response, the government of Cambodia implemented highly restrictive public health and social measures that have been criticised for leaving thousands of Cambodians at breaking point.[22] Additionally, despite reporting high levels of testing, data on testing had not been made available until April 2021.[20] However, Cambodia has reported one of the fastest

vaccination rates in the region- second behind only to Singapore as of September 2021.

Indonesia

Indonesia reported its first case on 2 March 2020. The early approach to disease control within the country utilised a diverse set of containment strategies, including international travel restrictions, school closures, movement restrictions and personal infection prevention measures that differed by region.[21-23] Transmission as such was never fully interrupted and has been comparatively one of the highest within the region. However, overwhelmingly high transmission led to the introduction of a national partial lockdown on 1 April 2021. The lockdown measures were eventually tiered into four levels, and as of 18 July 2021, Indonesia has been at level four; the highest stage of lockdowns in the country.[17] Additionally, testing rates have been one of the lowest within the region, and test positivity rates have been correspondingly higher than most other countries within the region.

Laos

Laos was the last country in ASEAN to report local transmission of COVID-19. The government began containment measures as early as 6 March 2020 and implemented restrictive public health and social measures on 29 March 2021.[24] These measures were followed by the phased reopening of almost all sectors, which led to only 23 cases being observed as of September 2020.[18] Despite no data being available on testing over this period, seroprevalence studies suggest that transmission was likely low in 2020.[24,25] However, beginning from April 2021, transmission began to increase, leading to restrictive public health measures being implemented again on 22 April 2021. Testing per capita is one of the lowest in the ASEAN region, suggesting potentially an undercounting of cases and deaths in 2021.

Malaysia

The first case of COVID-19 was detected in Malaysia on 25 January 2020. It was traced back to three Chinese nationals who previously had close contact with an infected person in Singapore.[26] They had travelled into Malaysia via Singapore on 24 January 2020. They were treated at the Sungai Buloh Hospital, Selangor, Malaysia.[26] Larger clusters were detected from those who attended a massive religious *(tabligh)* gathering at Masjid Sri Petaling Selangor between 27 February 2020 till 3 March 2020, which an estimated 15,000 or more participants attended. By 14 April 2020, there were 4,987 confirmed cases and 82 deaths.[27] The *tabligh* cluster had at that time contributed to the bulk of cases in Malaysia.

This increase in infections was met by rapidly implemented, high-intensity suppression measures that successfully terminated transmission.[28-29] A series of prison and immigration depot outbreaks coupled with the loosening of restrictions due to a state-elections led to a surge in cases within the country in September 2020.[30,31] Despite prolonged high-intensity suppression within the country, transmission was never fully interrupted leading to a third and fourth wave of infections in April and July 2021. Suppression was likely to have been ineffective due to several factors, including more transmissible variants, poor governance, and pandemic fatigue.[32-34] In comparison to all other countries within ASEAN, Malaysia has not performed well in terms of per capita deaths and cases. This burden of disease has led to a prioritisation of public health control measures. Malaysia reports the second-highest testing rate, the second-lowest test positivity, and the third-highest vaccination rate within the region. Additionally, recent thrusts by the Ministry of Health, Malaysia, in increasing data transparency has meant Malaysia now reports the most complete, publicly available surveillance data in the entire region.

Myanmar

Containment measures were implemented as early as 13 March 2020. The first case of local transmission was reported on 23 March 2020, and subsequent increases in transmission led to a nationwide implementation of restrictive public health and social measures as of 18 April 2020. These measures led to rapid decreases in local transmission of COVID-19.[35-36] A phased reopening was implemented beginning on 3 May 2020. However, a rise in cases within the state of Rakhine attributed to migrant movements with bordering Bangladesh led to an increase in the intensity of restrictions on 16 August 2020.[23,37] As transmission spread, different control measures were observed at the regional level. However, as reductions in transmission were observed in January 2020, a military coup was reported in Myanmar on 1 February.[37] Widespread social activism led to conflicts between the military and the public within the country.[38,39] The government, in response, imposed national movement restrictions and curfews.

In early July 2021, cases began increasing again, although cases have since begun decreasing, despite regional strife and limited resources.[40] Myanmar has been transparent with testing data. As of July-September 2021, Myanmar has reported nearly three times the number of tests per capita rate of neighbouring Laos and Cambodia.

Philippines

The Philippines has utilised sustained and intense public health measures since 10 March 2020. The government utilised a five-level system of staged restrictions suppressing transmission across the country.[41] Despite the sustained restrictions, transmission was one of the highest in the region, with one of the highest CFRs.[42,43] Additionally, test positivity was one of the highest within the region, with testing rates being one of the lowest.[44]

Singapore

Drawing lessons from the SARS 2003 pandemic, Singapore had a well organised public health preparedness and response during the COVID-19 pandemic, potentially one of the best in the region.[23] Implementation of control measures started on 2 January 2020, one of the earliest in the region. A robust policy consisting of early detection, contact tracing and isolation of infected individuals remained cornerstones of effective containment of infection. Early detection and management of cases has resulted in a low mortality rate, one of the lowest rates in the world.[43] A "Circuit Breaker" to ensure safe distancing was implemented on 3 April 2021, and with a gradual decrease in cases, a controlled reopening continued from June 2020 to May 2021. A state of

"Heightened Alert" was initiated due to an increase in the number of cases in May 2021.[17] Singapore has commenced a four-step plan to gradually open up the economy, progressively emerging as a ''COVID-19 resilient'' nation. Travel restrictions have been eased for fully vaccinated individuals, progressing to increase in size limits for events and further reduced strict border controls. The ultimate goal is to reach a new normal life with optimal vaccination, and sporadic cases of COVID-19 infection occurring without disrupting community life. Singapore's preparedness and response to COVID-19 have been exemplary within the region and globally.[42]

Thailand

Thailand reported its first COVID-19 cases on 13 January 2020- the first case reported outside of China. Three major clusters of super-spreaders seeded large outbreaks in March 2020, leading to the implementation of strong public health and social measures that successfully interrupted transmission.[45,46] A phased reopening of all sectors began on 1 May 2020 and transmission remained well controlled until outbreaks seeded by migrants in December 2021 led to increased transmission.[47] An increase in restrictions decreased transmission, which led to the loosening of restriction on 4 February 2021. However, the circulation of a more transmissible variant in July 2021 led to an increase in restrictions aiming to stifle transmission.[17] Despite being considered as having one of the most mature public health systems in the region, the more transmissible delta variant has led to an overwhelmed healthcare system in Thailand.[23]

Vietnam

The first case within Vietnam was reported on 23 January 2020. In response to the increasing transmission, the government utilised several strong public health measures to interrupt the transmission.[48] As cases quickly decreased, the government attempted a phased reopening of all sectors high degrees of success, leading to almost 100 days with no local transmission.[49,50] Despite cases being reported after 25 July 2020, the magnitude of transmission remained low until July 2021.[50] Transmission in July 2021 surged as the more transmissible delta began increasing the number of cases and deaths being reported. In response, increased restrictions were imposed to reduce the transmission. Despite relatively low resources, Vietnam remains one of the best performing countries within the region with regards to surveillance, testing, vaccinations, good governance and high population trust.[42,51,52]

DISCUSSION

The ASEAN region reported distinct differences in the COVID-19 pandemic profile compared to the rest of the world. As the pandemic started in 2019 in China and spread westwards, the magnitude of cases in ASEAN countries remained relatively low when compared with the rest of the world in 2020. This could be attributed to the presence of pandemic preparedness, and population memory of a lesson learnt from the SARS 2003 pandemic which had caused significant mortality in Asia. This promoted a quick and consolidated response which was publicly accepted, and adhered to.

The B.1.617.2 - Delta variant was first detected in India in December 2020, and by May 2021, became the predominant COVID-19 strain globally. With the emergence of the COVID-19 Delta variant in ASEAN countries, we saw an upsurge in cases and increasing mortality. However, the mortality rate in ASEAN still remained below the average world mortality of 65 deaths per 100,000 population. Demographic differences like younger population and genetic susceptibility could account for this difference. In 2020, most countries in ASEAN had higher case fatality rates especially between January–March 2020 but lower mortalities per population when compared to the peak of new cases during the period between July-September 2021 where higher mortalities per population were observed but with similar case fatality rates.

Some of the ASEAN countries launched large scale screening and testing while some nations conducted tests based on higher probability of infection, accounting for the differences in detection rates as those with higher testing rates detected larger proportions of asymptomatic cases, and those testing more severe cases were less likely to detect mildly symptomatic or asymptomatic cases. Higher detection of asymptomatic cases likely leads to lower case fatality rates, while there is also evidence that early detection, supportive management, and treatment leads to less severity and mortality. In addition, the case fatality rate may also be affected by factors such as population risk factors, population density, availability and effectiveness of quality healthcare infrastructure.

Tests per million people, and tests per confirmed case, weakly correlates with population mortality and case fatality rate. The proportion of critical cases moderately correlates with tests per confirmed case and tests per million people. Test positivity rate and proportion of severe disease in the nonvulnerable groups may be useful in predicting upsurge in cases and an increasing trend should act as an indicator to heighten control measures.

During the COVID-19 wave in 2021, Brunei, Malaysia, Singapore, and Thailand detected more than 30 cases per 100,000 population, with a high total cumulative testing rate ranging from 195-3,303 tests per 1,000 population, resulting in a cumulative case fatality rate ranging from 0.1% for Singapore to 1.7% for Thailand. Meanwhile, Cambodia, Indonesia, Myanmar, Philippines, and Vietnam had less than 25 cases per 100,000 population, conducted 25 - 224 tests per 1,000 population, and with a cumulative case fatality rate ranging from 1.6% (Philippines) to 3.6% (Indonesia). The countries with higher caseloads did not have higher mortality, as a higher testing rate would likely detect more asymptomatic and mild cases. Selective testing of symptomatic or severe cases could have contributed to lower case numbers in the countries with an apparent lower case load, lower testing rate, and higher mortality. The slow initiation of vaccination programs was found to be the key factor leading to the high incidence and case fatality rate in most ASEAN countries. This was shown by the low vaccination rates (below 20%) in the second quarter year (except Singapore) before the peak of new cases in the third quarter of 2021.

CONCLUSION

In 2020, most countries in ASEAN had higher case fatality rates but lower mortality rates per population when compared to the third quarter of 2021 where higher mortality rates per population and lower case fatality rates were observed. Lower testing rates have been one of the factors leading to higher test positivity rates. Delayed initiation of vaccination programs may be a key factor for the recent higher incidence rates in many ASEAN countries.

A varied set of responses have been implemented within the ASEAN region to interrupt the transmission of COVID-19. The World Health Organization (WHO) has developed strict guidelines to adhere to during the pandemic. Thus far, there remains no safe and effective medicine against COVID-19. Every nation within the ASEAN region leveraged heavily on strong public health and social measures in the early response to the pandemic, which was largely successful in each country. However, contextual factors such as political stability, public health preparedness, pandemic fatigue, and access to resources have led to different scenarios of transmission within individual countries.

Most of the ASEAN countries have been unable to contain the transmission despite the prolonged use of strong public health and social measures. All ASEAN countries have had periods with large increases in local transmission driven mainly by the more transmissible Delta variant since May 2021. The authorities should also continue looking out for new Covid-19 clusters to control the spread of the virus.

Benchmarking between nations in the ASEAN region highlights several important lessons. Effective public health measures can be very useful in interrupting the transmission of this novel virus. Nonetheless, maintaining strong public health measures over a prolonged period can be very challenging. Extraordinary demands on healthcare workers have intensified burnout among healthcare workers. The surging hospital admissions due to COVID-19 have led many national health care systems to the brink of collapse. Increasing the resources available to build preparedness within the region is critical in ensuring any future outbreaks can be dealt with collectively. As we continue to learn to live with this virus, it is critical that ASEAN nations increase information transparency and collaborative efforts, thus increasing the effectiveness of a collective regional response to the COVID-19 pandemic.

As the world continues to combat the COVID-19 pandemic, the way forward is through regional collaboration so that no country is left behind. The ASEAN countries should continue to share their experiences, resources and importantly provide timely support to fellow countries in need. Stronger regional partnerships and strategic pooling of resources may make ASEAN countries better prepared for the coming evolution of this pandemic.

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ORIGINAL ARTICLE

Determination of service key performance indicators for emergency departments of teaching hospitals in Malaysia: A fuzzy delphi method

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ABSTRACT

Introduction: The most crucial step in forming a set of key performance indicators (KPI) for emergency department's (ED) staff is deciding the appropriate items for the KPI. This article demonstrates Fuzzy Delphi Method (FDM) as a scientific approach to consolidate consensus agreement within a panel of experts pertaining to each service related KPI item's appropriateness for ED. We aimed to develop framework of service key performance indicators for emergency departments of tertiary centres by using FDM.

Materials and Methods: The panel consists of ten experts from ED that was randomly chosen from list of specialists obtained from the National Specialist Registry for Emergency Medicine. A set of questionnaires that contains item constructs related to KPI based on structure, outcome and process was developed from initial literature search from Pubmed Central, Google Scholar, Cochrane Database and Public Library of Sciences. The construct then used for FDM session in second phase of the study. In FDM phase, the experts will rank each of the items created from nominal group technique (NGT) session by using Likert Scale ranged from 1 to 5 ("1" totally disagree and "5" extremely agree). FDM prerequisite must include threshold value (d) ≤0.2, expert consensus of >75% and average fuzzy numbers ("A" value) of >0.5.

Results: The initial item construct has produced 22 items proposed for the service KPI. Post FDM analysis for service KPI, 16 out of the 22 (72%) satisfied first prerequisite "d" value ≤0.2. For the second prerequisite, ten items (45%) from service KPI domain had expert consensus of more than 75%. For the third prerequisite, 16 out of the 22 (73%) fit the criteria of average fuzzy number ("A" value) of more than 0.5. In final model of FDM, 13 items (59%) were discarded and the remaining (n=9 items) that fulfilled all three pre-requisites were retained for the final draft for content validation process.

Conclusion: This study introduces that FDM can be used to obtain experts' opinion and consensus in order to achieve a decision. The experts' consensus on the suitability of the pre-selected items on the KPI set were obtained, hence it is now ready for further applicability in the clinical setting in ED.

KEYWORDS:
Performance; quality, emergency department; KPI; service

INTRODUCTION

Emergency department (ED) serves as a vital role for any health care set up in providing care for variety of cases ranging from most critically ill to non-critical cases for whole range of population. Providing quality service in ED will enhance patients' outcome and generate trust among public who utilises the service.[1,2] Setting up key performance indicators (KPIs) in ED is crucial to ensure service provision is being monitored objectively and can serve as benchmarking for its performance against other set up within the same locality or abroad. KPIs also provide valuable information for institutions to set goals, support action plans, monitor implementation results, and to report results of their achievement. KPIs allow hospital stakeholders to identify critical points and problems that can be solved with low-cost actions, both in time and resources.[3,4] KPIs for ED in any given locality may be different from one to another as the need and capacity of its function may differ. For example, KPI framework for an ED of a tertiary teaching centre will be different from those KPI in non-academic ED centre or district hospitals.[5-7] Having a wrong KPI set up creates burden to an organisation resulting in poor compliance and in worst scenario waste financial and other resources. Hence setting up appropriate KPIs for an ED is crucial and it requires robust and reliable methods.

Unfortunately, at present time there are no standardised and common KPIs framework set up for emergency medicine service provision in teaching hospitals in the country and yet robust KPIs set up is essential to improve quality of teaching and learning whilst at the same time ensuring safety of patient care and staff. Therefore, given the vital role as well as the perpetual and indispensable service provided by the ED in teaching hospitals, it is necessary to evaluate the service provision in this unique setting in accordance to acceptable standards and criteria. Hence an effort was taken to create a framework of KPIs for service activities by using Fuzzy Delphi Method (FDM).[8,9] FDM uses expert opinion and consensus in reaching final decision of KPI contents for further construct validation before its final use in ED. The study was approved by local ethics and review board for

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human research and involved experts in emergency medicine throughout the country.

MATERIALS AND METHODS

The study utilised the Fuzzy Delphi Method (FDM) in obtaining consensus from experts on service KPI parameters of teaching hospitals in Malaysia. The principal investigator acted as the main facilitator who provided experts with online Google Form questionnaires. The experts were considered as experiencing in ED employment of >5 years as clinical specialists and involved in the scholarly activities in the specialty of Emergency Medicine. Our general approach was to select participants who have knowledge of the outcome and outcome assessment and with clinical and academic experiences in EM. For this reason, we used a purposive sampling approach for the participants based on the lists of EM staff employed in teaching hospitals obtained from administrative offices of the institutions. Currently, there are three major teaching hospitals in the country that provide specialty training program in EM. The selection expert members should reflect the population that is intended to use the KPIs. The Google form was sent directly to the experts handphone via WhatsApp® and Telegram® messaging to ensure the form reached the intended experts. This was followed by phone calls and messaging confirmation carried out by the investigators.

OUTCOME MEASURE & ANALYSIS

The study involved two phases:

Phase 1 (Literature Analysis)

The principal investigator listed out all potential initial draft KPIs to be assessed by the chosen experts. The initial draft was based on literature review and evidence based obtained from sources such as The PubMed Central, Google Scholar and Cochrane Library and Public Library of Science. The initial item constructs consist of three domains namely "Structure", "Outcome" and "Process" (SPO). Structure describes the context in which clinical care are delivered, including hospital buildings, staff, financing, and equipment. Process denotes the transactions between patients and providers throughout the delivery of healthcare activities. Finally, outcomes refer to the effects of healthcare on the health status of patients such as morbidity and mortality.

Phase 2

The FDM was used to obtain expert consensus on the feasibility and ranking top priority KPI parameters obtained from literature search for final use in the EM department of teaching hospitals. A set of KPI parameter assessment form was created by using a five-point Likert scale. (Table I) The pre-requisites to reach expert consensus consists of three elements. The first prerequisite required each item in the domain achieves threshold value (d) ≤0.2. The second prerequisite requires each item within the construct must achieve expert consensus of more than 75%.[10,11] The third prerequisite was used to rank the items within the constructs by calculating the average fuzzy numbers ("A" value). Items were accepted if the "A" value is more than 0.5.[12] The number of Fuzzy scales must be selected in odd numbers such as 3, 5, 7 and 9. The higher the Fuzzy scale value indicates the data is obtained more accurately. The survey was distributed to the experts in Google Form format via WhatsApp or Telegram text messaging platform.

Fuzzy Delphi Method (FDM) implementation steps.

Step 1

Selection of experts:

In the selection of experts, good results can be obtained even with small panels of 10-15 homogenous individual.[13] The concept of experts in FDM comprises of any of the following criteria such as individual having vast working experience in the field, those who are known for extensive scholarly work in the field of study and being recognized by certified bodies for his/her expertise. In this study the investigator had chosen ten experts within the field of EM and currently serve as EM specialists of >5 years' experience in a teaching hospital in the country. All of respondents are registered with the National Specialist Registry (NSR), Malaysian Medical Council and actively served as members of specialty conjoint member of EM trainee programme.

Step 2

The next step involved the conversion steps of all linguistic variables into triangular fuzzy numbers. A Triangular Fuzzy Number represents the value of m1, m2, m3 and is symbolised like (m1, m2, m3). The m1 value indicates the minimum value, the m2 value indicates a reasonable value and the m3 indicates the maximum value. Figure 1 shows the values of m1, m2, m3 for the Triangular Fuzzy Number. The m values represent the percentage likelihood the experts agree that the KPI parameters are important. (i.e., for Likert Scale 3: m1=minimally 20% agree it is important; m2=reasonably average likely 40% of experts agree it is important; m3=at most 60% of expert will agree it is important).

Step 3

The following step is identifying the value of threshold 'd'. The threshold value is very important in the step of identifying the level of agreement among experts. To obtain expert agreement for each item, the threshold value must not exceed 0.2 (14). However, the mathematical experts in FDM have always considered three decimal point value for inclusion of item acceptance due to minute value of fuzzy numbers evaluation ranging from 0 to 0.99999.[15,16] Therefore, if the d value is ≤0.299, it means experts reach an agreement on the item, otherwise the second round should proceed to survey whether the item is needed or not.

To obtain the threshold value (d), is calculated based on the formula:

$$d(\bar{m},\bar{n}) = \sqrt{\frac{1}{3}\left[(m1-n1)^2 + (m2-n2)^2 + (m3-n3)^2\right]}$$

Step 4

The second requirement for the FDM involves the step of determining the experts' agreement whether it is ≥75% for each item. If the percentage of expert agreement is ≥75% agreement for each item, then the item is assumed to reach the expert agreement. The percentage of expert's agreement can be calculated by using the formula:

Table I: Level of agreements and Fuzzy scale (5 points)

Linguistic Variables	Likert Scale	Fuzzy Scale
Not appropriate at all	1	(0.0, 0.0, 0.2)
Minimally appropriate	2	(0.0, 0.2, 0.4)
Moderately appropriate	3	(0.2, 0.4, 0.6)
Very appropriate	4	(0.4, 0.6, 0.8)
Extremely appropriate	5	(0.6, 0.8, 1.0)

Table II: Initial item constructs based on literature analysis outcomes for service KPI parameters

DOMAIN/ITEMS	KPI ITEM DESCRIPTION (SERVICE STRUCTURE-SS)
SS-1	BLS/ACLS/ATLS/PALS certification for all medical doctors working in Emergency Department (KPI outcome 80% of all doctors per any one certification)
SS-2	Minimum nursing to bed ratio in red zone (KPI: target 1:2)
SS-3	Minimum doctors to bed ratio in red zone (KPI: target 1:3)
SS-4	Maximum duration ambulances downtime annually (KPI: twice breakdown per ambulance per year)
SS-5	Annual budget allocation for point of care test (KPI: adequate to fulfill all tests request)
SS-6	Amount of Personal Protective Equipment provided and supplied annually (KPI: adequate to fulfil the use requirement)
	KPI ITEM DESCRIPTION (SERVICE PROCESSES-SP)
SP-1	Door to time to be seen by doctors/nurses in Critical (Red) Zone (KPI: 0 minute)
SP-2	Door to time to be seen by doctors/nurses in Semi Critical (Yellow) Zone (KPI: maximum 30 minutes)
SP-3	Door to time to be seen by doctors/nurses in Non-Critical (Green) Zone (KPI: maximum 120 minutes)
SP-4	Door to CT scan for CVA patient (KPI: within 30 minutes of arrival)
SP-5	Door to needle for thrombolysis in CVA (KPI: within 90 minutes of arrival)
SP-6	Door to thrombolytics for AMI (KPI: within 30 minutes of arrival)
SP-7	Ambulance response time (KPI: 15 minutes from call received at dispatch centre for hospital based ambulance services)
SP-8	Number of working hours per week for medical officers (KPI: maximum 70 hours per week)
SP-9	Number of working hours per week for nurses (KPI: maximum 60 hours per week)
SP-10	Hand hygiene practice among staff (KPI: 100% compliance)
	KPI ITEM DESCRIPTION (SERVICE OUTCOME-SO)
SO-1	Percentage of success thrombolysis in AMI (KPI: 70% of all cases thrombolysed)
SO-2	Percentage of success thrombolysis in CVA (KPI: 70% of all cases thrombolysed)
SO-3	Staff happiness index (KPI: 80% of staff is satisfied working in the department at any time)
SO-4	Number of patient/public complaints (KPI: maximum 5 complaints annually)
SO-5	Incidence of needle prick injury in department (KPI: zero incidence annually)
SO-6	Incidence of nosocomial infection among staff (KPI: zero incidence)

$$\frac{\text{Numbers of Item d} \leq 0.2 \times 100\%}{\text{Total Items}}$$

Step 5

The third criteria for the FDM, the α-cut is ≥0.5, indicates the item will be accepted as it shows the consensus of experts to receive the item. The calculation and determination of fuzzy values is by using as the formula below:

$$A = (1/3)*(m1 + m2 + m3)$$

If the value of A is more than the value of α-cut=0.5, then the item will be accepted as it shows the consensus of the expert to receive the item (17).

Step 6

The step of ranking or sub phases for the item. The ranking steps is by selecting the item based on defuzzification value (Value 'A" as above) based on expert agreement where the highest value of the item is determined by the most important ranking in the model.

The data entry from the Likert Scale obtained was translated into Fuzzy number data and analysed using FDM program in Microsoft Excel software. This data analysis technique is known as the Fuzzy Delphi or FDM technique. The study was approved by the host institution in accord to Declaration of Helsinki on ethical principles regarding human experimentation developed for the medical community by the World Medical Association (WMA).

RESULTS

A total of 22 item constructs for KPI service were identified at end of literature search for all three domains (Structure, Outcome, and Process). (Table II) All the items within the domains had scored average Likert scoring of three to five, which was in the scale of moderately appropriate to extremely appropriate. These scores were converted into fuzzy numbers. Sixteen out of the 22 items satisfied first prerequisite of "d" value ≤0.2. For the second prerequisite, ten items (45%) from service KPI domain had expert consensus of >75%. For the third prerequisite, 16 out of the 22 items (73%) fit the criteria of average fuzzy number ("A" value) of >0.5. Thirteen items (59%) were discarded and the remaining (n=9; 41%) that fulfilled all three prerequisites were retained. Apart from discarding items based on these prerequisites, little modification of items in terms of the structure, position and

Tabel III: Summary of all three prerequisite post Fuzzy Delphi analysis findings for Service KPI domain

Domain/Items	Average Likert Score	Threshold Value d < 0.2	Percentage Of Expert Consensus	Average Of Fuzzy Numbers (A value)	Ranking	Verdict***
Service Structure (SS)						
SS-1	4.7	0.147	90	0.740	2	Retained
SS-2	4.0	0.360	80	0.613	4	Discarded
SS-3	3.9	0.343	30	0.587	5	Discarded
SS-4	3.2	0.267	60	0.447	6	Discarded
SS-5	4.4	0.147	100	0.680	3	Retained
SS-6	4.8	0.098	100	0.760	1	Retained
Service Process (SP)						
SP-1	4.3	0.257	70	0.660	4	Discarded
SP-2	4.3	0.196	80	0.640	5	Retained
SP-3	3.6	0.387	30	0.527	8	Discarded
SP-4	3.9	0.344	30	0.593	6	Discarded
SP-5	4.5	0.214	90	0.700	3	Retained
SP-6	4.9	0.055	100	0.780	1	Retained
SP-7	3.1	0.225	70	0.427	10	Discarded
SP-8	3.3	0.370	50	0.473	9	Discarded
SP-9	3.9	0.227	60	0.587	7	Discarded
SP-10	4.8	0.098	100	0.760	2	Retained
Service Outcome (SO)						
SO-1	3.1	0.220	70	0.420	5	Discarded
SO-2	3.2	0.208	70	0.440	4	Discarded
SO-3	3.8	0.313	50	0.567	3	Discarded
SO-4	1.9	0.213	70	0.207	6	Discarded
SO-5	4.4	0.251	90	0.687	1	Retained
SO-6	4.3	0.252	90	0.667	2	Retained

***Prerequisite for retaining items based on expert consensus:

i. Threshold value (d) ≤ 0.2 (3 decimal points is accepted)
ii. Percentage expert agreement > 75%
iii. Average fuzzy value ("A" value) > 0.5

All three must be satisfied to retain the items

wordings were one based on the comments by the experts. These were some minor changes, and it did not alter the objective and nature of the items. Column for comments was provided in the last section of the Google Form as open questions and statements. Most of the comments were on simplifications of sentence structure and text format such "bold and italics". The whole findings were summarized in Table III and Figure 2.

DISCUSSION

This study introduces that FDM can be used to obtain experts' opinion and consensus in order to achieve a decision. This method can be used as a tool to select suitable items or content validation process before subjecting it to construct validation process. More importantly, this method provides a better quantitative approach compared to usual group discussions or meetings that are in a qualitative manner.[18,19] In addition, FDM approach does not require experts to meet physically and discuss topic of interest, hence agreement can be achieved via electronic platform that is most suitable during pandemic outbreak. The developed KPI framework can be considered as a prototype that was established and consented by experts without any bias; and it can be used in targeted setting after confirmatory or construct validation process. However currently, medical researchers rarely use FDM to obtain expert consensus on any subject matter. Delphi method should be widely used in medical related studies to obtain consensus among experts especially in developing a protocol, module or guidelines related to medical practices.[20-22] The Delphi method is well suited for research related to health education and health promotion campaigns, setting up guidelines or choice of clinical management.

FDM has an advantage of being able to rank the importance of selected items and remove the unfit items based on expert consensus and hence served as content validation process.[23,24] This study found that the average Likert scale scoring by the experts for all the items are from moderately to extremely appropriate range. However, in post FDM analysis, only nine items fulfilled all the pre-requisites. About 59% of the items did not match the terms, hence those items were regarded as failure to achieve consensus from the expert panel. These unfit items were the fuzziness or uncertainty among the expert panels that were not detected by the usual Likert Scale scoring system. Each expert has his/her own uncertainty towards certain variable, which often regarded as the "grey area". The use of FDM is to minimize those "grey area" effect and hence ensuring robust analysis. This method also catered for all experts' opinion, considering some experts are more experienced, some are more knowledgeable, some with relevant skills and some has the policy making authority in the field.[25,26] Variety of opinions is merged together to support each other's deficiency to derive at the desirable outcome. Moreover, the final draft of KPI framework was arranged based on priority ranking. Obviously, statement of items may have been interpreted differently among the experts. Any one

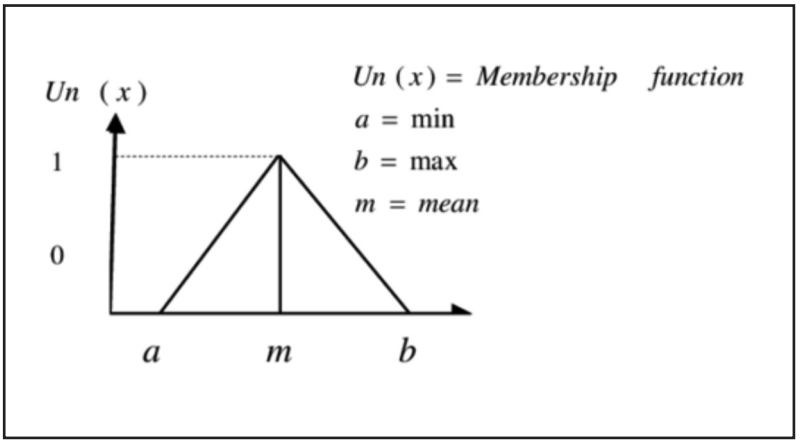

Fig. 1: The Triangular Fuzzy numbers.

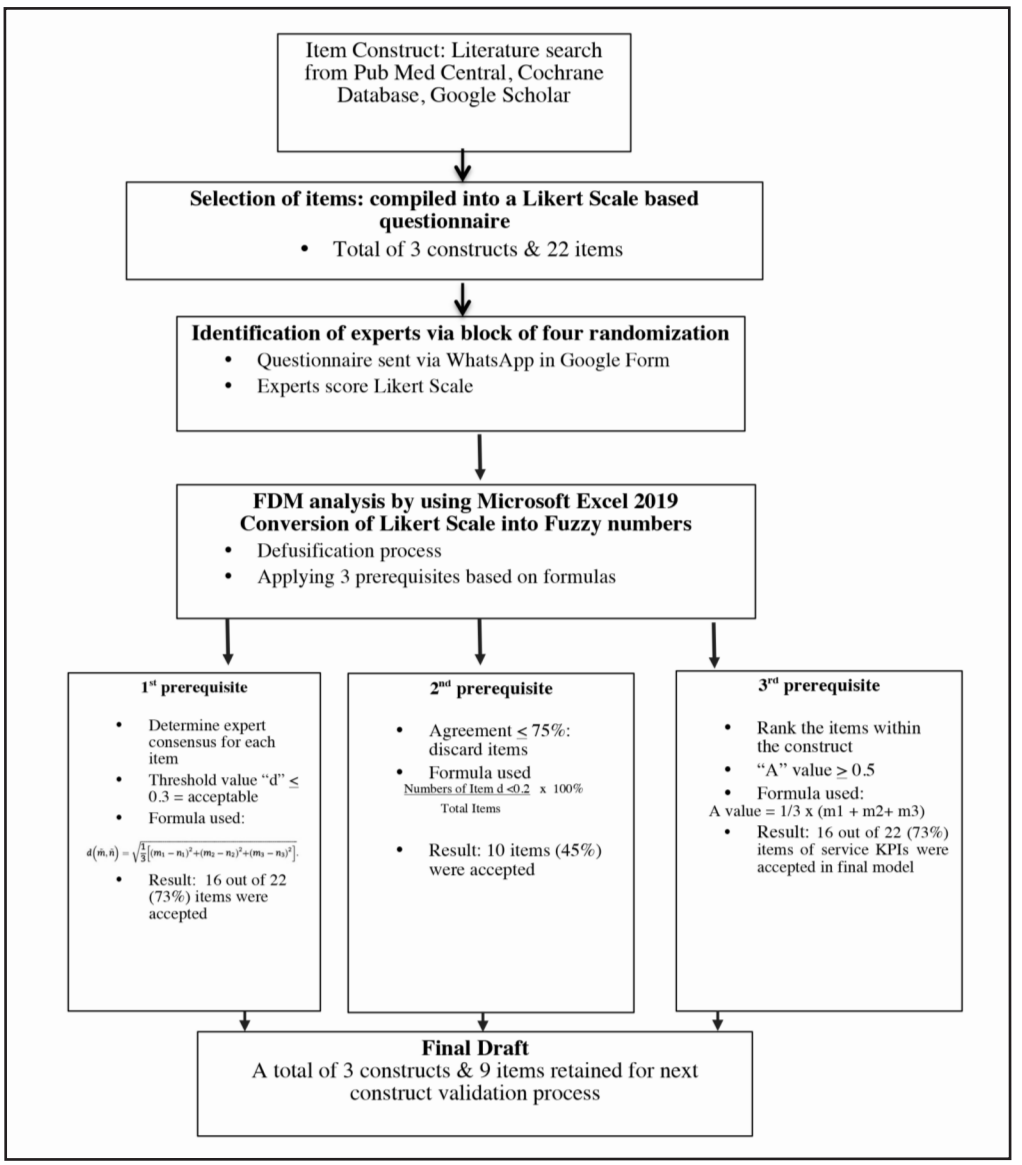

Fig. 2: Summary of content validation using Fuzzy Delphi Method for service KPI.

statement may have been well practiced KPI by the particular expert whereas the same KPI statement may deem to be non-crucial for other experts due to differences in set up of the ED of teaching hospitals. Additionally, the view of the experts may have been limited to their own and did not represent the view of whole fraternity. Unfortunately, no comments were obtained from experts on why they have put low marks on discarded items as by principle FDM works by giving Likert scale scoring without any commentary section or reasoning.

However, in the current pandemic situation, it is no doubt that FDM offers a very practical and safe method of getting expert opinion by a robust scientific technique and it is hoped that this study can serve as a guide for any future medical or health related research that intends to use FDM for their studies. The developed KPIs serve as a quality assurance tool for ED of teaching hospitals and can be replicated for similar use in non-teaching hospitals if deem suitable base on individual needs. KPIs allow stakeholders to identify critical issues that can be solved with low-cost actions, both in time and resources. The final outcome is to serve public and staff alike so that both sides gain benefit out of service provision in most efficient manner such as satisfaction, happiness index, and reduction in mortality and morbidity.

STRENGTH AND LIMITATIONS

However, the use of FDM in reaching expert consensus has its own strengths and limitations. The method can be used as a pre-construct validation tool to select the suitable items before subjecting it to a construct validation process. Most importantly, this method gives a proper quantitative approach to usual group discussions or meetings that are in a qualitative manner. The developed KPI items can be considered as accepted by the experts without any prejudice and it can be used for the targeted population after confirmatory validation process. The FDM process of obtaining expert consensus avoids the logistics issues pertaining to gathering of all experts such as tedious preparation, starting from the calling letter, arranging the venue and travelling expenses.[27] This method will certainly reduce the risk of bias by ensuring anonymity and welcoming the opinion of atypical views among the experts and the responses are totally independent without the fear of being judged by others that usually present in any routine group discussions or meetings. On the other hand, weaknesses of FDM include requirement of constant reminder to the experts to give their response and lead to the emotional bias among the experts. The KPI framework established in this study might not be applicable to other setting elsewhere. Different organisation may have other priorities in the KPI development that is more suited to their needs. The KPI developed has not been tested into real clinical setting hence it can be considered as a prototype. Further analysis is required for its applicability in the real setting before any improvement can be carried out.

CONCLUSION

FDM is applicable in medical research in obtaining experts' consensus on suitability of pre-selected items. The KPI set were obtained, hence it is now ready for further construct validation process and tests for its applicability in the real clinical service setting in teaching hospitals throughout the country.

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High prevalence of central hypothyroidism among patients with transfusion dependent thalassemia in Hospital Pulau Pinang: A cross sectional study

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ABSTRACT

Introduction: Thalassemia is the most common heritable haematological disorder in Malaysia. Hypothyroidism is one of the complications of the transfusion dependent thalassemia (TDT) patients as a result of iron overload.

Materials and Methods: All registered TDT patients attending Haematology day care, Hospital Pulau Pinang from January 2019 to January 2020 were included in the study. Hypothyroidism was defined according to TSH and FT4, or based on the history of treatment for diagnosed hypothyroidism.

Results: There were 51 TDT patients, with 24 (47%) males and 27 (53%) females. Most of the patients were Malays (27, 53%) followed with Chinese (23, 45%) and Indonesian (1, 2%). Beta thalassemia major and HbE beta thalassaemia accounted for 35 (68.8%) and 14 (27.5%) TDT patients respectively, while two (3.9%) were HbH Constant Spring. Eleven (21.6%) had hypothyroidism; of which seven (63.6%) had central hypothyroidism, three (27.3%) had subclinical hypothyroidism, the remaining one (9.1%) had primary hypothyroidism. Three (27.3%) had concomitant hypogonadism, one (9.1%) had hypocortisolism and another (9.1%) had both diabetes mellitus and hypogonadism. There was no statistical relationship between the prevalence of hypothyroidism and age, serum ferritin, splenectomy history and iron chelation therapy.

Conclusion: High prevalence of central hypothyroidism is reported. Measurement of both TSH and FT4 is recommended as initial screening for thyroid dysfunction among patient with TDT.

KEYWORDS:
Transfusion dependent Thalassemia, hypothyroidism, prevalence

INTRODUCTION

Thalassaemia represents a heterogeneous group of recessively inherited haemoglobin disorder characterised by defective synthesis of one or more globin chains. The World Health Organization (WHO) estimates about 56,000 births are affected with major thalassaemia annually and at least 30,000 are transfusion dependent.[1] The total number of living Thalassemia patients in Malaysia is 7984 according to the Malaysia Thalassemia Registry updated in November 2018. HbE-beta thalassaemia forms the majority of thalassaemia patients in Malaysia with 2744 patients (34.37%), followed by beta thalassaemia major with 2676 patients (33.52%), HbH disease with 1458 patients (18.26%), beta thalassaemia intermedia with 748 patients (9.37%), while the remaining 358 patients (4.48%) have others forms of haemoglobinopathies.[2]

Thyroid dysfunction is a frequently occurring endocrine complication among transfusion dependent thalassemia (TDT) patients. The prevalence of hypothyroidism ranges from 4-29% in various countries, largely in the form of subclinical hypothyroidism.[3-8] High incidence of central hypothyroidism among thalassemia major patients was observed in some centers.[9,10] Tan K.A et al., reported the prevalence of hypothyroidism among Malaysian children with TDT, including subclinical and overt hypothyroidism as 18.3%.[11] Hypothyroidism among TDT patients is associated with iron overload,[12-14] which is the primary therapeutic complication for polytransfused thalassaemic patients, and is linked to hemosiderosis of thyroid and pituitary gland.[15]

Screening for thyroid dysfunction among TDT patients should be performed annually, beginning at the age of nine years old.[16] Most of the laboratory guidelines recommend a two-step approach (the thyroid cascade) in screening for thyroid dysfunction; in which TSH should be measured first, followed by free thyroxine (FT4) only if TSH is out of reference range.[18-21] In this study, we explore the adequacy of screening for hypothyroidism among TDT patient by using the similar approach.

MATERIALS AND METHODS

This is a retrospective cross-sectional study carried out on all TDT patients aged 18 years and above at the Haematology unit, Hospital Pulau Pinang. All thalassaemic patients who received 2-6 weekly transfusions in the Haematology Unit day-care were included in this study. The study looked into demographic data, data on ferritin level, iron chelation therapy, history of splenectomy and thyroid function profile from January 2019 to January 2020 over a period of 13 months. For TDT patient with hypothyroidism, data on the age of diagnosis hypothyroidism and associated endocrinopathies were analysed.

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Table I: Demographic data of study population (n= 51)

Characteristic	Value	
	Number (n)	Percentage (%)
Gender		
Male	24	47.0%
Female	27	53.0%
Ethnic		
Malay	27	53.0%
Chinese	23	45.0%
Indian	0	0.0%
Others	1	2.0%
Classification of thalassemia		
Beta major	35	68.6%
HbE/ Beta	14	27.5%
Others	2	3.9%

*Mean±SD

Table II: Number of study population with Hypothyroid

	Number (n)	Percentage
Hypothyroid		
No	40	78.4%
Yes	11	21.6%

Table III: Clinical characteristics of TDT patients (both hypothyroidism and euthyroidism groups)

Parameters	Euthyroidism (n=40)		Hypothyroidism (n= 11)		
	Mean±SD		Mean±SD		p value
Age	30±7		28±6		0.400
Ferritin (ng/ml)	3012±3047		3902±2531		0.073
	n	Percentage	n	Percentage	
Splenectomy					0.466
Yes	14	35.0%	2	18.2%	
No	26	65.0%	9	81.8%	
Iron chelation therapy					0.372
Single iron chelation agent (Total)	15	37.5%	6	54.5%	
DFO	6	15.0%	2	18.2%	
DFP	5	12.5%	4	36.3%	
DFX	4	10.0%	0	0.0%	
Two iron chelation agents (Total)	25	62.5%	5	45.5%	
DFO+DFP	20	50.0%	5	45.5%	
DFO+DFX	4	10.0%	0	0.0%	
DFP+DFX	1	2.5%	0	0.0%	

Table IV: Clinical characteristics of TDT patients with Hypothyroid (n= 11)

Characteristic	Number (n)	Percentage (%)
Mean age of diagnosis (years)	22.8±6.9*	
Hypothyroid subtype		
Primary	1	9.1%
Subclinical	3	27.3%
Central	7	63.6%
On treatment for Hypothyroid		
Yes	3	27.3%
No	8	72.7%
Associated endocrinopathies		
Hypogonadism	3	27.3%
Hypocortisolism	1	9.1%
Diabetes mellitus and Hypogonadism	1	9.1%

Table V: Hypothyroidism rate among TDT patients reported in various centres

Centre/country	Hospital Pulau Pinang	Indonesia[28]	India[26]	Malaysia (UMMC)[11]	Greece[5]	Pakistan[27]	Iran[8]
Age (years)	29.7±6.9*	10.8±4.1*	9.0±4.6*	13.7 (2.5-25.3)**	23.6±6.8*	7.6±2.5*	21.0±7.8*
Hypothyroid (Total)	21.6%	26.8%	15.6%	16.5%	16.5%	25.7%	14.6%
Primary	2.0%	1.7%	0.0%	3.7%	4.0%	1.4%	1.5%
Subclinical	5.9%	25.1%	10.0%	13.4%	12.5%	24.3%	10.8%
Central	13.7%	0.0%	5.6%	1.2%	0.0%	0.0%	2.3%

*Mean±SD
**Median (Range)

Ethical approval and informed consent for this study was approved by the Medical Research and Ethics Committee, Malaysia (approval NMRR no. NMRR-20-968-53107).

Hypothyroidism was defined according to TSH and FT4, or based on the history of treatment with levothyroxine for previously diagnosed hypothyroidism. Thyroid dysfunction was defined as follows: primary hypothyroidism (FT4 <12pmol/L with TSH >5mIU/L), subclinical hypothyroidism (normal FT4 with TSH >5mIU/L), and central hypothyroidism (FT4 is <12pmol/l with low or normal TSH).[10] Thyroid function test was routinely performed on all TDT patients at six monthly intervals. At least two consistent abnormal measurements of thyroid hormones were taken into account for the newly diagnosed hypothyroid cases, in order to reduce the possibility of misdiagnosing hypothyroidism due to individual circadian variation of secretion of thyroid hormone.[22,23]
Data were analysed using Statistical Package for Social Sciences (SPSS) software version 26, independent t-test and Fisher's exact test. Numerical data were presented as mean±standard deviation (SD). A p-value <0.05 was considered significant.

RESULT

This study surveyed all 51 TDT patients receiving regular transfusion under Haematology Unit day-care, in Hospital Pulau Pinang, 24 (47%) were males and 27 (53%) females. Most of the patients were Malays (27, 53%) followed with Chinese (23, 45%) and Indonesian (1, 2%). Their mean age at the time of study was 29.7±6.9 years. Beta thalassemia major and HbE beta thalassaemia accounted for 35 (68.8%) and 14 (27.5%) TDT patients respectively, while the remaining two (3.9%) were HbH Constant Spring (Table I).

As shown in Table II, eleven (21.6%) of the 51 patients, with a median age of 30.6±6.2 years, had hypothyroidism. Out of these 11 patients, seven (63.6%) had central hypothyroidism, three (27.3%) had subclinical hypothyroidism, while another (9.1%) had primary hypothyroidism. Mean age for TDT patients with hypothyroidism was 28±6years, appeared to be younger as compared to 30±7years for the euthyroidism group. There was no statistical relationship between the two groups (95% Confidence Interval, 95%CI: -6.8, 2.8).

The relationship between ferritin level, iron chelation therapy, splenectomy and hypothyroidism were analysed. The mean ferritin level was 3902±2531ng/ml for the hypothyroidism group. A higher ferritin level trend of was observed among TDT patients with hypothyroidism, compared to the euthyroid group who had mean ferritin level of 3012±3047ng/ml, however the relationship was not statistically significant (95%CI: -250.8, 5340).

The iron chelation regimen was divided into monotherapy or combination therapy. The monotherapy regimen included either Desferrioxamine (DFO), Deferiprone (DFP) or Deferasirox (DFX); combination therapy on the other hand consisted of DFO plus DFP, DFO plus DFX or DFP plus DFX. As shown in Table III, for TDT patients with normal thyroid function, 15 (37.5%) were on monotherapy, another 25 (62.5%) were on combination therapy. Meanwhile, six (54.5%) patients were on monotherapy, and another five (45.5%) were on combination therapy under the group with hypothyroidism. Data analysis failed to show statistical relationship between iron chelation therapy and hypothyroidism (p=0.327).

Out of the 40 TDT patients who were euthyroid, 14 (35%) had history of splenectomy; only two (18.2%) of the hypothyroidism group were splenectomised. Statistically, there was no significant relationship between splenectomy and hypothyroidism (p=0.466). The prevalence of other endocrine complications was also reviewed among TDT patients with hypothyroidism; three (27.3%) of them had hypogonadism, one (9.1%) had hypocortisolism and another (9.1%) had concomitant diabetes mellitus and hypogonadism (Table IV).

DISCUSSION

Combination of blood transfusion and iron chelation therapy significantly improve the life expectancy of TDT patients. Iron overload among polytransfused thalassaemic patients is associated with multiple endocrine complications, including hypogonadism, short stature, osteoporosis, adrenal insufficiency, hypoparathyroidism, hypothyroidism, diabetes mellitus and impaired glucose tolerance.[16,24] Differences in the age of first exposure to iron chelation therapy, the degree and type of chelation, the haemoglobin level attained before blood transfusion, and the continuing improvement in survival in well-chelated patients are among the factors that complicate the ascertainment of prevalence of endocrine complications.[17] Thus, wide ranges of hypothyroidism prevalence among TDT patients have been reported, from 4-29 % among different centers.[3-8] Routine screening for hypothyroidism among TDT patients is essential, as the classical clinical signs of hypothyroidism in TDT patients are subtle, non-specific and are frequently attributed to anaemia or associated diseases, especially for mild cases.[25]

Eleven (21.6%) TDT patients were reported to have hypothyroidism. Our centre reported 7 (13.7%) of central hypothyroidism, which is higher compared to most of the other centres in Indonesia (0%), India (5.6%), Greece (0%), Pakistan (0%) and Iran (2.3%) and another centre in Malaysia (1.2%), as shown in Table V. In fact, most of the other centres reported higher incidence of subclinical hypothyroidism.[6,8,11,26-28] High prevalence of central hypothyroidism among TDT patients was also reported by Soliman et al.,[9] which is linked to slow progressive dysfunction of the thyroid gland with pituitary insensitivity to the low FT4 level. Pituitary hemosiderosis significantly correlates with serum ferritin level.[31] The anterior pituitary gland is particularly sensitive to iron deposition and free radical oxidative stresses. Even a modest amount of iron deposition within the anterior pituitary can interfere with its function.[31-33] In terms of screening for hypothyroidism, most of the studies and laboratory guidelines recommend TSH as sole initial screening test for thyroid dysfunction, to reduce unnecessary burden on patients and health care systems from economic point of view.[17,18,21] However, normal TSH does not reflect euthyroidism in pituitary disease, including central hypothyroidism among TDT patients.[21] Thus, both FT4 and TSH are necessary in screening for hypothyroidism among TDT patients, as recommended in WHO guidelines for TDT.[16]

Advanced age is reported to be associated with hypothyroidism among TDT patients.[3,10,28] This can be linked to defective hypothalamic-pituitary-thyroid axis in the secretion of thyroid hormones over time. Relationship between hypothyroidism and serum ferritin level varies among different studies, Al-Hader et al., and Chirico et al., reported high prevalence of hypothyroidism correlates with high ferritin level.[14,15] Similar to other studies, this study shows no statistical relationship between ferritin level and hypothyroidism[3,10,28] One of the limitations in our study is that we did not look into the hypothyroidism risk factors in the past, including age of first exposure to iron chelation therapy, pre-transfusion haemoglobin level attained, previous intensity and type of iron chelation.

Previous studies have shown that good compliance to iron chelation therapy reduces prevalence of endocrinopaties, including hypothyroidism.[7,34] Our study shows no correlation between hypothyroidism and mono or combination iron chelation therapy (p=0.327), which was a similar finding to a study by Bazi et al.[3] Splenectomy was identified as one of the risk factors for hypothyroidism among TDT patients in some studies.[3,34] Belhoul et al., reported higher serum ferritin level among TDT patients with splenectomy history.[35] The finding may be related to the role of intact spleen as reservoir of excess iron as well as scavenging effect on iron free fractions, including non-transferrin bound iron.[10,35] In this study, there was no statistical relationship between prevalence of hypothyroidism and age, serum ferritin, iron chelation therapy as well as splenectomy history. This is probably related to our small sample size, which is the limitation of this study.

Other endocrinopathies were also observed among the TDT patients with hypothyroidism in this study, including three (27.3%) cases of hypogonadism, one (9.1%) case of hypocortisolism and another one (9.1%) with co-existence of diabetes mellitus and hypogonadism. These associated endocrinopathies were reported in other studies as well, which is related to iron overload from regular packed cells transfusions.[3,4,5,34]

CONCLUSION

High prevalence of hypothyroidism with predominance central hypothyroidism was reported in our study. Early detection and treatment of hypothyroidism in polytransfused thalassaemic patients is crucial as part of the holistic management of the disease. Dependence on TSH as the sole initial screening of thyroid dysfunction might miss out central hypothyroidism cases. Hence, measurement of both TSH and FT4 is recommended during the initial screening for thyroid dysfunction among patient with TDT.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Assessment of Implementation of Pre-pregnancy care services in Negeri Sembilan, Malaysia

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ABSTRACT

Introduction: Pre-pregnancy care (PPC) is an established health care program for women of reproductive age that has been widely implemented globally. The implementation of these services varies between countries based on the guidelines advocated. Thus, a standard level of assessment on measuring the performance of the service was difficult. This study aimed to measure the status of implementation PPC services among health workers using the transtheoretical model framework.

Methods: A cross-sectional study was conducted among 445 healthcare workers using a validated questionnaire based on local PPC guideline published by the Ministry of Health Malaysia (MOH).

Results: The results showed that many respondents were in the implementation action stage (57%), followed by the maintenance stage (20%), preparation stage (19%), contemplation stage (4%) and pre-contemplation stage (<1%). Further categorisation showed that only 43% of the respondents are successfully implementing PPC according to the standard of MOH. Clinics lead by the Family Medicine Specialist (Adjusted Odds Ratio, AOR 2.845; 95% Confidence Interval, 95%CI: 1.839, 4.40), daily usage of tele-primary care system (TPC) in the clinic (AOR 1.563; 95%CI: 1.019, 2.397), and attended TPC training (AOR 3.358; 95%CI: 2.221, 5.075) were significantly determining the success of PPC implementation.

Conclusion: The emphasis on motivation and rewards among the healthcare workers, provision of good internet connection at health clinics and developing a comprehensive model of PPC training targeting the specific healthcare workers are mandatory to enhance the PPC services implementation.

KEYWORDS:
Pregnancy, healthcare, telehealth, competencies, transtheoretical

INTRODUCTION

Pre-pregnancy care (PPC) is a health care programme that utilises the concept of disease prevention management targeting women of reproductive age to achieve a good health status before they embark on pregnancy. Various organisations and countries have issued PPC services guidelines for global and local use, such as the World Health Organization, Australia, and? New Zealand, Canada, the United States of America, Scotland, India, and China.[1-7] However, the content of the guidelines and implementation methods vary according to the country.[8,9] PPC was introduced to Malaysia in 2002 and has expanded throughout its public health facilities, clinics, and hospitals by 2012. The Ministry of Health Malaysia (MOH) begin developing guidelines and standard operating procedure protocol for these services since 2011.[10] Currently, these services are freely available whereby the patients were recruited from the various entry points, and further health screening was done before specific counselling treatments were provided to prepare them for their subsequent pregnancies. In line with the improvement of services, the PPC guidelines in the first section of the Perinatal Care Manual have undergone several revisions. The latest policies used are in the third edition published in 2013, and it has been used as the standard reference for healthcare workers in Malaysia.[11]

The parameter to evaluate the implementation of the PPC services should be incorporated as a process indicator since the beginning of the programme. Although PPC was globally practiced, studies on the assessment of PPC services are still insufficient.[12,13] Comparative analysis of the PPC guideline available showed that evaluating the implementation of the services is not being emphasised.[14] Factors such as the difference in service policies and procedures make the evaluation process challenging to be implemented.[15,16] A different method of PPC delivery used at the clinic level also contributes to the difficulty of the evaluation process. There are no specific procedures for measuring the implemented services as the guidelines provided do not include measurement components or indicators in performing these services. The Malaysian government had difficulty implementing assessments due to complexity among the programme user and not having appropriate tools to assist the process.[17,18] The absence of guidelines to evaluate the performance of this service not only occurs in Malaysia but also reported in other countries.[13,19]

A behavioural model called the Transtheoretical Model (TTM) was developed in the last three decades.[20] TTM explains that behaviour change is a different process that everyone goes through, leading to a particular stage of change. Therefore, the TTM model used as a domain in this study, and the stage of change is the domain used to

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represent the status of the implementation of PPC services. The stage of change was constructed based on three main domains: change, self-efficacy, and decision-making.[21] Studies showing interventions using the TTM used previously in smoking cessation intervention, controlling obesity, physical activity intervention, chronic illness monitoring and drug addiction recovery.[22-26] TTM also measures six individual's stages of change during program implementation. However, we only used five stages of change for this study as the PPC services should be sustained in the system and not end to the termination stage.[27]

As there are various issues and differences in PPC programmes, the implementation of this service needs to be reviewed as no specific indicators are specified in the reference manual. Moreover, different effectiveness evaluations done between facilities cause the actual level of achievement to be questioned. Therefore, this study aimed to measure status of implementation of the PPC services among health workers using the TTM to improve service quality.

MATERIALS AND METHODS

Design and Data Collection

The is a cross-sectional study conducted from January to June 2019 involving 445 healthcare workers (HCW). The sample frame was HCW from the categories of doctors, nurses, and assistant medical officers engaged in PPC services in public health clinics. The list of members involved was obtained from the State and District Health Offices according to the type of clinic and position. Two health districts in Negeri Sembilan were randomly selected. All clinics in these two districts (16 clinics) were included. The HCW from the three categories were universally included in the study. The inclusion criteria are that the HCW who are permanent staff working at the selected public health clinics for at least six months and can communicate either in Malay or English. The exclusion criteria are that HCW who worked as a replacement staff in the chosen clinic, doing practical training or on maternity leave or on prolonged medical leave of >1-month duration. Implementation status of PPC services is the dependent variable of this study, and age, gender, education, occupational type, working experience, active PPC service providers, head of the clinic, clinic operation system, frequency of PPC services delivery, perception, knowledge, attitude, decisional balance, self-efficacy, the process of change and PPC training are the independent variables.

Study Instrument

Data was collected using a validated structured self-administered instrument named the Pre-pregnancy care services questionnaire (PPCQuest). Total items in the questionnaire are 59, divided into six sections; background (10-item), perception on PPC (4-item), knowledge on PPC (5-item), attitude on PPC (2-item), PPC training (7-item) and TTM (stage of change, 18-item, process of change, 5-item, self-efficacy, 5-item, and decisional balance, 3-item). The composite content validity index (CVI) was 95% and was tested among 200 samples with the Cronbach alpha range from 0.749 to 0.928 for the exploratory factor analysis (EFA). The reliability measurements in the confirmatory factor analysis (CFA) where composite reliability (CR) values range between 0.606 and 0.915. The average variance extracted (AVE) value range between 0.501 and 0.754. There are 18 items in the domain stage of change (SOC) comprising four subdomains named service delivery (6-item), clinic set up (5-item), standard operating procedure (SOP) (5-item) and agency cooperation (2-item). Each item uses a range of scores between 1 and 5, giving a minimum score of 18 and a maximum of 90. Based on the cumulative scores obtained, the HCWs were divided into five groups. The groups were categorised as pre-contemplation, contemplation, preparation, action, and maintenance. The pre-contemplation stage is defined as HCW who never performed PPC services with cumulative scores range from 1 to 18. The HCW who intended to implement the PPC services and scores between 19 to 36 was grouped as the contemplation stage. HCW who scores from 37 to 54 were categorised as a preparation group. The action stage group was defined as HCW, who practiced the PPC services and scored between 55 and 72. The maintenance stage group was defined as HCW who implement the PPC services into their daily work with a cumulative score of 73 to 90.

The HCWs were categorised into two groups based on items recorded in the stage of change domain. First, an item with a scale of 1 (never) and 2 (will consider) encoded to 0. Second, items with scale 3 (in preparation), 4 (in practice), and 5 (routine) coded to 1. This coding was decided based on Prochaska's suggestion that the respondent in the category of being prepared (equivalent to score 3) needs to be in an action-oriented group (Prochaska et al., 2015). For the present study, action-oriented groups were defined as respondents who successfully implemented PPC services. Therefore, based on the new code for items within the change domain, the minimum score for all 18 items is 0, and the maximum score is 18.

Percentages converted from the cumulative scores made by re-categorisation of HCWs to the successful implementation group (score >80) and unsuccessful implementation groups (score ≤80). The cut-off score of 80 was chosen as advised by the ten expert panels. The expert panel consisted of Family Medicine Specialist, a Public Health Specialist, a medical officer in charge of the clinic, a medical officer, matrons, nurses, assistant medical officer, and community nurse.

Data Analysis

Data was entered and cleaned using the SPSS version 21. First, bivariate analysis was done using the Chi-square test and simple logistic regression resulting in the p-value and the crude odds ratio (COR) with 95% confidence intervals (95%CI). Subsequently, multivariate analysis was done by performing multiple logistic regression analysis to determine adjusted odds ratio (AOR). Variables from simple logistic regression with a value of $p<0.20$ were included in the multivariate logistic regression analysis.

RESULTS

A total of 445 HCWs aged between 22 and 59 years old participated in the study, with a response rate of 92.7%. About 84% of the participants were women, and 77% had either a diploma or degree. Half were from the nursing

Table I: Sociodemographic characteristic of study respondents (n=445)

Characteristic	n (%)	Mean (S.D)	Min, Max
Age (years)		36 (7.41)	22, 59
Gender			
Male	71 (16.0)		
Female	374 (84.0)		
Education			
Secondary school	101 (22.7)		
Diploma	168 (37.7)		
Degree/master	176 (39.6)		
Occupation			
Family Medicine Specialist	8 (1.8)		
Medical Officer	161 (36.2)		
Matrons	21 (4.7)		
Nurses	111 (24.9)		
Community Health Nurses	101 (22.7)		
Assistant medical officer	43 (9.7)		
Working experience(years)		8 (6.47)	0.5, 39
< 2 years	94 (21)		
2 to 5 years	107 (24)		
> 5 years	244 (55)		
Head of the clinic			
Medical officer	193 (43.4)		
Family Medicine Specialist	252 (56.6)		
Clinic Operation system			
Manual	235 (52.8)		
Tele-primary care (TPC)	210 (47.2)		
Active PPC service			
None	151 (33.9)		
Present	294 (66.1)		
Frequency of PPC services delivery			
More than once a week	84 (18.9)		
Once a week	82 (18.4)		
Once a month	180 (40.4)		
Less than once a month	99 (22.2)		

Table II: Description of HCW based on the stages of change for the Implementation of PPC Services

Factors	Stage of Change n (%)				
	Pre-contemplation n (%)	Contemplation n (%)	Preparation n (%)	Action n (%)	Maintenance n (%)
Age					
<45 years (n=379)	1 (0.2)	15 (3.4)	76 (17.1)	219 (49.2)	68 (15.3)
≥45 years (n=66)	1 (0.2)	2 (0.4)	8 (1.8)	33 (7.4)	22 (4.9)
Gender					
Male (n=71)	1 (0.2)	10 (2.2)	11 (2.5)	38 (8.5)	11 (2.5)
Female(n=374)	1 (0.2)	7 (1.6)	73 (16.4)	214 (48.1)	79 (17.8)
Education					
Secondary level (n=101)	0 (0.0)	2 (0.4)	20 (4.5)	59 (13.3)	20 (4.5)
Tertiary level(n=344)	2 (0.4)	15 (3.4)	64 (14.4)	193 (43.4)	70 (15.7)
Service group					
Support (n=255)	2 (0.4)	12 (2.7)	38 (8.5)	141 (31.7)	62 (13.9)
Management and professional (n=190)	0 (0.0)	5 (1.1)	46 (10.3)	111 (24.9)	28 (6.3)
Working experience					
< 5 year (n=201)	0 (0.0)	8 (1.8)	46 (10.3)	117 (26.3)	30 (6.7)
> 5 year (n=244)	2 (0.4)	9 (2.0)	38 (8.5)	135 (30.3)	60 (13.5)

category (52.3%), while doctors were 44.2%, and only 9.7% hold the position as an assistant medical officer. The length of the service period was between 6 months and 39 years. However, most of them have served in their current place for more than five years (55%). More than half (56.6%) of the HCW works in health clinics led by Family Medicine Specialists (FMS).

Slightly more than half (52.8%) used manual services. The rest used the Tele primary care system (TPC), a type of digital health services. Our study found that 66.1% of the respondents are working in health clinics that actively provide PPC services. About 37% of delivered the PPC services for a minimum of at least once a week. Table I shows the sociodemographic characteristics of study respondents.

Assessment of the stage of change among the HCW for implementing PPC services was presented in Table II. Most respondents were in the action stage (57%), followed by the maintenance stage (20%), preparation stage (19%),

Table III: Statistical analysis of the PPC services implementation status

Factors	Implementation Status			
	Not Successful n (%)	Successful n (%)	X2	P-value
Age				
< 45 years	224 (88)	155 (81)	4.274	0.039
≥ 45years	30 (12)	36 (19)		
Gender				
Men	39 (15)	32 (17)	0.159	0.69
Women	215 (85)	159 (83)		
Education				
Secondary level	60 (24)	41 (22)	0.289	0.591
Tertiary level	194 (76)	150 (79)		
Service Group				
Support group	141 (56)	114 (60)	0.776	0.378
Management & professional	113 (45)	77 (40)		
Working experience				
< 5 years	119 (47)	82 (43)	0.676	0.411
≥ 5 years	135 (53)	109 (57)		
Active PPC service presenters				
None	87 (34)	64 (34)	0.270	0.87
Present	167 (66)	127 (67)		
Head of the clinic				
Medical officer	141 (56)	52 (27)	35.517	<0.001
Family Medicine Specialist	113 (46)	119 (73)		
Clinic Operation system				
Manual	151 (59)	84 (44)	10.469	0.001
Tele-primary care (TPC)	103 (41)	107 (56)		
Frequency of PPC services delivery				
less than once in a month	165 (65)	114 (60)	1.297	0.255
more than once in a month	89 (35)	77 (40)		
Perception				
poor	147 (58)	80 (42)	11.150	0.001
good	107 (42)	111 (58)		
Knowledge				
low level	151 (59)	102 (53)	1.378	0.202
high level	103 (41)	89 (47)		
Attitude				
poor	145 (57)	84 (44)	7.499	0.006
good	109 (43)	107 (56)		
Decisional balance				
poor	146 (58)	94 (49)	2.998	0.083
good	108 (42)	97 (51)		
Self-efficacy				
poor	146 (58)	107 (56)	0.095	0.758
good	108 (43)	84 (44)		
Process of change				
poor	141 (56)	91 (48)	2.704	0.100
good	113 (45)	100 (52)		
PPC Training				
poor	168 (66)	71 (37)	36.798	<0.001
good	86 (34)	120 (63)		
TOTAL	**254(100)**	**191(100)**		

contemplation stage (4%) and pre-contemplation stage (<1%). The HCW who achieved action stage and above were those aged less than 45 years old, received education up to the tertiary level (diploma and degree), and worked as a support group (health matrons, nurses, and assistant medical officer) with working experience of more than five years. We further categorised the HCWs into two groups. The result shows that 43% of the HCWs successfully implemented the PPC group as tabulated in Table III. Bivariate analysis from the Chi-square shows the relationship between the independent variable and the dependent variables. The age factors (p=0.039), HCW's perception (p=0.001) and HCW's attitude (p=0.006) showed significant relationships with the implementation status of PPC services. In terms of organisational behaviour, the type of the clinic's leader (p<0.001), the clinic mode operation system (p=0.001) and the training on PPC services (p<0.001) are significant factors found associated with the implementation of PPC services.

Table IV shows that the clinic led by the Family Medicine Specialist (AOR 2.845; 95%CI: 1.839, 4.40), daily usage of TPC system in the clinic (AOR 1.563; 95%CI: 1.019, 2.397) and attended PPC training (AOR 3.358; 95%CI: 2.221, 5.075) were significantly determining the success of PPC implementation.

Table IV: Simple and multiple logistic regression analysis on the PPC services implementation status

Factors	Simple Logistic		Regression Multiple Logistic Regression		
	Crude OR (95%CI)	P-value	Adjusted OR (95%CI)	Wald	P-value
Clinic head					
Medical officer	1	<0.001	1	22.057	<0.001
Family Medicine Specialist	3.335 (2.228, 4.993)		2.845 (1.839,4.40)		
Operation system					
Manual	1	0.001	1	4.182	0.041
TPC system	1.867 (1.277, 2.731)		1.563 (1.019, 2.397)		
PPC Training					
Poor PPC training	1	<0.001	1	33.026	<0.001
attended a good PPC training	3.302 (2.231, 4.886)		3.358 (2.221, 5.075)		
Age					
<45 years	1	0.040	-	-	-
≥45 years	1.734 (1.025, 2.935)		-		
Perception of PPC services					
Low perception	1	0.001	-	-	-
Good perception	1.906 (1.303, 2.788)		-		
Attitude towards PPC service					
Poor Attitude	1	0.006	-	-	-
				-	-
Good Attitude	1.695 (1.16, 2.475)		-		

DISCUSSION

The study found that PPC implementation among the HCWs can be assessed using the validated PPCQuest questionnaire. They were categorised into five groups as action stage (57%), followed by maintenance stage (20%), preparation stage (19%), contemplation stage (4%) and pre-contemplation stage (<1%). Successful implementation of PPC was noted highest among the nursing staff (84%), who act as the primary gatekeeper of PPC services. On the other hand, the percentage of successful PPC implementation was reported lower among the doctors (71%) and assistant medical officers (63%).

No similar studies are available for comparison. In this study, four subdomains were studied under the stage of change; (1) PPC service provision, (2) standard operating scope, (3) clinic provision and (4) inter-agency cooperation. The PPC services include pre-pregnancy risk factor identification activities, risk factor screening activities, and service monitoring activities. This study focuses on folic acid supplementation, optimal sugar level control, screening for complications in chronic patients, counselling and contraceptive pill administration, and referral to pre-pregnancy clinics in the subdomain standard operating scope. Subdomain clinic preparation emphasises infrastructure factors, service schedule, task rotation, service flow chart and service target group. Finally, outreach activities and cooperation with other ministries are focused on subdomain agency cooperation.

The present study has successfully measured the implementation of PPC services from the stage of clinic preparation to service implementation with collaboration planning involving other agencies to ensure service sustainability. In addition, the objectives of the study have been achieved using the stage of change in the TTM model, which is different from measures done earlier in other programs.

A study conducted in Ethiopia recorded only 31% demonstrated a good level of PPC implementation.[28] Another study in Iran described PPC implementation findings into three stages: low, moderate, and adequate.[29] They have reported that 25% of respondents were in the middle and 64.7% at a low PPC implementation level. However, that study did not record any prevalence for adequately PPC implementation. Lower prevalence rates were recorded in Ethiopia, Africa, with the prevalence rate for successful PPC implementation was 15.3%.[16] Having inadequacy of guidelines and policy to adhere by health personnel has shown relationships with the PPC implementation stage. Our study measured the prevalence rate of successful implementation of PPC services based on adherence to the MOH manual.[11]

Three factors determined the success of the PPC implementation in our study sites: clinics led by the family medicine specialist (FMS), usage of the TPC system in the management of clinic services, and HCW who have attended PPC service training. FMS have been recognised as the primary health care coordinator and primarily deliver services to complicated cases. Clinics led by FMS have an advantage in terms of the number of health personnel and equipment over clinics led by medical officers.[30] The length of the service period helps them plan and monitor various types of health services and implement training or conduct continuous medical education (CME), including PPC.[31] Having a TPC system in the clinic helps in the registration process, documentation of client databases and accessibility by other health clinics for continuity of care. TPC was first developed in Negeri Sembilan in 2014 and fully utilised by

the clinics in the district of Seremban in 2017.[32] TPC system were able to identify unscreened and dropped out PPC clients as the system using the real-time data management. The effectiveness of this system has been reported elsewhere.[33] Continuous support from superiors is needed to boost staff morale to support and ensure full utilisation of TPC.[34]

Proper PPC training is an investment to ensure the development, consolidation, and sustainability of the PPC health programmes. This study found that 46.3% of HCW at the action stage and 90% of HCW at the maintenance stage received the PPC training. Another study done in 2018 in rural India demonstrated that services performances could be increased by regular comprehensive and continuous training.[35]

STRENGTH AND LIMITATION OF THE STUDY

This strength of this study is forming a validated instrument (PPCQuest) for measuring PPC implementation based on existing guidelines used for the services. Therefore, the PPCQuest tool can better measure the performance of the PPC services and is suitable as a quality practice indicator if used for periodic monitoring. Clinic administrative provision, PPC implementation and service delivery, involvement of other agencies, and activities implemented were essential items used in the measurement. Therefore, PPCQuest is comprehensively reflected in the PPC services' implementation of PPC services in Malaysia. The study has its limitations in relation to the selection of the study site. Variation in the PPC service implementation in other areas of Malaysia may depend on human resources and primary health care types. The type of PHC facility has been used as a factor to be measured in the assessment.

CONCLUSION

The transtheoretical model framework used in developing the PPCQuest instrument is shown to outline a comprehensive approach in measuring the implementation of PPC services among the HCW in primary healthcare clinics. In clinics led by FMS, good network connecting systems between clinics and data management, and comprehensive periodic PPC training targeting specific healthcare workers are mandatory to enhance the services.

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ETHICAL CONSIDERATION

This study obtained approval from the Research Ethics Committee of the National University of Malaysia (FF-2017-396), Medical Research and Ethics Committee Ministry of Health Malaysia (NMRR-16-2800-33618) and permission to conduct the study in the State Health Director of Negeri Sembilan.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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A retrospective audit of endoscopic duodenal biopsies to uncover undetected Coeliac disease in Malaysian patients

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ABSTRACT

Background: Coeliac disease, an autoimmune enteropathy related to gluten sensitivity was hitherto thought to be rare in Asia. Recent data however suggests that Celiac disease may be under-diagnosed in Asia.

Objective: The aim of this audit was to determine the frequency of histological changes compatible with Coeliac disease among patients undergoing elective diagnostic oesaphago-gastro-duodenoscopy (OGDS) under the care of a single practitioner in a Malaysian hospital.

Materials and methods: The archived endoscopically obtained duodenal biopsy specimens of 241 consecutive Malaysian subjects undergoing elective diagnostic (OGDS) were reviewed by a pathologist blinded to the clinical data. Based on intra-epithelial lymphocyte counts, crypt hyperplasia and villous atrophy, each subject was assigned to one of the categories of the Modified Marsh classification for the histological diagnosis of Coeliac disease. The clinical charts of all subjects were reviewed by a single gastroenterologist blinded to the findings of the histological review.

Results: Of the 241 study subjects, 132 (54.8%) were females. There were 56 (23.2%) Malays, 90 (37.3%) Chinese, 88 (36.5%) Indians and seven (2.9%) from the other category. The median age of the study sample was 49 years (range 15-88 years). The OGDS was done as part of screening in 15(6.2%) subjects while in the remaining it was part of the investigation of a clinical problem. Based on histological findings, none of the subjects could be assigned to a modified Marsh class of >1. The prevalence of histological changes compatible with Coeliac disease in the study was 0% (binomial exact one-sided 97.5 % confidence interval 0-1.52%).

Conclusion: In conclusion, this audit provides no evidence that active Coeliac disease is significantly under-detected among symptomatic patients presenting for diagnostic OGDS. The possibility that a significant number may have potential coeliac disease cannot be excluded.

KEYWORDS:
Coeliac disease, prevalence, Malaysia

INTRODUCTION

Coeliac disease is an autoimmune enteropathy with systemic and gastrointestinal manifestations.[1] The primary mechanism is an immune mediated reaction to fractions of wheat protein in genetically predisposed individuals.[1] The condition is diagnosed on the basis of clinical features, serology and small intestinal biopsy. The condition has traditionally been thought to be rare in Asia and indeed that is the prevailing perception among gastroenterologists in Malaysia. Recent data however suggests that Coeliac disease may be under-diagnosed, and placed the global pooled prevalence of serologically determined and biopsy proven Coeliac disease in the general population at 1.4% and 0.7% respectively.[2] A recent seroprevalence study among healthy young adults in Malaysia determined the prevalence of Coeliac disease at 1.25%.[3] There has however been no published histological study on Coeliac disease in Malaysia. Our study essentially reports the results of an audit of all duodenal biopsies undertaken at diagnostic oesaphago-gastro-duodenoscopy (OGDS) by a single gastroenterologist in Pantai Hospital Kuala Lumpur (PHKL), Kuala Lumpur, Malaysia. The objective was to determine the prevalence of histological abnormalities compatible with Coeliac disease in the study sample with a view to test the hypothesis that Coeliac disease is under-diagnosed.

MATERIALS AND METHODS

It was the personal routine practice of the gastroenterologist in PHKL to take mucosal biopsies of the second part of the duodenum in all patients undergoing elective diagnostic oesophago-gastro-duodenoscopy. The rationale for this was that non-specific gastrointestinal symptoms are sometimes due to small intestinal mucosal disease and the availability of a biopsy eliminates the necessity for repeat endoscopy if small intestinal disease was considered a diagnostic possibility at a later stage in the clinical evaluation. Biopsies were not routinely taken if the endoscopy was undertaken as an emergency, if the indication was primarily therapeutic or if the patient was on anticoagulant or antiplatelet drugs. The archived histology slides of the duodenal biopsy specimens of 289 such patients who underwent diagnostic oesophago-gastro-duodenoscopy in 2019 were retrieved and re-examined by a single experienced pathologist who was blinded to the clinical data of the subjects. Two hundred and forty-one of these patients who were Malaysian nationals

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Table I: Frequency of symptoms and anaemia among study subjects.

Clinical feature	Frequency (%)
Abdominal pain, discomfort or dyspepsia.	180 (74.7)
Chronic diarrhoea.	20 (8.3)
Altered bowel pattern not attributable to a specific cause.	25 (10.4)
Symptoms fulfilling criteria for irritable bowel syndrome.	17 (7.1)
Weight loss.	23 (9.5)
Anaemia.	38 (15.8)
Chronic iron deficiency.	10(4.1)

and constituted the study subjects. The subjects were predominantly from in and around the city of Kuala Lumpur. None of the subjects had a prior diagnosis of Coeliac disease nor had any of the subject been given previous instructions to be on a gluten free diet. Endoscopic biopsies were taken using standard pinch biopsy forceps and stored in formalin overnight. The biopsy specimens were embedded in paraffin wax, microtomed and stained with haematoxylin and eosin. The biopsies were scrutinised methodically for intraepithelial lymphocytes (IEL) counts, crypt hyperplasia and villous atrophy. The clinical records were reviewed for details on demographic data, symptom profile and the eventual diagnoses in the study cohort. IEL counts were expressed as more than 30 per 100 enterocytes or less than or equal to 30 per 100 enterocytes. Based on the IEL counts, crypt hyperplasia and villous atrophy each subject was assigned to one of the categories of the Modified Marsh classification for the histological diagnosis of Coeliac disease.[4]

The binomial exact confidence interval for the prevalence of histological features compatible with Coeliac disease was determined using an online statistical calculator (sampsize.sourceforge.net © Phillipe Glaziou 2003-2005). This retrospective observational study was approved by the Hospital Research and Ethics committee.

RESULTS

Of the 241 study subjects, 132 (54.8%) were females. With regard to ethnicity, 56 (23.2%) were Malays, 90 (37.3%) were Chinese, 88 (36.5%) were Indians and seven (2.9%) were others. The median age of the study sample was 49 years (range 15-88 years). The symptom profile and frequency of anaemia in the group is shown in table I. In 6.2% (15/241) of the subjects, OGDS was undertaken as part of screening while in the rest OGDS was undertaken as part of the investigation of a clinical problem.

