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The Medical Journal of Malaysia
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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.
NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021; 11; 398(10304): 957-80.

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

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

Corporate Author
World Health Organization, Geneva. 2019. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: seventh report of a WHO study group. WHO Technical Report Series, No. 1015.

NCD Risk Factor Collaboration (NCD-RisC). Rising rural body-mass index is the main driver of the global obesity epidemic in adults. Nature 2019; 569: 260–64.

World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report 85, April 14, 2020. [cited April 2020] Accessed from: https://www.who.int/docs/defaultsource/coronaviruse/situationreports/20200414-sitrep-85-covid-19.

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

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All original papers which are accepted for publication by the MJM, will be considered for the 'Best Paper Award' for the year of publication. No award will be made for any particular year if none of the submitted papers are judged to be of suitable quality.

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Original Articles

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Characteristics of patients with tuberculosis and the associated factors with TB-related mortality in a rural setting in Sarawak, Malaysia: A single-centre study

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ABSTRACT

Introduction: Tuberculosis (TB) in Malaysia has estimated incidence and mortality rates of 81 cases per 100,000 people-year and 4.9 per 100,000 populations, respectively. This study aimed to study the characteristics of rural TB patients and their mortality outcomes.

Materials and methods: This is a retrospective observational study involving real-world data analysis, looking into TB patients in Lubok Antu Health Clinic by obtaining data through clinic cards, from 1 January 2019 till 31 December 2020. Statistical significance was $p < 0.05$.

Results: Eighty-four patients were included. Fifty-two (61.9%) were male. Median age was 58.5 (39–67). Forty-six (54.8%) had smear-positive TB. Seventy-eight (92.9%) were alive at treatment completion. Fifteen (17.9%) experienced adverse drug reactions. Estimated prevalence and mortality rate were 7.1% and 10.7 per 100,000 populations, respectively. Regression analyses revealed that drug reaction was significantly associated with compliance [OR = 8.38 (95% CI: 1.26, 55.53), $p = 0.029$]. Patients compliant with treatment were more likely to survive [OR = 12.5 (95% CI: 1.61, 97.34), $p = 0.028$].

Conclusion: Compliance with TB treatment should be emphasised to reduce TB-related mortality.

KEYWORDS:
Compliance; prevalence; mortality; rural; tuberculosis

INTRODUCTION

Tuberculosis (TB) remains a disease of public health importance in Malaysia. According to World Health Organization (WHO) Global Tuberculosis Report 2020, there were 25,837 cases of the disease nationwide in 2018 with an estimated incidence of 81 cases per 100,000 people-year in this developing country.[1] Although it is lower as compared to worldwide incidence of 130 cases per 100 000 people-year in 2019,[2] more work still needs to be done in this field. It is one of the top 10 causes of death worldwide, ranking above HIV/AIDS as a leading cause of death from a single infectious agent. Around 1.3 million deaths among HIV-negative individuals were attributed to TB globally in 2019, with an addition of around 208,000 deaths among HIV-positive people.[2] South-East Asia has 44% of worldwide TB cases among WHO regions, which has important weightage in TB prevalence.[2] Malaysia being in among South-East Asia countries has to contribute to this nationwide effort in curbing the expansion of disease. While TB-related mortality in Malaysia showed a reducing trend,[3] the number of TB incidence is still significant and has yet to achieve the global end TB milestone.[4]

WHO and the International Union Against TB and Lung Disease recommend the effort of contact tracing in order to improve the detection of TB cases.[5] Hence, local studies on the epidemiology and population dynamic of the disease need to be supported in order to curb this important public health problem. The risk of developing or reactivation of TB is reported to be higher in high-risk population with predisposing factors such as HIV, DM, and immunocompromised.[6] Hence, regular screening for asymptomatic high-risk population in high-risk area might be a wise step in TB detection.

Few recent studies have been done to study the local epidemiology and characteristics of TB population in rural area, especially in Sarawak, Malaysia where the incidence of TB is staggering with the high inflow of immigrants, causing TB incidence to be difficult to control. Hence, this study aims to study the characteristics of rural TB patients and their mortality outcomes to supplement the effort of national TB program, in line with the global effort to expand TB care and control. The objectives of this study include determining the prevalence and mortality rate among TB patients in Lubok Antu district; and determining factors associated with TB mortality, factors associated with compliance with anti-tuberculous therapy, factors associated with the development of symptoms and factors associated with the development of adverse drug reactions.

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MATERIALS AND METHODS

Study Patients

This is a retrospective observational study (case series) looking into patients who were diagnosed with TB and receiving treatment in primary healthcare facility in a rural setting, comparing the factors between patients who died from TB and patients who survived.

Data of all patients diagnosed with TB and received treatment in Lubok Antu Primary Healthcare Clinic, Sri Aman Division, Sarawak, Malaysia were obtained retrospectively through a review of their medical records. Lubok Antu Health Clinic is the mother clinic that covers all TB patients within Lubok Antu district which consisted of eight health clinics, namely Lubok Antu Health Clinic, Engkelili Health Clinic, Batang Ai Health Clinic, Merindun Health Clinic, Nanga Kesit Health Clinic, Nanga Stamang Health Clinic, Nanga Delok Health Clinic, and Nanga Patoh Health Clinic. Hence, although this study only involved data collection from a single centre, it represented a wide coverage of the local rural population.

Information collected include patients' age, sex, race, marital status, smoking status, alcohol history, new cases versus previous TB, HIV status, types of TB, chest X-ray findings, sputum smear status, drug resistance status, treatment duration, compliance to treatment, clinical symptoms at presentation, adverse drug reactions upon receiving TB treatment, and TB-related outcomes. Compliance to treatment was assessed by reviewing patients' directly observed treatment (DOT) record.

The inclusion criteria of this study were all patients diagnosed with TB, either through symptom or contact screening, and received treatment in Lubok Antu Health Clinic, from 1 January 2019 till 31 December 2020. The exclusion criteria include patients who were initially treated as TB but later confirmed to be other diagnosis.

Outcome Measure

The end-point of this study was TB-related mortality prior to or upon completion of treatment.

Statistical Analysis

This study was analysed using the IBM SPSS Statistics version 20.0. Quantitative variables are presented in frequency (percentage) for categorical data and median (interquartile range) for continuous data with skewed distribution. Analysis of quantitative variables in comparison between groups was done using Mann-Whitney U test (non-parametric). Analysis of categorical variables was performed through Pearson's chi-square test or Fisher's exact test wherever applicable. Statistical significance was set at $p < 0.05$. Logistic regression analysis was done to determine the independent variables associated with TB mortality.

RESULTS

Patients' Characteristics

A total of 84 patients were recruited into this study, 40 (47.6%) from year 2019 and 44 (52.4%) from year 2020. They consist of 52 (61.9%) males and 32 (38.1%) females, with a median age of 58.5 (39–67) years. Eighty (95.2%) were Iban, while the rest consisted of 1 (1.2%) Chinese, 2 (2.4%) Bidayuh and 1 (1.2%) foreigner. There was a total of 78 (92.9%) new cases within the 2-year period, 5 (6.0%) with previous pulmonary tuberculosis (PTB) who completed treatment, and 1 (1.2%) with previous PTB but did not complete treatment.

Forty-six (54.8%) had smear-positive TB, while 38 (45.2%) had smear-negative TB. All patients had TB sensitive to a common anti-tuberculous drug regime, and none were rifampicin-resistance or multi-drug resistance (MDR).

Other characteristics of TB patients are stated in Table I.

Sixty-seven (79.8%) received anti-TB treatment for 6 months, 12 (14.3%) received non-standard treatment duration, ranges from 7 to 10 months. Of this group of patients, three were due to delayed sputum conversion, hence prolongation of intensive phase; two were due to the development of hepatitis as a result of adverse drug reaction from standard HREZ regime, hence were changed to alternative anti-tuberculous regime; one was due to development of rash from hypersensitivity to rifampicin and later restarted treatment with HZO regime; one defaulted treatment and needed to restart intensive phase; two were persistently symptomatic despite compliance to treatment, hence prolongation of total duration of treatment; three had persistent chest radiography (CXR) changes.

Seventy-nine (94.0%) were compliant with treatment. One was deemed treatment failure for persistent CXR changes upon completion of standard regime and needing to restart anti-tuberculous therapy. There were 5 (6.0%) who were non-compliant with treatment. Among those, three received treatments under the classification of treatment after default in accordance with Malaysia Clinical Practice Guidelines.[7]

Seventy-eight (92.9%) patients were alive at the end of treatment, while 6 (7.1%) died prior to or upon completion of treatment.

TB-Associated Mortality Outcomes and Associated Factors

Factors involved in TB-associated mortality outcomes are stated in Table II.

Odds of mortality in non-compliant patients is 12.5 times more than those compliant to treatment with statistical significance of p value=0.028.

Other factors such as age, gender, marital status, smoking history, alcoholic, immunocompromised status, chest X-ray findings, sputum smear results, symptoms and drug reactions were found to be insignificant in their association with TB-related mortality.

We explored the crude relationship between TB mortality and each independent variable using simple logistic regression (univariate analyses). Those factors with p value <0.1 were selected for the multiple logistic regression analysis but the sample size was underpowered for the analysis.

Table I: Characteristics of patients with tuberculosis (n=84)

Characteristics	n (%)
Median age (Q1–Q3) – years	58.5 (39–67)
Gender	
Male	52 (61.9)
Female	32 (38.1)
Ethnics	
Iban	80 (95.2)
Chinese	1 (1.2)
Bidayuh	2 (2.4)
Foreigners	1 (1.2)
Marital status	
Married	63 (79.7)
Single	11 (13.9)
Widowed	4 (5.1)
Divorced	1 (1.3)
Smoker	26 (32.5)
Alcoholic	10 (12.2)
Case category	
New case	78 (92.9)
Previous PTB completed treatment	5 (6.0)
Previous PTB has not completed treatment	1 (1.2)
TB contact	51 (62.2)
Immunocompromised status	
Nil	65 (77.4)
Diabetes mellitus	18 (21.4)
Malignancy	1 (1.2)
HIV	0 (0.0)
ESRF	0 (0.0)
Others	0 (0.0)
CXR findings	
Normal	16 (19.0)
Mild PTB changes	27 (32.1)
Moderate PTB changes	27 (32.1)
Advanced PTB changes	14 (16.7)
Sputum smear	
Positive	46 (54.8)
Negative	38 (45.2)
Drug resistance	
Nil	84 (100.0)
Rifampicin resistance	0 (0.0)
MDR	0 (0.0)
Treatment duration	
6 months	67 (79.8)
Non-standard regime	12 (14.3)
Did not complete treatment (dead)	5 (6.0)
Compliance	
Yes	79 (94.0)
No	5 (6.0)
Outcomes	
Alive	78 (92.9)
Dead	6 (7.1)

CXR, chest radiography; ESRF, end-stage renal failure; HIV, human immunodeficiency virus; MDR, multi-drug resistance; PTB, pulmonary tuberculosis.

Symptoms of TB Experienced by Patients

TB symptoms experienced by patients are stated in Table III.

At diagnosis, 73 (86.9%) patients were symptomatic, while 11 (13.1%) were asymptomatic. The most common symptom experienced was cough, followed by loss of weight, fever, loss of appetite, night sweats and haemoptysis - 59 (70.2%) had cough, 44 (52.4%) had loss of weight, 33 (39.3%) had fever, 30 (35.7%) had loss of appetite, 15 (17.9%) had night sweats and 10 (11.9%) had haemoptysis. None experienced dyspnoea.

Adverse Drug Reactions

Adverse drug reactions experienced by patients are stated in Table IV.

Of the total patients treated, a minority of 15 (17.9%) experienced adverse drug reactions. From the most common to the least, 10 (11.9%) had hepatitis, 3 (3.6%) experienced gout, and 2 (2.4%) had rash. None develop peripheral neuropathy, visual impairment, hearing deficit or thrombocytopenia.

Table II: Factors associated with TB-associated mortality outcomes (n=84)

Factors	Outcomes		Simple logistic regression	
	Alive n (%)	Dead n (%)	Crude OR (95% CI)	*p* value[a]
Age*				
≤60yo	42 (97.7)	1 (2.3)	1	0.068
>60yo	36 (87.8)	5 (12.2)	5.83 (0.65,52.3)	
Gender				
Male	49 (94.2)	3 (5.8)	1	0.539
Female	29 (90.6)	3 (9.4)	1.69 (0.32,8.93)	
Marital Status*				
Married	59 (93.7)	4 (6.3)	1.02 (0.11,9.78)	0.988
Single/Widow/Divorcee	15 (93.8)	1 (6.2)	1	
Smoking				
Yes	24 (92.9)	2 (7.1)	1.42 (0.22,9.04)	0.716
No	51 (94.8)	3 (5.2)	1	
Alcohol				
Yes	8 (80.0)	2 (20.0)	5.75 (0.83,39.74)	0.100
No	69 (95.8)	3 (4.2)	1	
Immunocompromised*				
Yes	17 (89.5)	2 (10.5)	1.79 (0.30,10.64)	0.553
No	61 (93.8)	4 (6.2)	1	
Chest X-ray				
Normal	15 (93.8)	1 (6.3)	1	0.876
Abnormal	63 (92.6)	5 (7.4)	1.19 (0.13,10.96)	
Sputum smear				
Positive	44 (95.7)	2 (4.3)	0.39 (0.07,2.24)	0.273
Negative	34 (89.5)	4 (10.5)	1	
Compliance				
Yes	75 (94.9)	4 (5.1)	1	0.028
No	3 (60.0)	2 (40.0)	12.5 (1.61,97.34)	
Symptoms*				
Yes	68 (93.2)	5 (6.8)	0.74 (0.08,6.96)	0.794
No	10 (90.9)	1 (9.1)	1	
Drug Reaction*				
Yes	12 (80.0)	3 (20.0)	5.50 (0.99,30.55)	0.060
No	66 (95.7)	3 (4.3)	1	

[a] Likelihood Ratio (LR) test.
Factors marked with '*' allowed for non-binary response during data collection.

Table III: Symptoms of TB (n=84)

Symptoms	n (%)
Cough	59 (70.2)
Loss of weight	44 (52.4)
Fever	33 (39.3)
Loss of appetite	30 (35.7)
Night sweats	15 (17.9)
Haemoptysis	10 (11.9)
Dyspnoea	0 (0.0)

Table IV: Adverse drug reactions (n=84)

Adverse drug reactions	n (%)
Hepatitis	10 (11.9)
Gout	3 (3.6)
Rash	2 (2.4)
Peripheral neuropathy	0 (0.0)
Visual impairment	0 (0.0)
Hearing deficit	0 (0.0)
Thrombocytopenia	0 (0.0)

Table V: Factors associated with compliance to anti-tuberculous therapy (n=84)

Factors	Compliance		Simple logistic regression	
	Yes n (%)	No n (%)	Crude OR (95% CI)	*p* value[a]
Age				
≤60 years old	41 (95.3)	2 (4.7)	1	0.605
>60 years old	38 (92.7)	3 (7.3)	1.62 (0.26,10.22)	
Gender				
Male	50 (96.2)	2 (3.8)	1	0.307
Female	29 (90.6)	3 (9.4)	2.59 (0.41,16.40)	
Marital status				
Married	61 (96.8)	2 (3.2)	1	0.172
Single/widow/divorcee	14 (87.5)	2 (12.5)	0.23 (0.03,1.77)	
Smoking				
Yes	24 (92.3)	2 (7.7)	2.17 (0.29, 16.31)	0.457
No	52 (96.3)	2 (3.7)	1	
Alcohol				
Yes	8 (80.0)	2 (20.0)	8.75 (1.08, 70.89)	0.055
No	70 (97.2)	2 (2.8)	1	
Drug reaction				
Yes	12 (80.0)	3 (20.0)	8.38 (1.26, 55.53)	0.029
No	67 (97.1)	2 (2.9)	1	

[a] Likelihood Ratio (LR) test.

Drug Compliance and Associated Factors

Factors associated with drug compliance are stated in Table V.

This study also explored factors which are associated with compliance to anti-TB treatment. Odds of non-compliance in those having drug reaction is 8.38 times more than those without drug reaction, *p* value=0.029. Odds of non-compliance among smoker and alcohol drinker were 2.17 and 8.75 times more than odds of non-compliance among non-smoker and non-alcohol drinker, respectively. However, these associations were not statistically significant with *p* value=0.194 and *p* value=0.055, respectively.

We explored the crude relationship between drug compliance and each independent variable using simple logistic regression (univariate analyses). Those predictors of non-compliance with *p* value <0.1 were selected for the multiple logistic regression analysis but the sample size was underpowered for the analysis.

DISCUSSION

Lubok Antu is a district with 27,984 populations in the state of Sarawak in Malaysia, consisting of mainly Iban ethnic.[8] Hence, majority of the patients in this study were Iban. The disease burden in the local area can be translated into 139 cases per 100,000 people-year. This incidence is much higher compared to our national statistic of 81 per 100,000 people-year.[1] Furthermore, there might be under-reporting of the local incidence of TB as some patients attend follow-up in clinics of neighbouring district. There is a slight increment in the number of TB cases from year 2019 to year 2020 (40 and 44 in respective years). It is a disease of male predominance (61.9% male), which is consistent with WHO data of 56% TB cases worldwide being men.[2]

Note that among the study population, only 28 (32.5%) were smoker, and 10 (12.2%) were alcoholic. This might be due to under-reporting of patients' social history. Not all patients who contracted TB had TB contact. Hence, healthcare worker needs to be extra vigilant in screening for potential TB patients even for those who were not previously in contact with any known PTB patients.

In this study, 38 (45.2%) patients were smear-negative and 16 (19.0%) had normal chest X-ray. This makes diagnosis of TB difficult and easy to be missed. Moreover, not all TB patients were symptomatic. Hence, high clinical suspicion is necessary to come to the diagnosis for this asymptomatic group. Further work-up might need to be done to ascertain the diagnosis if sputum was smear-negative and CXR was normal but clinical suspicion of TB remains high.

Fortunately for the community, all the TB cases were sensitive to standard anti-tuberculous regime. MDR strain had not evolved among the local community. Further effort to ensure compliance is necessary to maintain the status of drug-sensitive strain. Better compliance was shown to significantly improve mortality from this study, further supporting the findings from other studies.[9-11] Social and mental support can help to improve compliance among patients, which had previously been highlighted by other studies.[12-17] Hence, early referral to a psychologist for those who were non-compliant with treatment will most likely be beneficial. Education of patients' family in supervising patients and to provide mental support might play a role in improving compliance among patients.

In this rural setting, many patients were from more remote areas which were far away from clinic, requiring hours of boat ride to reach. Hence, logistic challenges to attend clinic follow-up for continuation of treatment remains an important factor. Hence, in our clinic setting, free boat services will be arranged for those patients who were unable to afford transport to attend clinic. Infrastructure development in curbing logistic challenge should be prioritised in order to make patients' attendance at clinic convenient. In our setting, for this group of patients with logistic concern, daily DOT will be supervised by an in-charge

appointed by the clinic staffs among the local villagers. These are exemplary steps to further improve patients' compliance to treatment in rural setting.

Adverse drug reaction should not be a hindrance to compliance with treatment. The minority patients (17.9%) who developed drug reactions were of non-fatal reactions and steps had been taken to ensure subsequent compliance after recovery from the adverse effects.

In this study, we were unable to form a stable model to predict the associated factors. This can be due to two possibilities - inadequate sample size which could inflate the standard error and widen the 95% CI; or the number of event for mortality was very small (6 deaths versus 78 alive). Therefore, the model did not fit.

TB mortality rate in Lubok Antu district was 10.7 per 100,000 populations, which was more than double the national TB mortality rate of 4.9 per 100,000 populations; but half of that of the global TB mortality rate of 20.0 per 100,000 populations.[1] There is still room for improvement in reducing TB mortality with the aim to achieve the global end TB milestone.

TB is an important public health problem in our country. Especially for rural community, TB is often under-diagnosed and under-treated where awareness among the community is low and further complicated by logistic challenges. This has important implications to the rural community as TB is a contagious disease. It can easily spread to involve a large number of people when the local community in rural area usually lives in close proximity within longhouses and have frequent close physical interaction. Steps need to be taken to educate the community in early seeking of treatment for those with symptoms suspicious of TB and to be compliant with treatment once diagnosed. This can help to improve TB-related mortality in the community. The importance of mental support should not be undermined, and thus should be part of the treatment alongside pharmacological therapy.

CONCLUSION

TB mortality prevalence in Lubok Antu population was fortunately low (7.1%), although steps need to be taken to raise the standard of TB care to further reduce mortality and morbidity. Compliance with treatment was found to be significantly associated with mortality and is especially needed to be emphasised in the effort of curbing TB since it is a modifiable factor that carries a significant impact on TB outcome.

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REFERENCES

1. World Health Organization. 2019. Global Tuberculosis Report 2019. Geneva: World Health Organization.
2. World Health Organization. 2020. Global Tuberculosis Report 2019. Geneva: World Health Organization.
3. Iyawoo K. Tuberculosis in Malaysia: problems and prospect of treatment and control. Tuberculosis 2004; 84(1–2): 4-7.
4. World Health Organization. 2018. The end TB strategy: global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organization. Available from: https://www.who.int/tb/strategy/End_TB_Strategy.pdf?ua=1. Accessed June 2021.
5. World Health Organization. Chapter 4: childhood contact screening and management. Int J Tuberc Lung Dis 2007; 11(1): 12-5.
6. Swarna NY. A review of tuberculosis research in Malaysia. Med J Malaysia 2014; 69: Suppl. A, 88-102.
7. Malaysia Clinical Practice Guidelines. 2012. Management of Tuberculosis (3rd edition). Available from: https://www.moh.gov.my/moh/attachments/8612.pdf. Accessed June 2021.
8. City Population: Lubok Antu District, Malaysia (2010). Available from: https://www.citypopulation.de/en/malaysia/admin/sarawak/1308__lubok_antu/. Accessed June 2021.
9. Kliiman K, Altraja A. Predictors and mortality associated with treatment default in pulmonary tuberculosis. Int J Tuberc Lung Dis 2010; 14(4): 454-63.
10. Abdool Karim S, Naidoo K, Grobler A, Padayatchi N, Baxter C, L. Gray A, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med 2011; 365: 1492-501.
11. Uyei J, Coetzee D, Macinko J, Weinberg SL, Guttmacher S. The influence of integrated tuberculosis and human immunodeficiency virus service delivery on patient outcomes. Int J Tuberc Lung Dis 2014; 18: 315-21.
12. Deshmukh RD, Dhande DJ, Sachdeva KS, Sreenivas AN, Kumar AMV, Parmar M. Social support a key factor for adherence to multidrug-resistant tuberculosis treatment. Indian J Tuberc 2018; 65(1): 41-7.
13. Priedeman Skiles M, Curtis SL, Angeles G, Mullen S, Senik T. Evaluating the impact of social support services on tuberculosis treatment default in Ukraine. PLoS One 2018; 13(8): e0199513.
14. Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med 2007; 4(7): e238.
15. Chen X, Du L, Wu R, Xu J, Ji H, Zhang Y, et al. The effects of family, society and national policy support on treatment adherence among newly diagnosed tuberculosis patients: a cross-sectional study. BMC Infect Dis 2020; 20(1): 623.
16. Van Hoorn R, Jaramillo E, Collins D, Gebhard A, van den Hof S. The effects of psycho-emotional and socio-economic support for tuberculosis patients on treatment adherence and treatment outcomes - a systematic review and meta-analysis. PLoS One 2016; 11(4): e0154095.
17. Jakubowiak WM, Bogorodskaya EM, Borisov SE, Danilova ID, Lomakina OB, Kourbatova EV. Social support and incentives programme for patients with tuberculosis: experience from the Russian Federation. Int J Tuberc Lung Dis 2007; 11(11): 1210-5.

Intravascular imaging-guided treatment of severe coronary artery calcification with orbital atherectomy: A prospective single-centre registry

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ABSTRACT

Introduction: Coronary artery calcification can lead to suboptimal results when performing coronary angioplasty with conventional techniques. The presence of severe coronary artery calcium increases the complications of percutaneous coronary intervention as it may impede stent delivery and optimal stent expansion. The purpose of this study was to determine the procedural success and safety of orbital atherectomy (OA) in calcified lesions.

Materials and Methods: This was a prospective single-centre study regarding the utility of OA in the treatment of calcified coronaries. Intravascular ultrasound (IVUS) or optical coherence tomography (OCT) was used in all cases to characterise the severity of calcium pre-procedure, guide vessel sizing and assess procedural success. The primary endpoint was procedural success, defined by successful stent implantation following OA treatment. The secondary endpoint was in-hospital and 30-day major adverse cardiovascular event (MACE).