Only one patient had an IEL count of more than 30 per 100 enterocytes but crypt hyperplasia or villous atrophy was not observed in this particular case. This case was a fifteen-year-old female patient admitted with clinical features suggestive of acute enteritis coupled with a background of recurrent abdominal discomfort and an iron deficiency anaemia. The clinical features were not typical of Coeliac disease and she was negative for anti-tissue transglutaminase and anti-endomysial antibodies. All other patients had an IEL count of less than 30 per 100 enterocytes. One patient had mild villous atrophy with an IEL of less than 30 per 100 enterocytes. This particular patient had a definitive diagnosis of chemotherapy induced acute enterocolitis. Seven other patients had focal crypt hyperplasia with an IEL of less than 30 per 100 enterocytes and no villous atrophy. None of the subjects could therefore be assigned to a modified Marsh class of greater than one. The prevalence of histological changes compatible with Coeliac disease in the sample study was therefore 0% (binomial exact one-sided 97.5 % confidence interval 0-1.52%).

DISCUSSION

The key finding of the current study is that the prevalence of histological changes compatible with Coeliac disease in this sample of Malaysian subjects who underwent diagnostic OGDS for a variety of reasons was 0% with a Binomial exact one tailed 97.5% confidence interval of 0 to 1.52%. It is acknowledged at the outset that there are a number of limitations to this study. The sample size was limited and the demographic profile of the sample reflected the local referral pattern rather than being representative of the general Malaysian population. Furthermore, in the majority of subjects only one or two endoscopic biopsies was taken from the second part of the duodenum. Nonetheless when taken into context with other data, it does permit some insight into the likelihood of Coeliac disease being under-diagnosed locally. The study sample consisted of a symptomatic population that included patients with dyspepsia or abdominal discomfort, weight loss, chronic diarrhoea, and anaemia. Screening for Coeliac among patients with dyspepsia,[5] symptoms of irritable bowel syndrome[6] or iron deficiency anaemia[7] has shown prevalence rates higher than among control subjects. Furthermore, surveys of patients with established Coeliac disease have revealed that between 35 and 77% of patients have at least one gastrointestinal symptom including abdominal discomfort.[8,9] It is therefore not unreasonable to presume that the frequency of histologically defined Coeliac disease in a symptomatic population would be higher than in the general population. This makes the 0% prevalence rate of in the current study all the more significant. The rate in our study is lower than the rates of Coeliac disease reported in similar studies among selected and unselected patients undergoing OGDS and duodenal biopsy in a number of other countries including Canada (2.2%),[10] Romania (2.2%),[11] Northern Ireland (5%),[12] Spain (2.2%),[13] Australia (1.4%),[14] the US (1.8%)[15] and the Netherlands (1.0%).[16] Given the confidence interval of the observed prevalence in our study, it would seem that histologically proven Coeliac disease among our subjects is truly lower than similar studies from elsewhere in the world.

It cannot be discounted that the rate of Coeliac disease in our sample may have been underestimated because only 1-2 biopsies were taken in most subjects as opposed to the

minimum of four biopsies recommended to maximise the detection rate of Coeliac disease.[17] However this limitation was mitigated to some extent by the careful scrutiny for elevated counts of IEL during the histological audit; raised IEL being recognised as a sensitive albeit non-specific marker of Coeliac disease. To put this into perspective, the odds ratio of detecting an elevated IEL count when ≥4 biopsies are taken as opposed to fewer biopsies has been shown to be in the order of 1.24 (95% confidence interval, 95%CI: 1.09, 1.40).[17] Furthermore entirely normal findings have been reported to be unlikely in patients with Coeliac disease.[18] Clearly, larger multicentre prospective studies in which ≥4 duodenal biopsies are taken with concurrent serological testing would be optimum to establish the incidence of Coeliac disease unequivocally.

The limitations of our study notwithstanding, the results do not provide any evidence that Coeliac disease is significantly under-diagnosed at least PHKL. Indeed, the failure to detect any cases is compatible with the general clinical experience of most gastroenterologists in Malaysia who rarely encounter newly diagnosed cases of Coeliac disease among Malaysian subjects. However, the possibility that Coeliac disease is underdiagnosed even by gastroenterologists in Malaysia cannot be entirely excluded as duodenal biopsies and serological markers for Coeliac may be underutilised.

An important question that needs to be addressed is how our results can be reconciled with the relatively high Coeliac seroprevalence rate of 1.25% reported among young healthy Malaysian adults.[3] One explanation is that there may be a significant number of subjects with potential Coeliac in the Malaysian population who do not manifest either the clinical or histological features of Coeliac disease because of insufficient exposure to wheat in their diet. Potential Coeliac disease refers to the condition whereby the subject is seropositive for Coeliac antibodies and HLA DQ2 or DQ8 but does not have either the clinical features or histological features of Coeliac disease.[1] An insight into the possible cause of this discordance between the seroprevalence and histological rates of Coeliac disease can be gained by examining the results of the study by Ramakrishna et al., from India[19] who reported marked differences in the prevalence of Coeliac disease between the North and South of India despite no perceptible regional differences in genetic susceptibility to the condition. The difference in Coeliac disease between the North and South of India was attributed largely to differences in wheat consumption between the regions.[19]

It is also notable that in the recently reported Malaysian seroprevalence study there was no association between seropositivity and gastrointestinal symptoms.[3] The only symptom that was found to be associated with seropositivity was chronic fatigue. This is therefore concordant with the absence of histologically active Coeliac disease in our own cohort of patients with predominantly gastrointestinal symptoms. The implication of our findings taken in conjunction with the previous seroprevalence study is that active case finding of Coeliac disease in Malaysians may have to focus on patients with non-localising symptoms such as chronic fatigue.

In conclusion this audit of duodenal biopsies provides no evidence that active Coeliac disease is being significantly under detected in symptomatic patients presenting for diagnostic oesaphago-gastro-duodenoscopy.

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ORIGINAL ARTICLE

Development of a validated instrument on socio-cultural and religious influences during menstruation in Malaysia

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ABSTRACT

Introduction: Although menstruation is a physiological process, it is shrouded with socio-cultural and religious beliefs. Healthcare providers should be aware that these influences may affect how women perceive their menstrual disorders. The primary objective of this study was to develop a validated questionnaire measuring the sociocultural and religious beliefs during menstruation.

Methods: In the first stage, a preliminary list of items measuring socio-cultural and religious beliefs during menstruation was generated. In the second stage, exploratory factor analysis was performed. Finally, confirmatory factor analysis using reflective measurement model and structural equation modelling was performed using partial least squares. The practices of these beliefs were included as mediating effect. Biological symptoms of menstruation were added in as another factor.

Results: A total of 400 female students from the Universiti Malaysia Sarawak, Malaysia were recruited. A preliminary list of 22 items was first generated. From the confirmatory factor analysis, two factors were iteratively removed due to poor factor loadings. Four factors were retained, i.e., i) "religious beliefs"; ii) "unpleasant (or dirty) nature of menstruation"; iii) "personal restrictions (dietary and behavior)"; and iv) "restrictions of interactions with male gender". In structural equation modelling, only 2 factors, i.e., the practices of "personal restrictions (dietary and behavioural)" and "restriction of interactions with males" had significant negative impact on quality of life.

Conclusion: Menstruation should not be viewed purely from a biological lens as there are layers of sociocultural and religious beliefs surrounding it.

KEYWORDS:
Menstruation, socio-cultural belief, religious belief, quality of life

INTRODUCTION

Although menstruation is a physiological process, it is often coated with layers of socio-cultural and religious beliefs.[1,2] Compounding this issue is the pervasive stigma in many cultures that women are discouraged to discuss menstruation matters openly.[3] This is because menstruation is often perceived as an "embarrassing" issue that should be kept hidden and private.[3] This kind of social shroud can be particularly "thick" in an Asian society like Malaysia.[2]

According to Young and Bacdayan (1965),[4] menstrual sociocultural beliefs can largely be categorised into the following categories: i) the general belief that menstrual fluid is unpleasant, contaminating or even "dangerous"; ii) menstruating women may not have sexual intercourse or engaging in sexual activities; iii) personal restrictions imposed upon a menstruating woman such as food taboos, restriction of movement, talking, etc.; iv) restrictions imposed upon contact with men and things that belong to men, e.g., personal articles, weapons in ancient times, craft tools, religious emblems and shrines (where men are considered the guardians of these religious emblems); v) a menstruating woman may not cook for men; and vi) a menstruating woman should be confined to a restricted space such as menstrual huts for the duration of their periods.

Many studies (including Asian studies) have been conducted on the impact of the physiology of menstruation on a woman's quality of life.[1,5-7] However, as alluded by Lu,[1] menstruation impact is a multi-dimensional construct. Other dimensions that have not been conspicuously described are the socio-cultural and religious dimensions. In this regard, it is imperative for healthcare providers to be aware of the impact of these influences which may affect how women perceive their menstrual disorders as well as their health seeking behaviour particularly with regards to the alleviation of menstrual symptoms. Furthermore, by knowing these influences, healthcare providers, can play a pivotal role in helping women to destigmatize and to develop a more positive attitude toward menstruation.[8]

The primary objective of this study was to develop and validate a questionnaire measuring the sociocultural and religious beliefs during menstruation. The secondary objective was to evaluate the influences of these sociocultural and religious beliefs and practices on female university students' quality of life.

MATERIALS AND METHODS

Participants

Female medical and economic students from Universiti Malaysia Sarawak (UNIMAS), Malaysia were recruited voluntarily for this study. Sample size was estimated using

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the population-based sampling method by Krejcie and Morgan.[9] Based on the total number of approximately 500 female medical students from Year 1 to Year 5 (with confidence interval of 95% and the margin of error 0.05), the estimated sample size for female medical students was 210. Based on the total number of approximately 400 female economic students from Year 1 to Year 3 (with 95% confidence interval and the margin of error 0.05), the estimated sample size for female economic students was approximately 190.

Materials

Exploratory factor analysis (EFA) was performed using Statistical Package for the Social Sciences (SPSS) statistical software with principal axis factoring as the extraction method. Partial least squares structural equation modelling (PLS-SEM) using the SMART-PLS software was performed to measure the impact of various sociocultural and religious factors as well as common biological symptoms on quality of life (QoL) during menstruation. The list of common biological symptoms during menstruation was adapted from a previous study by Wong and Khoo.[6] The validated Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (also known as Q-LES-Q-SF) by Endicott et al.[10] was adapted to measure quality of life. Q-LES-Q-SF had been similarly used before to measure the impact of menstrual pain[11] and the impact of pre-menstrual related disorders on quality of life. This instrument had also been shown to have good internal consistency and reliability.[12]

Procedures

Stage 1: Generation of preliminary list of items using Modified Delphi Technique

Adopting the classification by Young and Bacdayan4 described above as our conceptual framework, personal communications with female friends and family members were first conducted by authors KEP, AKH, NZ and NALY to identify common sociocultural and religious beliefs and practices during menstruation in our local communities. In addition, literature search was also conducted using keywords such as "menstruation", "menstruating", "menstrual", etc. to skim for information in academic journals, webpages, blogs, etc. From this initial search, a preliminary list of socio-cultural and religious beliefs during menstruation among the various ethnic groups in Malaysia were listed and categorized according to the categories described by Young and Bacdayan.[4]

Following that, opinions and suggestions were sought from several female lecturers in UNIMAS to validate and further refine our preliminary list using modified Delphi technique. Modified Delphi technique is a structured iterative process aimed to obtain consensus from individuals through a series of communication until agreement is reached.[13,14] The lecturers who participated in validation process consists of different ethnicities. They were asked to comment on the representativeness of the preliminary list factors to measure common sociocultural and religious beliefs during menstruation. Based on the inputs, the list was further refined and some additional items were also added. A cut-off point of 70% agreement was set as the minimum level for an item to be included in the edited list.[13]

Stage 2: Exploratory Factor Analysis (EFA)

A preliminary set of questionnaires was developed based on the list generated in Stage 1. In this stage, 100 female medical economic students were asked to rate their agreement for each item using a 5-point-Likert scale ("1 = strongly disagree" to "5 = strongly agree. For EFA, construct validity was determined using principal axis factoring as the extraction method using the SPSS software. An initial run of factor analysis was performed in order to determine the number of factors to be extracted. Factors with eigenvalues >1.0 would be retained.

Once the number of factors was determined, repeated runs of factor analysis were then performed to determine the factor loadings of the items as well as to identify problematic items that may need to be removed. Varimax rotation was used with a cut-off factor loading value of 0.4 as the criteria to determine whether an item was to be removed or not.[15] Pattern coefficient values of less than 0.5 were suppressed. The communality value, which indicates convergent validity of the items, was set at 0.25. Finally, the Cronbach's alpha coefficients were then checked to evaluate the degree of internal consistency of the items in each construct or factor. A cut-off point of Cronbach's alpha >0.6 was set as the criteria of a satisfactory degree of internal consistency.[16] The questionnaire was revised based on the EFA results.

Stage 3 Confirmatory Factor Analysis (CFA) and Structural Equation Modelling

CFA was then performed on the revised questionnaire. In this stage, another 300 females medical and economic students were asked to rate their agreement for each item using a 5-point-Likert scale, "1 = strongly disagree" to "5 = strongly agree". Reflective measurement model was performed using partial least square (PLS) method in SMART-PLS software. For internal consistency of the items, three parameters were analysed, i.e., i) Cronbach alpha; ii) composite reliability (CR) index; and iii) the rho A (ρA) coefficient (also known as Dijkstra Henseler's rho).[17,18] For convergent validity, the factor loadings of all items were obtained, as well as the Average Variance Extracted (AVE) values for each factor or construct. AVE refers to the grand mean value of the squared loadings of all items associated with a factor. AVE of >0.5 is generally acceptable for an item to be included even if its loading is between 0.4 and 0.7.[15] Factor loading of >0.7 was considered as acceptable, whereas factor loading of <0.4 was deleted. For factor loading with values between 0.4 and 0.7, the AVE would then be used to determine whether the item should be accepted. For discriminant validity, Fornell and Larcker criterion,[19] cross loadings of items as well as the Heterotrait-Monotrait ratio of correlations (HTMT) proposed by Henseler et al.[20] were obtained. All these measurements were generated from the SMART-PLS software.

Structural equation modelling was then performed to evaluate the influences of these various sociocultural and religious beliefs and practices on the students' quality of life. In this regard, the practices of these various beliefs were considered as the mediating effect on the quality of life (as measured using Q-LES-Q-SF). The reason to include practices of these beliefs as mediating effect is because beliefs without practices are unlikely to affect their quality of life.

Table I: Final version of the Factor Loadings and Cross-loadings of items of Socio-cultural and Religious Beliefs During Menstruation

	Religious	Interactions with male	Personal	Unpleasant
Religious				
Not allowed to enter holy places	0.938	0.214	0.092	0.247
Not allowed to read or cite holy book	0.859	0.274	0.038	0.237
Restrictions on the interactions with male				
Not allowing the male gender to touch used sanitary pad	0.196	0.449*	0.154	0.167
Not allowed to sit around and mingle with male	0.177	0.893	0.418	0.373
Not allowed to touch properties and belongings of the male gender	0.263	0.912	0.443	0.413
Personal Restriction				
Not allowed to eat cold food	-0.029	0.260	0.788	0.212
Not allowed to take iced water	-0.070	0.239	0.801	0.226
Not allowed to eat brinjal	0.203	0.466	0.736	0.459
Not allowed to eat papaya	0.211	0.477	0.706	0.498
Not allowed to eat pineapple	0.160	0.363	0.749	0.373
Not allowed to use any medications to relieve pain	0.133	0.425	0.625	0.361
Not allowed to wash hair and taking cold shower	-0.102	0.287	0.770	0.329
Unpleasant (or dirty) nature of menstruation				
Not allowed to step over plants	0.133	0.292	0.391	0.839
Not allowed to throw fallen hair into trash bin	0.311	0.443	0.400	0.848
Not allowed to throwing clipped fingernail into trash bin	0.297	0.404	0.358	0.813
Not allowed to touch flowers	0.216	0.309	0.370	0.860
Need to wrap used sanitary pad properly before disposing	0.023	0.188	0.229	0.463

Note: *Although the loading for this item was slightly low (0.449), but the AVE >0.5, indicating that the item was acceptable to be included (according to Hair et al. 2017 [15]).

Table II: Cronbach's Alpha, Composite Reliability (CR) and Average Variance Extracted (AVE) values of the Retained Four Factors in CFA

Belief Factors	Cronbach's Alpha	CR	AVE
Religious	0.772	0.894	0.809
Restrictions of interactions with male gender	0.661	0.813	0.610
Personal restrictions	0.864	0.895	0.550
Unpleasant nature of menstruation	0.826	0.882	0.608

Table III: Path Coefficients from Structural Equation Modelling

	Path coefficients	Standard deviation	T-statistics	P-values
Biological symptoms → QoL	-0.34	0.05	7.29	<0.001
Menstruation Practices → QoL	-0.17	0.05	3.67	<0.001
Religious beliefs → Menstruation Practices	0.00	0.03	0.15	0.88
Beliefs about restrictions of interactions with male gender → Menstruation Practices	0.12	0.04	3.00	<0.001
Beliefs of personal restrictions → Menstruation Practices	0.74	0.04	18.18	<0.001
Beliefs of the unpleasant nature of menstrual blood → Menstruation Practices	0.12	0.04	3.00	<0.001

Furthermore, not all beliefs is translated as practices. Besides that, we also included the impact of five common biological symptoms of menstruation (i.e., fatigue, abdominal pain/cramp, mood swing, headache, and irritability) [6] into consideration. These biological symptoms were measured on a 5-piont-Likert scale where 1=strongly disagree that this symptom is common for me, and 5=strongly agree that this symptom is common for me.

Institutional ethics approval was obtained prior to starting this research (reference no UNIMAS/NC-21.02/03-02 Jld.3(51)). All participants were assured that their data would be kept confidential, no personal identification data would be revealed. Participants were recruited voluntarily and they were informed that they could withdraw their participation at any time.

RESULTS

A total of 400 female students from UNIMAS were recruited, i.e., 228 medical students and 172 economic students. One hundred (i.e., 47 medical and 53 economic students) out of the 400 participants were recruited in the EFA stage. The remaining 300 participants were recruited for the CFA. The mean (Standard Deviation, SD) age of these 400 participants was 21.42 (±0.855) years old. With regards to their religious beliefs, 178 of them (44.5%) were Muslims, 106 participants (26.5%) were Christians, 78 (19.5%) were Buddhists, 33 (8.25%) were Hindus and five (1.25%) of other religious affiliations. Following sessions of discussion using the modified Delphi technique, a preliminary list of 22 items was generated for EFA. In the EFA stage, the Kaiser-Meyer-Olkin (KMO)21,22 measure of sampling adequacy was 0.744, which indicates that the sample was adequate for factor analysis. The p-value for Bartlett's test of sphericity was

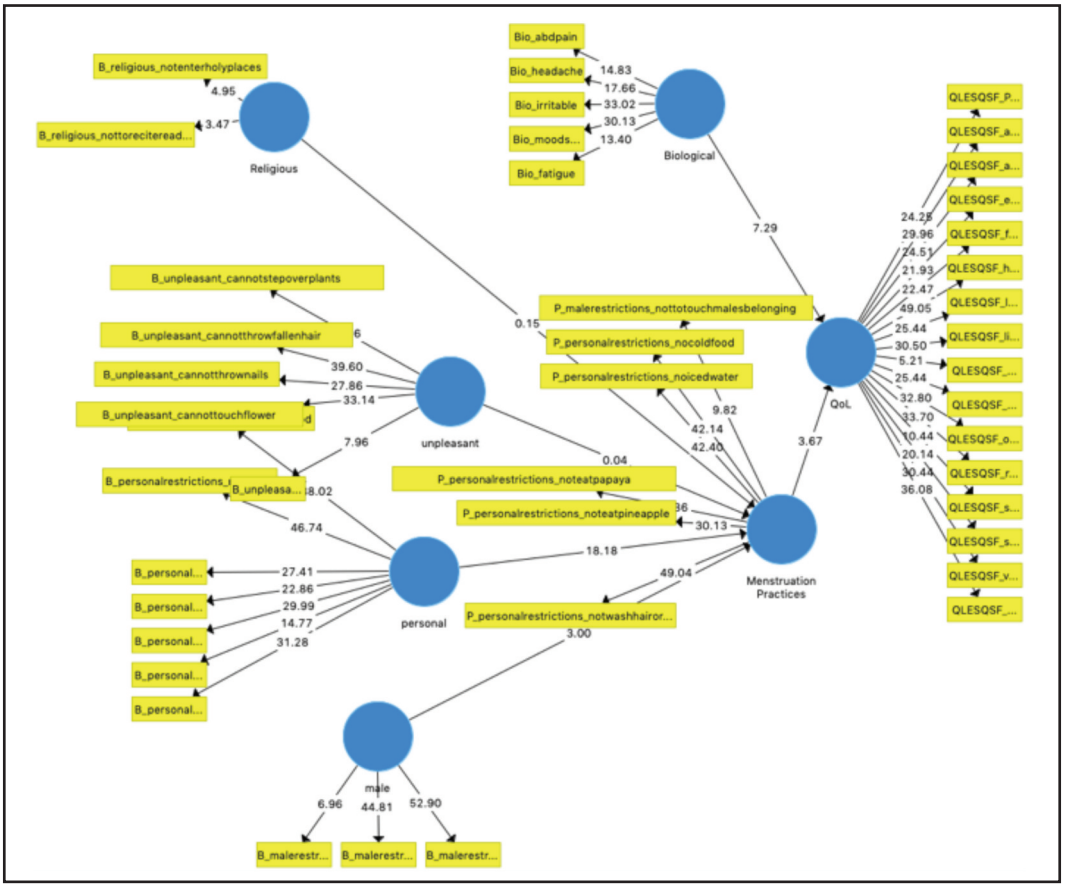

Fig. 1: Path model of sociocultural and religious beliefs and practices during menstruation among Malaysian university students.

<0.001, indicating that there are worthwhile correlations among the items. Based on initial eigenvalue>1, six factors were identified. With cut-off point of communalities value set at 0.25 to indicate good convergent validity of the items, re-runs of EFA subsequently performed showed that all items were loaded unto the various factors with good factor loadings of more than 0.5. No cross-loading was noted. Cronbach's alpha for these six factors (Factor 1 to 6) are 0.908, 0.898, 0.826, 0.855, 0.875 and 0.661 respectively. The inter-rater reliability measured using intra-class correlation coefficient (ICC) was 7.90 (95% Confidence Interval, 95%CI: 0.723, 0.848). Based on the items loaded unto them, Factor 1 was labelled as "Religious beliefs", Factor 2 as "Restriction on cooking and utensils", Factor 3 as "Unpleasant (or dirty) nature of menstruation", Factor 4 as "Personal restrictions (dietary and behaviour)", Factor 5 as "Spatial or movement restrictions" and Factor 6 as "Restrictions of interactions with male gender".

In the CFA stage, four items in Factor 2 "Restriction on cooking and utensils" and four items in Factor 5 "Spatial or movement restrictions" were iteratively removed due to poor factor loadings. Similarly, two items in Factor 1 "Religious beliefs", one item in Factor 3 "Unpleasant (or dirty) nature of menstruation" and three items in Factor 4 "Personal restrictions" were deleted due to low loadings. The factor loadings of all other items were acceptable and adequate. All factors achieved adequate convergent validity as the AVE was more than 0.5. The final result of the factor loadings is tabulated in Table I. The Cronbach alpha values, CR indices as well as the AVE values were satisfactory, indicating good convergent and divergent validity (Table II). The ρA of this study was 0.7, further suggesting good convergence and internal consistency.

In the structural equation modelling stage, the items in the four belief factors were subjected to the mediating effect of the practices of these beliefs. By bootstrapping the path coefficients, it was found that only two factors, i.e., "restriction of interactions with males" and "personal restrictions" are significant, t-statistics of 3.00 and 18.18 respectively. In particular, the path coefficient of factor "Restrictions of interactions with male gender" is weaker (0.12) compared to that of factor "Personal restrictions" (0.74). The path coefficients of both "menstruation practices" and "biological symptoms" in turn, had significant negative effects on the quality of life. Furthermore, biological symptoms were shown to have greater negative impact on the quality of life (path coefficient -0.34; t-statistics 7.29) compared to the practices of these sociocultural and religious beliefs (path coefficient -0.17; t-statistics 3.67) (Table III). The final path model for this study was shown in Figure 1.

DISCUSSION

Our study showed that sociocultural and religious beliefs during menstruation among university students can be broadly divided into four categories: i) religious restrictions;

ii) restrictions of social interactions with the male gender; iii) personal restrictions (with regards to dietary and behaviour); and iv) unpleasant (or dirty) nature of menstrual blood. A similar study on such restrictive behaviours during menstruation was similarly conducted in Fiji, Papua New Guinea and Solomon Islands.[23] In that study, the authors found that there were four overarching, but interacting themes. Three of out these four themes are very similar to the four categories of beliefs that we identified (with the exception of the category of religious beliefs which was not listed in that paper). The first theme is the belief that menstrual blood is 'dirty'. According to this belief, menstruating women are prevented from doing certain household tasks including food preparation, cooking and doing housework. This is similar to the category of the belief of the "unpleasant or dirty nature of menstrual blood" in our study. The second theme is the belief that menstrual blood and menstruating women can bring 'bad luck' to men and boys. According to this belief, menstruating women are prevented from, or should refrain from working in the garden, picking up fruits and avoiding contact with men and boys. This is similar to the belief of "restrictions of social interactions with the male gender" in our study although we classify the restriction to work in the garden under the category of the "unpleasant or dirty nature of menstrual blood" in our study. The third theme in that study is the belief of "shame and secrecy that surrounds menstruation". This refers to the need of secrecy in washing, cleaning and changing of sanitary pad and to ensure that the opposite gender do not see their menstrual blood. In our study, the need to wrap soiled sanitary pad and to dispose it properly is also an important belief although we classify this belief under the "unpleasant or dirty nature of menstrual blood" category. The fourth theme of belief addressed in that study by Mohamed et al.[23] is the belief of the impact of certain prohibitive behaviours on menstruation, health and well-being (similar to the category of "personal dietary and behavioural restrictions" in our study). In particular, this refers to certain restrictive beliefs to prevent heavy menstrual flow or menstrual cramps including the prohibition to drink iced or cold water, to eat sour things, or to wash hair using cold water|. Indeed, the similarities of these socio-cultural and religious beliefs is likely a reflection of the universality of some of these beliefs across the globe.

Nonetheless, although we have demonstrated the pervasiveness of some of these sociocultural and religious beliefs similar to the findings reported in some studies done outside of Malaysia,[23,24] we found that only the practices of "personal restrictions (dietary and behavioural)" and "restriction of interactions with males" had significant negative impact on their quality of life.

Interestingly, the practices of religious restrictions during menstruation do not seem to be significant. This might be due to the ethnic diversity of our sampled population, reflecting the varying degree of compliance to these restrictions. For the majority Muslim participants, they are restrained from performing religious rituals[25] including the restriction to enter mosque as well as the prohibition to pray or fast during the Ramadan fasting month.[26] The second largest religious group among our participants were the Christians. For the Christians community, generally they do not have restrictions during menstruation except for those from some Orthodox churches where menstruating women are prohibited to partake communion.[27] Among the Hindus, menstruating women are forbidden from entering "pooja room" (the prayer area in a house) and the temple.[28] Among Buddhists, menstruating women are restricted from performing certain religious rituals and ceremonies in temples as well as meditation.[29] Menstruation is also believed to make a woman loses her 'qi' (or inner energy).[29]

LIMITATIONS

Our study has a number of limitations. First, this study was conducted in only one centre in Malaysia, i.e., UNIMAS in the state of Sarawak. The demographic characteristics as well as the socio-cultural beliefs in Sarawak may not be generalizable to the demographic characteristics in other parts of Malaysia. Should this study be repeated in other parts of Malaysia where the percentage of Muslims may be higher, the impact of religious beliefs may be more significant. Secondly, because the initial stage of this study (Stage 1) involved getting opinions from friends and family members of some of the co-authors of this study, this might have introduced implicit, personal biases to the questionnaire development, e.g., soliciting answers just to conform to our personal beliefs. Thirdly, this study was only conducted among young university students. The perceptions, compliance and the impacts of these beliefs on quality of life may be different among those from the older age groups. For example, a study done by Lawlor and Choi30 showed that younger women generally have a more positive attitudes towards menstruation as they perceived menstruation as a natural physiological process rather than a process shrouded with taboos and myths. Fourthly, this study was solely conducted from a quantitative perspective. To better capture the emotions, concerns and fears surrounding these sociocultural and religious beliefs during menstruation, an added qualitative dimension may add more richness and colour to our findings.

CONCLUSIONS

In conclusion, menstruation should not be viewed purely from a biological lens. Instead, it should be viewed from a biopsychosocial lens due to the fact that there are layers of sociocultural and religious beliefs surrounding it. Four categories of sociocultural and religious beliefs have been identified in this study but only the practices of "personal restrictions (dietary and behavioural)" and "restriction of interactions with males" had significant negative impact on quality of life.

ETHICAL APPROVAL

Institutional ethics approval was obtained prior to starting this research (reference no UNIMAS/NC-21.02/03-02 Jld.3(51)). Participant's information sheet was given and written consent was obtained from participants prior to their participation. All participants were assured that their data would be kept confidential, no personal identification data such as name, personal identity number, etc. would be

revealed and their data would only be used anonymously solely for the purpose of this research. Participants were recruited voluntarily, and they were informed that they could withdraw their participation at any time.

Permissions were also obtained from the participants to publish their data anonymously without revealing their names and identities.

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ORIGINAL ARTICLE

Risk factors and outcome of community onset *Pseudomonas aeruginosa* bacteraemia in two Malaysian district specialist hospitals

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ABSTRACT

Introduction: Despite the ever-growing number of community onset (CO) *Pseudomonas aeruginosa (P. aeruginosa)* bacteraemia, there is a dearth of district hospital-based research examining this significant infection, which is associated with high mortality. The objectives of this study were as following: (1) to determine the risk factors of CO *P. aeruginosa* bacteraemia, (2) to compare the 30-day mortality rate between *P. aeruginosa* and *Escherichia coli* bacteraemia and (3) to identify the predictors of 30-day mortality for CO gram negative bacteraemia.

Methods: This is a retrospective case control study in Hospital Seri Manjung and Hospital Teluk Intan, Perak, Malaysia. *P. aeruginosa* bacteraemia cases that occurred between 1st January 2015 to 31st December 2019 were included, whilst *E. coli* bacteraemia cases that occurred within the same period were recruited successively until 1:2 case control ratio was achieved. Subjects below 12-year-old and those with polymicrobial bacteraemia were excluded. Demographic, clinical and treatment data were collected using pre-tested data collection forms by trained investigators.

Results: A total of 61 patients with *P. aeruginosa* bacteraemia and 122 patients with *E. coli* bacteraemia were included. Recent admission in the earlier three months, regular haemodialysis, immunosuppressive therapy in the past 30 days, chronic wound/pressure sore at presentation and indwelling urinary catheter at presentation were identified as independent predictors of CO pseudomonal bacteraemia. Whilst older age was identified as a negative predictor of CO Pseudomonal bacteraemia (all $p<0.05$). The 30-day mortality rate was 34.4% in subjects with *P. aeruginosa* bacteraemia and 27.0% in those with *E. coli* bacteraemia ($p=0.302$). Predictors of 30-day mortality for community onset gram negative bacteraemia were as follow: older age, underlying solid tumours, neutropaenia at presentation, in-patient mechanical ventilation, and in-patient nasogastric tube insertion. Unexpectedly, receipt of inappropriate empirical antibiotics which was switched later (delayed and non-delayed switching) was identified as the negative predictors of mortality (all $p<0.05$).

Conclusion: It is prudent to restrict the usage of empirical anti-pseudomonal antibiotics among individuals at risk as liberal usage of broad-spectrum antibiotics engenders emergence of drug resistant organism, particularly in district setting where community onset pseudomonal bacteraemia remains scarce. Subjects with elevated risk of mortality should receive early escalation of care as per sepsis management guidelines.

KEYWORDS:
Risk factors, Outcome, Community onset, Pseudomonas aeruginosa bacteraemia

INTRODUCTION

Pseudomonas aeruginosa, which is a gram negative aerobic bacilli, displays a predilection for infecting immunocompromised individuals and systemic pseudomonal infections are associated with dismal outcomes, with mortality rate reported as high as 46%.[1] In recent years, community onset (CO) *P. aeruginosa* bacteraemia has been increasingly reported.[2,3] This poses great challenges to the clinicians as differentiating pseudomonal bacteraemia (PB) from non-pseudomonal bacteraemia infection are difficult due to the lack of pathognomonic signs and their inherent resistance to a wide-ranged of antibiotics.[4]

Considering the deleterious outcomes associated with delayed effective antibiotics therapy in systemic pseudomonal infection, the notion of maintaining a low threshold for the usage of anti-pseudomonal may seem to be an appealing pursuit. Yet, the harms of injudicious usage of anti-pseudomonal antibiotics are also equally notable. The unguided and rampant use of broad-spectrum antibiotics would lead to emergence of multi-drug resistant organisms which would increase the costs of care and ultimately deplete the already very limited armamentarium we have in the present post-antibiotic era.[5] From a theoretical point of view, characterisation of pseudomonal blood stream infection would enable an educated and restrictive use of anti-pseudomonal antibiotics among the at-risk individuals.

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To our best knowledge, the literature on the risk factors of community onset *P. aeruginosa* bacteraemia is limited to studies conducted in tertiary hospitals, which has a distinct population demography compared to our district populations.[1] In view of this, we undertook this study with the following objectives (1) to determine the risk factors of CO *P. aeruginosa* bacteraemia, (2) to compare the 30-day mortality rate between *P. aeruginosa* and *Escherichia coli* bacteraemia and (3) to identify the predictors of 30-day mortality for CO gram negative bacteraemia.

MATERIALS AND METHODOLOGY

In the capacity of being specialist district hospitals in the state of Perak, both Hospital Seri Manjung (HSM) and Hospital Teluk Intan (HTI) receive referral cases from peripheral district hospitals who require in-patient attention. HSM receives transfer cases from Hospital Changkat Melintang, Perak whereas HTI receives referrals from Hospital Tapah and Hospital Sabak Bernam, which are located in the neighbouring state of Selangor, Malaysia.

Study Design and Data Collection

This is a retrospective 1:2 matched case-control study involving two healthcare centres, HSM and HTI. The investigators reviewed records of hospitalised patients with reported *P. aeruginosa* growth in blood culture between 1st January 2015 to 31st December 2019, whilst *E. coli* bacteraemia cases that occurred within the same period were recruited in an accumulative manner until 1:2 case control ratio was achieved. *E. coli* bacteraemia was selected as the controls because these were the most reported Gram-negative organism in both centres. Data from these patients were cross-checked with admission data and were included if positive cultures occurred within 48 hours after hospitalisation.

Their clinical data during the admission were obtained via electronic or physical copies. Demographic data including age, gender and residential status were recorded. Clinical characteristics including previous admissions, fever, use of vasoactive drug therapy, pre-existing comorbidities, use of immunosuppressive therapy, presence of indwelling devices, biochemical indices on admission, blood transfusions, mechanical ventilation, invasive procedures performed, antibiotic usage, antibiotic susceptibility for index blood culture, and clinical outcome were recorded. Investigators also recorded changes in antibiotics during the duration of hospitalisation, whether or not it was done before 48 hours, between 48 hours to 5 days, or after 5 days of admission. Data from previous admissions occurring within the last 3 months were also reviewed for past infection, antibiotic use, previous procedures, or long-term healthcare exposure for wound dressing, catheter change, or haemodialysis.

All subjects aged 12-year-old and above with a positive growth of either *P. aeruginosa* or *E. coli* on the index blood culture upon admission within the first 48 hours were included. Cases with incomplete clinical data or polymicrobial bacteraemia were excluded. Demographic, clinical and treatment data were collected using pre-tested data collection forms by trained investigators.

CO bacteraemia was defined as positive bacteria growth detected within 48 hours of hospital admission. Cases which were readmitted within 48 hours after being discharged from the hospitals would be considered as hospital onset bacteraemia and hence would not be included in this study. Previous admission was defined as admission that occurred within the last three months prior to the index admission.

The presence of *P. aeruginosa* bacteraemia or *E. coli* bacteraemia was defined by the identification from one or more sets of blood culture bottles collected using standard sterile techniques. Index blood culture was defined as the first blood culture that grew *P. aeruginosa* or *E. coli*. Index blood cultures also included patients who were transferred from peripheral district hospitals whose cultures were obtained within the first 48 hours of presentation to their respective hospitals.

Sequential Organ Failure Assessment (SOFA) scores were tabulated based on available laboratory and clinical data from patients' medical records on the same day as index blood culture date. In the event multiple blood samples or clinical assessments were made, investigators recorded the most abnormal value available from the said date. When specific parameters required in measuring SOFA scores were unavailable on the date of index blood culture, investigators used the parameters nearest to the date in measuring SOFA scores. A primary diagnosis of the source of *P. aeruginosa* or *E. coli* was obtained based on clinical findings, radiological data or other cultures obtained within 48 hours of the index incident blood culture drawn.

Microbiological Data

In both centres, blood cultures were processed using BACTEC fluorescent series instrument 9120 and 9240 (BMS diagnostics (M) Sdn. Bhd.). Organisms were identified to species level by Vivek 2 – Compact Machine (Biomerieux) (Diagnostic System (M) Sdn. Bhd.). Routine antibiotic susceptibility testing was performed according to CLSI (Clinical and Laboratory Standards Institute). Antibiotics tested for *P.aeruginosa* included Ceftazidime, Gentamicin, Amikacin, Cefoperazone, Meropenem, Imipenem, Piperacillin/Tazobactam, Ciprofloxacin and Cefepime. Antibiotics tested for *E.coli* included Ceftazidime, Cefotaxine, Ciprofloxacin, Gentamicin, Imipenem, Meropenem, Ampicillin, Amoxicillin/Clavulunate, Amikacin, Ampicillin/Sulbactam, Piperacillin/Tazobactam, Cefuroxime, Cotrimoxazole and Ceftriaxone. Non-susceptible include antibiotics that are reported as 'intermediate' and 'resistance' in susceptibility testing results. Multidrug resistance is defined as resistance to more than three of the following agents: anti-pseudomonal carbapanems, anti-pseudomonal beta-lactams (penicillins and cephalosporins), aminoglycosides, and fluroquinolones.

We considered empirical antimicrobial therapy as appropriate when: a) administered within 48 hours after index blood culture samples, and b) the regimen contains at least one antibiotic that is active against blood isolates in vitro. The dosage, frequency and route of antibiotics administered were reviewed. Delay in appropriate antimicrobial therapy referred to an initial inappropriate empirical antibiotics against isolate, which was later switched to an appropriate antibiotic after a lapse of more

than 48 hours from the time which blood culture samples were obtained.

All the data were analysed using Statistical Package for the Social Sciences (SPSS) Version 20. Demographic data and clinical profiles of study subjects were presented descriptively. Categorical variables between cases and controls were compared using Pearson Chi-Square or Fisher's Exact test while continuous variables were compared using Student t test or Mann-Whitney U test. Kaplan-Meier curve was used to compare the 30-day mortality rates among patients with *P.aeruginosa* bacteraemia and *E.coli* bacteraemia. The event of interest was death cases that occurred within 30 days after the index blood culture date.

Multiple logistic regression was used to identify variables independently associated with *P. aeruginosa* bacteraemia and variables independently associated with 30-day mortality among all the subjects studied. All variables associated with *P. aeruginosa* bacteraemia and 30-day mortality in the univariate analysis ($p<0.25$) were included at model entry. A stepwise approach was used to identify independent risk factors of *P. aeruginosa* bacteraemia and independent predictors of 30-day mortality. Variables were retained in the final model if the p value was <0.05. The results of multiple logistic regression analysis were reported as adjusted odd ratios with 95% Confidence Intervals (95%CI). For all statistical comparisons, a p-value <0.05 was deemed significant.

RESULTS

Study populations and clinical characteristics

A total of 61 patients with blood culture proven *P. aeruginosa* bacteraemia were identified and included in the analysis as case group. The cases were matched with 122 patients with blood culture confirmed *E. coli* bacteraemia during the study period to generate a 1:2 ratio between case subjects and control subjects (Table I). Among the 18 cases that were excluded, 10 cases were mixed growth, four cases were below 12-year-old and four cases due to missing clinical notes.

A review of the baseline characteristics revealed that gender distribution was relatively equal in the case subjects as opposed to the control subjects which were predominantly females (50.8% vs. 70.5%; $p=0.009$). Also, case subjects are generally younger compared to the control subjects (mean age in years 59.2 vs. 64.5; $p=0.019$). The commonest comorbidities among pseudomonal group were cardiovascular disease (36 cases), diabetes mellitus (DM) (28 cases) and chronic kidney disease or end stage renal disease (26 cases). The prevalence of chronic kidney disease or end stage renal failure (42.6% vs. 10.7%; $p<0.001$), haematological malignancy (8.2% vs 0.0%; $p=0.004$) and autoimmune disease (4.9% vs. 0.0%; $p=0.036$) in case groups were significantly higher compared to control groups. Noticeably, haematological malignancy, autoimmune disease and human immunodeficiency virus infection were only present in the case cohort but at a very small number. In contrast, DM (66.4% vs. 45.9%; $p=0.008$) was more prevalent among control group compared to case group (Table I).

The percentage of recent immunosuppressive treatment (11.5% vs. 0.8%; $p=0.002$) and presence of pre-existing chronic wound or pressure sore (19.7% vs. 4.9%, $p=0.002$) were higher among pseudomonal group. Furthermore, indwelling central venous line (23.0% vs. 0.8%, $p<0.001$), urinary catheter (11.5% vs 2.5%; $p=0.017$) and Tenckhoff catheter (3.3% vs. 0.0%; $p=0.110$) were also more frequently observed among pseudomonal group (Table I).

There was a significant difference between case subjects and control subject in terms of regular healthcare exposure (44.3% vs. 6.6%; $p<0.001$) and recent admission (52.5% vs. 14.8%; $p<0.001$) during the last three months prior to index admission. Further analysis revealed that types of healthcare exposure were due to long term haemodialysis (16 cases), wound dressing (5 cases), urinary catheter exchange (4 cases) and Ryle's tube exchange (2 cases) as shown in Table I.

On the other hand, past admission treatment review indicated a higher exposure rate to penicillin (18.0% vs 4.1%; $p=0.002$) and cephalosporin (24.6% vs. 5.7%; $p<0.001$) among pseudomonal group. In this report, multi-drug resistant organisms exclusively occurred in the control subjects which recorded 22 cases of extended spectrum beta-lactamase producing *E. coli* ($p<0.001$) despite lower exposure rate to penicillin and cephalosporin. Notably, central venous line insertion (14.8% vs. 2.5%; $p=0.003$), haemodialysis (16.4% vs. 1.6%; $p<0.001$), blood products transfusion (18.0% vs. 5.7%; $p=0.008$) and surgery (9.8% vs. 0.0%; $p=0.001$) were more often performed on the case subjects during the recent admission (Table I).

Clinical Outcomes

Pseudomonal subjects were more ill during presentation as evidenced by the higher median SOFA score (5.0 vs. 3.0; $p=0.002$). They also demonstrated higher rate of shock during first 48 hours of presentation (32.8% vs. 26.2%; $p=0.354$) although this was not statistically significant. Interestingly, the proportion of intensive care unit (ICU) admission were higher among *E. coli* group (9.8% vs. 4.9%; $p=0.253$) although this was not statistically significant (Table I).

Evaluation of biochemical parameters showed that median haemoglobin (8.95g/dL vs. 11.71g/dL; $p<0.001$) and mean albumin level (24.0g/dL vs. 27.1g/dL; $p=0.010$) were remarkably lower in the pseudomonal group. On the other hand, the serum creatinine (303.0µmol/L vs. 154.5µmol/L; $p<0.001$) levels were significantly higher in the pseudomonal group. Neutropaenia only occurred in pseudomonal group (8.2% vs. 0.0%; $p=0.004$). Examination of the bacteraemia sources identified central venous catheter infections (23.0% vs. 0.0%; $p<0.001$), and skin and soft tissue infections (11.5% vs. 1.6%; $p=0.007$) more frequent implicated in the pseudomonal group, whereas urinary tract infections (41.8% vs 24.6%; $p=0.022$), gastrointestinal tract infections (16.4% vs. 4.9%; $p=0.027$) and hepatobiliary tract infections (4.1% vs. 0.0%; $p=0.171$) were more common among the *E. coli* group. Presence of concomitant bacteria growth were conspicuously lower in the *E. coli* cohort (13.1% vs. 32.8%; $p=0.002$) as depicted in Table I.

Table I: Comparison of clinical characteristics of community onset bacteraemia (*P. aeruginosa* Vs. *E. coli*)

Characteristics	*P.aeruginosa* (n=61)	*E.coli* (n=122)	*p* value
Admission ward specialty, n(%)			0.582[a]
Medical	54 (88.5)	113 (92.6)	
Non-medical	6 (9.9)	7 (5.8)	
ICU	1 (1.6)	2 (1.6)	
Multidrug-resistant organism, n(%)	0 (0.0)	22 (18.0)	<0.001[b]
Age in years, mean (SD)	59.2 (15.5)	64.5 (13.6)	0.019[c]
Male gender, n(%)	30 (49.2)	36 (29.5)	0.009[b]
Admitted in the past 3 months, n(%)	32 (52.5)	18 (14.8)	<0.001[b]
Previous admission: Antibiotic use, n(%)			
Cephalosporin	15 (24.6)	7 (5.7)	<0.001[b]
Penicillin	11 (18.0)	5 (4.1)	0.002[b]
Nitroimidazole	3 (4.9)	2 (1.6)	0.335[a]
Macrolide	1 (1.6)	2 (1.6)	1.000[a]
Carbapenem	2 (3.3)	0 (0.0)	0.110[a]
Previous admission: In-patient treatment, n(%)			
Urinary catheter	13 (21.3)	13 (10.7)	0.052[b]
Blood product transfusion	11 (18.0)	7 (5.7)	0.008[b]
Haemodialysis	10 (16.4)	2 (1.6)	<0.001[a]
Central venous line	9 (14.8)	3 (2.5)	0.003[a]
Nasogastric tube	4 (6.6)	5 (4.1)	0.484[a]
Surgery	6 (9.8)	0 (0.0)	0.001[a]
Endoscopy	3 (4.9)	2 (1.6)	0.335[a]
Regular healthcare exposure in the last 3 months, n(%)	27 (44.3)	8 (6.6)	<0.001[b]
Types of regular healthcare exposure in the last 3 months, n(%)			
Haemodialysis	16 (26.2)	1 (0.8)	<0.001[b]
Wound dressing	5 (8.2)	2 (1.6)	0.042[a]
Urinary catheter change	4 (6.6)	2 (1.6)	0.096[a]
Ryle's tube change	2 (3.3)	3 (2.5)	1.000[a]
Had shock during index blood culture, n(%)	20 (32.8)	32 (26.2)	0.354[b]
Comorbidities, n(%)			
Cardiovascular disease	36 (59.0)	81 (66.4)	0.327[b]
Diabetes mellitus	28 (45.9)	81 (66.4)	0.008[b]
Chronic kidney disease/end stage renal disease	26 (42.6)	13 (10.7)	<0.001[b]
Old stroke	4 (6.6)	15 (12.3)	0.230[b]
Respiratory disease	6 (9.8)	10 (8.2)	0.711[b]
Solid tumour	6 (9.8)	9 (7.4)	0.568[b]
Genitourinary disease	4 (6.6)	7 (5.7)	1.000[a]
Chronic liver disease	4 (6.6)	4 (3.3)	0.444[a]
Orthopaedic disease	3 (4.9)	4 (3.3)	0.688[a]
Haematological malignancy	5 (8.2)	0 (0.0)	0.004[a]
Autoimmune disease	3 (4.9)	0 (0.0)	0.036[a]
Human immunodeficiency virus	2 (3.3)	0 (0.0)	0.110[a]
Others*	13 (21.3)	14 (11.5)	0.077[b]
Immunosuppressive therapy in the past 30 days, n(%)	7 (11.5)	1 (0.8)	0.002[a]
Chronic wound/pressure sore at presentation, n(%)	12 (19.7)	6 (4.9)	0.002[b]
Indwelling devices at presentation, n(%)			
Central venous line	14 (23.0)	1 (0.8)	<0.001[b]
Urinary catheter	7 (11.5)	3 (2.5)	0.017[a]
Tenckhoff	2 (3.3)	0 (0.0)	0.110[a]
Laboratory findings at index blood culture date			
Haemoglobin, g/dL, mean (SD)	8.95 (2.63)	11.71 (2.27)	<0.001[c]
White cell count, x10^3/µL, median (IQR)	13.20 (14.90)	17.20 (11.08)	0.103[d]
Albumin, g/L, mean (SD)	24.0 (7.7)	27.1 (7.5)	0.014[c]
Creatinine, µmol/L, median (IQR)	303.0 (416.5)	154.5 (143.0)	<0.001[d]
Neutropaenia, i.e. neutrophils < 0.5x10^3/µL	5 (8.2)	0 (0.0)	0.004[a]
SOFA score on / nearest to index blood culture date, median (IQR)	5.0 (5.0)	3 (6.0)	0.002[d]
Current admission: In-patient treatment, n(%)			
Central venous line	28 (45.9)	20 (16.4)	<0.001[b]
Blood product transfusion	27 (44.3)	12 (9.8)	<0.001[b]
Haemodialysis	23 (37.7)	11 (9.0)	<0.001[b]
Mechanical ventilator	11 (18.0)	20 (16.4)	0.780[b]
Surgery	5 (8.2)	6 (4.9)	0.510[a]
Appropriate empirical antibiotic use on index bacteraemia date, n(%)	30 (49.2)	95 (77.9)	<0.001[b]

cont..... pg 824

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Table I: Comparison of clinical characteristics of community onset bacteraemia (*P. aeruginosa* Vs. *E. coli*)

Switching of inappropriate empirical antibiotic, n(%)			0.001[b]
Not applicable	30 (49.2)	95 (77.9)	
Non-delayed switching	5 (8.2)	3 (2.4)	
Delayed switching	14 (22.9)	15 (12.3)	
Not switched	12 (19.7)	9 (7.4)	
Index blood culture source, n(%)			
Urinary tract	15 (24.6)	51 (41.8)	0.022[b]
Respiratory tract	21 (34.4)	42 (34.5)	1.000[b]
Gastrointestinal tract	3 (4.9)	20 (16.4)	0.027[b]
Central venous catheter	14 (23.0)	0 (0.0)	<0.001[a]
Skin & soft tissue	7 (11.5)	2 (1.6)	0.007[a]
Hepatobiliary tract	0 (0.0)	5 (4.1)	0.171[a]
Unknown	1 (1.6)	2 (1.6)	1.000[a]
Other samples with concomitant bacteria growth, n(%)	20 (32.8)	16 (13.1)	0.002[b]
ICU admission, n(%)	3 (4.9)	12 (9.8)	0.253[b]
In-hospital death, n(%)	20 (32.8)	28 (23.0)	0.154[b]
30-day mortality, n(%)	21 (34.4)	33 (27.0)	0.302[b]

SD, Standard deviation; IQR, Interquartile range; SOFA, Sequential Organ Failure Assessment; ICU, Intensive Care Unit
* psychiatric disorder, migraine, haemorrhoids, gastritis, hypothyroidism, Bell Palsy, cholelithiasis, pancytopenia, idiopathic thrombocytopenic purpura, epilepsy, recurrent pyogenic cholangitis with hepatolithiasis, deep vein thrombosis
[a] Fisher's Exact test
[b] Pearson Chi-square test
[c] Independent t-test
[d] Mann Whitney U test

Table II: Comparison of SOFA score on / nearest to index blood culture date with regards to empirical antibiotic use and its switching vs. mortality

Empirical antibiotic & its switching	SOFA score, median (IQR)	*p* value	30-day mortality rate	*p* value	Empirical antibiotic & its switching	SOFA score, median (IQR)	*p* value	30-day mortality rate	*p* value
***Pseudomonas aeruginosa* bacteraemia (n=61)**		0.226[a]		0.087[b]	***Escherichia coli* bacteraemia (n=122)**		0.613[a]		0.093[b]
Appropriate empirical antibiotic (n=30)	6.5 (4.3)		36.7%		**Appropriate empirical antibiotic (n=95)**	3.0 (6.0)		28.4%	
Inappropriate empirical antibiotic & Non-delayed switching (n=5)	4.0 (8.5)		0.0%		**Inappropriate empirical antibiotic & Non-delayed switching (n=3)**	5.0 (5.0)		66.7%	
Inappropriate empirical antibiotic & Delayed switching (n=14)	4.5 (6.5)		21.4%		**Inappropriate empirical antibiotic & Delayed switching (n=15)**	4.0 (5.0)		6.7%	
Inappropriate empirical antibiotic & Not switched (n=12)	4.0 (5.3)		58.3%		**Inappropriate empirical antibiotic & Not switched (n=9)**	2.0 (4.5)		33.3%	

SOFA, Sequential Organ Failure Assessment
[a] Kruskal-Wallis H test
[b] Fisher's Exact test

Table III: Independent risk factors for community onset *Pseudomonas aeruginosa* bacteraemia

Variable	Multivariate analysis		
	Adj. OR	95% CI	*p* value[a]
Age	0.97	(0.94, 1.00)	0.048
Admitted in the past 3 months	4.06	(1.73, 9.53)	0.001
Regular healthcare exposure: Haemodialysis	44.13	(5.36, 363.27)	<0.001
Immunosuppressive therapy in the past 30 days	13.82	(1.41, 135.43)	0.024
Chronic wound/pressure sore at presentation	4.49	(1.32, 15.32)	0.016
Urinary catheter at presentation	7.17	(1.30, 39.49)	0.024

Adj. OR, Adjusted Odd Ratio; CI, Confidence Interval
[a]Wald test

Table IV: 30-day mortality predictors of community onset gram negative bacteraemia

Variable	30-day mortality, n (%)			Multivariate analysis	
	No	Yes	Adj. OR	95% CI	*p* value[a]
Age in years, mean (SD)	60.3 (14.7)	68.6 (11.9)	1.06	(1.02, 1.10)	0.005
Solid tumour					0.004
No	121 (72.0)	47 (28.0)	1.00		
Yes	8 (53.3)	7 (46.7)	7.80	(1.91, 31.82)	
Neutropaenia, i.e. neutrophils < 0.5x10^3/μL					0.021
No	127 (71.3)	51 (28.7)	1.00		
Yes	2 (40.0)	3 (60.0)	23.10	(1.62, 328.88)	
In patient treatment: Mechanical ventilator					<0.001
No	125 (82.2)	27 (17.8)	1.00		
Yes	4 (12.9)	27 (87.1)	14.43	(3.54, 58.80)	
In patient treatment: Nasogastric tube					<0.001
No	116 (86.6)	18 (13.4)	1.00		
Yes	13 (26.5)	36 (73.5)	10.88	(3.49, 33.92)	
Switching of inappropriate empirical antibiotic					0.037
Not applicable	87 (69.6)	38 (30.4)	1.00		
Switched (Non-delayed & Delayed)	31 (83.8)	6 (16.2)	0.20	(0.05, 0.83)	0.026
Not switched	11 (52.4)	10 (47.6)	1.74	(0.46, 6.57)	0.414

Adj. OR, Adjusted Odd Ratio; CI, Confidence Interval
[a]Wald test

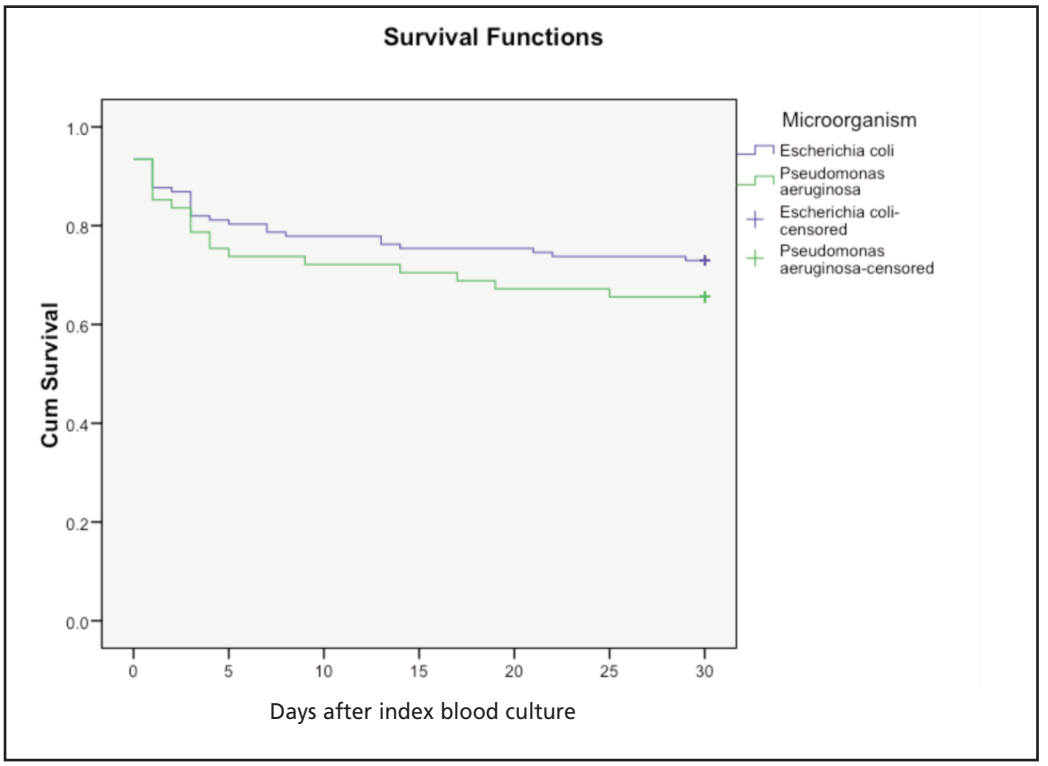

Fig. 1: Kaplan-Meier survival curve for patients with *Pseudomonas aeruginosa* versus *Escherichia coli* bacteraemia.

Additionally, there was a significant difference in term of empirical antibiotics prescription where pseudomonal case subjects recorded higher rates of inappropriate empirical antibiotics (50.8% vs. 22.1 %), delayed switching to appropriate antibiotics (23.0% vs. 12.3%) and inappropriate definite antibiotics (19.7% vs. 7.4%) as demonstrated in Table I. Among the 21 subjects who received inappropriate definite antibiotics, the reasons of not switching to appropriate antibiotics were as follow: subjects improved with initial inappropriate empirical antibiotics (10 subjects), blood culture reports not reviewed (4 subjects), subjects died before availability of blood culture (5 subjects) and subjects took at-own-risk discharge (2 subjects).

Interestingly, the 30-day mortality rate was lower among pseudomonal subjects who received inappropriate empirical antibiotic with subsequent non-delayed or delayed switching compared to those who received appropriate empirical antibiotics (0.0% vs. 21.4% vs. 36.7%; p=0.087). Further analysis revealed that the later had the highest median SOFA score compared to subjects who received inappropriate empirical antibiotic with subsequent non-delayed or delayed switching (6.5 vs. 4.0 vs. 4.5; p=0.226). In contrast, a higher 30-day mortality rate among *E. coli* subjects was observed in the cohort who had non-delayed switching to appropriate antibiotics (66.7%) and who had inappropriate definite antibiotics (33.3%) as shown in Table II.

The in-hospital mortality rate (32.8% vs. 23.0%; p=0.154) and 30-day mortality rate (34.4% vs 27.0%; p=0.302) were higher among *Pseudomonal* group. The 30-day survival rates, stratified according to types of organisms were presented in Kaplan-Meier curve as illustrated in Figure 1. It demonstrated 34.4% and 27.0% mortality rate in *P. aeruginosa* group and *E. coli* group respectively. The former group had a lower survival probability of 30-day survival.

Risk Factors of Community Onset *Pseudomonas aeruginosa* bacteraemia

Multiple logistic regression analysis identified following as independent predictors of CO PB: recent admission in the last three months (Adj. Odds Ratio, OR=4.06; 95%CI: 1.73, 9.53), regular haemodialysis (Adj. OR=44.13; 95%CI: 5.36, 363.27), immunosuppressive therapy in the past 30 days (Adj. OR=13.82; 95%CI: 1.41, 135.43), chronic wound/pressure sore at presentation (Adj. OR=4.49; 95%CI: 1.32, 15.32) and indwelling urinary catheter at presentation (Adj. OR=7.17; 95%CI: 1.30, 39.49). Whilst older age was identified as a negative predictor of CO PB (Adj. OR=0.97; 95%CI: 0.94, 1.00) as shown in Table III.

30-Day Mortality Predictors of Community Onset Gram Negative Bacteraemia

Multiple logistic regression analysis identified following as 30-day mortality predictors of community onset gram negative bacteraemia: older age (Adj. OR=1.06; 95%CI: 1.02, 1.10), underlying solid tumours (Adj. OR=7.80; 95%CI: 1.91, 31.82), neutropaenia at presentation (Adj. OR=23.10; 95%CI: 1.62, 328.88), in-patient mechanical ventilation (Adj. OR=14.43; 95%CI: 3.54, 58.80) and in-patient nasogastric tube insertion (Adj. OR=10.88; 95%CI: 3.49, 33.92). Interestingly, receipt of inappropriate empirical antibiotics which was switched later (delayed and non-delayed switching) was identified as the negative predictors of mortality in comparison with receipt of appropriate empirical antibiotics (Adj. OR=0.2; 95%CI: 0.05, 0.83) as shown in Table IV.

DISCUSSION

Currently, PB is proven to be a rare occurrence as only 61 episodes of CO PB were recorded over a span of five years period in two district hospitals in Malaysia. Nevertheless, PB still poses an existential threat as it is associated with high morbidity and mortality.[1,6,7] In spite of this, standard of care for hospital acquired infection, which entails broad spectrum antibiotics with anti-pseudomonal coverage cannot be applied to all patients presenting with community onset gram negative bacteraemia, especially in the setting where pseudomonal infections are only few and far between. Restrictive use of anti-pseudomonal antibiotics is vital as rampant use of such broad-spectrum antibiotics would lead to selective pressure of the ambient microorganism, which would ultimately lead to the nascence and spread of multi-drug resistant organism.[5]

Identification of predictive factors for PB is crucial as it enables judicious use of anti-pseudomonal antibiotics among at risk population. Our data revealed that recent admission, regular haemodialysis, immunosuppressant use, chronic wound and indwelling urinary catheter to be significantly associated with PB. These results corroborated with previous the study by David et al., which was conducted in two district hospital in the United Kingdom (UK) that bears close resemblance to our population.[3] Yet, haematological malignancy, solid tumours and neutropenia, which are well established risk for PB was not associated with increased risk of pseudomonal infection in this report.[2,8] The foremost cause of this discrepancy would be that previous studies were conducted in tertiary hospital where there was a high burden of haemato-oncological subjects.

The absence of sporadic multi-drug resistant *P. aeruginosa* in this report strengthens our conviction that empirical antimicrobial therapy that encompass either third generation cephalosporin or piperacillin/tazobactam are generally adequate in district setting. Another marked observation that emerges from this report was that nearly half of the pseudomonal cohort had pre-existing chronic renal disorder with an increased trend towards haemodialysis treatment during the hospitalisation. Considering this, we caution the use of aminoglycoside in PB due to its nephrotoxicity side effects and highlight the importance of close renal function monitoring.

In previous published studies, the source of infection is determined based on clinical grounds and concomitant growth from the causative system is not mandated.[2,3,9] It is intriguing that majority of gram-negative bacteraemia did not have demonstrable concomitant cultures from other sources. The numbers could be partly contributed by subjects with hepatobiliary tract infection, which only occurred in *E. coli* cohort as attempt of culture collection from the causative organ system are deemed as both high risk and implausible. Notwithstanding, concomitant yield from sputum samples and urine samples remained low despite accounting for majority of the sources. Therefore, it is reasonable to suggest that a negative microbial work-up from non-blood-based

culture does not preclude the presence of blood stream infection among the at-risk populations. We recommend blood culture as the gold standard in ruling out blood stream infections in patients who present with sepsis, especially those with aberrant immune system.

The preponderance of pre-existing chronic kidney disease or end stage renal failure among the pseudomonal cohort explains the increased rate of profound anaemia, blood product transfusion and haemodialysis among the case subjects. Although anaemia was more commonly seen among the pseudomonal cohort, our numbers were not significant enough to draw a meaningful conclusion, yet this observation sheds potential research interest exploring the relationship between anaemia, septicaemia, and potentially poorer clinical outcome.

Interestingly, despite the high burden of morbidity and excess mortality in case subjects, PB was not identified as the predictors of mortality in comparison to *E. coli* bacteraemia. In fact, this report identified clinical features like older age, pre-existing solid tumours, neutropaenia at presentation, mechanical ventilation requirement and nasogastric tube insertion to be the risk factors of gram-negative bacteraemia mortality. We can conceivably hypothesize frailty and life-shortening chronic conditions such as malignancy have a major influence on the outcome of survival. These demographic and clinical features are not incorporated in SOFA scoring, despite contributing significantly to increased mortality.

The intuitive concept about appropriate empirical antibiotics would lead to better survival in gram negative bacteraemia was not substantiated in this report.[10] On the contrary, we identified administration of inappropriate empirical antibiotics, which was switched later to be a predictive factor for survival. This contradictory observation emphasizes that appropriate empirical antibiotics is not the sole determinant of sepsis survival as this involves an inter-play of multiple factors. In our opinion, we emphasize that the enthusiasm of choosing appropriate empirical antibiotics should not overshadow the importance of timely fluid resuscitation, sepsis source control, nutrition therapy, as well as judicious use of blood products and life support in ICU which deserve equal attention.[11]

Inevitably, due to the retrospective design, missing data in this study could lead to underestimation or missing out certain significant variables. The upshot of this study is that it represents the first study examining CO pseudomonal bacteraemia that was conducted Malaysian district hospitals. Also, the data were collected pro forma by trained data abstractors who were experienced clinicians, thus reducing the likelihood of data collection error.

CONCLUSION

In summary, the clinical characteristics of pseudomonal bacteraemia in this study differ from previous research that have been undertaken in tertiary hospitals. Interestingly, observations from our data did not support the preconceived notion that *P. aeruginosa* bacteraemia and delayed appropriate antibiotics were more commonly associated with increased odds of mortality. In fact, host factors display a higher influence on the mortality rate as opposed to type of infections and timeliness of antibiotics. Lastly, we recommend judicious use of anti-pseudomonal antibiotics among at risk groups keeping in mind that community onset pseudomonal bacteraemia remain a rare condition in district setting.

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ETHICAL APPROVAL

This study was registered with National Medical Research register (NMRR) and approved by the Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH). MREC Approval Letter: KKM/NIHSEC/ P20-28 (6) dated 16 Jan 2020. NMRR ID: NMRR-19-3400-51985

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ORIGINAL ARTICLE

Comparing various cut-offs of aspartate aminotransferase-to-platelet ratio index (APRI) in liver cirrhosis diagnosis among hepatitis C patients in Malaysia

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ABSTRACT

Introduction: A major challenge in providing hepatitis C virus (HCV) treatment at primary healthcare clinics is the lack of radiological facilities to guide the decision making of liver cirrhosis (LC). This study aimed to compare the performance of three commonly used cut-offs of the aspartate aminotransferase-to-platelet ratio index (APRI) in diagnosing LC among hepatitis C patients in Malaysia.

Methods: This cross-sectional study was based on the data collected from the Hepatitis C Elimination through Access to Diagnostics (HEAD-Start) study in 25 primary healthcare clinics across three regions of Malaysia. The findings of biochemical tests were used to calculate the APRI for each study participant. Transient elastography was used as a standard reference for the diagnosis of cirrhosis. The area under the receiver operating curve (AUROC) was used to determine the discriminative ability of APRI in both HCV mono-infected and HCV/HIV co-infected patients. The diagnostic performance of APRI at three different cutoffs (>1.0, ≥1.5 and >2.0) were also evaluated.

Results: This study included 867 HCV-RNA-positive patients, 158 (16.1%) were co-infected with HIV. For the HCV mono-infected patients, the sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) for the cut-off of >1.0 were 61.8%, 88.7%, 73.8% and 81.9%, and for the cut-off of ≥1.5, 45.6%, 97.0%, 88.7% and 77.6%, respectively. A much lower sensitivity (29.9%) was observed for the cut-off of >2.0. The diagnostic accuracy of APRI at the cut-off of ≥1.5 in the HCV/HIV co-infected patients was relatively suboptimal.

Conclusion: APRI, with a cut-off of ≥1.5, can more accurately predict LC among hepatitis C patients in Malaysia. However, additional physical examination and laboratory assessment are likely to be required to support the diagnosis, especially in those with HCV/HIV co-infection.

KEYWORDS:
Aspartate aminotransferase-to-platelet ratio index, cirrhosis, hepatitis C, transient elastography

INTRODUCTION

Liver cirrhosis (LC) is the advanced stage of liver fibrosis. It is characterised by extensive scarring, altered microarchitecture, disruption of blood circulation, and nodularity in the liver.[1] Globally, LC is ranked thirteen among the leading causes of death in 2017.[2] Hepatitis B and C infections, alcohol-related liver disease, and non-alcoholic steatohepatitis (NASH) are among the common causes of LC. The concurrent occurrence of hepatitis C and NASH has also been shown to increase the risk of liver fibrosis.[3] Identifying LC in chronic hepatitis C (HCV) infection prior to the treatment with direct-acting antivirals (DAAs) is essential to guide the decision making of the treatment duration and follow-up intervals of patients.[4,5]

The diagnosis of LC is made through biopsy. However, the use of such an invasive method is often limited by its poor accessibility and the risk of complications following the procedure.[6,7] While the liver biopsy is the gold standard, the World Health Organization (WHO) hepatitis testing guidelines recommend non-invasive tests such as radiological imaging and biomarker testing for the assessment of liver staging.[8]

Since 2018, the Ministry of Health (MOH) Malaysia has been encouraging decentralised hepatitis C screening and treatment at primary healthcare clinics in an effort to improve access to care.[9] Both hepatitis C rapid diagnostic test (RDT) kits and DAAs are available in the health clinics. Nevertheless, one of the major challenges to providing hepatitis C treatment at health clinics is the lack of radiological facilities. As a result, the aspartate-to-platelet ratio index (APRI), a non-invasive biomarker, is recommended for the diagnosis of LC.[10]

APRI is formulated by using aspartate aminotransferase and platelet, two routinely tested parameters. These two biochemical tests are widely available in Malaysia's primary healthcare clinics and the test results were kept in each patient's note for future references. This makes the APRI a simple yet handy tool for use in resource-limited settings. Although APRI does not allow staging of fibrosis,[11] its ability to determine the status of cirrhosis enables its use in guiding hepatitis C treatment.[12,13] Many diagnostic studies confirmed

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the accuracy of an APRI score in this context, reporting an AUROC ranging between 0.80 and 0.84.[12-15] Several cut-offs of the APRI score were also suggested for the diagnosis of liver cirrhosis.

In Malaysia, the Clinical Practice Guidelines on the management of adult hepatitis C patients indicate that an APRI score of 1.5 and above is indicative of LC.[16] However, a higher score of 2.0, the cut-off recommended by WHO, could help keep the discriminative ability of APRI above 80%.[10] A lower APRI cut-off of 1.0 has also been used in several studies.[13,17] Given the discrepancy in recommendations and the limited local evidence regarding the external validity of APRI, this study compared the above-mentioned cut-offs for diagnosis of LC among hepatitis C patients in Malaysia.

MATERIALS AND METHODS

Ethics, study design and participants

This cross-sectional study was approved by the Medical Research and Ethics Committee of the Ministry of Health Malaysia (NMRR-18-2282-43132) and was based on the data collected in a study for the Hepatitis C Elimination through Access to Diagnostics (HEAD-Start) Malaysia. HEAD-Start Malaysia was a collaborative study between the Foundation for Innovative New Diagnostics (FIND), the Drugs for Neglected Diseases initiative (DNDi), the MOH and the Clinical Research Malaysia (CRM).

In brief, the HEAD-Start Malaysia study took place between December 2018 and December 2019 with the aim to improve access to hepatitis C screening services in all the 25 primary healthcare clinics across three regions (States of Kedah, Kelantan and the Region of Kuala Lumpur/Putrajaya/State of Selangor). Adult individuals aged between 18 and 70, who had a positive HCV serological rapid diagnostic test (RDT) results were referred to one of the five nearby tertiary care centres for an HCV RNA test, which was performed using the reverse transcription polymerase chain reaction technique, and an assessment of their status of cirrhosis through transient elastography (Fibroscan®, EchoSens, Paris). They also received biochemical assessments enabling the calculation of APRI. Those who had the HCV infection confirmed and were fit for treatment were subsequently offered DAAs, either under standard hospital care or by participating in a clinical trial. Information regarding their socio-demographics, laboratory test results and radiological findings was collected using a standardized data collection form.

Transient elastography

Transient elastography (TE), the reference standard used for the diagnosis of LC in this study, is a rapid, painless, and reproducible method to measure liver stiffness. The measurement is based on the estimated velocity of a shear wave through liver tissue.[18] The procedure was performed by a trained operator in each of the tertiary care centres. The median values of a minimum ten valid readings were taken for each patient and expressed in kilopascals (kPa). Liver stiffness was then categorised as either cirrhosis (≥12.5 kPa) or non-cirrhosis (<12.5 kPa).[18,19] This approach is shown to be highly reliable in the assessment of liver fibrosis in patients with chronic hepatitis C.[20,21] Using liver biopsy as a reference, a meta-analysis of 38 studies indicated that TE can be performed with excellent accuracy to differentiate cirrhosis and non-cirrhosis, with a mean AUROC of 94%.[22]

Data collection and APRI calculation

We retrieved the data of 981 patients who received an assessment regarding the individual socio-demographics, HCV RNA test results, HIV status, TE findings, and levels of AST and platelets from the database of the HEAD-Start Malaysia study. The APRI score was calculated using the following formula: [(AST level / ULN) / platelet count (10^9/L)] x100.[23] The upper limit of normal AST varied across the participating sites, ranging between 34IU/L to 50IU/L. This value varied depending on laboratory use at each site defined reference populations therein to establish their own reference ranges for AST test.

Statistical analysis

All patients were grouped into either HCV mono-infection or HCV/HIV co-infection, as the latter group has a higher risk of developing LC.[24] Categorical variables were presented as numbers and percentages, and numerical variables as the mean or standard deviation. Receiver operating curves (ROCs) were used to determine the discriminative performance of APRI in the diagnosis of liver cirrhosis. An AUROC of 1.0 could be judged as a perfect discrimination, ≥0.90 as excellent, a ≥0.80 as good, ≥0.70 as fair, and <0.70 as poor.[25] The diagnostic accuracy of APRI test was evaluated based on the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at different cut-offs (>1.0, ≥1.5 and >2.0). All the data was analysed using the R statistical software version 3.5.2.[26]

RESULTS

Demographic and clinical characteristics

Of the 981 patients who received an assessment of their cirrhosis status through TE and a APRI score in the HEAD-Start Malaysia study, 114 had unknown HIV infection status and were excluded from our study analysis. Finally, findings from a total of 867 patients were analysed. 709 patients included in this study were mono-infected with HCV. This mono-infected group was mainly males (95.8%) and in the age group of 40-49 years (40.1%). Their mean AST levels and platelet counts were 65.3±45.46IU/L and 223.2±78.80x10^9/L, respectively. The HCV/HIV co-infection group consisted of 158 patients, predominantly males (96.8%), and more than half were 40-49 years in age (51.3%). The mean AST levels and platelet counts were 62.6±47.97IU/L and 237.0±86.98 x10^9/L, respectively. The TE scores indicated that 34.2% of the HCV mono-infected and 21.5% of the HCV/HIV co-infected patients had cirrhosis. The demographic characteristics, laboratory test results, and radiological findings of all the patient are presented in Table I.

Discriminative ability of APRI

Figure 1 shows the AUROC of the APRI for HCV mono-infected patients and Figure 2 for HCV/HIV-co-infected patients. Applying APRI in all HCV mono-infected patients showed good discrimination between cirrhotic and non-cirrhotic cases, indicated by an AUROC above 0.8. However,

Table I. Demographic characteristics, laboratory test results and radiological findings of HCV mono-infected and HCV/HIV co-infected patients

Characteristic	HCV mono-infected	(%)	HCV/HIV co-infected	(%)
Total	709		158	
Age (year), mean (SD)	45.9	(9.74)	43.5	(6.94)
Age group				
20-29	26	(3.7)	2	(1.3)
30-39	153	(21.6)	45	(28.5)
40-49	284	(40.1)	81	(51.3)
50-59	174	(24.5)	25	(15.8)
60+	72	(10.2)	5	(3.2)
Gender				
Male	679	(95.8)	153	(96.8)
Female	30	(4.2)	5	(3.2)
Aspartate Aminotransaminase (IU/L), Mean (SD)	65.3	(45.46)	62.6	(47.97)
Platelet (109/L), Mean (SD)	223.2	(78.80)	237.0	(86.98)
Fibrosis grading by TE				
F0-F1	220	(31.0)	66	(41.8)
F2	152	(21.4)	31	(19.6)
F3	95	(13.4)	27	(17.1)
F4 / Cirrhosis	242	(34.2)	34	(21.5)

SD, standard deviation; TE, transient elastography.

Table II: Diagnostic accuracy of the APRI to diagnose liver cirrhosis among HCV infected individuals at different cut-offs using transient elastography as reference standard (n=709)

	HCV mono-infected patients		
	APRI >1.0	APRI ≥1.5	APRI >2.0
Sensitivity, % (95% CI)	61.8 (55.4, 68.0)	45.6 (39.2, 52.2)	29.9 (24.2, 36.1)
Specificity, % (95%CI)	88.7 (85.5, 91.4)	97.0 (95.0, 98.4)	98.5 (96.9, 99.4)
PPV, % (95%CI)	73.8 (68.2, 78.7)	88.7 (82.2, 93.1)	91.1 (82.8, 95.7)
NPV, % (95%CI)	81.9 (79.3, 84.2)	77.6 (75.5, 79.6)	73.2 (71.5, 74.8)
No. of patients matched the finding of TE, n(%)	564 (79.6)	564 (79.6)	533 (75.2)
False positive cases, n(%)	53 (7.4)	14 (2.0)	7 (1.0)
False negative cases, n(%)	92 (13.0)	131 (18.5)	169 (23.8)

HCV, hepatitis C virus; HIV, human immunodeficiency virus; APRI, aspartate aminotransferase-to-platelet ratio index; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; TE, transient elastography; 95%CI, 95% Confidence Interval

Table III: Diagnostic accuracy of the APRI to diagnose liver cirrhosis among HCV/HIV co-infected individuals at different cut-offs using transient elastography as reference standard (n=158)

	HCV/HIV co-infected patients		
	APRI >1.0	APRI ≥1.5	APRI >2.0
Sensitivity, % (95%CI)	32.4 (17.4, 50.5)	26.5 (12.9, 44.4)	20.6 (8.7, 37.9)
Specificity, % (95%CI)	87.1 (79.9, 92.4)	94.4 (88.7, 97.7)	96.8 (92.0, 99.1)
PPV, % (95%CI)	40.7 (26.1, 57.3)	56.3 (34.1, 76.2)	63.6 (35.2, 84.9)
NPV, % (95%CI)	82.4 (78.7, 85.7)	82.4 (79.2, 85.2)	81.6 (78.9, 84.1)
No. of patients matched the finding of TE, n (%)	119 (75.3)	126 (79.7)	127 (80.4)
False positive cases, n (%)	16 (10.1)	7 (4.4)	4 (2.5)
False negative cases, n (%)	23 (14.6)	25 (15.8)	27 (17.1)

HCV, hepatitis C virus; HIV, human immunodeficiency virus; APRI, aspartate aminotransferase-to-platelet ratio index; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; TE, transient elastography; 95%CI, 95% Confidence Interval

a slightly lower AUROC of the APRI for HCV/HIV co-infected patients (0.762) was observed.

Diagnostic performance of APRI

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the APRI at different cut-offs for the 709 HCV mono-infected patients is shown in Table II. Generally, using a cut-off of >1.0 yielded a sensitivity, specificity, PPV and NPV of 61.8%, 88.7%, 73.8% and 81.9%, respectively. The cut-off ≥1.5 showed a sensitivity of 45.6%, specificity of 97.0%, PPV of 88.7% and NPV of 77.6%. Using a cut-off of >2.0 made the APRI slightly more specific (98.5%) but much less sensitive (29.9%). It was also found that the lower cut-off resulted in a greater NPV. An APRI cut-off of >1.0 and ≥1.5 resulted in a similar number of patients that matched the finding of TE (564 patients, 79.6%), as compared to using cut-off >2.0 (533 patients, 75.2%).

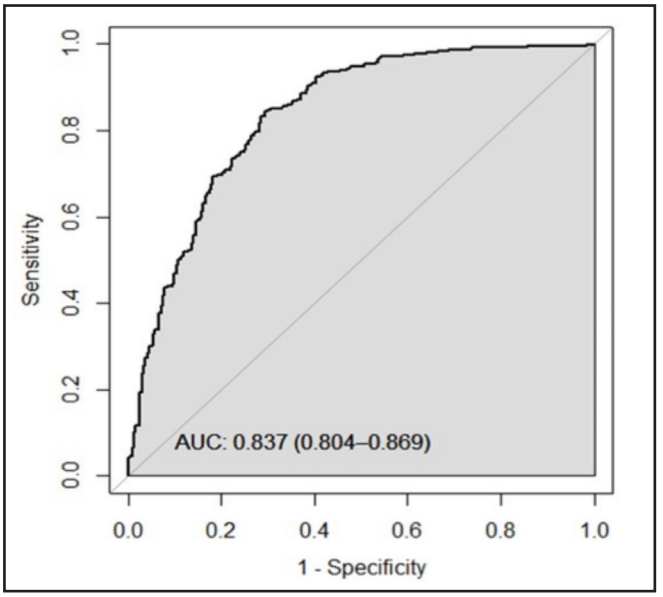

Fig. 1: Receiver operating characteristic analysis for the accuracy of APRI to diagnose cirrhosis (transient elastography ≥12.5kPa) in patients with chronic hepatitis C mono-infection (n=709).

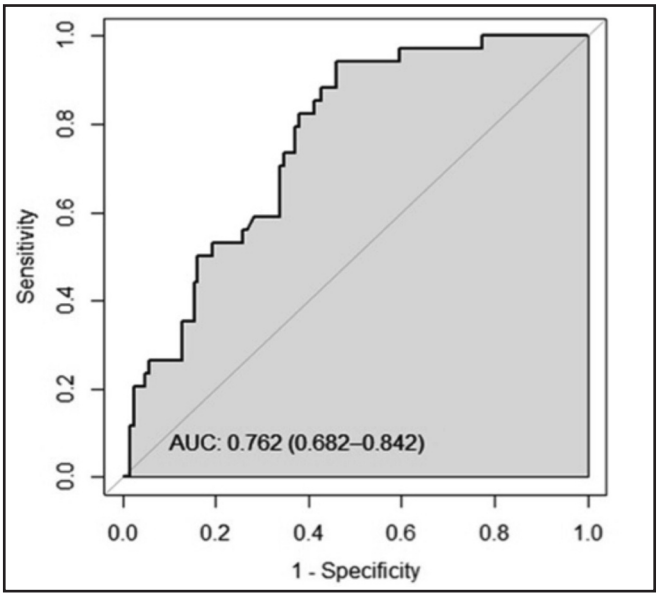

Fig. 2: Receiver operating characteristic analysis for the accuracy of APRI to diagnose cirrhosis (transient elastography ≥12.5kPa) in patients with HCV/HIV co-infection (n=158).

For the 158 HCV/HIV co-infected patients, the cut-off >1.0 showed a sensitivity of 32.4%, a specificity of 87.1%, a PPV of 40.7%, and a NPV of 82.4%, with 119 patients (75.3%) matching TE findings. A ≥1.5 cut-off matched TE findings in 126 patients (79.7%). The sensitivity, specificity, PPV and NPV were 26.5%, 94.4%, 56.3% and 82.4%, respectively (Table III). The number of patients that matched TE findings was 127 (80.4%), when considering the cut-off of >2.0 giving sensitivity, specificity, PPV and NPV of 20.6%, 96.8%, 63.6% and 81.6%, respectively.

DISCUSSION

Although this study presents the findings of an external validation on APRI using a local HCV-infected population as in most of the previous studies, our focus was on the evaluation of commonly used cut-off points used to diagnose LC using TE as the standard reference rather than suggesting a new one. A cut-off giving a good diagnostic accuracy to APRI would facilitate the treatment of HCV infection in primary health clinics without needing to refer patients to hospitals for further investigation. In addition, this would enable full-scale decentralised treatment of the disease.

The current study findings on the AUROC of APRI for discriminating between cirrhosis and non-cirrhosis cases among HCV mono-infected patients were consistent with those in a meta-analysis of 26 studies (>80%).[13] The meta-analysis also showed that AUROC of APRI for the HCV/HIV co-infection group was lower (0.79), but still better than the current study findings on similar groups of patients (0.76). Nevertheless, all studies included in the meta-analysis used liver biopsy as the standard reference to determine the status of the cirrhosis.[12]

In HCV mono-infected patients, our study shows that all three cut-off points yielded a good specificity (range 88.7-98.5%) but a relatively low sensitivity. However, the cut-off of >2.0 recorded the lowest sensitivity (29.9%), as well as the largest number of false negative cases. Although the cut-offs of >1.0 and ≥1.5 produced findings which agreed with those of TE for the same number of patients, the latter cut-off led to a smaller number of false positive cases. Therefore, as far as overtreatment of non-cirrhotic patients is concerned, 1.5 is the most clinically acceptable cut-off for LC screening in HCV mono-infected patients.

A similar observation was made when APRI was used on HCV/HIV co-infected patients. The use of 1.0 and 2.0 as the cut-offs were, respectively, limited by the high number of false positive and the high number of false negative cases. Even though APRI with a cut-off of ≥1.5 also seems to have a fair discriminative ability in detecting liver cirrhosis, this result should be interpreted with caution. A value of APRI below the threshold 1.5 could accurately indicate the absence of cirrhosis (NPV of 82.4% HCV/HIV co-infected patients). However, due to its relatively low sensitivity, additional physical examination and laboratory assessments are recommended to support the diagnosis of LC. The presence of chronic liver disease stigmata on physical examination, and low serum albumin or high bilirubin, were among the abnormal parameters that indicate LC.[1] Other non-invasive biomarkers, such FIB-4 index, can also be used along with APRI to enhance the accuracy of diagnosis.[27] A recent study suggests that the combined use of both biomarkers could increase the sensitivity, specificity, PPV and NPV up to 82.0%, 89.5%, 87.0% and 85.5%, respectively.[28]

The strengths of this study include the large study population, its multi-center design, as well as the high proportion of cirrhotic patients in the study. Nevertheless, the results from this study may not applicable to other HCV-infected populations such as patients co-infected with hepatitis B virus or have concomitant NASH. Another

limitation is that each participating centre had a different upper limit normal (ULN) value for AST. This could contribute to a lower diagnostic capacity for the APRI score.

CONCLUSION

In conclusion, APRI showed a fair to good discriminative ability in the diagnosis of liver cirrhosis among HCV mono-infected and HCV/HIV co-infected patients in Malaysia. The findings of this study favour a cut-off of 1.5, yet further assessment is likely to be required when the tool is used for diagnosing liver cirrhosis in HCV/HIV co-infected patients.

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Detection of foetal anomaly in advanced maternal age

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ABSTRACT

Objective: The aim of this study was to assess the prevalence of foetal anomaly diagnosed during a detailed ultrasonography amongst patients of advanced maternal age (AMA) and to identify the related anomalies in these age groups.

Method: A retrospective observational study amongst AMA mothers was done in Universiti Kebangsaan Malaysia Medical Centre, a Malaysian teaching hospital. The data over a period of three years (January 2013 – December 2016) obtained from the Maternal Foetal Medicine clinic registry was analysed. AMA mothers with singleton pregnancy presenting for foetal structural anomaly scan was included. They were later subdivided into 2 groups (35-39 years and ≥ 40 years). The logistic regression analysis was used to analyse the association of the chromosomal anomalies and the age groups.

Results: In all 486 patients were recruited and 84 patients were identified with foetal anomaly (17.3%). There was no significant difference in the prevalence of foetal anomalies or significant association with a specific structural foetal anomaly identified (p>0.05). However, the number of follow-ups for these patients are significantly higher (p<0.001).

Conclusion: The prevalence of structural foetal anomalies identified in detailed ultrasonography was low in AMA mothers. Hence, referral criteria for detailed anomaly ultrasonography need to be re-looked.

KEYWORDS:
Advanced maternal age, foetal anomaly, detailed foetal ultrasonography

INTRODUCTION

Childbearing above the age of 35 years old regardless of their parity is considered to be at an advanced maternal age (AMA). There has been an increase in number of pregnancies reported amongst women of advanced maternal age in the past two decades.[1] This increase is also seen amongst women in the high-income countries.[2] Many studies have also reported an association between AMA and higher outcome of adverse maternal and foetal outcome.[3-5]

Some of the adverse effects are low birth weight, preterm deliveries, stillbirth and unexplained foetal death.[6-11] Apart from these, the devastating effects of chromosomal and structural abnormalities are well known correlations.[12]

However, in recent years, studies have suggested that younger maternal age (19 years and less) may have a stronger risk factor resulting in congenital anomalies in comparison with AMA.[13,14] Many studies are now directed towards this. Nevertheless, we are still lacking data in our local population with limited resources available.

Most of the Maternal Foetal Medicine services in Malaysia screen patients from the AMA for structural anomalies from 18 weeks of gestation. However, the numbers are on a rise due to increasing rates of AMA mothers embarking in pregnancy. Against this background, the aim of this study was to examine the prevalence of structural anomalies amongst the AMA and to deduce the ideal AMA group patients who would benefit from screening. This would serve as a basis to concentrate on these particular groups in hospitals with limited resources and to reduce the number of unnecessary referrals to tertiary hospitals with a Maternal Foetal Medicine speciality.

MATERIALS AND METHODS

Study design

This was a retrospective observational study. This study was conducted in the Universiti Kebangsaan Malaysia Medical Centre (UKMMC), a tertiary teaching hospital, in the Department of Obstetrics and Gynaecology. Data over the period of three years (January 2013-December 2016) was obtained from the Maternal Foetal Medicine Registry of UKMMC. Approval from the UKM Research Ethics Committee was obtained (FF-2017-456).

The inclusion criteria were all mothers above ≥35 years old at the time of foetal anomaly ultrasonography with a singleton gestation. The mother had to undergo at least one foetal anomaly ultrasonography by the team in Maternal Foetal Medicine Unit who is credentialed to perform foetal anatomical survey. The exclusion criteria were patients aged below 35years old and multiple gestation.

Those participants who were included in the study was further subdivided into two age groups, i.e., 35-39 years and ≥40 years. Maternal demographic information and obstetrical history was entered in the database. Foetal anomalies identified were also included in the database for further analysis.

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Table I: Maternal ethnicity and foetal anomaly

Variable	Foetal anomaly in age group 35-39 years		P value	Foetal anomaly in age group ≥40yrs		p value
	Yes	No		Yes	No	
Malay	51	254	0.747	12	57	0.291
Chinese	12	63		7	13	
Indian	2	7		0	2	
Others	0	5		0	1	

*Pearson chi-square was applied for categorical data. p-value of <0.05 is significant.

Table II: Maternal parity and foetal anomaly

Variable	Age group 35-39 years	Age group ≥40yrs	P value
Parity 0	62 (15.7%)	9 (9.8%)	0.058
Parity 1-5	327 (83.0%)	79 (85.9%)	
Parity >5	5 (1.3%)	4 (4.3%)	

*Chi-Square test

Table III: Foetal structural anomaly identified in the compared group

Variable	n	Age 35-39yrs	Age ≥40yrs	OR (95%CI)	aOR (95%CI)	P Value
Nervous systems	13 (2.67%)	10 (2.54%)	3 (3.26%)	1.294 (0.349, 4.800)	1.133 (0.296, 4.334)	0.855
Urinary system	11 (2.26%)	8 (2.03%)	3 (3.26%)	1.626 (0.423, 6.253)	2.295 (0.572, 9.212)	0.241
GIT	19 (3.91%)	16 (4.06%)	3 (3.26%)	0.796 (0.227, 2.792)	0.808 (0.224, 2.923)	0.746
Limbs	6 (1.23%)	5 (1.27%)	1 (1.09%)	0.855 (0.099, 7.407)	1.152 (0.129, 10.256)	0.899
Hearts	26 (5.35%)	19 (4.82%)	7 (7.61%)	0.289 (0.662, 3.990)	1.601 (0.639, 4.011)	0.315
Others	30 (6.17%)	21 (5.33%)	9 (9.78%)	1.926 (0.851, 4.357)	1.989 (0.861, 4.595)	0.107

[a]Adjusted for ethnicity and parity. Logistic regression analysis was used. p-value of <0.05 is significant.
Note: The findings might be overlapped in a single patient.

Table IV: Association between foetal structural anomaly versus follow-ups

Variable		Foetal anomaly in age group 35-39 years		P value	Foetal anomaly in age group ≥40yrs		p value
		Yes	No		Yes	No	
Follow up	Yes	24	14	<0.001	12	0	<0.001
	No	41	315		7	73	

Pearson chi-square was applied. p-value of <0.05 is significant.

Table V: Association foetal anomaly identified versus amniocentesis

		Foetal anomaly in age group 35-39 years		P value	Foetal anomaly in age group ≥40yrs		p value
		Yes	No		Yes	No	
Amniocentesis done	Not done	59	326	<0.001	14	72	0.001
	Done	6	3		5	1	
Results	Normal	2	2	0.810	4	1	0.667
	Abnormal	4	1		0	1	

Pearson chi-square was applied. p-value of <0.05 is significant.

The primary outcome was to assess the prevalence of foetal anomalies diagnosed during the detailed ultrasonography. Structural anomalies were categorised by organ systems such as central nervous system, genitourinary system, gastrointestinal system, cardiovascular and musculoskeletal.

The secondary outcome of the study was to determine the relationship between foetal anomalies and the AMA, hoping to establish any particular system involved as per the age groups subdivided. Our hypothesis was that prevalence of foetal anomalies was higher with increasing maternal age.

Statistical analysis

The baseline maternal characteristics and the prevalence of chromosomal abnormalities between groups were compared using Chi square test and Mann-Whitney test. The logistic regression analysis was used to analyse the association of the prevalence of chromosomal anomalies and the subdivided age groups. All collected data were analysed using IBM Statistical Package for Social Science (SPSS) version 25. A p value <0.05 was considered statistically significant.

RESULTS

Four hundred and eighty-six women were included in our study where 394 women were in the age group of 35-39 years and the remaining 92 women were ≥40 years. The majority of patients were from the Malays 76.9%, followed by Chinese 19.5% and the Indians 2.2%, most likely due to catchment area, and this distribution concurs with the demographic breakdown of ethnicity in Malaysia (Table I)

As per our data, the patients from parity 1-5 were the largest number referred for detail anomaly scan and most of them belonged to the age group 35-39 years of age.

Mothers in their first pregnancy ≥40 years were nine patients comprising 9.8% of the same age group and 1.8% of the entire sample size. There is no statistical significance of AMA with the parity (Table II).

Eighty-four patients were identified with foetal anomalies, 65 patients of age group 35-39 years, i.e., 13.3% and 19 (3.9%) in ≥40 years group. There is no significant difference in the numbers seen in both groups.

Most of the foetal anomalies were noted in the cardiovascular system out of which 20 were identified having echogenic foci in the ventricles. Three had ventricular septal defect, one with tetralogy of Fallot and two with pericardial effusion.

The most common abnormality in the gastrointestinal system was the presence of hyperechoic bowel. This was identified in 16 patients and the remaining three were dilated bowel.

Nine foetuses were identified to have dilated renal pelvic calyces, one with suspected dysplastic kidney and one foetus was identified to have hydrocele.

As for the central nervous system, two foetuses were noted to have choroid plexus cyst, two foetuses with ventriculomegaly, one with a Blake's pouch cyst, two with absent of the vermis, three with enlarged cisterna magna and three had thickened nuchal fold.

There were six foetuses with shortening of the limbs and one with congenital talipus. Ten foetuses were identified to have abnormalities in more than one system. The distribution of anomalies by organ systems in both the AMA groups showed no significant association in the two groups (Table III)

There is a significant difference between follow up and structural anomaly status. Patients with identified foetal anomaly required more follow-up as they require further evaluation, counselling and plan (Table IV).

The patients who required further follow up to the Maternal Foetal Medicine Unit after structural anomaly identified was 42.8%, hence increasing the workload of the clinic further.

Even though there were four hundred and eighty-six patients recruited in this study, only 15 patients agreed for amniocentesis. The causes of this low uptake were unfortunately not documented in the registry (Table V).

DISCUSSION

AMA is reported to be associated with decrease in the risk of major congenital abnormalities in the absence of aneuploidy.[15] There is a four -fold increase in the risk of chromosomal abnormalities in older women. In comparison to mother in the age 25-29 years old, the mother above 35 years was four to seven times greater in foetuses having chromosomal abnormalities.[16] Our study similarly demonstrates that the prevalence of foetal anomalies was low despite the large group of patients screened (17.3%) with 2.04% having foetal anomalies involving more than one system. Hence, chromosomal and genetic disorders require screening that is more stringent rather than structural survey of foetus in AMA mothers. This is an important point that should be considered when deciding on methods of screening of all AMA mothers.

Based on the findings in our study, perhaps we should be looking at other methods of screening AMA mothers, since the prevalence of structural anomalies is not significantly higher. Therefore, there should be a shift in screening patients for structural anomaly to a more aggressive screening of aneuploidy by NICC or amniocentesis.

Amniocentesis even though invasive is relatively safe and more so in the hands of well-trained Maternal Foetal Medicine specialists. The risk of infection, i.e., chorioamnionitis is less than 0.1%. The rate of foetal lost related to amniocentesis is also low at around 0.5%. In our study, the number of patients that agreed for amniocentesis was low whereby only 15 patients agreed for the test in spite of a large number of 486 patients: undergoing foetal anomaly ultrasonography. Issues related to affordability, cultural, religious, or even poor counselling needs to be analysed to identify the reason. Unfortunately, the reason for refusal was unavailable in our data to make a conclusion.

In the recent years, cell free foetal DNA technology being a non-invasive test may be an option to consider in screening for aneuploidy in AMA mothers. In case where the test was abnormal, an amniocentesis is still required for confirmation. Bianchi et al. 2014 reported that invasive testing managed to identify 93% of trisomy 21, 64% with trisomy 18, 44% with trisomy 13 and 38% with sex chromosomal abnormalities in those with abnormal cell free foetal DNA results.[19] Hence, more studies looking into these choices of screening in AMA mothers may be more beneficial.

The age of screening pregnant mothers with a foetal anomaly ultrasonography is not standardised across the globe, similar discrepancies in different centres in Malaysia were also recognised. This may be due to the lack of expertise or the high load of cases in the tertiary centres making individual screening criteria different. In our study, we attempted to identify the ideal screening age group amongst the AMA mothers, hoping to concentrate more on these groups of mothers. Unfortunately, in our study, we could not identify the ideal age for screening AMA mothers for foetal anomalies as well as establish any relationship between foetal anomalies and the subdivided AMA groups. Perhaps future studies will guide us to identify the ideal age and focus on targeted systems.

Counselling is essential to ensure the patients truly understand the significance and importance of screening. Any doubts and uncertainties should be tackled during those sessions. The difference of screening for structural anomalies and chromosomal abnormalities, as well screening versus confirmatory test needed to be explained for further understanding. This may help patients being more willing for NICC or improve the uptake of amniocentesis if required as the uptake is rather poor based on our study. The primary care centres play a pivotal role in counselling, as the initial encounter with patients starts here.

This will significantly reduce the major bulk of the referrals for AMA to our Maternal Foetal Medicine Specialist and enable other high-risk obstetrics case to be given the importance. Indirectly improving the quality of care of these patients.

Our study has limitations, including its retrospective nature, being from a single tertiary centre and newer advances that may not be available in Maternal Foetal Medicine practice during the study period. More multi-centred studies are required to explore the ideal method and age groups for screening AMA mothers hoping to improve the quality of care for these women. More study on NICC and amniocentesis amongst AMA may also be beneficial. We hope that in future an appropriate screening will avail for these AMA mothers.

CONCLUSION

The prevalence of structural foetal anomalies identified in detailed ultrasonography was low in AMA mothers.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest. The authors alone are responsible for the content and the writing of the paper.

ETHICAL APPROVAL

The study was approved by the UKM Research Ethics Committee was obtained (FF-2017-456).

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The prevalence of Dysphagia among head and neck cancer patients in tertiary public hospitals in Malaysia

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ABSTRACT

Introduction: Dysphagia is the most common problem among head and neck cancer patients. It can occur before, during, and/or after cancer treatment due to cancer growth or side effects from cancer treatment. To date, the data on the prevalence of dysphagia in Malaysia is very limited. Therefore, the present study aimed to examine the prevalence and contributing factors of dysphagia.

Materials and Methods: A total of 240 patients (mean age 53.1, 167 males and 73 females) from Hospital Kuala Lumpur and the National Cancer Institute were enrolled in this research. All patients were interviewed individually in which they completed a thorough case history and swallowing screening test, including the water swallow test.

Results: The results revealed that 43.3% of patients had dysphagia. In multivariate logistic regression, occupation of the patients was found to be associated with dysphagia, i.e., working in service and sales sector (adjusted Odds Ratio, aOR=0.36, 95% Confidence Interval, 95%CI: 0.13, 0.99). Compared to patients without treatment, those who had chemoradiotherapy (aOR=4.45; 95%CI: 1.10, 17.99) were at an increased odd of developing dysphagia.

Discussion: This study showed that occupation, cancer stage, and type of treatment received by the head and neck cancer patients were crucial factors associated with the development of dysphagia. These findings guide the clinicians in identifying head and neck cancer patients who are at greater risks of developing dysphagia.

KEYWORDS:
Deglutition disorders, head and neck cancer, dysphagia, the prevalence

INTRODUCTION

Head and neck cancers are defined as an abnormal growth in the nasal, pharyngeal, and/ or laryngeal structures, including the salivary glands.[1] Collectively, these cancers are the sixth and tenth most frequently occurring cancers in men and women worldwide.[2] It is also one of the most crucial obstacles influencing the life expectancy of every country in the 21st century. In 2018, an estimated 887,659 new cases of head and neck cancer (excluding thyroid cancers) were reported worldwide. Cancer of the thyroid was not included due to the differences in treatment modality. Cancers of the lip and oral cavity are highly prevalent in southern Asia. They are also the leading cause of cancer death among men in India and Sri Lanka.[2]

In general, cancer is the second leading cause of death in Malaysia.[3] According to GLOBOCAN (2020), the cumulative incidence of head and neck cancer (nasopharynx, thyroid, lip, oral cavity, larynx, salivary glands, hypopharynx, and oropharynx) was 9.97% of the overall new cancer cases. The cumulative number of cases placed head and neck cancer as the third most common cancer in Malaysia, after breast and lung cancer, with total cases of 4,075. The previous report stated a total of 2,884 cases of head and neck cancer cases in Peninsular Malaysia in 2006.[4] The number increased to 11,920 cases in 2012.[5] The number of new cases could be attributed to the ageing population and sedentary lifestyle habits.[6]

Malaysia is a multicultural country with people of three major ethnic groups: Malays, Chinese, and Indians. The incidence of head and neck cancers varies by ethnicity; Indians have the highest incidence of laryngeal, oral, and pharyngeal cancers, followed by Malays and Chinese. On the other hand, nasopharyngeal cancer is most common among Chinese, followed by Malays, indigenous East Malaysians, and Indians.[3] Males were 1.2 times more likely to be affected with head and neck cancer in terms of gender distribution. Nasopharyngeal, laryngeal, and pharyngeal cancers were all more prevalent in men.[3]

Dysphagia is a common problem among head and neck cancer patients due to the abnormal growth of cancer cells and/or the side effects of cancer treatment such as surgery and radiotherapy.[7,8] Previous studies have shown that the prevalence of dysphagia was 40-60% in head and neck cancer patients[9-11] including post-operative patients, or had received chemotherapy, radiotherapy, chemoradiotherapy, or a combination of surgery with these therapies. Certain risk factors may worsen the severity of dysphagia among these cancer patients. For example, occupational exposure to dust, smoke, or polycyclic aromatic hydrocarbon was found to contribute to the risk of head and neck cancer development. At the same time, these particles can also act as irritants that may lead to inflammation in the neck area, subsequently

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affecting the swallowing mechanism.[12] Thus, it is vital to assess the types of occupation or the potential exposure at the workplace to estimate the risk of dysphagia and its severity among the patients.

To date, the vast majority of head and neck cancer epidemiological studies focused on dysphagia post-radiotherapy and chemoradiotherapy.[13-15] Factors including age, type of cancers, cancer location, type of cancer treatment, primary sites of cancer, and surgical location were reported to contribute to dysphagia.[16] In addition, the presence of comorbidities such as diabetes or hypertension may also influence the disease severity. For example, diabetes is often associated with periodontal infection, resulting in tissue destruction, altered inflammatory response, and subsequently cast a negative impact on the swallowing mechanism.[17] Another study reported that hypertension doubled the odds of dysphagia among patients with comorbidities[18] but this was not confirmed particularly among cancer patients. Although dysphagia is recognised as a head and neck cancer symptom at presentation, it is still necessary to comprehensively examine dysphagia before initiating cancer treatment so that its effects can be compared across all treatment modalities. By identifying the associated factors of dysphagia, necessary actions can be taken to prevent or reduce its severity so that the quality of life of the cancer patients can be improved.

In Malaysia, studies on the prevalence of dysphagia among patients with head and neck cancers are still scarce. Most of the studies are confined to a single centre or a single type of cancer such as nasopharyngeal cancer.[10,19] A study showed that 59.1% of patients complained of dysphagia before, during, or after the treatment of head and neck cancers.[10] To date, in Malaysia, dysphagia was mainly explored as the outcomes of oesophageal cancer,[19,20] stroke,[21] and malnutrition[22] while existing studies on the prevalence did not assess the associated factors.[10,20] A study on the prevalence of the health-related condition is crucial in the planning of human resources, facilities, and budget distribution in public hospitals.[20] This study, therefore, aimed to investigate the prevalence of dysphagia and its associated factors among head and neck cancer patients.

MATERIALS AND METHODS

Study Location

Data collection was carried out at the National Cancer Institute, Putrajaya (NCI), and Hospital Kuala Lumpur (HKL). NCI is the national referral centre for cancer patients[23] and HKL is the largest public hospital equipped with radiotherapy facilities. HKL is also the main referral hospital for head and neck cancer patients from other hospitals under the Ministry of Health, Malaysia.[24]

Patient selection

This was a cross-sectional study involving 240 patients with histologically-confirmed head and neck cancer from HKL and NCI. Newly diagnosed head and neck cancer patients and those who were on follow-up were recruited from both institutions. The sample size for this study was calculated using Daniel (1999) formula with a 10% non-response rate.[25] The research was carried out from November 2018 to May 2019. Head and neck cancer patients who were above 18 years old and could give consent to participate in the study were eligible to be recruited as study subjects. Patients were excluded if they had been diagnosed with dysphagia in conjunction with another medical condition such as a stroke or severe respiratory problems, if they had another type of cancer, or if they had low consciousness level and cognitive problems.

Study Instrument

A medical history form and swallowing screening form, i.e., the Modified Mann Assessment of Swallowing Ability (MMASA) developed by Antonios et al.,[26] was used in this study. The medical history form was created to assess previous and current medical histories, as well as the presence of comorbidities such as hypertension or obesity. It also recorded cancer characteristics such as primary sites of cancer, cancer stage, cancer treatment, side effects of radiotherapy, method of feeding, and types of diet. Data regarding age, gender, ethnicity, education level, and occupation level were also recorded.

The MMASA is one of the four most widely used dysphagia screening tests in the world. It has adequate reliability and validity with a sensitivity and specificity of more than 90%.[27] MMASA included 12 main indicators (alertness, ability to cooperate, comprehension of auditory, respiration, dysphasia, dysarthria, saliva, palate, tongue movement, tongue strength, gag, and ability to cough voluntarily) and one optional indicator (water swallow test). The maximum score is ten for each indicator. While administering MMASA, overall alertness level, oral preparation, oral and pharyngeal integrity (tongue strength, soft palate function, and gag reflex) of the patients were assessed. For the optional indicator, all patients were required to drink consecutive sips of 90ml of water. Patients showing signs of choking, coughing, or wet voices were asked to stop drinking. Patients with a score of less than 95 were considered as having dysphagia.[27,28] Their condition would be informed to their primary care doctors to be referred to speech and language therapists for dysphagia management.

Study procedures and analyses

Institutional approval and ethics clearance from the Universiti Kebangsaan Malaysia, Ministry of Health of Malaysia (NMRR-17-3460-34710), the NCI, and the HKL were obtained. On the day of data collection, potential patients were identified and approached. The purpose, procedure, and role of the patients as study subjects were explained clearly. The information sheet was provided to the potential study subjects, and they were screened based on the inclusion and exclusion criteria. Informed consent was obtained from all eligible study subjects before data collection.

All the data were obtained during the interview session with the patients. Next, they underwent the MMASA screening test followed by drinking 90ml of water. The test was conducted by a speech language therapist in the research team. For safety purposes, the patient was asked to drink the water in stages, starting from 2ml, 5ml (one teaspoon), followed by 10ml, 20ml, and a maximum of 90ml of water in a cup. Any patients who showed signs of aspiration when the fluid entered the airway at any stage were refrained from further

participation. Significant signs of aspiration included coughing and wet voice 7. During the swallowing trial, the researcher used the standard clinical bedside swallowing assessment by the Ministry of Health Malaysia.[29] During the procedure, the researcher would palpate the area at the level of the thyroid notch to examine laryngeal elevation during the swallow response. A normal laryngeal elevation is between 2 to 4 centimetres.[7] At the same time, the researcher placed the stethoscope at the side of the neck to auscultate for any acoustic information of the swallow response.

Patients were scored based on their swallowing ability. At the end of the test, the patient's scores were summed up and the maximum score would be 100. If the patient scored 95 and above as well as passing the water swallow test, the patient would be classified as having no dysphagia. In contrast, if the patient failed the water swallow test and obtained a score below 95, the patient would be classified as having dysphagia. For patients with dysphagia, the researcher informed the medical officer in charge to refer the patients for further dysphagia assessment by a speech language therapist in the same hospital.

All the data were entered and analysed using SPSS version 23. The categorical data were described in frequency and percentage. Chi-square analysis was conducted to assess the association of the study variables and the presence of dysphagia. In addition, univariate and multivariate logistic regression analyses were conducted to determine the strength of the variables in contributing to the odds of the presence of dysphagia among head and neck cancer patients.

RESULTS

Patient Demographics, Prevalence of Dysphagia and its characteristics

A higher proportion of patients were aged 51-60 years old (32.5%), males (69.6%), Chinese (43.4%), had secondary school education (50.0%) and were unemployed, pensioners, or housewives (42.1%). In this study the prevalence of dysphagia among the head and neck cancer patients was 43.3% (n=104). The majority of study subjects were able to feed orally (76.9%), and 10.6% had the nasogastric tube. The percutaneous gastrostomy tubes were used by 9.6% of the study subjects while only 2.9% of them had oral and nasogastric tubes. Only 18.1% consumed a normal diet, while a higher proportion (32.5%) had either a blended or a soft diet. Another 14.5% had a minced diet while 2.4% depended on nourishing fluid. A higher proportion of the patients had xerostomia (62.8%), while 22.1% reportedly had pain, followed by trismus (12.0%) and dysgeusia (9.4%) (Table I).

A higher proportion of patients had cancer of the pharynx, specifically nasopharynx (53.3%), followed by lip and oral cavity cancer (22.9%), larynx (9.6%), paranasal sinuses cancer (5.4%), and major salivary glands cancer (2.9%).

The proportion of patients with dysphagia was significantly higher among Indians (60.0%), followed by Malays (44.9%) and Chinese (34.6%). Type of occupation was found to be significantly associated with dysphagia among head and neck cancer patients (p=0.026). Majority of the study subjects were inpatients (61.7%), while outpatients mainly came from ENT and Oncology clinics. The type of admission was not associated with the presence of dysphagia. The presence of dysphagia was significantly higher among patients with lip and oral cavity cancer (67.3%) (p=0.001) as well as among patients with stage IV cancer (47.8%) (p=0.021). More than one-third of the head and neck cancer patients had chemoradiotherapy (CCRT) (37.5%). Another one-quarter received chemotherapy only (26.3%). There was a significant association between the types of cancer treatment and the presence of dysphagia (p=0.038). A higher proportion of patients who underwent surgery and chemotherapy presented with dysphagia (66.7%), followed by those who had surgery and radiotherapy (59.1%), radiotherapy only (50.0%), and CCRT (45.6%). A higher proportion of head and neck cancer patients presented with comorbidities such as hypertension or diabetes at the time of diagnosis (53.8%). However, it was not significantly associated with the presence of dysphagia.

The univariate logistic regression showed that patients' occupation, especially those from the service and sales sector (Odds Ratio, OR=0.37; 95% Confidence Interval, 95%CI: 0.15, 0.92) or those working as labourers (OR=0.45; 95%CI: 0.23, 0.89) were significantly associated with reduced odds of dysphagia compared to other types of occupations. As for types of cancer, patients with lips and oral cavity cancer were almost four times more likely to present with dysphagia compared to NPC patients (OR=3.92; 95%CI: 2.01, 7.68). On the other hand, stage II head and neck cancer patients were significantly associated with reduced odds of dysphagia compared to stage IV cancer patients (OR=0.15; 95%CI: 0.03, 0.66). Besides the three significant factors (types of occupation, sites of cancer, and stage of cancer), gender, ethnicity, type of admission, type of cancer treatment, and presence of comorbidity were also included in multivariate logistic regression as these variables showed a p-value of less than 0.25.

In multivariate logistic regression, occupation, especially those working in service and sales sector (adjusted Odds Ratio, AOR=0.36; 95%CI: 0.13,0.99, p=0.048) remained significantly associated with reduced odds of dysphagia compared to other types of occupations. The multivariate logistic regression also showed that patients who had chemoradiotherapy (AOR=4.45; 95%CI: 1.10, 17.99) were significantly associated with increased odds of dysphagia, as compared to patients without treatment, those.

DISCUSSION

This study showed that the prevalence of dysphagia among all head and neck cancer patients was 43.3%, inclusive of those before the treatment procedure and patients across all treatment modalities (Table III). This was consistent with a study by Pezdirec, Strojan, and Boltezar,[11] in which 41.3% of their head and neck cancer patients who underwent surgery, radiotherapy, chemoradiotherapy, or combined surgery and radiotherapy complained of dysphagia. On the other hand, Garcia-Peris et al.,[9] reported a higher prevalence of 50.6%. Similarly, Linn et al.,[10] who conducted a similar study among

Table I: Patient Demographics, Prevalence and Characteristics of Patients with Dysphagia

	Frequency (n)	Percentage (%)
Age		
≤40 years	38	15.8
41 to 60 years	135	56.3
≥61 years	67	27.9
Gender		
Male	167	69.6
Female	73	30.4
Race		
Malay	98	40.4
Chinese	104	43.4
India	35	14.6
Others	3	1.6
Education		
No Formal Education	26	10.8
Primary	58	24.2
Secondary	120	50
Post-secondary	36	15
Occupation		
Professional	19	7.9
Technicians and Associate Professionals	17	7.1
Service and Sales Workers	29	12.1
Craft and Related Trade Workers	16	6.7
Plant and Machine-operators and Assembler	25	10.4
Elementary Occupations	19	7.9
Unemployed/ pensioner	82	34.2
Housewife	19	7.9
Others	14	5.8
Dysphagia		
Yes	104	43.3
No	136	56.7
Method of Feeding (n=104)		
Oral	80	76.9
Nasogastric Tube	11	10.6
Percutaneous Gastrostomy Tube	10	9.6
Oral and Nasogastric tube	3	2.9
Types of Diet (n=104)		
Regular diet	15	18.1
Pureed diet	27	32.5
Soft and bite-sized diet	27	32.5
Minced and moist diet	12	14.5
Liquidised diet	2	2.4
Side Effect of Radiotherapy and Chemoradiotherapy*		
Pain	19	22.1
Xerostomia	54	62.8
Trismus	21	12.0
Dysgeusia	16	9.4
Completed Radiotherapy	55	59.1
Undergoing Radiotherapy	38	40.9
Week 1	10	26.3
Week 2	3	7.9
Week 3	7	18.4
Week 4	6	15.8
Week 5	5	13.2
Week 6	3	7.9
Week 7	4	10.5

*Multiple selection variable

head and neck cancer patients in dental clinics also reported a higher prevalence of 59.1% of dysphagia. These differences in prevalence could be attributed to the variation in study population and study design. Furthermore, some centres are equipped with more advanced treatment options that can reduce acute and late toxicities. On the other hand, some of the previous studies only included patients who were undergoing the treatment or had completed the treatment as compared to our study that also included patients who had yet to undergo treatment. In terms of study design, as a cross-sectional study, this is the most appropriate design in assessing the prevalence of health condition.[30]

In this study, age and gender were not associated with the presence of dysphagia. Thus, all age groups had a similar chance to be diagnosed with dysphagia due to head and neck

Table II: Association between sociodemographic, cancer characteristics, and presence of dysphagia among head and neck cancer patients

Parameter	All	Dysphagia		χ^2	p	OR	95% CI	p
	n(%)	Yes n(%)	No n(%)					
Age (years)				2.36	0.500			
≤40	38 (15.8)	18 (47.4)	20 (52.6)			1		
41-50	57 (23.8)	20 (35.1)	37 (64.9)			0.60	0.26, 1.39	0.233
51-60	78 (32.5)	37 (47.4)	41 (52.6)			1.00	0.46, 2.18	0.995
≥61	67 (27.9)	29 (43.3)	38 (56.7)			0.85	0.38, 1.89	0.686
Gender				1.53	0.216			
Male	167 (69.6)	68 (40.7)	99 (59.3)			1		
Female	73 (30.4)	36 (49.3)	37 (50.7)			1.42	0.82, 2.46	0.217
Ethnicity								
Malay	98 (40.4)	44 (44.9)	54 (55.1)	11.20	0.008	1		
Chinese	104 (43.4)	36 (34.6)	68 (65.4)			0.65	0.37, 1.15	0.136
India	35 (14.6)	21 (60.0)	14 (40.0)			1.84	0.84, 4.04	0.127
Others	3 (1.6)	3 (100.0)	0					
Education								
No formal education	26 (10.8)	14 (53.8)	12 (46.2)	1.85	0.605	1.30	0.47, 3.59	0.607
Primary	58 (24.2)	23 (39.7)	35 (60.3)			0.73	0.32, 1.7	0.471
Secondary	120 (50.0)	50 (41.7)	70 (58.3)			0.80	0.38, 1.69	0.555
Tertiary	36 (15.0)	17 (47.2)	19 (52.8)			1		
Occupation								
Professional	36 (15.9)	17 (47.2)	19 (52.8)	8.50	0.037	0.87	0.41, 1.88	0.736
Service and Sales	29 (12.8)	8 (27.6)	21 (72.4)			0.37	0.15, 0.92	0.033*
Labourer	60 (26.5)	19 (31.7)	41 (68.3)			0.45	0.23, 0.89	0.021*
Unemployed/ Pensioner/ housewife	101 (44.7)	51 (50.5)	50 (49.5)			1		
Type of admission				1.70	0.192			
Outpatient	92 (38.3)	35 (38.0)	57 (62.0)			1a		
Inpatient	148 (61.7)	69 (46.6)	79 (53.4)			1.42	0.84, 2.42	0.193**
Primary Sites of Cancer				19.79	0.001*			
NPC	128 (53.3)	44 (34.4)	84 (65.6)			1a		
Lip and oral cavity	55 (22.9)	37 (67.3)	18 (32.7)			3.92	2.01, 7.68	<0.001*
Larynx	23 (9.6)	7 (30.4)	16 (69.6)			2.55	0.83, 7.80	0.102**
pharynx	14 (5.8)	6 (4.4)	8 (7.7)			0.84	0.32, 2.18	0.713
Paranasal sinuses	13 (5.4)	5 (38.5)	8 (61.5)			1.19	0.37, 3.87	0.768
Major Salivary Glands	7 (2.9)	3 (42.9)	4 (57.1)			1.43	0.31, 6.68	0.648
Cancer Stages				8.76	0.021*			
Stage I	4 (1.7)	1 (25.0)	3 (75.0)			1a		
Stage II	17 (7.1)	2 (11.8)	15 (88.2)			0.40	0.03, 5.96	0.506
Stage III	62 (25.8)	26 (41.9)	36 (58.1)			2.17	0.21, 22.0	0.513
Stage IV	157 (65.4)	75 (47.8)	82 (52.2)			2.74	0.28, 26.9	0.387
Cancer Treatment				13.31	0.038*			
No Treatment	16 (6.7)	5 (31.3)	11 (68.8)			1a		
Radiotherapy only	10 (4.2)	5 (50.0)	5 (50.0)			2.20	0.43, 11.22	0.343
Chemotherapy only	63 (26.3)	19 (30.2)	44 (69.8)			0.95	0.29, 3.11	0.932
Surgery only	8 (3.3)	2 (25.0)	6 (75.0)			0.73	0.11, 4.99	0.751
Surgery and Chemotherapy	9 (3.8)	6 (66.7)	3 (33.3)			4.40	0.77, 25.15	0.096**
Surgery and Radiotherapy	44 (18.3)	26 (59.1)	18 (40.9)			3.18	0.94, 10.72	0.062**
Chemoradiotherapy	90 (37.5)	41 (45.6)	49 (54.4)			1.84	0.59, 5.73	0.292
Comorbidity				1.64	0.200			
No	111 (46.2)	51 (39.5)	78 (60.5)			1a		
Yes	129 (53.8)	53 (47.7)	58 (52.3)			1.40	0.84, 2.34	0.201**

Note: χ^2, chi-square; OR, Odds Ratio; 95%CI, 95% Confidence Interval.

cancer or the subsequent treatment. This was supported by Pezdirec et al.,[11] and Teguh et al.[31] Both studies revealed no statistically significant relationship between dysphagia with age and gender. There is a lack of studies on the ethnicity preponderance of head and neck cancer. To date, there is no data on overall head and neck cancer incidence across ethnicity reported in Malaysia. The National Cancer Registry (2019) reported that the incidence of nasopharyngeal cancer was relatively lower among Indians (age-standardised rate= 0.6 among males and 0.4 among females per) compared to Malays or Chinese. Overall, 57.5% of global cases of head and neck cancers are reported in Asia, especially in India.[32] Therefore, Indians in Malaysia may share the same genetic susceptibility of head and neck cancer. Our study was based in a multicultural country, and Indians were found to have a significantly higher proportion of dysphagia compared to

Table III: Multivariate logistic regression of factors associated with dysphagia among head and neck cancer patients

Variables	B	S.E.	AOR	95% CI		P
				Lower	Upper	
Gender						
Male			1a			
Female	-0.13	0.37	0.88	0.43	1.80	0.722
Ethnicity						
Malay			1a			
Chinese	-0.67	0.36	0.51	0.26	1.03	0.062
India	-0.38	0.53	0.69	0.24	1.94	0.479
Occupation						
Professional	0.03	0.44	1.03	0.43	2.47	0.940
Service and Sales	-1.02	0.52	0.36	0.13	0.99	0.048*
Labourer	-0.75	0.41	0.47	0.21	1.05	0.067
Unemployed/ Pensioner/ housewife			1a			
Type of admission						
Outpatient			1a			
Inpatient	0.14	0.36	1.15	0.57	2.32	0.694
Primary Sites of Cancer						
NPC			1a			
Lip and oral cavity	-0.18	0.95	0.83	0.13	5.39	0.848
Larynx	1.58	0.98	4.84	0.72	32.84	0.106
Pharynx	0.74	1.09	2.11	0.25	17.74	0.494
Paranasal sinuses	-1.07	1.02	0.34	0.05	2.55	0.296
Major Salivary Glands	-0.32	1.08	0.73	0.09	6.01	0.768
Cancer Treatment						
No Treatment			1a			
Radiotherapy only	0.67	0.99	1.95	0.28	13.73	0.501
Chemotherapy only	0.73	0.73	2.08	0.50	8.67	0.317
Surgery only	-0.50	1.11	0.60	0.07	5.38	0.652
Surgery and Chemotherapy	0.55	1.02	1.74	0.24	12.88	0.588
Surgery and Radiotherapy	1.44	0.77	4.20	0.92	19.12	0.063
Chemoradiotherapy	1.49	0.71	4.45	1.10	17.99	0.036*
Comorbidity						
No			1a			
Yes	0.55	0.33	1.80	0.95	3.43	0.074

other ethnicities. This showed that even though Indians in Malaysia have a lower incidence of head and neck cancer, they may be predisposed to a higher odd for advanced cancer or treatment outcomes such as dysphagia due to their genetic susceptibility. Nevertheless, this association needs be confirmed with genetic studies in the future. Other possibilities are late presentation due to poorer health education.

In addition, patients who were diagnosed with lip and oral cancers were three times more likely to have dysphagia. This is in agreement with studies by Pezdirec et al.,[11] and Valdez & Brennan,[33] both of whom detected a higher frequency of dysphagia among oral and/or oropharyngeal cancer patients.

Although the majority of the patients with dysphagia in this study (76.9%) were able to eat orally, only 18.1% of them were on a normal diet. The majority of them were unable to consume a normal diet as before after their cancer treatment due to swallowing difficulties. In a study among long-term head and neck cancer survivors, Kamal et al.,[34] found that only 28% were on normal diet.

The majority of the patients in the current study had xerostomia (62.8%), followed by pain (22.1%) due to the side effects of cancer treatment. Xerostomia is a common side effect of radiotherapy due to the damage to the salivary glands that results in reduced salivary flow and altered salivary composition [13]. Saliva plays an essential part in the formation of boluses [7]. It also moistens the food during chewing to ease the formation of a cohesive bolus that can facilitate swallowing. A study by Dirix et al., [13] found that more than half (54%) of head and neck cancer patients with xerostomia complained of eating problems, and 65% of them experienced restrictions in the amount and types of diet they consumed.

In this study, the head and neck cancer patients who worked in the service and sale sectors showed reduced odds of dysphagia. One possible reason was that patients with these types of occupations were generally more physically active at the workplace. The intensity of their daily physical activity can help them to develop higher resistance towards the toxicity of treatment. Another study highlighted that physical activity helped to maintain muscle structure and swallowing function in patients undergoing chemoradiotherapy for head and neck cancer [35].

Furthermore, many studies emphasised the need for all patients with head and neck cancer to undergo swallowing assessment as early as possible as they are more likely to

develop various degrees of dysphagia before starting the cancer treatment as well as throughout the disease and treatment. Past studies have shown that head and neck cancer patients who underwent early swallowing rehabilitation were associated with improved swallowing function.[11,16]

In this study cancer stage was not associated with dysphagia. In contrast to currrent finding, a study by Starmer et al.,[36] found that patients with stage IV cancer were more likely to have dysphagia than those at the early stages of cancer. Current study finding was in line to the findings by García–Peris et al.[9] also established that multimodality treatment was more likely to contribute to dysphagia compared to single treatment modality. Burnip, Owen, Barker, & Patterson[37] documented poor swallowing efficiency in patients who had both surgery and chemoradiotherapy. Mittal et al.,[38] explained that during the first few months, surgery is more likely to cause dysphagia, while after six months, the effect of neuromuscular damage and oropharyngeal fibrosis from radiotherapy is more obvious.

There are some limitations to our study. Firstly, only a water screening test was used to detect oropharyngeal dysphagia. In this study, consecutive sips of 90 ml of water during swallowing screening were used. A systematic review study by Brodsky et al.,[39] showed that consecutive sips of 90 ml during water swallow test were 91% sensitive (95%CI: 89%, 93%) and 53% specific (95%CI: 51%, 55%). Therefore, the water swallow test is useful for the early identification of dysphagia and screening for aspiration.[40] However, the test alone may not be adequate to predict aspiration.[40] For future studies, water screening tests should be complemented by the Fiberoptic Endoscopic Evaluation of Swallowing (FEES) or Modified Barium Swallow (MBS) to objectively rule out aspiration and to diagnose pharyngeal dysphagia.7 Furthermore, this study involved only two of the national referral hospitals. Other hospitals including university hospitals and private hospitals were not included. Thus, the prevalence of dysphagia might not be generalisable to the entire population of head and neck cancer patients in Malaysia. Therefore, future studies should consider a longitudinal study involving all referral hospitals in the country. Apart from examining the swallowing problems of head and neck cancer patients, future studies should also focus on eating difficulties, diet modification, and psychosocial effects following dysphagia to safeguard their physical wellbeing and quality of life.

CONCLUSION

In conclusion, the current study showed a relatively high prevalence of dysphagia in this study. More emphasis should be placed on early cancer detection or health-seeking behaviour. Our study highlighted that early detection significantly reduced the likelihood of dysphagia among head and neck cancer patients, thus producing a better quality of life. Due to environmental and workplace exposures, the occupation and lifestyle of patients are associated with the development of dysphagia after cancer diagnosis. Furthermore, the interaction between genetic and clinical factors should not be overlooked because they can produce a synergistic or confounding effect on the development of dysphagia in head and neck cancer. A longitudinal prospective study should be performed to determine the true effects on dysphagia or other treatment toxicities in patients with head and neck cancer using robust statistical analysis.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

This study received the ethical approval from the Medical Research & Ethics Committee of the Universiti Kebangsaan Malaysia and the Ministry of Health Malaysia.

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A retrospective cross-sectional study on the risk factors and survival outcome of End Stage Kidney Disease patients receiving regular maintenance haemodialysis with COVID-19 infection in Hospital Enche' Besar Hajjah Khalsom, Kluang

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ABSTRACT

Introduction: COVID-19 pandemic has affected healthcare services around the globe as hospitals were turned into designated hospitals to accommodate high risk groups of patients with COVID-19 infection including end stage kidney disease (ESKD) patients. In Malaysia, there was insufficient data on COVID-19 infection among ESKD patients. This study aims to determine factors and survival outcomes associated with COVID-19 infection among ESKD patients in a designated COVID-19 hospital in Malaysia.

Methods and Materials: A retrospective cross-sectional study involving 80 haemodialysis (HD) patients recruited from March 2020 till March 2021. Patients' information and results was retrieved and evaluated. Risk factors affecting the COVID-19 mortality were analysed using a one-way analysis of variance (ANOVA) and binary logistic regression.

Results: The mean age of the patients was 54 years who were predominantly Malays (87.5%) and living in rural areas. Majority of them had comorbidities such as diabetes mellitus (71%) and hypertension (90%). The most common presentations were fever (46%) and cough (54%) with chest radiographs showing bilateral lower zone ground glass opacities (45%). A quarter of the study population were admitted to the intensive care unit, necessitating mechanical ventilation. This study found that 51% of the patients were given steroids and 45% required oxygen supplementation. The COVID-19 infection mortality among the study population was 12.5%. Simple logistic regression analysis showed that albumin, Odd Ratio, OR=0.85 (95% Confidence Interval, 95%CI: 0.73, 0.98)) and absolute lymphocyte count OR=0.08 (95%CI: 0.11, 0.56) have inverse association with COVID-19 mortality. C-reactive protein OR=1.02 (95%CI: 1.01, 1.04), lactate dehydrogenase OR=1.01 (95%CI: 1.00, 1.01), mechanical ventilation OR=17.21 (95%CI: 3.03, 97.67) and high dose steroids OR=15.71 (95%CI: 1.80, 137.42) were directly associated with COVID-19 mortality.

Conclusion: The high mortality rate among ESKD patients receiving HD was alarming. This warrants additional infection control measures to prevent the spread of COVID-19 infection among this vulnerable group of patients. Expediting vaccination efforts in this group of patients should be advocated to reduce the incidence of complications from COVID-19 infection.

KEYWORDS:
ESKD, haemodialysis, COVID-19 infection, end stage kidney disease, Malaysia

INTRODUCTION

As the world marches into the year 2021 with the introduction of COVID-19 vaccines, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to devastate health and livelihoods worldwide. This enveloped RNA betacoronavirus, first identified at the end of 2019 in Wuhan, has since rapidly turned into a pandemic affecting countries throughout the world including Malaysia.[1] The disease burden of COVID-19 is high and has crippled most of the healthcare system worldwide.

The clinical presentation of COVID-19 varies widely. Most of the patients infected remain asymptomatic while others develop acute respiratory distress syndrome (ARDS) and multiple organ failures.[2] Many risk factors have been found which may influence the prognosis of patients with COVID-19. Poor prognosis is linked to risk factors such as old age, kidney diseases, hypertension, diabetes mellitus, cancer, chronic respiratory and cardiovascular diseases.[3]

The COVID-19 pandemic has not spared patients with end stage kidney disease (ESKD) . As these patients have multiple other comorbidities, they are more vulnerable and susceptible to COVID-19 infection. This is more apparent in the higher risk of cross infectivity in respective haemodialysis (HD) centres due to recurrent physical presence at healthcare facilities and physical proximity among patients during HD.[4] At the same time, patients needing dialysis have abnormalities in their innate and adaptive immune systems, which put them at a higher risk of adverse outcomes.

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In the Malaysian, almost 86.2% of the 45,937 ESKD patients receive renal replacement therapy (RRT) in the form of haemodialysis.[5] These patients have been receiving regular dialysis primarily from privately owned HD centres (50.2%), and government centres (30.0%) and centres run by non-governmental organisation (19.7%). Since the start of the pandemic, various recommendations and standard operating procedures by local experts have been drafted to prevent the emerging clusters of COVID-19 infection among dialysis patients and staffs.[6] Despite these efforts, incidences of COVID-19 infection among ESKD patients remain worrying.

This study explored the clinical condition, management, and survival outcomes of ESKD patients who had contracted COVID-19 infection and were admitted to a designated COVID-19 hospital in Johor, Malaysia.

MATERIALS AND METHODS

Study design and methodology

A retrospective cross-sectional study was conducted to assess the risk factors and survival outcome of End Stage Kidney Disease (ESKD) patients receiving regular maintenance haemodialysis with COVID-19 infection at Hospital Enche' Besar Hajjah Khalsom, Kluang (HEBHK).

Study area

HEBHK is a 268-bed hospital located in the district of Kluang, Johor which serves a population of 320,000. It is a hospital with intensive care units and has several major disciplines such as internal medicine, surgical, orthopaedics, paediatrics, and obstetrics and gynaecology. Since March 2020, HEBHK had been converted to a centralised COVID-19 hospital for the whole state of Johor. The objective was to pool these patients in a hospital for better monitoring and treatment.

Patients who tested positive via nasopharyngeal or oropharyngeal real-time polymerase chain reaction (RT-PCR) COVID-19 swab test were contacted and sent to HEBHK. Patients admitted to the hospital were isolated in the designated isolation wards with full history clerking and blood taken upon admission (within 24 hours) by the attending medical officer. They were stratified according to the protocol guidelines "COVID-19 Training Slides", implemented by the Ministry of Health, Malaysia. These guidelines were set by a team of experienced infectious disease consultants in Malaysia to help clinicians with risk stratification, monitoring of patients and monitoring of blood parameters, use of steroids and antiviral therapy in COVID-19 patients. The guideline also categorised COVID-19 patients into 5 categories. Category 1 is defined as asymptomatic, Category 2 as symptomatic with no evidence of pneumonia, Category 3 as symptomatic with evidence of pneumonia, Category 4 as symptomatic with evidence of pneumonia and requiring oxygen supplementation, and lastly, Category 5 as critically ill with multiorgan failure. Blood investigations taken included also for full haematology profiles, renal profiles, liver function tests, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin and arterial blood gas. A chest radiograph was ordered to determine the stage of pneumonia. Demographic information (age, gender, weight, height, body mass index, and pre-existing medical diseases) was also collected.

Patients were reviewed on a daily basis until they were discharged from the COVID-19 treatment pathway (transferred to another hospital for continuation of therapy for non-COVID-19 related health issues). All the patients were observed for at least 10-14 days depending on each individual's clinical condition of individual patient, chest radiograph changes and severity of the disease. They were given an appointment in the outpatient clinics of their respective district hospitals for health evaluation 1 month after discharge.

Inclusion and exclusion criteria

The inclusion criteria are ESKD patients tested positive for SARS-CoV-2 age ≥18 years old and who have received >3 months of regular HD admitted to HEBHK. Those who are on continuous ambulatory peritoneal dialysis (CAPD) were excluded.

Patient Recruitment

Data of patients who were admitted to HEBHK from March 2020 to March 2021 and met the inclusion and exclusion criteria were retrieved.

Definition of variables

Patients were classified as being from an urban area if the combined population of the area is greater than 10,000 people and at least 60% of the population is engaged in non-agricultural activities.

Ethics, consents and permissions

In compliance with ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline, all patients in this study were anonymised and numbered accordingly. No identifiers of patients were collected or used in the analysis.

This study was reviewed and approved by the Malaysian Medical Research Ethics Committee (NMRR-20-2729-57507). This is a study involving data collection through medical records, therefore informed consent from patients is not required.

Statistical Analysis

The statistical analysis was performed using SPSS Statistics for Windows, version 17.0 (SPSS Inc, Chicago, IL, USA). All data were presented as a mean±standard deviation (SD), while non-normal distributed variables were shown as median and interquartile range (IQR). Categorical variables have been shown as n (%). The continuous variables' differences in outcomes were measured using a one-way analysis of variance (ANOVA), while the categorical variables were measured using the chi-square test. For non-parametric variables, Mann-Whitney test was used. Multiple regression for all significant factors on univariate analysis was not done. The sample size for this study was 80 with 16 significant factors. The application of multivariate regression analysis requires over 100 cases for the model to have sufficient power (around 0,80).[7] Simple binary logistic was applied with stepwise forward selection [odds ratio, OR; 95%

Table I: Demography, Radiological Imaging and Management of 80 haemodialysis patients

Patient's characteristics	All (N, %)	Alive (n, %)	Dead (n, %)	p-value
Age, mean±SD	54.41±12.3	54.13± 2.57	56.40±10.34	0.588
Gender				0.035
Female	41 (51.2)	39 (55.7)	2 (20.0)	
Male	39 (48.8)	31 (44.3)	8 (80.0)	
Race				0.613
Malay	70 (87.5)	61(87.1)	9 (90.0)	
Chinese	5 (6.3)	5 (7.1)	0 (0)	
Indian	5 (6.3)	4 (5.7)	1 (10.0)	
Place of Residence				0.104
Urban	26 (32.5)	25 (35.7)	1 (10.0)	
Rural	54 (67.5)	45 (64.3)	9 (90.0)	
BMI (kg/m^2), mean±SD	26.43±5.7	26.62±5.90	25.13±3.75	0.441
Causes of ESKD				0.816
Diabetes Mellitus (DM)	3 (3.8)	3 (4.3)	0 (0)	
Hypertension (HTN)	17 (21.3)	14 (20.0)	3 (30.0)	
Glomerulonephritis	4 (5.0)	4 (5.7)	0 (0)	
Others	1 (1.3)	1 (1.4)	0 (0)	
DM and HTN	55 (68.8)	48 (68.6)	7 (70.0)	
COVID-19 category (on admission)				0.002
Category 1	10 (12.5)	10 (14.3)	0 (0)	
Category 2	9 (11.3)	9 (12.9)	0 (0)	
Category 3	33 (41.3)	31 (44.3)	2 (20.0)	
Category 4	18 (22.5)	15 (21.4)	3 (30.0)	
Category 5	10 (12.5)	5 (7.1)	5 (50.0)	
Comorbids				
Diabetes	57 (71.3)	50 (71.4)	7 (70.0)	0.926
Hypertension	72 (90)	63 (90.0)	9 (90.0)	1.000
Dyslipidaemia	35 (43.8)	30 (42.9)	5 (50.0)	0.670
Cerebral vascular events	3 (3.8)	1 (1.4)	2 (20.0)	0.004
Cardiovascular diseases	10 (12.5)	7 (10.0)	3 (30.0)	0.074
Others	16 (20)	15 (21.4)	1 (10.0)	0.398
Duration of dialysis (years)a, mean±SD	3.0 (4.85)	2.4 (5)	4.5 (4.0)	0.153
Education level				0.382
None	5 (6.2)	5 (7.1)	0 (0)	
Primary	22 (27.5)	21 (30.0)	1 (10.0)	
Secondary	43 (53.8)	36 (51.4)	7 (70.0)	
Tertiary	10 (12.5)	8 (11.4)	2 (20.0)	
Symptoms on admission				
Fever	37 (46.2)	30 (42.9)	7 (70.0)	0.107
Fatigue	7 (8.8)	4 (5.7)	3 (30.0)	0.011
Cough	43 (53.8)	37 (52.9)	6 (60.0)	0.672
Shortness of breath	25 (31.2)	18 (25.7)	7 (70.0)	0.005
Chest pain	2 (2.5)	2 (2.9)	0 (0)	0.588
Nausea	6 (7.5)	5 (7.1)	1 (10.0)	0.748
Radiological imaging				
Pneumonia/Consolidation				0.028
Left	8 (10.0)	7 (10.0)	1 (10.0)	
Right	8 (10.0)	6 (8.6)	2 (20.0)	
Bilateral	11 (13.8)	7 (10.0)	4 (40.0)	
None	53 (66.2)	50 (71.4)	3 (30.0)	
Ground glass opacities				0.193
Left	11 (13.8)	9 (12.9)	2 (20.0)	
Right	9 (11.3)	9 (12.9)	0 (0)	
Bilateral	36 (45.0)	29 (41.4)	7 (70.0)	
None	24 (35.0)	23 (32.9)	1 (10.0)	
Treatment and Management				
Antibiotics usage	46 (57.5)	37 (52.9)	9 (90.0)	0.026
Antibiotics duration (Days), mean±SD	9.5±4.5	9.5±4.9	9.7±2.8	0.916
Steroid usage				0.004
Low dose steroid	8 (10.0)	8 (11.4)	0 (0)	
High dose steroid	33 (41.2)	24 (34.3)	9 (90.0)	
None	39 (48.8)	38 (54.3)	1 (10.0)	
Steroid duration throughout hospitalisation (days), mean±SD	14.32±5.83	15.38±5.72	10.56±4.75	0.026
Oxygen supplementation	36 (45)	26 (37.1)	10 (100)	<0.001
ICU admission	20 (25)	13 (18.6)	7 (70.0)	<0.001
ICU duration (Days) (only 20 patients), mean±SD	11.7±7.0	12.3±8.1	10.6±4.8	0.612
Mechanical ventilation	19 + 1*(25)	12 (17.1)	7 + 1*(80.0)	<0.001
Inotrope usage	20 (25)	12 (17.1)	8 (80.0)	<0.001
Total days of hospitalisation (Days) , mean±SD	15.93±7.41	16.43±7.43	12.40±6.62	0.108

* Patient demised at Emergency Department

[a] Data not normally distributed, median and IQR reported, non-parametric- Mann-Whitney test was used

Table II: Laboratory parameters of 80 haemodialysis patients

Laboratory Parameter	All (N=80)	Alive (n=70)	Dead (n=10)	P=value
Sodium (mmol/L)	135.21±4.0	135.30±3.88	134.60±4.81	0.604
Potassium (mmol/L)	4.18±0.8	4.20±0.76	4.05±1.06	0.573
Urea (mmol/L)	19.41±8.5	18.87±8.26	23.19±9.99	0.136
Chloride (mmol/L)	95.47±4.7	95.94±4.59	92.2±3.94	0.017
Creatinine (µmol/L)	850.81±367.1	841.61±365.41	914.30±392.54	0.562
Heamoglobin (g/dl)	9.88±1.7	9.80±1.64	10.39±2.07	0.309
White blood cell (10^3/µL)	7.16±2.9	7.10±2.87	7.58±2.94	0.625
Absolute Lymphocyte Count (ALC) (10^3/µL)	1.27±0.7	1.35±0.644	0.70±0.49	0.003
Platelet (10^3/µL)	239.03±115.7	244.49±121.54	200.8±48.72	0.267
Absolute Neutrophil Count (ANC) (10^3/µL)	5.22±3.0	4.96±2.83	7.03±3.47	0.038
Monocytes (10^3/µL)	0.55±0.3	0.57±0.25	0.37±0.24	0.021
Total Bilirubin (µmol/L)	10.25±4.0	10.00±3.86	11.96±3.96	0.145
Total Protein (g/L)	75.78±6.9	75.86±6.86	75.20±7.32	0.780
Albumin (g/L)	35.96±4.6	36.42±4.32	32.80±5.12	0.018
AST (U/L)[a]	21.00 (16.00)	19.00 (10.00)	35.50 (99.75)	0.009[c]
ALT (U/L)[a]	13.00 (14.00)	12.00 (13.00)	24.50 (39.75)	0.008[c]
ALP (U/L)	119.67±76.7	122.28±79.19	101.00±55.67	0.413
Ferritin (µg/L)[b]	1865.70 (2469.25)	1455.00 (2815.00)	3132.20 (3226.50)	0.063[c]
CRP (mg/L)[a]	30.70 (66.10)	23.75 (49.58)	187.50 (168.50)	<0.001[c]
LDH (U/L)	292.74±195.8	264.37±128.66	482.80±195.78	0.001

[a] Median and IQR is reported for this variable.
[b] Ferritin levels are available for 40 subjects, 31 of whom are alive and 9 of whom are deceased.
[c] Mann-Whitney test was used for non-parametric data

Table III: Simple logistic regressions of mortality risk factors in 80 haemodialysis patients

Factor	OR	95% CI	p-value	Adjusted OR*	Adjusted 95% CI	Adjusted p-value
Age (years)	1.02	0.96, 1.08	0.583			
Gender	0.20	0.39, 1.00	0.520			
High dose steroid	14.25	1.70,119.70	0.050	15.71	1.80,137.42	0.045
BMI (kg/m^2)	0.95	0.84,1.08	0.437	0.96	0.83, 1.12	0.608
Fever	3.11	0.74,13.04	0.121	2.83	0.64, 12.51	0.169
Cough	1.34	0.35, 5.16	0.672	2.23	0.52, 10.10	0.271
Mechanical Ventilation	19.33	3.64,102.65	0.001	17.21	3.03, 97.67	0.001
ALC (10^3/µL)	0.08	0.01,0.50	0.007	0.08	0.11, 0.56	0.011
Albumin (g/L)	0.85	0.74,0.98	0.025	0.85	0.73,0.98	0.027
CRP (mg/L)	1.02	1.01,1.03	<0.001	1.02	1.01, 1.04	0.001
LDH (U/L)	1.01	1.00, 1.01	0.031	1.01	1.00, 1.01	0.041

Age and gender adjustments were made.
* Adjusted odds ratio (OR) to age and gender

confidence interval (95%CI)] to identify factors associated with mortality among ESKD COVID-19 patients in this study. Based on national COVID-19 data, adjustments were made for age and gender because age and gender were known to affect mortality.[8] A p-value of <0.05 was considered significant.

RESULTS

A total of 80 ESKD patients who were admitted to HEBHK for COVID-19 infection from March 2020 to March 2021 were enrolled into the study. There was almost an equal distribution of male and female patients. The mean age was 54 (±12) years old with 67% of them staying in rural areas. Malays made up the largest cohort of patients at 87.5%, followed by Chinese (6.3%) and Indians (6.3%). Their level of education was mostly up to primary (27.5%) and secondary school level (53.8%). In terms of comorbidities, 68.8% of the participants developed ESKD due to both hypertension and diabetes mellitus. A total of 35 (43.8%) patients had dyslipidaemia. The mean BMI was 26.43kg/m^2. Ten patients (12.5%) had a history of cerebrovascular accident (CVA) and another three (3.8%) had a history of cardiovascular disease (CVD). The median duration of patients receiving haemodialysis was 3 years with an interquartile range of 4.85 years.

The majority of the patients admitted to the hospital were categorised as Stage 3 (with pneumonia changes) and above; 41.3% of them had stage 3 COVID-19 infections, 22.5% is in stage 4 (requiring oxygen supplementation) and 12.5% in stage 5 (multi-organ failure). Most common reported presenting symptoms were cough (53.5%), fever (46.2%) and shortness of breath (31.2%).

The mean total white cell count was 7.16x10^3/µL with mean absolute lymphocyte count of 1.27x10^3/µL. Mean ferritin level (n=40) was high with 3621.87µg/L, mean CRP value was 62.83mg/L. Radiographic abnormalities, especially ground glass opacities were common among ESKD patients in this study. On chest radiographs, 36 (45%) patients had bilateral ground glass opacities, 11 (13.8%) had left sided

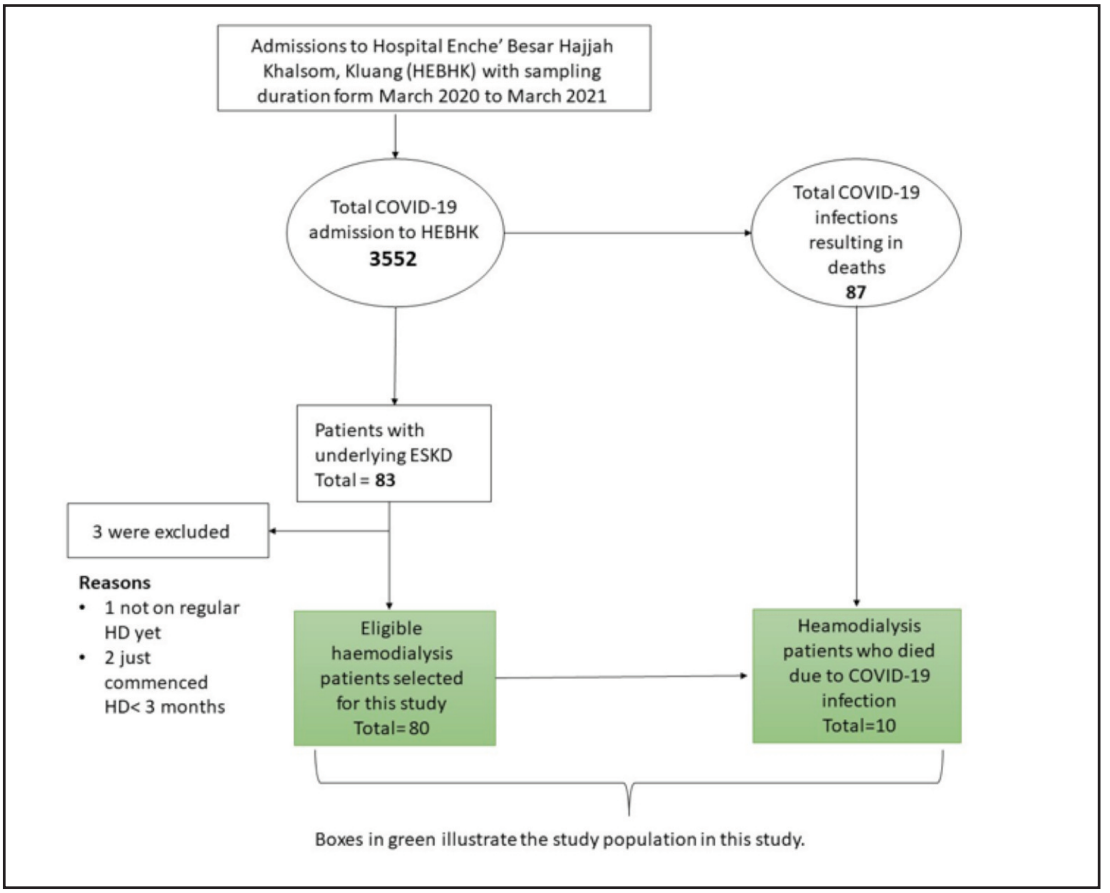

Fig. 1: Selection of study population from March 2020 to March 2021 in HEBHK.

ground glass opacities and 9 (11.3%) had right sided ground glass opacities. About one third of those 27 (33.8%) had concomitant pneumonia or consolidation changes.

A total of 46 (57.5%) ESKD patients had received antibiotics for a mean duration of 9.5 days. A total of 33 (41%) required high dose steroid (intravenous methylprednisolone 1mg/kg/day) while eight (10 %) were given low dose steroid (intravenous dexamethasone 6mg daily) during the hospitalisation. Almost half (45%) required oxygen therapy during their stay and a quarter (25%) required intubation and inotropes. The mean duration of hospitalisation and ICU stay were 15.92 days and 11.7 days respectively. Twenty (20) ESKD patients were admitted into the ICU; 19 of whom required mechanical ventilation.

A total of 10 (12.5%) ESKD patients in this cohort succumbed due to COVID-19 infection. Seven deaths were reported in the intensive care unit (ICU) and two deaths were reported in the COVID-19 ward. There was one ESKD male patient who died in the emergency department after contracting category 5 COVID-19 infection. His COVID-19 PCR swab test later turned out to be positive after his demise. All the patients who died from COVID-19 infection received mechanical ventilation except for two patients in the COVID-19 ward. One of the two patients who were not ventilated refused active resuscitation or intubation, while the other patient's clinical condition rapidly deteriorated in the ward despite prompt resuscitation.

In this cohort, high dose steroid (intravenous methylprednisolone 1mg/kg/day) was given to ill patients (Category 4 and 5) who developed warning signs or required ICU admission. Low dose steroid (intravenous dexamethasone 6mg daily) was served to Category 3 patients with raised inflammatory markers. Following consultation with the infectious disease team, steroids were administered (high or low dose) for five days before being tapered down based on their clinical responses, inflammatory markers and chest radiographs. Steroids were either extended in terms of duration or escalated (change from dexamethasone to methylprednisolone) if patients deteriorated. Antibiotics were administered to 57% of the cohort for secondary bacterial infection. This was due to prolonged steroid usage or hospital acquired infections as they generally spent an average of 15 days in HEBHK.

Table III shows several factors associated with mortality using simple logistic regression. Absolute lymphocyte count (ALC), OR=0.08 (95%CI: 0.11, 0.56) and serum albumin, OR=0.85 (95%CI: 0.73, 0.98) have an inverse association with COVID-19 mortality. COVID-19 mortality was directly associated with C-reactive protein, OR=1.02 (95%CI: 1.01, 1.04), lactate dehydrogenase, OR=1.01 (95%CI: 1.00, 1.01), mechanical ventilation, OR=17.21 (95%CI: 3.03, 97.67), and high dose steroids, OR=15.71 (95%CI: 1.80, 137.42). There was no correlation between age, gender, BMI, or clinical symptoms and mortality rate in this study.

DISCUSSION

Given their immunocompromised nature, high comorbidity burden and impracticable social distancing restrictions in haemodialysis centres, ESKD patients with various comorbidities were among the most vulnerable population to be infected with COVID-19 infection.[9,10] Several risk factors such as advanced age >65 years old, chronic systemic diseases namely hypertension, diabetes mellitus, and cardiovascular diseases had been attributed to the increased risk of developing severe type and mortality of COVID-19 infections.[11,12] Mortality rates vary between 16-32% based on reported cases around the world.[13] Herein, our study describes the experience in managing ESKD patients with COVID-19 infection in a COVID-19 hospital setting. The cohort in this study represents 1.12% of total haemodialysis patients in the state of Johor, Malaysia.

The initial presentation of COVID-19 infections varies from being asymptomatic to developing severe acute respiratory distress. However, there were some reported cases of atypical presentation involving gastrointestinal symptoms.[14,15] The most common presenting symptoms in our cohort were cough (53.8%) and fever (46.2%). These findings were similar to several other studies conducted in dialysis centres around the world.[16-18] Approximately 12.5% of our cohort remained asymptomatic throughout hospitalisation. Radiological imaging via chest radiograph showed more than half of our cohort had bilateral infiltrates attributed to active COVID-19 infection or chronic underlying volume overload. Thirty three percent (33%) of them developed consolidations probably from the disease itself or secondary bacterial infection due to their immunocompromised state.