Results: Ten patients with severely calcified lesions were successfully treated with OA. The primary endpoint was achieved in all patients. All of the lesions were severely calcified with concentric calcium. None of the patients suffered in-hospital or 30-day MACE. The average minimal luminal diameter at baseline was 1.7 ± 0.3 mm and the post-PCI luminal diameter was 3.0 ± 0.3 mm, with a significant luminal gain of 1.3 ± 0.3 mm ($p < 0.01$). Slow flow during procedure occurred in 2 (20%) cases and dissection occurred in 1 (10%) case during procedure. These were successfully treated with stent delivery to achieve TIMI III flow. There were no cases of stent thrombosis or vessel perforation.

Conclusion: Our experience demonstrates the feasibility and safety of OA in the management of calcified coronary stenosis. Intravascular imaging is an important adjunct to the use of OA to assess the severity of calcified coronary lesions, success of OA treatment and to aid sizing of the vessel for stent implantation. OA is an effective treatment approach to disrupt coronary calcification, facilitating stent implantation with optimal results. It is a safe procedure with good success rate and low rate of complications.

KEYWORDS:
Orbital Atherectomy; Intravascular Imaging; Intravascular Ultrasound; Optical Coherence Tomography; Coronary artery calcification

INTRODUCTION

Coronary artery calcification occurs due to the deposition of calcium in the arterial wall and is associated with increasing age and co-morbidities.[1,2] Severe calcification occurs in 10–20% of cases of ischaemic heart disease.[3] Severe coronary artery calcification is associated with an increased risk of major adverse cardiac events (MACE), including death and myocardial infarction.[4,5] Calcification poses difficult challenges to coronary angioplasty since plaques are difficult to cross and pre- dilate with conventional devices.[6] Severe calcification may also limit optimal stent expansion thus leading to increased risk of restenosis and stent thrombosis. The difficulty in dilating a calcified lesion may require the use of high-pressure non-compliant (NC) balloons and cutting balloons which pose risks of dissection or arterial perforation.[7,8] Additionally, inadequate stent expansion may lead to malapposition of stent struts[9] and subsequent stent thrombosis and early stent restenosis.[10] There has thus been a need for alternative calcium modification techniques, including rotational atherectomy, orbital atherectomy (OA) and intravascular lithotripsy.[11]

The Diamondback 360 Coronary orbital atherectomy system (Cardiovascular Systems, Inc., Saint Paul, MN, USA) consists of a diamond-coated crown which spins (orbits) and removes a thin layer of plaque as it comes into contact with a lesion. OA is designed to selectively ablate calcium while minimising treatment of soft non-calcified plaque.[12] Preparation prior to percutaneous coronary intervention (PCI) of calcified lesions with OA can improve changes of optimal stent delivery and stent expansion. Although atherectomy devices have classically been used for calcified lesions which are difficult to cross, the focus has more recently shifted to lesion preparation in order to optimise results in PCI. The aim of lesion preparation is to modify the plaque and change its morphology with the aim of achieving good stent expansion. Intravascular imaging techniques such as intravascular ultrasound (IVUS) or optical coherent tomography (OCT) are often performed alongside OA treatment to evaluate the

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extent of calcification and post-procedure as well as to demonstrate calcium fractures and evaluate procedural success.[13]

The use of OA is gradually increasing but currently there is limited real-world data published in Asia. In this study, we describe the data of a prospective registry in a single centre for the use of OA to treat severely calcified coronary artery lesions.

MATERIALS AND METHODS

Patients and Study Design

The Prospective Registry of Calcified Coronary Artery Lesions undergoing Atherectomy is a single-centre registry. Approval for the study was granted by Independent Ethics Committee of Ramsay Sime Darby Healthcare. Anonymised data between Mar 2021 and Mar 2022 was collected by medical record review and all patients gave written informed consent for inclusion into the registry. Baseline characteristics of patients including age, cardiac risk factors, clinical presentation, left ventricular ejection fraction (EF) and baseline renal function were documented.

Intravascular Imaging

Intravascular imaging with either OCT or IVUS was used in all OA cases. Calcium on OCT was defined as a signal-poor region with sharply delineated borders.[14] Calcium on IVUS was defined as a (hyperechoic) lesion with brighter shadow than reference adventitia.[15] Measurements of pre and post-PCI minimal luminal diameter (MLD), minimal luminal area (MLA) and stent cross-sectional area (CSA) were recorded. Calcium scoring systems were used in both intravascular imaging modalities to ascertain the severity of calcium to determine the need for OA treatment.

The OCT-based calcium scoring system (Fig. 1, Table I) is calculated with the following criteria (also known as Rule of 5s): 2 points for maximum calcium angle > 180° (i.e. >50% vessel arc), 1 point for maximum calcium thickness > 0.5 mm, and 1 point for calcium length > 5 mm, for a total calcium score of 0–4 points.[16] Severe calcium with an OCT score of 3 and above predicts an 80% chance of stent underexpansion.

The IVUS-based scoring system (Fig. 1, Table I) is calculated with the following: 1 point for circumferential calcium = 360°, 1 point for calcium arc > 270° that is > 5 mm in length, 1 point for vessel size (media-to-media) ≤ 3.5 mm adjacent to the maximum calcium, and 1 point for a calcific nodule (convex shape on luminal side of calcium).[17] Severe calcium with an IVUS score of 3 and above predicts a significant risk of stent underexpansion.

A score of ≥ 3 for both OCT and IVUS scoring systems is regarded as an indication for OA.

IVUS or OCT were also used to assess the effect of atherectomy. Effective post-OA calcium modification is identified on IVUS or OCT as the presence of a new disruption or discontinuity in the calcium arc (fractures).

Percutaneous Coronary Intervention

All patients were given dual-antiplatelet therapy and received intra-arterial heparin for anticoagulation during the PCI procedure. The coronary OA device (Cardiovascular Systems, Inc. [CSI], St Paul, MN) is advanced over a 0.014 guidewire (ViperWire, CSI) with the concomitant use of a lubricant, ViperSlide (CSI). OA was commenced with low speed (80,000 rpm) in all cases with some cases requiring subsequent high-speed (120,000 rpm) atherectomy. The recommended duration of each OA pass was 20 seconds or less. After atherectomy, predilatation angioplasty and PCI were performed with stent implantation. Following PCI, all patients were given dual antiplatelet therapy with either aspirin 100 mg, clopidogrel 75mg or ticagrelor 180 mg/day for 12 months.

Endpoints

The primary end point was procedural success, defined as successful OA treatment and stent implantation with <30% residual stenosis. The secondary endpoint was in-hospital MACE, including cardiac death, myocardial infarction (MI), or target-vessel revascularisation (TVR) and 30-day MACE.[18] Safety outcome was procedural complication, defined as coronary dissection, slow or no reflow, stent thrombus or vessel perforation.

Statistical Analysis

Descriptive statistics including mean and percentages were used. Categorical variables are presented as counts (%) and continuous variables are presented as mean ± standard deviation (SD). The paired t-test was used for the comparison of MLD at baseline and after PCI. A p value of ≤ 0.05 was considered significant.

RESULTS

Baseline Characteristics

Between March 2021 and March 2022, 10 patients with severely calcified lesions were treated with OA. The baseline characteristics of the patients are shown in Table II. Mean age was 57 ± 11 years, with a high prevalence of risk factors of hypertension and hypercholesterolaemia. The mean ejection fraction on echocardiogram was 60.4 ± 4.9%.

Procedural Characteristics

The procedural characteristics are shown in Table III. Femoral vascular access was preferred in majority of cases. The target artery was the left anterior descending coronary artery in all patients and the left main was treated in two patients. All of the lesions were severely calcified with a calculated OCT or IVUS score of 3 and above. 6 (60%) cases had one stent used, while two stents were used in 4 (40%) of cases. The median number of OA passes was 4 per case. OCT and IVUS cases pre- and post-OA showing effective atherectomy are shown in Figure 2. The angiogram images for a case of heavily calcified LAD artery effectively treated with OA are shown in Figure 2.

Clinical Outcomes

The primary endpoint of procedural success was achieved in all patients. There were no in-hospital MACE and 30-day

Table I: Intravascular imaging: determination of severity of coronary artery calcium with OCT and IVUS scoring systems (corresponding to images in Figure 1)

OCT score	OCT Characteristic	Score
Calcium depth	≤ 0.5 mm	0
	> 0.5 mm	1
Calcium arc	≤ 90 °	0
	90-180 °	1
	> 180 °	2
Calcium length	≤ 5 mm	0
	> 5 mm	1

IVUS score	IVUS Characteristic	Score
Calcium arc	< 360 °	0
	360 °	1
Length of calcium > 270	≤ 5 mm	0
	> 5 mm	1
Diameter	> 3.5 mm	0
	≤ 3.5 mm	1
Calcified nodule	Absent	0
	Present	1

Table II: Baseline characteristics (n=?)

Characteristic	Number
Male, n (%)	5 (50)
Age (mean ± SD)	57 ± 11
Hypertension, n (%)	5 (50)
Hypercholesterolemia, n (%)	7 (70)
Smoking, n (%)	3 (30)
Family history of cardiac disease, n (%)	4 (40)
Diabetes mellitus, n (%)	6 (40)
LVEF (mean ± SD)	60.4 ± 4.9
eGFR (ml/min/1.73 m^2)	83 ± 21
Stable angina/positive stress test	5 (50)
Unstable angina	5 (50)

LVEF - Left ventricular ejection fraction
eGFR - Estimated glomerular filtration rate

MACE events (Table III). The average stenosis diameter at baseline was 1.7 ± 0.3 mm and the post-PCI diameter was 3.0 ± 0.3 mm, with a significant acute luminal gain of 1.3 ± 0.3 mm ($p < 0.01$). Slow flow during the procedure occurred in 2 (20%) cases and dissection occurred in 1 (10%) case during the procedure. These were successfully treated with stent delivery to achieve TIMI III flow. There were no cases of stent thrombosis or vessel perforation.

DISCUSSION

OA is a relative new technology for calcium modification in complex angioplasty. We sought to prospectively assess the in-hospital safety and efficacy of treatment using intravascular imaging guidance and OA in a real-world population. The main finding of this study was that OA could be performed safely and relatively easily with successful stent delivery in all cases. In our patient cohort, there were no major angiographic complications with OA and none of the patients had in-hospital and 30-day follow-up MACE.

Orbital Atherectomy

The Diamondback 360 Coronary OA System (Cardiovascular Systems, Inc., St. Paul, Minnesota) is a device that modifies calcific lesions by a sanding mechanism.[19] The system uses a 1.25-mm diamond-coated crown which can be advanced bidirectionally over a 0.014" ViperWire coronary guidewire.[20,21] The continuous flow of lubricant, combined with small particle size of 2 µm, leads to low incidence of thermal injury, heart block, and no reflow.[22] In our study, there was a low rate of complications with the OA device, with slow flow during the procedure in 2 (20%) cases during procedure. Additionally, this improved following stent delivery to achieve TIMI III flow.

The OA crown is moved by the operator in both directions a slow movement at a speed of 1 to 3 mm/s for ablation.[23] During atherectomy, softer tissue flexes away from the crown while superficial and deep calcium is treated.[24] The OA console has speed selection options for low speed (80,000 rpm) and high speed (120,000 rpm). The small amount of luminal gain from debulking is not the main objective of OA treatment. Treatment with OA can hence increase the vessel diameter and reduce the risk of stent underexpansion, stent thrombosis, and stent restenosis.[25] Among our study patients, it was found that OA improved the vessel diameter from baseline of 1.7 mm to a post-PCI diameter of 3.0 mm, with a significant luminal gain of 1.3 ± 0.3 mm.

Safety of OA

Infrequent complications of OA may include slow coronary blood flow or no flow, distal embolisation, coronary artery perforation, and vessel dissection. Coronary vessel perforation is a serious complication that can occur 0.7% to 2% of OA cases.[20] Avoiding highly tortuous vessels can help to reduce the risk of coronary vessel perforation. OA should

Table III : Procedural characteristics and clinical outcomes (n=?)

Characteristic	Number
Vessel treated	
LMS, n (%)	2 (20)
LAD, n (%)	10 (100)
LCX, n (%)	0 (0)
RCA, n (%)	0 (0)
Lesion characteristics	
Proximal, n (%)	8 (80)
Mid, n (%)	5 (50)
Length (mean ± SD), mm	34.7 ± 11.1
Severe calcification, n (%)	10 (100)
Procedural characteristics	
Procedural time (min ± SD)	125.2 ± 34.4
Fluroscopy time (min ± SD)	27 ± 10.5
Femoral vascular access, n (%)	9 (90)
Number of orbital atherectomy runs (median)	4
Largest diameter of predilatation balloon, mm (mean ± SD)	2.6 ± 0.2
Mean pressure of predilatation, atm (mean ± SD)	14.6 ± 2.5
Largest diameter of postdilatation balloon, mm (mean ± SD)	3.4 ± 0.4
Mean pressure, of postdilatation, atm (mean ± SD)	14.2 ± 1.7
2 stents/lesion, n (%)	4 (40)
1 stent /lesion, n (%)	6 (60)
IVUS or OCT characteristics	
IVUS or OCT score ≥ 3	10 (100)
Baseline MLD (mm ± SD)	1.7 ± 0.3
Post-PCI MLD (mm ± SD)	3.0 ± 0.3
Baseline MLA (mm2 ± SD)	3.5 ± 0.8
Post-PCI-stent CSA (mm2 ± SD)	7.5 ± 1.3
Post-PCI-luminal gain (mm ± SD)	1.3 ± 0.3
Angiographic and clinical outcomes	
Procedure success with facilitated stent delivery	10 (100)
Slow flow during procedure	2 (20)
Coronary dissection during procedure	1 (10)
Stent thrombosis	0 (0)
Vessel perforation	0 (0)
In-hospital MACE (MI/TVR/death)	0 (0)
30-day MACE (MI/TVR/death)	0 (0)

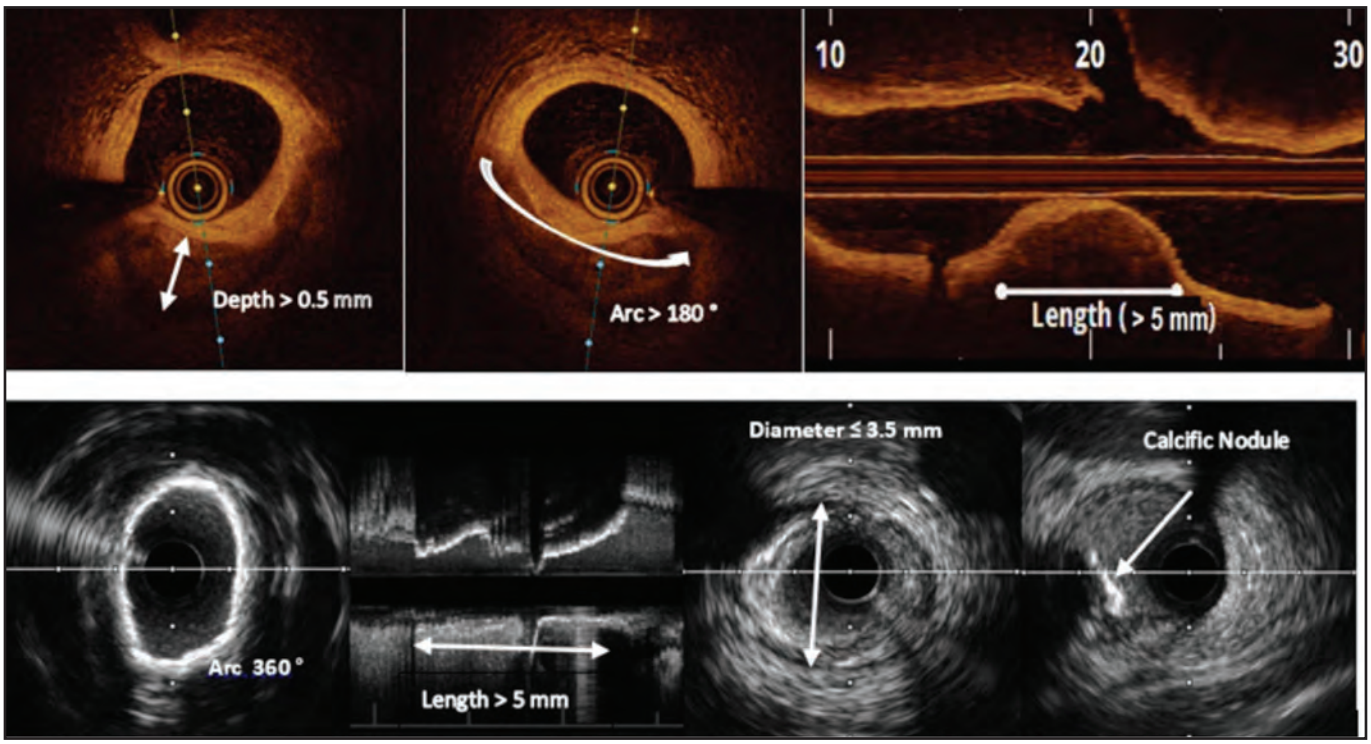

Fig. 1: OCT Images (row above) demonstrating measurements of depth, arc and length. IVUS images (row below) demonstrating measurements of arc, length, vessel diameter and calcific nodule

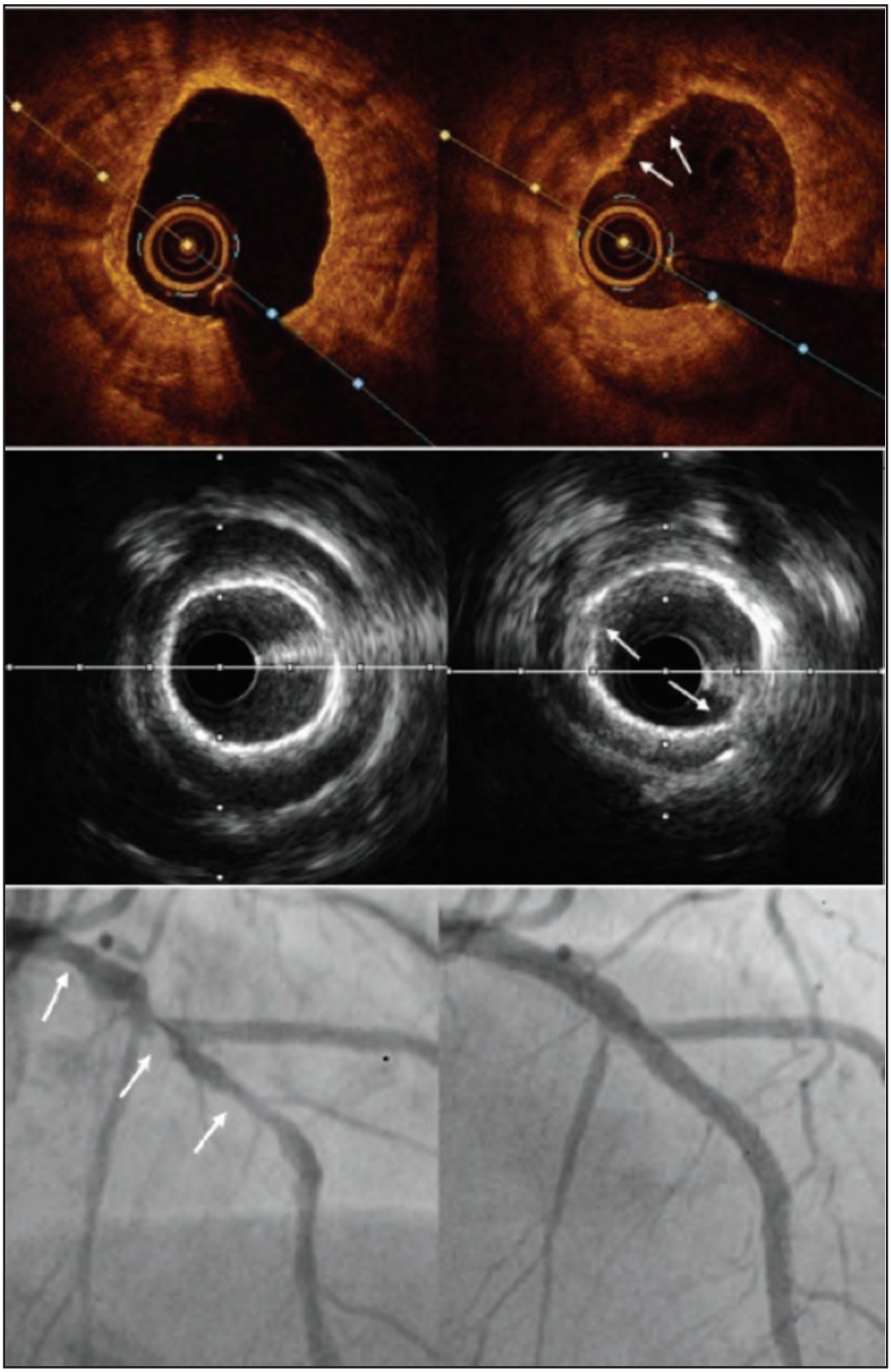

Fig. 2: OCT cross-section images (above left) demonstrating severe concentric calcification. Post-OA images (above right) demonstrating the mechanism of action of OA - polishing of the calcified surface, with characteristic smooth, concave ablation (arrows). IVUS cross-section images (middle left) demonstrating concentric arc of calcium and post-OA images on the (middle right) showing plaque modification with thinning and disruption of calcium ring (arrow). Coronary angiogram showing heavy calcification (arrows) at the proximal to mid LAD (below left). Post-treatment with OA and successful PCI of the LAD with stent implantation (below right)

be avoided in vessel anatomy with greater than 2 bends exceeding 90° angulation. We found that using OCT or IVUS guidance for careful patient selection and also monitoring of complications intraprocedure helped to minimise complications from OA. There was a low rate of acute complications in our study cohort with dissection occurring in 1 (10%) case during the procedure.

Trial Evidence for OA

The early clinical trial assessing OA in coronary arteries was the ORBIT I study. The study examined the safety and feasibility in 50 patients, demonstrating procedural success in 94% of patients.26 Complications included six cases of coronary artery dissection and one case of perforation. The MACE rate was 6% at 30 days.

Following this, the ORBIT II trial, a multicenter, prospective trial studied 443 patients from 49 sites with severely calcified coronary disease.[27] The primary endpoint of 30-day MACE and cerebrovascular events was 1.7%. Angiographic complication rates were low: perforation was 0.7%, dissection 0.9%, and no- reflow 0.7%; emergency coronary artery bypass graft surgery was performed in 0.2% of patients. There was a low rate of 1-year target vessel revascularisation (5.9%), cardiac death (3.0%), and peri-procedural MI (2%). The trial demonstrated that OA was safe and effective for the treatment of severely calcified coronary lesions.

Our study findings are comparable to such larger trials, with a low rate of MACE events post-OA in our study (0%) at 30 days as compared to 1.7% at 30 days with the ORBIT II trial.

Intravascular Imaging

Both IVUS and OCT provide good resolution for severity assessment of coronary calcification compared with visualisation during coronary angiography. The calcium arc on IVUS[28] and OCT[29], which indicates severity of calcification, is a measure of risk of stent under expansion. With IVUS, ultrasound waves reflect off calcium instead of penetrating calcium, making it difficult to assess calcium depth.[30] The thickness of calcium can influence the likelihood of calcium fracture during balloon angioplasty.[31] Lesions with calcium thickness exceeding a depth of 0.24 mm can benefit from atherectomy-induced calcium modification to avoid stent underexpansion.[32] Treatment of calcified lesions with OA leads to ablation of calcified plaque which may be seen on intravascular imaging.[33]

Calcium scoring algorithms with intravascular imaging allow a structured approach in routine practice to help minimise the likelihood of stent restenosis and stent thrombosis.[34] We found that OCT and IVUS scoring algorithms to assess for severity of calcium have been important for judicious selection of appropriate cases for the use of OA in angioplasty. Additionally, it has been essential to perform intravascular imaging post-OA treatment to aid in accurate stent diameter sizing and to demonstrate success with documentation of MLD, luminal gain, post-stent CSA with the use of either OCT or IVUS.

LIMITATIONS

This was a prospective, single-arm registry with short-term follow-up period of 30 days. Larger randomised studies or clinical registries of OA with long-term follow-up will be of significant clinical value.