From March 2020 to March 2021, Malaysia recorded 1,272 mortalities out of 345,500 confirmed COVID-19 patients representing 0.37%. Data from HEBHK showed a total admission of 3,552 COVID-19 patients with 87 deaths over a similar period. This represented a 2.44% overall mortality rate. On the other hand, this study has shown that the mortality rate from COVID-19 infection among haemodialysis patients stands at 12.5%. Of the ten deaths recorded in HEBHK, four were classified as deaths due to COVID-19, while the remaining six were due to death with COVID-19. In comparison to the overall national mortality rate in Malaysia and HEBHK, the mortality rate among ESKD patients receiving haemodialysis with COVID-19 is 33.8 times and 5.1 times higher respectively. This mortality rate, however, was lower as compared to the meta-analysis done by Kooman et al., on the outcome of dialysis patients with COVID-19 infections in different centres around the world which recorded a mortality rate that ranged from 16.2% to 32.8%.[13]

There were several relevant factors that may have contributed to the lower mortality rate observed in our cohort. ESKD patients who were unwell with warning signs were detected early and alerted to the healthcare authorities for initial surveillance and hospitalisation. Contact tracing of family members of patients and staff was performed swiftly to contain the spread of COVID-19 infections. Admission of this group of patients was prioritised to enable closer monitoring in wards and to minimise the risk of transmission to other ESKD patients or staff at respective HD centres. Strict adherence to national guidelines in managing ESKD patients with COVID-19 infection was practised. In addition, they were monitored for a period of 2 weeks with regular HD in a designated ward. As the majority of our study population presented with Category 3 and above, early detection of warning signs, prompt referral to intensivists and availability of ICU care with mechanical ventilation improved the overall survival rate as well.

This study found several risk factors associated with increased risk of mortality. This is similar to findings by Tortonese et al., where CRP and LDH showed a direct association with mortality[18]. Patients with high inflammatory markers were more likely to deteriorate as the cytokine storm may lead to severe respiratory distress. Absolute lymphocyte count has an inverse association with mortality as lymphopenia marked the activation of pro- inflammatory cytokines that lead to increased disease severity.[18] Albumin has been a predictor of mortality in various studies dated to the pre-COVID-19 era. Malnutrition, particularly among the dialysis population has been linked to increased deaths during this pandemic.[20] Multivariate analysis of our cohort showed albumin had an inverse association with mortality. The need for mechanical ventilation also increases the risk of death. Our study did not find an association between age, gender or clinical symptoms with mortality.

Systemic corticosteroid administration has been the mainstay treatment of COVID-19 infection especially during the cytokine storms.[21] The initiation of steroid therapy for COVID-19 patients with Category 4 and above was discussed with infectious disease (ID) consultants and based on the national guideline- Clinical Management of Confirmed COVID-19 Case in Adult and Paediatric, Annex 2e.[22] The duration of steroid administration varied based on clinical condition and inflammatory markers after consulting the ID team. In managing ESKD patients with COVID-19, it was found that administering high doses of systemic corticosteroid such as methylprednisolone was associated with a higher mortality risk. This is likely due to an increased risk of nosocomial infections; either ventilator related or prolonged hospitalisation. High doses of systemic corticosteroid were used mainly among ill patients with severe clinical conditions, those who required oxygen supplementation, longer hospitalisation, ICU care and inotropic support.

The introduction of drugs such as hydroxychloroquine, lopinavir, ritonavir and interferon were hotly discussed and debated by experts around the world. These drugs were suggested as a mode of therapy for patients in the first and second waves of the COVID-19 pandemic in Malaysia. Our cohort was recruited mainly from the third wave of the COVID-19 pandemic in Malaysia whereby steroids and oxygen therapy were the mainstay. The data showed only one ESKD patient received hydroxychloroquine as part of COVID-19 treatment whereas two ESKD patients with SLE had their hydroxychloroquine continued during hospitalisation. Three patients received tocilizumab in this cohort (two died, one alive). Tocilizumab was given to patients with severe disease in the ICU based on ID recommendation. In view of the small number of

prescriptions for hydroxychloroquine and tocilizumab, no proper conclusion or data can be analysed to substantiate the effectiveness of these drugs.

The limitations of this study include a small sample size, the retrospective nature of our data and missing laboratory test results of some patients. The true total number of ESKD patients infected with COVID-19 could not be depicted because ethical approval was only obtained for HEBHK. Although this cohort reflected the true demography of multiethnicity disposition in Malaysia, more data was needed to determine the association between various ethnic groups and the need for hospitalisation based on COVID-19 severity. As this cohort only included patients on regular haemodialysis, no data could be compared between haemodialysis, peritoneal dialysis, and transplant patients.

CONCLUSION

The findings from this study demonstrates a higher mortality rate among hospitalised patients with ESKD receiving haemodialysis. Several risk factors were identified which contributed to higher mortality rate in this study. These factors were low actual lymphocyte count, low albumin, increased CRP, increased LDH and patients who required mechanical ventilation and high dose steroid. Therefore, patients undergoing haemodialysis are at a high risk of mortality. Strict infection control measures and compliance with standard operative protocols are necessary to limit the spread of COVID-19 among this population in order to lower the risk of mortality in ESKD patients. Advocating and expediting vaccination programmes should be encouraged to reduce the severity and mortality of COVID-19 infections.

ETHICS APPROVAL

This study has been approved by Malaysian Medical Research Ethics Committee (NMRR-20-2729-57507). This is a study involving data collection through medical records, therefore informed consent from patients is not required.

CONSENT FOR PUBLICATION

We would like to thank the Director-General of Health, Malaysia for his permission to publish this report.

AVAILABILITY OF DATA AND MATERIALS

The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

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AUTHORS' CONTRIBUTIONS

CHH, CYH and YYL designed the study. CHH, CYH, YYL and TPS executed and analysed the study. TXT, HY and CPW drafted the manuscript. All the authors read and approved the final manuscript.

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Clinical manifestations of early childhood dengue virus infection in Thailand

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ABSTRACT

Introduction: Clinical manifestations of dengue infection has a wide spectrum. This study aimed to describe and compare the clinical aspects of dengue infection in early childhood and those in older children.

Materials and Methods: All dengue patients hospitalised at King Chulalongkorn Memorial Hospital, Bangkok, Thailand during 1987-2008 and aged 0-15 years were included. All parameters were compared between patients in two groups: aged 0-2 years and >2-15 years.

Results: Of the 2,221 children who were diagnosed with dengue, 179 were children aged 0-2 years compared with 2,042 children aged >2-15 years. The early childhood group presented significantly more frequently with hepatomegaly, drowsiness, diarrhoea, rash, convulsions, splenomegaly, and unusual manifestations. Dengue fever (DF) was more common in the early childhood group and dengue haemorrhagic fever (DHF) was less common. The mortality rate of the early childhood group was 1.67%, which was significantly higher than that of the comparative group. Approximately 65% of study subjects were serologically proven to have primary infection, compared to 9.8% of older children.

Conclusions: Clinical manifestations of dengue infection in early childhood are different in some aspects from those of dengue infection in older children, and mortality is higher. To effectively prevent dengue infection morbidity and mortality in children, it is essential that clinicians correctly recognize and diagnose dengue infection, particularly in early childhood.

KEYWORDS:
Dengue infection, Early childhood, Morbidity, Mortality, Thailand

INTRODUCTION

Dengue infection is a major health problem of Southeast Asia and the West Pacific.[1] Estimates of the disease burden suggest that there are nearly 100 million symptomatic dengue infections worldwide every year with the majority (75%) occurring in Asia and the West Pacific.[2] Disease incidence and deaths remains highest in children ≤15 years and case fatality rates were highest in young children.[3] The clinical manifestations of dengue virus infections have a wide spectrum, ranging from mild acute febrile illness to classical dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS).[4]

In Thailand, rate of dengue infection in children is significantly increasing each year.[5] Additionally, a growing number of dengue infections are related to unusual manifestations in children with dengue, such as severe involvement of the liver, brain, kidney, or heart.[6-10] It has been shown that clinical manifestations of dengue infections during early childhood differ from those that occur in older children; furthermore, the case-fatality among infants with severe dengue disease is higher than that in older children.[5] Because of the bigger sample size, it should have a power in determining the mentioned difference. And there is no specific treatment for dengue infection, and the outcomes depend on early recognition of infection and careful monitoring of the patients. Therefore, we conducted this study to describe the clinical aspects and complications of dengue infection in early childhood and compare them with those in older children.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand from 1987 to 2008. Inclusion criteria included 1) children aged 0-15 years who were admitted to King Chulalongkorn Memorial Hospital, 2) clinical diagnosis and disease severity of dengue virus infection, using the 1997 World Health Organization (WHO) criteria[11], and/or 3) confirmed dengue serological diagnosis, using hemagglutination inhibition test and/or an enzyme-linked immunosorbent assay (ELISA).

Patients were classified into two groups: children aged 0-2 years (early childhood group) and children aged >2-15 years (comparative group). Primary and secondary dengue virus infections were classified according to the serological criteria.[12] Data collected from medical records included symptoms and signs and laboratory findings of the patients. All parameters were compared between groups.

This study obtained ethics approval from the Forum for Ethical Review Committees of Srinakharinwirot University. Descriptive data were analyzed using SPSS 18.0. Variables were compared by chi-square test. A $p < 0.05$ was considered to be statistically significant.

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Table I: Symptoms and signs of the early childhood group (aged 0-2 years) in comparison to older children (aged >2-15 years) with dengue virus infections

Symptoms	0-2 years (n=179)	>2-15 years (n=2,042)	p-value
Days of fever prior to admission	4.4	4.9	NS
Hepatomegaly (%)	82.1	74.3	0.02
Coryza (%)	5.0	3.4	NS
Vomiting (%)	50.8	69.0	<0.0001
Drowsiness (%)	62.0	30.9	<0.0001
Diarrhoea (%)	31.2	18.0	<0.0001
Rash (%)	73.1	40.0	<0.0001
Convulsions (%)	17.8	1.3	<0.0001
Positive tourniquet test (%)	17.7	33.1	<0.0001
Splenomegaly (%)	3.3	0.7	<0.0001
Abdominal pain (%)	10.0	44.1	< 0.0001
Bleeding (%)	23.3	30.9	0.034
Unusual manifestations (%)	3.9	1.0	0.001

Table II: Laboratory findings of the early childhood group (aged 0-2 years) in comparison to older children (aged >2-15 years) with dengue virus infections

	0-2 years (n=179)	>2-15 years (n=2,042)	p-value
Hct max (vol%)	40.93	44.18	NS
Hct min (vol%)	33.19	37.18	NS
WBC min (cells/mm^3)	8,627.36	5,037.09	<0.0001
Platelet min (cells/mm^3)	62,473.57	76,167.42	<0.0001
Lymph max (%)	55.42	36.54	0.04
AL max (%)	10.29	10.71	NS
PMN max (%)	30.94	49.39	0.0039

Hct = hematocrit, max = maximum, min = minimum, mm^3 = cubic millimetre, Lymph = lymphocyte, AL = atypical lymphocyte, PMN = polymorphonuclear cell

Table III: Severity of dengue disease and serological response to dengue infections in all patients

Severity of dengue disease	0-2 years (n=179)	>2-15 years (n=2,042)	p-value
DF (%)	26.25	16.89	0.001
DHF (%)	73.74	82.85	0.002
DSS (%)	27.93	34.52	NS
Mortality rate	1.67	0.14	<0.0001
Serological response	**(n = 165)**	**(n = 1,872)**	
Primary infection (%)	107 (64.85)	185 (9.88)	<0.0001
Secondary infection (%)	58 (35.14)	1,687 (90.12)	<0.0001

Table IV: Severity of dengue disease classified by serological response

Primary infection	0-2 years (n=165)	>2-15 years (n=1,872)	p-value
DF (%)	30.84	44.32	<0.0001
DHF (%)	69.16	55.68	0.029
DSS (%)	26.17	5.41	0.004
Secondary infection			
DF (%)	22.41	14.38	<0.0001
DHF (%)	77.59	85.62	<0.0001
DSS (%)	31.03	36.51	<0.0001

RESULTS

Of the 2,221 children aged 0–15 years and diagnosed with dengue, 179 were aged 0–2 years. Of these, 88 and 91 were males and females respectively. Prior to admission, nearly all patients had a fever for an average of 4.4 days. Compared with 2,042 children aged >2-15 years, the early childhood group presented significantly more frequently with hepatomegaly, drowsiness, diarrhoea, rash, convulsions, splenomegaly and unusual manifestations (Table I).

In the early childhood group, the mean maximal haematocrit value (Hct max) was 40.93 volume%; the mean minimal value of the white blood cell (WBC min) count was 8,627 cells/mm^3; the mean of maximal percentage of lymphocytes, atypical lymphocytes, and polymorphonuclear cells was 55.42%, 10.29% and 30.94%, respectively, and the mean minimal value of the platelet count was 62,473 cells/mm^3 (Table II).

DF was more common in the study group and DHF was less common, but there was no significant difference in rates of DSS between groups. The mortality rates of the early childhood group was 1.67%, which was significantly higher than that of the comparative group. Approximately 65% of children aged 0-2 years were serologically proven to have primary dengue infection, while only 9.8% of older children had primary dengue infection (Table III).

DHF comprised approximately 70% of cases with primary infection among children aged 0-2 years. Moreover, DSS comprised approximately 26% of cases in the early childhood group who were serologically proven to have primary infection (Table IV).

DISCUSSION

Dengue virus is the causative agent of a wide spectrum of clinical manifestations and is transmitted to humans by *Aedes aegypti* and *Aedes albopictus* mosquito species. This mosquito-borne arboviral infection is endemic in Asia, the Eastern Mediterranean, the Americas, and Africa. The common manifestations of dengue infection is fever, vomiting, macular rash, myalgia, hepatomegaly, haemorrhagic manifestations including a positive tourniquet test, petechiae, purpura, ecchymosis, epistaxis, gum bleeding, and hematemesis and/or melena with no apparent symptoms or signs of respiratory tract infection.[4,13] Our study showed the early childhood group presented significantly more frequently with hepatomegaly, drowsiness, diarrhoea, rash, convulsions, splenomegaly and unusual clinical manifestations than comparative group. Patients with unusual manifestations tended to be younger and to have higher mortality rate than older children. The other common manifestation of dengue infection in early childhood is hepatomegaly but splenomegaly is uncommon. As previous studies have reported splenomegaly as an atypical presentation of dengue infection; the frequency of splenomegaly among childhood cases of dengue infection varies between studies.[14-18] In this study, we found that splenomegaly was more common in the early childhood group than in older children. In addition, 18% of the early childhood group in this study developed convulsions, which also are more common due to high grade of fever.

Children aged 0-2 years of age tend to have higher WBC counts and a higher percentage of lymphocytes and polymorphonuclear cells.[19] In contrast, our study showed that patients in the early childhood group had the mean minimal value of the WBC count and the mean of maximal percentage of lymphocytes more than those in the older age group. However, the mean maximal percentage of polymorphonuclear cells in patients aged 0-2 was lower than that in the older age group. The mean minimal value of the platelet count in the early childhood group was significantly lower than of the comparative group; however, we found that clinical of bleeding was significantly less common in the early childhood group than in the older age group in this study. Clinical of bleeding in dengue infection may be caused by thrombocytopenia, vasculopathy, platelet dysfunction, or coagulopathy.[20]

In addition, we have only one case of congenital dengue patient (vertical transmission) in the early childhood group.[21] Coinfections in dengue patients have been seen in our study, these may lead to missed diagnosis and treatment of dengue infection.[22]

Explanatory hypotheses for the mechanism of DHF/DSS have remained a topic of debate for decades.[4] Two distinct hypotheses to explain this mechanism have been debated between secondary infection or antibody enhancement and viral virulence. Antibody enhancement hypothesis was first described in 1977.[23] According to this hypothesis, a pre-existing antibody to dengue virus plays an important role in the development of severe disease symptoms; additionally, patients with secondary infection tend to be significantly more likely to develop shock compared to those with primary infection.[24] Although secondary dengue infection remains the strongest known hypothesis for explaining the mechanism of DHF/DSS, our study shows that various severities of dengue diseases, as well as both primary and secondary dengue infection, can occur in all age groups among children. This confirmed the observation that DSS can occur with primary infection in all age groups.

Dengue infection can only be prevented through controlling the mosquito vectors and administering the dengue vaccine.[25] The first dengue vaccine (CYD-TDV; Dengvaxia®, Sanofi Pasteur, Lyon, France) was licensed for use in individuals aged 9-45 years old in Thailand on October 2016, where dengue is endemic.[25,26] This vaccine has shown good efficacy in older children; however, in this study the mortality rate of children aged 0-2 years old who were infected with dengue was 1.67%, which was a significantly higher rate than that of older children. This finding is similar to mortality rates reported in a previous study.[5] As the licensed dengue vaccine is not indicated for use in this age group, development of new dengue vaccines with a good efficacy and favourable safety for use in younger children are necessary.

DISCUSSION AND CONCLUSIONS

Dengue virus infection during early childhood is not uncommon. The majority of children aged 0-2 years in this study acquired primary dengue infection. Clinical manifestations and complications of dengue infection vary between age groups. To effectively prevent dengue infection

morbidity and mortality in children, it is essential that clinicians correctly recognize and diagnose dengue infection, particularly in early childhood. Further studies to increase the understanding of dengue pathogenesis and disease severity in a well-defined cohort population between age groups is warranted.

CONFLICT OF INTEREST

None to declare.

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Compliance of Malaysian healthcare workers towards tuberculosis prevention programmes in workplace: An exploratory sequential mixed method study protocol

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ABSTRACT

Introduction: The World Health Organization (WHO) stated that the incidence of tuberculosis among healthcare workers is increasing yearly and exceeds the incidence of tuberculosis in the community in almost all the countries that report to the WHO. The problem is greater in countries with high burden of tuberculosis disease in the community. The cause of this problem may be contributed by the attitudes of the healthcare workers themselves, such as non-compliance of the procedures at their work tasks meant to prevent them from contracting the disease. Therefore, this study aims to assess the perceptions and the behaviours of healthcare workers in relation to compliance towards prevention activities on tuberculosis at their workplace.

Materials and Methods: We plan to conduct a two-phase exploratory sequential mixed method study to determine the factors affecting compliance of Malaysian healthcare workers towards tuberculosis prevention programmes in their workplace based on the guidelines of the Ministry of Health, Malaysia. Phase one is a qualitative study with a focus group discussion and questionnaire development and phase two is a quantitative study where data will be collected among healthcare workers in government clinics and hospitals in Selangor. The data from phase one will be analysed using Atlas.Ti software for thematic analysis and data from phase two will be analysed using SEM AMOS software for structural equation modelling.

KEYWORDS:
Compliance, adherence, health personnel, tuberculosis, prevention and control

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease that has existed for centuries throughout the world. This disease is caused by the rod-shaped non-spore forming aerobic bacterium, namely *Mycobacterium tuberculosis* which can infect all human organs, especially the lungs. Tuberculosis germs measuring between 0.5 to 3.0 micrometres and classified as acid-fast bacilli which has a unique cell wall structure and is spread through airborne particles by untreated individuals and is contracted when in contact with them for a period of time.[1] Tuberculosis infection is almost exclusively an airborne transmitting disease as it was initially an infection of the alveolar macrophage.[2] The World Health Organization (WHO) had estimated that in 2019, 1.2 million people died from tuberculosis worldwide including 208,000 deaths reported among people with HIV due to tuberculosis, whereas 10 million people fell ill with tuberculosis in 2019 worldwide.[3] Malaysia is categorised as an intermediate country of tuberculosis burden. In 2019, WHO had estimated the burden of tuberculosis in Malaysia was 29,000 cases with tuberculosis incidence rate between 79 to 106 cases per 100,000 population.4 The exact number of tuberculosis cases being reported to the Ministry of Health Malaysia in 2020 were 23, 644 cases with the incidence rate of 72 cases per 100,000 population.[5]

The incidence of tuberculosis among healthcare workers is increasing since many years but are being minimally highlighted and it has exceeded the incidence of tuberculosis in the community in almost all of the countries that report to the WHO.[6] Tuberculosis began to be recognized as an occupational hazard in early 1950s.[7,8] A systematic review conducted by Rajnish J et al., in 2006 stated that tuberculosis was a significant occupational problem among healthcare workers in low-middle income countries and there was a need to design and implement several recommended tuberculosis infection control strategies in healthcare facilities.[9] Control strategies and prevention measures are very important to be implemented, especially in a high-risk workplace, to prevent and reduce the risk of healthcare workers contracting tuberculosis disease from their workplace. The WHO has outlined measures for the control and prevention of tuberculosis in congregate spaces and health facilities comprising management or administrative control, engineering control and respiratory protection control.[6] Ministry of Health (MOH), Malaysia has published a guideline to prevent healthcare workers from contracting tuberculosis disease from the workplace based on the WHO guidelines in 2010 and was fully implemented in all their government health facilities in 2012.[10] The guidelines and standard operational procedures of the activities pertaining to prevention of tuberculosis transmission in the workplace were created and established in order to prevent Malaysian healthcare workers who are at risk of contracting the disease, where it is in line with the Occupational Safety and Health

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Act 1994, which states "It is the duty of every employer and every self-employed person to ensure, as far as practicable, safety, health and welfare while working of all its employees".[11]

Tuberculosis among healthcare workers is a long-standing global health problem. The risk of transmission of tuberculosis between an infected individual to a healthcare worker and vice versa has been identified from the previous studies, especially in high-risk areas or places such as health facilities or health institutions.[9,12-15] The healthcare workers are at higher risk for developing tuberculosis due to their association with patients from a variety of health backgrounds. Several studies stated that even in a controlled environment for airborne infection transmissions, such as hospitals or health clinics, the risk of a healthcare worker to contract tuberculosis infection is similar to the community where they live.[14,15] Tuberculosis among healthcare workers is a health issue that is given less attention than tuberculosis in the community. Tuberculosis among healthcare workers is a serious and persistent threat worldwide.[9,12] Many studies focus on the prevention and control for tuberculosis in the community, while the issue of tuberculosis among healthcare workers has received less attention in terms of implementation methods and effectiveness by most countries, especially low-income countries.[9]

Several studies have stated that the incidence rate of tuberculosis among healthcare workers is higher compared to the incidence rate of tuberculosis among the community which is between 25 to 5,361 per 100,000 health workers per year.[9,12] A higher burden of tuberculosis in a country can also lead to a higher incidence rate of tuberculosis among their healthcare workers, for example, in China which is one of the countries with a high burden of tuberculosis, Wang et al., stated that the prevalence rate of tuberculosis among healthcare workers in China was 760 per 100,000 healthcare workers.14 Jones et al. also noted that in 2013, four percent of new tuberculosis cases reported yearly in the United States of America (USA) were among health workers.[16] In Thailand, a total of 109 health workers were diagnosed with tuberculosis in a five-year period between 2011 to 2014 with an incidence rate ranging from 1.35 to 2.53 per 1,000 healthcare workers.[13]

Various behavioural theories are used to study the relationship between human behaviour and the tendency of a person to perform that behaviour, especially in health-related studies.[17] Human factors such as attitudes or compliance of healthcare workers are major factors that contribute to or are associated with occupational risk to healthcare workers. Several studies stated that poor adherence or compliance of healthcare workers towards standard operating procedures to prevent them from contracting occupational tuberculosis disease was significant.[18-21] Taking this into consideration, limited studies were conducted to examine the relationship between the behaviour of healthcare workers who are responsible for delivering health services to the community with occupational tuberculosis. Hence, these situations require research and further analysis related to the factors that influence the compliance of healthcare workers to the control and prevention activities, specifically on tuberculosis transmission in the workplace.

However, studies conducted in several countries proved that poor and incomplete implementation as well as non-compliance with the guidelines were among the main causes of the increase in tuberculosis cases among healthcare workers.[13,22,23] Although healthcare workers do know and are aware of the risks of contracting tuberculosis infection in their workplace, the absence of policies and guidelines as well as the lack of training given to them made it difficult for them to implement and adhere to preventive measures. Studies conducted in several countries pertaining to the implementation of tuberculosis prevention activities among healthcare workers also proved that the increase in the incidence of tuberculosis among healthcare workers are in line with the failure to comply to preventive measures as outlined.[14,22,24] Studies conducted in countries with high burden of tuberculosis, such as South Africa and Lagos, Nigeria, found that although tuberculosis prevention guidelines are available and the knowledge of the disease are high among the healthcare workers, the infection control practices among them are still low.[25,26]

The latest guidelines on preventing tuberculosis among healthcare workers in the workplace by WHO was published in 2009,[6] in which the management of controlling and preventing the spread of tuberculosis disease can be divided into three main controls, namely administrative controls, environmental controls and respiratory protective control. Administrative controls are defined as managerial or administrative measures in managing the tuberculosis program as a whole, including early identification of tuberculosis cases, and early separation and treatment of tuberculosis patients to reduce the risk of transmission to healthcare workers.[6,10] Environmental factors as defined by the WHO and MOH are the activities or methods to reduce the concentration of infectious aerosols (example: droplet nuclei) in the air and methods to control the direction of infectious air in the workplace.[6,10] Respiratory protective control or personal protective equipment are methods that should be used together with administrative controls and environmental controls to ensure complete protection and prevention to healthcare workers who are exposed.

Issues on tuberculosis among healthcare workers were identified in the early 1950s,[7,8] and various guidelines were published by the WHO as early as the 1990s but only focusing on management of tuberculosis in the community with establishment of tuberculosis treatment and high-risk group management. Guidelines on tuberculosis in the workplace and occupational tuberculosis were initially introduced by the WHO in 2003,[27] focusing more on managing the workplace if there were tuberculosis cases identified. The guidelines focusing on preventing healthcare workers in the workplace were initially published in year 2009 by WHO,[6] and in 2012 by MOH.[10] Although tuberculosis prevention and control policies and guidelines have been strengthened since 1997 in Malaysia, the burden of tuberculosis in this country is still high with a case notification rate of between 65 to 81 cases per 100,000 population over the past 10 years, as shown in Figure 1.[28] For

tuberculosis cases among healthcare workers, it shows a very significant increment over the past 10 years with the notification rate of tuberculosis cases among healthcare workers between 100 to 126 cases per 100, 000 health workers from 2010 to 2018, as shown in Figure 2.[28] The WHO stated that up to 80 per cent of tuberculosis cases among healthcare workers were contracted from the workplace. Close contact activities among healthcare workers with tuberculosis patients during their work task is a major factor that places healthcare workers at a high risk of getting occupational tuberculosis.[29] The risks get higher when healthcare workers do not comply to the prevention and activity guidelines.

In Malaysia, the initial guideline for preventing tuberculosis among healthcare workers were introduced in 2012, but despite that, the incidence and numbers of tuberculosis cases among healthcare workers increased significantly, as shown in Figure 2. The MOH had stated that the incidents of tuberculosis among healthcare workers in this country is likely to be work-related, since their investigation showed that the source of infection was found to be more from healthcare facilities than the community.[10]

OBJECTIVES

This study aims to explore and identify factors that influence and contribute to the compliance of healthcare workers in implementing tuberculosis prevention programs or activities in their workplace. This study will also determine the level of compliance of healthcare workers towards tuberculosis prevention programmes and the factors associated with it based on the theory of planned behaviour and self-protective behaviour in the workplace.

Research Questions

i. Why is the incidence of tuberculosis cases among healthcare workers increasing even though various guidelines and programmes related to tuberculosis prevention activities in the workplace have been issued?

Phase 1: Qualitative study

ii. What are the behavioural factors that influence the compliance of healthcare workers in implementing tuberculosis prevention programs in the workplace?

Phase 2: Quantitative study

iii. What are the occupational factors that influence the compliance of healthcare workers in implementing tuberculosis prevention programs in the workplace?
iv. What are the environmental factors that influence the compliance of healthcare workers in implementing tuberculosis prevention programs in the workplace?

MATERIALS AND METHODS

We will conduct an exploratory sequential mixed method study design comprising a qualitative study as the phase one, followed by a quantitative study as the phase two. We plan to conduct the study in Selangor since this state have the highest cases of tuberculosis among healthcare workers in Malaysia, as shown in Table I.[28]

Variables

In this study, we plan to explore and analyse several variables according to the three main factors, namely individual factor (based on the theory of planned behaviour such as intention, perceived control behaviour, attitude and subjective norm), knowledge related to the disease (tuberculosis and tuberculosis prevention measures in the workplace), environmental factors and organizational factors. Healthcare workers in this study is defined as those workers in the health institution who are doing clinical and administrative tasks pertaining to managing tuberculosis patients.

Individual factors will be defined as attitudes and perceptions of the healthcare workers in complying to the guidelines based on the Theory of Planned Behaviour (TPB). Intentions according to TPB is defined as the desire or willingness to perform a behaviour including a person's positive or negative beliefs and the individual's assessment of the behaviour outcome.[17,30] Intentions may be influenced by attitudes, perception-controlled behaviour and subjective norms of an individual. Attitudes will be defined as a behaviour or practice that will be implemented against a certain behaviour. Attitudes can be influenced by beliefs and outcome evaluation of the behaviour. The attitude in this study indicates the degree of inclination of an individual to perform and comply to the activities in the guidelines. Perceived control behaviour will be defined as the response of an individual to that particular behaviour whether the response is positive or otherwise. Subjective norms will be defined as social responses and pressures experienced by an individual in initiating the behaviour.

Organisational factors that will be anticipated in this study are the activities provided by management of the facilities as in the guidelines to reduce and halt the transmission of tuberculosis in the workplace, such as initiating a tuberculosis control committee, monitoring the implementation of the activities, designating a liaison officer or person in charge of the programmes for a better implementation as well as providing training to the healthcare workers and conducting surveillance programmes for tuberculosis among healthcare workers in the workplace.

Environmental factors that will be anticipated in this study are the activities conducted to reduce the concentration of the tuberculosis bacteria in the air, such as controlling the source of the infection by providing and using local exhaust ventilation and diluting and removing contaminated air by proper ventilation. Other measures in these environmental factors are controlling the airflow to prevent contamination of air areas adjacent to the source and cleaning the air using "high efficiency particulate air" (HEPA), filtration or 'ultraviolet germicidal irradiation" (UVGI). All the variables that will be studied in this research are based on the Ministry of Health Malaysia's guidelines.[10]

Patient and Public Involvement

Patients and/or public are not involved in this study. We will recruit the healthcare workers as the participatory subjects in this study.

Study Design

Phase 1

This study will be conducted based on the Theory of Planned Behaviour by Ajzen,[17,31] and Self-Protection Behaviour in Workplace by DeJoy.[32] We will identify factors related to the compliance of healthcare workers towards the tuberculosis prevention program in their workplace. In the phase one of this study, a qualitative approach will be conducted to explore and determine the factors that influence healthcare workers' adherence towards tuberculosis prevention programs in the workplace according to the theory of planned behaviour and the "Self-Protective Behaviour at Workplace" model.

A focus group discussion (FGD) will be conducted involving a group of health experts selected via purposive sampling methods to produce a set of survey questions. A total of 11 informants or experts involved in the development and implementation of the tuberculosis prevention program in the Disease Control Division, MOH and Occupational Health Unit and Tuberculosis Unit, Selangor State Health Department will be included. The discussion will be conducted in two sessions involving 4 and 7 informants. Each of the session will be conducted in a suitable selected private meeting room with around two and half hours or more time provided. All the sessions will be conducted using a semi-structured questionnaire which will involve two of the research officers as interviewer and co interviewer for note taking. The information and data gathered in this phase will then be analysed using Atlas.Ti to generate thematic analysis. Subsequently, a set of questionnaires will be developed from the thematic analysis and will be validated before being used in phase two.

Phase 2

Phase two of this study will be conducted in selected government hospitals and primary health clinics in the state of Selangor. A total of five government district hospitals and eight primary health clinics in the Selangor Health State Department were purposively selected in this study based on the burden of tuberculosis among healthcare workers at their facilities. This phase will be conducted using a self-administrated questionnaire that is given to the respondents.

Sampling Size and Sample Population

Phase 1

A total of 11 informants will be selected through purposive sampling based on their expertise and involvement in the tuberculosis prevention program of healthcare workers to undergo this FGD session. The informants that will be considered to participate in this session are Medical Officers, Supervisors/Head Nurses, Assistant Medical Officers, Environmental Health Officers or Assistant Environmental Health Officers from the Tuberculosis/Leprosy Unit or Occupational Health Unit in the Disease Control Division, Ministry of Health and Selangor Health State Department.

Phase 2

For quantitative studies, there will be several sample size calculations that will be proposed according to several guidelines in order to find out the best and the most accurate way of determining the sample size required for this study and to reduce the error of the parameter estimate. The first calculation is using the Sample Size Calculation Software Epi Info 7 Statcalc and based on the formula of Kish. L (1965) as follows:

n = (Z) 2 X [P (1-P) / D2]
n = Sample size
Z = 1.96 (For CI of 95%, Z = 1.96; normal distribution)
P = prevalence of tuberculosis of health members
D = precision of study

From the data obtained from the MOH, the prevalence of tuberculosis among health workers in 2018 was 126 per 100,000 health workers. Therefore, according to the above calculation, the estimated sample size is 169 respondents, in which the minimum sample size required is 202 samples (additional 20% for dropout of respondents). The second calculation is based on the number of sample size required from previous literature searches and according to the factors to be studied, the highest sample size reported was 236 respondents as reported in the study by Engelbrecht,33 and the smallest sample size was 20 respondents as reported by Barker.[34] The third calculation to be considered is by the Structural Equation Modelling method. In this study, there will be five constructs to be studied, therefore the sample size required based on the structural equation modelling method is 100 samples.[35]

From the three ways of calculations proposed, the sample size that was selected for this study is 236 respondents based on the previous literature searches as this calculation gave the highest numbers of sample size required, thus bringing the total number of respondents required to 283 respondents including an additional 20% dropout of respondents.

The respondents to be selected are those healthcare workers that work in the tuberculosis unit or involved in managing tuberculosis patients directly or indirectly at their respective facilities. The respondents will be selected through the simple random sampling technique. A list of respondents will be requested from the Human Resource Unit, Selangor State Health Department.

The inclusion criteria for this study are all healthcare workers involved in the management of tuberculosis cases in selected health facilities during the study period and are Malaysian citizens. While the exclusion criteria decided for this study are all healthcare workers who are on leave or do not agree to participate in the study during the study period as well as healthcare workers who are former tuberculosis patients or close contact of tuberculosis patients.[26]

Data Analysis

Phase 1

The entire interview session will be recorded using an audio recorder and will be analysed to produce a thematic analysis. Each response from the informant will be rewritten in the form of notes along with responses from the researcher's initial observations and research assistants. All answers will be typed into Microsoft Word for analysis and will be transcribed using ATLAS.ti TM software (ATLAS. Ti Inc. Berlin, Germany).

Table I: Table showing the number of tuberculosis cases among healthcare workers reported to the Ministry of Health Malaysia 2016 to 2018

STATE/YEAR	2016	2017	2018
Johor	24	33	35
Kedah	16	14	21
Kelantan	21	12	19
Melaka	7	7	3
Negeri Sembilan	18	10	11
Pahang	11	19	15
Perak	23	20	25
Perlis	1	2	2
Pulau Pinang	11	11	15
Sabah	58	34	48
Sarawak	20	24	22
Selangor	47	50	60
Terengganu	10	17	14
WPKL	24	27	32
WP Labuan	2	1	1
TOTAL	293	281	323

Source: Ministry of Health Malaysia, 2019

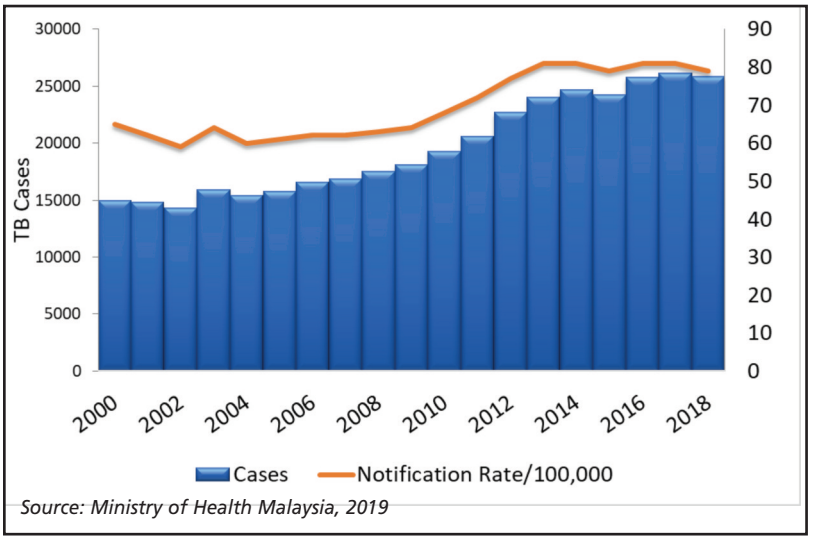

Fig. 1: Graph showing the total cases reported and notification rate of tuberculosis cases 2000–2018.

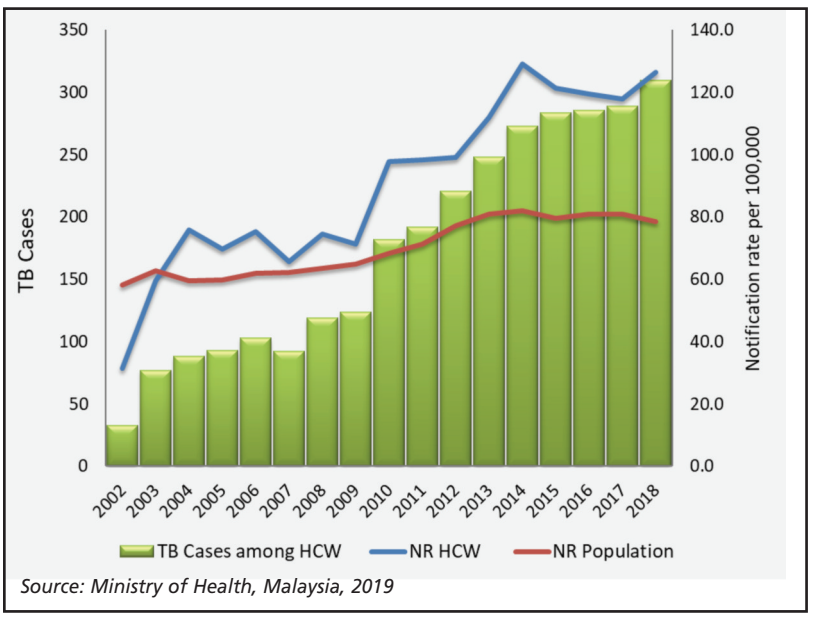

Fig. 2: Graph showing the total cases reported and notification rate of tuberculosis among healthcare workers 2000–2018.

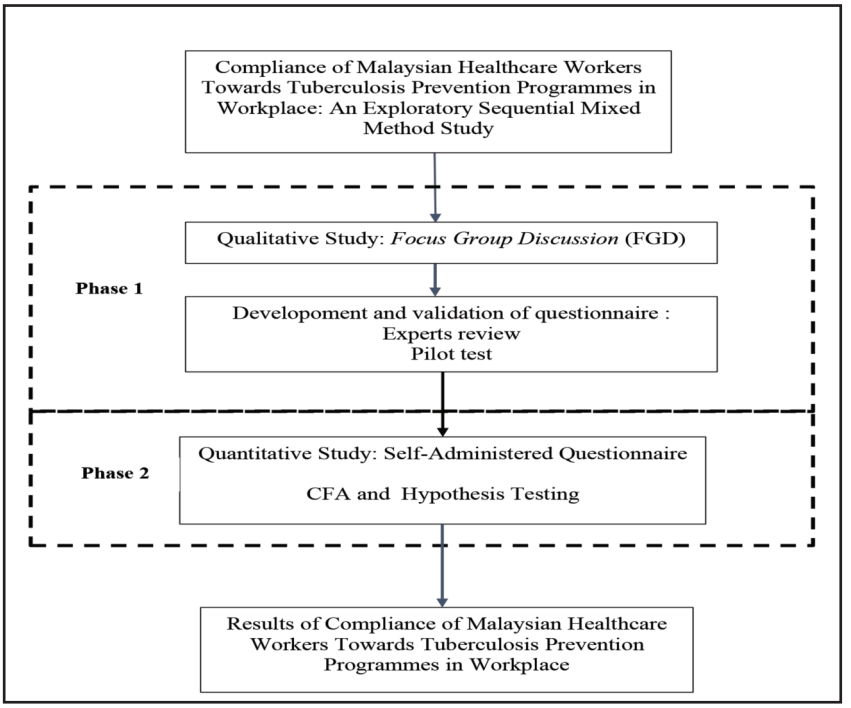

Fig. 3: The study flow chart.

At the early stage, the researcher and research assistants will give a code to each of the significant answer recorded in a text conferring to the objectives of the study. Then, the codes will be analysed, given a meaning and combined as appropriately as possible to form the basic theme. Subsequently, these basic themes will then be formed according to the appropriate clusters to produce the main theme. The main themes that have been formed will be analysed, coordinated and discussed again together with the research assistants in order to reduce bias. A total of 20 main themes will be needed to be agreed upon and will be used to design and develop the questionnaire.

The questionnaire that has been developed will be sent for evaluation by experts for the triangulation process. The Content Validation Index (CVI) will be calculated after all the experts completed their reviews and the questionnaire will be edited accordingly to ensure that the questions produced are truly inclusive and relevant to the objectives of this study. The number of experts proposed in this study are minimum of six experts with acceptable CVI values of at least 0.83.[36] Then the questionnaire edited will be used in pilot study using 150 respondents from another group of healthcare workers. The questionnaire will then be analysed using Cronbach's Alpha analysis in determine the internal consistency reliability. The cut-off points of Cronbach's Alpha more than 0.7 is opted. The feedback received in this validation and reliability process will be used to improve and strengthen this questionnaire.

Phase 2

The second phase is a field study via a quantitative cross-sectional method where the data will be collected via a self-administered questionnaire based on the model of Self-Protection Behaviour at Workplace in determining the compliance of healthcare workers towards tuberculosis prevention activities in their workplace. Factors that will be studied are individual, organisational and work environment factors. This phase will be using a Confirmatory Factor Analysis (CFA) test to proof the model via Structural Equation Modelling (Structural Equation Modelling).

DISCUSSION AND CONCLUSIONS

This study aims to determine the compliance of Malaysian healthcare workers towards tuberculosis prevention activities in their workplace based on the guideline provided by the WHO and MOH, Malaysia. This is the first study that explores Malaysian Healthcare workers' compliance towards tuberculosis prevention programs based on a behavioural theory (Theory of Planned Behaviour). The contribution of this study may improve the current tuberculosis prevention program in government health facilities. However, this study is limited to Selangor and the generalizability may not be applicable.

In summary, this study will be conducted in the following steps, qualitative data collection and analysis, then based on the findings in the qualitative data analysis, the questionnaire will be prepared for quantitative data collection, pilot testing followed with data collection in the field. The collected data in quantitative study finally will be analysed for reliability, confirmatory factors analysis (CFA) with hypothesis testing and interpretation. We will reach our conclusions based on findings after the interpretation and connect the qualitative and quantitative results to evaluate the compliance of Malaysian healthcare workers towards tuberculosis prevention activities in their workplace. The flow

chart of the study process is shown in figure 3. The conclusions can be used as measurement or key performance of current tuberculosis prevention programmes in Malaysia, especially focusing on the healthcare worker group. This conclusion can be used as a guideline for improvement or restructure of the current programmes. Our implications for the research will suggest priorities for future research and outline the remaining uncertainties in the area of occupational hazards or occupational diseases among the group of healthcare of workers.

Ethics and Dissemination

Ethical approval from National Medical Research Register, Ministry of Health Malaysia and ethical community board of National University of Malaysia was obtained in August 2020 *(NMRR-20-1270-55199, PPUKM-FR 20-084)*. Currently, this study is in phase one, in which data collection have just been completed and currently in designing and validating the questionnaire. We plan to use the findings of this study to update the Tuberculosis Prevention Sector and Occupational Health Sectors, Disease Control Division in Ministry of Health Malaysia for further improvement of the programmes. All findings will be shared and disseminated at any local or international conferences, including preliminary findings to the Disease Control Division of Ministry of Health Malaysia.

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Health services, pregnancy history and tetanus toxoid vaccination uptake among pregnant women in Cambodia

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ABSTRACT

Introduction: This study aimed to determine the coverage of tetanus toxoid vaccination (TT) among pregnant women in Cambodia, and its association with health services and pregnancy factors.

Methods: A cross-sectional study was conducted by utilising the data from the Cambodia Demographic Health Survey (CDHS). The records of 5901 pregnant women who fulfilled the inclusion criteria were reviewed. Multiple logistic regression was used to identify the association on the influence of health services and pregnancy factors on incomplete TT vaccination while controlling other co-variates. Adjusted odds ratio (aOR) and 95% confidence interval (95%CI) was reported.

Results: More than one-third of the respondents had incomplete TT vaccination (38.25%, 95%CI: 37.00, 39.48%). Health services as well as pregnancy factors were statistically associated with incomplete TT vaccination such as received antenatal care (ANC) from other health personnel beside midwife (aOR=1.83; 95%CI: 1.49, 2.24), had <ANC visits (aOR=1.76; 95%CI: 1.53, 2.03), being late for the first ANC visit (aOR=1.65; 95%CI: 1.41, 1.92), unwanted pregnancy (aOR=1.30; 95%CI: 1.11, 1.51), aged ≥30 years at delivery (aOR=1.45; 95%CI: 1.15, 1.46) while controlling other factors like; including age, occupation, husband's age, occupation, financial status, maternal age at delivery, birth order, wanted pregnancy and accessing health facility.

Conclusion: More than one-third of pregnant women in Cambodia had not completed tetanus toxoid vaccination. Health services and pregnancy related factors had significance role on incomplete tetanus toxoid vaccination.

KEYWORDS:
Cambodia, health services, pregnancy history, tetanus toxoid vaccination

INTRODUCTION

Maternal and neonatal tetanus is often considered as a silent killer.[1] The World Health Organisation-United Nations Children's Fund (WHO-UNICEF) estimates of tetanus toxoid vaccination coverage in South East Asia for 2013 included Brunei Darussalam (99), Thailand (99%), Malaysia (97%), Singapore (97%), Indonesia (92%), Philippines (89%), Lao People's Democratic Republic (87%), Cambodia (86%), Myanmar (75%), and Viet Nam (59%).[2] Maternal tetanus is defined as tetanus that occur during pregnancy or within six weeks after the end of pregnancy. Neonatal tetanus is defined as tetanus that occur within 28 days of life among neonates. Tetanus among neonates usually occur among infant born to unvaccinated mother and infection of unhealed umbilical stump from non-sterile instruments.[3] Worldwide, an estimated number of neonate death was between 180,000 and 300,000 annually.[4] Antenatal care (ANC) practice does not only provided maternal cares but also informs and encourages pregnant women on the advantages of health facility delivery as well as the principle of clean cord care and importance of vaccines.[5,6] ANC provides the convenient opportunity for vaccination among pregnant women. However, expensive expense causes insufficient ANC.

Previous studies and reports indicated a low coverage of tetanus toxoid (TT) in Cambodia. Only 62.4% of pregnant women received two or more TT injection during pregnancy.[7] Many reports and research identified the influence of geographic settings and socioeconomic factors on tetanus coverage. In addition, access to adequate health services was the important factor that affects vaccination. Previous studies found that the distance from home to vaccination providers significantly affected immunisation rates.[8,9] However, those findings provided only the descriptive information.10 Exploration on the magnitude of the problems and factors associated with incomplete tetanus toxoid is still limited in Cambodia. Therefore, this study aimed to describe tetanus toxoid vaccination pattern and identify the relationships of health services as well as pregnancy factors associated with incomplete tetanus toxoid vaccination among pregnant women in Cambodia. The hope is these findings will be evidence-based health for policymaking and designing intervention programs to improving low tetanus uptake among pregnant women in Cambodia.

MATERIALS AND METHODS

Study design

This cross-sectional study was utilised the data of the Cambodian Demographic and Health Survey 2014.

Population and samples

We performed two-stage cluster sampling method to select the participants which represent the whole pregnant women population. The inclusion criteria were women aged between

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15 and 49 years old, pregnant and gave birth between 2009-2014 and had completed data on tetanus vaccination. There were 5901 records of individuals who were selected for the analysis.

Factors of interest

The main outcome variable of this study was tetanus toxoid vaccination uptake (complete/incomplete). Dependent variable was categorised into incomplete TT (coded as 1) referring to had <2-time during their latest pregnancy (no injection or only one doses of TT) against completed TT vaccination (coded as 0) which referred to at least two TT injections. Health services including health insurance, health facility for ANC, health providers, pregnancy factors covering birth order, age at first birth, and wanted pregnancy. Socio-economic factors of which ages of women and spouses, education, financial status was considered as independent factors.

Statistical analysis

A simple logistic regression was carried out to identify the association of each independent variable with incomplete tetanus toxoid vaccination uptake. The independent variable that had p-value <0.25 were processed to the multivariable analysis using the multiple logistic regression to identify the association between health services, pregnancy history factors and incomplete tetanus toxoid vaccination when controlling other covariates. The magnitude of association was presented as adjusted odds ratio (aOR), 95% confidence interval (95%CI) and a statistically significant level was $p<0.05$.

Ethical consideration

This study was approved by the Ethics Committee in Human Research of Khon Kaen University, Khon Kaen, Thailand (Reference no. HE622190).

RESULTS

Among the 5,901 respondents, their average age was 28.78±6.22 years old and almost all were married. About a quarter were illiterate (25.11%), and almost half finished only primary education (49.38%). Their mean age of the spouses was 32.13±7.31 years old. Less than a quarter were from the household with less deficiency wealth category (22.25%), 34.94% were self-employed and 45.42% had spouse working in agricultural sectors. Most of them did not have health insurance (83.83%). Almost all had health services from public health facilities (92.32%) and services provided by midwifes. About 80% of respondents had ANC first visit before 12 weeks and received >4 visits. Almost two-third had health expense problems (63.09%) whereas the permission, distance, accompanied person to health facility were not a serious problem. Concerning pregnancy factors, the average age at first birth was 21.77±3.98 years old, whereas the average age at the latest delivery was 27.07±5.96 years old. Most of them wanted to have more children (85.01%). However, half terminated pregnancy by abortion. About two-third had less than two years birth interval from the first delivery. Nearly half made decision on health service utilisation by themselves (41.81%).

As high as 38.25 % (95%CI: 37.00, 39.48) had incomplete tetanus toxoid vaccination during their latest pregnancy (Table I).

Our univariate analysis performed by using simple logistic regressions revealed that independent variables that were potentially associated with incomplete TT were ages of women, education, occupation, financial status, residence, literacy, spouse's age, education, occupation, health insurance, health facility for ANC, first ANC visit, number of ANC visit, accessibility to health services, maternal age at delivery, birth order, wanted pregnancy and terminated pregnancy. The factors that had p-value <0.25 in the bivariate analysis were processed to the multiple variable analysis (Table II).

The multiple logistic regression indicated factors that were statistically associated with incomplete TT was received ANC from other health beside midwife (aOR=1.83, 95%CI: 1.49, 2.24), had less than 4 ANC visits (aOR=1.76, 95%CI: 1.53, 2.03), being late for the first ANC visit (aOR=1.65, 95%CI: 1.41, 1.92) and did not to pregnant (aOR=1.30, 95%CI: 1.11, 1.51), Mother whose ages were 30 years or older at delivery (aOR=1.45, 95%CI: 1.15, 1.46) when controlling other factors including age, occupation, husband's age, occupation, financial status, maternal age at delivery, birth order, wanted pregnancy and accessing health facility (Table III).

DISCUSSION

This study observed that 38.25% of Cambodian pregnant women had incomplete tetanus toxoid vaccination. Therefore, the proportion of complete TT during pregnancy in this study was similar with many studies reported the coverage of two times TT vaccination during pregnancy was between 33 to 68%.[11-13] Our study also identified the linkage between health service factors and incomplete tetanus toxoid uptake. Those who received ANC provided by other health personnel not midwife were 1.83 times more likely to have incomplete tetanus toxoid than those who got ANC provided by midwife. This finding was similar to other studies which revealed that health care provider was one of the predictors on the coverage of tetanus toxoid vaccination.[14-17] However, another study in rural Bihar reported that having nurse as a provider was the predictor of receiving two TT doses.[17] This may be due to the packages of health services were mostly provided by midwife and nurse especially the ANC.[18] In case of ANC provided by other health personnel beside midwife, they might get the service at private sectors, the pregnant women would have missed the chance to be reminded about the ANC package which included TT vaccination.[19,20] Moreover, the result also indicated that had ANC <4 times and late first ANC visit had influence on incomplete tetanus toxoid. Other studies agreed that ANC was strongly associated with tetanus toxoid immunization among pregnant women.[12,13,21,22] Late first ANC made pregnant women having shorter time to get services, resulted in getting <4 ANC visits. ANC is the source of knowledge to TT injection.[12,21] Therefore, the new recommendation of ANC package is minimum eight time, and the first visit schedule should be taken at least within 12 weeks of gestation.[23] Another finding of this study was that the pregnant women

Table I: Tetanus toxoid vaccination uptake among pregnant women in Cambodia (n=5,901)

	Number	Percentage	95%CI
Tetanus toxoid vaccination (During Last Pregnancy)			
At least two time (Complete)	3644	61.75	60.52, 63.00
Less than two time (Incomplete)	2257	38.25	37.00, 39.48

Table II: Univariate analysis for factors associated with incomplete TT of sample among the pregnant women in Cambodia (n=5900)

Factors	Number	% Incomplete TT	Crude OR	95%CI	p-value
Socio-Economic Factors					
Age (Year)					0.004
<30	3,406	10.13	1		
≥30	2,495	11.78	1.18	1.00, 1.39	
Educational Attainment					<0.001
≥Secondary school	2,184	5.72	1		
≤Primary school	3,717	13.83	2.64	2.15, 3.23	
Marital status					0.011
Married	5,558	10.56	1		
No Married	343	15.16	1.51	1.11, 2.05	
Occupation					<0.001
With skill	2,428	7.87	1		
Without skill	3,473	12.90	1.73	1.45, 2.07	
Spouse Age					0.001
<35	3,936	9.40	1		
≥35	1,965	13.69	1.52	1.29, 1.80	
Spouse Education					<0.001
≥Secondary school	2,812	6.54	1		
≤Primary school	3,089	10.83	2.46	2.06, 2.95	
Spouse Occupation					<0.001
With skill	3,114	8.54	1		
Without skill	2,787	13.38	1.65	1.40, 1.95	
Financial Status					<0.001
Rich	2,530	6.76	1		
Poor	3,371	13.88	1.22	1.16, 1.27	
Residence					<0.001
Urban	1,628	7.56	1		
Rural	4,273	12.08	1.68	1.36, 2.06	
Literacy					<0.001
Can read some	4,420	8.39	1		
Cannot read at all	1,481	18.10	2.41	2.03, 2.85	
Health Services Factors					
Health insurance coverage					0.037
No	4,947	10.45	1		
Yes	954	12.79	1.25	1.01, 1.55	
ANC first visit					
Appropriate (<4 month)	4,622	6.38	1		<0.001
Late visit (≥4months)	1,279	26.90	5.39	4.54, 6.40	
ANC visit time					<0.001
Adequate (≥4times)	4,391	5.97	1		
Not adequate (<4 times)	1,510	24.97	5.24	4.42, 6.22	
Health Facility for ANC	0.896				
Public	5,566	10.82	1		
Private	335	11.04	1.02	0.72, 1.45	
ANC provided by					<0.001
Midwife	5,405	7.97	1		
Beside midwife	496	41.94	8.33	6.79, 10.21	
Accessibility to Health services: permission to go health facility					0.001
No problem	4,656	8.59	1		
Have problem	1,245	11.43	1.37	1.10, 1.70	
Accessibility to Health services: Distance to health facility					<0.001
No problem	3,786	9.88	1		
Have problem	2,115	12.58	1.30	1.10, 1.54	
Accessibility to Health services: Go alone to health facility					<0.001
No problem	3,420	9.50	1		
Have problem	2,481	12.66	1.37	1.17, 1.62	

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Table II: Univariate analysis for factors associated with incomplete TT of sample among the pregnant women in Cambodia (n=5900)

Factors	Number	% Incomplete TT	Crude OR	95%CI	p-value
Accessibility to Health services: Getting money for treatment		0.167			
No problem	2,562	10.10	1		
Have problem	3,723	11.25	1.12	0.94, 1.34	
Pregnancy History					
Maternal age 1st birth					<0.001
≥20	4,075	9.18	1		
<20	1,826	14.51	1.67	1.41, 1.98	
Maternal age at delivery					<0.001
<30	4,054	9.52	1		
≥30	1,847	13.70	1.50	1.27, 1.78	
Birth order					<0.001
≥3rd	3,898	8.49	1		
1st & 2nd	2,003	15.38	1.95	1.65, 2.31	
Wanted pregnancy					<0.001
Now	5,015	9.95	1		
Later	886	15.80	1.69	1.38, 2.08	
Interval from marriage to first birth					0.021
≤1year	2,144	9.61	1		
≥2year	3,757	11.53	1.22	1.02, 1.46	
Terminated Pregnancy					0.016
Never	4,222	10.21	1		
Ever	1,679	12.39	1.24	1.04, 1.48	
Social Cultural Factor					
Decide on respondent health care					0.801
Co-decide with partner	3,567	10.46	1		
Decide alone	2,334	11.40	1.10	0.93, 1.30	

Table III: Multivariable analysis of factors associated with incomplete TT, by using multiple logistic regression (n=5,901)

Factors	Number	% incomplete TT	Crude OR	Adj OR	95%CI	p-value
Health Services						
ANC provided by						<0.001
Midwife	5,405	35.87	1	1		
Other health personnel beside midwife	496	64.11	3.19	1.83	1.49, 2.24	
ANC visit						<0.001
Adequate (≥4times)	4,391	32.45	1	1		
Inadequate (<4 times)	1,510	55.10	2.55	1.76	1.53, 2.03	
ANC first visit						<0.001
Appropriate(<4months)	4,622	33.10	1	1		
Late visit (≥4 month)	1,279	56.84	2.66	1.65	1.41, 1.92	
Pregnancy History						
Wanted pregnancy						0.001
Now	5,015	36.61	1	1		
Later	886	47.52	1.69	1.30	1.11, 1.51	
Maternal age at delivery						<0.001
<30	4,054	35.42	1	1		
≥30	1,847	44.45	1.45	1.29	1.15, 1.46	

aged 30 years and older for the first delivery were more likely to have incomplete tetanus toxoid uptake. Many studies reported that tetanus immunisation during pregnancy was affected by maternal age at delivery.[11,22,24] It could be due to unwanted pregnancy as well. Unintentional to have baby was associated with ANC contact.[25-27] ANC contact does not only provide maternal cares but also informs on advantages and encouraging health facility delivery, the principle of clean cord care and importance of vaccines.[5,6]

CONCLUSION

More than one third of pregnant women in Cambodia had incomplete tetanus toxoid vaccination. Health services and pregnancy factors had influences on incomplete tetanus toxoid vaccination. Therefore, maternal health programs especially ANC should be strengthened and more effort put on the readiness of women to be pregnant in terms of information and services.

This study was a cross-sectional analysis that could show only the association. Using secondary, some variables are missing into analysis because of difference objectives and as well as difference data collection.

CONFLICT OF INTEREST

No conflicts of interest to declare.

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ORIGINAL ARTICLE

Outcome of acute ischaemic stroke patients after intravenous alteplase in Hospital Universiti Sains Malaysia

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ABSTRACT

Introduction: Intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rt-PA) is effective in treating acute ischaemic stroke. Our primary objective is to assess the outcome of these acute ischaemic stroke (AIS) patients after IV alteplase with the modified Rankin scale (mRS).

Methods: This is a cross-sectional study in which patients receiving IV alteplase in Hospital Universiti Sains Malaysia, from January 2017 to April 2020 were recruited. Demographical data, National Institutes of Health Stroke Scale (NIHSS) scores, door-to-needle time were recorded. Modified Rankin scale (mRS) scores were evaluated at 90 days after initial therapy. Good and poor functional outcomes were defined as 0-2 and 3-6, respectively.

Results: A total of 30 patients were included in the study with a mean age of 59±11.47 years old. 76.7% of them were male and the rest were female. From the study, onset-to-needle time was 197.47±51.74 minutes, whereas door-to-needle time was 120.93±53.63 minutes. Seventeen (56.3%) patients achieved a favourable score of 0-2 on the mRS at 90 days after treatment. Haemorrhagic transformation occurred in eight (26.7%) of the patients with a mortality rate of 13.3%.

Conclusion: 56.7% of our patients showed improvement in the mRS at 90 days post thrombolysis for AIS. Higher baseline NIHSS scores and diabetes mellitus were associated with poorer functional outcomes after thrombolysis.

KEYWORDS:
Acute ischaemic stroke, rt-PA, door-to-needle time, functional outcomes, thrombolysis

INTRODUCTION

Stroke is one of the leading non-communicable diseases that carry a heavy social and economic impact on individuals and their immediate families.[1] Thus, it has the most significant burden of disease, based on the disability-adjusted life years.[2] It is estimated that 14 million people worldwide will suffer their first stroke and 80 million live with the burden of stroke. Stroke also accounts for 116 million years of healthy life lost to the disease.[1] This equates to roughly 14.7 million disability-adjusted life years affecting patients aged 20 to 64 years old, with the majority occurring in the developing countries.[3]

In Malaysia, stroke is one of the top ten causes for hospitalisation,[2] and the mean age of stroke patients in Malaysia is 62.5 years.[4] With a population of approximately 32.5 million in 2019, a majority (69.8%) of them fall into the 15 to 64 years old age group.[5] This increased ageing of the population indirectly leads to a higher number of stroke cases and an associated increase in the healthcare expenditure.

Management of acute ischaemic stroke (AIS) had undergone three stages of evolution, including the introduction of intravenous (IV) thrombolysis. Recombinant tissue plasminogen activator (rt-PA) is an IV thrombolysis for AIS, was licensed to be used since 1996 following the results from the National Institute of Neurological Disorders and Stroke trials.[6] The efficacy of the rt-PA treatment has been shown to improve functional outcomes of patients receiving the therapy within three hours of the onset of the symptoms. Functional outcomes of stroke patients are measured with the modified Rankin scale (mRS) and a score of 0 to 1 is considered as a favourable outcome, whereas a score of 0 to 2 means that the patient is alive and independent.[7,8] International guidelines unanimously agreed upon the safe and effective therapeutic window for treating AIS patients within 4.5 hours from onset of symptoms.[9,10] This study aims to evaluate the outcomes of AIS patients from January 2017 to April 2020. The onset-to-needle and door-to-needle time were also analysed.

METHODS

This cross-sectional study was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM), Kubang Kerian. Data from medical records were collected from January 2017 to April 2020.

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The inclusion criteria were all AIS patients who presented through the Emergency Department (ED) and received IV alteplase therapy within 4.5 hours of symptoms onset. The demographic data included the age, gender, ethnicity and underlying medical comorbidities of patients. The timing of the onset of symptoms to the administration of IV alteplase (incident-to-needle time) and the registration time at the ED to the treatment time (door-to-needle) were also collected. The door-to-needle time is inclusive of assessment, stabilising and ordering CT scan for the patient from ED, reviewing the CT scan by the radiologist and neurologist before the administration of the treatment. Comorbidities like diabetes mellitus, hypertension, atrial fibrillation and underlying ischaemic heart disease were also included.

Patients received the standard dose of 0.9mg/kg IV alteplase (maximum of 90mg). The initial dose of 10% was administered as a bolus dose and the remaining 90% was a continuous infusion over one hour. Patients' mRS at the point of treatment were also assessed and compared against their respective mRS at 90 days post-therapy during follow-up at the Neurology Clinic or telephone interview with the patient or caregiver. A mRS of 0-2 was considered as a good clinical outcome, whereas a score of 3-6 was considered as a poor outcome.

Patients who developed haemorrhagic transformation post-therapy were managed accordingly and classified as a complication of the IV alteplase therapy. Symptomatic or fatal haemorrhagic transformation is also known as symptomatic intracerebral haemorrhage (SICH). SICH was defined as local or remote parenchymal haemorrhage within 36 hours posttreatment associated with deterioration of four points or more based on the National Institutes of Health Stroke Scale (NIHSS) or from the lowest NIHSS value between baseline and 24 hours or leading to death.[11] Mortality due to other causes was also recorded.

Data of the study was analysed using the IBM SPSS Statistics version 24. The numerical values seen in the tables are expressed as mean (standard deviation, SD) and percentages. Association between the variables and functional outcomes were analysed using the independent Student's t-test, Chi-square or Fisher's exact test. A p-value of <0.05 was considered as statistically significant. To determine the predictors of functional outcome, multiple logistic regression analysis was performed.

RESULTS

The demographic data of the patients recruited during the study period is shown in Table I. A total of 30 patients received IV alteplase. The duration of the study was approximately 40 months; hence, the treatment frequency is less than 1 case per month. Hospital USM (USM) is one of two centres in the state of Kelantan, Malaysia that offers IV alteplase therapy.

Based on Table I, out of the 30 patients enrolled, 23 were males and seven were females. The mean age of the patients was 59 years old (SD±11.47), with the youngest patient at 36 years of age, whereas the oldest patient was 79 years of age. All the patients were Malays. Hypertension (56.6%) and diabetes mellitus (33.3%) form the major comorbid suffered by these patients. The mean onset time to treatment (incident-to-needle) was 197.47 minutes (SD±51.74), whilst the door-to-needle time was 120.93 minutes (SD±53.63). All but one of the patients suffering from a stroke in the territories supplied by the middle cerebral artery, with the odd one out suffering from a posterior circulation stroke. A mean NIHSS score prior to IV alteplase was 10.60 (SD±4.61)

The mean mRS during admission was 3.43 (SD±1.331) and there was no significant difference with the mRS of 2.93 (SD±1.929) at 90 days after the therapy. Figure 1 shows the percentages of the patients based on their pre-treatment and post-treatment of mRS scores.

Table II shows a breakdown of all the variables assigned to two different outcomes, one being those with a good outcome (mRS 0-2)[10] and the other being a poor outcome (mRS 3-6). A total of 17 patients (56.7%) had a good outcome (mRS 0-2) at 90 days after the IV alteplase therapy in which 7 (23.3%) of them were able to return to pre-stroke functional activities. Patients with good outcomes have a pre-treatment NIHSS score of 9.53 (SD=4.78) compared to 11.89 (SD=4.05) in those who had a poor outcome.

A total of eight patients (26.7%) developed haemorrhagic transformation after the IV alteplase of which four (13.3%) passed away following the insult and four patients recovered with some functional outcome. Two patients suffered haemorrhagic transformation during the treatment but after 90 days, they were able to achieve good outcomes (p=0.049). The other four patients (13.3%) who had passed away were due to hospital-acquired pneumonia, acute coronary event, sepsis and the last patient passed away at home due to unknown causes, respectively. Table IV shows the breakdown of patients with haemorrhagic transformation according to year, with zero cases in 2020.

However, there were no statistically significant outcomes between the ages, gender, hypertension, area of infarct, incident-to-needle, door-to-needle before IV alteplase and the functional outcomes after 90 days of patients. Table III shows that for each increment in the pre-treatment NIHSS score, patients had 20% lower odds of achieving a good outcome (OR=0.80, 95%CI: 0.640, 0.995). Diabetes mellitus (p=0.034) and NIHSS scores (p=0.045) have a statistically significant association with the functional outcomes.

DISCUSSION

Thrombolysis in AIS is a relatively new service with limited experience among physicians in Malaysia, particularly in Hospital USM. Hospital USM had the stroke thrombolysis protocol since 2012 but very few patients had been thrombolysed. With the initiative of the acute stroke team in Hospital USM, the number of AIS patients being thrombolysed has increased slowly. Only 23.3% of our patients achieved a mRS of 0-1 (excellent outcome)[7] at 90 days post treatment from our study. This is comparatively lower than other published data in the Southeast Asia region, where the improvement ranges were from 26.1% to 59%.[12-15] European studies had achieved excellent outcomes ranging from 31% to 53%[16,17] whereas one study in the United States

Table I: Baseline characteristics of patients treated with IV rt-PA (n=30)

Characteristics	n (%) / mean (SD)
Age (years)	59.0 (11.47)
Gender	
Male	23 (76.7)
Female	7 (23.3)
Ethnicity	
Malay	30 (100.0)
Mode of transport to ED	
By Self	28 (93.3)
By Ambulance	2 (6.7)
Hypertension	17 (56.6)
Diabetes Mellitus	10 (33.3)
Ischaemic Heart Disease	2 (6.7)
NIHSS score pre rt-PA	10.60 (4.61)
Onset-to-treatment time	197.47 (51.74)
Door-to-needle time	120.93 (53.63)
Modified Rankin Scale (Admission)	
0-1	
0-2	7 (23.3)
3-6	23 (76.7)
Modified Rankin Scale (90 Days)	
0-1	7 (23.3)
0-2	17 (56.7)
3-6	13 (43.3)
Modified Rankin Scale at Admission	3.43 (1.331)
Modified Rankin Scale at 90 Days	2.93 (1.929)
Haemorrhagic Transformation	4 (13.3)
Minor haemorrhagic complications	4 (13.3)
Mortality	
Due to haemorrhage	4 (13.3)
Other causes	3 (10.0)
Area of Infarct	
Left Middle Cerebral Artery	18 (60.0)
Right Middle Cerebral Artery	11 (26.7)
Posterior Circulation	1 (3.3)

Table II: Analysis of factors determining functional outcome

Parameters	n (%) / mean (SD)		p-value
	Good Outcome (n=17)	Poor Outcome (n=13)	
Age (years)	57.18 (12.98)	61.38 (9.06)	0.328[a]
Gender			0.666[b]
Male	14 (46.7)	9 (30.0)	
Female	3 (10.0)	4 (13.3)	
NIHSS score pre rt-PA	9.35 (4.72)	12.23 (4.09)	0.091[a]
Onset to Needle (minutes)	190.94 (51.96)	206.00 (52.25)	0.439[a]
Door to Needle (minutes)	123.41 (64.17)	117.69 (37.95)	0.763[a]
Haemorrhagic Transformation			0.049[c]
Yes	2 (6.7)	6 (20.0)	
No	15 (50.0)	7 (23.3)	
Mortality			0.001[c]
Death due to SICH	0 (0.0)	4 (13.3)	
Death due to other causes	0 (0.0)	3 (10.0)	
No	17 (56.7)	6 (20.0)	
Hypertension			0.785[b]
Yes	10 (33.3)	7 (23.3)	
No	7 (23.3)	6 (20.0)	
Diabetes Mellitus			0.255[c]
Yes	4 (13.3)	6 (20.0)	
No	13 (43.3)	7 (23.3)	
Ischaemic Heart Disease			0.492[c]
Yes	2 (6.7)	0 (0.0)	
No	15 (50.0)	13 (43.3)	
Ischaemic Area			0.452[c]
Left MCA	10 (33.3)	8 (26.7)	
Right MCA	7 (23.3)	4 (13.3)	
Posterior Circulation	0 (0.0)	1 (3.3)	

[a]independent t-test, [b]Pearson chi-square, [c]Fisher Exact test

Table III: Multiple logistic regression of factors determining functional outcome

Parameter	β	p-value	OR	95% CI
Age	-0.04	0.360	0.96	0.88-1.05
NIHSS pre rt-PA	-0.23	0.045	0.80	0.64-0.99
DM	-2.60	0.034	0.08	0.01-0.82
HPT	1.35	0.214	3.85	0.29-32.36

Table IV: Breakdown of haemorrhagic transformation according to year

Year	Haemorrhagic Transformation	Total Number of Patients Receiving IV Alteplase
2017	2	6
2018	2	10
2019	4	10
2020	0	4

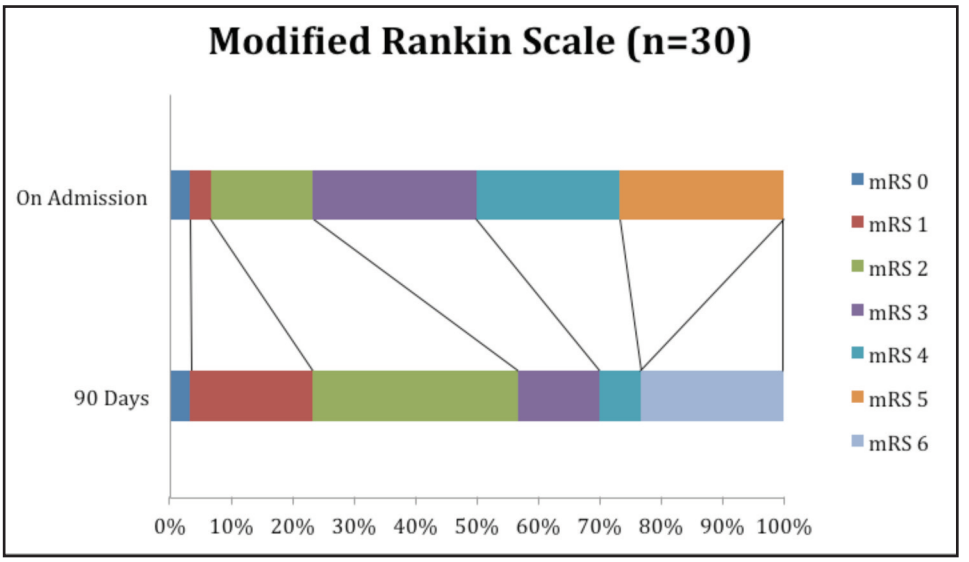

Fig. 1: Modified Rankin Scale on Admission and at 90 Days post IV rt-PA.

of America had achieved 78.2% of excellent outcome.[18] However, 56.7% of our patients had a good outcome with functional independence (mRS of 0-2). This is comparable with another local study at the University of Malaya Medical Centre where 55.6% of their patients had achieved a similar outcome.[13]

Many studies trying to predict the functional outcome of AIS patients.[19-21] For example, one local study found poor functional outcome was associated with higher baseline NIHSS scores and the presence of DM.[13] On the other hand, one Australian study found that age is a significant predictor of good functional outcomes independent of stroke severity.[22]

Symptomatic intracranial haemorrhage (SICH) is a major complication following thrombolysis.[23] In our study, 13.3% of our patients had SICH and this incidence was higher than the findings of a local study.[12,24] A study in Hong Kong had a much lower SICH rate of 4%.[25] Clinical trials such as NINDS and ECASS II had 6.4% and 8.8% incidence of SICH.[23] Published reports have identified a few risk factors for SICH, such as age more than 70 years old,[26] National Institute of Health Stroke Scale (NIHSS) more than 20,[27] diabetic patients with high serum glucose levels,[28] international normalized ratio (INR) ≥1.028 and history of coronary artery disease or atrial fibrillation.[29] Many risk factors and predictions have been proposed for the risk of SICH, including computerised tomography (CT) based scale, MRI-based technique and plasma biomarkers.[22]

In our study, the overall mortality rate at three-month was 23.3%, which is higher than regional studies that range from 3.2% to 15.0%.[12-15,25] However, SICH as the main cause of death (13.3%) is comparable to another study.[30] Our study also did not explore the risk factors associated with haemorrhage, which could be related to various factors such as the size of cerebral infarct, the ASPECT score at presentation, late-timing of alteplase infusion or other relative contraindications. The pathogenesis of intracerebral haemorrhage after thrombolysis are probably due to pre-existing microbleeds and leukoaraiosis, as the majority of patients had either diabetes or hypertension.[23]

The concept of "time is brain"31 has become more significant as shorter onset-to-needle time is associated with better functional outcomes.[32,33] Our onset-to-needle time was

197.47±51.74 minutes, which is longer than the guideline.[34] However, this result is comparable with a Malaysian study where the mean onset-to-needle time was 211 minutes.[13] Studies from Hong Kong and Vietnam had a shorter mean onset-to-needle time of 143 minutes,[15,25] whereas another study from Singapore had a median onset-to-needle time of 165 minutes.[12] Our door-to-needle time is at 120.93±53.63 minutes which is comparable to the Malaysian Stroke Registry's time of 132 minutes.[4]

Nevertheless, the time is still beyond the target in the guideline.[34] One of the major proponents for reduced mortality and improved outcomes is the door-to-needle time. Patients receiving IV alteplase within 45 minutes have a lower mortality rate. Conversely. every increment of 15 minutes up to 90 minutes of door-to-needle time is significantly associated with worse outcomes.[32]

In order to improve the time to thrombolysis, proven strategies have been identified[35] and separated into three distinct categories: pre-hospital, in-hospital and post-treatment decision strategies. The pre-hospital component is mainly directed at public education, stroke awareness and early arrival to the hospital. In Malaysia, stroke awareness is segregated into urban and rural areas, whilst the city dwellers are competent in their knowledge[36] and the opposite is for those coming from the rural areas.[37] Recognition of stroke symptoms is one of the crucial keys to early access to medical therapy.[38] This is followed by in-hospital strategies inclusive of a fast-track system for thrombolysis.[12,39] Easy availability of IV alteplase and simplification of informed consent prior to treatment at the ED must also be streamlined.[35]

There are several limitations to our study. Firstly, it is a cross-sectional study and information was taken from medical records and follow-up notes. Thus, interobserver variability of the mRS score would remain a substantial bias.[40] Secondly, the small sample size (n=30) from a single-center does not show the complete picture of the disease. Finally, the racial composition of the patients was 100% from the Malay ethnic group, which does not reflect the national population.

CONCLUSION

Our study has shown that 56.7% of our patients showed improvement in the mRS at 90 days post IV alteplase for AIS patients in Hospital USM, which is on par with Malaysian reports. However, as a newly established service, we had a SICH complication rate of 13.3%. In addition, higher baseline NIHSS scores at presentation and the presence of diabetes mellitus were associated with poorer functional outcomes.

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ORIGINAL ARTICLE

Impact of virtual brief wellness based psychosocial intervention on mental wellbeing of stable hospitalised COVID-19 patients – A pilot study

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ABSTRACT

Introduction: The Optimal Health Program (OHP) is a collaborative self-management program that promotes clients to be actively involved in their own healthcare and overall wellbeing. Program Kesihatan Optimum (SANUBARI) is a Malay version of the OHP after a translational process and cultural adaptation by psychiatrists, clinical psychologist and family medicine specialists in 2017. The program is of a low intensity, patient-centred program, advocating self-health management to improve health literacy by enhancing self-efficacy, building strengths and values, and initiating change and planning, ultimately enhancing wellbeing of people. The programme can be used as a form of early psychosocial intervention during the current pandemic in maintaining the general mental wellbeing of COVID-19 patients.