CONCLUSION

Calcified coronary lesions are challenging to treat and are associated with an increased risk of acute complications and poor long-term outcomes. Our experience demonstrates the feasibility and safety of OA in the management of calcified coronary stenosis. Intravascular imaging is an important adjunct to the use of OA to assess the severity of calcified coronary lesions, success of OA treatment, and aid in sizing the vessel for stent implantation. OA has an important role in lesion preparation of calcified lesions before stent implantation to best ensure optimal results for adequate stent expansion. OA is a safe procedure with good success rate and low rate of complications.

REFERENCES

1. Mori H, Torii S, Kutyna M, Sakamoto A, Finn AV, Virmani R. Coronary artery calcification and its progression: what does it really mean? JACC Cardiovasc Imaging 2018; 11(1): 127-42.
2. Goel R, Garg P, Achenbach S, Gupta A, Song JJ, Wong ND, et al. Coronary artery calcification and coronary atherosclerotic disease. Cardiol Clin 2012; 30: 19-47.
3. Bourantas CV, Zhang YJ, Garg S, Iqbal J, Valgimigli M, Windecker S, et al. Prognostic implications of coronary calcification in patients with obstructive coronary artery disease treated by percutaneous coronary intervention: a patient-level pooled analysis of 7 contemporary stent trials. Heart 2014; 100(15): 1158-64.
4. Shlofmitz E, Khalid N, Hashim H. Seeing is believing: Imaging-guided treatment of calcified lesions. Cardiovasc Revasc Med 2020; 21: 1106-7.
5. Copeland-Halperin RS, Baber U, Aquino M, Rajamanickam A, Roy S, Hasan C, et al. Prevalence, correlates, and impact of coronary calcification on adverse events following PCI with newer-generation DES: findings from a large multiethnic registry. Catheter Cardiovasc Interv 2018; 91(5): 859-66.
6. Onuma Y, Tanimoto S, Ruygrok P, Neuzner J, Piek JJ, Seth A, et al. Efficacy of everolimus eluting stent implantation in patients with calcified coronary culprit lesions: two-year angiographic and three-year clinical results from the SPIRIT II study. Catheter Cardiovasc Interv 2010; 76: 634-6.
7. Genereux P, Madhavan MV, Mintz GS, Maehara A, Palmerini T, Lasalle L, et al. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes: pooled analysis from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) and ACUITY (acute catheterization and urgent intervention triage strategy) trials. J Am Coll Cardiol 2014; 63: 1845-54.
8. Bittl JA, Chew DP, Topol EJ, Kong DF, Califf RM. Meta-analysis of randomized trials of percutaneous transluminal coronary angioplasty versus atherectomy, cutting balloon atherectomy, or laser angioplasty. J Am Coll Cardiol 2004; 43: 936-42.
9. Kini AS, Vengrenyuk Y, Pena J, Motoyama S, Feig JE, Meelu OA, et al. Optical coherence tomography assessment of the mechanistic effects of rotational and orbital atherectomy in severely calcified coronary lesions. Catheter Cardiovasc Interv 2015; 86: 1024-32.
10. Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. J Am Coll Cardiol 2010; 56: 1897-907.

11. Barbato E, Shlofmitz E, Milkas A, Shlofmitz R, Azzalini L, Colombo A. State of the art: evolving concepts in the treatment of heavily calcified and undilatable coronary stenoses - from debulking to plaque modification, a 40-year-long journey. EuroIntervention 2017; 13: 696-705.
12. Abdel-Wahab M, Richardt G, Joachim Buttner H, Toelg R, Geist V, Meinertz T, et al. High-speed rotational atherectomy before paclitaxel-eluting stent implantation in complex calcified coronary lesions: the randomized ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) trial. JACC Card Interv 2013; 6(1): 10-9.
13. Wang X, Matsumura M, Mintz GS, Lee T, Zhang W, Cao Y, et al. In vivo calcium detection by comparing optical coherence tomography, intravascular ultrasound, and angiography. JACC Cardiovasc Imaging 2017; 10(8): 869-79.
14. Amemiya K, Maehara A, Yamamoto MH, Oyama Y, Igawa W, Ono M, et al. Chronic stent recoil in severely calcified coronary artery lesions. A serial optical coherence tomography study. Int J Cardiovasc Imaging. 2020; 36(9): 1617–1626. doi: 10.1007/s10554-020-01876-8.
15. Ueki Y, Otsuka T, Hibi K, Räber L. The value of intracoronary imaging and coronary physiology when treating calcified lesions. Intervent Cardiol 2019; 14: 164-8
16. Fujino A, Mintz GS, Matsumura M, Lee T, Kim SY, Hoshino M, et al. A new optical coherence tomography-based calcium scoring system to predict stent underexpansion. EuroIntervention 2018; 13(18): e2182-e9.
17. Zhang M, Matsumura M, Usui E, Noguchi M, Fujimura T, Fall K, et al. IVUS predictors of stent expansion in severely calcified lesions. J Am Coll Cardiol 2019; 74(13): B51.
18. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, et al. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium-2 consensus document. Circulation 2018; 137: 2635-50.
19. Genereux P, Lee AC, Kim CY, Lee M, Shlofmitz R, Moses JW, et al. Orbital atherectomy for treating de novo severely calcified coronary narrowing (1-year results from the Pivotal ORBIT II Trial). Am J Cardiol 2015; 115(12): 1685-90.
20. Lee MS, Nguyen H, Philipson D, Shlofmitz RA. Single-operator technique for advancing the orbital atherectomy device. J Invasive Cardiol 2017; 29(3): 92-5.
21. Chambers JW, Diage T. Evaluation of the Dia mondback 360 coronary orbital atherectomy system or treating de novo, severely calcified lesions. Expert Rev Med Devices 2014; 11: 457-66.
22. Sotomi Y, Shlofmitz R, Colombo A, Serruys PW, Onuma Y. Patient selection and procedural considerations for coronary orbital atherectomy system. Interv Cardiol 2016; 11(1): 33-8.
23. Shlofmitz E, Martinsen BJ, Lee M, Rao SV, Généreux P, Higgins J, et al. Orbital atherectomy for the treatment of severely calcified coronary lesions: evidence, technique, and best practices. Expert Rev Med Devices 2017; 14(11): 867-79.
24. Galougahi KK, Shlofmitz RA, Ben-Yehuda O, Généreux P, Maehara A, Mintz GS, et al. Guiding light: insights into atherectomy by optical coherence tomography. JACC Cardiovasc Interv 2016; 9: 2362-3.
25. Lee MS, Shah N. The impact and pathophysiologic consequences of coronary artery calcium deposition in percutaneous coronary Interventions. J Invasive Cardiol 2016; 28: 160-67.
26. Parikh K, Chandra P, Choksi N, Khanna P, Chambers J. Safety and feasibility of orbital atherectomy for the treatment of calcified coronary lesions: the ORBIT 1 trial. Catheter Cardiovasc Inerv 2013; 81(7): 1134-9.
27. Chambers JW, Feldman RL, Himmelstein SI, Bhatheja R, Villa AE, Strickman NE, et al. Pivotal trial to evaluate the safety and efficacy of the orbital atherectomy system in treating de novo, severely calcified coronary lesions (ORBIT II). JACC Cardiovasc Interv 2014; 7(5): 510-8.
28. Vavuranakis M, Toutouzas K, Stefanadis C, Chrisohou C, Markou D, Toutouzas P. Stent deployment in calcified lesions: can we overcome calcific restraint with high-pressure balloon inflations? Catheter Cardiovasc Interv 2001; 52(2): 164-72.
29. Kobayashi Y, Okura H, Kume T, Yamada R, Kobayashi Y, Fukuhara K, et al. Impact of target lesion coronary calcification on stent expansion. Circ J 2014; 78(9): 2209-14.
30. Ali ZA, Karimi Galougahi K, Maehara A, Shlofmitz RA, Ben-Yehuda O, Mintz GS, et al. Intracoronary optical coherence tomography 2018: current status and future directions. JACC Card Interv 2017; 10(24): 2473-87.
31. Maejima N, Hibi K, Saka K, Akiyama E, Konishi M, Endo M, et al. Relationship between thickness of calcium on optical coherence tomography and crack formation after balloon dilatation in calcified plaque requiring rotational atherectomy. Circ J 2016; 80 (6): 1413-9.
32. Fujino A, Mintz GS, Lee T, Hoshino M, Usui E, Kanaji Y, et al. Predictors of calcium fracture derived from balloon angioplasty and its effect on stent expansion assessed by optical coherence tomography. JACC Cardiovasc Interv 2018; 11(10): 1015-7.
33. Sotomi Y, Cavalcante R, Shlofmitz RA, Suwannasom P, Tateishi H, Tenekecioglu E, et al. Quantification by optical coherence tomography imaging of the ablation volume obtained with the orbital atherectomy system in calcified coronary lesions. EuroIntervention 2016; 12(9): 1126-34.
34. Shlofmitz E, Shlofmitz RA, Galougahi KK, Rahim HM, Virmani R, Hill JM, et al. Algorithmic approach for optical coherence tomography-guided stent implantation during percutaneous coronary intervention. Interv Cardiol Clin 2018; 7(3): 329-44.

ORIGINAL ARTICLE

Predicting successful live birth from single serum hCG measurement in assisted reproductive technology cycle

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ABSTRACT

Introduction: Assisted reproductive technology may result in various outcomes, causing a significant stress both physically and emotionally to the patients. This study aims to determine the level of serum human chorionic gonadotrophin (hCG) following embryo transfer in predicting successful live births in in vitro fertilisation (IVF) cycles.

Materials and Methods: This is a retrospective analysis of 407 IVF pregnancies in Hospital Sultanah Bahiyah Kedah from 2014 to 2019. Serum hCG was withdrawn on either (i) day 16 post-oocyte retrieval for fresh IVF cycle or (ii) day 16 from the addition of progesterone in frozen embryo cycles. Outcomes of IVF pregnancies were analysed in relation to the level of serum hCG.

Results: The overall median hCG level in singleton live birth was 304.7 IU/L, 547.10 IU/L for multiple live births, and early pregnancy loss level was 77 IU/L. When the ROC graphs were plotted, serum hCG level of 152.85 IU/L predicted singleton livebirth with a sensitivity of 81.3%. Serum hCG of 322.40 IU/L predicted multiple live births with sensitivity of 78.6% and a specificity of 64.3%. In the subgroup analysis comparing prediction hCG level in singleton live birth; the cut-off point in frozen cycle was found to be higher as compared to fresh cycle, 277.05 IU/L vs 117.5 IU/L. Blastocyst pregnancies recorded overall higher predictor hCG level as compared to cleavage state in all the outcomes measured; singleton live birth (372.30 IU/L), early pregnancy loss (107.60 IU/L), and multiple pregnancies (711.40 IU/L).

Conclusion: A single reading of serum hCG taken at day 16 post-oocyte retrieval or day 16 from the addition of progesterone in a frozen cycle will help to determine the outcomes of IVF pregnancies and direct the physicians during counselling sessions and plan for further follow-up of the patients.

KEYWORDS:
Human chorionic gonadotrophin; assisted reproductive technology; livebirth; frozen embryo transfer

INTRODUCTION

Counselling is very important in assisted reproductive technology (ART) as patients endure high level of stress; both emotionally and physically.[1] In vitro fertilisation (IVF) is associated with multiple adverse pregnancy outcomes including biochemical pregnancies, failing pregnancies, miscarriages and ectopic pregnancies. In a good-quality blastocyst transfer study of 370 patients, the incidence of miscarriage was reported as 6.2%, biochemical pregnancies 8.1% and 1.1% ended with ectopic pregnancies.[2]

An easily available and reliable predictor of successful IVF pregnancies will help to reduce anxiety among patients awaiting the final results of their treatment. Many biomarkers have been evaluated to predict the outcomes of early pregnancies including serum oestradiol,[3] progesterone[4,5] and pregnancy-associated plasma protein A (PAPP-A).[6] One of the makers linked to a successful live birth in IVF pregnancies is the higher mean level of human chorionic gonadotrophin (hCG) on day 12 following embryo transfer.[7]

hCG is a hormone unique to pregnancies and has been used to confirm and monitor pregnancy outcomes. The hCG RNA expression occurred as early as eight cell stage embryo state[8] and is detectable in the serum 10 days after fertilisation.[9] Following blastocyst stage, hCG is mainly produced by the syncytiotrophoblast and serves as an important element in maintaining pregnancy. hCG then is detectable in the urine following 2–3 weeks of fertilisation; when the invasive trophoblastic activity is at maximum, and the levels continue to reach its peak at 10–11th week gestation.

As implantation is a complex process, a proper synchronisation of the blastocyst hormones, biomarkers and endometrial receptivity state is paramount in ensuring good pregnancy outcomes. hCG has been shown to be favouring endometrial tolerance towards the embryo and promoting angiogenesis to result in successful pregnancies.[10] It also plays a vital role in maintaining uterine quiescence by regulating gap junctions in myometrial smooth muscles and enhancing the expression of the progesterone receptors on these cells.[11] Immunomodulator properties of hCG have been well documented by mediating inhibitory properties to Th1 response leading to fetal survival.[12]

The objective of this study is to determine the level of hCG in predicting livebirth and early pregnancy loss in IVF pregnancies.

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MATERIALS AND METHODS

All patients who underwent ART in Hospital Sultanah Bahiyah Alor Setar from 2014 to 2019 were enrolled in this study. Patients' age, infertility factor, stimulation protocol and outcomes were analysed retrospectively. Cases with incomplete data were excluded from this analysis.

IVF Protocol in Fresh Cycle

In fresh IVF stimulation, the majority of the patients were stimulated with an antagonist cycle, except for cases of endometriosis where the ultra-long protocol was used. For antagonist protocol, stimulation typically began on day 1–2 menses, using recombinant follicle stimulation hormone (rFSH) alone or in combination with urinary or recombinant leutinizing hormone (LH), with an average dose of 150–350 iu daily. Trigger of ovulation in form of recombinant hCG was given once three or more leading follicles measured at least 17 mm from transvaginal scan. For patients who were at risk of ovarian hyperstimulation syndrome (OHSS), gonadotrophin releasing hormone (GnRH) agonist was used instead, followed by intensified luteal support (Humaidan protocol) after the oocyte retrieval (OR). In endometriosis patients, pituitary suppression was achieved by administrating long-acting GnRH agonist 3 months prior to IVF stimulation. A mixture of rFSH and urinary or recombinant LH was used, with a continuation of short-acting GnRH agonist for the rest of the stimulation protocols. Recombinant hCG 6500 iu (ovidrel) was used to trigger the oocytes, followed by oocyte retrieval after 36 hours. All patients had intracytoplasmic sperm injection (ICSI) procedures regardless of the cause of infertility.

Frozen Embryo Transfer Stimulation

In frozen embryo transfer, patients were randomly allocated to natural, mild stimulated or hormone replacement cycle. Patients were monitored transvaginally, and once the endometrial thickness reached 8 mm with trilaminar appearance, we started vaginal progesterone, followed by embryo transfer according to the age of embryo. Most of the patients were intended for blastocyst transfer, however in some cases we proceeded with cleavage state embryo transfer in avoidance of public holiday or weekends. Patients then continued their luteal support according to the protocol regime.

Embryo Transfer

All procedures were done as outpatient, using a Wallace or Emtrac embryo transfer catheter, both consisting inner and outer catheter. We transferred either 1–3 embryos at cleavage state or 1–2 blastocyst stage embryo based on the quality of the embryo and age of the patients.

Luteal Support

The luteal support consists of vaginal progesterone 90 mg daily, and 1,000 u hCG injection on days 0, 3, 6 following the oocyte retrieval for antagonist cycle. In patients who were stimulated with ultra-long protocol, oral oestrogen (estradiol valerate 2 mg BD) together with 1000u of hCG on days 0, 3, 6 and twice a day application of 90 mg vaginal progesterone was used for luteal support. For intensified luteal phase support, we followed Humaidan protocol whereby IM hCG injection of 1500u were given on the oocyte retrieval day, and day 5 post-OR along with vaginal progesterone 90mg BD and oestradiol valerate 2 mg TDS.

hCG Analysis

Serum hCG was taken on (i) day 16 post-oocyte retrieval or (ii) day 16 from the addition of progesterone in a frozen cycle.

The results were analysed in our biochemistry laboratory using the standard immunoassay method, and the level of 10 IU/L or more had been used to define biochemical pregnancy. For low level of HCG 10–20 IU/L, repeated samples were performed to determine the outcome of pregnancy. All pregnancies that ended with miscarriage, ectopic or failing biochemical pregnancy were recorded. Once the serum hCG was reported as biochemical pregnancy, we continued the luteal support and transvaginal ultrasounds were performed 3–4 weeks following the positive result to confirm the location and viability of pregnancy. Clinical pregnancies were confirmed with the presence of fetal heart activity from the scan and ongoing pregnancy was defined as pregnancy that lasted at least 12 weeks of gestation.

Statistical analysis

Statistical analysis was performed with SPSS version 25. The data were analysed separately, broadly divided into IVF outcomes – singleton livebirth and early pregnancy loss (miscarriage, ectopic pregnancy, and failed biochemical pregnancy). A separate analysis was performed for multiple pregnancy, knowing that the result would affect the overall level of hCG. Median values of hCG were computed and compared with non-parametric test (Mann–Whitney U test). Non-parametric receiver operating characteristics (ROC) curve was drawn to determine the cut-off value of hCG for predicting live birth in fresh and frozen cycle, multiple pregnancies with adequate sensitivity and specificity. For all the statistical test, the level of < 0.05 was taken as significant.

RESULTS

A total of 407 IVF pregnancies were analysed; 297 were fresh IVF cycles stimulation with 110 cases of frozen embryo transfers. Most of the embryo transfers were performed at cleavage state (D2-D3 embryo), comprised of 299 cases while the rest of 108 patients had blastocysts transfer.

Majority of the patients were diagnosed with male infertility; 122 patients (30%), followed by 81 cases of endometriosis (20%), 70 patients with PCOS and unexplained infertility (17% each group) and lastly tubal factors; 64 patients (16%). The mean age of the patients who attended our clinic was 32 years old. 13 patients (3%) were 40 years old and above; and 38% of them had early pregnancy loss despite of having good quality embryo transferred. Almost 70% of the IVF pregnancies ended with live birth, with the incidence of multiple pregnancies at 24%. Out of 129 patients who had early pregnancy loss, 18% had failing biochemical pregnancies, 8% had ectopic pregnancies and majority of the patients had miscarriages.

Table I: Median hCG level in all IVF outcomes (n=?)

	All pregnancies (cleavage and blastocyst) (n=407)	Cleavage embryo pregnancies (n= 299)	Blastocyst embryo pregnancies (n= 108)
	hCG level IU/L Median (QR)	hCG level IU/L Median (QR)	hCG level IU/L Median (QR)
Overall singleton livebirth (fresh and frozen cycles)	304.70 (267.40)	219.70 (257.00)	372.70 (424.78)
Fresh cycle singleton livebirth	223.00 (233.53)	208.00 (189.03)	312.95 (320.77)
Frozen cycle singleton livebirth	415.40 (398.70)	300.00 (393.90)	450.15(563.73)
Multiple live births	547.10 (584.20)	524.00 (349.90)	711.40 (1182.40)
Early pregnancy loss	77.00 (146.00)	53.55 (115.27)	107.60 (268.50)

hCG Prediction Level of IVF Outcomes
HG: human chorionic gonadotrophin, IUL: International Units Per Liter (IU/L)

Table II: hCG predictor level in of IVF outcomes

	All pregnancies (cleavage and blastocyst) (n=407)			Cleavage embryo pregnancies (n=299)			Blastocyst embryo pregnancies (n=108)		
	hCG level IU/L	Sen %	Spe %	hCG level IU/L	Sen %	Spe %	hCG level IU/L	Sen %	Spe %
Overall singleton live birth (fresh and frozen)	152.85	81.3	71.9	198.00	54.8	60.7	291.35	61.5	60.7
Fresh cycle singleton live birth	111.75	71.9	29.6	202.20	51.5	51.2	304.50	53.61	53.8
Frozen cycle singleton live birth	277.05	66.0	64.6	245.55	60.0	63.3	361.85	62.5	61.9
Multiple live births	322.4	78.6	64.3	303.75	78.0	77.9	553.30	72.7	76.3
Early pregnancy loss	174.50	61.5	60.7	153.55	77.6	77.6	265.95	71.1	71.4

Sen = sensitivity; Spe=specificity.

Median hCG Level in IVF Outcomes
Table I shows the median hCG level measured in this study. The overall median of hCG level in singleton livebirth was 304.70 IU/L with 267.40 IU/L of interquartile range. When subgroup analysis was performed, the serum hCG level was significantly higher in frozen cycles, as compared to fresh cycles; 415.40 IU/L vs 223.00 IU/L (p 0.002). Patients with multiple live births showed a higher median hCG level of 547.10 I IU/L, and the median hCG level in early pregnancy loss was 77.00 IU/L.

Analysis was then further divided according to the state of embryos; cleavage vs blastocyst. Blastocysts pregnancies recorded overall higher median hCG level as compared to cleavage state in all the outcomes measured.

Singleton livebirth
Figure 1 shows ROC curve plotted the predicted value of hCG level in total singleton livebirth (fresh and frozen cycle) as 152.85 IU/L, with the area under the ROC curve (AUC) of 0.822, a sensitivity of 81.3% and a specificity of 71.9%.

Blastocysts embryos recorded a higher level of hCG; 291.35 IU/L (sensitivity 61.5% specificity 60.7%) as compared to the cleavage embryos. (Table II).

Fresh vs frozen cycle singleton livebirth
The optimal hCG prediction level in singleton livebirth for the frozen group was higher; 277.05 IU/l (Figure 2) with area under the ROC curve (AUC) of 0.647 (sensitivity 66.0% specificity 64.6%) vs 111.75 IU/l in fresh cycle transfer (sensitivity of 71.9% and a specificity 29.6%)

Blastocysts pregnancies recorded a higher singleton livebirth predicted level in both fresh and frozen cycles. The prediction level of in frozen was 361.85 IU/L (sensitivity 62.5%) as compared to 304.50 IU/L in fresh cycle with a sensitivity of 53.61% (Table II).

Multiple live births
The ROC curve analysis showed the predicted value of hCG level in multiple pregnancies as 322.40 IU/l with area under the ROC curve (AUC) of 0.758, a sensitivity of 78.6% and a specificity of 64.3% (Figure 3). The cut-off point in cleavage embryo is lower as compared to blastocysts multiple livebirth; 303.75 IU/L (sensitivity 78% specificity 77.9%) vs 533.30 IU/L (sensitivity 72.7% specificity 76.3%), as seen in Table II.