Methods: This is an open labelled interventional study of a virtual brief psychosocial intervention, called SANUBARI. The program was conducted among COVID-19 patients hospitalized in the COVID-19 wards of two centres from May 2020 until August 2020. Inclusion criteria include patients aged eighteen years and above, diagnosed with COVID-19, medically stable, speaking and reading Bahasa Melayu or English. All study subjects attended two sessions on OHP via telecommunication method and answered questionnaires (General Self-Efficacy (GSE) Scale, Patient Health Questionnaire and Generalized Anxiety Disorder Questionnaire) via computer-assisted self-interview. Data collection was done before the start of the intervention, at the end of the intervention and a month post-intervention.

Results: A total of 37 patients were recruited and more than half of the subjects were males (62.2%), single (75.5%) and from the Malay ethnicity (78.4%). Seventy-three per cent of subjects had received tertiary education, and most of them were students reflecting a higher unemployment status (73%). Most subjects have no comorbid chronic medical illness (89.2%), and none has a comorbid psychiatric illness. Comparison of the GSE score across 3-time points (pre-intervention, immediate post-intervention and a month post-intervention) showed statistically significant improvement in the mean total GSE score immediate and a month post-intervention as compared to the pre-intervention; from mean total GSE score of 29.78 pre-intervention to 34.73 (mean difference 4.946, 95% Confidence Interval 95%CI: 3.361, 6.531) immediate post-intervention and 33.08 (mean difference 3.297, 95%CI: 1.211, 5.348) a month post-intervention. There was no significant association between the socio-demographic or clinical data, depressive and anxiety symptoms, and changes in GSE scores over three time points.

Conclusion: COVID-19 patients improved their self-efficacy levels after the virtual brief OHP intervention, and it maintained a month post-intervention, protecting them from psychological stress and ultimately enhances wellbeing during this coronavirus pandemic.

INTRODUCTION

The COVID-19 has taken us all globally by storm and it has resulted in changes in our lives and economies, such as unemployment and financial insecurity. Along with the implementation of social distancing and isolation, the pandemic has created tremendous stress. There is the uncertainty of how long it will last and how this pandemic will ultimately play out. It is evident that this current COVID-19 pandemic has led to an increase, in a range of mental health issues such as abnormal stress reactions, depression, anxiety, and even post-traumatic stress disorders.[1]

Many studies have shown that during a pandemic, the prevalence of mental illness remains high. The prevalence of depression among Middle East Respiratory Syndrome (MERS) CoV patients during the outbreak was 40.7%.[2] Studies on were needed during the hospital stay for some of these patients. Past pandemics have found that general stress and adverse psychological effects were increased in infected patients.[3] Depression, anxiety and anger feelings were noted high among patients requiring quarantine and isolation.[4] Psychiatric consultations and prescriptions of medications were needed during the hospital stay for some of these patients.

The first three COVID-19 cases were reported in Malaysia on the 25th of January 2020.[5] All confirmed cases in Malaysia were admitted to the hospital for treatment and subjected to isolation for days to weeks, depending on their medical condition. In times like this, a focus on this mental health of the affected individuals is all the more critical. Some form of early psychosocial intervention should be in place even during hospital quarantine or isolation stage. Mental health interventions should begin not when one starts developing mental disorders but earlier.

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The existing Mental Health and Psychosocial Services (MHPSS) in Malaysia are already providing mental health intervention to aid those affected. Examples of the MHPSS intervention given are psychological first aid, relaxation techniques and art therapy. Optimal Health Program (OHP) can be an excellent addition to the existing efforts of the MHPSS teams. OHP is a structured psychological intervention that can fill in the gap of care. It focuses on the physical, emotional, intellectual, spiritual, social and occupational aspects of health. It draws upon many evidence-based practices that sit within collaborative therapy, positive psychology and wellbeing. It fosters critical thinking and self-regulation, increases capacity for health-seeking behaviour and self-care behaviour. The OHP has been shown to be effective in improving health and social functioning in patients with mental health problems by building their self-efficacy in managing the impact that mental health has on their wellbeing.[6]

Trained health professionals can provide effective OHP. The program consists of five modules, and it can be delivered individually or in groups. It adopts a person-centred approach focussing on health as defined by the clients, also a self-efficacy enhancing self-management program. The critical components of the program include education, coping strategies and skills development. With data showing the usefulness of OHP in helping people to achieve and maintain optimal health, we are now looking into its effectiveness among the COVID-19 patients during the pandemic.

The existing OHP is given face to face over five sessions. However, in this study during the current pandemic situation, we modified the program into a brief intervention, done over two sessions, and we provided it virtually. Data obtained from this research will allow us to evaluate whether this modified intervention is still effective and beneficial in increasing the self-efficacy of COVID-19 patients when dealing with the current pandemic situation. Perhaps from here, we can expand this provision of a psychosocial intervention to help other groups of populations deal with this pandemic and explore the possibility of having a helpful early psychosocial intervention in preventing mental health problems in the future outbreak.

MATERIALS AND METHODS

Study design and subjects

This study is an open labelled interventional study involving a brief psychosocial intervention, SANUBARI, Malay version of OHP that was conducted via telecommunication method among COVID-19 patients hospitalised in wards of the Low-Risk COVID-19 Quarantine and Treatment Centre, Malaysia Agro Exposition Park Serdang (MAEPS), Serdang and Hospital Sungai Buloh from May 2020 until August 2020. The inclusion criteria include patients aged eighteen years and above, diagnosed with COVID-19, speaking and reading Bahasa Melayu or English. The exclusion criteria is medically unstable patients (clinical category 3 to 5).7

The sampling frame is list of all the COVID-19 patients admitted to the wards who were in a stable condition (clinical category 1-2). Sampling method used is convenient sampling. The first 37 eligible patients (study sample size) who responded will be recruited in this study. The research team members received list of COVID-19 patients from the matron in charge of the stable COVID-19 wards (clinical category 1 or 2) after getting verbal consent from them. All these COVID-19 patients admitted were offered the OHP intervention and screened for the study. Patients were contacted through phone by a research team member and provided with information on the intervention and explained about the study. Patients were given sufficient time to consider their participation in the study. After they agreed to participate, they were given a link to the google form by the research team member. The google form was used for consent and data collection. The front page (first part) of the google form is the Patient Information Sheet and Consent page. The second part of the google form is the socio-demographic profile of study subject (Section A). The third part (Section B) is the GSE to assess self-efficacy. The fourth part (Section C) is the Patient Health Questionnaire (PHQ-9) to assess for probable depression and the fifth part (Section D) consists of Generalised Anxiety Disorder questionnaire (GAD-7) to assess for probable anxiety. Study subjects answered questionnaires used in the study via computer-assisted self-interview. Data collection was done before the intervention, at the end of the intervention and a month post-intervention.

Study instruments

The three measurement tools used in this study to measure study outcomes were the GSE, PHQ- 9 and GAD- 7.

The GSE is a 10-item psychometric scale designed to assess optimistic self-beliefs to cope with various challenging demands in life. For example, item 4 in the GSE assesses self-perceived confidence to respond to unexpected events efficiently. A total score is calculated by finding the sum of all items. The total score ranges between 10 and 40, with a higher score indicating more self- efficacy or confidence in your ability to manage an illness or follow through with behaviour change successfully.[8] The PHQ-9 is an instrument for screening, monitoring and measuring the severity of depressive symptoms. It is brief nine self-report tools consisting of nine questions based on the nine DSM-IV criteria for major depression. The tool rates the frequency of the symptoms into the scoring severity index, each of which is scored 0 to 3, providing a 0 to 27 severity score. PHQ scores of 5, 10, 15 and 20 represent mild, moderate, moderately severe and severe depression.[9] The GAD-7 is a practical self-report tool to measure anxiety symptoms. There are seven items, each of which is scored 0 to 3, providing a 0 to 21 severity score. Scores of 5, 10, and are taken as the cut-off points for mild, moderate and severe anxiety, respectively.[10]

SANUBARI

As explained earlier, a brief version of the program was used in this study. Instead of the regular weekly sessions over five weeks, patients in this study had the sessions twice, covering all five modules. The two OHP sessions lasted an hour each and were arranged a day apart. This shortened duration of the intervention during the current pandemic catered for study subjects and program facilitator who were unable to commit to the regular weekly sessions. The outline of the two OHP sessions is shown in Table I.

Table I: The Program Kesihatan Optimum (SANUBARI)

Session	Module	Session Outline
1.	Module 1: Optimal health	- Introduction to collaborative therapy in OHP - TOOL: Optimal health wheel - Reflection and exploration of one's satisfaction level within each health domains - Identify possible area for change
	Module 2: - I-CAN-DO Model	- TOOL: I-CAN-DO-MODEL - Identify one's strengths and vulnerabilities - Identify one's source of stress and how the stress may impact overall wellbeing - Identify and building one's own strategies to cope with stressors
2	Module 3: Factors on wellbeing	- TOOL: Eco-mapping - Identify collaborative partners and their roles in maintaining one's health
	Module 4: Collaborative partners; Visioning and goal setting	- TOOL: Timeline activity - Identify past events and its impact on health - Problem solving and setting SMARTER goals - Problem solving and setting SMARTER goals
	Module 5: Maintain well-being	- Stages of health: Optimal health(1), Suboptimal health(2) and Episode of illness(3) - TOOL: Health plans 1,2,3 - Building skills and strategies at different stages of health

Table II: Distribution of study subjects according to sociodemographic and clinical characteristics (n=37)

Characteristic	
Mean age (SD)	26.35 (8.567)
Gender, n (%)	
Male	23 (62.2)
Female	14 (37.8)
Ethnicity, n (%)	
Malay	29 (78.4)
Chinese	3 (8.1)
Indian	2 (5.4)
Others	3 (8.1)
Marital status, n (%)	
Single	28 (75.5)
Married	9 (24.3)
Educational level, n (%)	
Secondary	10 (27)
Tertiary	27 (73)
Employment status, n (%)	
Employed	10 (27)
Unemployed	27 (73)
Household income group, n (%)14	
B40 < RM4850	25 (67.6)
M40 RM4850 - 10959	10 (27.0)
T20 > RM10959	2 (5.4)
Comorbid chronic medical illness, n (%)	
Yes	4 (10.8)
No	33 (89.2)

n=frequency, %=percentage, SD=standard deviation

Table III: Comparison of mean GSE scores across 3-time points (pre-intervention, immediate post-intervention and one-month post-intervention)

GSE score	Mean (SD)	Mean difference (95% CI)	P value
Pre-intervention	29.78 (3.845	4.946 (3.361, 6.531)	<0.001
Immediate post-intervention	34.73 (2.883)		
Pre-intervention	29.78 (3.845)	3.297 (1.211, 5.348)	0.003
1 month post-intervention	33.08 (4.418)		
Immediate post-intervention	34.73 (2.883)	-1.649 (-3.396, 0.098)	0.064
1 month post-intervention	33.08 (4.418)		

GSE= General Self-efficacy, SD=Standard deviation, CI=Confidence Interval

All study subjects attended two OHP sessions via telecommunication method (video calls), facilitated by a psychiatrist trained as OHP facilitator. The sessions were done with the study subjects located in a designated room inside the quarantine ward to maintain privacy and confidentiality. Study subjects were provided with the OHP workbook and the necessary stationaries during the sessions.

Sample size calculation Formula

$$= \frac{\sigma^2 \left[Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right]^2}{(\mu_1 - \mu_2)^2}$$

where n
- Z = level of confidence,
- σ = standard deviation,
- α = alpha,
- β = beta,

1. $\mu 1$ = mean in Time 1, and
2. $\mu 2$ = mean in Time 2.

= 0.532 [1.96 + 0.85]2 (2.9-3.2)
= 29 samples

Sample size estimation was calculated using two means formulae.[11] Prior data indicate that the mean GSF score prior to intervention was 2.9 (standard deviation = 0.53) and the mean of post-intervention expected from the expert opinion is 3.2 (standard deviation = 0.53).[12] Thus, a minimum sample size of 29 samples to reject the null hypothesis with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. The paired t-test statistic will be used to evaluate this null hypothesis. With an additional 20% dropout rate, the sample size is 37 samples.

Statistical analysis and ethical consideration

The data analysis was done using the SPSS (statistical package for social studies) statistical software. Descriptive data were presented in mean (SD) and frequency (%) unless otherwise stated. For comparison between 2-time points, paired t-test was used for the numerical outcome, and McNemars' test was used for the categorical outcome. Multivariate analysis using general linear models (GLM) repeated measures was performed to look for the association between studied variables (socio-demographic or clinical data) with the change in GSF scores over time from baseline to account for confounding factors. A value of $p<0.05$ with a confidence interval of 95% is considered statistically significant.

The study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guidelines. Ethical approval was obtained from Malaysian Research Ethics Committee (MREC), and all relevant ethical boards before starting any study-related activities. Cases with significant psychological issue are referred to the psychiatric clinic for further management.

RESULTS

Of the 37 patients, male patients consisted of 62.2%. Most of the patients were single (75.5%), from the Malay ethnicity (78.4%) and received tertiary education (73%). Seventy-three per cent of the patients were unemployed during the study period. Most of the subject have no comorbid chronic medical illness (89.2%), and none has a comorbid psychiatric illness.

The mean GSE score pre-intervention was 29.78, whereas immediate post-intervention was 34.73 and a month post-intervention was 33.08. The comparison of the GSE score across 3-time points (pre-intervention, immediate post-intervention and a month post- intervention) done revealed statistically significant improvement as shown in Table III.

Multivariate analysis performed to look for the association between the socio-demographic or clinical data, depressive (PHQ-9) and anxiety (GAD-7) symptoms, and changes in GSE scores over three-time points did not reveal significant association.

DISCUSSION

This is the first study that has looked into the effect of a more structured psychosocial intervention, SANUBARI, Malay version of OHP, on COVID-19 patients during COVID-19 pandemic. It examines the effect of a brief version of OHP intervention in the self-efficacy of study subjects to deal with the current pandemic situation and also on depressive and anxiety symptoms of the study subjects.

Self-efficacy, the belief in our abilities in dealing with various situations, has a significant role in our lives. Perceived efficacy can affect behaviour in several ways. Individuals who steer clear of enriching activities and environments fail to develop their potentialities and shield their negative self-conceptions from corrective change.[13] Individuals with higher self-efficacy tend to view challenging conditions as only another task to be mastered. They tend to have a more heightened sense of commitment to their activities, and when they are faced with obstacles, they recover more quickly. In short, strong self-efficacy helps to protect oneself from psychological stress in times such as during this coronavirus pandemic.

The established preliminary findings in this study may create a path in planning future advanced research that may benefit the patients during a similar disease outbreak. This study had shown improvement in self-efficacy among those COVID-19 patients who participated in the intervention immediately and a month post-intervention. As the COVID-19 patients in the study were those from clinical category 1 or 2 (asymptomatic or have only mild symptoms with no pneumonic changes),[7] these changes in the GSE scores were likely not related to the patients COVID-19 disease condition. This finding could be due to patients having more insights on optimal health, their strengths and vulnerabilities, learned better coping strategies to deal with difficulties and stressful situations that increase their confidence in themselves.

This brief OHP intervention provided in teleconsultation has a potential use as an intervention for hospitalized COVID-19

patients. OHP can fill in the gap of care here to address patients with psychological distress. More staff can be trained to deliver OHP to cope with the increasing number of patients during this pandemic.

The slight decline in mean total GSE score (not statistically significant) a month post-intervention compared to immediate post-intervention can be explained by the fact that knowledge acquired may be liable to forgotten over time if there's no continuous practice or applicability in daily life. With this finding, it will be helpful to provide a booster OHP session, which may be a month after intervention, for patients to maintain a positive outcome. In the booster session, patients can reflect on the application of knowledge and skills learnt or practised. Also, to review health plans and discuss possible barriers or strategies to improve wellbeing.

Some of the limitations in the current study are that the sampling was limited to two centres where patients may be characteristically different from other parts of Malaysia. There are also other confounders in examining self-efficacy not looked into due to the constraint of various resources. The confounders that were likely to affect the measurement included perceived social support, premorbid personality, coping skills, and life events.

CONCLUSION

Optimal health is a holistic approach to health. The coronavirus pandemic has affected all aspects of our health. In times like this, an early focus on mental wellbeing is critical, and actions to achieve and maintain optimal health should begin. COVID-19 patients in this study improved on their levels of self-efficacy after the brief virtual version of OHP intervention and the improved level of self-efficacy is maintained a month after the intervention, protecting themselves from psychological stress and ultimately enhances wellbeing during this coronavirus pandemic.

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Vitamin D and COVID-19 Infection

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ABSTRACT

Introduction: The COVID-19 pandemic has prompted the medical world to look at factors that may influence outcomes. There have been connections made between vitamin D and COVID-19, as vitamin D has previously been shown to play a role in the maintenance of immune homeostasis.

Materials and Methods: We performed a prospective cohort study on 103 patients at Wigan Wrightington and Leigh NHS Foundation Trust looking at serum vitamin D levels of patients with positive COVID-19 swabs. Results were collated and correlations were made to compare vitamin D levels with age; severity of illness; hospital outcomes; and frailty. Comparisons were also made between frailty and outcome.

Results: The results showed that there was a significant statistical difference between vitamin D levels and severity of infection: those who were treated in the intensive care units (ICU) (severe symptoms) had lower vitamin D levels than those treated on the ward (p=0.0446). There was also a correlation between vitamin D levels and frailty: those who were more frail had higher vitamin D levels than fitter patients (P=0.005). Vitamin D and frailty had no effect on hospital outcomes of COVID-19 infection.

Conclusion: Ultimately, we concluded that low vitamin D can increase susceptibility of contracting COVID-19, increase severity of infection but does not affect mortality.

INTRODUCTION

The COVID-19 pandemic has stimulated the medical community to investigate factors which could affect outcomes.

Coronavirus Disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which has led to hundreds of thousands of deaths globally. During the infection, it is thought to use the immune evasion process followed by hyper reaction and cytokine storm as a pathogenic process of acute respiratory disease syndrome (ARDS). To enter the alveolar and intestinal epithelial cells, it uses the angiotensin-converting enzyme 2 as the host receptor, which in turn causes dysregulation of the system, thus excess cytokine production ultimately causing ARDS.[1]

There have been many hypothesises on what can affect the replication of the virus; one thought is that vitamin D has a significant role in maintenance of immune homeostasis by stimulating exhibition of antimicrobial peptides or by directly interfering with the viral replication.[2]

It is known that deficiency in vitamin D can lead to promotion of the renin-angiotensin system leading to ARDS and chronic cardiovascular disease.[3] This may explain why susceptibility to COVID-19 is increased.

Vitamin D, known as calciferol, is a fat-soluble steroid hormone that can be produced endogenously by the effect of ultraviolet radiation on the skin or it can be absorbed from food and dietary supplements. Due to changes in our lifestyle with increased working hours, more sedentary life and imbalanced diet, there has been a reduction in vitamin D levels.[4] Vitamin D deficiency is widely linked to skeletal disorders, such as rickets or osteoporosis. It can also be attributed to other health conditions such as certain cancers, cardiovascular disease, inflammatory bowel diseases, psychological disorders as well as autoimmune diseases and infections.

Previous studies have found that Vitamin D has an immunomodulatory role, increasing innate immunity by secretion of antiviral peptides, which improves mucosal defences.[1] Some studies have also linked vitamin D insufficiency to respiratory tract infections including epidemic influenza and one meta-analysis showed those with low serum vitamin D levels had 64% more risk of developing community acquired infections.[5-8]

We aimed to further understand the relationship between vitamin D deficiency and COVID-19 outcomes.

In order to answer the hypotheses of whether vitamin D levels have any correlation with outcome or severity of COVID-19 infection, a prospective cohort study on patients admitted with positive viral swabs was undertaken to compare levels with length of stay, mortality and clinical frailty scoring (Rockwood score).

MATERIALS AND METHODS

A prospective cohort study was undertaken between March 2020 and May 2020 of patients admitted to Wrightington, Wigan and Leigh NHS Foundation Trust. Patients were tested routinely for both COVID-19 and serum vitamin D levels on admission to hospital. Information was collected from electronic patient records concluding on 21/05/2020. The audit was registered with the local audit department, ethics approval was not required.

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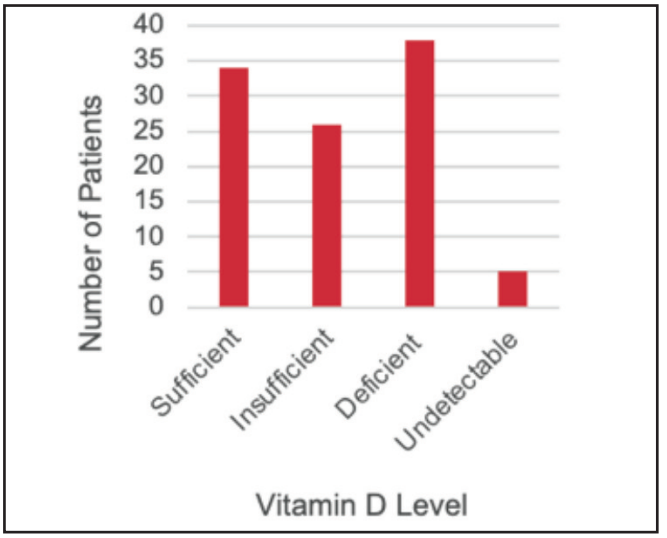

Fig. 1: Vitamin D levels of cohort.

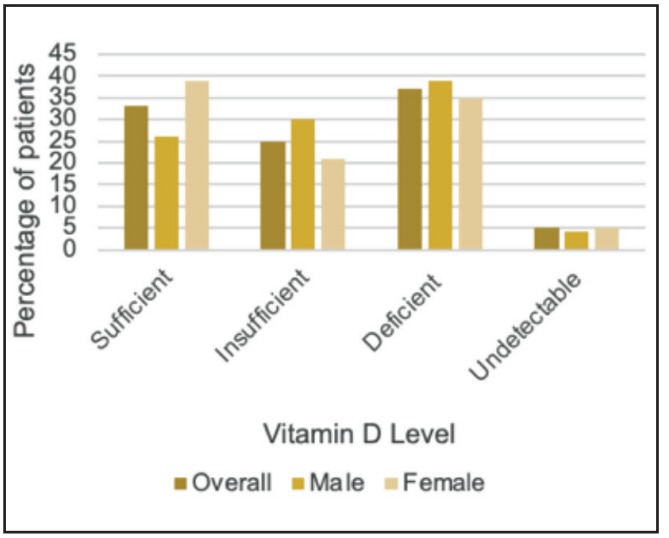

Fig. 2: Vitamin D levels in relation to gender.

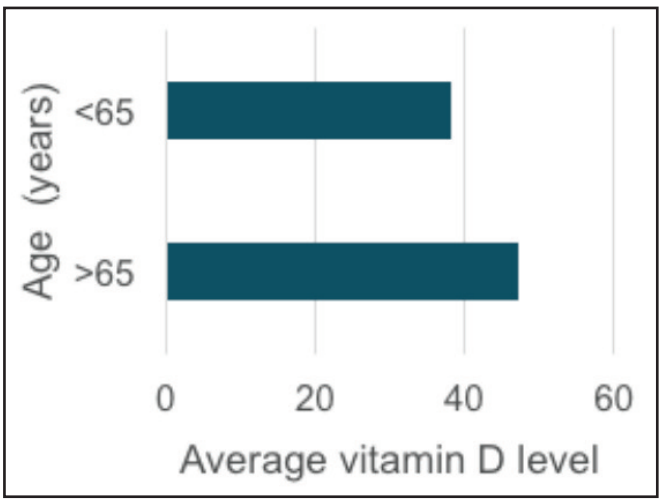

Fig. 3: Average vitamin D in relation to age.

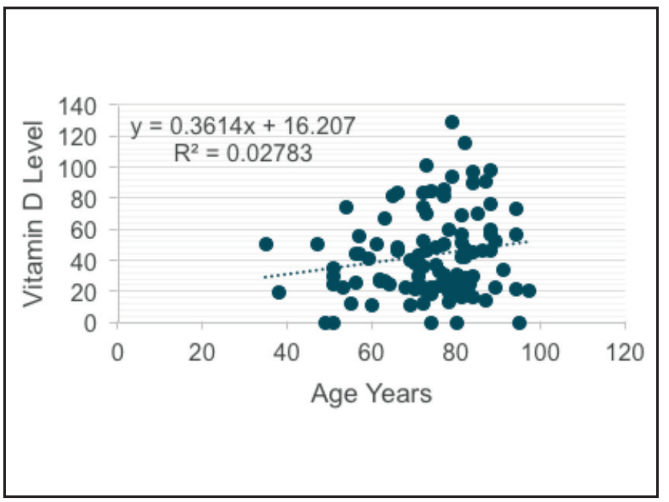

Fig. 4: Vitamin D in relation to age in linear regression.

The National Institute of Health and Care Excellence (NICE) classifies those with serum 25-hydroxyvitamin D (25[OH] D) levels >50nmol/L to have adequate vitamin D levels. Those with 25[OH] D levels between 25 and 50 are insufficient and those with levels less than 25 are deficient of vitamin D.9

Statistical analysis was performed (graph pad prizm). Unpaired T test was used to compare groups. A statistically significant difference was considered when the $p<0.05$.

RESULTS

Of the 103 patients who were COVID-19 swab positive, there were 57 females (55%), there was a mean age of 73.6 years (range: 35-97 years). The majority of the patients identified as White British 95 (92.2%), one Indian, one Arab, and six had not declared their ethnicity. The mean length of stay of the all patients was 15.3 days. At the time of data collection, 10.7% of patients were still admitted, 41.7% patients were discharged, and 47.6% died. Of the cohort, 17 patients (16.5%) were admitted to ICU; of which, 13 (76.5%) died, the remaining 4 (23.5%) were still admitted.

Vitamin D and age

For patients who were older than 65 (n=79), the average vitamin D level was 47.4. However, for those younger than 65 (n=24), the average vitamin D level was 38.4 (Figure 3). An unpaired t-test revealed p=0.1854. Linear regression – p=0.1140 (Figure 4)

Vitamin D and severity of illness

Those who required intensive care treatment had a mean vitamin D level of 27.6 nmol/L as opposed to the average of those treated at ward level care being 45.6nmol/L (p=0.0446).

Vitamin D levels and hospital outcomes

Those who were discharged had mean vitamin D level of 45.2nmol/L compared to 41.0 nmol/L for those who died (p=0.5297). Of those discharged; 15 patients were sufficient, 11 insufficient, 16 deficient, 1 undetectable. Of those who died; 14 were sufficient, 13 insufficient, 19 deficient and 3 undetectable. (Figure 5)

Vitamin D and frailty
Out of the 103 patients, 87 patients (85%) had a documented Rockwood Clinical Frailty Score (CFS). Those with sufficient vitamin D levels had a higher mean Rockwood score (5.7) than patients with insufficient levels (4.9), deficient patients (4.3) or undetectable vitamin D levels (4.5). Comparing those with sufficient versus those with low Vitamin D levels (insufficient, deficient and undetectable) the average CFS was 5.7 versus 5.4 with a p-value of 0.005. (Figure 6)

Frailty and outcome
Comparing the CFS with patient outcome, those who were discharged had a CFS average of 4.97 compared to those who died with an average of 5.1, p=0.39.

DISCUSSION

Understanding how to improve the outcomes for COVID-19 patients is currently a worldwide endeavour. Our results show that most patients who were COVID-19 positive had deficient vitamin D levels. Moreover, 40.2% of patients had vitamin D levels less than 25nmol/L which is deficient. According to the National Diet and Nutrition Survey; 24% of men and 21.7% of women between the ages of 19 and 64 years old had vitamin D concentration below 25nmol/L, this was also true for 16.9% of men and 24.1% of women aged 65 years and over.[10] This suggests that patients admitted with COVID-19 had in fact had significantly lower levels of vitamin D than the general population. Our patient cohort contained mainly patients of a White British background (92%) in comparison to 80.5% average of the United Kingdom population.[11]

The overall outcomes of patient treatment were not greatly affected by the concentration of vitamin D, patients who died had a marginally lower vitamin D level than those who were discharged. This was not a statistically significant difference.

It has to be noted that whilst vitamin D levels had no effect on final outcomes, the severity of illness did correlate to vitamin D levels. Those who required intensive care had a significantly lower concentration of vitamin D (27.6nmol/L) as opposed to those not requiring ICU treatment (45.6nmol/L) p=0.0446.

There was also a correlation between vitamin D concentration and Rockwood clinical frailty scores. Interestingly, those with sufficient vitamin D had a statistically significantly higher Rockwood score than those with low levels. This means that patients who were frailer (higher CFS) had better vitamin D levels than those who were fitter. A suggestion to explain this could be that the elderly/frail population are generally more investigated, i.e., regular bloods and therefore, vitamin D may have been monitored and replaced as necessary. We recommend further studies to explore the relation of vitamin D levels and clinical frailty. Patients who died compared to those who were discharged had no significant difference in their frailty scores, thus suggesting there was no effect of frailty on outcome of COVID-19 infection.

There were a few limitations to this study: this is a single centre study with limited numbers which wasn't adequately powered to look at the effects of corrected Vitamin D levels on hospital outcomes.; there was no control group to compare the levels of vitamin D of those with COVID-19 infection against the normal population; there was also no data on the comorbidities to compare patients who required treatment in ICU against those who received ward level care.

CONCLUSION

The Coronavirus pandemic has caused the death of hundreds of thousands of people worldwide. It is thought that lower vitamin D levels may increases the severity of COVID-19 infections and potentially increase susceptibility to contracting COVID-19. Our data suggests that lower vitamin D levels do not affect mortality. We found that low vitamin D levels potentially can lead to more severe disease requiring ICU level care. We therefore suggest that Vitamin D levels should be measured and corrected in those hospitalised with COVID. Studies that investigate the effect of Vitamin D correction on COVID outcomes are required.

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ORIGINAL ARTICLE

Interocular optical biometry differences as predictors of postoperative cataract surgery refractive outcomes: A retrospective cohort study

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ABSTRACT

Introduction: Few studies have reported the impact of preoperative interocular discrepancy in optical biometry (axial length, corneal power, white-to-white, central corneal thickness) on postoperative refractive outcomes. This study aims to investigate any predictive value of preoperative optical biometry differences between eyes on postoperative refractive outcomes.

Materials and methods: A retrospective cohort study of patients who have undergone optical biometry measurement before unilateral phacoemulsification in the Queen Elizabeth Hospital, Sabah, Malaysia from 2018 to 2020. Biometry data of interest includes axial length (AL), keratometry(K), white-to-white (WTW) and central corneal thickness (CCT). The postoperative outcomes of interest were the patient's preoperative refractive target, postoperative best-corrected visual acuity (BCVA), post-operative refractive outcomes, and optical biometry prediction error.

Results: The interocular biometry discrepancies which were associated with higher odds of prediction error >0.5D from the refractive target were Interocular Corneal Power Difference (IKD)-average≥0.8 D (Odds Ratio, OR=1.97; 95% Confidence Intervals, 95%CI: 1.06, 3.67) and Interocular WTW Difference ≥1.5 mm (OR=2.77; 95%CI: 1.11, 6.92). In cases with prediction error >1.0D, the measurements were Interocular AL Difference ≥0.4 mm (OR=2.99; 95%CI: 1.11, 8.06), IKD flat≥0.4D (OR=2.76; 95%CI: 1.31, 5.82) and Interocular CCT Difference ≥15μm (OR=3.53; 95%CI: 1.29, 9.64).

Conclusion: Interocular axial length difference ≥0.4mm and interocular central corneal thickness difference ≥15μm are associated with refractive error >1.0D from the pre-operative target. Interocular average corneal power difference ≥0.8D and interocular white-to-white difference ≥1.5mm have higher odds of refractive drift >0.5D from the refractive aim. The above cutoff values help clinicians to identify which patients have a higher risk of refractive shift post-cataract surgery and counsel the patient before cataract operation.

KEYWORDS:
Cataract, interocular discrepancy, interocular optical biometry differences, refractive outcomes

INTRODUCTION

Ocular biometry has become an important tool in pre-cataract surgery assessment. It is one of the parameters which determine the postoperative visual acuity of patients. Modern cataract surgery is no longer performed solely as a medical procedure; it is now considered a refractive surgery procedure on which both patients and surgeons have placed high expectations on a good outcome. Hence, reliable biometric measurements are of paramount importance to generate accurate Intraocular Lens (IOL) power calculations. Optical biometry has become the gold standard for the measurements of ocular Axial Length (AL), automated keratometry for Corneal Power (K), Anterior Chamber Depth (ACD), White-to-White (WTW) and Central Corneal Thickness (CCT).[1] Likewise, Lenstar (model LS 900, Haag-Streit AG, Koeniz, Switzerland) uses optical low coherence reflectometry technology for the above measurements.[2]

The axial length must be accurately estimated to ensure there are no errors. Inaccurate measurement of axial length by only 0.10mm can result in the skewed measurement of 0.27diopters (D) from the target refractive outcome in the standard eye.[3] This poses a significant impact on postoperative results. The variation of refractive error from the target refractive outcomes are proven to be wider in myopic and hyperopic eyes.[4] Similarly, deviation in the measurement of corneal power (K) by 1.0D causes 0.9D of refractive error.[3]

In daily clinical practice, one of the methods to ascertain the precision of biometry measurement is to compare the biometry measurements between both eyes to detect interocular discrepancies. Knox Cartwright et al suggest that biometry measurements should be repeated if an intraindividual asymmetry of axial length is more than 0.70mm or the mean keratometry difference is more than 0.90D.[5] Nonetheless, this figure is estimated based on 95%

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distribution of a large biometry dataset performed using the Zeiss IOLMaster (Carl Zeiss Meditec, Oberkocen, Germany) without taking into consideration of the postoperative refractive outcomes.[5]

There are limited studies in the literature that report the impact of Interocular Axial Length Difference (IALD) on visual outcome postoperatively. Lal et al., demonstrated an important relationship between IALD and visual outcomes in paediatric cataract patients.[6] Gochnauer et al., affirmed that best-corrected visual acuity (BCVA) ≥6/12 is associated with lower IALD in paediatric cataract population.[7]

However, these results might be confounded by amblyopia. In the adult population, there are two studies that investigate IALD; Rajan et al., concluded that in patients with age-related cataracts, the increase in AL is associated with increased IALD and postoperative anisometropia.[8] However, this study did not compare the IALD and refractive outcomes. Kansal et al., is the only published study to the best of our knowledge that found that IALD ≥0.2mm is associated with >0.5D of refractive error from the target, and at the same time correlates with worse uncorrected visual acuity.[9]

Studies exploring the relationship between preoperative Interocular Corneal Power Difference (IKD) and postoperative refractive error is lacking. The article published by Vinay et al is the sole article to the best of our knowledge who reported that IKD was not associated with worse refractive error from the target.[9]

The association of the Interocular White-to-White (IWTWD) and Interocular Central Corneal Thickness Differences (ICCTD) with the postoperative refractive error has not been explored. To our best knowledge, ours is the first study that study the impact of IWTWD and ICCTD on postoperative refractive outcome.

MATERIALS AND METHODS

The study was registered with the National Medical Research Registry and acquired ethical approval from the National Research and Ethics Committee of The Ministry of Health of Malaysia. This study was conducted in accordance with the tenets of the Declaration of Helsinki. This study received ethical approval from Medical Research & Ethics Committee of Ministry of Health Malaysia (NMRR-20-1022-54779).

Retrospectively, all electronic reports of the patients who had undergone optical biometry measurement in Queen Elizabeth Hospital (QEH), Kota Kinabalu, Sabah, Malaysia from January 2018 to January 2020 were extracted from the Lenstar in QEH (model LS 900, Haag-Streit AG, Koeniz, Switzerland). Lenstar optical biometry measurements were only performed on cataract that were not dense or mature by an experienced optometrist before cataract surgery. Bilateral eyes' biometry was measured by an experienced optometrist before the cataract surgery. The optometrist would repeat the optical biometry measurement when there were any discrepancies between the eyes to double check the accuracy of the data.

The demography, surgical details, the preoperative refraction target, and postoperative refractive outcomes of patients were extracted from the Malaysian Cataract Surgery Registry (CSR), a web-based password-protected surveillance system collecting data on eye diseases and clinical performance of the Ophthalmology Service in Malaysia. It consists of systematic data entry according to predefined sets of preoperative, operative and outcome forms by designated paramedical staff. Ministry of Health (MOH) Ophthalmology Departments nationwide contribute data to the CSR database. Details on the CSR have been published elsewhere.[10-12] Post-operative refractive outcomes were entered into the CSR 6 weeks post-cataract surgery. The optical biometry data from Lenstar and surgical details with post-operative refractive outcomes from CSR were matched and analysed.

Inclusion criteria were all patients in QEH who have undergone bilateral optical biometry measurement prior to unilateral phacoemulsification who underwent uncomplicated phacoemulsification with IOL implantation during the period from January 2018 to January 2020. Exclusion criteria were patients of age less than 40 years, any ocular co-morbidities (glaucoma, corneal pathology, diabetic retinopathy and others), traumatic or secondary cataract, history of cataract surgery on either of the eyes, previous strabismus, vitreoretinal and refractive surgery before the cataract surgery. Surgery performed by junior specialists or trainee were excluded.

Pre-operative biometry data of interest comprised Axial Length (AL), corneal keratometry (K), white-to-white diameter (WTW) and central corneal thickness (CCT). All data were compared between the right and left eye to identify any discrepancies. The outcome obtained were IALD, IKD-Flat (over flat meridian), IKD-Steep (over steep meridian), IKD-Average, ICCTD and IWTWD.

Different formulas to calculate the IOL power were used depending on the axial length. In AL of <22.0mm, Hoffer Q was used.[13] SRK-T was chosen for AL between 22.0mm and 24.99mm.[14] If the AL fell within 25.0mm to 25.99mm, Holladay was applied. SRK-T was utilized for eyes with long AL (26.0mm or more).[15] The monofocal posterior chamber intraocular lens was selected from the biometry.

Phacoemulsification surgery was performed by three experienced surgeons in the same centre. All 337 patients have only unilateral phacoemulsification done throughout the study. Only uneventful surgeries were included in the study. Complicated cataract surgeries were excluded to reduce the confounding effect on the results. The postoperative refractive assessment was done six weeks after cataract surgery; results were documented into the CSR on the same day.

The outcomes of interest in CSR were the preoperative refractive target, postoperative best-corrected visual acuity (BCVA), postoperative refractive outcomes and optical biometry prediction error of patients. The optical biometry prediction error is defined as the difference between postoperative refractive outcomes and preoperative refractive target.

Table I: Characteristics of the study population (N=337)

	n		(%)
Age (years):			
Mean (SD)		67.77 (8.22)	
Range		43.00, 94.00	
Age group:			
40-50 years	10		(3.0)
51-60 years	47		(13.9)
61-70 years	160		(47.5)
71-80 years	105		(31.2)
>80 years	15		(4.5)
Gender:			
Female	169	(50.1)	
Male	168	(49.9)	
Preoperative Visual Acuity, BCVA (logMAR):			
Median (IQR)		0.50 (0.30–0.60)	
Range		0.00, 3.00	
Preoperative Visual Acuity group:			
BCVA better than 6/15 (<0.4logMAR)	124		(36.8)
BCVA 6/15 or worse (≥0.4logMAR)	213		(63.2)
Preoperative Biometry:			
Axial length (mm):			
Median (IQR)		23.42 (22.75–24.13)	
Range		20.69, 30.79	
Interocular Axial Length Difference (IALD) (mm):			
Median (IQR)		0.10 (0.05–0.22)	
Range		0.00, 3.20	
Flat K (D):			
Mean (SD)		43.86 (1.47)	
Range		39.24, 48.37	
Steep K (D):			
Mean (SD)		44.78 (1.53)	
Range		40.58, 49.05	
Corneal Astigmatism (D):			
Median (IQR)		0.78 (0.45–1.21)	
Range		0.00, 3.65	
Interocular K Difference (D):			
Median (IQR)		0.33 (0.15–0.62)	
Range		0.00, 2.58	
Central Corneal Thickness (CCT) (μm):			
Mean (SD)		532.54 (33.43)	
Range		443.00, 614.00	
Interocular Central Corneal Thickness Difference (ICCTD) (μm):			
Median (IQR)		5.00 (2.00–8.00)	
Range		0.00, 80.00	
White-to-white Diameter (WTW) (mm):			
Median (IQR)		11.70 (11.36–12.02)	
Range		8.60, 12.86	
Interocular WTW difference (mm):			
Median (IQR)		0.16 (0.07–0.38)	
Range		0.00, 12.53	
Preoperative Refractive Target:			
Median (IQR)		-0.43 (-0.50, -0.35)	
Range		-2.04, +0.58	
Preoperative Refractive Target:			
+2.00 to 0.00 D	2		(0.6)
-0.01 to -0.25 D	23		(6.8)
-0.26 to -0.50 D	235		(69.7)
-0.51 to -1.00 D	72		(21.4)
<-1.00 D	5		(1.5)

SD = Standard deviation.
IQR = Interquartile range, reported as 25th percentile–75th percentile.
Range is reported as minimum, maximum

Table II: Relationship between Interocular Biometry Differences and Odds of Optical Biometry Predictive Error 0.5D

IALD (mm	≤0.5D (n=179)		>0.5D (n=158)		OR (95% CI)	P-value
	n	(%)	n	(%)		
<0.1mm	86	(56.2)	67	(43.8)	1.00	0.300
≥0.1mm	93	(50.5)	91	(49.5)	1.26 (0.82, 1.93)	
<0.2mm	132	(53.9)	113	(46.1)	1.00	0.648
≥0.2mm	47	(51.1)	45	(48.9)	1.12 (0.69, 1.81)	
<0.3mm	150	(53.8)	129	(46.2)	1.00	0.601
≥0.3mm	29	(50.0)	29	(50.0)	1.16 (0.66, 2.05)	
<0.4mm	164	(52.9)	146	(47.1)	1.00	0.791
≥0.4mm	15	(55.6)	12	(44.4)	0.90 (0.41, 1.98)	
IKD-Flat (D)						
<0.2D	56	(48.7)	59	(51.3)	1.00	0.242
≥0.2D	123	(55.4)	99	(44.6)	0.76 (0.49, 1.20)	
<0.4D	112	(56.6)	86	(43.4)	1.00	0.130
≥0.4D	67	(48.2)	72	(51.8)	1.40 (0.91, 2.16)	
<0.6D	147	(54.2)	124	(45.8)	1.00	0.401
≥0.6D	32	(48.5)	34	(51.5)	1.26 (0.74, 2.16)	
<0.8D	164	(53.9)	140	(46.1)	1.00	0.355
≥0.8D	15	(45.5)	18	(54.5)	1.41 (0.68, 2.89)	
IKD-Steep (D)						
<0.2D	64	(51.2)	61	(48.8)	1.00	0.588
≥0.2D	115	(54.2)	97	(45.8)	0.88 (0.57, 1.38)	
<0.4D	113	(52.3)	103	(47.7)	1.00	0.694
≥0.4D	66	(54.5)	55	(45.5)	0.91 (0.59, 1.43)	
<0.6D	149	(54.0)	127	(46.0)	1.00	0.496
≥0.6D	30	(49.2)	31	(50.8)	1.21 (0.70, 2.11)	
<0.8D	163	(53.6)	141	(46.4)	1.00	0.575
≥0.8D	16	(48.5)	17	(51.5)	1.23 (0.60, 2.52)	
IKD-Average (D)						
<0.2 D	66	(60.0)	44	(40.0)	1.00	0.079
≥0.2 D	113	(49.8)	114	(50.2)	1.51 (0.95, 2.40)	
<0.4 D	110	(57.0)	83	(43.0)	1.00	0.099
≥0.4 D	69	(47.9)	75	(52.1)	1.44 (0.93, 2.22)	
<0.6 D	133	(54.7)	110	(45.3)	1.00	0.339
≥0.6 D	46	(48.9)	48	(51.1)	1.26 (0.78, 2.03)	
<0.8 D	160	(55.6)	128	(44.4)	1.00	0.032
≥0.8 D	19	(38.8)	30	(61.2)	1.97 (1.06, 3.67)	
ICCTD (μm)						
<5μm	88	(54.0)	75	(46.0)	1.00	0.756
≥5μm	91	(52.3)	83	(47.7)	1.07 (0.70, 1.64)	
<10μm	148	(53.2)	130	(46.8)	1.00	0.923
≥10μm	31	(52.5)	28	(47.5)	1.03 (0.59, 1.81)	
<15μm	167	(53.4)	146	(46.6)	1.00	0.751
≥15μm	12	(50.0)	12	(50.0)	1.14 (0.50, 2.62)	
IWTWD (mm)						
<0.5mm	150	(83.8)	121	(76.6)	1.00	0.097
≥0.5mm	29	(16.2)	37	(23.4)	1.58 (0.92, 2.72)	
<1.0mm	166	(92.7)	137	(86.7)	1.00	0.070
≥1.0mm	13	(7.3)	21	(13.3)	1.96 (0.95, 4.05)	
<1.5mm	172	(96.1)	142	(89.9)	1.00	0.029
≥1.5mm	7	(3.9)	16	(10.1)	2.77 (1.11, 6.92)	

OR = Odds ratio; CI = Confidence interval; IALD = Interocular Axial Length Difference; IKD = Interocular Corneal Power Difference; ICCTD = Interocular Central Corneal Thickness Difference; IWTWD = Interocular White-to-White Difference

IBM SPSS Statistics 20 (IBM SPSS Statistics for Windows, IBM) was used for data analysis. Continuous variables were presented by the mean and standard deviation for normally distributed data. Skewed data were presented by the median and interquartile range (IQR). Categorical variables were described in frequency and percentage.

Simple logistic regression was used to estimate the Odds Ratio (OR) and 95% confidence intervals (95%CI) to determine the association between interocular biometry difference and optical biometry predictive error. P-values of less than 0.05 were considered statistically significant throughout the study.

The relationship between IALD and optical biometry prediction error was compared at 0.1mm, 0.2mm, 0.3mm and 0.4mm cutoffs. In the same way, the association between optical biometry prediction error and IKD-Flat, IKD-Steep and IKD-Average were tested at 0.2D, 0.4D, 0.6D, and 0.8D. Besides that, both IWTWD and ICCTD were compared to optical biometry prediction error at cutoff points of 0.5mm,

Table III: Relationship between Interocular Biometry Differences and Odds of Optical Biometry Predictive Error 1.0D

	≤1.0D (n=304)		>1.0D (n=33)		OR (95%CI)	P-value
IALD (mm)	**n**	**(%)**	**n**	**(%)**		
<0.1mm	137	(89.5)	16	(10.5)	1.00	0.708
≥0.1mm	167	(90.8)	17	(9.2)	0.87 (0.42, 1.79)	
<0.2mm	223	(91.0)	22	(9.0)	1.00	0.414
≥0.2mm	81	(88.0)	11	(12.0)	1.38 (0.64, 2.96)	
<0.3mm	254	(91.0)	25	(9.0)	1.00	0.264
≥0.3mm	50	(86.2)	8	(13.8)	1.63 (0.69, 3.81)	
<0.4mm	283	(91.3)	27	(8.7)	1.00	0.030
≥0.4mm	21	(77.8)	6	(22.2)	2.99 (1.11, 8.06)	
IKD-Flat (D)						
<0.2D	108	(93.9)	7	(6.1)	1.00	0.105
≥0.2D	196	(88.3)	26	(11.7)	2.05 (0.86, 4.87)	
<0.4D	186	(93.9)	12	(6.1)	1.00	0.008
≥0.4D	118	(84.9)	21	(15.1)	2.76 (1.31, 5.82)	
<0.6D	246	(90.8)	25	(9.2)	1.00	0.479
≥0.6D	58	(87.9)	8	(12.1)	1.36 (0.58, 3.16)	
<0.8D	276	(90.8)	28	(9.2)	1.00	0.281
≥0.8D	28	(84.8)	5	(15.2)	1.76 (0.63, 4.92)	
IKD-Steep (D)						
<0.2D	112	(89.6)	13	(10.4)	1.00	0.773
≥0.2D	192	(90.6)	20	(9.4)	0.90 (0.43, 1.87)	
<0.4D	196	(90.7)	20	(9.3)	1.00	0.660
≥0.4D	108	(89.3)	13	(10.7)	1.18 (0.56, 2.46)	
<0.6D	251	(90.9)	25	(9.1)	1.00	0.337
≥0.6D	53	(86.9)	8	(13.1)	1.52 (0.65, 3.54)	
<0.8D	276	(90.8)	28	(9.2)	1.00	0.281
≥0.8D	28	(84.8)	5	(15.2)	1.76 (0.63, 4.92)	
IKD-Average (D)						
<0.2D	102	(92.7)	8	(7.3)	1.00	0.282
≥0.2D	202	(89.0)	25	(11.0)	1.58 (0.69, 3.62)	
<0.4D	179	(92.7)	14	(7.3)	1.00	0.073
≥0.4D	125	(86.8)	19	(13.2)	1.94 (0.94, 4.02)	
<0.6D	222	(91.4)	21	(8.6)	1.00	0.256
≥0.6D	82	(87.2)	12	(12.8)	1.55 (0.73, 3.29)	
<0.8D	263	(91.3)	25	(8.7)	1.00	0.102
≥0.8D	41	(83.7)	8	(16.3)	2.05 (0.87, 4.86)	
ICCTD (μm)						
<5μm	148	(90.8)	15	(9.2)	1.00	0.725
≥5μm	156	(89.7)	18	(10.3)	1.14 (0.55, 2.34)	
<10μm	253	(91.0)	25	(9.0)	1.00	0.287
≥10μm	51	(86.4)	8	(13.6)	1.59 (0.68, 3.72)	
<15μm	286	(91.4)	27	(8.6)	1.00	0.014
≥15μm	18	(75.0)	6	(25.0)	3.53 (1.29, 9.64)	
IWTWD (mm)						
<0.5mm	248	(91.5)	23	(8.5)	1.00	0.107
≥0.5mm	56	(84.8)	10	(15.2)	1.93 (0.87, 4.27)	
<1.0mm	274	(90.4)	29	9.6)	1.00	0.684
≥1.0mm	30	(88.2)	4	(11.8)	1.26 (0.41, 3.83)	
<1.5mm	285	(90.8)	29	(9.2)	1.00	0.213
≥1.5mm	19	(82.6)	4	(17.4)	2.07 (0.66, 6.49)	

OR = Odds ratio; 95%CI = 95% Confidence interval; IALD = Interocular Axial Length Difference; IKD = Interocular Corneal Power Difference; ICCTD = Interocular Central Corneal Thickness Difference; IWTWD = Interocular White-to-White Difference

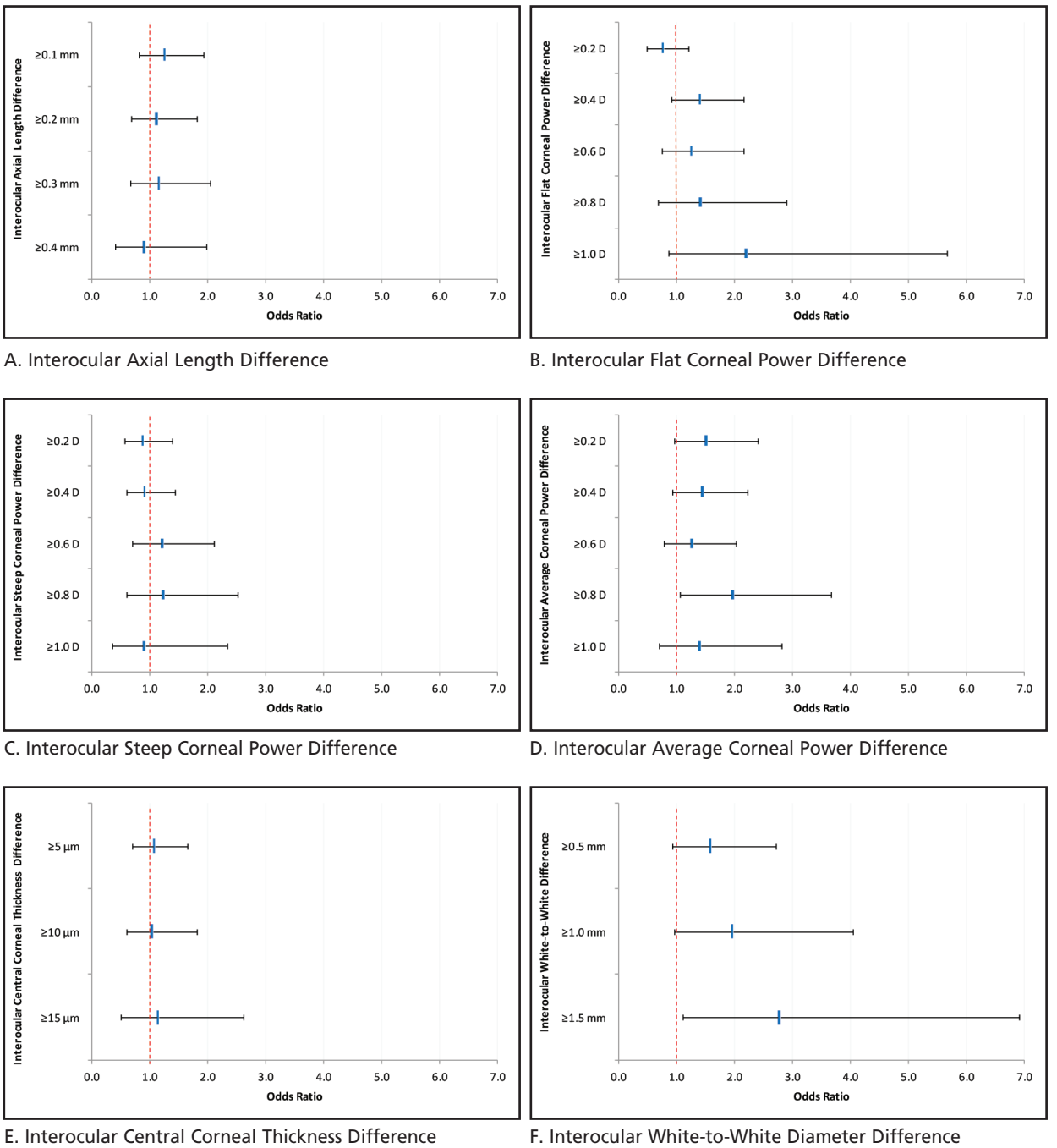
1.0mm, 1.5mm and 5μm, 10μm, 15μm respectively. The cutoff point was determined by using the histogram method.

Optical biometry predictive error was tested in both 0.5D and 1.0D for all of the parameters stated above.

RESULTS

Out of a total of 1012 patients who had undergone cataract surgery, only 337 patients were eligible for analysis. The mean age was 67.7±8.2 years with 160 (47.5%) within the age group of 61-70 years old. The percentage of surgeries with BCVA 6/15 or worse (≥0.4logMAR) was 213 (63.2%). Most of the surgeries were targeted to achieve slight myopia at -0.26 to -0.50D. (Table I)

Among the 337 patients who had undergone surgery, 179 patients (53.1%) were within 0.5D of the refractive target, and 304 patients (90.2%) were within 1.0D. A total of 33 patients (9.8%) had an optical biometry prediction error of more than 1.0D from the refractive target.



A. Interocular Axial Length Difference

B. Interocular Flat Corneal Power Difference

C. Interocular Steep Corneal Power Difference

D. Interocular Average Corneal Power Difference

E. Interocular Central Corneal Thickness Difference

F. Interocular White-to-White Diameter Difference

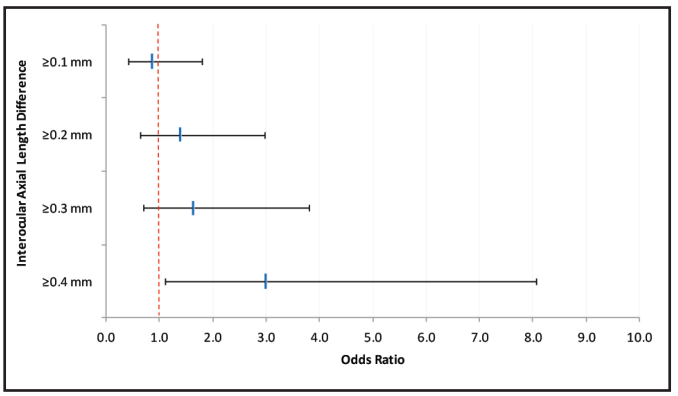
Fig. 1: Odds of Predictive Error >0.5D, By Each Interocular Difference.

Significant proportions of the interocular biometry measurements differences from the refractive target which were associated with higher odds of prediction error >0.5D were IKD-average ≥0.8 D (Odds Ratio, OR=1.97; 95%CI 1.06, 3.67) and IWTWD ≥1.5mm (OR=2.77; 95%CI: 1.11, 6.92) was observed. (Table II)

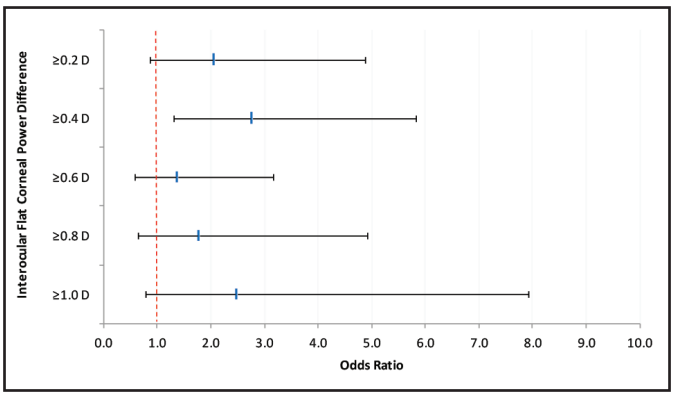
While for the prediction error >1.0D, the measurements were IALD ≥0.4mm (OR=2.99; 95%CI: 1.11, 8.06), IKD flat ≥0.4D (OR=2.76; 95%CI: 1.31, 5.82) and ICCTD ≥15µm (OR=3.53; 95%CI: 1.29, 9.64). (Table III)

DISCUSSION

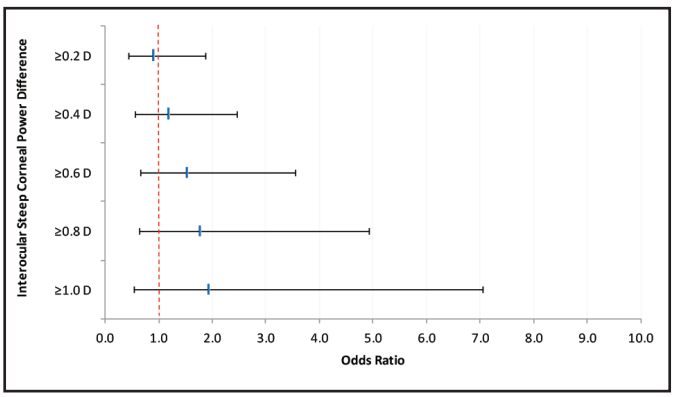
In cataract surgery, surgeons aim to achieve the refractive target which is determined preoperatively during IOL power measurement. Other important ocular biometry parameters are AL, K, CCT and WTW Distance. During the preoperative assessment, the discrepancy in interocular parameters should ideally be measured to determine the reliability of the ocular biometry to ensure quality visual and refractive outcomes. It is not done in practice due to a busy clinic setting and high-volume of surgeries. Besides, the evidence to recommend the routine evaluation of interocular differences for those



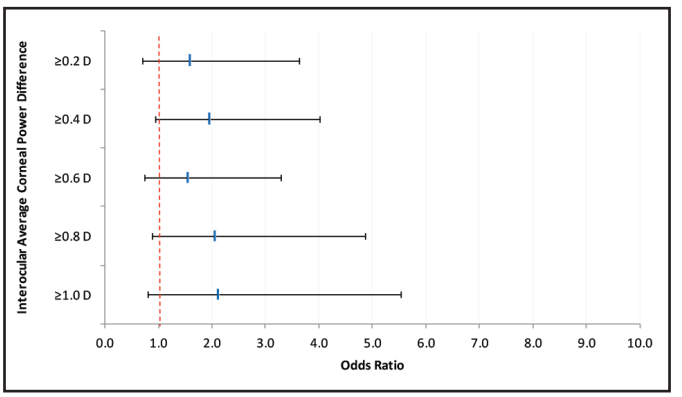
Interocular Axial Length Difference



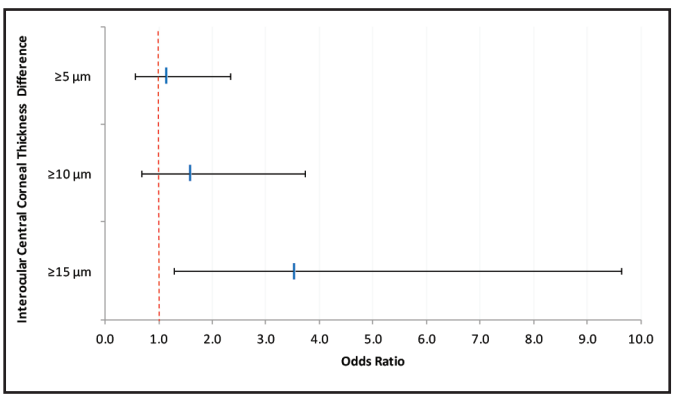
Interocular Flat Corneal Power Difference



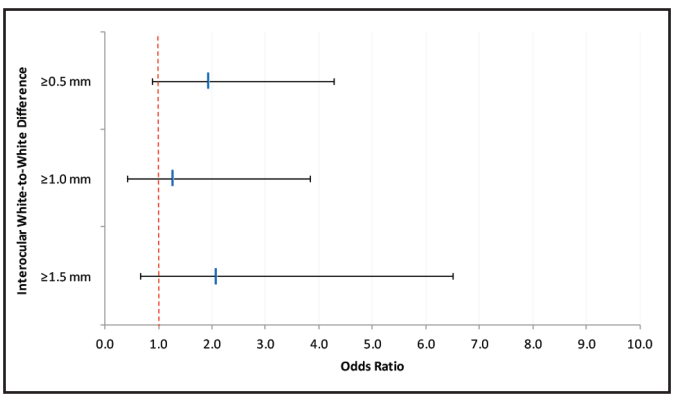
Interocular Steep Corneal Power Difference



Interocular Average Corneal Power Difference



Interocular Central Corneal Thickness Difference



Interocular White-to-White Diameter Difference

Fig. 2: Odds of Predictive Error >1.0 D, By Each Interocular Difference.

parameters are lacking. There are limited studies published in literature regarding the impact of interocular biometry discrepancy on refractive outcomes of cataract surgeries.

In our study, preoperative optical biometric data and postoperative refractive outcomes were analyzed in 337 patients. In the AL analysis, IALD of ≥0.4mm was found to be associated with a higher odds ratio for 1.0D residual refractive error from the target. None of the other subgroups in IALD was associated with a refractive error of 0.5D from the target.

The finding of an increased IALD associated with higher odds of refractive drift from the target is consistent with the previous study.[9] Kansal et al., found IALD of 0.2mm or more is associated with >0.5D of refractive error from the target[9]. Although the cutoff point of significant IALD and refractive error was slightly different from our results, the magnitude of IALD is still significant in predicting postoperative refractive error from the target. Kansal's study has a large number of patients who underwent femtosecond laser-assisted cataract surgery (52.8% of the sample), compared to our study which solely investigates phacoemulsification. This could attribute to the difference of our cut-off value.

The IKD analysis showed an average corneal power difference (IKD-average) of ≥0.8D has higher odds of residual refractive error of 0.5D from the target. Certain IKD cutoffs showed increased odds, however, the results were not significant. This result is incongruous with other studies, as they found no significant relationship between the IKD and refractive outcomes.[9] The reason may be due to different formulas selected according to AL in our study. Factors that can influence keratometry include ocular surface dryness, recent contact lens wear and gonioscopy should be taken into consideration. Interocular average corneal power astigmatism discrepancy of more than 0.8D could be one of the indicators of refractive drift from the target. However, more studies are needed to explore the reliability of this parameter.

The association of Interocular Central Corneal Thickness Difference (ICCTD) with the postoperative refractive outcome is a possibility that has not been explored in other studies. In this study, ICCTD of ≥15µm had the predictive error of 1.0D in the postoperative refractive outcome. To the best of our knowledge, there are no published reports in the literature on the relationship between ICCTD and postoperative prediction error. The limitation in this parameter's measurement is, ICCTD of ≥15µm cannot be labelled as abnormal because there is no reference range for normal ICCTD in literature. Thus, our inability to compare it with other studies. Further studies need to be done to find out the normal range of ICCTD and how ICCTD affects the postoperative refractive outcomes.

The IWTWD of ≥1.5mm was associated with >0.5D of refractive error from the target. To the best of our knowledge, the normal range of IWTWD and its impact on postoperative refractive is not normally evaluated or reported in practice. We hypothesized that an increased IWTWD could be attributed to inconsistent ocular biometry. Given the limited studies on IWTWD, we suggest clinicians repeat the optical biometric measurement if IWTWD is ≥1.5mm until the IWTWD is <1.5mm. If the measurement is persistently high despite repeating the biometry measurement, the possibility of postoperative refractive error of 0.5D from the target needs to be explained to the patient.

There are two limitations in our study that could be addressed in future research. Firstly, this study is a retrospective cohort study which may be biased due to confounders. Hence, a future prospective cohort study is needed to mitigate the possibility of bias. Secondly, the involvement of multiple surgeons in this study is another confounding factor that may induce performance bias.

The strength of this study is to explore the impact of IALD, IKD, ICCTD and IWTWD on postoperative refractive outcomes. There are only limited studies discussing this topic in the literature. To our best knowledge, this is the first paper exploring the impact of ICCTD and IWTWD on the postoperative refractive outcome. The predictive value of the parameters described above is useful for clinicians in decision making and during preoperative counselling of patients. To reduce postoperative refraction drift from the target, the preoperative interocular discrepancy should be reduced to the cut-off value as mentioned. Clinicians can perform biometry by using more than 1 type of instrument (immersion or other optical biometry) when in doubt. Whether repetitive ocular biometric measurements need to be done to reduce the interocular biometric discrepancy remains questionable. This study did not focus on eliciting repetitive ocular biometry consistency owing to the retrospective nature of the study design. Further directions for this investigation will be to establish the role of repetitive ocular measurement on patients who have interocular discrepancy exceeding the cut-off points as determined in this study.

CONCLUSION

The IALD ≥0.4mm and ICCTD ≥15µm are associated with increased odds of greater than 1.0D of postoperative residual refractive error, while both IKD-average ≥0.8D and IWTWD ≥1.5mm have a higher risk of greater than 0.5D of residual refractive error from the target after cataract surgery. To our best knowledge, this is the first study that evaluates the impact of interocular central corneal thickness difference and interocular white-to-white difference on postoperative refractive outcome. Future research is encouraged to narrow the gap in acceptable range of interocular discrepancy value. True interocular discrepancies above these values shall serve as indicators to alert ophthalmologists on the potential risk of postoperative refractive drift and advice patients accordingly.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest in this study.

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Renal Denervation in the treatment of Resistant Hypertension

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ABSTRACT

Hypertension is a risk factor for coronary artery disease and stroke. Only about half of the patients with hypertension are adequately controlled on medical therapy, and about a quarter may develop severe or resistant hypertension. Resistant hypertension is defined as failure to achieve target blood pressure of <140/90mmHg while on full doses of an appropriate three-drug regimen that includes a diuretic. Increasingly more attention has been paid to the potential of renal denervation (RDN) as treatment for resistant hypertension, guided by a better understanding of renal nerve anatomy.

RDN is undergoing transformation as a technology for the treatment of resistant hypertension. Early studies demonstrated efficacy in treating resistant hypertension patients with significant reduction in office blood pressure (BP). However, the randomised sham-controlled trial, Symplicity HTN-3, did not demonstrate any significant difference in BP reduction between the RDN and the sham control arm. Since then, further improvements have been made in developing second generation systems. Subsequent studies showed the importance of more distal and branch renal artery ablation, and multielectrode systems have been utilised. Two randomised sham-controlled trials, the SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED studies showed the effectiveness of RDN with the second-generation radiofrequency ablation system. These studies showed that RDN significantly reduced office and 24-hour ambulatory BP when compared with sham control treatment. The RADIANCE-HTN SOLO trial also demonstrated efficacy using an ultrasound-based catheter system for RDN treatment of resistant hypertension. These trials have reinvigorated current clinical interest in RDN as treatment for resistant hypertension.

There is increasing evidence for RDN as an effective treatment for uncontrolled or resistant hypertension. The RDN procedure has also evolved with time, with an improved practice of delivering a larger number of ablations to distal vessels in addition to main renal arteries. The RDN procedure has a low complication rate and may provide an approach that could potentially reduce the morbidity and mortality risks associated with resistant hypertension in Malaysia.

KEYWORDS:
Renal Denervation, resistant hypertension

Hypertension is a risk factor for coronary artery disease and stroke.[1,2] The Malaysian National Health and Morbidity Survey in 2019 has shown that the prevalence of hypertension was 6.4 million, and 3 out of 10 people in Malaysia have hypertension.[3] Having increased levels of blood pressure (BP) increases the mortality risk[4] and controlling hypertension reduces mortality related to ischaemic heart and cerebrovascular disease.[5] It has been shown that even modest reductions in BP are associated with significant reductions in the rates of cardiovascular mortality.[6] Only about half of the patients with hypertension are adequately controlled on medical therapy,[7] and about a quarter may develop severe or resistant hypertension.[8] Resistant hypertension is defined as failure to achieve target blood pressure of<140/90mmHg while on full doses of an appropriate three-drug regimen that includes a diuretic. One study found that in Malaysia, resistant hypertension is present in nearly one in ten hypertensive patients on treatment.[9]

It is important to have a treatment option for patients with treatment resistant hypertension, who may subsequently develop end organ damage from hypertension. Over time, our understanding of the pathophysiology of hypertension has progressively improved. Studies of hypertension models have demonstrated that renal afferent and efferent sympathetic nerves have a significant role in the pathophysiology of hypertension.[10] As a result, increasingly more attention has been paid to the potential of renal denervation (RDN) as treatment for resistant hypertension, guided by a better understanding of renal nerve anatomy.

Pathophysiology and Rationale for Renal Denervation

Over the years, there has been increasing evidence from studies that the sympathetic nervous system plays a significant role in the pathophysiology of hypertension.[11] It has been shown that reduced activity of the renin-angiotensin system and reduced renal vascular resistance is involved in the antihypertensive effect of RDN in experimental rat models.[12] Furthermore, canine models demonstrated that renal nerve stimulation in both proximal and middle regions of the renal artery increased systolic BP by >10mmHg.[13] RDN was therefore thought to be a method which can alter sympathetic activity, since surgical RDN has also previously been shown to reduce BP in several animal models of hypertension.[14]

The sympathetic nerves located around the renal arteries are derived from the celiac plexus, the lumbar splanchnic nerves,

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and the superior mesenteric ganglion.[15] These nerves lie close to the renal artery, allowing the possibility of denervation through an endovascular approach. Previous studies showed that more nerve fibres are present in the proximal artery when compared to the distal segment. About half of the nerve fibres around the main artery are located within 2.5mm from the intima of the artery.[16] In contrast, the nerves at the distal arteries are even closer to the lumen than those in the proximal segments, with a majority of the nerve fibres within 2mm from the intima.[17] This knowledge has led to techniques to optimise the clinical outcome for renal denervation by targeting nerve fibres.[18]

Renal sympathetic efferent nerves activate the renin-angiotensin-aldosterone system, hence leading to a decrease renal blood flow, as well as a decrease in urinary excretion of salt and water[19] (Figure 1). By decreasing efferent sympathetic nerve activity, RDN can lower BP. Additionally, sympathetic afferent activity also activates centrally, leading to further mediation of hypertensive response.[20] RDN can also reduce BP by decreasing centrally mediated renal afferent sympathetic nerve activity.[21] Both reductions of afferent and efferent renal nerve activity lead to a reduction in systemic vascular resistance which leads to the BP lowering effect.[22]

Renal Denervation Procedure in Early Clinical Trials

Since studies have shown that renal sympathetic nerves are located at a close distance to the renal arteries, radiofrequency ablation (RFA) via the intra-arterial route was first introduced to denervate sympathetic nerves in order to lower BP in patients with hypertension. The first-generation RFA system (Symplicity Flex; Medtronic, Minneapolis, Minnesota) is a catheter with single electrode. The system uses low power output (8W) to deliver RFA into the intraluminal surface of the renal artery via a single electrode catheter, with four to six ablations of 120 seconds each in the renal artery.[23] The early study (SIMPLICITY HTN-1 study) using this catheter was a proof of concept trial that included 45 patients who underwent RDN treatment.[24] Primary endpoints included safety and efficacy in lowering office BP. The patients had a mean baseline office BP of 177/101mmHg. The study demonstrated significant reduction in office systolic BP of 26mmHg in the RDN group compared to 12mmHg in the control group at six months (Figure 2).

Following this, a multicentre randomised controlled trial (SYMPLICITY HTN-2 study) studied patients with resistant hypertension with an office systolic BP of ≥160mmHg despite the prescription of ≥3 antihypertensive drugs, including a diuretic.[25] RDN was performed using the Simplicity Flex catheter and RDN treatment was compared to medical therapy in the study. The study found that the mean office BP at 6 months dropped by 32mmHg ($p<0.001$) in the RDN group (n=52) compared to BP drop of 12mmHg in the control group (n=54) (Figure 2). There was, however, some limitations for the first two Simplicity trials. Firstly, both studies were not blinded, and furthermore 24-hour ambulatory BP was not routinely tested. Hence, a further blinded randomised controlled trial, the Simplicity HTN-3 trial was conducted subsequently to overcome these limitations.

The Symplicity HTN-3 was a multicentre single blinded trial which randomised 535 patients to either RDN using Symplicity Flex or sham control (with 2:1 randomisation).[26] The trial compared an RDN group with a sham-controlled group of patients with an office systolic BP ≥160mmHg despite the prescription of ≥3 antihypertensive medications including a diuretic. The primary and secondary efficacy endpoints were the difference in office and 24-hour ambulatory BP reduction respectively between the two groups at 6-month. After six months following RDN treatment, there was a mean decrease in office systolic BP of 14.1mmHg in the RDN group (n=364) compared to a decrease of 11.7mmHg in the control group (n=171) (Figure 2). Since both RDN and sham-controlled groups showed significant decreases in the blood pressure, this raised doubt as to the genuine effectiveness of the RDN treatment. One possible reason for this could have been the lack of consistency in hypertensive medications taken, with medication changes occurring in 39% of patients over the period of the trial.[27] Another proposed reason for these differences was variable operator experience in delivering RDN treatment.[28]

Several other randomised controlled trials (RCT) have used RFA in renal denervation with variable results. The simplicity HTN-Japan trial was the first RCT of RDN in an Asian population involving RDN (n=22) and control (n=19) subjects.[29] The 6-month office SBP change was -16.6±18.5mmHg for RDN subjects ($p<0.001$) and -7.9±21.0mmHg for control subjects ($p=0.117$). Another trial, the French DENER-HTN trial was an RCT involving patients with resistant hypertension.[30] A group of patients on medications who were treated with RDN (n=48) was compared to a control group of patients treated with medication only (n=53). The mean change in daytime ambulatory systolic blood pressure at 6 months was -15.8mmHg (95% Confidence Interval, 95%CI: -19.7, -11.9) in the renal denervation group and -9.9mmHg (95%CI: -13·6, -6·2) in the group receiving antihypertensive medication. Another trial carried out in Denmark, the ReSet trial, is an RCT among patients with resistant hypertension. Sixty-nine patients with treatment-resistant hypertension were randomised to RDN (n=36) or a sham procedure (n=33).[31] In this trial however, there were no significant differences when comparing RDN to a sham procedure at 6-month [-6.1± 18.9 mmHg (RDN) vs. -4.3±15.1mmHg (SHAM)].

Developments in the Renal Denervation Technology

Since the publication of SYMPLICITY HTN-3 trial, further advances have been made in the technology for RDN. Studies have previously demonstrated that RF ablation was more effective when renal sympathetic nerves at the distal segment of the renal artery or the arterial branches are targeted.[32,33] One study randomised patients with uncontrolled hypertension to RFA at the main renal artery (n=26) compared RFA at the distal branches of the renal arteries (n=25).[34] At 6-month, the decrease in 24-hour ambulatory systolic BP (SBP) was greater in the distal branch treatment group compared to the main artery RFA group (22.6mmHg vs. 9.4mmHg; $p<0.03$). In another clinical study, there was better BP reduction at 3-month using the combined method compared to main vessel ablation only.[35] With the previous Simplicity Flex ablation system (Medtronic, Minneapolis, MN, USA) it was challenging to achieve circumferential ablation. Therefore, more advanced systems have since been

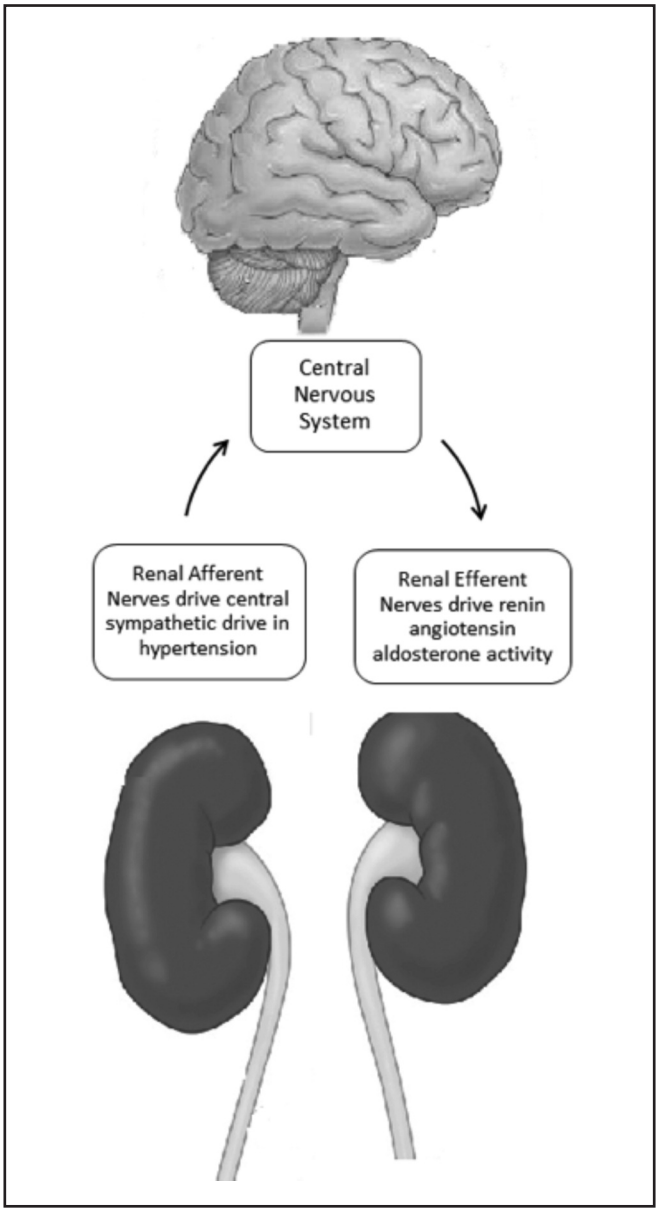

Fig. 1: Afferent and efferent renal sympathetic nerve targets for renal denervation.