Pregnancy loss
The overall pregnancy loss predicted hCG level was 174.50 IU/L with a sensitivity of 61.5% and specificity of 60.7%. Higher level was observed in blastocyst transfer at 265.95 IU/L as opposed to cleavage embryo transfer at 153.55 IU/L (Table II)

DISCUSSION

Multiple approach of measuring hCG post-embryo transfer has been proposed in predicting the IVF outcomes; including single measurement during peri-implantation period (day 5

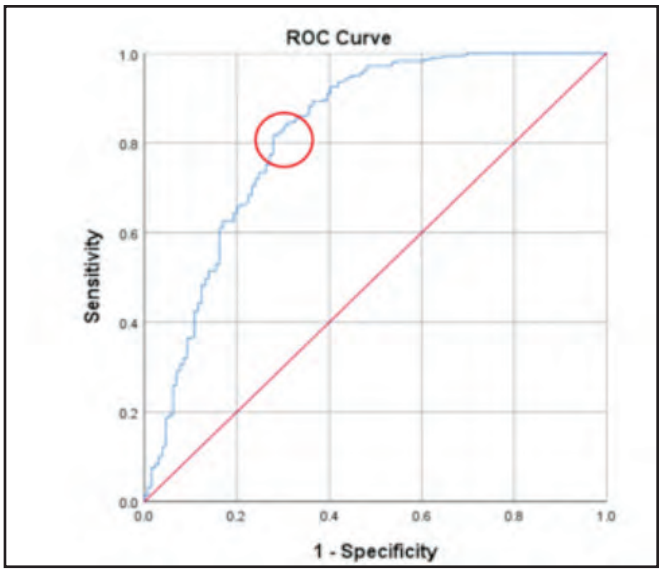

Fig. 1: ROC curve of hCG values predicting singleton livebirth in both frozen and fresh cycle

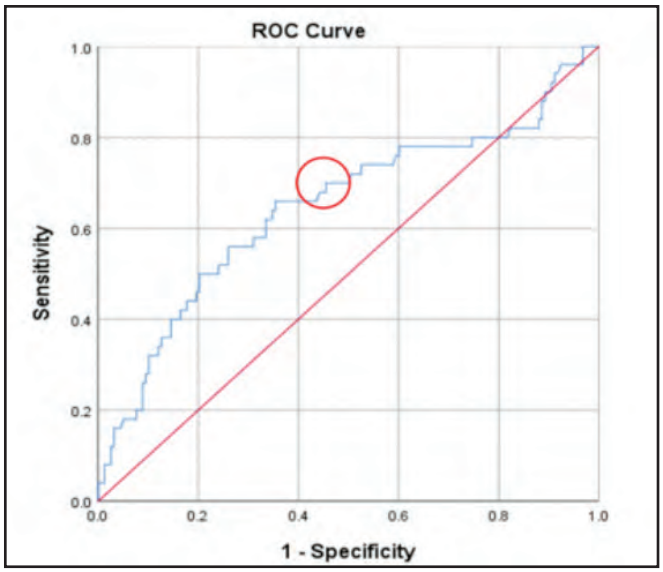

Fig. 2: ROC curve of hCG values predicting singleton livebirth in frozen cycle

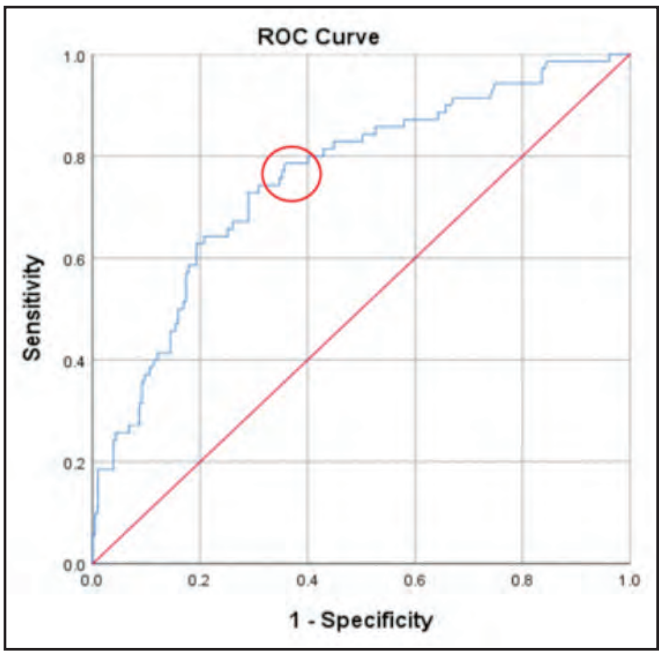

Fig. 3: ROC curve of hCG values predicting multiple pregnancies

post-transfer), day 12–14 post-embryo transfer and serial hCG measurement following embryo transfer. Saphiro et al[13] found that peri-implantation bHCG level of > 5IU/L (at day 5 following blastocyst transfer), resulted in 83% of ongoing pregnancy.

Few other researchers suggested comparing two levels of bhCG as a better predictor of IVF outcomes. For example, hCG index (day 12 hCG / day 8 hCG) of > 3.5 has been associated with 72.3% sensitivity and 100% specificity in predicting ongoing pregnancy.[2] Another paper by Hongbin et al suggested a hCG ratio on day 21 and day 14 post embryo transfer (hCG 21/hCG 14) as a predictor of viable pregnancy with level of >15 to be statistically significant.[14]

Considering cost-effectiveness and practicality point of view, majority of the practitioners still resort into single bHCG measurement at day 12–14 following embryo transfer. Even though the earliest serum bHCG is traceable in the serum at day 8–10 after fertilisation, it should be present and detectable from day 12 onwards. Based on the doubling level, measuring serum hCG on day 14–16 post-oocyte retrieval (fertilisation) represents the strength of implantation.[24]

In our centre, serum hCG is taken on day 16 post-oocyte retrieval (day 11–14 post-embryo transfer depending on the embryo age) not only for the reason mentioned above, but also for the fact that hCG injection was also used as part of the luteal support, and it takes 48–72 hours to be excreted from the system.[25] Meanwhile, for frozen embryo transfer, the day of progesterone commencement was referred to as the day of fertilisation.

In the present study, it is predicted that the overall median hCG level tends to be higher (304.70 IU/L) as the outcomes measured were singleton live birth. In a study by Poikkeus et al, a mean concentration hCG of 126 IU/L on day 12 post-embryo transfer was found to be associated with viable pregnancy; with a mean level of 115 IU/L in singleton and 201 IU/L in multiple pregnancies.[15] Kumbak et al3 further discussed a significant different levels of hCG in 2035 cycles for cleavage state embryo as compared to blastocyst transfer; with higher level found in D5 embryos.[3] Our result matched the previously published data with higher median hCG level recorded in blastocyst transfer as opposed to the cleavage state embryo; despite the small sample size.

Another interesting finding in this study is the mean hCG level of frozen embryo transfer was significantly higher than the fresh cycle. Even though the positive predictive values were low, the higher level of negative predictive values

indicates better accuracy of negative results. On the contrary, analysis in Sun Yat-Sen university hospital in Guangzhou reported a higher level of hCG predictor for live birth in both frozen (410.8 mIu/L) and fresh (222.86 mIU/L) cycle. However, their study only included blastocyst transfer which would eventually reveal a higher level.[16] Our blastocyst predictor hCG level was slightly lower; 361.85 IU/L for frozen cycle, and 304.50 IU/L for fresh cycle, most likely due to a smaller sample size.

Kalra et al[17] stated that the hCG rise level was noted to be higher in frozen embryo transfer even after adjustment of multiple pregnancies. They postulated the possibility of the best embryo surviving the whole thawing process together with physiologic endocrine environment during implantation might have influenced the outcomes and suggested further studies.[17] Previous studies also explained on the possibility of optimum endometrial receptivity in frozen cycle which result in better overall implantation rate, hence resulting in a higher hCG level.[18] The negative effect of the supra-physiological concentration of oestrogen and progesterone on the endometrium in fresh cycle may slow down the implantation process and release of hCG into the circulation. Another possible explanation is the rate of blastocyst growth during the transfer process, whereby some of the embryologist gave extra time for early blastocyst to grow in the thawing media and transfer a more mature embryo, therefore affecting the hCG result.[19]

Frozen embryo are also associated with higher birth and placental weight,[20] and previous data revealed that the level of hCG is also associated with fetal weight. A study by Barjaktrovic et al[21] found low level of bHCG in late first trimester has been associated with small gestational age in female fetus. On the other hand, Xiong et al[22] revealed a higher level hCG day 11 post blastocyst transfer in pregnant women with a male fetus in both fresh and frozen cycle. In our study, we did not look into the fetal weight and gender of the fetus to dispute or support this hypothesis.

In multiple live births, majority (90%) of our patients had twin pregnancies, followed by 9% of triplets and 1 % had quadruplets. Blastocysts pregnancies had a higher hCG level predictor as compared to cleavage embryos : 533.3 IU/L (sensitivity 72.7% specificity 76.3%) vs 303.75 IU/L (sensitivity 78.0% specificity 77.9%). A higher cut-off point was found in the study by Neeta Singh[23] with a level of 808 IU/L (sensitivity of 70% and specificity of 72%); however, the proportions of the higher order multiple gestations were not stated, which will affect the overall level of hCG.

A similar pattern was observed in pregnancy loss level, with a higher hCG level noted in blastocyst transfer; suggesting a need for closer monitoring with hCG level of 265.95IU/L or lower, as the sensitivity for miscarriage and ectopic pregnancy was 71%.

LIMITATIONS

This study has a few limitations. Firstly, it involves a small number of participants. Secondly, outcomes of the study may be less accurate as it involves both cleavage and blastocysts stage embryo transfer, therefore generating a slightly lower level of overall hCG. And lastly, a single study centre also serves as another limitation to the study, as it may increase the bias in result interpretation.

It is well known that there are many factors affecting the outcomes of IVF pregnancies; including the embryo qualities, endometrium, uterine factors and maternal age. However, for this study purpose, we focused on patients who were confirmed pregnant, based on single reading of hCG to further guide in monitoring and counselling.

We proposed a larger data collection involving only blastocyst transfer to capture the real value of predictive hCG level with consideration of other parameters such as the gender and birth weight of the babies which may affect the overall hCG level.

CONCLUSION

Single measurement of hCG on day 16 post oocyte retrieval (or day 16 from the addition of progesterone in frozen cycle) remains a practical and reliable approach to predict IVF outcomes. Not only it helps patients to understand the possibility of different IVF results at the end of treatment, it also serves as a guide for the practitioners in planning for further follow-up and subsequent management for the patients.

REFERENCES

1. Kee BS, Jung BJ, Lee SH. A study on psychological strain in IVF patients. J Assist Reprod Genet 2000; 17(8): 445-8.
2. De Neubourg D, Gerris J, Mangelschots K, Van Royen E, Vercruyssen M, Elseviers M. Single top quality embryo transfer as a model for prediction of early pregnancy outcome. Hum Reprod 2004; 19(6): 1476-9.
3. Kumbak B, Oral E, Karlikaya G, Lacin S, Kahraman S. Serum oestradiol and β-HCG measurements after day 3 or 5 embryo transfers in interpreting pregnancy outcome. Reprod Biomed Online 2006; 13(4): 459-64.
4. Martínez F, Coroleu B, Clua E, Tur R, Buxaderas R, Parera N, et al. Serum progesterone concentrations on the day of HCG administration cannot predict pregnancy in assisted reproduction cycles. Reprod Biomed Online 2004; 8(2): 183-90.
5. Ioannidis G, Sacks G, Reddy N, Seyani L, Margara R, Lavery S, et al. Day 14 maternal serum progesterone levels predict pregnancy outcome in IVF/ICSI treatment cycles: A prospective study. Hum Reprod 2005; 20(3): 741-6.
6. Yaron Y, Heifetz S, Ochshorn Y, Lehavi O, Orr-Urtreger A. Decreased first trimester PAPP-A is a predictor of adverse pregnancy outcome. Prenat Diagn 2002; 22(9): 778-82.
7. Bjercke S, Tanbo T, Dale PO, Mørkrid L, Abyholm T. Human chorionic gonadotrophin concentrations in early pregnancy after in-vitro fertilization. Hum Reprod 1999; 14(6): 1642-6.
8. Bondueue M-L, Dodd R, Liebaers I, Steirteghem A Van, Williamson R, Akhurst R. Chorionic gonadotrophin-/3 mRNA, a trophoblast marker, is expressed in human 8-cell embryos derived from tripronucleate zygotes. Human Reprod 1988; 3(7): 909-14
9. Makrigiannakis A, Vrekoussis T, Zoumakis E, Kalantaridou SN, Jeschke U. The role of HCG in implantation: A mini-review of molecular and clinical evidence Int J Mol Sci 2017; 18(6): 1305.
10. Tsampalas M, Gridelet V, Berndt S, Foidart JM, Geenen V, d'Hauterive SP. Human chorionic gonadotropin: A hormone with immunological and angiogenic properties. J Reprod Immunol 2010; 85(1): 93-8.

11. Horiuchi A, Nikaido T, Yoshizawa T, Itoh K, Kobayashi Y, Toki T, et al. HCG promotes proliferation of uterine leiomyomal cells more strongly than that of myometrial smooth muscle cells in vitro. Mol Hum Reprod 2000; 6(6): 523-8
12. Schumacher A, Costa SD, Zenclussen AC. Endocrine factors modulating immune responses in pregnancy. Front Immunol 2014; 5: 196
13. Shapiro BS, Daneshmand ST, Restrepo H, Garner FC. Serum HCG measured in the peri-implantation period predicts IVF cycle outcomes. Reprod Biomed Online 2012; 25(3): 248-53.
14. Chi H, Qiao J, Li H, Liu P, Ma C. Double measurements of serum HCG concentration and its ratio may predict IVF outcome. Reprod Biomed Online 2010; 20(4): 504–9.
15. Poikkeus P, Hiilesmaa V, Tiitinen A. Serum HCG 12 days after embryo transfer in predicting pregnancy outcome. Hum Reprod 2002; 17(7): 1901-5
16. Zhao W, Li Y, Ou J, Sun P, Chen W, Liang X. Predictive value of initial serum human chorionic gonadotropin levels for pregnancies after single fresh and frozen blastocyst transfer. J Huazhong Univ Sci Technol - Med Sci 2017; 37(3): 395-400.
17. Kansal Kalra S, Molinaro TA, Sammel MD. Viable pregnancies following fresh versus frozen embryo transfer: is there a difference in the rate of serum human chorionic gonadotropin (hCG) rise? Fertil Steril 2008; 90: S205.
18. Evans J, Hannan NJ, Edgell TA, Vollenhoven BJ, Lutjen PJ, Osianlis T, et al. Fresh versus frozen embryo transfer: Backing clinical decisions with scientific and clinical evidence. Hum Reprod Update 2014; 20(6): 808-21.
19. Zhu W, Yeung Q, Chan D, Chi L, Huang J, Wang Q, et al. Maternal β-HCG concentrations in early IVF pregnancy: association with the embryo development stage of blastocysts. Reprod Biomed Online 2019; 38(5): 683–90.
20. Pereira N, Baergen RN, Kelly AG, Pryor KP, Elias R, Rosenwaks Z. Birth weight differences of term singletons after frozen or fresh embryo transfer: what does placental histology reveal? Fertil Steril 2017; 108(3): e82.
21. Barjaktarovic M, Korevaar TIM, Jaddoe VWV, de Rijke YB, Visser TJ, Peeters RP, et al. Human chorionic gonadotropin (hCG) concentrations during the late first trimester are associated with fetal growth in a fetal sex-specific manner. Eur J Epidemiol 2017; 32(2): 135-44.
22. Xiong F, Sun Q, Li GG, Chen PL, Yao ZH, Wan CY, et al. Initial serum HCG levels are higher in pregnant women with a male fetus after fresh or frozen single blastocyst transfer: A retrospective cohort study. Taiwan J Obstet Gynecol 2019; 58(6): 833–9.
23. Singh N, Begum AA, Malhotra N, Bahadur A, Vanamail P. Role of early serum beta human chorionic gonadotropin measurement in predicting multiple pregnancy and pregnancy wastage in an in vitro et fertilization cycle. J Hum Reprod Sci 2013; 6(3): 213-8.
24. Lambers MJ, van Weering HGI, van't Grunewold MS, Lambalk CB, Homburg R, Schats R, et al. Optimizing hCG cut-off values: A single determination on day 14 or 15 is sufficient for a reliable prediction of pregnancy outcome. Eur J Obstetrics Gynecol Reprod Biol 2006; 127(1): 94-8.
25. Bjercke S, Tanbo T, Dale PO, Mørkrid L, Abyholm T. Human chorionic gonadotrophin concentrations in early pregnancy after in-vitro fertilization. Human Reprod 1999; 14(6): 1642-6.

ORIGINAL ARTICLE

Humoral response to SARS-CoV-2 vaccines among healthcare workers in a tertiary hospital in Malaysia

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ABSTRACT

Introduction: Healthcare workers (HCWs) were among the first to be fully vaccinated against SARS-CoV-2. However, the antibody responses to the vaccines and potential decline among Malaysian HCW are still unclear. The objective of this study is to follow-up anti-S antibody levels among HCW vaccinated with mRNA vaccine (BTN162b2) and inactivated vaccine (CoronaVac).

Materials and Methods: Plasma samples were collected pre-vaccination, 2 weeks and 6 months post-vaccination and tested for total immunoglobulin levels using ELISA method.

Results: A small percentage of HCW (2.2%, 15/677) had elevated anti-S antibody levels in their pre-vaccination plasma samples (median 20.4, IQR 5.8), indicating that they were exposed to SARS-CoV-2 infection prior to vaccination. The mRNA vaccine significantly increased anti-S levels of both previously infected and uninfected individuals to saturation levels (median 21.88, IQR.0.88) at 2 weeks post-second dose of the vaccine. At 6 months post-vaccination, the antibody levels appeared to be maintained among the recipients of the mRNA vaccine. However, at this time point, anti-S antibody levels were lower in individuals given inactivated vaccine (median 20.39, IQR 7.31, n=28), and interestingly, their antibody levels were similar to anti-S levels in pre-vaccination exposed individuals. Antibody levels were not different between the sexes.

Conclusion: Anti-S levels differ in individuals given the different vaccines. While further study is required to determine the threshold level for protection against SARS-CoV-2, individuals with low antibody levels may be considered for boosters.

KEYWORDS:
Anti-S COVID-19 antibody; healthcare workers; vaccination; mRNA vaccine; inactivated vaccine

INTRODUCTION

Healthcare workers (HCWs) were among the priority groups to be given vaccination against SARS-CoV-2. HCW are at-risk groups and prevalence of COVID-19 infection has been widely reported. A systematic review of 97 studies estimated the prevalence of SARS-CoV-2 infection was 11% (95% confidence interval (CI): 7, 15) and 7% (95% CI: 4, 11) based on molecular or serology tests, respectively.[1] Figures varied widely even within the same country in the United States, as 3.22% was reported in Seattle, Washington[2] while 57.06% in New York.[3] Vaccination among HCW in Malaysia was initiated on 24 February 2021 with the mRNA vaccine, BNT162b2 (Pfizer-BioNTech, US) followed by inactivated severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine CoronaVac® (Sinovac Biotech, China). Both are two dose vaccines, the second dose is given 2 weeks later. Clinical trials have shown an overall efficacy of 94.6% was achievable for BNT162b2 but figures varied from 50.38% to 91.25% for CoronaVac.[4]

General population studies detected significantly increased anti-spike SARS-CoV-2 antibodies, particularly after the second vaccination dose. Seroconversion was found in at least 99% of participants after the second dose vaccination with ChAdOx1 or BNT162b2.[5] The levels were even higher in individuals with previous COVID-19 infection.[5,6] Similar results were obtained with CoronaVac® with coverage of 97–99.4% response rate 28 days after the second dose vaccination of healthcare workers.[7,8] Serum antibody levels were maintained at positive levels for up to at least 6 months.[9,10] Comparative studies showed BNT162b2 induced higher levels of SARS-CoV-2 compared to ChAdOx1 levels[5,6] and CoronaVac.[10]

After an initial high, however, a decline in antibody levels was observed after receiving the second dose. Individuals provided with BNT162b2 vaccine demonstrated a substantially decreased humoral response.[11] Mean serum

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levels continued to decrease with times 10 at an estimated average of -60.05 BAU/ml with every 100 days.[6] There was no evidence that rates of antibody decline flattened over time where subjects were followed up to 119 days after second vaccination.[5]

On the one hand, the decline in IgG levels over time is expected since this occurs for all other vaccinations. However, there remain concerns about how long these antibodies remain reasonably effective[6] in addition to questions on adequate protection against mutant variants and variation in the efficacy of vaccines. Thus, the need to consider providing a booster dose is to be initiated 6 months following the completion of the second dose. Other considerations include increased adverse reactions and burnout among HCW with continued vaccination of the masses.[12,13]

The SARS-CoV-2 vaccines have been crucial in reducing the number of COVID-19 fatalities that have paralysed hospitals worldwide. Nevertheless, follow-up on seroconversion status is important as antibody levels are known to wane over time. The findings from serial measurements of antibody levels are important to policymakers, in deciding appropriate actions in terms of vaccination schedules to ensure long-term health and safety are maintained, including among HCWs.

The aim of this study was to determine anti-S antibody levels among HCWs before vaccination, 2 weeks after the first dose of vaccination and 6 months after the second dose of vaccination with the COVID-19 vaccines.

MATERIALS AND METHODS

Study Design

This was a prospective longitudinal cohort study conducted between May 2020 and December 2021. The participants were followed up until after the second vaccination with the COVID-19 vaccine.

Subjects

Study population was HCWs. Sampling population was HCWs in a tertiary teaching hospital in Malaysia. HCWs in this study were defined as individuals who work at this hospital, comprising of formal employees as well as medical and health sciences students. The distribution of the HCWs at this hospital was as follows: 18% were physicians, 27% were nurses or nurse aids, 21% were paramedical personnel, and 34% were in the non-medical areas such as administration and logistics. Sampling frame was obtained from the hospital's human resource unit. Minimum sample size required after anticipating 15% non-response rate was 695 participants. Sampling method was simple random sampling. The sampling frame was the numbered list of names of individuals who worked at this hospital obtained from the management office. The Microsoft Excel random number generator was used to provide the random numbers to select the participants.

Participants were eligible for inclusion in the study if they were Malaysian, aged 18 years or more, worked at the study location and received two doses of COVID-19 vaccine at the study location. Participants were excluded if they were pregnant, planning to get pregnant, breast-feeding, was less than 2 weeks after surgery/vaccination/body piercing, diagnosed with acute diseases or malignancy, not vaccinated against COVID-19, or only received a single dose COVID-19 vaccination.

This study's protocol was reviewed and approved by the Ethics Committee for Research Involving Human Subjects Universiti Putra Malaysia [JKEUPM-20201-197] and the Clinical Research Unit of the hospital. The participants provided their written informed consent to participate in this study.

Measurements

Participants who agreed to participate in the study were invited to provide peripheral blood samples before the first COVID-19 vaccine dose, 2 weeks after the second COVID-19 vaccine dose and 6 months after the second COVID-19 vaccine dose. These pre- and post-vaccination blood samples were tested for antibodies against SARS-CoV-2 receptor-binding domain (referred to as "anti-S antibody" in the subsequent paragraphs).

The total immunoglobulin detection kit (WANTAI SARS-CoV-2 Ab ELISA, Beijing Wantai Biological Pharmacy Enterprise, China) was used. The kit contained microwell strips pre-coated with a recombinant receptor-binding domain of SARS-CoV-2 spike protein. It has a sensitivity of 94.5% (293/310) and specificity of 100% (333/333). The protocol used was according to the manual provided in the kit by the manufacturer.

The results were calculated by relating each specimen absorbance (A) value to the Cut-off value (C.O.) of the plate and reported as OD ratio, according to the manufacturer's instruction.

Statistical Analysis

Shapiro-Wilks test demonstrated that data were not normally distributed. Independent Kruskal–Wallis test was used to test statistically significant differences between groups while pairwise comparisons were compared between two groups.

RESULTS

Subjects

Health care workers (HCW) from Hospital Pengajar, Universiti Putra Malaysia (HPUPM) were recruited for this study. A total of 666 HCWs provided pre-vaccination blood samples and almost 70% (466/666) provided a second sample 2 weeks post-vaccination. These HCW received the mRNA vaccine (BTN162b2). Majority of the sample was female. The participants' ages were similar. A smaller number (N=104) also provided a third sample 6 months after the second dose of vaccination. In addition, at 6 months post-vaccination, blood samples were also obtained from a subgroup of HCW (N=28) who completed two doses of the inactivated vaccine (CoronaVac). The summary of the results is presented in Table I.

Anti-S antibody levels

Among the pre-vaccinated samples, 2.2% (15/666) had positive levels of anti-S antibody, suggesting previous exposure to SARS-CoV-2 infection. In this group of

Table I: Healthcare workers' characteristics

	Pre-vaccine	2 weeks post-vaccine mRNA vaccine	6 months post-vaccine	
			mRNA vaccine	Inactivated vaccine
Total, N	666	466	104	28
Sex, N(%)				
Male	183 (27.5%)	121 (26.0%)	25 (24.0%)	18 (64.3%)
Female	483 (72.5%)	345 (74.0%)	79 (76.0%)	10 (35.7%)
Age, median (range)				
Male	31 (23–59)	31 (23–59)	30 (24–42)	
Female	31 (22–59)	31 (22–59)	30 (24–59)	

Table II: Anti-S antibody levels at pre-vaccination and post-vaccination among HCW who were naturally infected and uninfected

	Natural infection		Uninfected			
	Pre-vac	2 weeks post-vac mRNA vaccine	Pre-vac	2 weeks post-vac mRNA vaccine	6 months post-vac mRNA vaccine	6 months post-vac Inactivated vaccine
Total, N	15	13	651	453	104	28
M:F	4:11	3:10	179:472	118:335	25:79	18:10
OD ratio						
Median (IQR) (range)						
Total	20.4(5.8) (1.5-21.8)	21.9 (0.0) (21.7-21.9)	0.0(0.00) (0.0-0.5)	21.9(0.0) (11.9-21.9)	21.9(0.0) (21.4-21.9)	20.4(12.2) 1.9-21.9)
Male	19.8(3.8) (12.9-21.1)	21.9(0.1) (21.7-21.9)	0.0(0.0) (0.0-0.1)	21.9 (0.0) (14.5-21.9)	21.9 (0.0) (21.4-21.9)	20.4(12.3) (1.9-21.9)
Female	20.4(7.2) (1.5-21.8)	21.9(0.0) (21.9-21.9)	0.0(0.0) (0.0-0.5)	21.9 (0.0) (11.9-21.9)	21.9 (0.0) (21.6-21.9)	18.7(11.5) (2.7-21.9)

Abbreviations: OD- optical density.

individuals with previous exposure to COVID-19, their median anti-S antibody level was 20.4 (IQR 5.8). At 2 weeks post-vaccination, their median anti-S antibody levels increased slightly to 21.88 (IQR 0.06). Samples of infected subjects were excluded from further analysis.