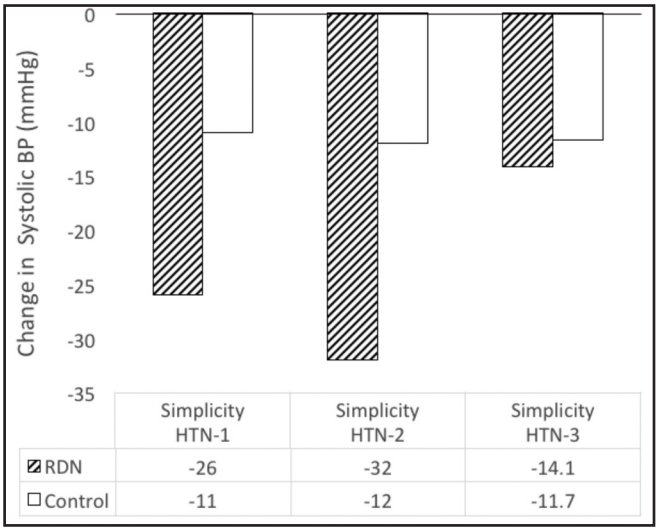

Fig. 2: The Simplicity HTN-1 and HTN-2 trials showed significant drop when comparing RDN and controls, but Simplicity HTN-3 trial did not show a significant difference.

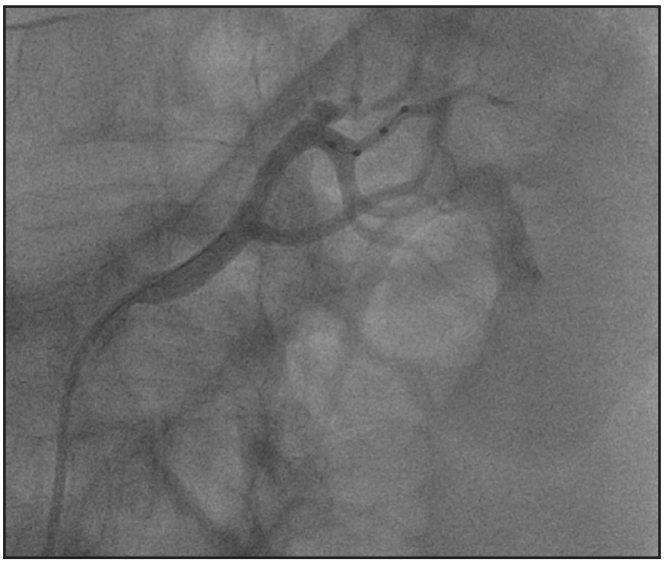

Fig. 3: Renal Denervation with the Spyral 4-electrode Catheter system.

developed with multi-electrode catheter design to increase the ease of use and reduce operator dependency. One such system, the Spyral catheter was designed as a 4-electrode system which delivers a maximum power of 6.5W for a duration of 60 seconds[36] (Figure 3).

The SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED, were designed as proof of concept studies for the Spyral catheter.[37,38] These trials assessed BP response to RDN in patients with mild to moderate hypertension (office SBP of 150-180mmHg, 24-hr ambulatory SBP of 140-170mmHg). The SPYRAL HTN-ON MED trial assessed patients who were on 1 to 3 antihypertensive medications. Patients were randomised (1:1) to RDN or sham treatment in both trials. In these trials, the Spyral catheter allowed a more comprehensive RDN procedure that involved ablation in the distal main renal artery and arterial branches. Additionally, the operators had previous RDN experience, and a standardised approach was used to target all accessible renal arterial branches with a diameter of 3 to 8mm.

The SPYRAL HTN-OFF MED showed that at 3-month following RDN, there was significant reduction in both office and 24-hour ambulatory BP from baseline in the treatment group (-10/-5.3mmHg and -5.5/-4.8mmHg) compared to the sham control group. Significant BP reduction in the RDN arm was also reported in the SPYRAL HTN-ON MED study at 6-month (-9.0/-6.0mmHg for 24-hr ambulatory BP) (Figure 4). A rigorous procedural technique was adopted in this study, including more extensive ablations involving the main vessel and the branches. The larger number of ablations was not associated with an increase in adverse events.

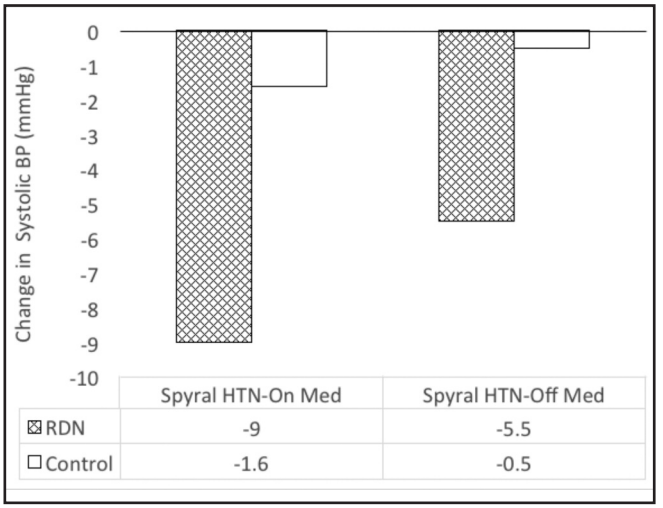

Fig. 4: Reduction of 24-hour Systolic BP in the Spyral HTN-On and HTN-Off Med trials.

Apart from RFA as described above, catheter-based ablation of renal nerves has also been shown to be effective using ultrasound. With this technology, ultrasound is emitted circumferentially via a piezoelectric crystal at the end of the catheter that is placed in the renal artery with the inflation of a water-cooled balloon (Paradise ultrasound system; ReCor Medical, Palo Alto, California). A multicentre, single-blind, sham-controlled trial (RADIANCE-HTN SOLO) studied catheter-based ultrasound in patients who were not on antihypertensive medications. The decrease in daytime ambulatory SBP (primary endpoint) from baseline to two months was greater in the RDN group (8.5mmHg, n=74) when compared to the sham group (2.2mmHg, n=72).[39] The successful treatment using this method in the RADIANCE-HTN SOLO trial suggests that interruption of the renal nerves in any segment of the renal artery may be sufficient to achieve effective RDN.

Two additional RCTs with ultrasound-based ablation systems are ongoing.[40] The RADIANCE-HTN TRIO trial is being conducted in the United States and Europe. The REQUIRE study is being conducted in Japan and Korea. Both trials aim to evaluate the safety and efficacy of the ultrasound RDN system in patients with uncontrolled hypertension (office BP >140/90mmHg despite treatment with three antihypertensive medications). The primary endpoint in both trials is the change in daytime ambulatory BP from baseline to six months.

Clinical Safety

Many studies have demonstrated a low complication and adverse event rate with RDN. Complications are commonly related to vascular access for example, haematoma and pseudoaneurysm at the femoral puncture site with an incidence of 1-2%.[41] Another complication is renal artery dissection with an incidence of <1%. There have also been reported cases of renal artery stenosis after the RDN procedure.[42] There has been no reports of significant deterioration of renal function after RDN.[43]

Potential Limitations of RDN trials

Although there are positive results from SPYRAL HTN-OFF MED, RADIANCE SOLO, and SPYRAL HTN-ON MED several limitations and unknown issues remain. Since RDN was performed in a small number of selected patients and follow-up was only up to six months in these studies, it is not clear whether the BP lowering effects can be sustained and also safety in the long-term is still not known. One other important factor is to determine whether RDN can reduce the number of antihypertensive drugs for long-term BP control, and this is currently not known.

CONCLUSION

There is increasing evidence for RDN as an effective treatment for uncontrolled or resistant hypertension. The RDN procedure has also evolved with time, with an improved practice of delivering a larger number of ablations including distal vessels in addition to main renal arteries. The RDN procedure has a low complication rate. In the future, randomised controlled trials in larger populations with longer follow-up may further add to current evidence for the effectiveness of RDN treatment. RDN technology may provide an innovative approach that could potentially reduce the morbidity and mortality risks associated with resistant hypertension in Malaysia.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Quantitative vestibular function tests in posterior circulation stroke patients: A review

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ABSTRACT

While specific bedside examinations are known to be sensitive in identifying stroke among acute vestibular syndrome patients, complementary quantitative vestibular function testing can be helpful to quantify vestibular loss due to stroke. In contrast to peripheral vestibular dysfunction, diagnosis of central vestibular dysfunction can be challenging for unskilful clinicians. This article presents a comprehensive overview of quantitative vestibular function test findings such as the video head impulse test (vHIT), cervical vestibular evoked myogenic potentials (cVEMPs), ocular vestibular evoked myogenic potentials (oVEMPs), videonystagmography (VNG) and caloric test among stroke patients. Vestibulo-ocular reflex (VOR) gain is usually found normal among posterior inferior cerebellar artery (PICA) stroke patients but varies among anterior inferior cerebellar artery (AICA) stroke patients. Abnormal contralesional posterior semicircular canal VOR gain can be observed due to lesions in the medial longitudinal fasciculus (MLF). AICA and PICA stroke can impair cVEMPs, oVEMPs, and VNG (i.e., smooth pursuit and saccade functions). Strokes, particularly those involving the vestibular nucleus, including both upper, lower brainstem and cerebellum, can result in various abnormalities of smooth pursuit, saccade or calorics testing. The combined evaluations of VNG, vHIT, and VEMPs can be accurately used to complement and quantify bedside vestibular evaluation in diagnosing central vestibular dysfunction. In addition, as most studies were conducted amongst acute vestibular syndrome (AVS) patients, future studies that investigate the prevalence of vestibular dysfunction in recovering stroke patients are required.

KEYWORDS:
Vestibular function tests, vestibular evoked myogenic potentials, vestibulo-ocular reflex, caloric tests, stroke

INTRODUCTION

An imbalance in the vestibular system tonic discharges following disturbances to the vestibular organs can be defined as vestibular dysfunction. Common vestibular symptoms are vertigo, dizziness, oscillopsia, and postural symptoms like unsteadiness involving peripheral vestibular organs, the vestibular ocular reflex (VOR) or both.[1,2] However, vestibular dysfunction can also be caused by a stroke. It was reported that 25% of posterior circulation stroke (PCS) patients had vertigo.[3] Among acute vertigo patients, 11%[4] to 59.5%[5] of vertigo incidences were associated with stroke. A study also found that 12.5% of emergency department visits related to vestibular symptoms were due to cerebrovascular accidents.[6] A national database survey in Taiwan reported that 3.1% of the Taiwanese adult population had vertigo, and 0.5% was having a stroke.[7]

PCS accounts for approximately 10% to 20% of annual stroke incidences.[8-10] Based on the Global Burden of Disease Study 2016 report, stroke was among the most common cause of death globally, with 80 million stroke survivors having permanent disabilities.[11]

Acute vestibular syndrome (AVS), characterised by a single episode, sudden onset of vestibular signs and symptoms can occur due to disorders and diseases as vestibular neuritis or stroke.[2] In contrast, the chronic vestibular syndrome usually occurs due to persistent symptoms and signs of vestibular disorders, such as bilateral vestibular loss or cerebellar degeneration.[2] Clinical bedside vestibular examinations have been used extensively to diagnose vestibular and oculomotor dysfunction associated with stroke. The clinical Head-Impulse-Nystagmus Test of Skew (HINTS) was introduced as the test for the angular horizontal VOR, nystagmus and skew deviation (to determine the otolithic function) to differentiate central vestibular disorders (which may be due to stroke) from a peripheral vestibulopathy.[12] Central vestibular lesions caused by a stroke can be identified by a normal head impulse test (HIT) VOR finding, presence of bilateral gaze-evoked or direction-changing nystagmus, and a positive skew deviation. Earlier studies reported these sensitivities and specificities for the HINTS battery: 94.1% sensitivity,[3] 96.5% sensitivity and 84.4% specificity,[5] 100% sensitivity and 96% specificity in diagnosing stroke in AVS patients, which is higher than the magnetic resonance imaging (MRI) within 48 hours of symptom onset.[12] Compared to HINTS, the early diffusion-weighted magnetic resonance imaging (DW-MRI) had lower sensitivity, 100% vs. 72%, and comparable specificity, 96% vs. 100%.[12]

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The HINTS algorithm was created and validated to triage vertigo patients in the acute setting, such as the emergency room. The HINTS is a highly sensitive bedside test that is quick and cost-effective to diagnose acute central vertigo (e.g., PCS), which has a high risk of mortality and morbidity. Quantitative vestibular testing such as caloric irrigation, vestibular evoked myogenic potentials (VEMPs), and videonystagmography (VNG) have also been used to complement clinical bedside testing measuring vestibular and oculomotor dysfunction. Quantitative vestibular function testing is usually used in laboratory or office settings, except for the video head impulse test (vHIT), which has also been used recently in the emergency room.[13] Quantitative vestibular testing can monitor the effects of rehabilitation and the course of recovery of chronic vestibular dysfunction over time.[14] However, quantitative testing, such as vHIT[15] and VEMPs[16] have been known to identify peripheral vestibular lesions. Recently, abnormal vHIT[13] and VEMPs[17] have also been reported among patients with central lesions such as stroke. Vestibular dysfunction can occur depending on the lesion involved in the posterior circulation (Fig. 1). This review aims to document recent clinical presentations and characteristics of quantitative vestibular test batteries among stroke patients.

METHODS

The present narrative review is based on searches from Pubmed, SCOPUS and Ovid databases with the following keywords; "(head impulse test or scleral search coil or video head impulse test or video-oculography or vestibular evoked myogenic potentials or electronystagmography or videonystagmography or caloric test) AND (stroke)". Google Scholar was also used to search for additional literature and other quantitative methods. Fifty-four, 134 and 553 articles were retrieved from Pubmed, SCOPUS, and Ovid web search engines. After excluding duplications, only 20 original articles involving quantitative vestibular testing studies were reviewed. This review includes only recent articles published from 2010 up to 2020.

RESULTS

Video Head Impulse Test (vHIT)

The vHIT concept is based on the VOR function among normal healthy individuals, which depict that the VOR moves the eyes with the same speed and contralateral direction to that of head movement, for the eyes to keep the object of interest in the fovea. The vHIT measures VOR, which originates from the semicircular canals (SCCs), i.e., part of the peripheral vestibular organs in the inner ear. Signals were then sent to the brainstem following head acceleration and deceleration. In peripheral vestibular lesions, the VOR gain is reduced, causing catch-up saccades, enabling the eyes to focus on the targeted image. From the SCCs, the VOR pathway projects to the vestibular nucleus and contralateral abducens nucleus.[18] The neurons then project to the oculomotor nucleus to activate eye muscles via the medial longitudinal fasciculus.[18]

In the early years before the availability of vHIT, the scleral search coils technique was used to measure the VOR gain. However, the coils require special equipment and are only available for research outside the standard clinical practice. A recent study reported that the VOR gain for the horizontal SCC is usually normal among PCS patients.1[9] The study indicated that quantitative HIT could distinguish between peripheral or central vestibular dysfunction among AVS patients in the emergency department. However, studies using vHIT and dual-search coils showed that, based on blood circulation territories, acute stroke patients had distinct VOR gain findings (Table I). The VOR gain for horizontal SCCs among anterior inferior cerebellar artery (AICA) stroke patients were bilaterally reduced[13,20-22] or varied[20-22] compared to normal individuals. The reduction or variation in the VOR gain findings was attributed to the level of involvement following ischemic insults in the labyrinth, vestibular nucleus or flocculus.[20] For example, floccular infarction could cause a more severe ipsilesional gain reduction.[20] However, due to the risk of misclassifying AICA stroke in diagnosing central vestibular dysfunction, HIT VOR gain should not be used in isolation but only when accompanied by other tests and clinical oculomotor examination.[21]

The VOR gain for the horizontal SCCs was within normal symmetrical ranges among PICA stroke patients.[21,22] But, in the dual-search coils study, 17 PICA and three superior cerebellar arteries (SCA) stroke patients with AVS had a 25% symmetrical mean gain reduction for the horizontal SCCs when compared with the control subjects.[20] Although there was only a slight reduction in the gain values, this finding indicates some cerebellar influence in the high-acceleration VOR.[20] Another study also found that, when a stroke involved PICA and SCA territories, the VOR vHIT gains for the horizontal SCCs revealed normal values.[13] Overall, among AVS patients, abnormal VOR gains for the horizontal SCCs typically indicate vestibular neuritis, while normal gains usually predict the likelihood of stroke.[13,20-22] The vHIT VOR gain for the horizontal SCCs has a sensitivity of 88%[21] to 94%[20] or accuracy of 100%[13,22] when identifying PCS among AVS patients. In another study among stroke patients with lesions in the lateral medulla, only three of fourteen patients had mild to moderate gain deficits for the horizontal or posterior SCCs.[23] The patients with abnormal VOR gain had lesions in the rostral medulla. However, most patients with lesions involving the caudal or middle medulla had normal VOR gain values. Overall, the study indicated that the VOR gain is usually normal for the horizontal SCCs in the lateral medullary infarct patients.[21,23]

The study using dual-search coils HIT also provided further saccade analysis for the horizontal SCCs.[20] Overall, the saccades for the horizontal SCCs in both AICA and PCA and SCA groups were small, with 97% of the patients in both groups had <61% saccade asymmetry.[20] Due to larger ipsilesional saccade amplitude after contralesional trials, there was also negative saccade asymmetry among 70% of PICA and SCA stroke subjects in the study.[20] The saccade asymmetry in PICA and SCA stroke was attributed to the hypometria of the infarcted dorsal vermis in the cerebellum, caused by refoveated eyes after saccade undershooting.[20] The fact that PCS patients had small saccades with amplitude asymmetry, more pronounced in PICA and SCA than AICA stroke, may warrant further investigation on saccade potential in diagnosing central vestibular dysfunction.[20] In a recent study that utilised vHIT in the assessment of PCS patients, it was reported that there was no significant difference in the saccades prevalence for the horizontal SCCs

Table I: Quantitative head impulse test findings in posterior circulation stroke (PCS) studies

Authors	Duration From Stroke Onset	Measurement Techniques	Subjects	Gain Findings	Saccade Amplitude Findings
Guler et al. (13)	Acute	vHIT	9 brainstem infarct (PICA-SCA stroke) patients	Horizontal SCC (mean±SD)= Ipsilesional 0.79±0.25; Contralesional 0.80±0.23	
			7 cerebellar infarct (PICA-AICA stroke) patients	Horizontal SCC (mean±SD)= Ipsilesional 1.02±0.13; Contralesional 0.97±0.16	
Calic et al., (19)	Mean 7 days	vHIT	22 PCS patients	Horizontal SCC (mean±SD)= 0.85±0.3	Horizontal SCC (mean±SD)= Amplitude 2.2±1.7°;
Chen et al., (20)	< 7 days	Dual-search coil	17 PICA and 3 SCA	Horizontal SCC (mean±SD)= Ipsilesional 0.75±0.09; Contralesional 0.74±0.08	Horizontal SCC (mean±SD)= Ipsilesional 2.1±0.4°; Contralesional 3.0±0.8°
			13 AICA	Horizontal SCC (mean±SD)= Ipsilesional 0.38±0.13; Contralesional 0.57±0.12	Horizontal SCC (mean±SD)= Ipsilesional 4.7±1.4°; Contralesional 3.3±0.7°
Mantokoudis et al. (21)	< 7 days	Video-oculography	7 PICA	Horizontal SCC mean (SE)= Ipsilesional 0.94 (0.04); Contralesional 0.93 (0.04)	
			3 AICA	Horizontal SCC mean (SE)= Ipsilesional 0.84 (0.10); Contralesional 0.74 (0.10)	
Newman-Toker et al. (22)	< 7 days	Video-oculography	3 AICA	Horizontal SCC: 2 patients with VOR gain 0.6-0.8, 1 patient with VOR gain <0.6	
Lee et al. (23)	Acute up to 16 days	vHIT	17 lateral medulla	3 patients had mild to moderately reduced VOR gain (1 patient with reduced ipsilesional horizontal and posterior SCC, 1 patient with ipsilesional horizontal, ipsilesional posterior SCC and contralesional posterior SCC, 1 patient with contralesional posterior SCC).	Covert saccades: Latency 84 -111 ms, Peak velocity 42-104°/s. Overt saccades: Latency 314-368 ms, Peak velocity 90 to 130°/s.
Choi et al. (24)	1-3 weeks	Magnetic search coil	10 patients with unilateral INO	90% had reduced VOR gain for the contralesional posterior SCC and 50% had reduced VOR gain for the ipsilesional horizontal SCC	
Lee et al. (25)	1-131 days	vHIT	16 unilateral INO	Horizontal SCC (mean±SD)= Ipsilesional 0.77±0.27; Contralesional 0.90±0.24 Anterior SCC (mean±SD)= Ipsilesional 0.75±0.17; Contralesional 0.76±0.19 Posterior SCC (mean±SD)= Ipsilesional 0.73±0.18; Contralesional 0.55±0.11	
			5 bilateral INO	Horizontal SCC (mean±SD)= 0.82±0.32 Anterior SCC (mean±SD): 0.58±0.19 Posterior SCC (mean±SD)= 0.43±0.11	

AICA: anterior inferior cerebellar artery; PICA: posterior inferior cerebellar artery; SCA: superior cerebellar artery; INO: internuclear ophthalmoplegia; SCCs: semicircular canals; SD: Standard Deviation; SE: Standard Error

between the standard healthy control and PCS.[19] However, in the study, the saccade metrics such as saccade amplitudes and velocities were smaller, with saccadic latency longer in the PCS than in the standard controls. The fact that the PCS patients had small saccade with amplitude asymmetry, more in PICA and SCA than AICA stroke, may warrant further investigation of the application of saccade potential in diagnosing central vestibular dysfunction.[20]

While HIT gain measured on lateral SCCs can sensitively differentiate peripheral from central vestibular dysfunction, the HIT can also be used to investigate angular VOR deficiency for the vertical SCCs. The medial longitudinal fasciculus (MLF) transmits the VOR signals from the vertical SCCs to the ocular motor nuclei.[24,25] In a study on unilateral internuclear ophthalmoplegia (INO) stroke patients, reduced VOR gains were found in contralesional posterior SCCs more

Table II: cVEMPs and oVEMPs abnormalities in posterior circulation stroke (PCS) studies

Authors (year)	Test Duration From Stroke Onset	Blood Supply Territories	Lesion Locations	cVEMPs	oVEMPs
Heide et al. (17)	The first week after symptom onset		Brainstem	12/29 (41%) patients had unilateral abnormal AC clicks cVEMPs	
Calic et al. (19)	Mean 7 days	PCS		38% had asymmetrical cVEMPs	9% had asymmetrical oVEMPs
Ahn et al. (27)		AICA	Brainstem, cerebellum or both	8/16 (50%) patients had abnormal clicks cVEMPs on the lesion side (absent or decreased amplitude)	
Weng and Young (28)		PICA, AICA	Brainstem, cerebellum or both	PICA group: (8/22) 36% were abnormal AICA group: 3/4 (75%) ear were abnormal	PICA group: 8/14 (57%) ears were abnormal AICA group: 1/2 (50%) ears were abnormal
Choi et al. (29)	10 -13 days	PICA, PICA & SCA, SCA, AICA	Unilateral cerebellum	11/27 (41%) patients had abnormal AC TB cVEMPs	9/27 (33%) patients had abnormal head tap oVEMPs
Kim et al. (30)	1-14 days		Lateral medulla	9/21 (43%) patients had abnormal AC TB cVEMPs (7 unilateral and 2 bilateral)	
Kim et al. (31)	1-11 days		Lateral medulla	13/45 (29%) patients had abnormal AC tone burst (9 increase IAD with 6 ipsilesional and 3 contralesional reduced amplitude; 4 increased p13 latency with 1 ipsilesional, 2 contralesional, 1 bilateral)	12/45 (27%) patients had abnormal had tap oVEMPs (absent in 3, 5 increased IAD with 4 ipsilesionally and 1 contralesionally reduced amplitude, 4 increased N1 latency)
Kim et al. (32)	2 days -3 years		Medial medulla	7/14 (50%) patients had ipsilesional abnormal AC TB cVEMPs	
Kim et al. (33)	1 week		Medial longitudinal fasciculus	3/12 (25%) patients had abnormal AC TB cVEMPs (2 reduced amplitude, 1 absent on lesion side)	8/12 (67%) patients had abnormal head tap oVEMPs (7 on lesion side, 1 bilateral)

cVEMPs: cervical vestibular evoked myogenic potentials; oVEMPs: ocular vestibular evoked myogenic potentials; AC: air conduction; TB: tone burst; IAD: interaural amplitude difference ratio; AICA: anterior inferior cerebellar artery; PICA: posterior inferior cerebellar artery; SCA: superior cerebellar artery

than the anterior SCCs. INO occurred due to damage in the MLF, resulting in impaired adduction of an ipsilesional horizontal eye and dissociated nystagmus from the contralesional abducting intact eye. These findings suggest that the MLF mediates the excitatory VOR from posterior SCCs to the ocular motor nuclei. As the VOR gain for the anterior SCCs is slightly affected than the posterior SCCs, it was postulated that the anterior SCCs input is also mediated outside the MLF. The VOR signal from the anterior SCCs can also be transmitted by the ventral tegmental tract and brachium conjunctivum and the MLF.[24,25]

Vestibular Evoked Myogenic Potentials (VEMPs)

Cervical VEMPs (cVEMPs) represent the vestibulo-collic reflex projections from the saccule in the inner ear to the vestibular nucleus in the brainstem that transmits through the inferior vestibular nerve.[16] The saccular projections later descend to the ipsilateral sternocleidomastoid (SCM) muscles through the medial vestibulospinal tract.[16] The cVEMPs consist of P13-N23 peak-to-peak waveforms attributed solely to the ipsilateral sacculo-colic reflex and N12-P20 waveforms from the contralateral SCM muscle, originating from the utricle.[26] cVEMPs can be abnormal among PCS patients (Table II). In a recent study among PCS patients, cVEMPs were found abnormal in 59% of patients.[19] Among 16 AICA stroke patients, cVEMPs stimulated using clicks stimuli were reported to be abnormal (six absent and two reduced amplitude) on the lesion side.[27] Those with abnormal cVEMPs also had canal paresis on caloric irrigation test and were found to have sensorineural hearing loss due to ischemia in the root of the entry zone to the eighth nerve of the inner ear.[27] cVEMPs were also reported to be delayed or absent in 36% of PICA and 75% of AICA groups, due to lesion in the lower brainstem.[28] Apart from the brainstem, lesions located in the cerebellum may also exhibit abnormal air-conducted cVEMPs responses. Eleven of 27 patients (41%) had increased interaural amplitude difference (IAD) ratio, absent or delayed responses with no cVEMPs directionality to the lesion side.29 The authors concluded that the asymmetrical cVEMPs responses might be related to the otolith lateralisation effect in the unilateral cerebellar lesions.[29] The absence of cVEMPs directionality may indicate that there are crossed or bilateral otolithic vestibular modulating pathways occurring within the cerebellum.[29] However, no lesion subtraction analysis was performed in the study to investigate the specific cerebellar structure involved in generating cVEMPs.[29]

Damage to the vestibular fascicles, vestibular nuclei, or its descending fibres in the brainstem can disrupt cVEMPs responses.[30] In one study among 21 lateral medullary infarct

Table III: Caloric irrigations and oculomotor tests findings in posterior circulation stroke (PCS) studies

Authors (year)	Test Durations From Stroke Onset	Test Durations territories	Lesion Locations	Oculomotor Testing using Electronystagmography (ENG) /Videonsytagmography (VNG)	Caloric irrigations
Ling et al. (35)	Acute	PCS		9/30 (23.7%) abnormalities in gaze testing, 12/30 (31.6% abnormalities in saccade testing, 57.9% abnormalities in smooth pursuit testing, 50% abnormalities in optokinetic testing	
Weng and Young (28)		AICA, PICA	Brainstem, cerebellum or both	Among the PICA group: 9/11 (82%) had abnormal pursuit, (8/11) 73% had abnormal saccade, (9/11) 82% had abnormal optokinetic nystagmus	Among PICA group patients: 14/22 (64%) ears had abnormal caloric, 8/14 (57%) had abnormal visual suppression test
				Among AICA group: (2/3) 67% abnormal pursuit, (2/3) 67% abnormal saccade, (3/3) 100% abnormal optokinetic nystagmus	Among AICA group patients: 3/6 (50%) ear had an abnormal caloric test, 2/4 (50%) had abnormal visual suppression test
Kim et al. (36)	1-7 days	19 PICA, 3 AICA, 1 pontine artery	18 cerebellar, 4 medulla, 1 pons	11/23 (48%) patients had direction-changing nystagmus, 6/23 (27%) periodic alternating nystagmus	7/23(30%) patients had fixation failure, 15/23 (65%) patients had spontaneous nystagmus without canal paresis
Kim and Kim (37)	1-18 days		Middle cerebellar peduncle	15/23 (65%) patients had horizontal gaze-evoked nystagmus (GEN), 14/19 (73%) abnormal smooth pursuit	14/18 (78%) patients with infarctions had canal paresis
Su and Young (38)	Acute		Posterior Fossa	19/22 (86%) patients had abnormal optokinetic nystagmus test, 21/22 (95%) abnormal eye tracking test	19/22 (86%) patients had abnormalities (1 hyperfunction; 8 canal paresis; 10 caloric areflexia), 22/22 (100%) patients had abnormal visual suppression test

AICA: anterior inferior cerebellar artery; PICA: posterior inferior cerebellar artery; SCA: superior cerebellar artery

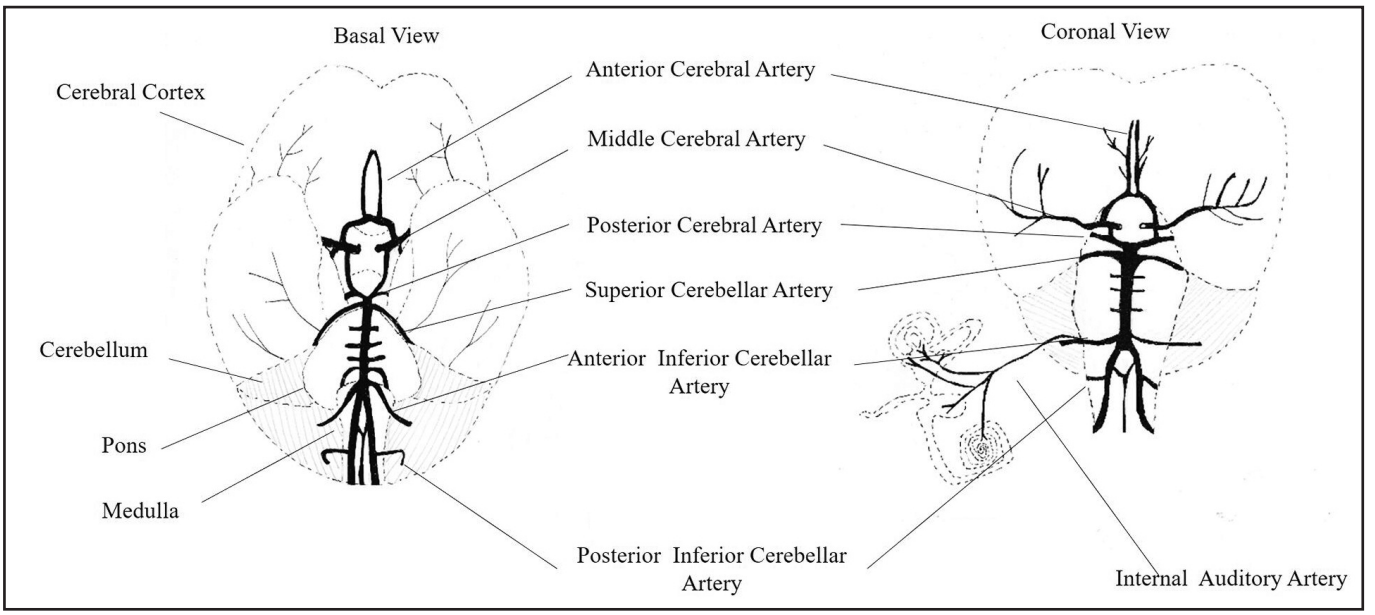

Fig. 1: Circle of Willis and blood supply to the inner ear. The posterior cerebral artery (PCA), anterior inferior cerebellar artery (AICA), posterior inferior cerebellar artery (PICA) and superior cerebellar artery (SCA) form the posterior circulation of the brain. The anterior cerebral artery (ACA) and middle cerebral artery from the anterior circulation of the brain. The internal auditory artery (ACA), a segment of AICA, also supplies the inner ear.

patients, nine subjects (43%) had abnormal air conduction (AC) tone burst cVEMPs (seven unilateral and two bilateral).[30] In this study, six ears had reduced amplitude, six ears had delayed latencies, and two ears had reduced and delayed latencies. Two patients exhibited abnormal cVEMPs responses on the contralesional side. These findings suggest that the commissural fibres had a role in modulating the contralateral sacculocollic input pathway in the brainstem.30 Any isolated or combined damage to the commissural fibres can result in abnormal contralesional or bilateral cVEMPs responses.[30] While decreased or absent cVEMPs both indicate the presence of ischemia, delayed latency can be a sign of demyelination following incomplete infarct.[30] Another study also reported that 29% of the patients with lateral medullary infarction also had abnormal cVEMPs with increasing IAD ratio or longer p13 latency.[31] The abnormalities were due to lesions in the caudal and rostral medulla, where the vestibular nuclei are located.[31] Most patients in the study also had abnormal ocular tilt reaction and subjective visual vertical on the ipsilesional side, but fewer of these patients reported abnormal cVEMPs and oVEMPs. These suggest the dissimilarities of otolithic substrates processing located in the dorsolateral medulla.[31]

In a study of 29 patients with brainstem lesions, 12 had unilateral abnormal cVEMPs (eight absent, four reduced amplitude) while seven had bilateral absent cVEMPs responses to AC clicks stimuli. This study shows that lesions in the lateral medulla and lateral lower pons where the spinal accessory nerve and vestibular nuclei are located, respectively, can impair the generation of cVEMPs. It was also determined that the pyramidal tract lesions, located in the upper pons, disrupt the cVEMPs output, suggesting that the abnormal cVEMPs can also be affected by lesions up to the mesencephalon, above the vestibular nuclei level.[17]

Infarcts occurring in the descending pathway can also impair cVEMPs. Seven of fourteen patients (50%) with medial medullary infarct had abnormal AC tone bursts cVEMPs responses (either absent, delayed or reduced amplitude) on the lesion side.[32] This study reported that damage in the medial medulla, which contains the MLF, could disrupt the vestibulospinal tract pathway that runs in the MLF to descend and contract sternocleidomastoid muscles in the neck.[32] This finding is supported by another cVEMPs study on 12 patients with isolated INO. Twenty-five per cent of the patients had abnormal cVEMPs responses (two decreased amplitude, one absent) on the side of the lesion, suggesting that the MLF played a role in mediating ipsilesional cVEMPs descending pathway.[33]

In contrast to cVEMPs, the oVEMPs reflect the function of a crossed utricular pathway that projects from the utricle in the inner ear to the vestibular nuclei via the superior vestibular nerve.[16] It later activates both the inferior oblique and inferior rectus muscles of the eyes.[16] The oVEMPs consist of the N10-P15 complex of the contralateral side.[26] Unlike cVEMPs, only a few studies have reported oVEMPs findings among stroke patients.

Abnormal oVEMPs were reported in 5% of PCS patients.[19] Among the PCS patients, abnormal oVEMPs have been found among PICA/AICA patients due to lesions in the upper brainstem.[28] oVEMPs in response to head tap were reportedly abnormal among 12 of the 45 patients with infarcts in the lateral medulla.[31] In the study, two patients with abnormal responses also had lesions in the rostral medulla, where the vestibular nucleus is located.[31] oVEMPs in response to head tap were also reported to be abnormal (four absent and three reduced amplitude on the lesion side; one absent bilaterally) among 12 patients with INO.[33] These findings indicate that the MLF mediates the ascending crossed otolith-ocular reflex signal.[33] More than 30% of unilateral cerebellar infarct subjects also had abnormal head tap oVEMPs responses (either delayed, reduced amplitude or absent), suggesting a cerebellar role, such as the nodulus and uvula, in mediating oVEMPS pathway. However, results did not show any directionality of abnormal response to the lesion side involved.[29] As PICA supplies the nodulus, uvula, inferior cerebellar hemisphere and medulla,[28] injuries to the surrounding areas can also cause abnormal VEMPs.

Electronystagmography (ENG) / Videonystagmography (VNG) Oculomotor Testing

Abnormalities of the saccades, smooth pursuit, gaze and optokinetic system can be reliably identified using bedside examination or measured quantitatively using video-oculography (VOG) or nystagmography. Saccades and gaze are modulated in the brainstem and cerebellum and project to the extraocular muscles of the eyes.[34] The smooth pursuit has a long pathway and is generated in many locations in the brain, from the brainstem and cerebellum towards frontal eye fields.[34] A study reported that eye movement abnormalities occurred in 78.9% of PCS patients.[35] Among the PCS patients, 23.7% had abnormal gaze testing, 31.6% had abnormal saccade testing and 57.9% had abnormal smooth pursuit testing. Fifty per cent of patients in the study also had optokinetic nystagmus. Another study found abnormalities of smooth pursuit, saccade and optokinetic nystagmus in both PICA and AICA stroke patients, indicating the presence of central vestibular dysfunction when tested using electronystagmography (ENG).[28] In a study among 19 PICA, three AICA and one pontine artery stroke patient tested using videonystagmography (VNG), 48% had direction-changing nystagmus, and 27% had periodic alternating nystagmus.[36] As most patients in the study did not have neurological signs and showed normal imaging during AVS onset, the study suggested that for examinations of delayed neurological signs, VNG can assist in diagnosing vertebrobasilar stroke among AVS patients.[36] In another study of patients with unilateral middle cerebellar peduncle infarction tested using video-oculography (VOG), 78% had horizontal gaze-evoked nystagmus, while 73% had abnormal smooth pursuit function.[37] An injury to the vestibular nucleus, flocculus and pontocerebellar fibres near the middle cerebellar peduncle (MCP) can disrupt the neural integrator responsible for holding gaze.[37] The pursuit function can be impaired as the MCP also carries fibres from the flocculus, uvula and dorsal vermis to the frontal eye field.[37] A study found that overall, 86% had abnormal optokinetic nystagmus among the patients with posterior fossa stroke, while 95% had abnormal eye-tracking tests.[38]

Caloric Irrigation Testing

The caloric irrigation test was used to identify the peripheral

vestibular lesion in the horizontal SCCs and central pathway in the brainstem.[27,28,34] Caloric thermal irrigation measures the velocity storage to the low-frequency signals.[34] The visual suppression test (VST) measures fixation's ability to reduce the nystagmus slow phase velocity.[34] VST overrides the VOR pathway in the parietal-occipital cortex, brainstem and cerebellum.[34] Visual lack of suppression is also a sign of disturbance in the cerebellum due to reduced inhibition of the superior and medial vestibular nuclei by the floccular Purkinje cells.[28] Previous studies have revealed abnormalities in the caloric irrigation test and VST measurements due to central vestibular dysfunction (Table III). In a study among PICA stroke patients, 64% of ears had either canal paresis, caloric areflexia or hyperactive responses to the irrigation.[28] Among the AICA stroke patients in the study, 50% of the ears had canal paresis or caloric areflexia.[28] The study concluded that the canal paresis or caloric areflexia in these PCS patients were due to reduced VOR following brainstem infarcts. The hyperactive caloric responses might also indicate cerebellar lesions.[28] Among 19 PICA, three AICA and one pontine artery stroke patient, 30% had fixation failure due to cerebellar lesion.[36] Eighty-six per cent of posterior fossa stroke patients in their study also had abnormal caloric responses, while one patient had hyperfunction, eight patients had canal paresis, and ten patients had caloric areflexia.[38] All patients in the study also had abnormal visual suppression tests, possibly due to unilateral floccular lesion.[38] In another study among patients with MCP stroke, 78% had caloric paresis due to the impairment in the vestibular nuclear complex, which is located adjacent to the MCP.[37]

Summary and future recommendations in the use of quantitative vestibular testing

Quantitative vestibular tests, along with clinical bedside examinations, can be used to identify central vestibular dysfunction among ischemic stroke patients. The presence of normal VOR gain for lateral SCCs using quantitative HIT among AVS patients can indicate a stroke, usually in the PICA, SCA or both. However, abnormal VOR gain, mainly in the posterior SCCs, can be observed when stroke involves the MLF. AICA stroke usually results in variable gain findings. Further investigations using vHIT as the latest VOR technology to identify the role of the central vestibular pathway in modulating saccades are needed. Compared to magnetic search coils, vHIT is less invasive and easier to use to measure VOR.

Both cVEMPs and oVEMPs are abnormal when the lesions involved the upper, lower, or parts of the brainstem, particularly the vestibular nuclei. However, the results varied with various lesion locations and parameters such as latencies, amplitudes and testing stimuli. Moreover, many subjects, particularly the healthy elderly, also exhibited reduced response rate, amplitude and prolonged latencies for both cVEMPs[39,40] and oVEMPs responses.[39] Therefore, it is difficult to ascertain whether the abnormal cVEMPs and oVEMPs are attributable to ageing or stroke.

There were only a few studies performed on stroke patients using caloric irrigation and VNG. Caloric irrigation may not be tolerated well by stroke patients.[28] However, VNG is a sensitive test of oculomotor function and can be used along with HIT and VEMPs to measure central vestibular dysfunction quantitatively. On the other hand, the bedside approach is still mandatory as it is a quick, cheap, and highly sensitive method to diagnose stroke during the acute stage. In contrast to clinical bedside testing, quantitative vestibular testing may not be readily available in acute care settings and is costly, time-consuming and requires trained personnel. Quantitative VFT, such as VNG, is also prone to artefacts. Besides, appropriate control group or normative clinical data and standardised parameters for VEMPs and VNG are necessary to ensure an accurate diagnosis of central vestibular dysfunction. Therefore, quantitative measures can be used as supplementary, complementary and subordinate tests to clinical bedside testing to identify central vestibular dysfunction or topographic mapping of vestibular lesions. Also, quantitative VFT may be more applicable to chronic vestibular symptoms or when quantitative information of central vestibular dysfunction is required.

There are several limitations of this narrative review. This type of review has a less systematic method approach with potential bias in selecting and reporting findings. However, given the complexity and broad research topic, a narrative review was proposed to present the overall patterns of findings and to provide a greater depth of the research topic to the clinicians. Given the limitations, broader and systematic search databases were used and only original research articles specific to the research topics were presented. This allowed comprehensive sources with a relevant and in-depth selection of articles to the study subject.

Most studies measured vestibular function during acute stroke. A study found that vertigo and nystagmus may be reduced within one week of stroke onset.[41] However, persistent unsteadiness or dizziness among recovering stroke patients, without known causes, may occur even months following stroke onset.[42] Future studies are required to quantify vestibular dysfunction among stroke patients to understand the progression or adaptation of vestibular disorders in stroke patients.

In summary, when a stroke involves the vestibular nucleus, both the upper and lower brainstem and cerebellum can produce various abnormalities during quantitative VFT. Thus, quantitative VFT can be used to complement bedside vestibular testing in identifying vestibular dysfunction among PCS patients. Future studies to investigate the prevalence of vestibular dysfunction in post-stroke patients are required.

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SHORT COMMUNICATION

Surgical subspecialty training outside Malaysia during COVID-19 Pandemic: Perspectives and experiences of Trainees

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SUMMARY

Subspecialty surgical training is an integral part of continuous professional development. It represents a unique opportunity for surgeons to enhance and develop specific advanced skills in their sub-disciplines. Hence, hands-on training in an international training centre abroad allows one to bring home new technical and management skills in the expansion of Malaysian surgical services to raise to be on par with the international standards. The unexpected onset of the COVID-19 pandemic brought in previously unknown hindrances to the training both locally and abroad but our success in engagement with international centres despite the pandemic restrictions serves as a valuable experience towards maintaining international networking for future collaborations.

KEYWORDS:
subspecialty surgical training, Covid-19, experience, Malaysia

INTRODUCTION

The practise of general surgery is constantly evolving. Numerous factors such as advances in surgical knowledge, techniques, and technology, as well as patient and physician preferences, have driven an increasing number of surgeons to specialisation.[1] It is important to recognise that training is part of the continuum of learning in medicine.[2] It allows surgeons to develop niche-specific skills set beyond the scope of basic general surgery training. Thus, to achieve competency in order to improve patient outcomes with subspecialisation, it is prudent that trainees are adequately exposed to high-volume cases[3] during their three-year program under the Ministry of Health (MoH), with the option of an overseas attachment in the final year. As the MoH has no formal international collaboration with centres overseas for fellowship training positions, the procedure was purely self-initiated by the trainees. The process turned out to be tedious with the emergence of the COVID-19 pandemic. Many affected ones resorted to continue training in local universities. The trainees' supposed timeframe of program completion was also inevitably extended. However, we were successful in our continued pursuit for a fruitful training program in European and Asian centres, respectively. Not only did we achieved significant operative case volumes exposures despite the global slow-down in non-emergent surgeries, but we also witnessed their mitigation of the disease while maintaining continuous oncological surgery services during the pandemic.

Tan Yee Ling: Breast Surgery Fellowship at National Oncology Institute of Budapest, Breast and Sarcoma Surgery Unit, Hungary.

I was accepted as a training Associate Clinical Fellow post in Breast Surgery at the Hong Kong Queen Elizabeth Hospital in January 2020 but was denied entry at the onset of the COVID-19 outbreak. The process of re-application for another training centre, while the world was affected by the outbreak, was daunting and tedious. Fortunately, I was granted a second observership post in Hungary in July 2020. The legislation process took double the time during the pandemic, and I was further delayed for another three months. At the time of my arrival, Hungary was managing 5000-6000 cases of COVID-19 patients per day and the country was in a state of medical crisis. I had no clear information on the quarantine duration amidst the chaos. I was deemed safe to report for duty after two serial COVID-19 Rapid Antigen Kit tests. As the institute provides purely oncological services, the elective cases were conducted as usual; up to 40 primary breast cancer surgeries per week despite the pandemic, a total of 1260 cases by December 2020.

All breast cases were subjected for discussion in Multi-Disciplinary Team (MDT) pre- and post-surgery. The unit has a high bed turnover time, with a maximum length of inpatient stay of two days if surgery was uneventful. An observation worth highlighting was the use of intravenous propofol infusion as induction and maintenance for all breast surgeries. This facilitated a rapid patient turnover time in the operation theatre. All patients were discharged with drains and reviewed weekly in the outpatient clinic. Histopathological results were reported within two weeks and adjuvant treatment commenced within four weeks from surgery. For patients with positive COVID-19 PCR test results, they were rendered hormonal treatment if feasible, until two new negative swabs were achieved before they were allowed to proceed with elective surgery three months later. On the other hand, the hospital healthcare workers were screened weekly for COVID-19 infection and were all inoculated with two-dose vaccination by the end of January 2021.

Out of the initial 486 breast surgeries done during my first four months of stay, 70% comprised of oncoplastic breast-conserving procedures (BCS), 25% were skin/nipple

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preserving mastectomies with immediate two-stage reconstruction using silicon expanders implants, 4% was conventional modified radical mastectomies without reconstruction and 1% delayed reconstruction (permanent implant change and contralateral symmetrisation procedures). Axillary surgeries were sentinel node biopsies (85%) and axillary clearance (15%). This large volume of cases was equivalent to my one year of case volume in Malaysia.

On top of the operative skills, theoretical learning was fully virtual and seemed to be well incorporated into the Europeans Surgical Society. I was able to participate in numerous local online conferences and webinars, organised by the institute as well as the European Society of Surgical Oncology. The social environment during my stay was very different from the pre-pandemic time. As there was no complimentary dormitory provided by my institution due to the pandemic, I resorted to a single apartment rental which incurred half of my monthly scholarship allowance. A sense of desolation was inevitable, but I had to adapt quickly. My time after work was used to learn a second language (Hungarian) for the need of communication with patients and colleagues.

Given that the rate of breast-conserving surgery was reportedly low in Malaysia as influenced by independent factors such as the presence of breast sub-specialist surgeons,[4] this large volume of operative knowledge gained would certainly benefit the subsets of Malaysian women with early breast cancers treatable by oncoplastic breast surgery. The adversity encountered during the entire training in an unprecedented time of pandemic made me more resilient and adaptive, which are all important non-operative technical skills as a modern time surgeon.

Elaine Hui Been NG: Colorectal Surgery Fellowship, China Medical University Hospital Taiwan

I went for my Colorectal Surgery Fellowship focusing on minimally invasive surgery (laparoscopic and transanal approaches) in Taiwan just when COVID-19 started making headlines in East Asia. The first five months were saddled with lower number of cases operated per week due to control of non-emergent patient entry to hospitals and limitation of travel between hospitals in different districts given that I was originally assigned to train in both Hsinchu and Taichung. Despite this, we were still operating on average eight cancer cases per week. At this juncture, laparoscopic surgery was also not recommended globally as a precaution for intraoperative aerosolization of COVID-19 viral particles. However, my centre carried on performing laparoscopic surgeries with careful preoperative COVID-19 patient screening and extra precautions during surgery, successfully maintaining a 90% laparoscopy rate monthly with no positive case or exposure. I was able to learn hands-on laparoscopic colectomies and rectal resections with different anastomotic techniques, transanal minimally invasive surgery (TAMIS), transanal total mesorectal excision (TaTME) and lateral pelvic node dissection (LPLND).

On a personal front, I had trouble procuring face masks and gloves. I was rationed with only 1 mask per workday and had no privilege to purchase face masks from pharmacies as a foreigner. Experience of loneliness with travel restriction was difficult especially when one is still new to the country. Thankfully, the unit and hospital staff were helpful to ensure we were well taken care of in the dormitory especially during quarantine and kept teaching us despite the limitations.

The successful pandemic control in Taiwan was evident by the resumption of normal daily activities and local tourism by June 2020. We were operating 10 to 15 cancer cases per week notwithstanding the minor benign cases by May. I was able to resume training in my second centre by June. Face-to-face meetings resumed in July, and I participated actively in their tumour board meetings and academic teachings along with sponsored participation to various colorectal surgical conferences all over the country. I also participated in combined surgeries and visited other centres including Koo Foundation Sun Yat-Sen Cancer Centre in Taipei. My trainers also encouraged me to write papers with them.

The strict pandemic measures include heavy fines for violating rules such as not wearing face masks on public transportation adopted by the Taiwan Centre for Disease Control (CECC). Daily news updates from the Ministry of Health and Welfare helped to ensure that the public abides by the rules. The Taiwanese displayed an astounding resilience against COVID-19, largely due to their experience with SARS in 2003. What amazes me most is how they were able to maintain their pursuit of excellence in patient care and yet steadfastly teach foreign fellows despite restrictions when every other country is struggling with the pandemic

I count myself very blessed to be in Taiwan for the last 12 months of my fellowship. As I departed from Taiwan, I returned home armed with skills and determination to encourage a laparoscopic-first initiative in my hospital. I would eventually like to expand the scope of laparoscopic colorectal surgery to include pelvic node dissection and hybrid transanal surgery that I learnt during my training in optimising rectal cancer treatment, which are now hardly performed in Malaysia. It is time for my country to move forward in minimally invasive colorectal surgery.

Diong Nguk Chai: Thoracic Surgery Clinical Fellowship, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan

My 12-month fellowship in thoracic surgery, Koo Foundation Sun Yat-Sen Cancer Center (KFSYSCC), Taiwan started on the 1st of March 2020 when the COVID-19 pandemic struck two weeks later and forced closures of all international borders, including Taiwan. As thoracic elective surgeries were heavily debated on whether they should be allowed to resume during a pandemic, I was fortunate that my centre was not affected. My objectives were to learn minimally invasive surgery (MIS): video-assisted thoracoscopic surgery (VATS) and minimally invasive esophagectomy (MIE). We operated four days a week with an average of two cases per day or a case a day for MIE, under two thoracic surgeons. The cases we operated on were lobectomy, segmentectomy, subsegmentectomy, wedge resection, thymectomy, esophagectomy, all by MIS where VATS were all uniportal. I was given hands-on experience gradually from assisting initially to operating. My supervisors

were passionate about teaching and keen to share all their valuable knowledge possible to ensure my objectives were met and my training a fruitful one.

As low-dose chest computed tomography (LDCT) was widely performed as a part of medical checkups, many ground glass opacity (GGO) were detected as early lung cancers and were therefore treated with surgery. I learned to reconstruct 3D images based on CT images using software like Horos, RadiAnt and Synapse, as part of the pre-operative preparations for segmentectomies for these lesions. Throughout the preparation, I learned and managed to master the complicated pulmonary anatomy better so as the surgery.

Webinars have become the best substitute for regular scientific meetings/conferences during the pandemic. Fortunately, I attended a few thoracic conferences physically and managed to meet and communicate with other thoracic surgeons. I had the opportunity to be on stage to give a presentation in Mandarin, which was a great experience for me. I also participated in the weekly Tumour Board Meeting by presenting and discussing cases. This reflected how wholesome and thoughtful the fellowship program was by creating all possible opportunities to maximize my exposure here, including learning outside the hospital.

My entire year of overseas fellowship training moulded both my mind and skills towards betterment indefinitely, despite being struck by the unexpected pandemic. The situation has thought me to be resilient to fight the pandemic yet not to compromise the cares for cancer patients at the same time. I am determined to move together with my team back in Malaysia to face the challenges ahead with all that I have acquired, be it with or without the pandemic.

CONCLUSION

Subspecialty surgical training overseas had broadened our experiences and perspectives on how to overcome the enforced pandemic restrictions and yet continue to deliver optimum clinical and academic services for oncological surgery. Apart from gaining invaluable surgical skills, these overall experiences strengthened the non-operative skills in us as well. The good connection established with international colleagues would serve as a platform for potential networking and collaboration, to benefit the future generations of Malaysian surgeons.

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Coping with uncertainties for medical students

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Sir,

The article in the Medical Journal of Malaysia, clearly highlights the effects of anxiety on medical students.[1] The COVID-19 has disrupted the physical, mental, and social well-being of the medical students causing stress, anxiety, depression, fear, loneliness, and uncertainty about their futures.

We propose here some helpful tips for the much-challenged medical students of this time of uncertainties. The strategies are grouped into the three cyclical phases of self-regulated learning, viz forethought, performance, and self-reflection.[2,3] However, not all may benefit from these guidelines as everyone is unique and has different coping strategies.

Forethought

Plan

Plan the day ahead taking due consideration of the online classes timetable, self-study, nonetheless giving due importance for self-care and social time.

Routine

Having an orderly routine frames the day better granting a sense of control. Get up every working day at the same time. Step into the day with the "serenity prayer" and blessings from parents. Follow your morning routine, a walk in the open (if possible), dress-up, have a good breakfast.

Performance

Effective Study environment

Wherever you study make the surroundings conducive. Keep the phone/distractions out of reach. Inspirational quotes, good lighting, comfortable seating may help.

Make notes

Making notes saves time and energy for the second reading. This is the best time to make mnemonics. Visuals and auditory methods help in retaining better.

Exercise, eat healthy and good sleep hygiene

Exercise is to body what reading is to mind. Dedicate 20-30 minutes for exercise, it can be as simple as walking/jumping. Healthy mind in a healthy body. Healthy food is associated with general wellbeing.

Practice good sleep hygiene as it acts as an energising fuel for the next day.

Mindfulness

Enjoy every moment. Live in the moment. There may be a list of tasks waiting to be ticked but be mindful of the task at present. For instance, while eating relish and taste every bite.

Free time

All work and no play, makes Jack a dull boy. Keep some time free to have fun, laugh out loud, watch a movie. So, you have something to look forward to.

Social time

Spend time socializing with friends and family and invest in healthy relationships. Share your feelings and emotions.

Self-reflection

Keep a diary

Pen down your golden moments of the day. It is good to write at least one-two things you were grateful for that day, the topics you covered etc. Note your mistakes and blunders to avoid in future.

Gratitude and Help

Start and finish the day with gratitude. Thank God for the new opportunity and show gratitude towards teachers, advisors, parents, and siblings.

Offer help to ones in need. At the same time, do not be reluctant to ask for help when needed.

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Case series: Vaginal pessary for pelvic organ prolapse and its association with vaginal cancer

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SUMMARY

Vaginal pessaries have long been used in the management of pelvic organ prolapse as an alternative option for surgery. Vaginal cancer is a very rare form of gynaecological malignancy, and its association with vaginal ring pessaries has yet to be clearly established. We examined the cases of vaginal cancers in a tertiary state hospital for the last three years and found four cases of vaginal cancers, in which three of these cases were associated with a long history of using vaginal ring pessary for pelvic organ prolapse. Two of them had defaulted follow- up and presented with a vaginal mass and vaginal bleeding. These two cases did not have evidence of distant metastases, one of them underwent surgical removal of the tumour and radiotherapy, whilst the other case was initially given neoadjuvant chemotherapy, but the patient died prior to her planned surgery. The third patient declined further investigation and treatment after she was diagnosed with vaginal cancer. In conclusion, such potential serious long term complication from vaginal pessary should be informed prior to its insertion, it is also imperative to ensure compliance to regular follow- up for patients on vaginal pessaries, and to biopsy any suspicious chronic vaginal ulcers.

KEYWORDS:
Vaginal pessary, ring pessary, vaginal carcinoma, pelvic organ prolapse

INTRODUCTION

Vaginal pessaries have long been used in the management of pelvic organ prolapse as an alternative option for surgery. One of the earliest documented use of such pessary was around 400 B.C. in which half a wine-soaked pomegranate was inserted into the vagina to reduce a prolapse.[1] Pessaries are now synthetically made from medical grade silicone with various shapes and sizes.[1] Vaginal cancers are rare and constitute about 2% of all gynaecological malignancies.[2,3] In order for a tumour to be considered a primary vaginal carcinoma, the primary site of growth should only be in the vagina; the cervix and vulva should not be involved and there should be no evidence of metastases from elsewhere.[2] There has been limited evidence for the exact aetiology of vaginal cancers. However, it is known to be more common in older women, and the other factors that are associated with vaginal cancer include Human Papilloma Virus (HPV) infection, chronic irritation, and irradiation. The commonest type of vaginal cancer is squamous cell carcinoma.[2] Vaginal intra- epithelial neoplasia (VAIN) is the precancerous stage for such cancer but there has not been any established routine screening programme for vaginal cancer.[2,3] As vaginal cancers are rare, the treatment for such cancers is often complex, individualised and drawn from previous experience in the centre.[3] We examined the cases of primary vaginal cancers in our centre since 2018 and found four of such cases, in which three of them were associated with long term use of the vaginal ring pessary; we have outlined these cases and our management approach in the following case description.

CASE DESCRIPTION

Case 1

An 81-year-old Malay woman who initially presented to our urogynaecology clinic 4 years ago with complaints of prolapse symptoms. She had noted a mass protruding through the vagina for 10 years which had been worsening in the past two years. There was no history of per vaginal bleeding, urinary incontinence, or pain. She had four previous vaginal deliveries in the past and had been menopausal 30 years ago. Her other medical illnesses include diabetes mellitus and hypertension. Her body mass index (BMI) was 26. Her last pap smear done more than 10 years ago was normal. Upon vaginal examination, there was a Stage 4 uterine prolapse which was completely reducible. There was no evidence of ulceration, cystocoele or rectocoele.

Subsequently, after counselling, a size 80mm ring pessary was inserted into the vagina for the management of the prolapse. She was then seen every 4-6 months in the urogynaecology clinic for routine change of pessary and vaginal examination. During each visit, she did not complain of any vaginal bleeding and the vaginal examination was unremarkable.

However, after about two years of regular follow-up with the urogynaecology clinic, she defaulted her subsequent clinic appointments. Around two years later, she presented to the emergency gynaecology services for having acute onset of vaginal bleeding. Upon vaginal examination, a neglected ring pessary was removed and there was a vaginal wall ulcer in the posterior fornix measuring 3x3cm. An urgent biopsy was taken, and the histopathological examination results showed a well differentiated squamous cell carcinoma.

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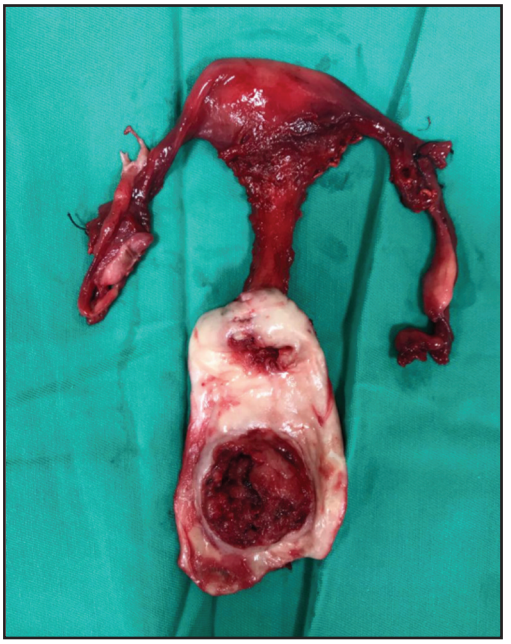

Fig. 1: The uterus, fallopian tubes, ovaries, cervix and vaginal tumour specimen from the surgery showing that the tumour is confined to the vaginal mucosa away from the cervix.

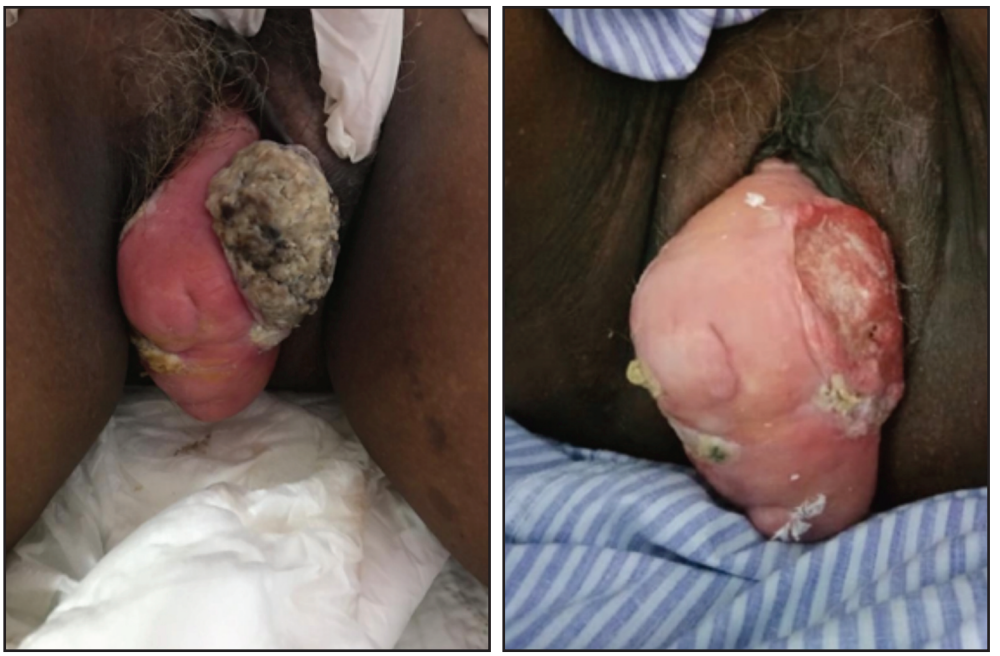

Fig. 2: Vaginal tumour before chemotherapy (left) and after chemotherapy (right).

CT scan showed bulky and heterogenous cervix with poor demarcation with base of urinary bladder. Presence of a heterogenous lesion possibly in the uterine wall which may represent a uterine fibroid. There were also bilateral ovarian cysts. Cystoscopy showed no tumour invasion to the bladder.

She subsequently, underwent a vaginal hysterectomy and bilateral salpingo-oophorectomy, sacrospinous fixation, anterior and posterior pelvic floor repair, as shown in Figure 1. Histopathological examination showed that the tumour was a moderately differentiated keratinising squamous cell carcinoma with clear surgical margins, the paravaginal tissue was not involved, the ovaries, uterus and other structures were negative for malignancy. Subsequently, she underwent vaginal brachytherapy and 25 fractions of external beam radiotherapy.

However, a repeat CT scan done four months after completion of radiotherapy showed that there was a tumour recurrence at the vaginal vault with bilateral hydronephrosis. She declined further treatment or investigations, and eventually died at home a few months later.

Case 2
A 72-year-old Indian woman para 6, who presented with a mass protruding through the vagina for two days with one week history of dry cough. She has history of uterine prolapse for 15 years which was managed with vaginal ring pessary however this pessary was removed five years ago due to a vaginal ulcer and she had defaulted follow-up subsequently. She attained menopause at the age of 50 years and had no regular pap smears done previously. Her relevant medical illnesses include hypertension on amlodipine, bisoprolol, and dyslipidaemia on simvastatin. She had two previous surgeries in the past- one previous lower segment caesarean section and one midline laparotomy for renal calculi. She was a widow for the past 30 years and was currently living with her eldest daughter. She was a non-smoker and did not take alcohol. Her BMI was 19.

Upon examination of the vagina there was a Stage 3 uterine prolapse with a foul smelling friable fungating mass on the left vaginal wall measuring 5x3cm. There was presence of stress urinary incontinence. A biopsy of the specimen showed a well differentiated squamous cell carcinoma of the vagina. CT scan showed squamous cell carcinoma confined to a uterine prolapse with no distant metastases. Cystoscopy showed no tumour invasion of the bladder.

She was planned for neoadjuvant chemotherapy with paclitaxel and carboplatin prior to a vaginal hysterectomy, bilateral salpingo-oophorectomy, colporrhaphy and sacrospinous fixation. After completing the first and second cycle of neoadjuvant chemotherapy, the tumour size significantly reduced as shown in Figure 2. She went on to complete six cycles of neoadjuvant chemotherapy, and was then planned for a vaginal hysterectomy, bilateral salpingo-oophorectomy and pelvic floor reconstruction. Unfortunately, prior to the planned surgery, she had atrial fibrillation, and she was eventually found unconscious and died at home before the surgery.

Case 3:
A 98-year old Malay woman, para 7 who was initially admitted seven years earlier for symptoms of acute urinary retention, was found to have a stage 4 uterine prolapse. Speculum examination was otherwise normal, and a ring pessary size 71mm was inserted. She has a known history of Alzheimer's disease, and requires a wheelchair to mobilise. She had good social support from her daughter for outpatient follow-up. She was given regular follow- up in the urogynaecology outpatient department. She was seen every 4 to 6 monthly by the urogynaecology team, her ring pessary was cleaned and changed during each visit and there were no abnormalities documented throughout her follow-up.

After having been on the pessary for seven years, she was admitted to the gynaecology ward for complaints of vaginal bleeding. Upon further assessment by the gynaecology team, after removal of the ring pessary, a friable induration measuring 4x3cm was seen in the posterior fornix. The parametrium was normal, the cervix appeared atrophied. The mass was biopsied, and the histopathological examination showed a well differentiated squamous cell carcinoma of the vagina. She was then offered further imaging investigation but both patient and her daughter declined this. She died about a year later.

DISCUSSION

Vaginal ring pessary is one of the commonest managements for women with pelvic organ prolapse. It has been regarded as one of the first line treatment due to its simplicity and widespread availability.[4] Superficial vaginal erosion is the most common reported complication from vaginal pessary, 8.9%, vaginal discharge and infection occur in around 2.5% of women using vaginal pessaries.[4,5]

There are several types of pessaries and they can generally be classified as supportive or space occupying pessaries. These two types of pessaries may come with or without support to reduce urinary incontinence.[4,5] Ring pessaries comes under supportive pessaries and are easier to dislodge compared to space- occupying pessaries such as Gellhorn or shelf pessaries.[4,5] Serious complications such as fistulas, vaginal or cervical cancers are rare but have been reported in cases of neglected vaginal pessary users.[4] Formation of vesicovaginal fistulas is in fact more common with the use of Gellhorn and shelf pessaries.[4]

Much controversy has remained with regards to the optimal follow-up for the use of such pessary. In a recent prospective cohort study done in 2020, they examined for the most optimal duration for follow-up and the effectiveness of cleaning the vaginal pessary in reducing the risk of vaginal pain, discharge and irritation.[6] The authors found that there was no difference for cleaning the vaginal pessary and not cleaning it, there was also no difference for pessary related side effects for the studied change intervals of 3 months and 9 months.[6]

For our three cases, we suspected that the cancer actually originated from a non-healing ulcer on the vaginal tissue which resulted from the use of vaginal pessary. This factor combined with age, existing medical illness such as diabetes, and poor follow-up may have given the opportunity for the tissue to undergo chronic inflammatory changes, metaplasia, and subsequently dysplastic changes. There may have been the presence of concomitant Human Papillomavirus (HPV) infection which may have contributed to such cellular changes as well. Clinicians should always take into consideration the potential complication of vaginal cancer whenever vaginal pessaries are used to treat pelvic organ prolapse. During speculum examination, the vagina should be thoroughly examined for any ulcers or erosions, and consideration given for a tissue biopsy in such circumstances. Women with pelvic organ prolapse who are unable to attend follow-up should be offered other management options such as surgery. Clinicians should also be aware that such vaginal tumour can potentially occur even with regular follow-up.

CONCLUSION

It is therefore imperative to ensure that patients on vaginal pessary for pelvic organ prolapse is compliant to follow- up, they should also be informed regarding the potential serious long term complications from the use of vaginal pessary prior

to its insertion. The vagina should also be thoroughly examined during each follow- up for any suspicious vaginal ulcers, and such ulcers should be biopsied.

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CASE REPORT

Hepatic Sarcoidosis: Diagnostic approach and management

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SUMMARY

Sarcoidosis is a multi-systemic, non-caseating granulomatous disorder with an idiopathic aetiology. We report a 58-year-old Malay woman, with underlying type II diabetes mellitus, hypertension and history of stage II pulmonary sarcoidosis presenting with incidental finding of multiple hypodense liver lesions. Her recent contrasted enhanced computed tomography of the abdomen and pelvis demonstrated multiple intra-abdominal lymphadenopathies with evidence of liver and splenic infiltrations. Her age-appropriate malignancy screening was negative while liver biopsy showed non-caseating granulomatous hepatitis consistent with hepatic sarcoidosis. In view of her normal liver enzymes and normalised serum calcium levels, no immunosuppressive therapy was commenced. She remains asymptomatic and is currently under our close monitoring.

INTRODUCTION

Sarcoidosis is a multi-systemic, non-caseating granulomatous disorder. It remains an enigma due to its idiopathic aetiology, wide-ranged presentations and unpredictable prognosis. Sarcoidosis is more prevalent among female compared to male, with an incidence of 6.3 and 5.9 cases per 100,000 populations respectively.[1] The lifetime risk for Caucasians in the United States of America is estimated at 0.85 percent.[1] However, sarcoidosis is less common among Asian communities. The estimated annual incidence of sarcoidosis in Singapore was 0.56 per 100,000.[1] Currently, there is no up-to-date information of sarcoidosis in Malaysia and literature search showed around 10 reported cases from year 2000 till 2021 (Table I). The onset of sarcoidosis can be insidious, and abnormalities may be discovered only on routine chest radiograph while skin involvement is seen in 25% of patients and may be the only site of involvement.[1] Hence, clinical suspicion is vital in reaching the diagnosis.

CASE REPORT

A 58-year-old Malay woman, with underlying type II diabetes mellitus and hypertension for 10 years was initially referred from the local community clinic three years ago for bilateral hilar lymphadenopathy from a screening chest radiograph done for chronic cough. Her contrasted enhanced computed tomography (CECT) thorax demonstrated bilateral hilar and mediastinal lymphadenopathies. Endoscopic ultrasound (EUS) guided biopsy of her mediastinal lymph nodes revealed multiple non-caseating granulomatous lesions and she had a negative mycobacterium tuberculosis work-up. She was diagnosed with stage II pulmonary sarcoidosis with disturbing respiratory symptoms and deteriorating lung function results (FVC and DLCO) on her serial follow-up. She was prescribed with oral prednisolone 0.5mg/kg per day for four weeks and taper upon improvement of her symptoms and lung function test. She achieved successful resolution of her bilateral hilar lymphadenopathy and her lung function test improved back to normal over one year duration. Unfortunately, she missed her appointments subsequently due to resolved symptoms.

One year later, she was referred by her primary care doctor for asymptomatic hypercalcemia (Table II). There were fine crepitations on her bilateral lung fields with hepatosplenomegaly on clinical examination. There was no palpable lymphadenopathy. Otherwise, there was absence of erythema nodosum, arthritis and parotid swelling. A repeated CECT thorax (Figure 1) showed mediastinal and intra-abdominal lymphadenopathy with infiltrations into her liver, spleen, and lung parenchyma. There was no evidence of portal hypertension. She remained asymptomatic. Her six minutes walking test yielded a good total walking distance of 228 metres without desaturation. Her latest lung function test showed a severe restrictive pattern with FEV_1 of 49% and FEV_1/FVC of 0.9. In view of hypercalcemia and raised alkaline phosphatase, an extrapulmonary sarcoidosis workup was commenced. Her serum Angiotensin Converting Enzyme was raised at 172U/L. A CECT abdomen and pelvis (Figure 1) demonstrated multiple intra-abdominal lymphadenopathies with evidence of liver and spleen infiltrations. A liver biopsy was performed to rule out malignancy or tuberculosis. Histopathological examination of her liver biopsy (Figure 2) showed non-caseating granulomatous hepatitis consistent with hepatic sarcoidosis in view of her past history of pulmonary sarcoidosis. Both Ziehl-Neelson stains for acid-fast bacilli and Periodic Acid-Schiff (PAS) indicate glycogenation for presence of fungi were negative. Liver biopsy for tuberculous polymerase chain reaction (PCR) and *Mycobacterium tuberculosis* culture were negative. Her age-appropriate malignancy screening, human immunodeficiency virus and autoimmune workup were all negative. Echocardiography showed a normal left ventricular ejection fraction of 60% with no evidence of pulmonary hypertension. Her attending hepatologist decided to monitor her first as she was asymptomatic. She had no evidence of nephrocalcinosis, nephrolithiasis, ocular, neurologic and myocardial sarcoidosis involvement.

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Table I: Sarcoidosis case reports in Malaysia from year 2000-2021

No.	Study, year	Age/sex	Site of sarcoidosis	Management
1.	Wan Muhaizan WM, 2004[2]	26/male, 47/male	Pulmonary, cardiac	Nil
2.	Ismail S et al., 2005[3]	40/male	ocular	Oral and topical steroids
3.	Ramlee N et al., 2007[4]	42/female	conjunctiva	Oral steroids and surgery
4.	Ling PK, 2009[5]	43/male	Abducens nerve, cervical lymphadenopathy, cardiac	Steroids
5.	Ahmad Y et al., 2010[6]	29/male	Pulmonary, liver, parotids, lymphadenopathy	Steroids
6.	Sazliyana Shaharir S et al., 2017[7]	59/male	Proximal myopathy, lymphadenopathy	Steroids and azathioprine
7.	Chang A et al.,2018[8]	27/male	Pulmonary	Observation
8.	Noorhafini AS et al., 2020[9]	43/female	Pulmonary, liver , facial nerve	Steroids and azathioprine
9.	Tan WJ et al., 2021[5]	38/female	Pulmonary , myocardium	Steroids
10.	Low QJ et al, 2021[10]	30/female	Pulmonary	Steroids

Table II: Laboratory investigations

Blood parameters	Reference range	Pulmonary sarcoidosis diagnosis at 2017	Hepatic sarcoidosis diagnosis at 2020	On discharge
Haemoglobin	12-18g/dL	13	13.1	14
Platelets	150 x 10^3- 450x10^3/microlitre	200	350	300
White Cell Counts	4 x 10^3- 9x10^3/microlitre	7	6.44	5
Sodium	135-145mmol/L	132	133	134
Potassium	3.5-5.1mmol/L	4	4.4	3.9
Urea	2.8-7.2mmol/L	3.9	8.5	5.8
Creatinine	59-104micromol/L	52	157	128
Corrected calcium	2.2-2.65mmol/L	2.66	3.03	2.40
Total protein	66-83g/L	80	89	92
Albumin	35-52g/L	31	33	35
Globulin	28-36g/L	45	55	57
Total Bilirubin	5-21micromol/L	10	12.9	11.4
Alanine Transferase	0-50U/L	37	18	21
Alkaline Phosphatase	30-120U/L	291	346	429
Gamma Glutamyl Transferase	0-38U/L			173
Magnesium	0.73-1.06mmol/L	0.8	0.85	0.89
Inorganic Phosphate	0.81-1.45mmol/L	1.0	1.12	1.03
Erythrocyte Sedimentation Rate	0-20mm/hour		79	
Sputum for AFB direct smears x1 x2 x3		No AFB seen	No AFB seen	No AFB seen
Liver biopsy for TB PCR			Negative	
Liver biopsy for *mycobacterium tuberculous* culture and sensitivity			Negative	
HIV			Negative	
ANA		Negative	Negative	
24 hours urine calcium	0-7.7mmol/L		8.9	
6-minute walking test			Total walking distance= 228 meters, no desaturation, normal recovery	
Lung function test			Severe restrictive pattern with FEV_1 49% and FEV_1/FVC of 0.9	

DISCUSSION

Sarcoidosis has an estimated worldwide prevalence of 2-60 per 100,000 people.[1] It affects all ethnicities especially the Scandinavian and rarely in patients of Chinese and Taiwanese background.[1] There is currently no detailed data on sarcoidosis available in Malaysia. Globally, more females are affected with sarcoidosis compared to males with a peak among the age group around 20-40 years old.[1]

Sarcoidosis is a great mimicker with numerous differential diagnoses including mycobacterium infection, viral, fungal, protozoan, autoimmune diseases, and haematological malignancy. As mycobacterium tuberculosis is more prevalent in Malaysia, often clinicians would have to extensively investigate and rule out tuberculosis prior to confirming sarcoidosis histologically. Table I list the reported sarcoidosis cases in Malaysia published over the last two decades. Among the local cases reported, majority were

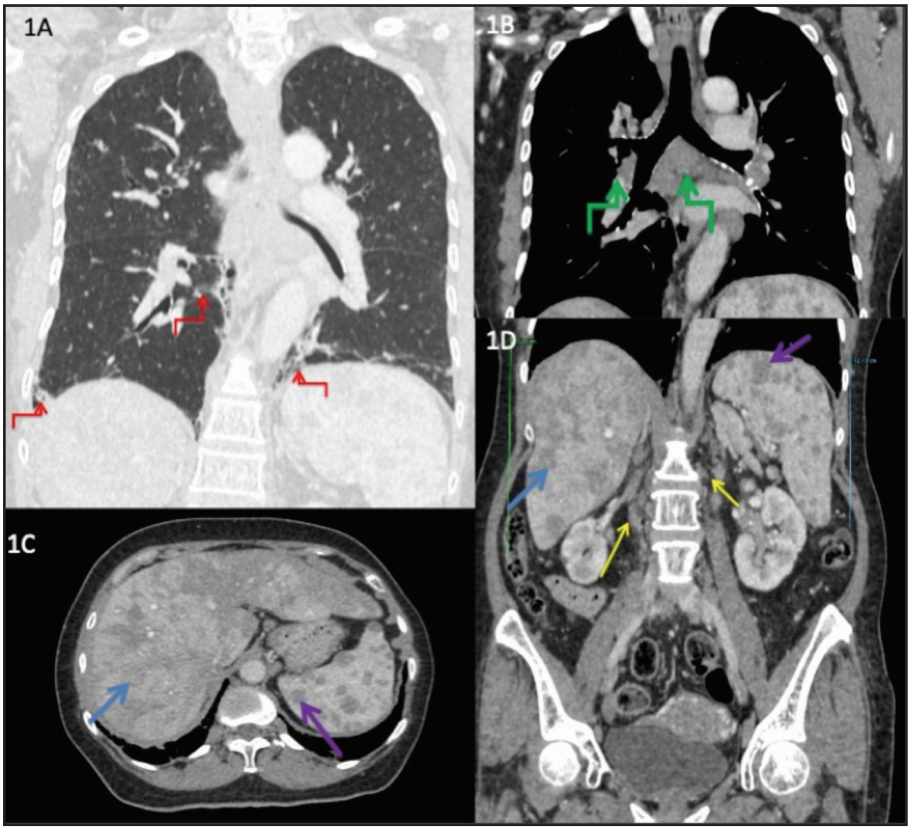

Fig. 1: CT Thorax (coronal view) in mediastinal and lung window. Multiple mediastinal and hilar lymph nodes (green arrows), with no calcification or center necrosis. Fibrosis and early honeycombing changes are also present at the periphery of the lung (red arrows) suggestive of stage 4 pulmonary sarcoidosis. CT Abdomen (mediastinal window) at axial and coronal view. There is diffuse heterogeneous enhancement of the liver (blue arrows) and multiple hypodense nodular lesions scattered in the spleen (purple arrows). Multiple subcentimeter para-aortic lymph nodes are also present (yellow arrows).

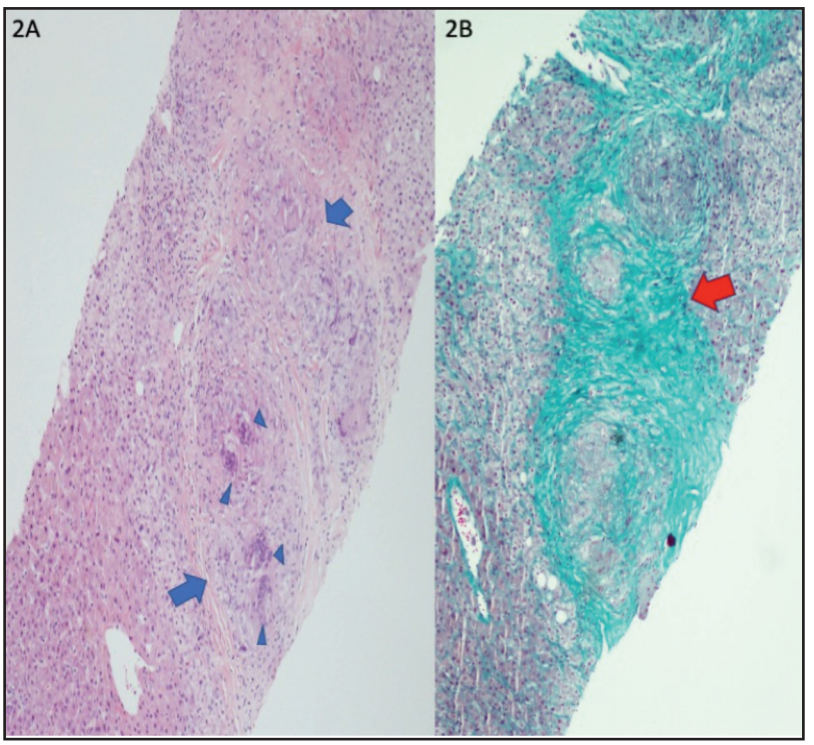

Fig. 2: Hematoxylin-eosin stain revealed multiple epitheloid granulomata (blue arrow) with multinucleated giant cells (blue arrowhead). Masson Trichrome stain revealed epithelioid granulomata surrounded by concentric hyalinized collagen (red arrow).

pulmonary sarcoidosis consistent with reports from international literatures. Most of the local papers described of the difficulty in arriving at the diagnosis of pulmonary sarcoidosis in view of its rarity and the prevalence of tuberculosis in Malaysia. Among the cases reported locally, there were two cases of hepatic sarcoidosis for the past twenty years. Hepatic involvement is seen in around 50% of cases of sarcoidosis as reported but it is rarely here.[7] Most patients are asymptomatic, with around 20% presenting with clinically significant disease.[7] While half of the patients have biopsy-proven hepatic sarcoidosis, approximately 20% had palpable hepatosplenomegaly, 10-30% developed elevated liver enzymes and 15% reported abdominal pain and pruritus.[7] Granulomatous lesions are always found in liver biopsy typically around the portal and periportal zones of hepatic sinuses.[7]

Serum angiotensin converting enzyme is usually elevated but not pathognomonic. Hypercalcemia occurs in 10-20% of patients as seen in our patient, attributed to the overproduction of 1, 25-dihydroxycholecalciferol from activated macrophages.[7]

Our patient was initially treated successfully with steroids when diagnosed with stage II pulmonary sarcoidosis three years ago. However, her disease progressed to stage IV pulmonary sarcoidosis and involved the extrapulmonary sites as she had missed her appointments. Her raised alkaline phosphatase levels had driven the investigation of extrapulmonary sarcoidosis. The American Thoracic Guidelines recommends that in patient with sarcoidosis who have neither hepatic symptoms nor hepatic sarcoidosis, a baseline alkaline phosphatase need to be reviewed as a screening for hepatic sarcoidosis.[1] Patients who are asymptomatic with mild elevations of liver enzymes, and normal synthetic liver function will only require close monitoring without any immunosuppressive agents.[1] Hepatomegaly alone from physical examination or radiographic investigation in the absence of symptoms is not an indication for treatment. In asymptomatic patients, the mild hepatitis often resolves spontaneously or remains stable for years.[1] Our patient did not fulfil the treatment criteria. Generally, the indications to start treatment include being symptomatic, or presence of significant number of granulomas on biopsy. The first line medical therapy is oral prednisolone 0.5mg/kg per day with gradual taper. Corticosteroids reduce the number of hepatic granulomas by suppressing the inflammatory response.[7] Ursodeoxycholic acid can be used to reduce cholestasis by decreasing the biliary secretion of cholic and chenodeoxycholic acids.[7] Second line treatment involves methotrexate.[7] Albeit liver involvement is common in sarcoidosis, end-stage liver disease remains a rare indication for orthotopic liver transplantation. Investigators from the University of Tennessee Health Sciences Center had found statistically significant graft and patient survival on the long-term outcomes of liver transplantation in end stage hepatic sarcoidosis when compared to other cholestatic diseases.[8]

CONCLUSIONS

Sarcoidosis remains idiopathic and heterogenous in manifestations. A suspicion of extrapulmonary sarcoidosis should warrant extensive investigations for associated liver disease, as this may impact on the prognosis. Asymptomatic patients with gastrointestinal sarcoidosis generally do not need treatment. Liver transplantation is a plausible option if there is a risk of progression to end-stage liver disease. Our case illustrates the importance for clinicians to follow up sarcoidosis patients regularly as they may progress to pulmonary or extra-pulmonary sarcoidosis. Hepatic sarcoidosis is rare but remains a common manifestation of extra-pulmonary sarcoidosis and often there are many other differential diagnoses with the similar presentation.

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CASE REPORT

Concurrent COVID-19 and dengue with hyperferritinaemia: A case report

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SUMMARY

The current pandemic of coronavirus disease 2019 (COVID-19) poses a bigger challenge to the population in tropical countries where dengue fever is also endemic as both diseases share similar clinical and laboratory features. In COVID-19, hyperferritinaemia is associated with severe disease and clinical outcome while in dengue fever, hyperferritinaemia is a key feature of haemophagocytic lymphohistiocytosis (HLH), which is a complication with high mortality. In this case report, we present a case of co-infection of COVID-19 and dengue with hyperferritinaemia in Queen Elizabeth Hospital, Sabah, Malaysia.

INTRODUCTION

The ongoing COVID-19 global pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA betacoronavirus. Clinical features of COVID-19 such as fever, myalgia, fatigue and skin rash, and laboratory abnormalities such as lymphopaenia, thrombocytopaenia, increased liver enzymes and raised inflammatory markers are also seen in dengue fever, caused by the dengue virus (DENV). This poses a diagnostic challenge especially during the current pandemic when the healthcare system is strained by the large numbers of ill patients requiring treatment for COVID-19. Here, we report a case of a patient afflicted with both polymerase chain reaction (PCR) proven COVID-19 and dengue with hyperferritinaemia.

CASE REPORT

A 41-year-old man, non-smoker with underlying hypertension, was admitted to the Queen Elizabeth Hospital, Sabah, Malaysia for asymptomatic COVID-19 which was detected as part of contact screening. Nasopharyngeal swab for SARS-CoV-2 PCR was positive eight days prior to admission. PCR detection was done with BGI real-time fluorescent rt-PCR assay (SLAN-96S, China) with a cycle threshold value of 27.71 (RdRp gene) and 28.86 (N gene). There was no history of recent travel. On the 3rd day of admission, he started having fever (henceforth referred to as day-1 of fever). On day-3 of fever, he required nasal cannula oxygen supplementation due to desaturation. Oxygen saturation was 94% on ambient air. Lungs were clear on auscultation. Blood investigations revealed lymphopaenia (0.59 x10^3/uL) and raised C-reactive protein (CRP) (45.3mg/L) and ferritin (6381ng/mL). Procalcitonin was 0.58ng/mL. Chest radiography showed ground glass opacities over bilateral lung fields (Figure 1). In view of diagnosis of COVID-19 with pneumonia requiring oxygen therapy, he was started on dexamethasone 6mg once daily. He was also started on piperacillin-tazobactam for empirical treatment of hospital-acquired infection.

He was weaned off oxygen supplementation within 24 hours. However, he remained febrile with multiple spikes of temperature in the ward. He also had an episode of unprovoked gum bleeding. Clinically he was normotensive with good peripheral perfusion with no signs of plasma leakage. Serial blood investigations showed decreasing platelet and white blood cell counts and increasing liver enzymes (aspartate aminotransaminases more than alanine aminotransaminases) (Table I). He was thence screened for dengue fever. Dengue screening taken on day-4 of febrile phase revealed a positive dengue NS1 and negative dengue IgM and IgG, and multiplex real-time reverse transcriptase PCR (rt-PCR) for dengue revealed the detection of DENV serotype 3 (Bio-Rad CFX96, USA). Human immunodeficiency virus and hepatitis screening was negative. Blood smears for malarial parasites were also negative.

Serum ferritin showed an increasing trend to >40000ng/ml, serum triglyceride was 3.65mmol/L and fibrinogen was 225.2mg/dL. He was also noted to have splenomegaly of two fingerbreadths below the costal margin. In view of marked hyperferritinaemia, a diagnosis of dengue-related haemophagocytic lymphohistiocytosis was considered. HScore for reactive haemophagocytic syndrome was 199, which translated to an 80-88% probability of haemophagocytic syndrome, while HLH-2004 score was 4 (fever, splenomegaly, hypertriglyceridaemia and hyperferritinaemia).

Dexamethasone therapy was increased to 8mg 12-hourly (10mg/m^2 per day) on day-7 of illness. Subsequently his blood parameters improved, and dexamethasone was then tapered off over a total of 14 days. He remained stable throughout his hospitalisation, and he was discharged home on the 19th day of admission. A follow-up review at a health clinic after 1 week revealed a recovered liver function with normalising serum ferritin.

DISCUSSION

The hyperinflammatory phase of COVID-19 manifests as systemic inflammation resulting in multiorgan and respiratory failure, and elevation of inflammatory cytokines

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Table I: Serial blood investigation of patient during admission. The last temperature rise was on day-5 from fever onset. The last column refers to blood parameters during post-discharge review at the health clinic. TWBC denotes total white blood count, ALT alanine aminotransferase, AST aspartate aminotransferase, CRP C-reactive protein, and LDH lactate dehydrogenase.

Day from fever onset	2	3	4	5	6	7	8	9	10	13	15	24	Normal range
Haemoglobin (g/dL)	15.1	16.3	15.6	14.2	14.3	14.6	15.5	13.6	13.0	14.3	13.1	12.7	13.0-17.0
TWBC (x10^3/µL)	4.66	5.57	3.36	3.53	4.41	8.15	11.87	12.46	11.93	10.48	10.65	6.8	4.0-10.0
Neutrophil (x10^3/µL)	3.46	4.27	2.16	2.25	2.11	4.47	7.22	8.96	9.00	6.82	7.27	4.5	2-7
Lymphocyte (x10^3/µL)	0.59	0.71	0.83	0.81	1.80	3.01	2.74	1.85	1.35	2.24	2.08	1.9	1-3
Platelet (x10^3/µL)	165	147	66	20	13	35	75	133	197	263	241	261	150-410
Haematocrit (%)	43.2	44.9	44.9	39.8	41.4	41.0	43.4	38.7	36.7	41.8	39.4	35.9	40-50
Urea (mmol/L)	5.3	5.6	6.0	5.0	5.3	5.6	6.2	6.3	6.5	7.1	5.6	3.9	3.2-7.4
Creatinine (µmol/L)	93.7	104.2	105	77.9	68.5	65.5	72.3	66.4	70.9	68.7	66.3	82	63.6-110.5
ALT (U/L)	95	102	110	130	167	214	196	172	156	190	128	46	0-55
AST (U/L)	90	116	171	256	355	270	171	124	90	73	43	-	5-34
CRP (mg/L)	45.3	34.2	18.5	11.1	8.1	6.2	6.2	4.2	3.2	2.3	5.7	11.1	<5
LDH (U/L)	404	482	585	831	810	551	487	411	382	335	231	-	125-220
Ferritin (ng/mL)	6381	-	23118	>40000	>40000	31543	16073	11300	7584	5043	4078	959	21.8-274.7
Fibrinogen (mg/dL)	286.0	-	280.9	-	228.4	225.2	-	202.1	-	-	-	-	200.1-442.6
Triglyceride (mmol/L)	-	-	2.70	-	-	3.65	-	-	2.37	-	-	-	<1.7

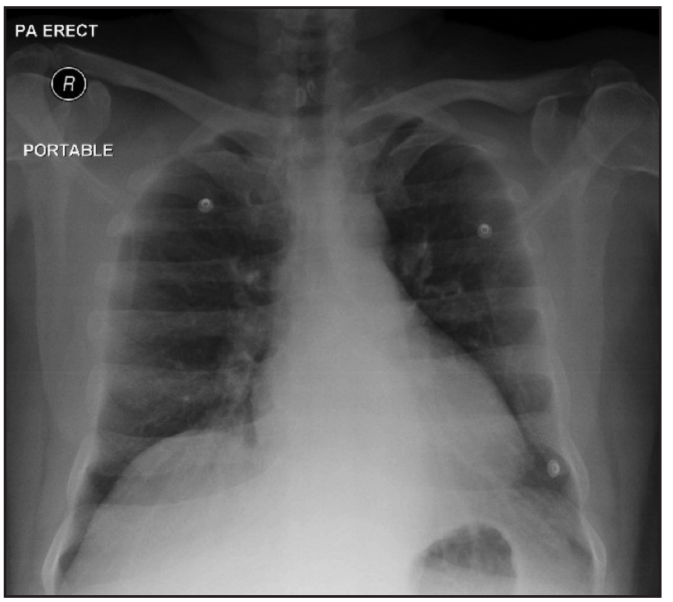

Fig. 1: Chest X-ray showing ground glass opacities with interstitial infiltrates over bilateral lung fields.

and markers such as interleukin-6, CRP, LDH, ferritin and D-dimer. Current data suggest that this phase is caused by a dysregulated host innate immune response. The hyperinflammatory response in COVID-19 shares similar clinical characteristics with dengue-associated HLH, which is a state of uncontrolled hyperinflammation caused by persistent stimulation of lymphocytes and histiocytes resulting in hypercytokinaemia. Ferritin levels have been used as a prognostic tool for COVID-19 as they have been shown to be significantly higher in patients with severe disease, though concentrations rarely exceed the HScore threshold of 2000ng/mL within 16 days after the symptom onset.[1]

There are many case reports of co-infection of dengue and COVID-19 worldwide,[2,5] however, as of writing, none had reported hyperferritinaemia or suspected HLH. It is unknown if a concurrent infection of both diseases results in a more severe clinical course, or if it increases the risk of hyperinflammation. In this case, we hypothesised that the patient may be progressing to HLH in view of clinical findings of fever, splenomegaly, hypertriglyceridaemia and hyperferritinaemia. A diagnosis of HLH should be considered if the patient fulfils ≥4 of the 8 HLH-2004 diagnostic criteria, or if HScore probability of HLH is 70% or greater. However, bone marrow examination was not performed. Case reports have described findings of dyserythropoiesis and haemophagocytosis on bone marrow aspirates in patients with clinically diagnosed HLH, though it is not commonly performed in dengue fever due to risk of bleeding.

Dengue-associated HLH is also more commonly seen in severe dengue,[3] defined as the presence of severe plasma leakage leading to shock, haemorrhage, and organ involvement. DENV serotype 2 has also been associated with a higher prevalence of severe dengue by a study by Suppiah et al. Interestingly, our patient does not fulfil the criteria for severe dengue and serotyping had revealed infection with DENV serotype 3.

There is a marked heterogenicity of literature regarding management of acquired HLH. Various case reports of dengue associated HLH have shown clinical improvement in patients after a brief course of corticosteroids,[4] as opposed to a more prolonged corticosteroid therapy used for other forms of acquired HLH with a protracted course of disease trigger. Likewise, a meta-analysis by the World Health Organisation (WHO) Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group published in September 2020 have shown a reduction in mortality in COVID-19 patients with hypoxia with the use of systemic corticosteroids for 7-14 days. In our case, the patient responded well to treatment with just a short course of dexamethasone, and blood parameters had normalised at a reassessment 2 weeks after corticosteroids were stopped.

Concerns regarding serological cross-reaction of SARS-CoV-2 and DENV have been highlighted by case reports of false-positive results from serological testing for dengue IgM in patients with COVID-19. This was first reported in a case report from Singapore[5] in March 2020, which described two patients who initially tested positive for dengue IgM but later confirmed to have SARS-CoV-2 infection. In dengue-endemic areas, this carries serious consequences for the public health as a presumed diagnosis of dengue based on positive serological testing may result in a missed or delayed diagnosis of COVID-19. It is thus imperative that patients presenting with fever and a positive dengue serological test to be screened for COVID-19 especially during an active outbreak. Likewise, a co-infection of dengue fever should be considered in a patient with confirmed COVID-19 presenting with a constellation of persistent fever, leucopaenia and thrombocytopaenia, especially in tropical countries where dengue fever is prevalent.

CONCLUSION

A diagnosis of COVID-19 and dengue coinfection should always be considered in the setting of a dengue-endemic area. A high index of suspicion for dengue-related haemophagocytic lymphohistiocytosis is crucial in patients with hyperferritinaemia as mortality is greatly reduced by prompt initiation of corticosteroids. Further research is warranted to study the outcome of COVID-19 and dengue coinfection, and serological cross-reactivity between both conditions should be considered in the management of the ongoing pandemic.

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Littoral cell angioma disguised as huge ovarian cyst: A thought to ponder

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SUMMARY

Littoral cell angioma (LCA) of the spleen is a rare vascular tumour. It was thought to be a benign and incidental lesion. Given the relative lack of specific symptom in many cases, these tumours are found incidentally during abdominal surgery during a non-related procedure. Clinical manifestation of a huge adnexal mass and the atypical appearance of splenomegaly, explains the often misguided diagnosis. To the best of our knowledge, there has been no case of incidental finding of LCA disguised as a huge ovarian cyst in Malaysia. We present a case report of a focal solitary LCA incidental finding after splenectomy.

INTRODUCTION

Vascular tumours are the most common primary neoplasms of the spleen. Among these, littoral cell angioma (LCA) is a rare vascular tumour that occurs exclusively in splenic tissues and was first described by Falk et al. in 1991.[1] Due to its rarity, it may be mistakenly diagnosed as a benign cystic lesion, particularly resulting from a gynaecological disorder. In this paper, we present a case of LCA with clinically manifested as an adnexal mass in Hospital Sultanah Nora Ismail, Batu Pahat, Johor, Malaysia.

CASE REPORT

A 15-year-old young woman with no known premorbid illness was seen in Gynaecology Clinic at Hospital Sultanah Nora Ismail, Batu Pahat, Johor, Malaysia. The patient came with a two week history of abdominal distension and constipation. She also had a frequency of micturition. She denied any gynaecology symptoms and attained menarche at the age 12. During physical examination by our Gynaecologist, her abdomen was found to be distended with clinically manifested as huge adnexal mass with 20-week size, soft and non-tender. No hepato-splenomegaly was noted during during percussion. Bedside ultrasonography examinations by the gynaecologist revealed an uniloculated ovarian cyst with the size of 10x14cm with no significant abdominal free fluid. Ultrasonography studies done during the 2 week follow up was consistent with the first ultrasonography finding and normal uterus visualised anteverted position, sized 4x5cm. Her laboratory tests showed hypochromic microcytic anaemia. Her full blood picture had a non-specific finding. Her tumour marker shows elevated in CA125, but Alpha-fetoprotein and LDH were normal.

She was diagnosed with a symptomatic huge ovarian cyst and to ruled out malignancy. She was then scheduled for elective cystectomy keeping in view salphingo-oophorectomy.

Intra-operative findings noted a large splenic tumour occupying the inferior pole of the spleen. Uterus and both ovaries were normal. The case was subsequently referred to the surgical team during the operation. Splenectomy was performed. On gross pathological examination, a focal solitary mass of the anterior splenic capsule measuring 17×18cm with clear margins was found. Histological examination of the pathological specimen from the splenectomy specimen showed a low-grade vascular tumour compatible with LCA. A baseline contrast-enhanced CT scan of the thorax, abdomen and pelvis was done postoperatively and showed unremarkable findings. She was then given triple vaccination and was started on prophylactic penicillin until the age of 21 years old. She was under our surveillance follow up 6 monthly.

DISCUSSION

LCA of the spleen is a rare vascular tumour that was first described in 1991. LCA may occur at any age and have no gender predilection. However, in the original paper Falk et al., state that LCA affects both men and women (female: male ratio = 5:3) with no specific age predilection (1-77 years, median age: 50 years).[1] Majority of patients with LCA are usually asymptomatic and the lesion is discovered incidentally as in the case with our patient. Typically, patients with LCA are found to have a splenic abnormality, in which 50% of all patients present with signs of hypersplenism such as anaemia or pancytopenia. Other systemic symptoms such as fever, chills, weakness, fatigue, and pain have been reported.[1] Given the relative lack of specific symptoms, in many cases, these tumours are found incidentally during abdominal surgery during a non-related procedure. However, most of the cases were incidentally found during emergency settings, such as traumatic solid organ injuries and ruptured haemorrhagic ovarian cysts.[2,3]

In our case, LCA was clinically manifested as a huge adnexal mass causing abdominal distention and external compression symptom such as constipation. Considering the atypical manifestation of splenomegaly from gross pathological examination, that might explain the misguided diagnosis pre-operatively by our Gynaecologist. The gross

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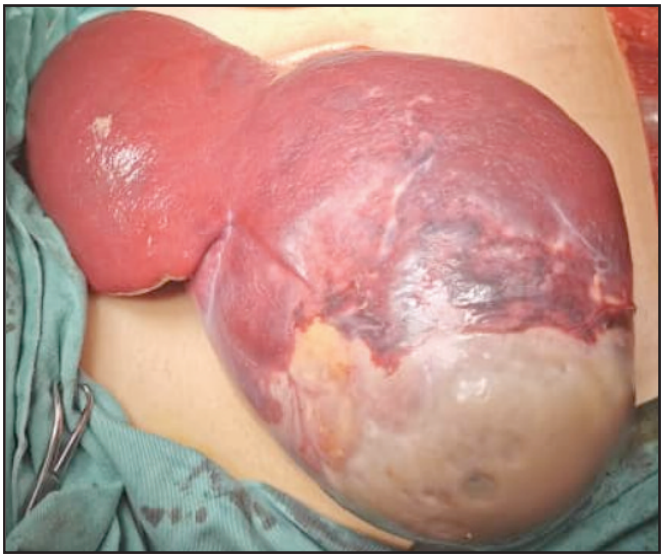

Fig. 1: Gross pathological examination shows uneven splenomegaly.

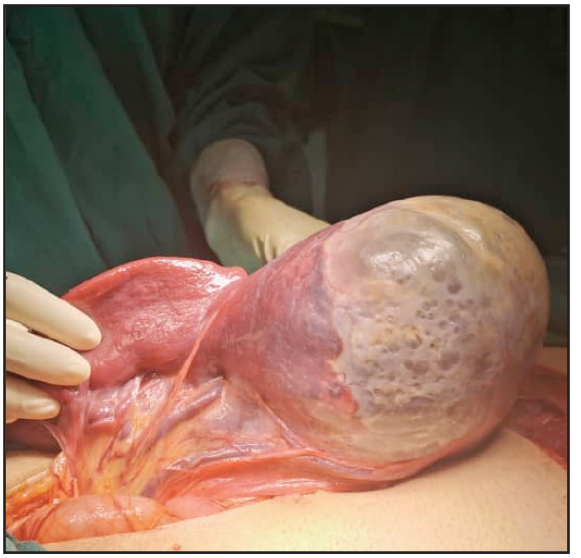

Fig. 2: Large splenic tumour occupying inferior pole of the spleen.

specimen showed a normal appearance of the superior pole and a huge tumour from the inferior splenic pole. Thus, leading to negative Traube's space during the examination finding.

Therefore, the case was referred by a primary health care team to evaluate the ovarian mass. The patient was seen first by our gynaecologist and transabdominal ultrasound were done twice. Based on the Royal College of Obstetrician and Gynaecologists Green-top guideline, a pelvic ultrasound is the single most effective way of evaluating an ovarian mass with transvaginal ultrasonography are preferred due to its higher sensitivity over transabdominal ultrasound. However, considering that the patient is a virgin adolescent, transvaginal ultrasonography was not performed. In addition, at present, the routine use of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) for the assessment of ovarian masses does not improve the sensitivity or specificity obtained by transvaginal ultrasonography in the detection of ovarian malignancy.[4] Nevertheless, in our case, a decision for cystectomy kept in view salphingo-oophorectomy was made for symptomatic relieve and need for tissue histopathological examination evaluation to confirm diagnosis.

On ultrasound, the findings for LCA or splenic tumours vary widely diversified, from heterogeneous echotexture without specific nodules to hyperechogenic, hypoechogenic or isoechogenic appearing lesions. However, the spleen has traditionally been regarded as an orphan organ.[5] In our case, ultrasound was misleading, suggesting a huge ovarian mass with uniloculated ovarian cyst.

Nonetheless, from the general surgery point of view, in most cases involving an abdominal mass, CT and MRI are adequate to establish a confident diagnosis. MRI is the best radiological imaging method to differentiate between LCA and other angiomatous vascular lesions [5]. Ultrasonography quality is operator dependent and subjective to interpretive error thus we must also recognize the clinically relevant limitations and pitfalls associated with the use of ultrasound. A definitive diagnosis of LCA requires histological examination. The differential diagnosis of lesions that can mimic LCA on imaging includes lymphangioma, hamartoma, lymphoma, Kaposi's sarcoma, and haemangioma. On gross examination at histopathology, an LCA will typically reveal splenomegaly. Macroscopically, splenic involvement is characterized by multiple, spongy, cystic blood-filled, circumscribed nodules. The nodules are often multifocal similar in size and are well delineated from the surrounding splenic tissue but do not have a surrounding capsule. It is characterised histologically by anastomosing vascular channels lined by tall or flat endothelial cells, which may anastomose with normal splenic sinuses at the periphery.[5]

However, our case showed atypical splenomegaly and a focal solitary mass measuring 17×18 cm of the anterior splenic capsule with clear margins. To the best of our knowledge, this shows an unusual presentation of splenomegaly that can mislead a diagnosis. Bhatt S et al. also stated that, less commonly, these lesions can be solitary or completely replace the splenic parenchyma. Therefore, a definitive diagnosis can only be obtained pathologically.[5]

Although this is a benign tumour, surgical removal is always indicated. Treatment for symptomatic LCA is splenectomy, but currently this is not recommended for asymptomatic LCA. Due to the association and reported cases of malignant transformation, the option for splenectomy should be considered. In our case, a decision was made for splenectomy made on table during surgery due to incidental findings by the gynaecology team.

CONCLUSION

Thus far, this is the first case of LCA presented as an incidental finding splenic tumour disguised as a huge

ovarian cyst reported in Malaysia. We believe that further imaging workup and multidisciplinary approach might be helpful to build up a harmonious environment and better healthcare service. A definite diagnosis is difficult to make preoperatively because histological examination is the only accurate means of making this diagnosis.

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CASE REPORT

Baby boy blue … and mommy too! A rare case of methaemoglobinaemia presenting simultaneously in a mother-neonate pair

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SUMMARY

Methaemoglobinaemia occurs when there is >1% methaemoglobin in erythrocytes. In an infant, they can present either congenitally or in an acquired form. We present a rare case of methaemoglobinaemia presenting simultaneously in a mother and infant pair. The mother and infant were discharged well on Day-4 post-delivery with both mother and baby recording oxygen saturation levels of 100%. On Day-7, during a routine clinic visit, they were incidentally found to be centrally cyanosed. There were no other abnormalities. On investigation, the methaemoglobin levels were elevated in the infant (23.9%) and mother (14.3%). Treatment with ascorbic acid normalised mother's methaemoglobin levels; but baby's levels remained high until the administration of oral methylene blue. Both baby and mother remained well and pink at last follow-up at 2 years 8 months of age. This case illustrates difficulties in ascertaining the cause of methaemoglobinaemia. Post-delivery, the mother-neonate pair were pink, and their haemoglobin electrophoresis were normal, hence it was unlikely to be congenital methaemoglobinaemia. The team could not identify any triggering factors for acquired methaemoglobinaemia. There was also the uncertainty of the necessity to treat the baby. This is because treatment is not without harmful effects and despite the high methaemoglobin levels, the infant was otherwise well. Only a single published paper recommended that high methaemoglobin levels must be treated, and the recommendation was not supported by evidence. Lessons learnt from our case are that neonates with methaemoglobinaemia can be safely treated with oral methylene blue, but more research is needed on the benefit-risk profile of treatment.

INTRODUCTION

While case reports of methaemoglobinaemia is not uncommon, there are no reports of methaemoglobinaemia presenting simultaneously in a previously well mother and her newborn baby boy a few days after delivery. We present this case to illustrate the difficulties in ascertaining the cause of methaemoglobinaemia in both mother and baby; and also the management dilemma in this otherwise well newborn.

Methaemoglobinaemia occurs when erythrocytes contain >1% methaemoglobin (metHb). This increases oxygen affinity of haemoglobin and shifts the oxygen dissociation curve to the left;[1] which reduces oxygen availability to tissues resulting in tissue hypoxia.[2]

Congenital methaemoglobinaemia is rare. It is commonly due to cytochrome-b5-reductase deficiency (Type I methaemoglobinaemia), sometimes due to Haemoglobin M disease and rarely due to cytochrome-b5 deficiency (Type II methaemoglobinaemia). Both Type I and Type II methaemoglobinaemia are autosomal recessive while Haemoglobin M disease is autosomal dominant. Type 1 methaemoglobinaemia is generally asymptomatic but Type II methaemoglobinaemia is associated with early infancy death or severe neurological impairment later in life.[3]

Acquired methaemoglobinaemia is more common but often under-reported.[4] Anaesthetic agents such as lidocaine and prilocaine (in topical creams) and benzocaine (in topical sprays) are the known metHb inducers.[1] These agents oxidize haemoglobin to metHb and are themselves metabolised into reactive metabolites that further oxidize haemoglobin to metHb. In individuals with high levels of gut coliforms, food and water with high nitrate levels can cause methaemoglobinaemia because coliforms convert nitrate to nitrite; and nitrite is a potent metHb inducer. Symptoms of methaemoglobinaemia range from mild cyanosis to life-threatening events such as renal failure, shock, seizures and death.[1]

Ascorbic acid and methylene blue are commonly used treatment modalities.[5] Ascorbic acid scavenges free radicals, thus decreases metHb formation[6] while methylene blue reduces metHb back to haemoglobin. Ascorbic acid may take more than 24 hours before its effect is seen, and several doses may be needed. There are concerns about kidney stone formation if high doses are used.[7] Conversely, methylene blue shows maximal effect within 30 minutes. However, it can cause hypotension, a paradoxical rise in metHb and in neonates it can also cause haemolytic anaemia and respiratory distress.[8]

CASE REPORT

A primigravida mother with uncontrolled hypertension, underwent emergency lower segment caesarean section at 37 weeks gestation. Bupivacaine was given for spinal anaesthesia and magnesium sulphate for her hypertension.

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Fig. 1: Pink at birth (left), cyanosed on Day 7 (top right), chocolate- brown coloured arterial blood (bottom right).

The delivery was uneventful. The baby boy weighed 2.5kg at birth and was pink. Throughout the surgery and post-operative period, the pulse oximetry saturation of the mother was 100% breathing room air.

The baby was exclusively breastfed from birth. While still in the hospital on Day-3 of life, phototherapy was started for neonatal jaundice. He did not have glucose-6-phosphate dehydrogenase (G6PD) deficiency. Before discharge on Day-5, his pulse oximetry saturation (SpO_2) breathing room air was 97%. On Day-7 of life, the baby's parents brought him to the paediatric clinic to review his bilirubin level. The paediatrician attending to the baby noticed that the mother and infant were centrally cyanosed. The mother and father had not realised this until it was pointed out by the attending paediatrician. The mother and baby's SpO_2 on air were 85% and 88% respectively and did not improve with a trial of supplemental oxygen. However, both mother and infant were otherwise well and did not look or feel sick.

Physical examination of mother and infant did not reveal any abnormal findings apart from the central cyanosis. The infant's echocardiogram and chest X-ray were also normal. Methaemoglobinaemia was suspected when the infant's arterial blood was found to be chocolate brown in colour and his arterial blood gasses were normal (pH 7.43, pO_2 83mmHg, pCO_2 36mmHg, HCO_2 23.6mmol/L) despite the low SpO_2. Further investigation confirmed elevated metHb levels in both mother (14.3%) and baby (23.9%). Haemoglobin electrophoresis of both mother and baby excluded Haemoglobin M.

Breastfeeding was temporarily stopped as we explored extensively for methaemoglobinaemia triggering substances, but none were found.

Mother was prescribed one dose of ascorbic acid orally and her metHb levels normalised (1.6%) after three days. The infant received three doses of ascorbic acid orally eight hours apart but metHb levels remained high (24.2%). Methylene blue (0.6mg/kg) was administered via a nasogastric tube and five hours later, metHb levels normalised (3%). Sixteen hours later, it rebound and a second dose (0.8mg/kg) was given. Over the next three days, metHb levels fluctuated between 2.9% and 6.9% before maintaining below 3%. Throughout this period, the infant was clinically well and had resumed breastfeeding four days later.

At six weeks of age, the infant underwent bilateral herniotomy under general anaesthesia uneventfully. His growth and development were normal at his last clinic visit at the age of two years eight months. Neither mother nor baby had recurrence of methaemoglobinaemia.

DISCUSSION

Our case illustrated an unusual simultaneous presentation of metHb in both mother and baby. Determining if this was congenital or acquired methaemoglobinaemia would be useful in the management of the case. Congenital methaemoglobinaemia would require genetic counselling as well as explanation of the long- term prognosis to the parents. On the other hand, acquired methaemoglobinaemia would require advice on avoidance of triggering factors. However, determining the cause proved to be very difficult in this case. We did not manage to test for cytochrome-b5-reductase levels because the parents did not consent for the test to be done. However, congenital methaemoglobinaemia was unlikely because both mother and baby had recorded normal oxygen saturations before discharge from hospital; their haemoglobin electrophoresis results were normal thus excluding Haemoglobin M disease; and there was no family

history of cyanosis. However, we could not be certain that this was acquired methaemoglobinaemia either because we could not identify any possible triggering agent apart from bupivacaine, the spinal anaesthesia administered to the mother before delivery. Bupivacaine has a half-life of three hours,[9] hence there should not be a lag time of seven days before symptoms manifested. Furthermore, its availability in breast milk is low[2] and the trial of breastfeeding cessation did not help improve the baby's condition. Detailed history taken from the mother also did not reveal any other possible sources of triggers. The mother was not on any medication after delivery and was staying in a house with many other people after discharge. None of them developed methaemoglobinaemia hence it was unlikely due to the environment, food or water she had consumed.

Extensive literature search did not come up with evidence on whether or not asymptomatic methaemoglobinaemia should be treated. The only information available was that metHb levels above 25% should be reversed[2] but there was no available research to support this recommendation. We were therefore faced with a dilemma on the justification to offer treatment as the neonate was otherwise not ill and had arterial blood gasses that were within normal limits. As stated earlier, treatment is not without risks. At the same time, we also did not know if there would be health consequences if the metHb levels were not brought down as literature on this was sparse. Therefore, a decision was made to treat the methaemoglobinaemia. Although reports suggested that methylene blue was first line treatment[10] given its faster mode of action, the doctors chose to have a trial with ascorbic acid first because it was thought to be relatively safer compared to methylene blue. However, although ascorbic acid had successfully normalised the mother's metHb levels, it failed to work for the baby. As the parents had been worried about the possible adverse effects with the use of intravenous methylene blue in their otherwise well child, the doctor gave the neonate a trial of oral methylene blue which successfully normalised the metHb level without any adverse effects. A nasogastric tube was used to administer the methylene blue to avoid discoloration to the tongue and the possibility of mucosal burns as per the warning in the medication leaflet.

LESSONS LEARNT

Methaemoglobinaemia can occur simultaneously in both mother and baby. Determining the cause is an important part of the management but it can be difficult. Oral methylene blue was used safely and effectively to reverse methaemoglobinaemia in this neonate. However, there is a lack of evidence to support treatment in asymptomatic patients. Therefore, research is needed to determine the benefit-risk profile of treatment for asymptomatic methaemoglobinaemia.

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Infected pancreatic pseudocyst following severe dengue infection

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SUMMARY

Severe dengue infection is life threatening as it can result in fatal complications such as intractable bleeding from coagulopathy, multiorgan failure from shock and haemophagocytic syndrome. There have been case reports of atypical manifestation of severe dengue infection such as pancreatitis, Guillian-Barre's syndrome, perforated viscus and myocarditis. However, to our knowledge, pancreatic pseudocyst from dengue-related pancreatitis has never been reported in the literature. We hereby report a case of infected pancreatic pseudocyst in a patient with persistent pyrexia, abdominal pain and raised inflammatory markers 10 weeks from the onset of severe dengue infection. Endoscopic ultrasound (EUS) guided transluminal drainage of the infected pancreatic pseudocyst with lumen-apposing metallic stent (LAMS) was performed with good clinical and radiological outcome.

INTRODUCTION

Dengue infection which is transmitted via the female Aedes aegypti mosquitoes remains a public health burden in tropical countries. The incidence around the world has increased in recent years with severe dengue infection as the leading cause of morbidity and mortality in the Asian continent.[1] Any dengue infection with either severe plasma leakage, severe haemorrhage or severe organ impairment is categorised as severe dengue. There have been case reports of dengue infection presenting with acute pancreatitis but the pathophysiology of pancreatitis in dengue infection is still not well understood till now despite several hypotheses being stated in the literature.[2] However, severe dengue infection with acute pancreatitis leading to pancreatic pseudocyst has never been reported.

In accordance to the revised Atlanta Classification 2012, pancreatic fluid collection (PFC) can be divided into acute peripancreatic collection, acute necrotic collection, pancreatic pseudocyst and walled-off pancreatic necrosis. Pancreatic pseudocysts are well-defined encapsulated homogenous fluid collections without necrotic debris that occur four weeks after the onset of interstitial oedematous pancreatitis. These fluid collections are termed acute peripancreatic fluid collection if they occur before four weeks from onset of pancreatitis. Both acute necrotic collection and walled-off pancreatic necrosis are the results of severe necrotising pancreatitis with the former occurring prior to four weeks from onset of pancreatitis and the latter, four weeks after. The indication of drainage of pancreatic pseudocyst includes abdominal pain, gastrointestinal obstruction, infection, obstructive jaundice and vascular compression. Modalities of PFC drainage include surgical cystgastrostomy, percutaneous drainage and endoscopic ultrasound (EUS) guided transluminal drainage with plastic or metallic stents.[3]

CASE REPORT

A 31-year-old woman with no past medical history was admitted to Hospital Kuala Lumpur, Malaysia with fever, malaise and vomiting. Dengue infection was confirmed in her with positive dengue non-structural protein-1(NS-1) and she was treated as severe dengue with multiorgan failure, hypotension and coagulopathy. In view of worsening organ failure and lactate acidosis, she was mechanically ventilated in the intensive care unit. She developed upper gastrointestinal bleeding during the critical phase of her dengue infection. Oesophagogastrodoudenoscopy was performed which revealed haemorrhagic gastric mucosa with multiple bleeding points throughout her stomach. Haemostatic powder was applied all over her stomach via gastroscope and bleeding resolved after two sessions of endoscopy. Her clinical condition improved with supportive treatment and was extubated after 54 days from onset of her illness.

At week 10 of the dengue infection, she however developed persistent pyrexia with abdominal pain. Abdominal examination revealed tenderness at epigastrium and left lumbar area with increased C-reactive protein (CRP) of 117.2mg/L and total white blood cell count (TWC) of 17 x 10^9/L. There was a drop of haemoglobin from 9g/dl to 7g/dl with no clinical evidence of gastrointestinal bleeding or hypotensive episode. She was treated as nosocomial sepsis and commenced on intravenous meropenem. Computed tomography (CT) of thorax, abdomen and pelvis was performed to locate the source of sepsis. CT showed large encapsulated homogenous peripancreatic collection around the head and uncinate process measuring 4.9x6.2x7.8cm (white arrow, Fig. 1A) with extension to the left intraabdominal cavity measuring 7.2x11.2x13.7cm (white arrow, Fig. 1B). We treated her for infected pancreatic pseudocyst from dengue-related pancreatitis in view of her symptoms of abdominal pain, persistent pyrexia and raised inflammatory markers.

Endoscopic ultrasound (EUS) guided transluminal drainage of pseudocyst was performed with electrocautery enhanced

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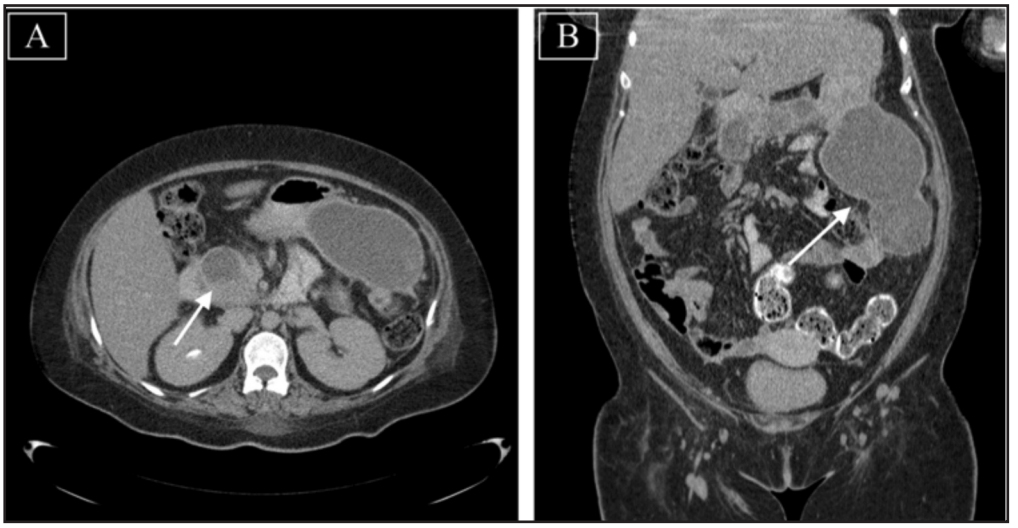

Fig. 1A and 1B: Axial and coronal CT showed well-defined and encapsulated homogenous collection at the head of pancreas extending into the left intraabdominal cavity and compressing the stomach anteriorly.

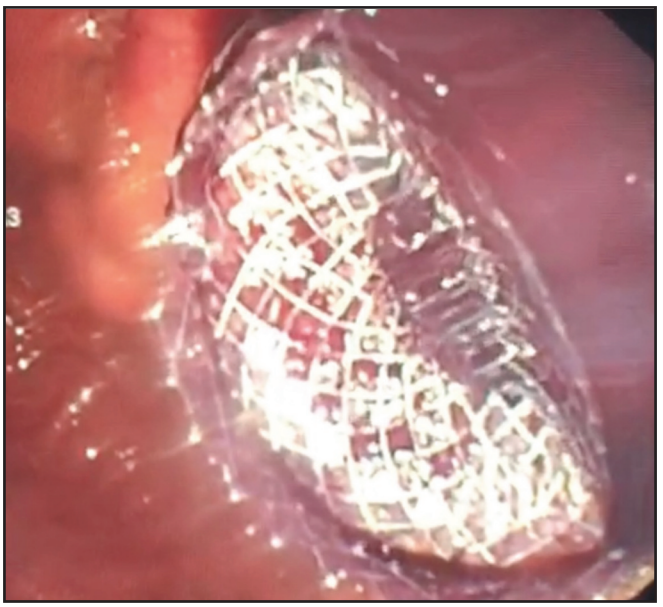

Fig. 2: Haemopurulent fluid was seen draining from the collection into the gastric lumen via the Lumen Apposing Metallic Stent (LAMS).

Lumen Apposing Metallic Stent (LAMS) (AXIOS; Boston Scientific) and haemopurulent fluid was seen draining from it (Fig. 2). Her fever and abdominal pain resolved five days after procedure. The LAMS was removed after four weeks, and she was discharged well from the hospital. Magnetic resonance cholangiopancreatography performed after 1 month following LAMS removal showed complete resolution of pancreatic pseudocyst. She remained well during her latest clinic follow-up.

DISCUSSION

Acute pancreatitis is considered one of the rare and atypical manifestation of dengue infection. In this case, pancreatitis was not suspected initially as the patient did not present with abdominal pain radiating to the back which is a typical feature of pancreatitis. We hypothesised that the pancreatitis in this case occurred during the critical phase of severe plasma leakage which had resulted in hypotension and multiorgan failure. The patient was already ventilated at that time and assessment for pancreatitis type of abdominal pain was not possible. Moreover, serum amylase may be elevated in dengue infection, and this also presents a challenge to the clinician in making the diagnosis of pancreatitis in dengue infection. Exact pathophysiology of pancreatitis in dengue infection remains unknown. Pancreatic acinar cell damage from viral invasion, pancreatic hypoperfusion from dengue shock syndrome, cellular injury from autoimmune process triggered by the virus and obstruction of pancreatic fluid outflow from oedematous ampulla of Vater are few hypotheses that have been mentioned as possible causes of pancreatitis in dengue infection.[4] The possibility of drug-induced pancreatitis could not be fully excluded in this case as there were multiple drugs administered to this patient throughout her admission. However, the drugs given to her have been reviewed and were thought to be of low risk in causing pancreatitis.

Clinical symptoms of persistent pyrexia, abdominal pain with raised inflammatory markers occurring weeks after dengue infection in this case indicated ongoing sepsis in the patient, likely from an intraabdominal source. This prompted radiological imaging in her which found an encapsulated peripancreatic collection. It takes more than four weeks for peripancreatic collection to have a well-defined wall and this correlated temporally with the patient's presentation of a symptomatic pancreatic pseudocyst 10 weeks following dengue infection. The maturity of the peripancreatic collection defined as the presence of a well-defined wall is one factor that needs to be considered before performing drainage. This allows easier access into the collection with reduction of risk of free perforation and greater adherence of collection to the gastrointestinal lumen for endoscopic drainage.[3]

The modality of choice in drainage of a pancreatic pseudocyst is dependent on factors such as the location of the cyst from the stomach or duodenum and availability of local expertise of therapeutic endosonographers, interventional radiologists and surgeons.[3] In our patient, drainage was preferred over surgical and percutaneous method as it is a minimally invasive method and the encapsulated collection was closely adherent to the stomach wall as illustrated in (Fig. 1A), allowing direct drainage into the stomach. A recent meta-analysis by Farias et.al., has shown that endoscopic drainage of pseudocyst was superior to surgical intervention in terms of cost-effectiveness and shorter hospitalisation.[5] Endoscopic drainage of pseudocyst can be performed using double pig tail plastic stents or metal stent such as the one illustrated in this case.[3]

CONCLUSION

Diagnosis of acute pancreatitis in severe dengue infection is challenging and may be missed given their overlapping features as well as being a rare presentation. Infected pancreatic pseudocyst from pancreatitis should be considered in a patient who develops persistent pyrexia, abdominal pain and raised inflammatory markers after recovering from severe dengue infection. Although EUS guided transluminal drainage is a feasible method of drainage in symptomatic pancreatic pseudocyst, a multidisciplinary approach is still necessary to manage such patients.

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CASE REPORT

Functional neurological disorder during the perinatal period: A case report

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SUMMARY

Functional neurological disorder (FND) is a rare neuropsychiatric illness that commonly presents to the medical setting as opposed to the psychiatric setting. FND is characterised by signs and symptoms affecting the voluntary motor or sensory function that cannot be explained by a specific neurological or general medical condition. FND in pregnancy and postpartum is rare. We report here a case of FND in a 32-year-old woman who presented with multiple medical problems during her perinatal period. She exhibited *'la belle indifference'*, history of vague unexplained medical symptomatology while all relevant investigations were normal. There were long-standing psychosocial and interpersonal difficulties with significant distress including multiple personal, marital, and family issues which stemmed from her childhood. This left her feeling inadequate as a mother to her infant. The diagnosis of FND was finalised by the multidisciplinary team consisting of a neurologist, physicians, and psychiatrists, based on longitudinal assessment. Psychological intervention for the patient included psychoeducation, supportive psychotherapy, stress management, and parental intervention. The key point in our management of the patient was the delivery of the diagnosis to help her understand the illness and treatment plan. For this patient, functional and psychological recovery is achievable with a good therapeutic alliance, early diagnosis of the illness, and the acceptance of her diagnosis.

INTRODUCTION

Functional neurological disorder (FND), or previously known as conversion disorder, is a neuropsychiatric disorder characterised by signs and symptoms affecting voluntary motor or sensory function that cannot be explained by a neurological or general medical condition.[1,2] Sigmund Freud hypothesised that the occurrence of these functional symptoms reflected a repressed idea or unconscious conflict.[3] The development of FND is in response to any stressor – mainly due to affective stress, impaired emotional processing, and maladaptive coping response.[4] Despite any definitive medical diagnosis, it is evident that these patients experience distressing physical symptoms that are not deliberate or controlled at will.[3] Risk factors of FND include women, lower educational level, lower socioeconomic background or coming from rural areas, and history of sexual or physical abuse.[3] FND is a low prevalence neuropsychiatric illness that often presents to medical settings as opposed to psychiatric settings.[4] FND symptoms can often be missed.[3,4] Approximately 30% of referred neurology outpatients have medically unexplained neurological symptoms.[3,4] It is estimated that up to 25% of patients in the general hospital have individual symptoms of FND, with 5% fulfilling the criteria of the disorder.[3,4] This case report highlights a lady, J, diagnosed with FND during the perinatal period.

CASE REPORT

Madam J is a newly wedded 32-year-old para 1 lady with a history of neurogenic bladder since she was 19 years old and multiple drug allergies. From her seventh month of pregnancy till her delivery, she was admitted to the obstetrics ward for inpatient treatment of recurrent urinary tract infection (UTI). She developed an anaphylactic reaction (evidenced by pruritic rash) and developed a seizure after being served mefenamic acid for pain management on the second day of delivery, which warranted a transfer to the medical ward for further observation. While she was in the medical ward, she developed an acute headache, vomiting, and fainting episode when discharge planning was made. Although there was no fever and sign of meningism, the medical team started intravenous ceftriaxone 2g BD as an empirical coverage for meningoencephalitis given the sudden onset of an unexplained seizure and fainting episode while waiting for the investigation results, including full blood count (FBC), C-reactive protein level (CRP), computed tomography (CT) of the brain, and video electroencephalography (EEG). Other than lumbar puncture which she refused, all investigation results were normal, and EEG showed no epileptic activities. Thus, ceftriaxone was stopped after five days, and she was referred to the psychiatric team for a psychological assessment.

During the first assessment, there was no psychopathology of major psychiatric illness identified. As J had the capacity and she refused to let the team speak to her family, the team was not able to corroborate the history of absence of significant psychosocial stressors although the team was aware that her newborn was taken care of by her mother-in-law throughout her admission. Since there was no safeguarding concern, she was discharged, and a psychiatric appointment was provided although she did not turn up.

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A week after her discharge, J was readmitted to the medical ward for multiple nonspecific symptoms, including generalised body weakness, headache, vomiting, and lethargy. Multiple episodes of sudden self-aborted unprovoked generalised jerky body movement with retained consciousness were observed on top of change of behaviour, where she became less communicative. Again, FBC, CRP, CT brain, and video EEG was repeated and it showed no abnormality. Given the inconsistently observed seizure semiology, the diagnosis of psychogenic non epileptic seizure (PNES) was made by the neurologist, and the psychiatric team was involved in her care again.

The longitudinal assessment of her previous admissions revealed the trend of J displaying new symptoms whenever she was scheduled for a discharge. Strangely, she was not distressed about the various 'medical problems', which indicated *'la belle indifference'*. With the improved therapeutic alliance, J finally consented the psychiatry team to contact her husband, which revealed that J had multiple personal, marital, and family issues which stemmed from her childhood. J came from a deprived large family which she did not have a close relationship since young and hence she rarely turned to them for support during her difficult times. This background had moulded her into an introvert who was self-reliant and internalise her problems as a form of coping. Childbirth was a major stressor for her given she was a first-time mother. As she was far from her extended family and her husband needed to go outstation for work, she experienced a sense of isolation in the new city, she had no role model to refer to and no support to turn to. Being a new mother had brought back painful memories of her childhood and reminded her of her own poor relationship with her parents. This resulted in poor bonding with her infant son, and she was unable to breastfeed him.

The diagnosis of FND was finalised by the multidisciplinary team consisting of a neurologist, physicians, and psychiatrists, based on the longitudinal assessment. Experts have highlighted that communication of the diagnosis of FND to the patient and their families is done by the neurologists with the early involvement of mental health professionals.[5] Psychoeducation of her diagnosis was given to both her and her husband and supportive psychotherapy was provided based on the strategies of LaFrance Jr and colleagues (2013). J was explained that her seizures were nonepileptic in nature, as evidenced in the EEG findings. Her seizures were precipitated by emotional stress, predisposed by her childhood experience rather than a medical condition. Her physical symptoms and psychological distress were validated and reassurance of the absence of a serious medical condition was provided. Outpatient psychological treatment was explained, and we offered to help her to process her emotional difficulty. As part of stress management, J was taught deep breathing exercises and progressive muscle relaxation techniques to be practiced daily. These techniques activate the natural relaxation response of the body to effectively combat stress. Parental intervention was done between the psychiatrists, J and her husband about the direction of care of her baby and her support system. This was done to ensure that both J, and her baby would be in a safe environment upon discharge and help her mobilize support from the people around her.

J accepted her diagnosis and she was successfully discharged without the development of further physical symptoms. Overall, J showed a fair prognosis in terms of a good therapeutic alliance, early diagnosis, and accepting her diagnosis, predicting a better outcome for her in this case.[6] As she was going to relocate, she was referred to another tertiary centre to continue her psychiatric treatment. Nevertheless, she did not attend the follow-up in the referred centre, and she had not turned up to seek treatment for any medical condition, which indicated her FND had resolved.

DISCUSSION

1. DIAGNOSIS

J had hallmarks of FND, a somatic symptoms disorder. J had *'la belle indifference'*, history of vague unexplained medical symptomatology including PNES. All relevant investigations were normal. Psychiatric assessment discovered long-standing psychosocial and interpersonal difficulties and significant distress of not being able to function as a mother to her infant and having lack of support.

2. MANAGEMENT OF FND

There is no algorithm or empirically supported guidelines in the treatment of FND.[3,4] The core feature is the absence of organic or neurological illness.[3,4] Patients like J may not be receptive to the diagnosis of FND nor will they accept the psychological explanations of FND. The key to successful treatment would be establishing a strong therapeutic alliance with J and incorporating psychotherapy into her management.

3. FND IN PERINATAL PERIOD

Psychiatric disorders during the perinatal period can have a significant impact on maternal health, birth outcomes, foetal development, and relationship with infant.[7] Studies on the management of FND in the perinatal period are limited, however, the management is similar to the standard of care of other FND cases with some adaptation considering the current post-natal state.[8]

The key step in the delivery of the diagnosis to the patient is to help them understand their illness and treatment plan.[8] The psychodynamics of the disorder and the role in pregnancy and motherhood should be explored, as well as the patient's gain from sick role.[8] Any stigma that the patient or her family might have in seeking psychiatric treatment during the perinatal period should be addressed and proper destigmatisation and psychoeducation are imperative.[9] Besides that, clinicians should also look out closely for common psychiatric disorders that tend to occur during the perinatal period including postpartum depression and psychosis.[7]

Experts have suggested a multidisciplinary involvement for the management.[7] Close communications between the psychiatric, neurology, and primary care team is important in the continuation of care of the patient with FND[8]. The

pregnant or postpartum women should be engaged to ascertain their emotional well-being and need for further psychiatric care.[9] The patient's maternal capacity to care for her child should also be regularly assessed to ensure that the baby and mother are in a safe environment for optimal childcare.[9]

CONCLUSION

This case highlights the physical manifestation of underlying psychological stress which was precipitated by childbirth and the key to helping the client is the supportive manner of delivering the diagnosis and further treatment plan.

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CONSENT

Written informed consent was obtained from the patient for publication of this case report.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

ESK, NS, and TT were part of patient's treating team and conceptualized the case with UAS's input. ESK and NS drafted the manuscript. ESK, NS, UAS, and JLL critically reviewed and revised the manuscript. All authors have read and approved the final manuscript.

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Iced towel – a novel method to revert supraventricular tachycardia in a paediatric patient

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SUMMARY

Supraventricular tachycardia (SVT) is the commonest tachyarrhythmia among paediatric age group. Modified Valsalva manoeuvre can be attempted in a stable child. We discuss here a case of a 6-year-old boy who presented with stable SVT and iced towel was applied to his face to revert the tachyarrhythmia. This method was well tolerated by the child without any complications. The SVT was successfully reverted, and pictures were taken to capture the simple but effective method.

INTRODUCTION

Supraventricular tachycardia (SVT) is the commonest tachyarrhythmia among paediatric cases, where it occurs about one case in every 250-1000 children.[1,2] Non-pharmacological methods like carotid massage and Valsalva manoeuvre (VM) can be applied to revert the stable SVT. We discuss in this report a case of a child who presented with SVT and the application of a non-pharmacological method was used successfully to revert his tachyarrhythmia. We share our method that is quick, safe, well tolerated, and less watery while still having good results and outcomes.

CASE REPORT

A 6-year-old boy was referred from a private hospital to the Emergency Department (ED) of the Hospital Universiti Sains Malaysia (Hospital USM), Kelantan, Malaysia, with acute onset of palpitation while studying. It was associated with

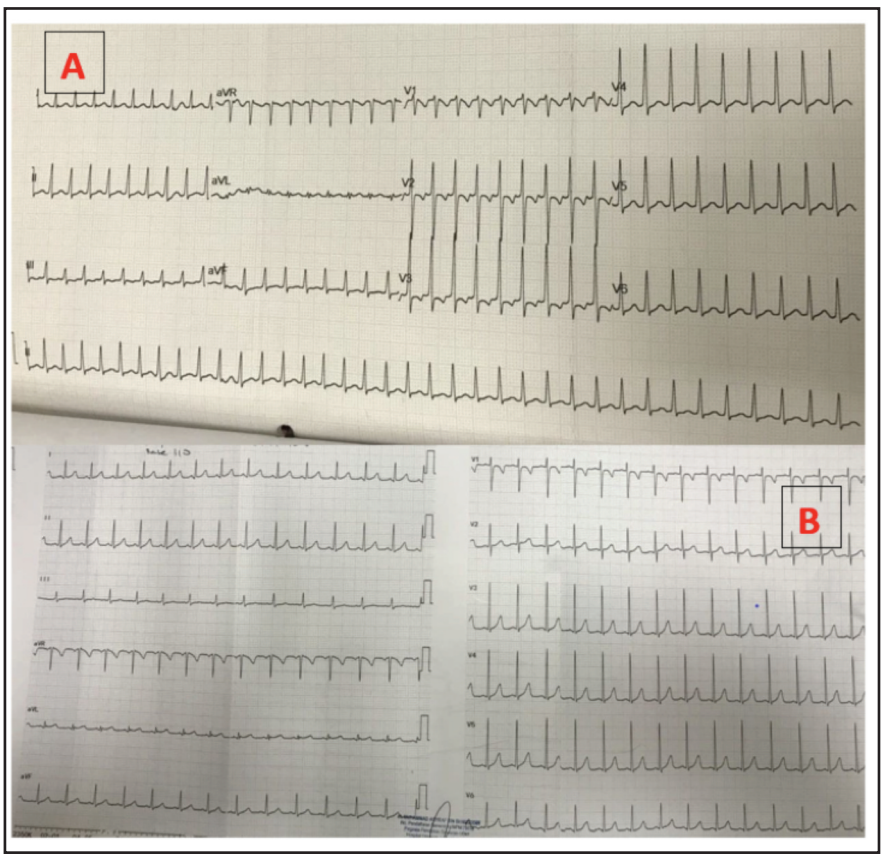

Fig. 1: A) Pre ECG: Regular narrow complex tachycardia with no P wave seen and a heart rate of 220 bpm. B) ECG post Valsalva manoeuvre showed sinus tachycardia with a heart rate of 110 bpm.

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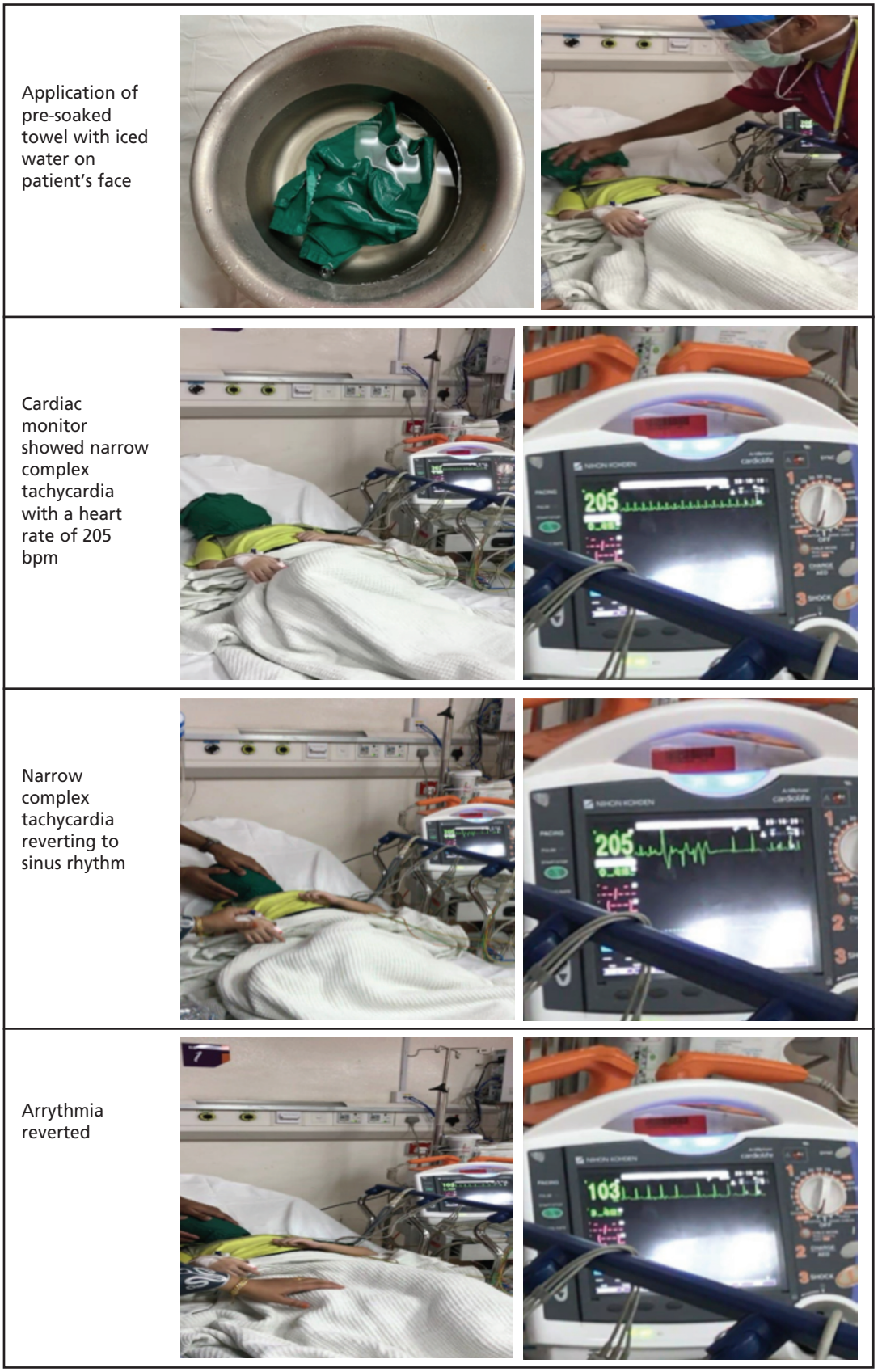
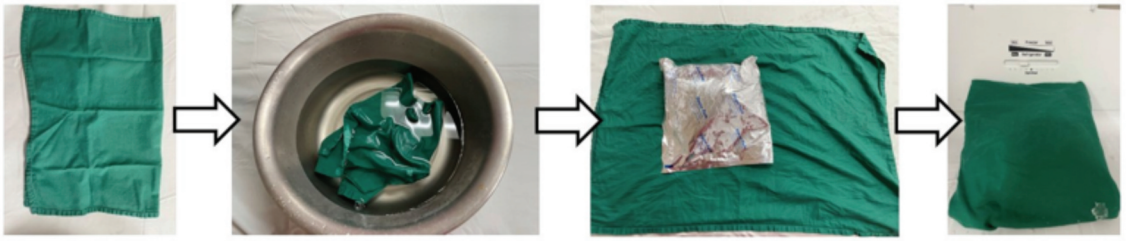


Fig. 2: Method of applying iced towel with cardiac monitoring at each stage.



A: A plain green towel
B: Green towel soaked in pipe water
C: Ice pack placed on the wet green towel
D: Wet green towel wrapped over ice pack was placed in freezer for 5 minutes (the iced pack was removed prior to application on patient's face)

Fig. 3: Step by step preparation of the iced towel.

mild central chest discomfort, profuse sweating and dizziness. He denied history of fever, abdominal pain, vomiting, diarrhoea or dysuria. He was born full-term without any complications. He did not have any significant medical or surgical history. There were no documented allergies, and he was not on any medication. All of his immunisations were up to date. His family history was not significant for any chronic illnesses.

On arrival, he was conscious and appeared comfortable. His blood pressure (BP) was 98/63mmHg with a regular heart rate (HR) of 228 beats per minute (bpm). His respiratory rate (RR) was 20 breaths/minute with oxygen saturation of 100% on room air. There was no documented fever. His extremities were warm and well perfused with normal capillary refill time and his capillary blood sugar was 5.9mmol/L. His heart sounds were normal without any murmur. Examination of other systems were unremarkable.
All of his laboratory results, i.e., renal function test, electrolytes, liver function test, full blood count, were within normal limits. His chest X-ray was normal. Bedside echocardiography showed a hyperdynamic heart with no gross structural abnormalities. An electrocardiogram (ECG) revealed regular narrow complex tachycardia with no P wave seen and a heart rate of 220bpm (Figure 1).

In view of the child's stable condition and appearing comfortable, we attempted a modified Valsalva manoeuvre by placing an iced towel over his face (Figure 2). Prior to that, supplemental oxygen was given to the child to avoid him from feeling suffocated. After about five seconds of application, the arrhythmia spontaneously reverted, and the child returned to sinus rhythm with a heart rate of 110 bpm (Figure 3). The child was then admitted to paediatric ward for observation. He was discharged well home with follow-up under the Cardiology Unit.

DISCUSSION

The management of SVT depends on the condition of the child on presentation. Advance Paediatric Life Support (APLS) guideline advocates the use of a non-pharmacological method for stable condition, in contrast to pharmacological and electrical (synchronised) cardioversion in hemodynamically unstable children.[1] VM with diving reflex is a known non-pharmacological method for a stable SVT.

This technique was first reported in 1979 when a 2-week-old infant with SVT was treated by placing the newborn's face in a basin of ice water for 5 seconds.[3] However, the ice-immersion method is not without its complication. Few case reports had been published where ice-immersion had caused subcutaneous fat necrosis and cold panniculitis. However, the complications are self-limiting and resolved over time.[4]

Another method with ice was tried by Grahame, where he applied ice cubes to the infant's lip and cheek.[5] The method was done mostly among newborns and infants. The cold temperature will stimulate afferent branch of a trigeminal cranial nerve which then causes efferent stimuli on the vagal nerve. In response to it, conduction through atrioventricular nodal is reduced.[2] A review by Marion showed that applying ice water to the face is an effective and non-invasive method in reverting SVT, compared to carotid sinus massage and VM.[6]

Applying an iced towel to treat stable SVT is a novel and modified diving reflex method. The aims are to be more tolerable to paediatric patients and minimising any potential complications. It also eludes the need to create the artificial environment of suffocating or being apnoeic to stimulate the afferent pathway and subsequently the vagal response. In our method, we used a green towel, soaked in pipe water then wrapped over an ice pack before being placed for about 5 minutes in a freezer. The iced towel was then applied gently to the face of the child covering his forehead and cheek. The child was asked to breathe as usual with oxygen supply through a nasal prong. This method reduces the possibility of the worst complication associated with suffocating or apnoeic conditions. Another complication, like cold panniculitis was also avoided as there was no direct contact of ice to the face while creating a comfortable situation for the patient. In addition, the process was less watery and yet, producing a similarly good results.

CONCLUSION

The use of an iced towel is a novel method that can safely be attempted in the ED or even in outpatient clinics. It is a quick, comfortable, safe and less watery technique while still achieving the intended results. This provides the treating doctors with another non-pharmacological intervention in stable SVT patient, thus potentially avoiding the use of medications.

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When polymyositis meets Graves' disease: A rare case report

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SUMMARY

Polymyositis is rarely associated with Graves' disease. A 22-year-old woman was admitted for progressively worsening proximal muscle weakness of both upper and lower extremities. One month prior to admission, she was diagnosed with thyrotoxicosis and prescribed carbimazole 10mg twice daily. Neurological examination confirmed proximal myopathy and blood investigations revealed marked elevation of muscle enzymes, particularly creatine kinase. Electromyography demonstrated myopathic changes while right quadriceps muscle biopsy showed only traces of inflammatory myopathy. She was treated with pulsed intravenous methylprednisolone followed by tapering doses of oral prednisolone, which was eventually down-titrated to 5mg daily during subsequent clinic visits. The initial clinical improvement that she exhibited did not persist despite being rendered euthyroid. She was re-admitted approximately one year later with the same complaint. A second course of intravenous methylprednisolone brought about clinical improvement as well as reduction of creatine kinase levels. A diagnosis of polymyositis was then made, for which she was managed with oral prednisolone 20mg daily in combination with gradual up-titration of azathioprine. She continued to show clinical and biochemical improvements during follow-ups. Polymyositis should be considered in the diagnostic workup of proximal myopathy in a patient with Graves' disease, especially in the setting of markedly raised muscle enzymes.

INTRODUCTION

Muscle involvement is common in hyperthyroidism and has been reported in about 80% of thyrotoxic patients.[1] However, polymyositis has rarely been described as the aetiology of proximal muscle weakness in a patient with Graves' disease.[2-5] We report a young lady who presented with proximal myopathy at diagnosis of Graves' disease which was eventually attributable to polymyositis.

CASE REPORT

A 22-year-old woman was admitted in March 2020 at Hospital Sultanah Aminah, Johor, Malaysia for further investigation and management of proximal muscle weakness. She experienced progressively worsening bilateral lower limb weakness since the end of January 2020, which hampered her ability to rise from a sitting or squatting position. This was associated with palpitations and hand tremors. She denied heat intolerance, weight loss or menstrual irregularity. There was no family history of thyroid disorder. A diagnosis of thyrotoxicosis was made at a primary care clinic based on her presentations, supported by a biochemical picture in keeping with hyperthyroidism (Table I). She was prescribed with carbimazole 10mg twice daily and subsequently referred for tertiary care in our centre.

Physical examination revealed a calm and thin (Body mass index, BMI 16.5 kg/m^2) woman who had exophthalmos, a diffuse goitre and bilateral hand fine tremors. Blood pressure was 117/72mmHg and pulse rate was 124 beats per minute. There was no evidence of heliotrope rash, shawl sign or Gottron's papules. Neurological examination showed a predominantly proximal muscle weakness: Medical Research Council (MRC) scale 3 for bilateral shoulder abduction and adduction as well as hip flexion and extension; scale 4 for muscle power over bilateral elbows, wrists, fingers, knees and ankles. Neck flexion and extension were MRC scale 3 and 5 respectively. There were no muscle wasting and fasciculations. Other systemic examinations were unremarkable.

Relevant investigations during this admission were detailed in Table I. Of note, free thyroxine (T4) was subnormal while thyroid-stimulating antibody (TSH) remained suppressed after one month of carbimazole treatment. Significant elevation of both thyroid autoantibodies indicated the diagnosis of Graves' disease. There was only mild hypokalaemia. Muscle enzymes, in particular creatine kinase (CK), were markedly elevated. Autoimmune markers including anti-nuclear antibody (ANA), extractable nuclear antigen (ENA) and rheumatoid factor (RF) were negative. Complement factors C3 was low while C4 was low normal. Inflammatory myopathy panel was not sent.

In view of raised muscle enzymes, she was treated with three days of pulsed intravenous methylprednisolone after right quadriceps muscle biopsy. Physiotherapy was also commenced. Slight improvement of upper limb proximal muscle power was observed following treatment and this was accompanied by a gradual decrease in CK levels (Figure 1). She was subsequently discharged with tapering doses of oral prednisolone. Carbimazole was withheld throughout admission due to very low free T4 level but resumed one month later when a repeat free T4 rose above normal range.