In the remaining pre-vaccination samples (n= 651), the median anti-S antibody levels were negligible (0.01, IQR 0.05), suggesting no prior exposure to COVID-19. However, at 2 weeks post-vaccination with the mRNA vaccine, the level of anti-S antibody levels in this group of samples increased to the median value of 21.9 (IQR 0.0).

A comparison of anti-S antibody levels in HCW 6 months post-vaccination showed significantly lower levels in individuals vaccinated with inactivated vaccine compared to mRNA vaccine (Figure 1). Interestingly, there was no difference in the anti-S antibody levels between individuals vaccinated with an inactivated vaccine (median 20.4, IQR 12.2) and individuals exposed to natural infection (at pre-vaccination) (median 20.4, IQR 5.8). However, a higher percentage of cases had an optical density (OD) ratio of less than 10 (n=8/28, 28.6%). Median COVID-19 antibody levels for natural infection and individuals vaccinated with an inactivated vaccine (post-6 months) were lower than mRNA-vaccinated individuals (Figure 1).

Comparison between sexes showed there was no statistical difference in the anti-S antibody levels between the sexes. These findings are summarised in Table II.

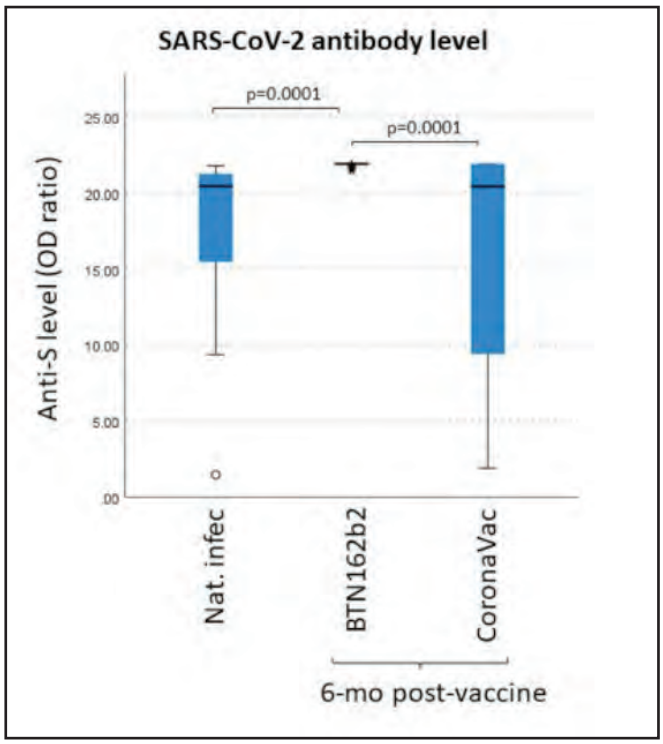

Fig. 1: Anti-S antibody levels in natural infection (N=15) and 6 months post-vaccination with the mRNA vaccine (N=104) and the inactivated vaccine (N=28). Pairwise comparisons followed Independent-samples Kruskal–Wallis test. $p<0.05$ considered significant. Significance values have been adjusted by the Bonferroni correction for multiple tests

DISCUSSION

A relatively high responder rate of 96% (666/695) and 65% (453/695) than expected, was achieved for pre-vaccination and 2 weeks post-vaccination, respectively. At 6 months post-vaccination, the number of respondents had reduced to 15% (104/695). Unfortunately, higher response rate could not be obtained due to insufficient time to recruit the numbers as the period of sample collection coincided with the commencement of the booster (third) dose, which took priority. As the majority of HCW received the mRNA (BTN162b2) vaccine, only 28 respondents who received two doses of the inactivated vaccine (CoronaVac) participated in the study at the final blood sampling exercise. Nonetheless, all participants in this study showed seroconversion post-vaccination with COVID-19 vaccine.

The spike protein has been identified as the immunodominant antigen of SARS-CoV-2 virus and thus is the main candidate vaccine. Anti-viral antibodies in COVID-19 patients that inhibit and neutralise virus entry were shown to target the receptor-binding domain (RBD) of the S1 subunit.[14] The Wantai SARS-CoV-2 Ab ELISA kit is suitable to detect antibodies in response to SARS-CoV-2 vaccines. As a matter of fact, a comparison of several serological diagnostic assay kits for COVID-19, identified Wantai total immunoglobulin (Ig) kit to have best overall characteristics including to detect the presence of protective antibodies.[15] The virus neutralization test is the gold standard to demonstrate the presence of coronavirus inhibitory antibodies. A high correlation (r=0.829) with the plaque-reducing neutralizing assay (PRNT50) was achieved with the Wantai Ig kit and protective neutralising antibodies was set at cut-off point at OD ratio > 10.[15] These suggested levels of anti-RBD antibodies detected by this kit are suitable alternative markers to detect the presence of anti-SARS-CoV-2 neutralizing antibodies. A limitation of the Wantai ELISA kit is the 'semi-quantitative' format which limits the range of reading, with a maximum read at 21.9 OD ratio. This, however, was comfortably way higher than the protective antibody cut-off value.

No differences were observed in the antibody levels in sex and age. This was in contrast to waning antibody seen following peak levels during days 4 through 30 in an Israel population vaccinated with mRNA vaccine, showing substantially lower levels of antibodies among males compared to female.[11] Older age and male sex were associated with substantially lower peak antibody levels in vaccinated participants[5] as seen also for age (>35 years old) among health care workers.[16] The discrepancy in the results here may be due to the higher number of younger (71%, 322/453, <35 years old) and small number of older (1.3%, 6/453, >55 years old) participants among our 2-weeks post-vaccination HCWs.

A prevalence of 2.2% (15/666) anti-S antibody positivity of responders in the pre-vaccination state among HCW was much lower than the estimated 7% (95% CI: 4, 11) in a meta-analysis of 97 studies.[1] A Malaysian study of 400 HCW from the National Public Health Laboratory and two COVID-19 designated public hospitals in Klang Valley between April 13, 2020, and May 12, 2020, on the other hand, detected zero prevalence even though a majority claimed exposure in the past month within respective workplaces.[17] Nonetheless, these findings may be explained by the exclusion of HCW previously confirmed for COVID-19 from the study population, as the aim of that study was to identify cases that were missed. Additionally, the low prevalence was due to high adherence to PPE. As for the current study, the low prevalence of anti-S antibody positivity in the pre-vaccination state among HCW could be due to the timing of data collection: it was conducted when the hospital had yet to receive COVID-19 cases.

Being infected with COVID-19 can result in several benefits for the individual. Previous infection can provide protection against the risk of subsequent infections by 80·5–100%[18] specifically with an estimated 60.2 to 97.6% against the alpha variant, 85.7% (95% CI, 75.8 to 91.7) against the beta variant, 92.0% (95% CI, 87.9 to 94.7) against the delta variant, but only 56.0% (95% CI, 50.6 to 60.9) against the omicron variant.[19] Previous infection is also an advantage to individuals vaccinated with CoronaVac as anti-S antibody levels were maintained at significantly higher levels compared to vaccinated HCW without prior infection.[8]

The results of the current study showed that HCWs vaccinated with BTN162b2 reached substantially high levels at median OD ratio of 21.9, 2 weeks post-vaccination and maintained this median level for at least 6 months. This increase supports earlier studies that were reviewed in individuals vaccinated with various SARS-CoV-2 vaccines.[5,6,7,8,9,10,11] Nevertheless, comparative studies on different vaccines demonstrated variation in levels of antibodies achieved. mRNA-1273 generated higher peak levels than BTN162b2 vaccinated individuals.[16] Studies in UK[5] and Kuwait[6] demonstrated higher antibody levels in BNT162b2 than ChAdOX1. Similar to our results, Kwok et al.[10] showed higher levels following BTN162b2 than CoronaVac. The important question, however, is whether all the vaccines provided a sufficient level of protection against later infections by SARS-CoV-2 and its various mutants. The SARS-CoV-2 surrogate virus neutralisation test[14] has been used to predict vaccine efficacy. Interestingly, although antibodies from ChAdOx1 individuals were lower than BNT162b2, the mean percentages of neutralizing antibodies were at similar levels,[6] suggesting lower levels per se should not be of immediate concern. As discussed above, OD ratio >10 is the cut-off value to imply the presence of neutralising antibodies with the Wantai Ig ELISA kit used here. OD ratio median values of 21.9 achieved here suggested neutralising antibodies were highly present, particularly after complete vaccination with BTN162b2.

Various studies have reported on the decline in SARS-CoV-2 antibody levels following initial peak after second dose of vaccine. The mean antibody half-life was estimated as 79 days. While prior infection extended the half-life by 13 days, very small reductions in half-life were observed at older ages, in non-white ethnicity and in having a long-term health condition.[5]

In this study, no significant reduction in antibody levels was detected at 6 months compared to 2 weeks post-vaccination, particularly among BTN162b2 vaccinated individuals. As expected, 6 months post-vaccination antibody levels in CoronaVac vaccinated participants were significantly lower than BTN162b2. Anti-S antibodies were observed to have decreased significantly by day 42 post-vaccination compared with day 14 post-vaccination, which were then maintained at

least for 98 days post-vaccination.[8] Here, at least 28% (8/28) of HCW vaccinated with CoronaVac appeared to no longer have sufficient protective neutralizing antibodies (OD ratio < 10). This result was similar to Kwok et al.[10] where median antibody levels of CoronaVac but not BTN162b2 vaccinated individuals fell below the cut-off protective antibody levels. Furthermore, it was shown this fall occurred 4 months after vaccination.[10] In this study, it was also demonstrated that among pre-vaccinated HCW with previous infection, a percentage, 13.3% (2/15) did not have the protective levels of neutralizing antibodies. Therefore, previously infected individuals also require vaccination.

Interestingly, the study by Nam et al.[9] observed significantly lower levels of anti-SARS-CoV-2 antibodies in individuals (N=50) with higher weight (>55 kg), and BMI (>22), 6 months post-second vaccination, suggesting another group to be recommended for booster does.

The main limitation of this study is its small sample size due to the high attrition rate. The high attrition rate could also be due to the high workload hence preventing the HCWs to participate in blood-taking exercise. Nevertheless, the findings in this study addressed the study objectives. Another limitation was the different SARS-CoV-2 antibody kits that were used in different studies making comparison difficult. This could be resolved by using the WHO international binding antibody unit per ml[5,6] although thresholds set may still differ. The ELISA kit used here also limited the detection of the range of antibody levels and is better to be replaced with quantitative kits.

CONCLUSION

There was a small percentage of HCW who were exposed to SARS-CoV-2 before the vaccination campaign started. The mRNA vaccination increased anti-S antibody levels to protective levels which were stably maintained at 6 months post-vaccination. Anti-S level at this time point was significantly lower among HCW vaccinated with the inactivated vaccinate, where more than a quarter did not have protective levels. This suggests a booster dose would benefit these individuals.

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REFERENCES

1. Gómez-Ochoa SA, Franco OH, Rojas LZ, Raguindin PF, Roa-Díaz ZM, Wyssmann BM, et al. COVID-19 in health-care workers: a living systematic review and meta-analysis of prevalence, risk factors, clinical characteristics, and outcomes. Am J Epidemiol 2021; 190(1): 161–75.
2. Roxby AC, Greninger AL, Hatfield KM, Lynch JB, Dellit TM, James A, et al. Detection of SARS-CoV-2 among residents and staff members of an independent and assisted living community for older adults — Seattle, Washington, 2020. MMWR Morb Mortal Wkly Rep 2020; 69(14): 416–18.
3. Breazzano MP, Shen J, Abdelhakim AH, Dagi Glass LR, Horowitz JD, Xie SX, et al. Resident physician exposure to novel coronavirus (2019-nCoV, SARS-CoV-2) within New York City during exponential phase of COVID-19 pandemic: report of the New York City residency program directors COVID-19 research group. Preprint. Posted online April 28, 2020. medRxiv.
4. Creech CB, Walker SC, Samuels RJ. SARS-CoV-2 vaccines. JAMA 2021; 325(13): 1318–20.
5. Wei J, Pouwels KB, Stoesser N, Matthews PC, Diamond I, Studley R, et al. COVID-19 Infection Survey team. Antibody responses and correlates of protection in the general population after two doses of the ChAdOx1 or BNT162b2 vaccines. Nat Med 2022 May; 28(5): 1072–82.
6. Ali H, Alahmad B, Al-Shammari AA, Alterki A, Hammad M, Cherian P, et al. Previous COVID-19 infection and antibody levels after vaccination. Front Public Health 2021; 9: 778243.
7. Şenol Akar Ş, Akçalı S, Özkaya Y, Gezginci FM, Cengiz Özyurt B, Deniz G, et al. Factors affecting side effects, seroconversion rates and antibody response after inactivated SARS-CoV-2 vaccination in healthcare workers. Mikrobiyol Bul 2021; 55(4): 519–38. Turkish
8. Cucunawangsih C, Wijaya RS, Lugito NPH, Suriapranata I. Antibody response to the inactivated SARS-CoV-2 vaccine among healthcare workers, Indonesia. Int J Infect Dis 2021; 113: 15–7.
9. Nam SY, Jeon SW, Lee HS, Lim HJ, Lee DW, Yoo SS. Demographic and clinical factors associated with anti-SARS-CoV-2 antibody levels after 2 BNT162b2 mRNA vaccine doses. JAMA Netw Open 2022; 5(5): e2212996.
10. Kwok SL, Cheng SM, Leung JN, Leung K, Lee CK, Peiris JM, et al. Waning antibody levels after COVID-19 vaccination with mRNA Comirnaty and inactivated CoronaVac vaccines in blood donors, Hong Kong, April 2020 to October 2021. Euro Surveill 2022; 27(2): 2101197.
11. Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, et al. Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months. N Engl J Med 2021; 385(24): e84.
12. Jang Y, You M, Lee H, Lee M, Lee Y, Han JO, et al. Burnout and peritraumatic distress of healthcare workers in the COVID-19 pandemic. BMC Public Health 2021; 21: 2075.
13. Mc Keaveney C, Reid J, Carswell C, Bonner A, de Barbieri I, Johnston W, et al. Experiences of renal healthcare practitioners during the COVID-19 pandemic: a multi-methods approach. BMC Nephrol 2021; 22(1): 301.
14. Tan CW, Chia WN, Qin X, Liu P, Chen MI, Tiu C, et al. A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2-spike protein-protein interaction. Nat Biotechnol 2020; 38(9): 1073–78.
15. GeurtsvanKessel CH, Okba NMA, Igloi Z, Bogers S, Embregts CWE, Laksono BM, et al. An evaluation of COVID-19 serological assays informs future diagnostics and exposure assessment. Nat Commun 2020; 11(1): 3436.
16. Steensels D, Pierlet N, Penders J, Mesotten D, Heylen L. Comparison of SARS-CoV-2 antibody response following vaccination with BNT162b2 and mRNA-1273. JAMA 2021; 326(15): 1533–535.
17. Woon YL, Lee YL, Chong YM, Ayub NA, Krishnabahawan SL, Lau JFW, et al. Serology surveillance of SARS-CoV-2 antibodies among healthcare workers in COVID-19 designated facilities in Malaysia. Lancet Reg Health West Pac 2021; 9: 100123.
18. Kojima N, Klausner JD. Protective immunity after recovery from SARS-CoV-2 infection. Lancet Infect Dis. 2022; 22(1): 12–4.
19. Altarawneh HN, Chemaitelly H, Hasan MR, Ayoub HH, Qassim S, AlMukdad S, et al. Protection against the omicron variant from previous SARS-CoV-2 infection. N Engl J Med 2022; 386(13): 1288-90.

Preventable stillbirths and neonatal deaths in Malaysia: An analysis of the under-five mortality surveillance data 2015–2017

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ABSTRACT

Introduction: The under-five mortality (U5M) trend in Malaysia significantly declined from 30.0 per 1000 live births (1980) to 8.0 per 1000 live births (2004), and the trend plateaued over the next two decades. Stillbirths and neonatal deaths were the major contributors to U5M. Scarce literature addressing factors associated with preventable U5M in Malaysia. The objective of this study was to describe preventable stillbirths and neonatal mortality, the associated factors and recommendation for improvement.

Materials and Methods: The U5M surveillance data from 2015 to 2017 was retrieved for Malaysian cases of stillbirths and neonatal deaths with multiple pregnancies as exclusion. Stillbirth and neonatal death cases were analysed descriptively for socio-demographic and clinical characteristics. Logistic regressions were performed to identify the associated factors.

Results: There were 15,444 cases selected for analysis, of which 55% of stillbirths and 45% of neonatal deaths. There were 21% of preventable deaths (U5M) and the major contributing causes of preventable stillbirths and neonatal deaths were classified as perinatal death (82.5%), infectious and parasitic diseases (4.1%) and congenital malformations (3.5%). The birth weight (aOR 6.03, 95% CI: 4.14–8.79), hypertensive mother (aOR 1.88, 95% CI: 1.66–2.12) and instrumental delivery (aOR 1.64, 95% CI: 1.16–2.31) were significantly associated with preventable stillbirths and neonatal deaths. Higher household income (>RM3000 per month) was noted as a protective factor (aOR 0.79, 95% CI:0.69,0.89). Mothers with ethnicities other thanBumiputera, single mothers and housewives were identified as the group of mothers with higher odds of poor perinatal services. Among the 3242 cases of preventable stillbirths and neonatal deaths with a complete documented level of adequacy and quality of healthcare, the most frequently identified factors were due to insufficient antenatal care (ANC) (20.4%), non-compliance with medical advice (12.3%) and unsuitable place of delivery (8.6%).

Conclusion: Increasing trend of preventable stillbirths and neonatal deaths was noted over 3 years (2015–2017), and one-fifth was related to insufficient ANC service-related factors. Remedial measures in improving the quality of ANC services with an emphasis on the targeted high-risk maternal socio-demographic group (other Bumiputera, older antenatal mothers, nonmarried, poor family income neglected family) and enhancing ANC competency skills among the healthcare provider through adequate training are required to decrease preventable stillbirths and neonatal deaths in Malaysia.

KEYWORDS:
stillbirths and neonatal death; preventable death; antenatal care; sustainable development goals

INTRODUCTION

Under-five mortality (U5M) rate is a primary indicator of the health status of a population. It was defined as the probability of a child dying between birth and exactly 5 years of age.[1] It was further categorised based on age classification, i.e., neonatal death, perinatal death and toddler deaths. Stillbirth is defined as births after 28 completed weeks or more of gestation without any sign of life during delivery.[2] Perinatal mortality refers to stillbirths and deaths of infants aged less than 1 week and meanwhile, neonatal death is defined as deaths of infants less than 28 days.[2] The global U5M rate declined by 61%, from 93 deaths per 1,000 live births in 1990 to 37 in 2020.[1] In Malaysia, the U5M rate decreased from 18 per 1000 live births in 1990 to 6 per 1000 live births in 2009.[2] However, rates have plateaued at 5.3 (stillbirth death rate), 8.3 (perinatal death rate) and 4.5 per 1000 live births (neonatal death rate) for the year 2020.[3-5]

Stillbirths and neonatal mortality have been linked to poor intrauterine conditions, insufficient healthcare services, poor socio-economic levels, and certain biological factors. It was found that antenatal and intrapartum complications, birth defects, infections, and maternal comorbidities, especially hypertension and diabetes, were the most common causes of stillbirths.[6,7] Preterm birth, intrapartum-related complications such as birth asphyxia, infections, and birth defects were the most common causes related to neonatal deaths.[7,8] Based on the U5M report,[5] the causes of stillbirths and neonatal deaths were related to conditions from the perinatal period, including congenital malformations, certain parasitic and infections, respiratory disease, nervous system and injuries, poisons and other external factors. Among these preventable

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deaths, 44% were reported in 2006, declining to 30% in 2019.[4,5]

Stillbirths were labelled as the 'forgotten catastrophe' and a global problem with significant disparities in rates as high as 23 times in the worst-affected countries.[9-11] Studies have shown that neonatal mortality is a significant subset of U5M globally.[11,12] Therefore, the Sustainable Development Goal (SDG) 3.2 aims to reduce the U5M rate to less than 25 per 1000 live births globally by 2030.[11] Current epidemiological knowledge of U5M rate helps to assess, prepare and monitor public health programs, especially for maternal and child health. The Malaysian U5M surveillance system collects the succumbed cases' characteristics and the health services factors. Up to present knowledge, scanty published literature came from Malaysia's U5M surveillance data. This study aims to describe the preventable stillbirths and neonatal deaths of Malaysia's U5M data from 2015 to 2017 and determine the associated factors and recommendations to improve maternal and child healthcare services in Malaysia.

MATERIALS AND METHODS

Study Design

This is a descriptive analysis of the Malaysia's U5M surveillance data for the years 2015–2017.

Study Setting

All U5M including stillbirth and perinatal death reported in Malaysia.

Case Definition

The U5M is defined as any child death from birth to age five, including the stillbirths notified to the Ministry of Health using the Stillbirth and U5M Form SU5MR-1/2012.[12] The inclusion criteria set were only the stillbirths and neonatal deaths were retrieved for data analysis. We excluded multiple pregnancies, non-Malaysians, and major incomplete cases.

Variables and Outcomes

The outcome measured was factors associated with the preventable cause of stillbirths and neonatal deaths. The preventable death was divided into (1) deaths through medical intervention, which includes modifiable factors that may have contributed to the death such as delayed referral, delayed diagnosis and treatment, inadequate management and (2) deaths due to non-medical conditions such as drowning, choking, teenage pregnancy, and non-accidental injury. Whereas non-preventable deaths refer to death due to life-limiting diseases, such as lethal congenital malformation and inborn error metabolism. The undetermined deaths referring to a situation when accurate/appropriate classification of death cannot be determined by the investigation committee members. The independent variables were socio-demographic (maternal age, ethnicity, education level, marital status) and clinical characteristics of the mother or baby (medical condition, birth weight, types of delivery).

Data Management and Analysis

All verified data were recorded in a line list of U5M. Statistical Package for the Social Sciences (SPSS) software version 22 was used for data analysis. The trend of stillbirths and neonatal deaths, causes of death and service-related factors were described descriptively. Socio-demographic, clinical characteristics of preventable stillbirths and neonatal death were analysed using univariate and multivariate analysis to examine factors that best predicted preventable stillbirths and neonatal deaths in Malaysia.

Ethical Approval

The present study obtained approval from the Medical Research and Ethics Committee Ministry of Health Malaysia (NMRR-19-426-46153(IIR) and the University Kebangsaan Malaysia Research Ethics (JEP-2019-283).

RESULTS

There were 18,013 stillbirths and neonatal deaths in the U5M dataset from 2015 to 2017. However, only 16,977 cases were identified after the exclusion of multiple pregnancies, non-Malaysians and cases with major incompleteness. Out of 16,977 deaths, 100% of deaths occurred in hospitals, 55% were stillbirths and 45% were neonatal deaths. The incidence rate of stillbirth was 5.98, 6.09 and 5.98 per 1000 births in 2015, 2016 and 2017, respectively. The neonatal death rate was 5.07, 4.86 to 5.02 per 1000 births for the same reported years. Further data cleaning, only 15,444 cases were written as preventable or not preventable and 15,094 cases were documented as hospital death or non-hospital death (Table I).

Causes of Stillbirths and Neonatal Deaths in Malaysia

3242 cases of preventable stillbirths and neonatal deaths were analysed. The conditions from the perinatal period (82.5%) was the commonest causes of preventable deaths followed by specific infectious and parasitic disease (4.1%), congenital malformation (3.5%), unknown (3.2%) and respiratory (2%) (Figure 1). Specific infectious and parasitic diseases showed an increment from 0.63% in 2015 to 3.4% in 2017.

Factors Associated with Preventable Stillbirths and Neonatal Deaths in Malaysia

Table II depicts factors associated with preventable stillbirths and neonatal deaths. The birth weight (aOR 6.03, 95% CI:4.14–8.79), hypertensive mother (aOR 1.88, 95% CI:1.66–2.12) and instrumental delivery (aOR 1.64, 95% CI:1.16–2.31) were significantly associated with preventable stillbirths and neonatal deaths. The household income of RM3001 and above (aOR 0.79,95% CI:0.69,0.89) was noted as a protective factor.

Adequacy and Quality of Healthcare Influencing Preventable Stillbirths and Neonatal Deaths

Insufficient ANC (20.4%), non-compliance with medical advice (12.3%) and unsuitable place of delivery (8.6%) were associated with preventable stillbirths and neonatal deaths (2015–2017) (Table III)

Association Between Health Services Factors and Maternal Characteristics

Table IV depicts the association of perinatal care service factors for preventable stillbirths and neonatal deaths reported for 2015–2017. Maternal ethnicity of 'Other Bumiputera' and 'Other Malaysian', aged 36 years old and

Table I: Characteristics of stillbirths and neonatal deaths in Malaysia (2015–2017)

Characteristics	Year		
	2015, n (%)	2016, n (%)	2017, n (%)
Preventable or not preventable (n=15,444)			
Preventable	808 (16.2)	1099 (22.1)	1335 (24.4)
Not preventable	4067 (81.5)	3747 (75.3)	4057 (74.1)
Undetermined	89 (1.8)	71 (1.4)	80 (1.5)
Unknown	29 (0.6)	61 (1.2)	1 (0)
Type of death (n=15,094)			
Hospital death	5221 (99.9)	5019 (100)	4850 (100)
Non-hospital death	4 (0.1)	0	0
Category of death by age (n=16,997)			
Stillbirth	3137 (54.3)	3116 (55.8)	3060 (54.5)
Stillbirth rate*	5.98	6.09	5.98
Neonatal death	2640 (45.7)	2471 (44.2)	2553 (45.5)
Neonatal death rate*	5.07	4.86	5.02

*Per 1000 births.

Table II: Factors associated with preventable stillbirths and neonatal mortality (2015–2017)

Variables	Regression coefficient[a]	Adjusted OR[b]	95% CI	Wald	*p* value
Birth weight					
500–999 g	0	1			
1000–1499 g	0.43	1.53	(1.29,1.82)	4.87	<0.001
1500–2499 g	0.63	1.88	(1.63,2.18)	8.52	<0.001
2500–4000 g	1.08	2.95	(2.56,3.39)	15.19	<0.001
4001 g and above	1.80	6.03	(4.14,8.79)	9.35	<0.001
Household income					
RM3000 and below	0	1			
RM3001 and above	-0.24	0.79	(0.69,0.89)	-3.72	<0.001
Maternal hypertension					
No	0	1			
Yes	0.63	1.88	(1.66,2.12)	10.11	<0.001
Type of birth					
Spontaneous vaginal delivery	0	1			
Instrumental delivery	0.49	1.64	(1.16,2.31)	2.82	0.005

[a]Adjusted; [b]Backward method was applied; Interacting variables were omitted from the mode; Mean VIF = 1.13, no multi-collinearity issues in the model.

Table III: Level of substandard care based on criteria of preventable death[12]

Adequacy and quality of healthcare (Level of substandard care)	Yes	No	Not Applicable
Insufficient antenatal care provided/unbooked (n=2879)	662 (20.4%)	2074 (64%)	141 (4.3%)
Delay/lack of referral/consultation for high-risk pregnancy (n=2873)	148 (4.6%)	2294 (70.8%)	430 (13.3%)
Not adherence to medical advice/treatment including follow-ups (n=2861)			
398 (12.3%)	1973 (60.9%)	490 (15.1%)	
Misinterpretation of test during ANC (n=2859)	23 (0.7%)	2282 (70.4%)	553 (17.1%)
Unsuitable place of delivery (n=2864)	280 (8.6%)	2233 (68.9%)	351 (10.8%)
Inadequate intrapartum monitoring (n=2847)	62 (1.9%)	2052 (63.3%)	733 (22.6%)
Delay/lack in referral/consultation during intrapartum (n=2849)	77 (2.4%)	2117 (65.3%)	655 (20.2%)
Inadequate/inappropriate resuscitation/stabilisation (n=1305)			
63 (1.9%)	1134 (35%)	108 (3.3%)	
Failure to transfer to appropriate care (n=1307)	91 (2.8%)	1077 (33.2%)	139 (4.3%)
Delay/lack consultation from senior/specialist (n=1306)	40 (1.2%)	1143 (35.3%)	123 (3.8%)
Family neglect or ignorance, (n=1308)	105 (3.2%)	1057 (32.6%)	146 (4.5%)
Healthcare provider staffing ratio not meeting MOH norms (n=1309)	24 (0.7%)	1152 (35.5%)	133 (4.1%)
Inadequate equipment (n=1296)	44 (1.4%)	1121 (34.6%)	131 (4%)

above, single mothers and housewives were identified as higher odds of poor perinatal health services ($p<0.05$). 'Other Malaysian' is defined as Malaysian other than Malay, Chinese and Indian that is made up of mostly Orang Asli, Bumiputera Sarawak and Bumiputera Sabah. High household income per month (>RM5000) and formal education (tertiary level) were noted as protective factors for preventable stillbirths and neonatal deaths ($p<0.05$).

DISCUSSION

The Malaysian child healthcare services were established under the National Rural Health Development Programme14 that clearly outlines a clinical management pathway between primary and tertiary hospitals for effective paediatric care. The neonatal retrieval teams were implemented in neonatal intensive care planning to support preterm and small gestational age foetus management.[15,16] The monitoring continued during the post-delivery period

Table IV: Association between health services factors and maternal characteristics (n=?)

		Regression coefficient (B)	Adjusted odds ratio	95% CI	Wald	*p*
Insufficient ANC supplied/unbooked[a]						
Maternal ethnicity	Malay	0	1			
	Other Bumiputera	0.461	1.586	1.12,2.24	6.901	0.009
	Other Malaysian	-1.637	0.194	0.05,0.80	5.173	0.023
Maternal age	18 years old and below	0	1			
	36–42 years old	0.657	1.929	1.04,3.58	4.328	0.037
	43 years old and above	1.927	6.867	2.605,18.10	15.183	<0.001
Marital status	Married	0	1			
	Unmarried	2.718	15.152	10.41,22.05	201.766	<0.001
	Widow/divorced	3.135	22.999	6.23,84.89	22.145	<0.001
	Unknown	1.914	6.78	3.00,15.31	21.221	<0.001
Household income	RM1000 and below	0	1			
	RM1001-RM5000	-0.574	0.563	0.34,0.94	4.935	0.026
	RM5001-RM7000	-0.867	0.42	0.20,0.87	5.443	0.020
Unsuitable place of delivery[b]						
Maternal ethnicity	Malay	0	1			
	Other Bumiputera	0.444	1.559	1.04,2.34	4.627	0.031
	Other Malaysian	-3.317	0.036	0.002,0.78	4.496	0.034
Maternal age	18 years old and below	0	1			
	Unknown	3.696	40.282	2.71,599.19	7.2	0.007
Marital status	Married	0	1			
	Unmarried	1.866	6.465	4.42,9.45	92.799	<0.001
	Widow/divorced	1.986	7.283	2.13,24.90	10.024	0.002
	Unknown	1.431	4.181	1.85,9.46	11.801	0.001
Failure to transfer to proper care[c]						
Maternal occupation	Working mother	0	1			
	Housewife	0.575	1.777	1.11,2.86	5.658	0.017
Family neglect or ignorance[d]						
Maternal ethnicity	Malay	0	1			
	Other Bumiputera	1.223	3.398	1.32,8.73	6.458	0.011
Maternal education	No formal education	0	1			
	Tertiary education	-1.526	0.217	0.06,0.75	5.859	0.016
	Unknown	-1.728	0.178	0.03,0.92	4.233	0.04
Marital status	Married	0	1			
	Unmarried	0.993	2.698	1.37,5.33	8.19	0.004
	Widow/divorced	3.006	20.21	1.14,357.75	4.204	0.04

[a] Backward method was applied, interacting variables were omitted from the model, mean VIF =1.32, no multi-collinearity issues in the model, correctly classified percentage 85.2%
[b] Backward method was applied, interacting variables were omitted from the model, mean VIF = 1.29, no multi-collinearity issues in the model, correctly classified percentage 90%
[c] Backward method was applied, interacting variables were omitted from the model, mean VIF = 1.15, no multi-collinearity issues in the model, correctly classified percentage 92.7%
[d] Backward method was applied, interacting variables were omitted from the model, mean VIF =1.30, no multi-collinearity issues in the model, correctly classified percentage 92.5%

with postnatal home visits by primary care midwives, routine health examinations by medical doctors, immunisations, child development and health monitoring in the primary care clinics to improve under-five outcomes.[17]

There are two databases under the Ministry of Health to collect data on U5M which are the Rapid Reporting System of Perinatal and Neonatal Deaths and the National Neonatal Registry.[18,19] The process of auditing the U5M including the stillbirths is documented based on level of care and time allocation. Having a regular monthly meeting at the district level and a 3-monthly meeting at the state level will ensure complete and finalise information of the death cases submitted for national reporting.[18] The quality assessment of the auditing system for U5M is determined by appointed committee members that consists of a paediatrician, obstetrics and gynaecology specialist, family medicine specialist, public health physician and related staff. They will be responsible for determining the causes of death, classifying the death into preventable or non-preventable death, determining the remedial action, and disseminating the findings.[18] The standard is at par with other countries on perinatal and U5M investigation of deaths.[1,11,13]

The U5M database system was separated into a notification and an investigation system to ensure the validity of the data collection process. The flow process was integrated at each healthcare level, from the district and state health officials to the national level. The International classification of disease (ICD) 10 coding was used for certification of death in the U5M reporting system to help in making international comparison. The U5M reporting format (SU5MR-I/2012) was used to distinguish stillbirths from U5M notifications to avoid duplication of reporting.

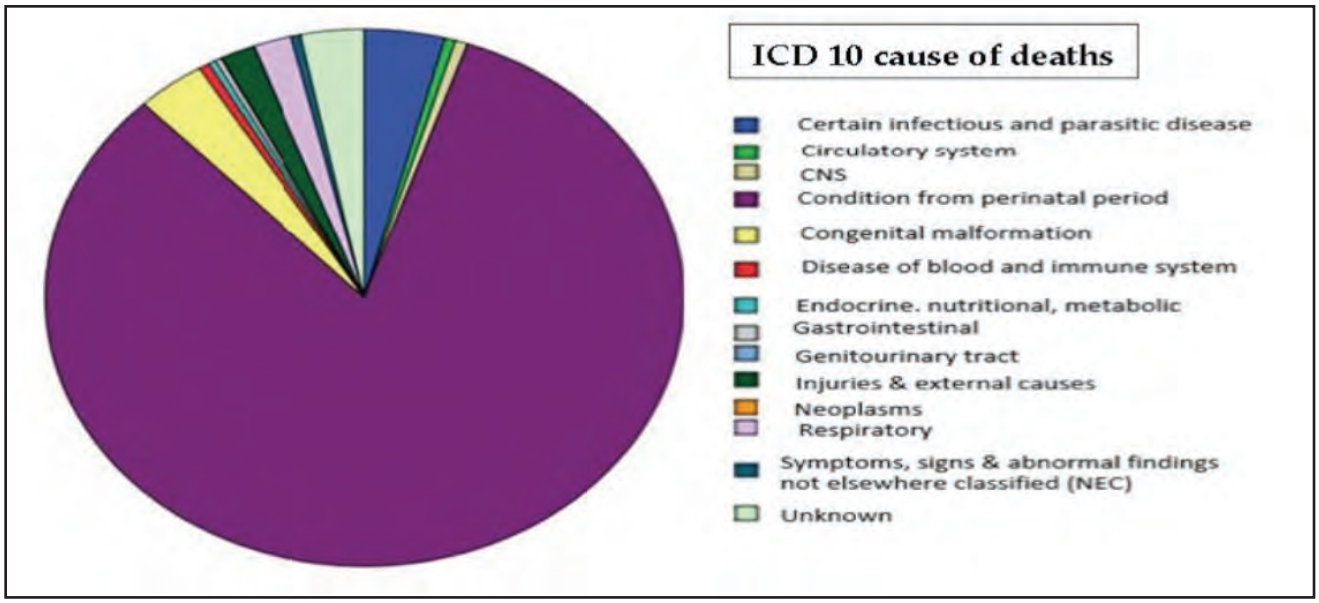

Fig. 1: Causes of preventable stillbirths and neonatal deaths in Malaysia, 2015–2017 (n=3242 cases)

The stillbirths rate calculated in the present study ranges from 5.98 to 6.09 per 1,000 births which are slightly higher from data reported by Statista20 ranging from 4.4 to 5.4 per 1,000 births. Similar pattern was seen for the neonatal death rate, which was found higher i.e. ranging from 4.86 to 5.07 per 1,000 live births compared to rate reported by the Department of Statistics Malaysia (DOSM) which showed ranging from 4.2 to 4.4 per 1,000 live births.[21,22] The difference is due to the method of data collation by the organisation and reporting. However, the trend seems to be plateaued compared to the post-independence era until the early 2000s. This study identified that the annual preventable stillbirths and neonatal deaths in Malaysia increases from 16% (in 2015) to 24% (in 2017). This is an alarming trend for Malaysian health services as child survival is one of importance health indicator for SDG monitoring.

The Lancet series on 'Ending preventable stillbirths' indicated that maternal and child healthcare quality improvement is necessary to prevent stillbirths and neonatal deaths.[13] Preventable means that death can be avoided by proper and adequate care, either by medical intervention or non-medical intervention.[23,24] Although the factors associated with preventable U5M are known, the references for Malaysia are scarce.[18] Determining the factors might help the health provider to improve the health services delivery to the targeted population. This study selected only stillbirths and neonatal deaths from the U5M group as they have a similar cause of death that is influenced by intrauterine and early-life conditions.[24]

Causes of Preventable Stillbirths and Neonatal Deaths in Malaysia
An U5M study in Malaysia5 in 2006 found that Most of the deaths (61.8%) occurred in the first year of life, and only 38.1% of preventable deaths occurred in hospital settings and these were caused primarily by patient and family factors (58%). Using a similar U5Msurveillance dataset, a report published for data collected in 2016 showed preventable U5M decreased to 31%, and the three most common causes were conditions originating in the perinatal period (27.5%); injuries, poisoning and external causes (17.0%); and certain infectious and parasitic diseases (14.5%).[19] Present study focussed only for stillbirths and neonatal deaths found that the preventable deaths for stillbirths and neonatal deaths were in increasing trend (16% to 24% over the period of 2015 to 2017). The major contributing causes of preventable stillbirths and neonatal deaths were classified as perinatal death (82.5%), infectious and parasitic diseases (4.1%) and congenital malformations (3.5%) which saw similar pattern as reported earlier.[5,19]

Studies within the last decade indicate that neonatal birth weight is the most common predictor of infant survival.[23-25] The lower an infant's birth weight, the higher the risk of mortality and morbidity. Conversely, mortality among normal birth weight babies is preventable. Inadequate foetal monitoring, sepsis or intrapartum unpreparedness causing asphyxia are preventable. In addition, maternal comorbidities such as hypertension cause adverse health outcomes for infants.[26] However, these conditions can be managed successfully if we can stabilise any women with a history of hypertension during the pre-pregnancy care clinic. Provision of good ANC share with mother to empower them on monitoring maternal weight gain, blood pressure, urine protein, diabetic screening, early urinary infections and administering intrapartum antibiotics for Group B Streptococcus. These antenatal management strategies ensure that infants are protected from life-threatening elements. Prevention of neonatal mortality is also associated with household income.[27] People with a household income above the poverty line have better health literacy and health-seeking behaviours. Studies show that increased health literacy and health-seeking behaviours reduces U5M. Implementation of first 100 days of life and Approach to Unwell Child Under Five Manual were parts of efforts to improve the trend of U5M in Malaysia.[28]

Service Factors Related to Preventable Stillbirths and Neonatal Death

Many countries, including Malaysia, practice shared care approach for pregnant women. Primary health care clinic is the first contact for pre-pregnancy and antenatal health screening. Using risk assessment checklist, cases were grouped as high and low risk and managed according to level of care and type of personnel and were assessed at every antenatal visit.[14,17] Although almost 97% of pregnant women make four or more antenatal visits as recommended by WHO, high-frequency antenatal visits alone are insufficient to lower infant mortality rates.[27] Furthermore, it is crucial to address the 3% of pregnant women with insufficient antenatal visits. The frequency of ANC check-ups is not representative of the quality of patient care. A study found that about half of all pregnant mothers were still not getting the desired ANC score documentation required.[30] It was reported that high-risk pregnancies with a lower ANC scores, influencing maternal and child health outcomes.[29-31]

Patient factors remain a significant contributor to preventable stillbirths and neonatal deaths. The preventable U5M in Malaysia found that 50–55% of deaths were caused by patient and family factors in 2008.[5] Consequently, non-compliance with medication and medical advice and delays in seeking treatment were identified as common patient factors that need to be addressed. Therefore, health education is essential for information dissemination, promoting awareness that can influence mother's attitude and behaviour for accessing antenatal care.[31]

In this study, we found that mothers from 'Other Bumiputera', 'other Malaysian', maternal age above 35 years old, housewives and single mothers have a higher risk of getting poor perinatal care service. Therefore, identifying early-risk groups of mothers for active health education intervention and monitoring can prevent adverse pregnancy outcomes. The maternal and child health programme is designed to be accessible and easily engaged even by the minority groups with limited accessed. Providing of mobile clinic for mother and child check-up in their village and area is known as the best to reach the need.[31] A comprehensive and effective pre-pregnancy care, which includes a family planning programme, were provided to guide the mother towards safer pregnancy and birth when they are ready and in a good health condition. Strengthening social supports by collaboration with social welfare, non-governmental organisation and community participation should be established to support single mothers, low income households during pregnancy and delivery.[32-34] Using digital health for empowerment and surveillance monitoring will help in broadening and efficiency of services provided.

Despite of low percentage of preventable stillbirth and neonatal death reported in the present study, it is critical to address the issues, particularly on service-related factors among preventable deaths. Remedial measures in improving the quality of ANC services with an emphasis on the targeted high-risk maternal socio-demographic group as found significant in this study such as other Bumiputera, older antenatal mothers, nonmarried, poor income family and neglected family. This group needs to be monitored closely by the medical doctor for proper health empowerment on the importance of ANC an early identification for referrals. Studies in Indonesia and Africa found that the mortality reporting system required constant re-evaluation and improvement to preserve information quality.[33,34]

More targeted intervention needs to be conducted to embark the modifiable non-service-related factors by upscaling health competency training among the healthcare providers. Revamping training module as digital education and promoting continues medical education for healthcare providers are important to improve healthcare quality and avoid substandard care in maternal and childcare.

LIMITATIONS

A well-maintained mortality reporting system is vital for epidemiological surveillance and sustaining good quality health services. The Malaysian U5M data collection system was established almost two decades ago and should be improved over time. However, deficiencies persist within this system, such as incomplete data reporting, with up to 60% missing data. Understandably, a child's delivery and death are significant events resulting in incomplete data retrieval from the mother. Due to such high vulnerability, monitoring perinatal health and children's epidemiological surveillance indicators is essential. In present study, the missing data were managed by the listwise deletion approach with an expectation of data missing completely at random (MCAR), representing a randomly drawn sub-sample of the original data as written in earlier publication.[33]

CONCLUSIONS

The U5M trends in Malaysia remained almost static for the years 2015–2017 with an increasing trend of preventable stillbirths and neonatal deaths. Healthcare service factors found related to preventable stillbirths and neonatal death. Providing a comprehensive yet targeted maternal and child health services is crucial in improving the equity of health and preventing delay in identification, referral and appropriate management. Revisiting the training capacity and approaches using digital education in strengthening the healthcare provider competency in managing ANC cases is timely. Enhancing health promotion to increase health literacy, increase awareness in practicing health lifestyles and early screening for non-communicable diseases are important to all women especially before there are entering their reproductive age.

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REFERENCES

1. World Health Organization. Under-five mortality rate. [cited 2022 Oct 14]. Available from: https://www.who.int/data/nutrition/nlis/info/under-five-mortality-rate
2. Department of Statistics Malaysia. Vital Statistics Tie Series Malaysia 1963-1998. 2001. 285 p.
3. UNICEF. Under-five mortality. 2021 [cited 2022 Oct 14]. Available from: https://data.unicef.org/topic/child-survival/under-five-mortality/
4. BPKK. Laporan Tahunan 2019. Putrajaya. 2020. [cited 2022 Oct 14]. https://fh.moh.gov.my/v3/index.php/component/jdownloads/send/47-bpkk/684-final-laporan-tahunan-bpkk-2019-primer-n-keluarga-25-ogos-2020-compressed?Itemid=0
5. Lan WS, Imam H. A study on under five deaths in Malaysia 2006. Kuala Lumpur 2008. [cited 2022 Oct 14]. Available from https://www.crc.gov.my/wp-content/uploads/documents/report/StudyOnUnder5DeathsinMsia_2006.pdf
6. Joseph KS, Kramer MS. The fetuses-at-risk approach: survival analysis from a fetal perspective. Acta Obstetricia et Gynecologica Scandinavica 2018; 97(4): 454-65.
7. Zhu X, Niu H, Wang H, Li X, Qi T, Ding W, et al. High risk pregnancy associated perinatal morbidity and mortality: A second birth population-based survey in Huai'an in 2015. BMC Pregnancy Childbirth 2019; 19(1): 1-15.
8. Ngoc NTN, Merialdi M, Abdel-Aleem H, Carroli G, Purwar M, Zavaleta N, et al. Causes of stillbirths and early neonatal deaths: Data from 7993 pregnancies in six developing countries. Bull World Health Organ 2006; 84(9): 699-705.
9. Sankar MJ, Natarajan CK, Das RR, Agarwal R, Chandrasekaran A, Paul VK. When do newborns die? A systematic review of timing of overall and cause-specific neonatal deaths in developing countries. J Perinatol 2016; 36(S1): S1-11.
10. Mengesha HG, Sahle BW. Cause of neonatal deaths in Northern Ethiopia: A prospective cohort study. BMC Public Health 2017; 17(1): 1–8.
11. UNICEF. A neglected tragedy the global burden of stillbirths. 2020 [cited 2021 May 8]. [cited 2022 Oct 14]. Available from: https://data.unicef.org/resources/a-neglected-tragedy-stillbirth-estimates-report/
12. Family Health Development Division MOH. Guideline on classification of under-five mortality into preventable and unpreventable death. 2017. [cited 2022 Oct 14]. Available from: https://fh.moh.gov.my/v3/index.php/component/jdownloads/send/20-sektor-kesihatan-kanak-kanak/447-preventable-26-5?Itemid=0
13. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional , and national causes of child mortality in 2000-13 , with projections to inform post-2015 priorities: an updated systematic analysis. The Lancet 2015; 385(9966): 430–40. [cited 2022 Oct 14].
14. Fadzil F, Jaafar S, Ismail R. 40 years of Alma Ata Malaysia: Targeting equitable access through organisational and physical adaptations in the delivery of public sector primary care. Primary Health Care Res Dev 2020; 21: 1-8.
15. Boo NY, Pong KM. Neonatal resuscitation training program in Malaysia: Results of the first 2 years. J Paediatrics Child Health 2001; 37(2): 118-24.
16. Boo NY. Neonatal resuscitation programme in Malaysia: An eight-year experience. Singapore Med J 2009; 50(2): 152-9.
17. BPKK. Manual Perkhidmatan Kesihatan bagi Anggota Kejururawatan di Perkhidmatan Kesihatan Awam bagi Anggota Kejururawatan di Perkhidmatan Kesihatan Awam. Vol. 15. 2016. [cited 2022 Oct 14]. Available from https://fh.moh.gov.my/v3/index.php/component/jdownloads/send/18-sektor-kesihatan-ibu/409-manual-perkhidmatan-kesihatan-ibu-anak-bagi-anggota-jururawat-di-perkhidmatan-kesihatan-awam-2016?Itemid=0
18. National Stillbirth and Under Five Mortality Technical Committee MOH. Guidelines for stillbirth and under-five mortality. 2013. [cited 2022 Oct 14]. Available from https://hdokpps.weebly.com/uploads/4/2/8/1/42813715/guideline_for_under_5_mortality.pdf
19. Choo HL, Abdul Manaf AM. A study on under five deaths in Malaysia in the year 2016. Putrajaya 2020. [cited 2022 Oct 14]. Available from https://fh.moh.gov.my/v3/index.php/component/jdownloads/send/20-sektor-kesihatan-kanak-kanak/698-technical-report-of-under-five-deaths-in-malaysia-2016-compressed?Itemid=0
20. Statista. Stillbirth rates in Malaysia from 2011 to 2020. [cited 2022 Oct 14]. Available from: https://www.statista.com/statistics/641958/malaysia-stillbirth-rates/
21. DOSM. Vital Statistics, Malaysia 2015. Department of Statistics Malaysia. 2016.
22. Ho MK. Department of Statistics Malaysia Press Release. Department of Statistics Malaysia 2018; 5-9.
23. Wilcox AJ. On the importance-and the unimportance-of birthweight. Int J Epidemiol 2001; 30(6): 1233-41.
24. Pirhadi M, Dehnavi ZM, Torabi F. The relationship between small for gestational age (SGA) at birth and developmental delay in children aged 4 to 60 months. Int J Pediatrics-Mashhad 2018; 6(11): 8595-603.
25. Shah NM, Shah MA, Khalaf AA, Mustafa MM, Al-Sayed A. Searching for socioeconomic risk factors in perinatal mortality in Kuwait: A case control study. Soc Sci Med 2000; 51(4): 539–50.
26. Kassar SB, Melo AMC, Coutinho SB, Lima MC, Lira PIC. Determinants of neonatal death with emphasis on health care during pregnancy, childbirth and reproductive history. Jornal de Pediatria 2013; 89(3): 269–77.
27. Dewey KG. Reducing stunting by improving maternal, infant and young child nutrition in regions such as South Asia: Evidence, challenges and opportunities. Maternal Child Nutrition 2016; 12: 27-38.
28. BPKK. Training Manual on Approach to Unwell Children. Vol. 18. [cited 2022 Oct 14]. Available from https://fh.moh.gov.my/v3/index.php/component/jdownloads/send/20-sektor-kesihatan-kanak-kanak/702-20200819-atucu5-20191018-fa-edit-11-11-2020-compressed?option=com_jdownloads
29. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. ISBN 978 92 4 1549912.2016. [cited 2022 Oct 14]. Available from http://apps.who.int/iris/bitstream/handle/10665/250796/9789241549912-websupplement-%20eng.pdf;jsessionid=D74DF9F2550E689BE3A7B748E9C15EBA?sequence=8
30. NHMS. National Health And Morbidity Survey 2016 : Maternal And Child Health (MCH) [Internet]. Vol. 2, Kementerian Kesihatan Malaysia. 2016. [cited 2022 Oct 14]. Available from: http://www.iku.gov.my/images/IKU/Document/REPORT/2016/NHMS2016ReportVolumeII-MaternalChildHealthFindingsv2.pdf
31. Yeoh PL, Hornetz K, Shauki NIA, Dahlui M. Assessing the extent of adherence to the recommended antenatal care content in Malaysia: Room for improvement. PLoS ONE. 2015; 10(8): 1-15.
32. Azreena E., Suriani I, Muhamad Hanafiah Juni FP. Factors associated with health literacy among Type 2 diabetes mellitus patients. Int J Public Health Clinical Sci 2016; 3(6): 50-64.
33. Bamford LJ, McKerrow NH, Barron P, Aung Y. Child mortality in South Africa: Fewer deaths, but better data are needed. South African Med J 2018; 108(3a): 25.
34. De Bernis L, Kinney MV, Stones W, Ten Hoope-Bender P, Vivio D, Leisher SH, et al. Stillbirths: Ending preventable deaths by 2030. The Lancet 2016; 387 (10019): 703-16.