During a follow-up visit in neurology clinic three months after discharge, our patient demonstrated clinical improvement as evidenced by her ability to rise from a sitting

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Table I: Blood investigations at initial presentation and on first hospital admission

Blood tests	Reference range	Initial Presentation	Admission
TSH (mIU/L)	0.27-4.20	<0.01	<0.005
Free T4 (pmol/L)	12.0-22.0	50.2	6.75
Free T3 (pmol/L)	3.1-6.8	17.9	
TPOAB (IU/ml)			1395.33
ATGAB (IU/ml)			1002.65
Hb (g/L)	120-150		100
WBC (10^9/L)	4.0-10.0		2.8
Platelet (10^9/L)	150-410		436
Sodium (mmol/L)	136-145		133
Potassium (mmol/L)	3.50-5.10		3.47
Urea (mmol/L)	2.8-8.1		1.5
Creatinine (µmol/L)	44-80		29
Albumin (g/L)	35-52		32
ALT (U/L)	5.0-33.0		68
ALP (U/L)	35.0-104.0		43
CK (U/L)	26-132		2514
AST (U/L)	5.0-32.0		193
LDH (U/L)	135-214		834
ESR (mm/hr)	0-20		57
CRP (mg/L)	<5		<0.3
RF (IU/ml)	<14		<10
C3 (g/L)	0.9-1.8		0.784
C4 (g/L)	0.1-0.4		0.109
Anti-Nuclear Antibody IF Test			
Anti-Nuclear Antibody			Negative
Anti-Double-Stranded DNA			Negative
Extractable Nuclear Antigen			
ENA			Negative
Anti-Smith			Negative
Anti-RNP			Negative
Anti-Sjogren's Syndrome A/Ro			Negative
Anti-Sjogren's Syndrome B/La			Negative
Anti-SCL-70			Negative
Anti-JO-1			Negative

TSH thyroid-stimulating hormone, T4 thyroxine, T3 triiodothyronine, TPOAB Thyroid Peroxidase Antibody, ATGAB Anti-thyroglobulin Antibody, Hb haemoglobin, WBC white blood cell, ALT alanine transaminase, ALP alkaline phosphatase, CK creatine kinase, AST aspartate aminotransferase, LDH lactate dehydrogenase, ESR erythrocyte sedimentation rate, CRP C-reactive protein, RF rheumatoid factor, C3 complement factor 3, C4 complement factor 4, IF immunofluorescence, ENA extractable nuclear antigen, Anti-RNP anti-ribonucleoprotein, Anti-SCL-70 anti-topoisomerase I, Anti-JO-1 anti-histidyl-transfer RNA (tRNA) synthetase

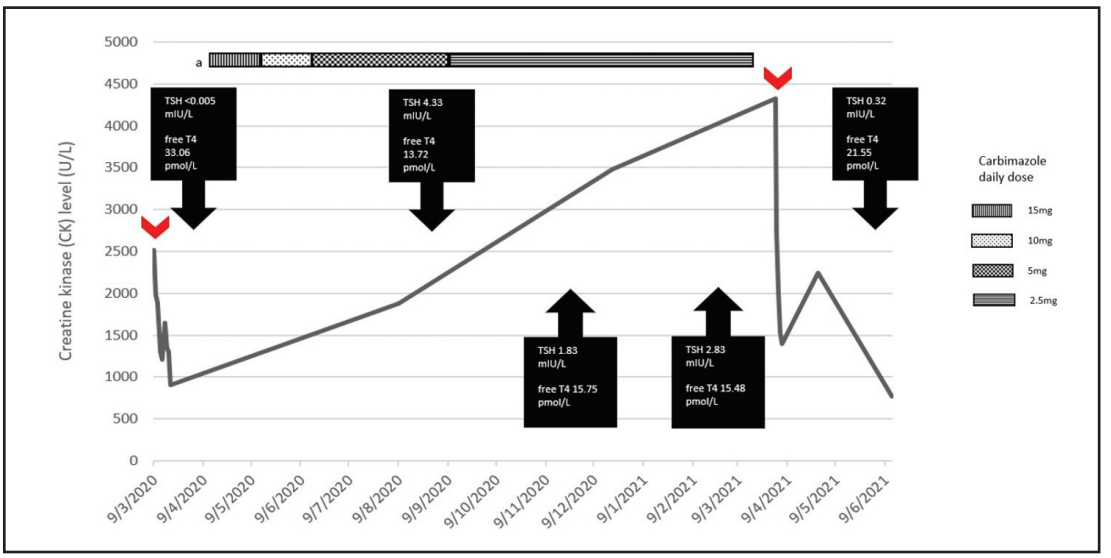

Fig. 1: Creatine kinase (CK) trend with corresponding thyroid function tests from first hospital admission till last clinic review. Arrow heads represent the timepoints of pulsed intravenous methylprednisolone.
[a]Doses of carbimazole at respective time intervals

position and gradual normalisation of proximal muscle power (MSC scale 4 in proximal muscle groups and scale 5 in distal muscle groups). Electromyography (EMG) showed motor unit potentials (MUPs) of small amplitude with short-duration waveforms and early recruitment pattern, which were in line with myopathic changes. Right quadriceps muscle biopsy was also reported as showing myopathic changes with marked variation in fibre size, few pyknotic nuclei, scattered atrophic fibres, and few necrotic and regenerating fibres. No lymphocytic infiltrate was seen. Her prednisolone dose was then down-titrated to 5mg daily in light of good clinical response.

Meanwhile, she attained euthyroid state while taking carbimazole. Approximately one year after her initial presentation, she was able to come off carbimazole and remained in remission of Graves' disease (Figure 1). However, this had not been the case for her proximal muscle weakness. Despite initial clinical improvement, complete recovery was not observed. She was readmitted in April 2021 due to worsening lower limb weakness, which again limited her movement from a chair. There was concurrent rise in her CK levels. A three-day course of pulsed intravenous methylprednisolone led to both clinical and biochemical improvements (Figure 1). She was discharged with oral prednisolone 20mg daily. Azathioprine was added during subsequent clinic visits.

DISCUSSION

Our patient presented with proximal muscle weakness at the onset of hyperthyroid symptoms. Differential diagnoses for such presentation include thyrotoxic periodic paralysis, thyrotoxic myopathy or co-existing polymyositis. The absence of profound hypokalaemia and protracted course of illness excluded thyrotoxic periodic paralysis.

Manifestation of thyrotoxic myopathy at the onset of thyrotoxic symptoms is, in fact, a rare occurrence. Commonly reported symptoms encompass predominantly proximal muscle weakness and wasting, although distal muscle involvement has also been described. The mechanism which underlies thyrotoxic myopathy likely involves upregulation of metabolic activity, which then accelerates catabolism of muscle cells. Muscle enzymes, including CK, are invariably normal while EMG generally exhibits a myopathic pattern. Muscle biopsy is frequently normal. Attainment of euthyroid state resolves thyrotoxic myopathy.[1]

Our patient's proximal myopathy was accompanied by marked elevation of CK levels, which responded to pulsed intravenous methylprednisolone followed by tapering doses of oral prednisolone. Despite initial improvement in her muscle symptoms, full regain of muscle power appeared to be delayed. To make matters worse, she had another episode of worsening proximal muscle weakness, which necessitated second hospital admission for pulsed intravenous methylprednisolone, approximately one year after her first hospitalisation. It is important to note that this recurrence of worsening muscle symptoms happened while she was euthyroid. In other words, restoration of euthyroid state did not seem to ameliorate her proximal muscle weakness. Hence, these findings clearly argue against the diagnosis of thyrotoxic myopathy.

All treatment modalities of hyperthyroidism, including antithyroid medications, radioactive iodine or total thyroidectomy, have been reported to cause abnormal increase in CK levels. Rapid reduction of thyroid hormone levels induced by these treatments has been implicated in creating a relative hypothyroid state which leads to muscular damage and thence release of muscle enzymes. In most reported cases where antithyroid drugs were used, muscle symptoms and elevated CK concentrations resolved with either dose reduction or discontinuation of antithyroid drugs, with or without addition of levothyroxine.[6] Our patient did have a rapid drop of free T4 from 50.2pmol/L at diagnosis of Graves' disease to 6.75pmol/L one month after carbimazole therapy. However, she did not have a baseline CK before initiation of carbimazole. Hence, it is unclear whether her CK levels were already elevated before or rose only after taking carbimazole. Additionally, her CK level was 19 times above upper limit of reference range during her first hospital admission. This degree of CK rise is in stark contrast to that reported by a Chinese group whereby majority of their patients, who were found to have increased CK concentrations while taking antithyroid drugs, had only mildly elevated CK levels (less than twice upper limit of normal range).[7] Moreover, dose reduction and eventually discontinuation of carbimazole did not result in a drop in our patient's CK concentrations. On the contrary, her CK continued to rise alongside worsening proximal muscle weakness, so much so that she needed to be hospitalised again, despite discontinuation of carbimazole one month prior (Figure 1). Therefore, we believe that carbimazole treatment is unlikely the aetiology which underlies her clinical symptoms and markedly high CK concentrations. Similarly, even though positive correlation between TSH and CK levels has been described,[7,8] we are of the opinion that the slightly raised TSH level in our patient four months after re-initiation of carbimazole could not have contributed to the increasing CK concentrations as subsequent normalisation of TSH did not abate CK rise (Figure 1).

Even though myopathic changes were demonstrated in our patient's EMG, these findings are actually non-specific and can be seen in both thyrotoxic and inflammatory myopathies. On the other hand, histopathological examination of our patient's right quadriceps muscle biopsy showed marked fibre size variability as well as few necrotic and regenerating fibres, which constitute some of the main features of polymyositis.[9] Lymphocytic infiltrate, another characteristic finding, was nonetheless absent in this muscle biopsy sample. All in all, putting clinical presentation and subsequent course of illness, muscle enzyme elevation, myopathic EMG pattern as well as presence of inflammatory features in muscle biopsy all together, a diagnosis of polymyositis co-existing with Graves' disease was made. She was treated with both oral prednisolone and azathioprine, and continued to experience improvement in her muscle symptoms and reduction in CK levels thereafter.

Coexistence of Graves' disease and polymyositis is rare.[2-5] A review of literature by Wang H et al. summarised the findings of seven cases of polymyositis with hyperthyroidism (five of which had positive thyroid autoantibodies). All patients were females, aged between 16 and 52 years, and were diagnosed with polymyositis and hyperthyroidism at mean age of 35.3 years and 32.7 years respectively. Hyperthyroidism was

frequently diagnosed before polymyositis. The most common complaint of polymyositis was proximal muscle weakness. Muscle enzymes were almost always elevated. Electromyography results were available in four cases and generally showed myopathic changes. Muscle biopsy in four patients demonstrated inflammatory infiltrate, variation of fibre size, fibre atrophy as well as fibre necrosis. All were treated with antithyroid therapy, out of which six received corticosteroid with or without additional immunosuppressive agents for polymyositis. Complete recovery of muscle dysfunction, as defined by clinical remission and/or normalisation of muscle enzymes, were seen in all but one. One patient experienced partial recovery, as indicated by clinical improvement short of a complete clinical response.[10] Our case is similar to those reported in the aforementioned review. Long term follow-up is imperative to monitor her progress, both clinically and biochemically.

The pathogenetic links between these two autoimmune conditions have yet to be discerned. Some of the proposed mechanisms include common environmental triggers of both conditions in genetically susceptible individuals, cross-reactivity between thyroid autoantibodies with antigens on other tissues or organs or vice versa, immunomodulatory effects of autoantibodies, cytokine imbalance, and possible genetic link between thyroid autoimmunity and predisposition to other autoimmune diseases.[10] More research in this area would be beneficial in providing a clearer picture on the pathogenesis behind the rare coexistence of Graves' disease and polymyositis.

In summary, polymyositis should be considered in the diagnostic workup of proximal muscle weakness in conjunction with markedly raised muscle enzymes in a patient with Graves' disease, despite the rare association. Muscle biopsy remains the gold standard to confirm the diagnosis. Timely management diminishes or eliminates inflammation, restores muscle function and thence accelerates recovery.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Idiopathic hyperprolactinemia - A challenge for primary care

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SUMMARY

Hyperprolactinemia is a condition of elevated serum prolactin, which usually occurs in women as compared to men. Most patients present to primary care clinics with a history of galactorrhoea, oligomenorrhea, amenorrhoea or infertility. Literature search reveals that there were few idiopathic causes of hyperprolactinemia, which resolved by itself without specific pharmacological or surgical treatment. This case is of a 39-year-old woman presented with amenorrhea for four months after Implanon removal and concomitantly noted to have galactorrhoea for four years without any medical attention. The condition persisted after cessation of breastfeeding. After undergoing several investigations including imaging studies, the underlying cause of hyperprolactinemia was noted to be idiopathic. Due to the unclear cause of its aetiology, this case caused various challenges to the primary care. Exhaustive physiological and pathological causes of hyperprolactinemia have been ruled out. Nevertheless, with adequate treatment, she gained her normal menstrual and resolved galactorrhoea symptoms.

INTRODUCTION

Prolactin is an anterior pituitary hormone that plays an important role in lactation during pregnancy and have many other functions such as osmoregulation, angiogenesis and immunoregulation.[1] Serum prolactin concentrations increment also known as hyperprolactinemia often manifests as amenorrhea and galactorrhoea in women and impotence in men. Most of the time, the causes can be identified. Normal serum prolactin levels vary between 5 and 25ng/ml in females. In pregnancy, the level can raise up to 200-500ng/ml.[2]

The mean prevalence of hyperprolactinemia is estimated to be around 30 per 100,000 in women and 10 per 100,000 in men; with peak prevalence in women aged 25 to 34 years.[3] The causes for hyperprolactinemia can be divided into physiological, pharmacological and pathological. Physiological causes that need to be considered are vigorous exercise, physical and psychological stress, chest wall diseases and stimulation, pregnancy, breastfeeding and sleeping. Pharmacological causes are prior intake of antidoparminegic drugs, oestrogen, calcium channel blocker, antipsychosis, and H2 receptor antagonist. Pathological causes can be due to hypothalamic and pituitary diseases compressing pituitary stalk, hypothyroidism and hepatorenal disorders. However, 29% of hyperprolactinemia cases has been classified as idiopathic as in this case report.

Patients with hyperprolactinemia can present with amenorrhea, low libido, erectile dysfunction, infertility, gynecomastia, or trivial fractures. They may have symptoms related to intracranial mass effect of a pituitary adenoma, such as headache or visual changes. Past medical history of thyroid disease, hepatorenal problems and drug history such as hormonal contraceptive, antipsychotic, antidepressant, cimetidine, verapamil is important. For example, if amenorrhea is persistent for more than two months after removal of Implanon, pregnancy must be excluded, and further workup need to be done to look for the cause of amenorrhoea. Therefore, verification on the last menstrual period is mandatory to rule out unplanned pregnancy. In terms of physical examination, it should be directed towards looking for signs of increased intracranial pressure and compressive symptoms. Visual field assessment, fundoscopy for papilloedema, cranial nerve examination and neurological examination are mandatory to be done. Respiratory examinations need to be performed to look for chest wall injury, thyroid status assessment clinically to look for hypothyroidism and genitalia examination for hypogonadism. Breast examination is also important to look for the nature of nipple discharge and exclude any breast pathology.

At the primary care level, to confirm the condition, serum prolactin levels need to be measured twice preferably in the early morning within three to four hours after waking up from sleep. Whenever the level is still high during subsequent follow up, serum thyroid stimulating hormone level needs to be measured to rule out concomitant hypothyroidism. The inadequate hormone needs to be treated. Patients usually can be followed up at primary care level for further workup together with serum prolactin monitoring. However, whenever a patient presents with red flag symptoms, or unclear diagnosis, then the referral to tertiary centre needs to be done. Among the red flags symptoms for hyperprolactinemia which occur due to mass effect of enlarged pituitary are headache, cranial nerve disturbance, and visual field defect classically bitemporal hemianopia due to compression of the optic chiasm.[4] Once patients manifest with these alarming features, further imaging studies are warranted. The imaging test is helpful in stratifying the size of pituitary gland into microadenoma (<10mm) or macroadenoma (>10mm). If the MRI findings are normal, then only the diagnosis of idiopathic hyperprolactinemia can be concluded. This can be summarised as in Figure 1 below:

The principle of management of hyperprolactinemia is based on the underlying aetiology.[5] For idiopathic hyperprolactinemia and for those due to pituitary

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Table I: Blood investigation results

Thyroid Function Test	Free T4 11.99pmmol/L TSH 2.229mIU/L
Fasting Lipid Profile	Total cholesterol 5.5mmol/L HDL 1.13mmol/L LDL 3.9mmol/L Triglyceride 1.1mmol/L
Renal Profile	Urea 3.2mmol/L Sodium 138mmol/L Potassium 4.0mmol/L Chloride 104mmol/L Creatinine 61µmol/L
Full blood count	Haemoglobin 12.9 White blood cell 5.7 Platelet 228
Fasting plasma glucose	FBS 4.3mmol/L
Liver function test	Total protein 70g/L Albumin 44g/L Globulin 26g/L Albumin globulin ratio 1.7U/L Aspartate aminotransferase 26U/L Alanine amino transferase 14U/L Alkaline phosphatase 73U/L Total bilirubin 12µmol/L Direct bilirubin 2.0µmol/L Indirect bilirubin 10µmol/L
Hormone	Oestradiol 117.4pmol/L FSH 8.83IU/L LH 4.56IU/L **Prolactin 77.21µg/L**

microadenoma, treatment is mainly by medical therapy and follow up. For hyperprolactinemia secondary to pituitary macroadenoma, both medical and surgical therapy can be initiated. Other miscellaneous causes of hyperprolactinemia such as systemic disorders, drugs, pituitary hypersecretion, and hypothalamic pituitary stalk damage must be properly identified and treated accordingly.

The pharmacological treatment that can be initiated after diagnosing idiopathic hyperprolactinemia is mainly dopamine receptor agonist, such as cabergoline. This drug is indeed very effective in in treating hyperprolactinemia.[6] Among the most common side effects of cabergoline that need to be informed include nausea, headache, dizziness or vertigo, weakness, low blood pressure, constipation, and abdominal pain.[6] Therefore, a shorter interval of appointment should be arranged to clarify the effects with patients. After initiating the medication, the patient also requires careful monitoring in terms of the symptoms progress and serum prolactin level. For patients who had idiopathic hyperprolactinemia and have had a persistent normal range of prolactin level while taking a low dose of dopamine agonist for at least two years, the medication can be gradually weaned off.

If there are no red flags and patient is well, primary care doctors can arrange for follow up to monitor serum prolactin level for six years and re-evaluate the need for imaging studies if sudden increment of serum prolactin detected.[7] Untreated hyperprolactinemia will end up with multiple complications. For example, for females in the reproductive age, they will end up with menstrual disorder especially amenorrhea and this will cause further anxiety and psychological impairment for the patient, as in our case. Other than that, amenorrhea and low oestradiol levels will lead to eventual bone loss and osteoporosis if untreated. In men, hyperprolactinemia may also be associated with erectile dysfunction and other symptoms of hypogonadism such as decreased libido, decreased energy, loss of sexual hair, loss of muscle mass, and osteoporosis.

CASE REPORT

A 39-year-old woman presented to our clinic with a complaint of persistent amenorrhoea since removal of Implanon for six months. She otherwise had no abdominal pain, headache, blurring of vision, nausea or vomiting, loss of appetite or loss of weight. On further questioning, she had underlying persistent galactorrhoea for the past four years since her last childbirth. The galactorrhoea was present upon milking, whitish in colour without any foul smell. Otherwise, there were no signs and symptoms of thyroid disorder and no history of taking supplements or over the counter drugs for milk booster. There was no significant past medical or surgical history. She never has had any gynaecological procedure, such as curettage for miscarriage. She otherwise had a family history of bone cancer, which is her late aunty.

She has been a divorcee for the past one year. She had seven children from her previous marriage. She was not sexually active. She works as a Science Officer and is not exposed to any chemical hazard. She is a non-smoker and non-alcoholic. Nevertheless, she did feel psychological and physical stress as she needed to take care of her children on her own. She benefited from good support from her family members.

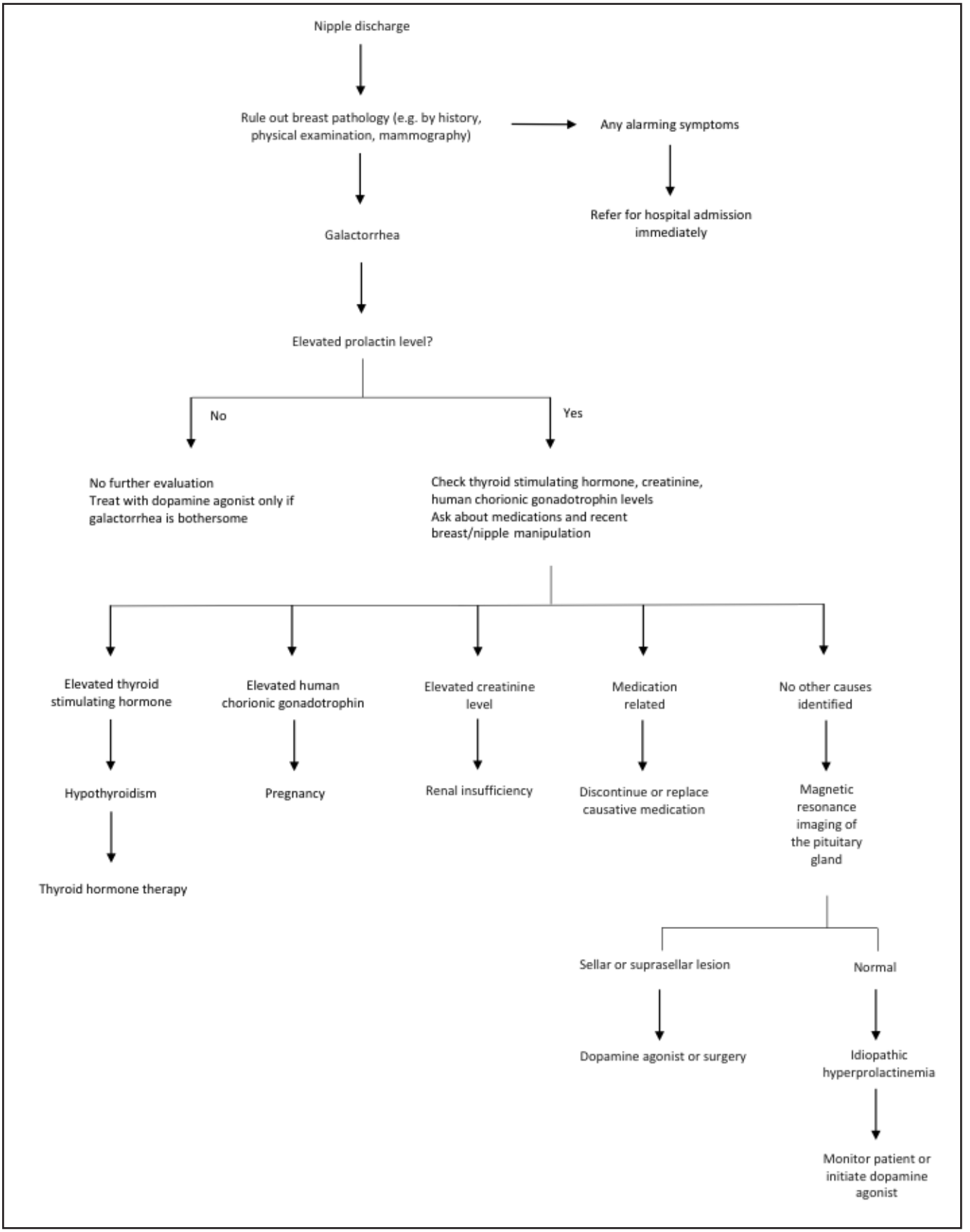

Fig. 1: Overview of hyperprolactinemia management approach (Modified from Huang 2012)[2].

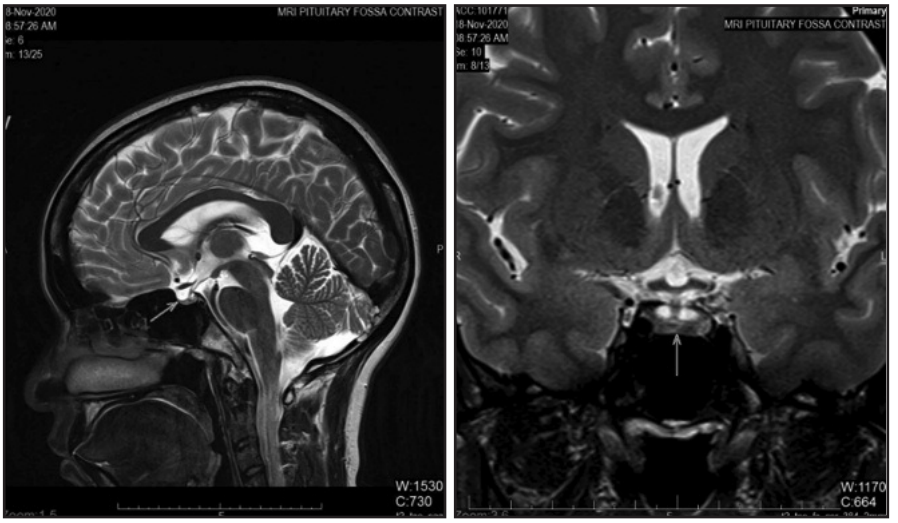

Fig. 2: MRI Pituitary Sagittal and Coronal View.

On general examination, she had a thin body build with a BMI of 22kg/m2. She had no features of hirsutism. Her blood pressure was 104/69mmHg and pulse rate was 88 beats per minute. Her thyroid was not palpable. Breast examination revealed no obvious lump, retracted nipple, or any skin lesion. However, there was an active secretion seen coming out from her both nipples upon milking, whitish in colour without any foul smelly or blood stain. Eye examination showed a normal visual field, fundoscopy, and 3rd, 4th and 6th cranial nerve. Neurology examination of the upper and lower limb was normal.

She was scheduled for blood investigation during the next visit together with opportunistic screening for cardiovascular disease. The blood investigations were listed as in Table I.

She was referred to an endocrinologist for further evaluation and expert opinion in terms of her condition. She benefited from regular follow up under primary care clinic for psychoeducation and continuous education regarding her problems. Initial abdomen and pelvic ultrasound were noted to be normal without any mass or structural abnormalities were seen to suggest ovarian pathology induced amenorhoea. She was referred to a psychiatry clinic for shared care due to her emotional stress. Repeated serum prolactin at the endocrine clinic during subsequent follow up showed increasing levels from 77.21 to 104µg/L within four months despite psychiatry intervention. She was then scheduled for MRI Pituitary to look for any mass or intracranial growth. The image is as below in Figure 2 that showed significant effacement of the anterosuperior aspect of the pituitary gland with downward displacement of the pituitary gland represent partial empty sella syndrome.

Patient was then started on tablet Cabergoline 500 mcg twice per week. She complied with the medication without any side effects. She also benefited from a counsellor follow up at a psychiatry clinic. She was then able to regain her normal menstrual cycle. Her nipple discharges were also resolved. She finally was able to experience back her usual good quality of life.

DISCUSSION

Hyperprolactinemia, despite being classically associated with gonadal dysfunction, its associations with psychological symptoms like anxiety, stress and depression has come into attention lately. For this case, she was initially diagnosed to have hyperprolactinemia with a high probability secondary to emotional stress as she was just divorced by her husband. She was referred to the psychiatry unit and was started on antidepressant, together with psychological therapy. The antidepressant that she was on is Tablet Escitalopram 20mg OD, a selective serotonin reuptake inhibitor (SSRI) with less potential to cause hyperprolactinemia. The repeated serum prolactin level after four months was noted to be increased from 77.21 to 104µg/L. Physiologically, stress from physical or psychological insult can cause an increase in the serum prolactin concentration with a magnitude of increase should not exceed 40µg/L. Women have greater increases than men, possibly due to the effect of their higher serum estradiol concentrations on the lactotroph cells with all stimuli of prolactin secretion. She decided to undergo magnetic resonance imaging of the pituitary because of the increased level despite psychological treatment.

For a patient who is found to have hyperprolactinemia, but typical symptoms and radiological abnormalities are absent, the condition of macroprolactinemia should be suspected. Macroprolactinemia is a term to describe a condition of aggregation of prolactin and prolactin antibodies in the vascular space, but not biologically active, thus, it causes no clinical symptoms abnormality. This condition can be misdiagnosed and treated as prolactin hypersecretion. However, the presence of galactorrhoea, menstrual problem, and other symptoms does not exclude the diagnosis of macroprolactinemia. The gold standard for the diagnosis of macroprolactinemia is gel-filtration chromatography, however, due to the cost and complexity of the test, polyethylene glycol (PEG) serum precipitation has been widely used as a screening method.[8]

In a condition of idiopathic hyperprolactinemia, one-third of the patients with elevated serum prolactin levels will resolve,

and in one-half of patients, the level will remain stable. But there is a study that founded a high prevalence of anti-pituitary antibodies (APA) in 25.7% of patients with idiopathic hyperprolactinemia.[9] These antibodies reduce prolactin bioactivity and delay its clearance, inducing macroprolactinemia. Antibody-bound prolactin is confined to vascular spaces and, therefore, macroprolactinemia seems to develop mostly due to the delayed prolactin clearance, rather than its increased production. It is not impossible that many cases initially diagnosed as idiopathic hyperprolactinemia were later confirmed as having macroprolactinemia.

In case of increase serum prolactin with presents of red flag symptoms, radio-imaging study is mandatory to confirm the diagnosis of prolactinoma. However, in the case of mildly elevated serum prolactin with absent of red flag symptoms, there are controversial whether to proceed with imaging or just monitor the serum prolactin level. It should be noted that microadenomas are present in about 10% of the normal population.[10] Like in this case, she might not have the symptoms of increased intracranial pressure but microadenoma cannot be excluded. Thus, radio imaging study is suggested to be done if the facility is available provided all the possible potential secondary causes of hyperprolactinaemia excluded.

As for the primary care perspective, the objectives of treatment of hyperprolactinemia are to restore and maintain the normal gonadal function, restoring normal fertility, and prevention of osteoporosis. There are benefits if primary care can monitor and manage the patient with suspected idiopathic hyperprolactinemia because the risk for macroadenoma is low, and the symptoms need to be resolved soon. Nevertheless, there is always a role for tertiary referral especially in a situation whereby the exact cause of the disease is not clear and when a patient developed alarming symptoms of increased intracranial pressure.

CONCLUSION

Diagnosis of hyperprolactinemia is challenging because of the endless list of secondary causes that can contribute to it. Primary health care may detect this condition and can manage it. However, for excluding other causes, especially for imaging studies, patients might need shared care with a tertiary setting. The prognosis of this condition is good if the cause is identified early, and patients can return to their normal life if they are properly treated. The screening for macroprolactinemia should often be considered for the correct identification of the aetiology of hyperprolactinemia.

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CASE REPORT

The effects of Goldenhar Syndrome on hearing and speech development

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SUMMARY

Goldenhar syndrome is a congenital abnormality with an incidence of 1 in 5,200 to 26,500 births. This syndrome is characterized by facial asymmetry, ear malformation, and/or defects in the eyes and vertebrae. The hearing disorder manifests as both conductive or sensorineural due to the abnormalities occurring in the inner and outer ear. We report a case of a 1-year-3-month-old child presenting with left anotia and right microtia, severe bilateral conductive hearing loss, and global delayed development. The patient was also found to have a hemifacial microsomia, a secundum atrial septal defect (ASD), and a ventricular septal defect (VSD). The patient was advised to use hearing aids and participate in speech therapy. The management of this Goldenhar syndrome patient should be done comprehensively, appropriate to the abnormalities found to achieve the best result.

INTRODUCTION

Goldenhar syndrome (GS) is a congenital condition presenting with facial, ear, and vertebral abnormalities. It is characterised by hemifacial microsomia and ear defects causing clinical manifestations such as hearing disorder due to the incomplete formation of various ear structures.[1,2]

Although this syndrome's exact etiology and pathogenesis have not yet been pinpointed, it is suspected that this condition arises from anomalies in the first and second brachial arc and/or neural crest. The interaction between genetic and environmental factors such as infection, drug use, and alcohol could play a role in this disease.[1,2]

As GS is a sporadic disease, genetic factor is not always acting as the primary determinant. Even though this disease is incurable, it is treatable according to the presenting symptoms. If GS is accompanied with hearing problems, thus a hearing aid and speech therapy are needed to increase patients' quality of life and self-esteem.[2,3]

CASE REPORT

A one-year-three-month-old male patient came to Cipto Mangunkusumo Hospital (CMH) Community ENT division, Universitas Indonesia, Indonesia, referred from the pediatrics department for a hearing examination. The patient presented with a congenital complaint of the absence of ear canals in both ears with no left earlobe, alongside a small right earlobe. The patient could only respond to loud noise such as a forcefully closed door. The patient had not been able to say meaningful words. In speech development, he started babbling at the age of 13 months. A delay in motor development was noted as the child had only been able to sit at 15 months and could not crawl, stand, or walk.

The mother denied any history of infections, hypertension, diabetes, and drug consumption during pregnancy. The patient was born at full term with a cesarean section due to breech presentation. He cried soon after delivery and weighed 2,300 grams. One week after the delivery, the patient suffered from hyperbilirubinemia and was treated with blue light therapy for two days.

At the age of three months, the patient was brought to the paediatrics clinic in CMH with complaints of dyspnoea; the patient was further found to have a leaky heart valve. The patient was then suggested to undergo routine visits as no further surgical management was deemed needed. When referred to our division, the patient weighed 9.7kg with a length of 54cm. No sign of dyspnoea was found, and vital signs were in the normal range. However, the physical examination found that the patient was normocephalic, had a hemifacial microsomia with micrognathia, right ptosis, and lagophthalmos of the left eye. In addition, ENT clinical examination found abnormalities of both ears; those are left anotia and a second-degree microtia of the right ear (Figure 1). Neurological examination revealed a global delayed development alongside left hemifacial VII cranial nerve paresis. A grade 3/6 parasystolic murmur at the left inferior sternal border with no gallop was found during cardiac diagnostic evaluation.

Brainstem-evoked response audiometry (BERA) examination—with a click stimulus rate of 27.7/second on the rarefaction—found no electrophysiological response of the fifth wave up until 80dB stimulus on both ears. Bone conduction BERA examination found an electrophysiological response of the fifth wave at 30dB on both ears (Figure 2). Masking was unable to perform due to bilateral ear abnormalities. In paediatric patients with bilateral atresia, a BERA examination is one of the best choices to identify any residual cochlear hearing function.

A secundum atrial septal defect and a small perimembranous ventricular septal defect were revealed during routine echocardiography (Figure 3).

A suspicion of vertebral deformities at level T8-10 arose from

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Fig. 1: The patient presented with hemifacial microsomia, left anotia, and right ear microtia.
Permission from the parents of the patient were obtained for the publication of this photograph.

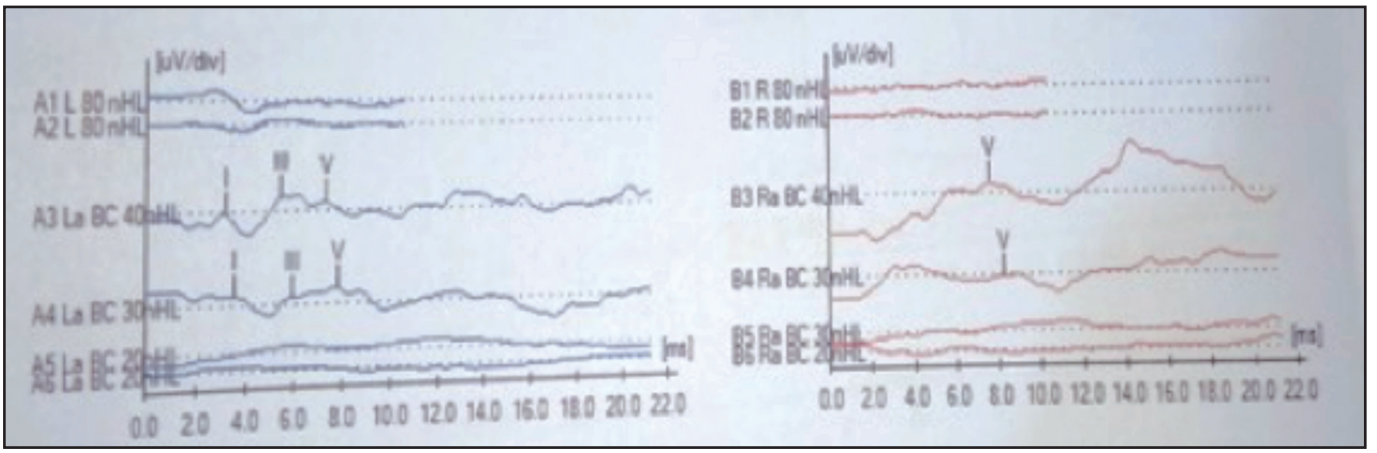

Fig. 2:

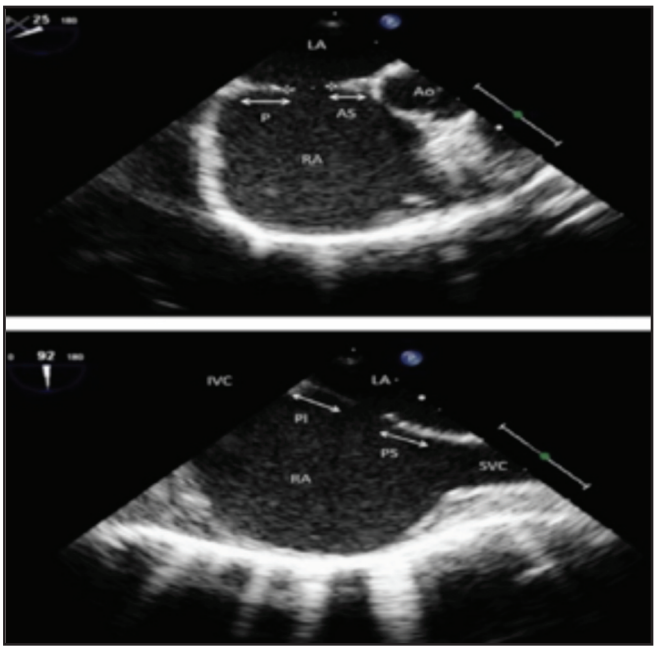

Fig. 3: Echocardiogram revealing an ASD and VSD found in the patient.

an abdominal x-ray examination (babygram with AP position). MRI imaging did not find any haemorrhage, infarction, nor intracranial lesion. However, simple contacts between the right anteroinferior cerebellar artery and V, VI, and VII right cranial nerve structures were found, albeit with no nerve compression.

The patient was diagnosed with GS based on deformities and abnormalities found on the face, ear, and heart, accompanied by global delayed development, left VII cranial nerve palsy, and severe bilateral conductive hearing loss. Therefore, by taking into account the clinical symptoms, physical examinations, and additional investigations such as the audiology examinations, the patient was confirmed to have GS, left anotia, second-degree right microtia, bilateral ear canal atresia, severe bilateral conductive hearing loss, secundum ASD and VSD.

DISCUSSIONS

The incidence of GS ranges from 1 in 3,500 to 5,600 live births and is found in 1 out of 1000 children with congenital hearing loss. There is a slight male preponderance with a ratio of 3:2 compared to that of females. Eighty-five percent of this syndrome presents unilaterally, while the remaining

10-33% occur bilaterally.[1,2] The exact aetiology of GS has not been yet fully elucidated, but it is found to be inherited in an autosomal dominant and/or recessive manner. This disease is thought to be a multifactorial condition involving interaction between genetic and environmental factors. Infectious features such as positive results of anti-CMV (cytomegalovirus) IgG, anti-rubella IgG, and anti-HSV (herpes simplex virus) IgG are thought to be the most probable cause of GS. Nevertheless, other factors such as alcohol consumption, smoking, and the use of vasoactive drugs (retinoic acid, tamoxifen, diabetes medications) during pregnancy could also contribute as precipitating factors.[4,5]

Typical clinical manifestations of GS include hemifacial microsomia, facial asymmetry, preauricular skin tag, epibulbar dermoid, and vertebral anomalies. Other craniofacial abnormalities include microsomia and outer ear, mandible, temporal bone, zygoma, outer ear, facial nerve, bones, and surrounding tissues malformation. Alternatively, the term 'oculo-auriculo-vertebral dysplasia is often used to depict this syndrome due to the accompaniment with epibulbar dermoid, auricle malformation, and fistule, alongside vertebral anomalies.[4-6]

In our case, abnormalities involving multiple organs such as eyes, ears, heart, and vertebrae were found. In addition, neurological examination revealed a VII cranial nerve palsy affecting the left side of the face, along with global delayed development.

Ear abnormalities that were found in this patient include left anotia and second-degree right microtia. It is worth noted that microtia is one of the most common abnormalities found in this syndrome, comprising 90% of all ear malformation in Goldenhar syndrome.[4,6] Other than that, the patient also had severe bilateral conductive hearing loss. The ear malformation found in this patient contributes to causing conductive hearing loss, which hindered auditory development before finally impacting speech development.[6,7]

Abdominal x-ray examination (babygram in AP position) revealed a suspicion towards T8-10 vertebral body deformities. The deformities that present in the thoracal segment contribute to the postural instability of the patient. This head-neck postural abnormality happened due to the typical craniofacial deformities of Goldenhar syndrome.[4] Poor postural control of the head, neck, and thoracal segment of the spine will negatively impact the breathing, speaking, and swallowing function. These postural problems are thus negatively affecting quality of life of the patient in the long run.[4,8]

It has been thoroughly researched and shown that postural stability and sensorimotor integration process play a vital role in the functional maturation of a child's speaking and swallowing abilities. Thus, concerns should be placed more upon the role of postural control and sensorimotor maturity.[8] Postural coordination exercises and interventions comprising postural modification have been extensively examined and proven to be correlated to a better upper airway sensorimotor integrity and ability. This, in turn, will support better sucking-breathing-swallowing cycle coordination alongside clearer and stronger speech articulation. In this case, it is also worth remembering that our patient also suffered from facial nerve palsy, adding further issues to what was an already compound problem. Many studies have reported that children with postural control failure had a higher risk of aspiration during feeding, due to the uncoordinated and non-integrated upper airway sensorimotor function. It will pose significant danger if not properly intervened.[8,9] Hence, collaboration with fellow clinicians from the medical rehabilitation division is needed to modify and exercise postural control therapy. The patient is also experiencing delayed motor development, making the importance of physiotherapy under the guidance of medical rehabilitation experts more prominent, besides the hearing aid use and therapy speech itself.

The parents have received information regarding treatment plans—specific to hearing problems—in which a conventional bone-conduction hearing aid, called bone-anchored hearing aid (BAHA), will be used. BAHA is chosen as it is a good option for hearing habilitation in bilateral microtia-atresia cases and can improve the quality of life of the patients significantly in the long run. Besides, BAHAs are relatively accessible in terms of availability and pricing.[5-7,10] The parents were also educated regarding speech therapy plans after hearing aid usage and the possibility of surgical intervention. One of the intervention choices is reconstruction surgery which will address the patient's microtia or ear malformation. It will only be done when the patient has reached the appropriate age.[4,6]

Hence, a solid collaboration between fellow clinicians in the field of ENT, medical rehabilitation, and paediatric neurology is of the utmost importance in ensuring the best possible development in children with GS.

CONCLUSIONS

Goldenhar syndrome is a congenital disease with a variety of risk factors and multi-organ involvement. The hearing disorder is one of the culprits behind the delayed speech and hearing development in patients. Therefore, an accurate diagnosis coupled with comprehensive multidisciplinary management is needed to achieve the best results for the patients.

ACKNOWLEDGEMENTS

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CASE REPORT

I think I have double vision? Or not? Internuclear Ophthalmoplegia following right lacunar infarct

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SUMMARY

Internuclear Ophthalmoplegia (INO) is an inability of the ipsilateral adduction with a contralateral horizontal abducting saccade on attempted gaze to the contra-lesion side. Injury to the medial longitudinal fasciculus (MLF) will obstruct the signalling pathway between the ipsilateral abducens nucleus and the contralateral medial rectus muscle. Infarction accounts for 38% of INO cases with mostly being unilateral (87%), followed by demyelination (34%), which mostly being bilateral (73%). Lacunar infarct is the most common ischemic stroke. INO can be easily missed due to its subtle presentation with no complaints from the patients. A full cranial nerves assessment, includes the extraocular muscles movement, is important. Ischemic and demyelinating INO typically recover. We present here of a case of INO following right lacunar infarct in a 72-year-old Malay woman. She had hypertensive crisis due to missed medications. Her blood pressure was well controlled throughout the hospital admission and finally she was discharged home with continuation of care at her primary facility.

INTRODUCTION

Internuclear ophthalmoplegia (INO) is a supranuclear eye movement disorder, characterized by the disorder in horizontal gazes. In the older patients, stroke is a common aetiology. Less common causes are traumatic, neoplastic, inflammatory or infectious aetiology. INO presents with an ipsilateral adduction deficit (partial or complete) with a contralateral, dissociated, horizontal abducting saccade on attempted gaze to the contra-lesional side.

CASE REPORT

A 72-year-old Malay woman presented to the Emergency Department (ED) of University Malaya Medical Centre (UMMC) with sudden onset of slurred speech, left sided body weakness and right sided facial asymmetry. Prior to this, she missed her antihypertensive medications for 4 days as she was travelling to another state in Malaysia. On arrival at the ED her blood pressure was 202/100mmHg, with reduced strength of her left lower limb. She noticed that she occasionally had double vision. Her daughter noted that the patient occasionally had some 'weird' movements of the eyes. Otherwise, she had no other ocular symptoms.

Her vision on the unaided Snellen was 6/24, pinhole 6/9. Both eyes were orthophoric. No ptosis noted (Figure 1A). On the extraocular movement examination, full dextroversion was seen (Figure 1B). However, limitations were noted on adduction of her right eye with left eye showed saccades on levoversion (Figure 1C). Convergence is preserved (Figure 1D). Confrontational visual field was normal on both eyes. The other ocular examinations were normal.

The patient was restarted on her antihypertensives and being put on ambulatory blood pressure monitoring. She was referred to our neuromedical team and underwent physiotherapy. Finally she was discharged home with continuation of care at her primary facility.

DISCUSSION

INO is an inability of the ipsilateral adduction with a contralateral horizontal abducting saccade on attempted gaze to the contra-lesion side.[1] According to the Herring's law of equal innervation, increased innervation to the underacting adducting muscle, results in an enhanced stimulus to the contralateral abducting muscle.[2]

INO is caused by damage to the interneuron between the two nuclei of cranial nerves VI and III. This interneuron is called the medical longitudinal fasciculus (MLF). The higher cortical centres such as the frontal eye field, occipital and parietal lobes send signals to the paramedian pontine reticular formation (PPRF). It further relays the information to the ipsilateral abducens nucleus (CN VI). The nuclei will send the signal through the MLF to the contralateral medial rectus muscle. The activation of the ipsilateral lateral rectus and contralateral medial rectus produces a horizontal conjugate movement. INO is named by the side of the adduction deficit, which is ipsilateral to the MLF lesion. Causes of damage are due to such as demyelinating, ischemic, neoplastic and inflammatory in the pons or midbrain. An ischemic INO is due to the ischemia in the vertebrobasilar system, which is supplied by branches of the basilar artery. Infarction accounts of 38% of INO cases, most of these are unilateral (87%). Demyelination is 34% and most of them (73%) are bilateral.[3]

The diagnosis is made clinically with the conjugate movements. From the computed tomography (CT) scan or Magnetic Resonance Imaging (MRI), the site of damage can be assessed. The prognosis of INO depends on its aetiology. Ischemic and demyelinating INO usually recover.

Lacunar infarct is the most common ischemic stroke, resulting from the occlusion of the small deep penetrating arteries that arise directly from Circle of Willis, cerebellar

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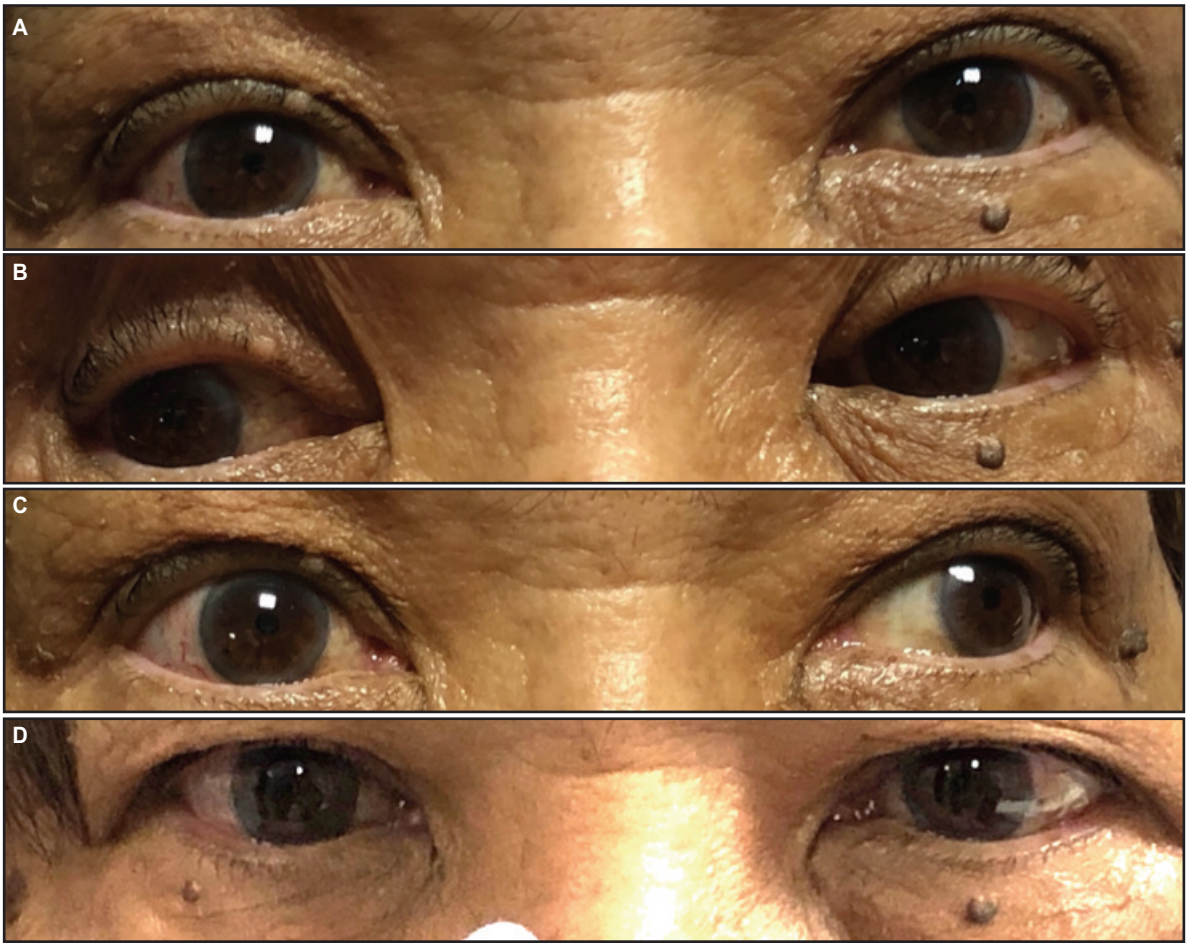

Fig. 1: Extraocular movement examination. A: A general appearance of the eyes were orthophoric and no ptosis, B: Full range of dextroversion, C: Limited levoversion of the right eye, D: Both eyes were able to adduct in the convergence test.

arteries and basilar artery. In the lacunar strokes, true cortical signs such as aphasia, visuospatial neglect, gaze deviation and visual field defects. Five classical lacunar syndromes are described: pure motor stroke, ataxic hemiparesis, dysarthria, pure sensory stroke, and mixed sensorimotor stroke.[4] Two proposed occlusive mechanisms are microatheroma and lipohyalinosis. An embolic cause is assumed, if no evidence of small vessel disease was found. Advanced age, chronic hypertension, smoking, diabetes mellitus and hypercholesterolemia are risk factors. In a study done by Linxin et al., the maximum BP in the 5 years before the stroke event, was higher in patients with lacunar events.[5]

Short-term high dose of aspirin can be given within 48 hours. For long term prevention of recurrence, the risk factors such as hypertension, and diabetes mellitus should be kept well controlled. Rehabilitation after stroke can be done through occupational therapy, speech therapy and physical therapy interventions. Family support plays an equal vital role in rehabilitation of INO patients.

CONCLUSION

INO can be easily missed during the acute presentation, with the subtle symptoms and signs. A full cranial nerves assessment, including the extraocular muscle movements, should be included. Lacunar stroke is the most common ischemic stroke, which has a high association in unilateral INO cases.

DECLARATION OF CONFLICTING INTEREST

The authors declared no potential conflicts of interest with respect to the authorship and/or publication to this article.

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Clots in tuberculosis

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SUMMARY

Tuberculosis (TB) is a common communicable disease. Active TB infection may be complicated by both venous and arterial thrombosis which are often under-recognised. We report two patients with incidental TB associated thrombosis involving different venous systems. Both responded to anticoagulant and anti-tuberculous therapy (ATT). Patients with tuberculosis are at risk of VTE and careful monitoring for venous thromboembolism (VTE) is needed during ATT. Our case illustrates the importance of having a high index of suspicion for silent VTE as it may complicate active TB infection.

INTRODUCTION

TB is a common communicable disease caused by Mycobacterium tuberculosis (MTB). The incidence appears to be rising worldwide.[1] Although all age groups are at risk, the frequency of tuberculosis (TB) appears to be highest in the 34 to 45-year age group, with an increased incidence in the elderly. The majority of patients with TB have involvement of one or more organs. The organs which are frequently involved are the lung, pleura, lymph nodes, gastrointestinal tract, spine, eyes and genitourinary tract. Active TB has been associated with venous thrombosis (VT) and less commonly arterial thrombosis. We report two patients diagnosed with TB who had incidental findings of VT. We describe the investigations, treatment and outcome.

CASE REPORT

Case No. 1

A 39-year-old woman was diagnosed with disseminated TB with involvement of the lungs and peritoneum. She presented with a 2-month history of intermittent fever and abdominal pain. On examination her vital signs were stable with coarse crepitation in the left lower zone of the lung with presence of ascites. The peritoneal fluid was exudative biochemically. Both sputum and peritoneal fluid were positive for MTB polymerase chain reaction. Computed tomography (CT) of the chest showed multiple small lung nodules, ground-glass opacification in both lungs with mediastinal lymphadenopathy (figure 1 A&B).

She was initiated on anti-tuberculous therapy (ATT, AKURIT-4). One week later, she developed acute hepatitis and required bridging therapy with streptomycin, ethambutol and moxifloxacin. Alanine transaminase increased from 44 U/L to 369 U/L with elevated bilirubin of 38 mmol/L. The serum albumin was 30 g/L. The platelet level and fibrinogen level were both normal. Due to persistent hepatitis and prolonged international normalise ratio of up to 2.69, ultrasonography (USG) of the hepatobiliary system (HBS) was performed. This revealed an incidental portal VT with normal liver architecture and the presence of ascites (figure 1 C&D).

Anti-cardiolipin, anti-beta 2 glycoprotein, anti-double-stranded DNA and anti-nuclear antibody tests were negative. We did not initiate anticoagulant therapy due to the presence of prolonged INR. Outpatient review at 2 weeks showed improvement in clinical symptoms with complete resolution of ascites and residual thrombus in the portal vein on ultrasonography (USG) of the abdomen. Oral warfarin was initiated at a dose of 3 mg daily. She achieved the therapeutic international normalise ratio without the need to increase the dose. A repeat USG at 3 months showed complete resolution of the thrombus and the warfarin was discontinued.

Case No. 2

A 55-year-old man with poorly controlled type 2 diabetes mellitus was diagnosed with smear-positive pulmonary TB. He presented with cough for 6 months and a 2-week history of intermittent fever and dyspnoea. On examination his temperature was 39°C, he was tachypnoeic with an oxygen saturation of 94% on room air. There were bronchial breath sounds in the right upper zone, coarse crepitation and stony dullness in the right lower zone of the lung. Chest radiograph revealed a right hydro-pneumothorax with pleural thickening. A small-bore chest drain was inserted.

Laboratory investigation revealed leucocytosis (white cell count of 28.4x109/L), normocytic normochromic anaemia (haemoglobin 10.4 g/dL), Erythrocyte sedimentation rate was 107 mm/hr and C-reactive protein was 11.24mg/dL. Sputum was positive for acid-fast bacilli which were later culture positive. Bacterial sputum and blood cultures were negative. We initiated ATT therapy consisting of isoniazid, ethambutol, rifampicin, and pyrazinamide.

There was persistent fever and poor resolution of the right pleural effusion. A contrast-enhanced computed tomography (CT) of the thorax revealed incidental findings of extensive thrombosis involving the right brachiocephalic, right internal jugular, subclavian and axillary veins (figure 1 E). Further aetiological investigations of thrombosis which included anti-nuclear antibody, protein S, protein C, and anti-thrombin levels were negative. An echocardiogram

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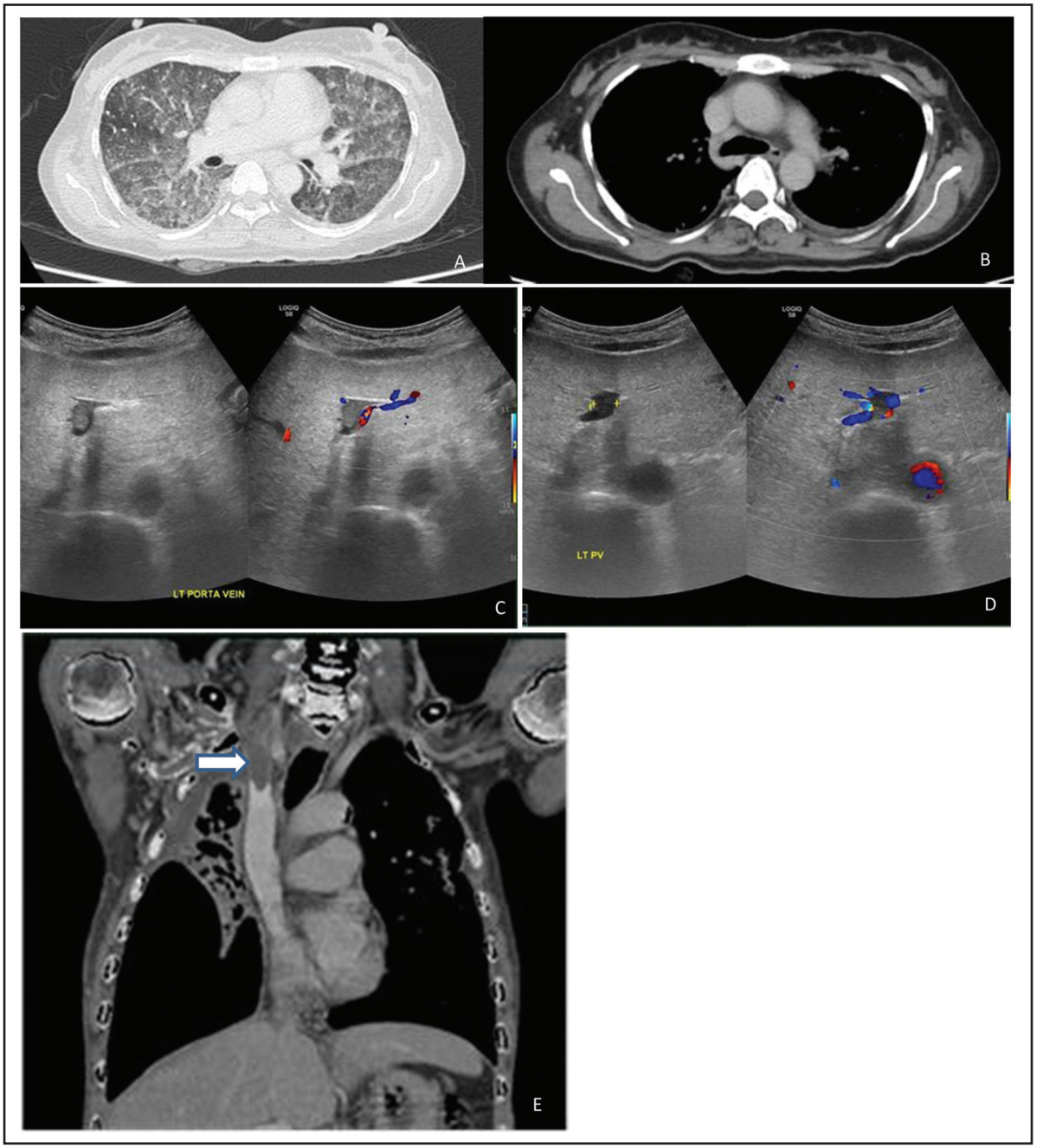

Fig. 1: (A) CECT thorax showed multiple small lung nodules, ground glass opacification in both lungs. (B) . CECT thorax showed mediastinal lymphadenopathy. (C&D) USG Doppler of the portal vein showed residual thrombosis at 2 weeks' interval. (E) CECT thorax showed filling defects in right brachiocephalic, right internal jugular, subclavian and axillary veins.

revealed a normal left ventricular ejection fraction. Ultrasound Doppler of both lower limbs excluded the presence of deep venous thrombosis. We initiated warfarin at a dose of 6 mg daily and continued the ATT for 6 months. He achieved the therapeutic INR. A repeat CT thorax at 6 months showed complete resolution of the thrombosis.

DISCUSSION

Active TB infection can result in a hypercoagulable state leading to an increased risk of both venous and arterial thrombosis. This thrombotic phenomenon is rare with a prevalence of 1.5 to 3.4 % and can occur as either a presenting feature, a complication or sequelae during the course of TB infection.[2] Up to a third of cases occur in the first week of disease.[2] TB is an independent risk factor for thromboembolism with the reported risk almost as high as that of malignancy.[3]

The thrombotic phenomena may involve the portal venous system.[4] This is likely a consequence of the tuberculous inflammation of the porta hepatis or systemic

prothrombotic.[4,5] Other postulations include periportal tuberculous lymphadenitis leading to portal venous thrombosis with portal hypertension.[6] Portal vein thrombosis can cause serious complications such as bowel ischemia and gangrene by extending to the superior mesenteric vein.[6]

It is postulated that TB associated thrombosis is caused by elevation of plasma fibrinogen coupled with impaired fibrinolysis, elevated fibrin degradation products, decreased prothrombin levels, anti-thrombin III and protein C level.[7] Active TB induces the expression of a tissue factor in monocytes-macrophages. It also causes a release of pro-inflammatory cytokines (tumour necrosis factor α, interleukin 1, and interleukin 6 which results in a chromogenic vascular endothelium.[7] Local compression by enlarged lymph nodes may cause venous obstruction or thrombosis. This hypercoagulable state is associated with raised antiphospholipid antibody levels in TB which usually normalises after a month of ATT. Both of our cases had CT evidence of severe pulmonary involvement with the presence of cavities in the second patient indicating a more severe inflammation and hypercoagulable state predisposing the patients to thrombosis.

The prompt initiation of ATT usually results in the improvement of haemostatic abnormalities as early as the first month of treatment.[8] Rifampicin is a potent inducer of hepatic cytochrome P450 and increases the catabolism of warfarin. Co-administration of rifampicin and warfarin may result in higher warfarin dose requirements. Rifampicin itself may induce thrombosis by binding to platelets and erythrocytes to form immune complexes. To date, no reported studies has addressed the benefit of novel anticoagulants in combination with ATT following the failure of vitamin K antagonists to achieve therapeutic INR.

There is a wide variation in treatment regimes in TB related thrombosis from published case reports.[4-8] The commonest reported regime is low molecular weight heparin (LWMH) followed by warfarin.[4-8] The earliest resolution of thrombus was reported at 3 weeks. A retrospective study showed that the majority of patients with concurrent pulmonary TB and deep VT required at least 3 months of anticoagulant treatment for the resolution of thrombus.[2] Both of our patients showed thrombosis in the different venous systems and resolved with warfarin treatment 3 and 6 months, respectively.

There is equipoise in the treatment of portal vein thrombosis (PVT). In cases of non-cirrhotic, non-malignant acute PVT, the American College of Chest Physicians recommends anticoagulation for symptomatic patients, whereas the American Association for the Study of Liver Disease advocates anticoagulation regardless of symptomatology.[9,10]

Our two cases describe silent VTE complicating tuberculosis. Patients with tuberculosis are at risk of VTE and careful monitoring for VTE is needed during the course of ATT.

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CASE REPORT

Infantile intracardiac thrombus in severe encephalo-myocarditis

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SUMMARY

Myocarditis is an uncommon disease in childhood and has a wide range of clinical presentations, from subtle to devastating and thus requires a high index of suspicion. Intracardiac thrombus formation following myocarditis is rare and thus its management remains challenging and not well defined. We report a child whom presented with a viral prodrome, rapidly deteriorated into multi organ failure and developed fulminant viral myocarditis with encephalitis that was complicated with an intracardiac thrombus formation. We describe the challenges faced, the successful medical treatment offered and propose factors that can help guide appropriate treatment.

INTRODUCTION

Myocarditis is an uncommon disease in childhood that often follows cardiotropic viral infections and can lead to significant morbidity including cardiac failure, thrombosis, arrhythmias, dilated cardiomyopathy, and sudden death. Intracardiac thrombus formation following myocarditis is rare and its management remains challenging and not well defined. We report a case of successful medical treatment of a 3-month-old previously well female infant with fulminant viral myocarditis and encephalitis that was complicated with an intracardiac thrombus formation and highlight the factors that can help guide appropriate treatment.

CASE REPORT

A 3-month-old previously well female infant was admitted to a peripheral hospital for high grade fever, recurrent vomiting, and papulovesicular rashes over the wrists and knees for three days. She was mildly dehydrated and there were no abnormal physical signs. Initial laboratory investigations revealed C-reactive protein 198.2g/dL, hemoglobin 10.9g/dL, white cell count 17.25 x 10^9/L (neutrophil 53%, lymphocyte 38%, monocytes 8%, eosinophil 1%), platelet count 783 x 10^9/L and transaminitis (aspartate aminotransferase 126 U/L, alanine transaminase 108U/L). She was treated for a presumed bacterial infection with intravenous (IV) ceftriaxone and IV hydration. On the third day, she experienced sudden clinical deterioration with increasing tachypnoea (58/min), tachycardia (170/min) and a brief seizure that aborted spontaneously. Following IV fluids resuscitation, her tachypnea and tachycardia worsened, she was electively ventilated and was transferred to our center for continued care.

Her ventilation was optimized on arrival. Blood pressure 90/45mmHg. Cardiovascular examination found shifted apex beat, tachycardia with gallop rhythm, and hepatomegaly 2.5cm from the right costal margin. Neurologically, she had sluggish pupil reactivity, hypertonia, and persistent thumb adduction with fisting. Faint healing papulovesicular rash visualised over knees and wrists bilaterally. Laboratory investigations revealed elevated biomarkers (troponin T 164.2ng/L, creatine phosphokinase 696U/L, creatine kinase-MB 9.4ng/mL, aspartate aminotransferase 2735U/L, alanine transaminase ALT 934, lactate dehydrogenase 3452U/L, ferritin 541.6ng/ml). Chest radiograph displayed bilateral interstitial opacities with mild cardiomegaly, consistent with pulmonary edema. Electrocardiography showed sinus tachycardia with right ventricular hypertrophy (Figure 1). Our preliminary diagnosis was fulminant viral myocarditis, pulmonary edema, and encephalitis.

The first echocardiogram demonstrated dilatation of left heart chambers, poor left ventricular function with left ventricular ejection fraction (LVEF) of 31%. There was mild to moderate mitral and tricuspid regurgitation with no evidence of ventricular non-compaction. No pericardial effusion or intracardiac thrombus was visible.

Cerebrospinal fluid and stool for polymerase chain reaction (PCR) and culture were negative for cardio-neurotropic viruses.

Electroencephalography showed diffusely attenuated background with lack of variability and consisted of low amplitude delta activity (up to 75uV) intermixed with theta activity and bilateral sleep spindles. Magnetic resonance imaging (MRI) brain showed multiple tiny punctate foci that was hypointense on T1 weighted imaging, hyperintense on T2 weighted imaging and restriction diffusion on ADC and DWI sequence, over the thalamus and cerebellum bilaterally (Figure 2). These changes are in keeping with an acute arterial ischemic insult.

Treatment initiated included IV acyclovir and IV ceftriaxone, and for congestive heart failure IV milrinone infusion, low dose IV dopamine and IV furosemide. Intravenous immunoglobulin (IVIG) (2g/kg) infusion was started as adjunctive treatment for viral associated encephalitis and myocarditis.

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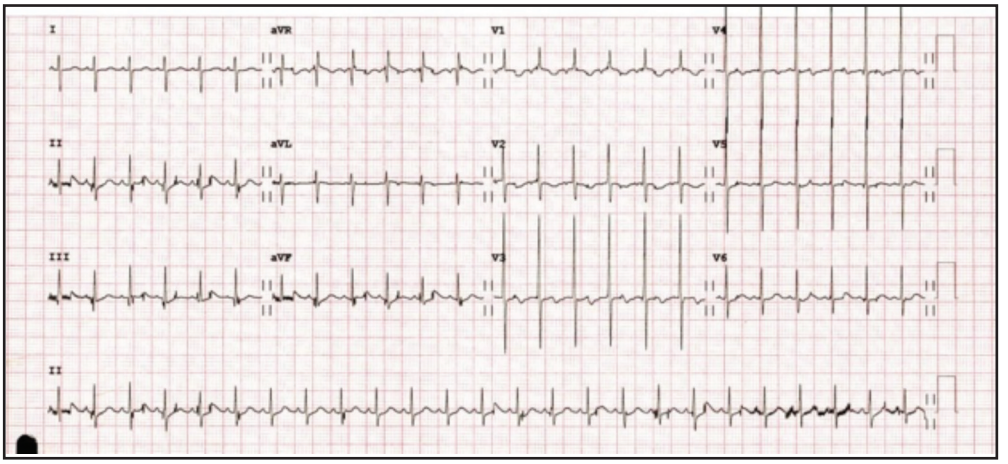

Fig. 1: Electrocardiography showing sinus tachycardia (heart rate 152/min) with right ventricular hypertrophy.

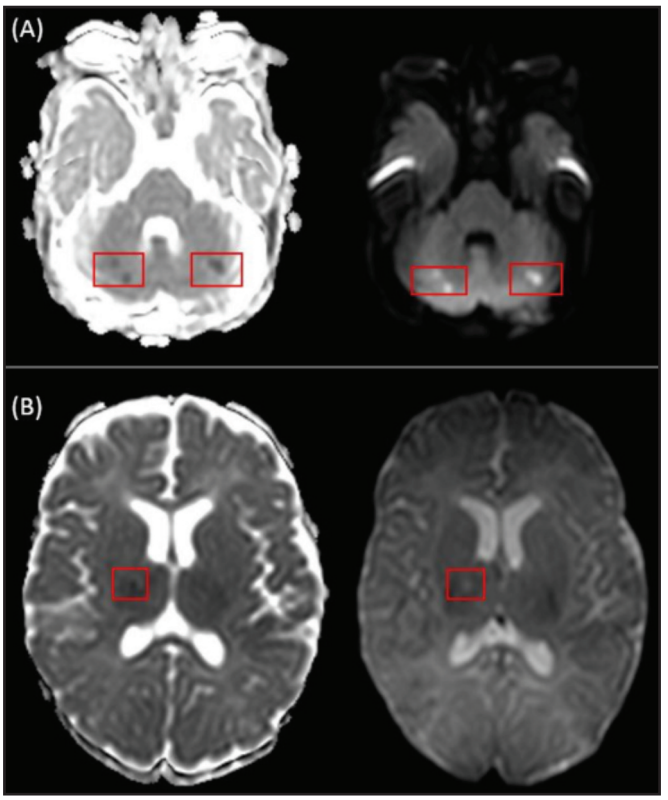

Fig. 2: MRI brain (Apparent diffusion coefficient/Diffusion weighted imaging sequence) showing restricted diffusion (red box) over bilateral cerebellar white matter (A) and right thalamus (B).

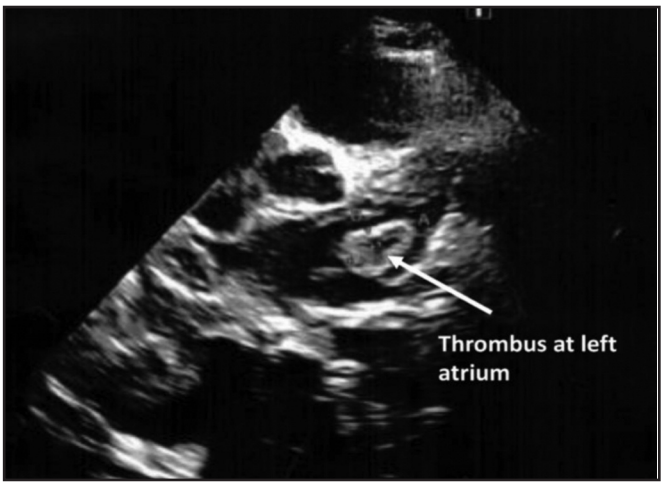

Fig. 3: Echocardiography on day 6 admission showed a large left atrial thrombus at the left atrial appendage and extending to the body of the left atrium, measuring 8mm x 11.4mm.

LA: left atrium, RA: right atrium, LV: left ventricle, RV: right ventricle, Ao: aorta

Video 1: https://drive.google.com/file/d/1h2Z1x4L3y8WRDx37LX6r67Lh5Heh-Vqu/view?usp=sharing

The patient was ventilated for eight days, then weaned to continuous positive airway pressure, and finally nasal oxygen that was discontinued at day 15 of admission.

Echocardiogram on day-6 of admission detected a large left atrial thrombus at the left atrial appendage and extending to the body of the left atrium, measuring 8mm x 11.4mm. It was pedunculated and non-mobile. Left ventricular function was impaired with LVEF of 44% (Figure 3 Video 1). Hematological investigations did not reveal hypercoagulopathy. The was no cardiac arrhythmia. The stasis of blood within the poorly functioning myocardium had likely resulted in the thrombus formation.

Surgical thrombectomy was initially considered given the risk of thromboembolism. However, as our patient remained critically ill with severe neurological insult and impaired cardiac function, a trial of medical treatment was jointly agreed upon. IV heparin infusion was commenced for the first two weeks followed by subcutaneous low molecular

weight (LMW) heparin. There was a consistent reduction in the size of the intracardiac thrombus over four weeks with improved cardiac function (LVEF of 62-70%). Complete resolution of the intracardiac thrombus was achieved at day 43 post-admission with no occurrence of thromboembolic events.

She made a gradual neurological recovery with no seizures witnessed throughout admission. She developed transient cerebral salt wasting requiring sodium chloride supplementation for 1 month. The long-term neurological prognosis remains guarded.

DISCUSSION

Myocarditis is defined as an inflammatory disease of the heart muscle diagnosed by established histological, immunologic, and immunohistological criteria. Patients of all ages may be affected, but the majority of cases occur in infants and teenagers; particularly in the first year of life.

In a Finnish national registry study of children, the incidence of myocarditis was approximately 2 in 100,000 patient-years.[1] There are nearly 20 known cardiotropic viruses that have been implicated as a cause for myocarditis, of which enteroviruses, particularly coxsackie group B serotypes, are the commonest. More recently, viral genomes from endomyocardial biopsies have shown parvovirus B19, human herpesvirus 6, and adenovirus to be increasingly common.[1]

The cardiotropic virus in myocarditis can be identified by viral PCR of endomyocardial biopsy, respiratory tract, blood, urine or stool samples. The absence of a positive PCR, however, does not exclude a viral cause as the viremic phase may have resolved before cardiac manifestations.

Clinical presentations of paediatric myocarditis can vary from subtle findings of tachypnoea and tachycardia to fulminant myocarditis and cardiogenic shock, within days to weeks of a viral infection. It is not unusual for the fulminant form to be mistaken for sepsis or severe dehydration in children, and commencement of large volumes of resuscitation fluids can lead to pulmonary oedema and cardiovascular collapse, as in our case. A high index of suspicion is necessary for early diagnosis as clinical judgment, with supporting ancillary tests, remains the mainstay of diagnosis.

The general approach for myocarditis is supportive. Some centres advocate the early use of intravenous immunoglobulin (IVIG) in children due to its antiviral and anti-inflammatory effects. One paediatric trial from the Cochrane Collaboration Review of 2015 (Bhatt 2012) suggested that benefits may be seen in children with acute encephalitis syndrome complicated by myocarditis.[2]

Treatment of congestive cardiac failure include diuretics, afterload reduction, inotropic support, anticoagulation, arrhythmia management, and ventilatory support. Low dose dopamine (≤5µg/kg/min), dobutamine and low-dose epinephrine (≤0.05µg/kg/min) help increase contractility via their actions on myocardial beta-adrenergic receptors while minimizing associated vasoconstriction. Milrinone has positive inotropic and vasodilatory effects without increasing myocardial oxygen consumption. Those with more severe cases of myocarditis may require circulatory support in the form of extracorporeal membrane oxygenation or ventricular assist devices.[1]

The risk of thrombotic events in children with myocarditis is currently unknown, leading to uncertainty regarding the need for antithrombotic therapy. A retrospective study of 28 paediatric patients with myocarditis reported that 11.1% experienced intracardiac thrombosis.[3]

Several factors place children with myocarditis at increased risk of thrombus formation, including stasis of blood in a poorly functioning heart, and inflammation of the myocardium and surrounding structures. Some studies in children with dilated cardiomyopathy suggest that those with severely diminished or rapidly deteriorating ventricular function are at highest risk of thrombus formation.[3] The biggest concern of intracardiac thrombus is its risk of peripheral embolization particularly to the brain and kidneys leading to high mortality with a reported embolisation risk of 13%.[4]

The treatment approaches for paediatric intracardiac thrombus described include thrombolytics (tissue plasminogen activator (t-PA), streptokinase, urokinase) and/or anticoagulants (classical/LMW heparin, warfarin) or surgical thrombectomy.[5] The traditional therapy for intracardiac thrombi in paediatric patients has been surgical thrombectomy, but there are increasing reports of successful non-surgical strategies.[4]

Patients with thrombus causing important hemodynamic abnormalities (obstruction to flow with symptoms or signs, interference with valve function) or at high risk of embolisation (poorly adherent or mobile thrombus, thrombus located in an area of high flow) should receive thrombolytic therapy or surgical thrombectomy.

Balancing the risk of surgical thrombectomy versus medical therapy is difficult. With anticoagulation therapy, a pedunculated thrombus risks becoming more unstable due to additional narrowing of the thrombus stalk and thus promoting embolism.

Conversely, the presence of underlying myocarditis with poor left ventricular function would lead to additional deterioration of myocardial function following cardiopulmonary bypass and cardioplegic arrest. Furthermore, patients with pre-operative neurological insult are vulnerable to cardiopulmonary bypass related neurologic injury. In view of this, we felt intravenous heparin infusion was the appropriate initial first line treatment option. Further, we decided against the use of thrombolytic therapy as this was an acute thrombus, and it has shown to be associated with higher mortality due to major bleeding in young infants.[5]

We recognise that the multiple punctate lesions with restricted diffusion seen in the MRI brain, may represent infarct of end arteries. Considering the clinical scenario, multiple factors could account for this, however embolic infarct would be the most likely pathology.

Intravenous (IV) heparin has been shown to be highly effective and safe for thrombi with high-risk features for embolization then once stable switch to low molecular weight (LMW) heparin.

The early use of IV immunoglobulins, inotropic and vasodilatory therapy, and aggressive anticoagulation therapy had likely contributed to the complete resolution of the intracardiac thrombus and normalization of left ventricular function.

Despite extensive investigations, we were unable to identify the causal organism. The distributive pattern of papulovesicular rashes over her limbs prior to the onset of neurological, and cardiovascular compromise though nonspecific, suggests the possibility of enterovirus infection. The rash in toxic shock syndrome due to Staphylococcal and Streptococcal infections usually present with mucosal and conjunctival hyperaemia, diffuse erythroderma, necrotizing fasciitis and desquamation of palms and soles, none of which was present in our case.

CONCLUSION

Intracardiac thrombus formation following fulminant myocarditis in children is rare but has potentially fatal consequences. Treatment decisions of such cases with medical anticoagulation or surgical thrombectomy should be guided on a case-to-case basis by the patient's hemodynamic status, cardiac function, and thrombus characteristics. The role of prophylactic anticoagulation therapy in children with myocarditis remains unclear and should be a focus of future research.

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