ORIGINAL ARTICLE

COVID-19 pandemic and its impact on emergency surgery in colorectal cancer: A single centre experience

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ABSTRACT

Introduction: The COVID-19 pandemic has led to major changes in the provision of surgical services and also affected patients' health-seeking behaviour. This contributes to delayed presentation of many surgical conditions resulting in poorer outcomes. Colorectal cancer (CRC) patients who present with acute surgical emergencies such as complete bowel obstruction, perforation, bleeding or sepsis often require immediate intervention. This study aimed to assess the impact of COVID-19 pandemic on the proportion of emergency surgery in CRC patients.

Materials and Methods: This is a retrospective cohort study. All CRC patients who underwent elective and emergency surgery from January until December 2019 (pre-COVID era) and September 2020 until August 2021 (COVID era) were included. Patient demographics, presentation, tumour stage, surgery performed and waiting time for surgery were collected. Data were then compared.

Results: Seventy-seven and 76 new cases of CRC underwent surgery before and during COVID-19, respectively. The proportions of emergency surgery before and during COVID-19 are 29% vs 33% (p=0.562). Of those who required emergency surgery, the proportions of patients who required stoma formation are 59% vs 72% (p= 0.351). There was no difference in median waiting time for patients requiring elective surgery (p= 0.668).

Conclusion: The proportion of emergency surgery for CRC patients is not statistically higher during the pandemic.

KEYWORDS:
Colorectal cancer; COVID-19; emergency surgery

INTRODUCTION

Worldwide, colorectal cancer (CRC) is the second most commonly diagnosed cancer in women and the third most in men.[1] The survival of CRC patients depends largely on the stage of disease upon diagnosis.[2] In addition, patients who present with acute surgical emergencies such as obstruction, perforation and bleeding are more likely to have locally advanced tumour and distant metastasis, thus conferring them poorer prognosis.[3]

Following the COVID-19 pandemic, changes in the pattern of general surgery admission have been observed. Patients tend to be older, more ill with organ dysfunction and have higher rates of bowel obstruction, perforation or incarcerated hernia.[4,5] In addition, an increased rate of large bowel obstruction and more T4 CRC have been reported in the United Kingdom during the pandemic.[6]

Malaysia, which is among the countries that are severely hit by the pandemic, has daily number of COVID-19 cases per 1 million population that ranks top ten worldwide in August 2021.[7] An increase in acute surgical emergencies (bowel obstruction, perforation, bleeding and sepsis) as initial presentation of CRC has been anecdotally observed. The primary aim of this study is to compare the proportions of surgery performed in emergency manner for all CRC patients that underwent surgery before and during COVID-19 pandemic.

MATERIALS AND METHODS

Study Design and Setting

This is a retrospective cohort study performed at a secondary hospital in Malaysia. All CRC patients that underwent surgery are divided into pre-covid and covid cohort. Pre-covid population is defined as patients operated on before the pandemic from January until December 2019. Covid population is defined as patients operated on from September 2020 until August 2021.

World Health Organization (WHO) declared the novel coronavirus (COVID-19) outbreak as a global pandemic on 11 March 2020.[8] Soon after, the Federal Government of Malaysia implemented a series of movement control orders which includes lockdown and quarantine. However, the sudden and exponential rise of daily confirmed cases, hospitalisations and deaths due to COVID-19 in Malaysia occurred during the latter half of the year 2020.[7] Thus, in this study, the Covid population was taken as patients operated on during September 2020 until August 2021. This is to allow the full impact of COVID-19 during the height of the pandemic to be captured.

Inclusion and Exclusion Criteria

All patients with new diagnosis of CRC including carcinoma in situ and anorectal carcinoma that underwent elective and emergency surgery during the study time period were included. Emergency surgery are surgery performed for CRC patient who presents with acute surgical emergencies such as obstruction, perforation, bleeding and sepsis that require immediate surgical intervention.

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Table I: Patient characteristics (n=?)

Patient characteristics	Pre-COVID (77)	COVID (76)	*p* value
Age (years)			
Mean (SD)	61 (13)	60 (14)	0.560[a]
Gender			
Male n (%)	52 (69)	52 (68)	0.906[b]
Female n (%)	25 (31)	24 (32)	
Race n (%)			
Malay n (%)	51 (66%)	51 (67)	0.893[b]
Chinese n (%)	23 (30%)	21 (28)	
Indian n (%)	3 (4%)	4 (5)	
Duration of symptoms (days)			
Median (IQR)	56 (84)	56 (84)	0.851[c]
Charlson Comorbidity Index			
0	10 (14%)	13 (17.5%)	0.779[b,d]
1	18 (24%)	13 (17.5%)	
2	18 (24%)	17 (23%)	
3	14 (19%)	13 (18%)	
≥4	14 (19%)	18 (24%)	
Tumour location			
Right-sided	13 (16%)	12 (16%)	0.697[b]
Left-sided	32 (42%)	35 (46%)	
Anorectal	32 (42%)	28 (37%)	
Synchronous (right and left)	0	1 (1%)	
Pathological staging			
pT1/T2	9 (15%)	11 (19%)	0.568[a,d]
pT3/T4	52 (85%)	48 (81%)	
pN0	25 (41%)	31 (53%)	0.204[a,d]
pN1/N2	36 (59%)	28 (47%)	

[a]Independent Student's t test. [b]Pearson's chi-squared test. [c]Mann-Whitney U test. [d]There were data missing for some variables. The percentages were derived by excluding the missing data from the variables.

Table II: Comparison of surgery performed (n=?)

	Pre-COVID	COVID	*p* value
Elective surgery	55 (71)	51 (67)	0.562[a]
Emergency surgery	22 (29)	25 (33)	
Acute intestinal obstruction	19	23	
Bowel perforation	3	2	
Formation of stoma in emergency surgery			
Yes	13 (59)	18 (72)	0.351[a]
No	9 (41)	7 (28)	

[a]Pearson chi-squared test.

Table III: Waiting time for elective surgery

	Pre-COVID (30)	COVID (40)	p-value
Waiting time (days)			
Median (IQR)	8.5 (10)	9 (15)	0.668[a]

[a]Mann–Whitney U test.

Operating theatre log and histopathological log were used to identify the cases. Outpatient clinic notes and inpatient admission notes were then retrieved from the hospital record office. Patients with high-grade dysplasia, neuroendocrine tumour, gastrointestinal stromal tumour and small bowel malignancy were excluded.

Statistical Analysis

Continuous variables were compared using Student's t test or Mann–Whitney U test; categorical variables using Pearson's chi-squared test. A p value of < 0.05 was considered statistically significant. Data analyses were performed using IBM SPSS Statistics for Windows (Version 23.0. Armonk, NY: IBM Corp.).

RESULTS

A total of 153 patients with newly diagnosed CRC underwent surgery during the study period, with an almost equal number of cases during the pre-COVID era, n=77 and COVID era, n=76. The patient demographics in terms of age, gender, race, Charlson Comorbidity Index, and tumour location and staging were comparable with all p value > 0.05 (Table I).

The proportions of CRC patients who underwent emergency surgery before and during COVID-19 are 29% vs 33%, p=0.562. The majority of them had complete large bowel obstruction. Among patients who underwent emergency surgery, the proportion of patients who required stoma formation is 59% vs 72%, p=0.351 (Table II).

The waiting time for patients that underwent elective surgery was also collected. Waiting time for surgery was calculated from the time decision was made for surgery until the day of surgery. There is no difference in median waiting time for elective surgery between the two groups of patients (Table III).

DISCUSSION

Across the world, various surgical services were heavily disrupted and significantly reduced during the COVID-19 pandemic. This includes clinic consultations, cancer screening programs, elective endoscopy procedures and surgeries. These are part of the strategies to channel the financial, personal protective equipment and manpower resources to combat the spread of COVID-19. At the same time, changes in healthcare-seeking behavior have also taken place. Some patients tend to dismiss their symptoms and are reluctant to seek earlier healthcare for fear of contracting COVID-19 from the hospital.[9,10]

In this study, similar numbers of CRC patients underwent surgery (77 vs 76) before and during the pandemic. There was no statistically significant difference in the proportions of emergency surgery (29% vs 33%, p=0.562). The majority of emergency surgery were due to bowel obstruction which requires immediate intervention. All patients were not previously diagnosed as having CRC. As part of the limitations of the retrospective design of this study, it is not possible to explore factors that could lead to delayed presentation in these group of patients.

A higher proportion of CRC patients with stoma-forming procedures has been reported in the UK during the pandemic.[11] In our local setting, comparing the proportions of stoma creation in emergency setting before and during the pandemic, the difference is not significant. However, we observed that during the pandemic, we tend to adopt staged surgery strategy in patients who had complete bowel obstruction. Emergency trephine diversion transverse or sigmoid colostomy were performed for CRC patients who had complete large bowel obstruction without peritonitis. Diversion stoma is a relatively shorter and lower risk surgery which can be performed even under local anesthesia. Patients were then scheduled for an elective tumour resection after they have returned to their physiological baseline and their medical condition optimised. Scarcity of ICU beds, ventilators and blood products during the COVID-19 pandemic has deterred us from performing upfront major tumour resection in these acutely ill patients. Nevertheless, in tertiary centres with available colonic stenting services, colonic stenting is suggested as the first treatment option in suitable intestinal obstruction cases during the COVID-19 pandemic.[12,13]

The waiting times for elective CRC surgery were similar (8.5 days vs 9 days, p=0.668). This is made possible by strongly adhering to both national and international guideline of prioritising malignant cases during the pandemic.[14] Benign non-urgent cases were postponed or referred to other hospitals. Interestingly, we also found a patient who chose to postpone surgery to complete COVID-19 vaccination. No complications occurred during the waiting period.

CONCLUSION

There was no statistically significant difference in the proportion of emergency surgery in CRC patients before and during the pandemic. Nevertheless, in the midst of heavy focus on combating the pandemic, both patients and healthcare providers should consider CRC diagnosis and make prompt surgical referral for patients with suspicious gastrointestinal symptoms.

REFERENCES

1. Dekker E, Tanis PJ, Vleugels JL, Kasi PM, Wallace MB. Colorectal cancer. Lancet 2019; 394 (10207): 1467-80.
2. Sant M, Aareleid T, Berrino F, Lasota MB, Carli PM, Faivre J,et al. EUROCARE-3: survival of cancer patients diagnosed 1990–94—results and commentary. Ann Oncol 2003; 14: v61-118.
3. Baer C, Menon R, Bastawrous S, Bastawrous A. Emergency presentations of colorectal cancer. Surg Clin. 2017; 97(3): 529-45.
4. McLean RC, Young J, Musbahi A, Lee JX, Hidayat H, Abdalla N, et al. A single-centre observational cohort study to evaluate volume and severity of emergency general surgery admissions during the COVID-19 pandemic: is there a "lockdown" effect?. Int J Surg 2020; 83: 259-66.
5. Cano-Valderrama O, Morales X, Ferrigni CJ, Martín-Antona E, Turrado V, García A, et al. Reduction in emergency surgery activity during COVID-19 pandemic in three Spanish hospitals. J Br Surg 2020; 107(8): e239.
6. Shinkwin M, Silva L, Vogel I, Reeves N, Cornish J, Horwood J, et al. COVID-19 and the emergency presentation of colorectal cancer. Colorectal Dis 2021; 23(8): 2014-9.
7. Malaysia: Coronavirus Pandemic Country Profile [cited August 2022]. Available from : https://ourworldindata.org/coronavirus/country/malaysia
8. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Bio Medica: Atenei Parmensis 2020; 91(1): 157.
9. Solis E, Hameed A, Brown K, Pleass H, Johnston E. Delayed emergency surgical presentation: impact of corona virus disease (COVID-19) on non-COVID patients. ANZ J Surg 2020; 90: 1482-3.
10. Lazzerini M, Barbi E, Apicella A, Marchetti F, Cardinale F, Trobia G. Delayed access or provision of care in Italy resulting from fear of COVID-19. Lancet Child Adolesc Health 2020; 4(5): e10-1.
11. Morris EJ, Goldacre R, Spata E, Mafham M, Finan PJ, Shelton J, et al. Impact of the COVID-19 pandemic on the detection and management of colorectal cancer in England: a population-based study. Lancet Gastroenterol Hepatol 2021; 6(3): 199-208.
12. Ren X, Chen B, Hong Y, Liu W, Jiang Q, Yang J, et al. The challenges in colorectal cancer management during COVID-19 epidemic. Ann Transl Med 2020; 8(7): 498.
13. Chen YH, Peng JS. Treatment strategy for gastrointestinal tumor under the outbreak of novel coronavirus pneumonia in China. Chin J Gastrointestinal Surg 2020; 23(2): I-V.
14. SAGES and EAES Recommendations Regarding Surgical Response to COVID-19 Crisis, published on 30th March 2020. [cited August 2022]. Available from: https://www.sages.org/recommendations-surgical-response-covid-19/

Outcome of tracheostomy among COVID-19 patients in a tertiary hospital setting: Our experience

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ABSTRACT

Introduction: The COVID-19 pandemic is unprecedented. Amongst those who contracted COVID-19, a number required intubation and prolonged ventilation. This increased the number of ventilated patients in the hospital and increased the requirement for tracheostomy of severe COVID-19 patients. Our objective is to study the outcome of patients with COVID-19 who underwent tracheostomy.

Materials and Methods: This study is a novel retrospective study in a tertiary centre in Malaysia. Case notes of COVID-19 patients who underwent tracheostomy in Hospital Ampang were collected using the electronic Hospital Information System. Data were analysed using the SPSS system.

Results: From a total of 30 patients, 15 patients survived. All patients underwent either open or percutaneous tracheostomy. The median age is 53 (range: 28–69) with a significant p-value of 0.02. Amongst comorbidities, it was noted that diabetes mellitus was significant with a p-value of 0.014. The median time from the onset of COVID-19 to tracheostomy is 30 days. The median duration of intensive care unit (ICU) stay is 30.5 days, with the median duration of hospital length of stay of 44 days (p = 0.009 and <0.001, respectively). No complications that contributed to patient death were found. Survivors had a median of 29.5 days from tracheostomy to oxygen liberation.

Conclusion: Tracheostomy in COVID-19 patients that requires prolonged ventilation is unavoidable. It is a safe procedure and mortality is not related to the procedure. Mortality is primarily associated with COVID-19.

KEYWORDS:
COVID-19; tracheostomy; survivors; non-survivors; prognosis

INTRODUCTION

The COVID-19 pandemic caused by SARS-CoV-2 has affected more than 500 million and caused the death of more than 6 million people.[1] As of September 2022, the number of cases in Malaysia had reached 4.8 million with 36,270 deaths.[2] As its name suggests the SARS-CoV-2 is known to affect the lungs, often including acute respiratory distress syndrome (ARDS), which is its primary morbidity.[3] Due to its transmissibility and sheer number of infected patients, COVID-19 placed a major burden on healthcare facilities, with 5–12% of cases requiring critical care and prolonged mechanical ventilation. Tracheostomy is traditionally performed to improve the chance of successful ventilation weaning and lower the risk of complications and mortality when compared to long-term endotracheal intubation.[4] Because tracheostomy is an aerosol-generating procedure, specific guidelines were denoted by the Ministry of Health Malaysia in select cases for proper donning of personal protective equipment and intraoperative procedures to reduce the risk of transmission to healthcare workers during the procedure.[5,6] Hospital Ampang was converted into a hospital devoted exclusively to the treatment of COVID-19 patients from January 2021 to February 2022. In this article, we would like to set forth our experience performing tracheostomies in a single hospital dedicated to COVID-19 and review tracheostomy outcomes in this population.

MATERIALS AND METHODS

This retrospective observational study evaluated adult COVID-19-positive patients who underwent tracheostomy between January 2021 and February 2022 (13-month period) in a single tertiary care hospital setting (Hospital Ampang). Patients were included if they had a positive polymerase chain reaction or antigen rapid test kit, whose primary diagnosis is COVID-19, and underwent either open tracheostomy or percutaneous tracheostomy from otorhinolaryngology or intensive care teams in the ICU or operating theatre setting. The indications for tracheostomy were prolonged ventilation and failure to wean off ventilation. Universal sampling was used. A total of 30 patients were included.

Data Collection

The electronic Hospital Information System was used to identify patients and review patient's notes. Patients who underwent tracheostomies were identified via their operative notes and intensive care unit (ICU) notes. Notes were reviewed by researchers for demographical data, comorbidities, vaccination status, hospital length of stay, ICU length of stay, days from intubation to tracheostomy, days from COVID-19 diagnosis to tracheostomy, days from tracheostomy to decannulation, days from tracheostomy to death and tracheostomy complications.

Data Analysis

Data were expressed as count (percentage, %) and median (interquartile range, IQR). Chi-squared test was used for categorical variables and Mann–Whitney U test/Wilcoxon rank-sum test for continuous variables. Survivability graphs

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Table I: Summary statistics including patient demographics, comorbidities, vaccination, CT values and tracheostomy types (n=?)

	Total (n=30) (%)		Survivors (n=15) (%)		Non-survivors (n=15) (%)		*p* value
Age, years	53.5	(28.0–69.0)	36.0	(28.0–69.0)	60.0	(35.0–69.0)	0.002
BMI, overall	28.7	(21.8–50.5)	28.4	(21.8–45.0)	29.0	(23.3–50.5)	0.836
BMI, Subgroups							0.361
Normal weight (BMI < 25.0)	6	20.0	4	26.7	2	13.3	
Overweight/obese (BMI > 25.1)	24	80.0	11	73.3	13	86.7	
Race							0.440
Malay	20	66.7	9	60.0	11	73.3	
Chinese	8	26.7	5	33.3	3	20.0	
Indian	1	3.3	-	-	1	6.7	
Others	1	3.3	1	6.7	-	-	
Sex						1.0	
Male	20	66.7	10	66.7	10	66.7	
Female	10	33.3	5	33.3	5	33.3	
Tracheostomy Type							0.456
Open Tracheostomy	18	60.0	8	53.3	10	66.7	
Percutaneous Tracheostomy	12	40.0	7	46.7	5	33.3	
Vaccination							0.068
Vaccinated	3	10.0	3	20.0	-	-	
Unvaccinated	27	90.0	12	80.0	15	100	
CT Value, overall	23.6	(8.0–38.0)	23.7	(15.0–36.0)	23.51	(8.0–38.0)	0.457
Smoking							1.0
Smokers	4	13.3	2	13.3	2	13.3	
Non-smokers	26	86.7	13	86.7	13	86.7	
Comorbidities (Total)							
n = 0	7	23.3	4	26.7	3	20.0	
n = 1	8	26.7	5	33.3	3	20.0	
n = 2	8	26.7	4	26.7	4	26.7	
n = 3	4	13.3	2	13.3	2	13.3	
n = 4	3	10.0	-	-	3	20.0	
Hypertension							0.256
No	19	63.3	11	73.3	8	53.3	
Yes	11	36.7	4	26.7	7	46.7	
Diabetes mellitus							0.014
No	25	83.3	15	100%	10	66.7	
Yes	5	16.7	-	-	5	33.3	
Cardiovascular illnesses							0.068
No	27	90.0	15	100	12	80.0	
Yes	3	10.0	-	-	3	20.0	
Respiratory illnesses							0.143
No	28	93.3	15	100	13	86.7	
Yes	2	6.7	-	-	2	13.3	
Other comorbidities							
No	21	70.0	10	66.7	11	73.3	
Yes	9	30.0	5	33.3	4	26.7	

CT - cycle threshold
BMI - Body mass index

Table II: Tracheostomy complications by mortality status

	Overall		Survivors		Non-survivors	
	n	(%)	n	(%)	n	(%)
Complications						
Major	-	-	-	-	-	-
Minor	3	11.1	1	6.7	2	13.3
None	27	88.9	14	93.3	13	86.7
Minor Complications						
Tracheostomy bleed	2	6.7	-	-	2	13.3
Tracheostomy tube blockage	1	3.3	1	6.7	-	-
None	27	90.0	14	93.3	13	86.7

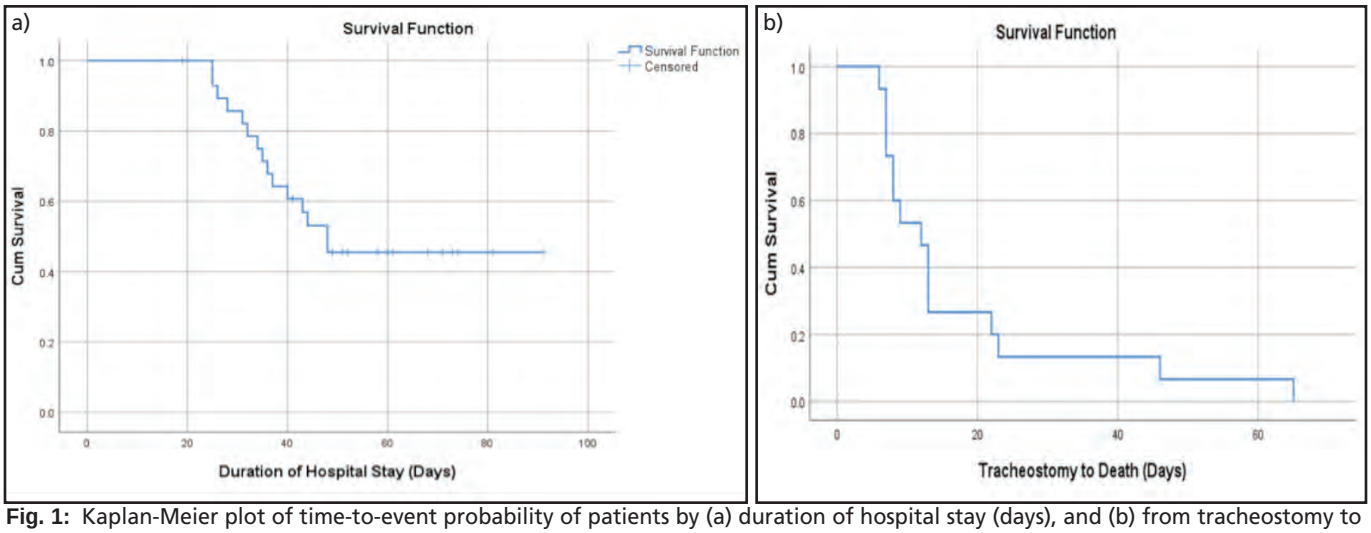

Fig. 1: Kaplan-Meier plot of time-to-event probability of patients by (a) duration of hospital stay (days), and (b) from tracheostomy to death (days)

were plotted using Kaplan–Meier method for duration of hospital stay and tracheostomy to death. Statistical analysis was performed using the SPSS version 26. A significant *p* value was taken at alpha < 0.05.

RESULTS

There were 30 patients who were COVID-19 positive, requiring mechanical ventilation, and underwent open or percutaneous tracheostomy between January 2021 and February 2022 in Hospital Ampang. The indications for tracheostomy were prolonged ventilation and failure to wean off ventilation. The median age was 53.5 (IQR 34.8–61.8) (p=0.002). Most patients were of the Malay race (66.7%) and male. Only three patients were fully vaccinated, and all non-surviving patients were unvaccinated. Of the comorbidities, diabetes mellitus had significance (p=0.014). All surviving patients had no underlying diabetes mellitus, cardiovascular disease, or prior respiratory disease. There was no significance (p=0.456) between percutaneous tracheostomy performed by the critical care team, and open tracheostomy performed by the otorhinolaryngology team in relation to death (Table I). The percutaneous tracheostomies were performed by a senior anaesthetist bedside in the ICU without scope guidance. Patients who had a higher BMI, hence thicker necks, or patients in deemed the critical care team as difficult for a percutaneous tracheostomy, were referred to the otorhinolaryngology team for an open tracheostomy. The median days from COVID-19 illness to tracheostomy was 30.0 (IQR 25.0–34.0), which is equal for survivors and non-survivors. The median ICU stay of 30.5 days (IQR 25.5–43.0) (p=0.009) and the median hospital stay duration of 44.0 days (IQR 33.0–60.5) (p=0.000) was significantly higher for patients who survived compared to non-survivors. Kaplan–Meier curves summarise the time-to-event data among COVID-19 patients, including probabilities of hospital length of stay and days from tracheostomy to death (Figures 1 A and 1B). There were only minor complications (n=3, 11.1%) of tracheostomy bleed (n=2) and tracheostomy tube blockage (n=1). No major complications such as haemorrhage, pneumothorax, tracheitis and/or tracheobronchitis, tracheal stenosis, or trachea-oesophageal fistula were noted (Table II). It is worth mentioning that no surgeons, anaesthetists or operating staff involved in the tracheostomy procedures developed COVID-19 symptoms.

DISCUSSION

This study shows our experience of open and percutaneous tracheostomies for patients who had COVID-19 that required prolonged ventilation and failed to wean off ventilation during the COVID-19 pandemic in a tertiary hospital dedicated solely to COVID-19 patients at the time. This is a novel study in Malaysia to the best of our knowledge. Mortality of COVID-19 patients who underwent tracheostomy in Spain was 20%,[7] in the United states 6–33%[8,9] and in Dubai 23.7%/.[10] Our study shows a mortality rate of 50%. The majority of non-survivors were non-vaccinated, had higher BMIs, comorbidities and higher risk of complications.[11–13] Our study also showed that age (p=0.002) and diabetes mellitus (p=0.014) were significant factors relating to the death of tracheostomised COVID-19 patients. All five patients in our study who had diabetes mellitus were non-survivors, as diabetes mellitus has been shown to be a factor for poorer prognosis.[14] In keeping with our data, it would be preferable to select patients for tracheostomy who are vaccinated, have a lower BMI, younger and without diabetes mellitus, as these patients had been shown to have a better outcome. Our patients underwent tracheostomy between 17 and 25 days from intubation. Due to this, we are unable to advise if performing a tracheostomy earlier or later is preferable. Similarly to Rovira et al. and Botti et al., our study does not show significance (p=0.456) between open and percutaneous tracheostomies in relation to death.[15,16] Selection of patients for percutaneous and open tracheostomy should be done on a case-by-case basis. We would recommend performing open tracheostomies in patients who have thicker necks, neck mass or risk of bleeding. When performing percutaneous tracheostomy, it should be performed by a senior anaesthesiologist and preferably scope guided. In our study, the duration of ICU stay and the duration of hospital stay is

double for that of survivors than non-survivors. With a median ICU stay of 20 days post-tracheostomy for survivors, it is likely tracheostomy did not assist in weaning the patient off the ventilator. However, this could possibly be due to several factors, including a difference in ventilator weaning thresholds by the critical care team, significant lung fibrosis, secondary bacterial infections and exacerbations of comorbidities that affected patient ventilation. The decreased length of stay for non-survivors is likely due to the overall poor prognosis of the patient. A study by Ahmed et al. found 9% of patients had minor complications and 9% of patients had major complications.[9] Another study by Tang et al. showed peristomal bleeding and tracheal bleeding were more common in COVID-19 patients at 13%.[17] Our study had only three minor complications and no major complications. For survivors, it took a median of 29.5 days to reach oxygen liberation from tracheostomy. It is recommended to have a multidisciplinary team approach when selecting a patient for tracheostomy to better evaluate the prognosis of the patient prior to performing a tracheostomy, which is an aerosolised procedure that may increase the risk of COVID-19 infection to health staff.

LIMITATIONS

This is a retrospective study with a small sample size and may not show some significant statistical values. Our study is performed in a single centre. The duration is only 13 months.

CONCLUSION

Tracheostomy in COVID-19-positive patients is essential for those dependent on a ventilator for an extended period. The tracheostomy procedure itself is safe to perform. However, the outcome of post-tracheostomised patients varies depending on multiple factors such as comorbidities, obesity, age and prognosis of COVID-19. A collaborative and cohesive multidisciplinary team approach is recommended. We propose tracheostomy (percutaneous or open) in select patients who are younger, vaccinated, with lower BMI and fewer comorbidities.

REFERENCES

1. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int
2. COVIDNOW in Malaysia. COVIDNOW. https://covidnow.moh.gov.my/
3. Machhi J, Herskovitz J, Senan AM, Dutta D, Nath B, Oleynikov MD, et al. The natural history, pathobiology, and clinical manifestations of SARS-CoV-2 infections. J Neuroimmune Pharmacol 2020; 15(3): 359-86.
4. Piazza C, Filauro M, Dikkers FG, Nouraei SAR, Sandu K, Sittel C, et al. Long-term intubation and high rate of tracheostomy in COVID-19 patients might determine an unprecedented increase of airway stenoses: A call to action from the European Laryngological Society. Eur Arch Otorhinolaryngol 2021; 278(1): 1-7.
5. Rohaizam J, Tham YS, Zakinah Y, Mohd Razif MY, Marina MB. Tracheostomy during the COVID-19 pandemic in Malaysia: A revised guideline. Med J Malaysia 2021; 76(Suppl 4): 23-6.
6. American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS). Tracheotomy Recommendations During the COVID-19 Pandemic [cited May 2022]. Accessed from: https://www.entnet.org/resource/tracheotomy-recommendations-during-the-covid-19-pandemic-2/
7. Martin-Villares C, Perez Molina-Ramirez C, Bartolome-Benito M, Bernal-Sprekelsen M, COVID ORL ESP Collaborative Group (*), Perez-Fernandez A, et al. Outcome of 1890 tracheostomies for critical COVID-19 patients: A national cohort study in Spain. Eur Arch Otorhinolaryngol 2021; 278(5): 1605-12.
8. Chao TN, Harbison SP, Braslow BM, Hutchinson CT, Rajasekaran K, Go BC, et al. Outcomes after tracheostomy in COVID-19 patients. Ann Surg 2020; 272(3): e181-86.
9. Ahmed Y, Cao A, Thal A, Shah S, Kinkhabwala C, Liao D, et al. Tracheotomy outcomes in 64 ventilated COVID -19 patients at a high-volume center in Bronx, NY. The Laryngoscope 2021; 131 (6).
10. Nadeem R, Zahra AN, Hassan M, Parvez Y, Gundawar N, Hussein MAM, et al. Prevalence and timing of tracheostomy and its impact on clinical outcomes in COVID-19 pneumonia patients in Dubai hospital. Dubai Med J 2021; 4(2): 151-55.
11. Ismail SN, Abdul Halim Zaki I, Noordin ZM, Md Hussin NS, Ming LC, Zulkifly HH. Clinical characteristics and risk factors for mortality in patients with COVID-19: A retrospective nationwide study in Malaysia. Proc Singap Healthcare 2022: 20101058221085744.
12. Assal HH, Abdel-hamid HM, Magdy S, Salah M, Ali A, Elkaffas RH, et al. Predictors of severity and mortality in COVID-19 patients. Egypt J Bronchol 2022; 16(1): 18.
13. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: A systematic review and meta-analysis of 42 studies and 423,117 patients. BMC Infect Dis 2021; 21(1): 855.
14. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020; 323(20): 2052-59.
15. Rovira A, Tricklebank S, Surda P, Whebell S, Zhang J, Takhar A, et al. Open versus percutaneous tracheostomy in COVID-19: A multicentre comparison and recommendation for future resource utilisation. Eur Arch Otorhinolaryngol 2021; 278(6): 2107-14.
16. Botti C, Lusetti F, Neri T, Peroni S, Castellucci A, Salsi P, et al. Comparison of percutaneous dilatational tracheotomy versus open surgical technique in severe COVID-19: complication rates, relative risks and benefits. Auris Nasus Larynx 2021; 48(3): 511-17.
17. Tang L, Kim C, Paik C, West J, Hasday S, Su P, et al. Tracheostomy outcomes in COVID-19 patients in a low resource setting. Ann Otol Rhinol Laryngol 2021: 00034894211062542.

The impact of prehabilitation in upper gastrointestinal cancer underwent major surgery

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ABSTRACT

Introduction: Several risk factors found to be associated with postoperative complications and cancer surgery, which carry a significant morbidity risk to cancer patients. Therefore, prehabilitation is necessary to improve the functional capability and nutritional status of a patient prior to surgery, so that the patient can withstand any postoperative activity and associated deterioration. Thus, this study aims to assess the effectiveness of prehabilitation interventions on the functional status of patients with gastric and oesophageal cancer who underwent esophagectomy and gastrectomy.

Material and Methods: An interventional study was carried out among oesophageal and gastric cancer patients who had undergone surgery at the National Cancer Institute of Malaysia. The prehabilitation process took a maximum of two weeks, depending on the patient's optimisation before surgery. The prehabilitation is based on functional capacity (ECOG performance status), muscle function (handgrip strength), cardio-respiratory function (peak flow meter) and nutritional status (calorie and protein). Postoperative outcomes are measured based on the length of hospital stay, complications, and Clavien-Dindo Classification.

Results: Thirty-one patients were recruited to undergo a prehabilitation intervention prior to gastrectomy (n=21) and esophagectomy (n=10). Demographically, most of the cancer patients were males (67.7%) with an ideal mean of BMI (23.5±6.0). Physically, the majority of them had physical class (ASA grade) Grade 2 (67.7%), ECOG performance status of 1 (61.3%) and SGA grade B (51.6%). The functional capacity and nutritional status showed a significant improvement after one week of prehabilitation interventions: peak expiratory flow meter (p<0.001), handgrip (p<0.001), ECOG performance (p<0.001), walking distance (p<0.001), incentive spirometry (p<0.001), total body calorie (p<0.001) and total body protein (p=0.004). However, those patients who required two weeks of prehabilitation for optimization showed only significant improvement in peak expiratory flow meter (p<0.001), handgrip (p<0.001), and incentive spirometry (p<0.001). Prehabilitation is significantly associated postoperatively with the length of hospital stay (p=0.028), complications (p=0.011) and Clavien-Dindo Classification (p=0.029).

Conclusion: Prehabilitation interventions significantly increase the functional capacity and nutritional status of cancer patients preoperatively; concurrently reducing hospital stays and complications postoperatively. However, certain cancer patients might require over two weeks of prehabilitation to improve the patient's functional capacity and reduce complications postoperatively.

KEYWORDS:
Prehabilitation; upper gastrointestinal; oesophageal cancer; gastric cancer; preoperative; postoperative

INTRODUCTION

Oesophageal and gastric cancers are lethal tumours which carry a high risk of morbidity and mortality. The number of new cancer cases and deaths for oesophageal and gastric cancers in the United States is estimated at 43 300 and 26 400 respectively.[1] Surgery is the cornerstone of curative intent treatment for localised or locally advanced oesophagogastric cancers and it is associated with important adverse events.[2,3] The combination of neo-adjuvant chemotherapy or chemoradiotherapy treatment for esophagogastric cancer has posed an enormous challenge to the patient. The current best surgical practice involves the Enhanced Recovery After Surgery (ERAS) program, which has been shown to have a positive association in terms of length of hospital stay, resource use and complications.[4,5]

Risk stratification optimisation of pre-existing organ function is essential in ERAS elements for preparing patients facing surgery. Hence, it is vital to avoid a silo mentality and require a multidisciplinary approach to prepare patients and prehabilitation prior to surgery. Another parameter that can measure the effectiveness of prehabilitation would measure walking distance, for example, the 6-minute walk test (6MWT).[6] This has been predicted to determine the rate of mortality in patients undergoing major surgery. It also correlates inversely with sarcopenia and peak flow oxygen consumption in predicting postoperative cardiopulmonary complications.[7]

Certain types of exercises with resistance training are considered fundamental elements in building patient functional capacity and it has a role in attenuating and even reversing adverse impact postoperative outcomes. Resistance

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training can counter myopenia and promote hypertrophic adaptation in skeletal tissue, increasing muscle mass, strength, and function. A handgrip test can assess these. Reduced handgrip strength has been a predictor of impaired short-term outcomes, such as increased postoperative complications, increased length of hospital stay, decreased physical status and increased readmission rate. Jamar dynamometer could measure the average value of three successive measurements of the dominant hand to determine the grip strength.[8]

Despite these advances, esophagogastric surgery is still associated with short-term and long-term adverse effects. It includes high rates of postoperative complications and mortality, decreased muscle strength and cardiorespiratory fitness, fatigue, depression, emotional distress, anxiety and poor quality of life.[9,10] Consequently, surgical complications and subsequent impaired (nutritional, physical, and performance status), most patients are not able to receive the complete sequence of perioperative or adjuvant therapy. Surgery alone is inadequate for loco-regional control in patients with locally advanced disease, and overall, 5-year survival remains poor. Therefore, optimising pre and perioperative functional capacity is an interesting aim in these patients.[11,12]

Interventions in the preoperative period are directed to enhance recovery after surgeries collectively called 'prehabilitation'. Prehabilitation is known to be the "new frontier" in preoperative care, especially for major upper gastrointestinal (GI).[13] It focuses on preoperative conditioning intervention to increase the physiological reserve before the stress of surgery to improve postoperative outcomes.[14] Prehabilitation aims to improve nutritional status, pre and postoperative fitness, and to reduce postoperative complications.[15] The prehabilitation is moving towards a multimodal approach, encompassing medical optimization, preoperative physical exercise, nutritional support, and stress/anxiety reduction.[16,17]

Prehabilitation of surgical patients seems to be better placed to cope after surgery compared to others. Increasing evidence shows that prehabilitation improves perioperative physical function in major abdominal surgery.[18,19] Integration of prehabilitation was found to improve hospital length of stay, postoperative pain, and postoperative complications.[20] Prehabilitation uses multimodal intervention which includes physical exercise, nutritional support, medical optimisation and psychological support.[21,22] The impact of the prehabilitation can be measured using the ECOG Scale of Performance Status developed by the Eastern Cooperative Oncology Group (ECOG) and is now part of the ECOG ACRIN Cancer Research Group.[23]

The effectiveness of the prehabilitation program has been demonstrated in several specialities, including cardiothoracic and bariatric surgery.[24] Nevertheless, upper GI surgery presents a unique challenge in clinical management because of the high-risk population and treatments. Furthermore, few trials in major abdominal surgery found a significant reduction in overall and pulmonary morbidity post-surgery with prehabilitation.[25] Prehabilitation through exercise therapy and chest physiotherapy seems to have improved the physical fitness of a patient and reduced pulmonary complications.[26] Since functional status is a key and modifiable factor in major upper GI surgery, prehabilitation is a notable intervention in these patients. Intervening with early prehabilitation rather than late or after surgery (rehabilitation) in this high-risk group appears to be more beneficial.[27]

Based on the Malaysia National Cancer Registry Report 2012-2016, the age-standardised incidence rate of stomach cancer is 3.1 and 1.9 per 100,000 populations for males and females, respectively. For oesophageal cancer, the age-standardised incidence rate is 1.4 and 0.5 per 100,000 populations for males and females, respectively.[28] Although it is a relatively small number compared to Korea, China and Japan, stomach cancer is still in the top ten lists of common cancers among males in Malaysia. A study by Zalina at Malaysia Hospital shows three over four gastrointestinal cancer patients are malnourished (moderately malnourished stage B (25.7%), severely malnourished stage C (48.6%)), two over five having low physical activity and one over three having a low quality of life.[29] A large cohort study by Jessica Spence among Canadians found that 44.9% of deaths within 30 days of post-surgery among 40,000 non-cardiac surgical patients were associated with 3 complications: major bleeding, MINS (myocardial injury after non-cardiac surgery) and sepsis.[30] Furthermore, this study suggested that preoperative identification and management of complications in patients is needed to reduce post-operative complications and mortality.

In Malaysia, the National Cancer Institute started the prehabilitation program for oesophageal and gastric cancer in October 2020. Prehabilitation is effective in certain surgeries, but a limited study was found on oesophageal and gastric cancer, including in Malaysia.16 This study would support the evidence and contribute to the knowledge of prehabilitation prior to upper gastrointestinal cancer surgery. Therefore, this study aimed to assess the effectiveness of prehabilitation on the functional status of patients with gastric and oesophageal cancer who underwent esophagectomy and gastrectomy in Malaysia.

MATERIALS AND METHODS

Design and Study Sample

This was an interventional study conducted using data collected from the surgical department among oesophageal and gastric cancer patients, who had undergone esophagectomy and gastrectomy surgery at the National Cancer Institute of Malaysia. Thirty-one patients' data from the Enhanced Recovery After Surgery (ERAS) assessment forms underwent esophagectomy or gastrectomy was retrieved from October 2020 to June 2021. The postoperative follow-up period is 30 days after the surgery. Therefore, patients recruited for this study started on 1st October 2020 until the end of May 2021, as the remaining 30 days will be the postoperative follow-up. Data collected includes demographic data, disease stage, nutritional status and functional status parameters, as in the ERAS assessment form.

Intervention

Nutrition

The dietician screened and assessed all the preoperative patients. Nutritional therapy was initiated according to a recommendation based on ESPEN practical guidelines in cancer 2021.[31] Total energy expenditure is calculated based on a predicted formula of 25-30kcal/kg/day, while protein requirement is aimed to be above 1.2g/kg/day, if possible, up to 1.5g/kg/day.

Exercise

During the hospital stay, patients were required to ambulate in the ward. The standard walking exercise was done to achieve over 10 meters per session. Thera band loops with different levels of resistance and colour coding (e.g.,: yellow, green, red, black, grey and orange) were supplied to the patient. These allow an individual to progress to gain muscle strength in the upper/lower limbs and abdominal muscles. The aerobic and resistance exercise supervised the physiotherapy unit, including the usage of these Thera bands for different types of muscle strengthening in our body. Meanwhile, cycling on an ergometer bike for 10-15minutes and weight-lifting exercises using dumbbells with different weights was also supervised by the physiotherapist. Training of inspiratory muscles was also associated with decreased postoperative respiratory complications. There was a set of standardised deep breathing exercises together with the use of an incentive spirometer. Patients were also required to practise coughing. Simple instructions and demonstrations were given during admission.

The standardised deep breathing exercise was instructed to do every hour, and the step includes:-

1) 10 deep inspiration/set x at least three times/day with thoracic cage stretching, followed by huffing/blowing out loudly,
2) Long, slow deep breathing using incentive spirometry,
3) Efficient coughing.

Outcome Measures

The overall outcome of the implementation exercise and its correlation with functional status improvement pre- and post-operation were assessed. In addition, subgroup analysis will be performed on the patient undergoing surgery post-neo-adjuvant therapy, elderly patients (>70years old) and in comparison, on disease stage and type of surgery. The difference between preoperative and postoperative physical performance and functional capacity was assessed using ECOG performance status, walking distance, handgrip strength, and peak flow rate on alternate days. However, ECOG Grade 3, 4 and 5 patients were not included (as not intended for surgery).

The parameters were filled into a standard ERAS assessment form with a duration of 1-2 weeks before surgery. For those who have good functional and nutritional status, the minimal duration of prehabilitation before surgery is 1 week. Clavien Dindo classification (CDC) was originally described in 2004 and is widely used throughout surgery for grading adverse events i.e. post-operative complication (POCs) which occurs as a result of surgical procedures.[32] It has become a standard classification system for many surgical specialities. The grading system is from grade 1 to grade V.

Statistical Analysis

Data were checked and cleaned before being analysed using the Statistical Package for the Social Science (SPSS) version 28. The data distribution before and after the intervention was not equally distributed. The normality test for this study was negative. Wilcoxon Signed-Ranks Test was used to determine the association between the baseline parameter and perioperative parameter (1st week and 2nd weeks after prehabilitation intervention). Furthermore, the relationships between postoperative outcomes after prehabilitation against the prehabilitation period were determined using the Chi-square test.

Ethical Consideration

This study was initiated by the Surgical Department of the National Cancer Institute of Malaysia, and it was self-funded. This study was registered under National Medical Research Registry (NMRR) (NMRR ID-21-1370-60445 (IIR) and approval were granted (21-1370-60445 (2)) by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia.

RESULTS

Thirty-one participants were recruited in the study who underwent major upper GI surgery, either gastrectomy and/or esophagectomy, as shown in Table I. The patients' mean age was 59.2 (SD±8.9) years old. The majority of patients who underwent major upper GI surgery due to cancer were males (67.7%) but they had an equal variation of BMI between males (23.8 ± 6.3) and females (22.9 ± 5.7). Meanwhile, most of the participants were SGA B (51.6%), had good ECOG status of 1 (61.3%) and were classified as ASA II (67.7%). Patients with SGA C (32.3%) and mediocre functional status with ECOG performance 2 (16.1%) were another extreme spectra of concern. Twenty-one (67.8%) studies of stomach cancer required gastrectomy and ten (32.3%) studies of cardio-oesophageal/oesophageal cancer required oesophagectomy. Most of the diseases were in stage III (54.9%), followed by stage II (29%), stage IV (9.7%) and last, stage I (6.4%) which is the least and usually benefits from the minimally invasive approach.

Table II shows a comparison of the outcome between baseline and preoperative parameters after a week of prehabilitation interventions. The perioperative parameters have shown a significant improvement (22.4%) on PEFR (p<0.001), 20.9% improvement on hand grip (p<0.001), 5.4% improvement on total body calorie (p<0.001) and 8.5% improvement on total body protein (p=0.004). There is also a positive development in ECOG performance (p<0.001), walking distance (p<0.001), and intensive spirometry (p<0.001).

The remaining patients after 1 week of prehabilitation were only 16 out of 31 patients. There were significant positive strong correlations between pre-intervention and two weeks post-interventions for PEFR (p<0.001), hand grip (p<0.001) and intensive spirometry (p<0.001). Meanwhile, other prehabilitation interventions (total body calorie, total body protein, ECOG performance) were found to have no association after two weeks of the prehabilitation process as shown in Table III.

Table I: Patients characteristics who had undergone gastrectomy or oesophagectomy (n=31)

Varibales	n(%)
Age (years), mean ± SD	59.2 ± 8.9
Gender	
Male, n (%)	21 (67.7)
BMI, mean ± SD	23.5 ± 6.0
Male	23.8 ± 6.3
Female	22.9 ± 5.7
ASA grade, n (%)	
I	8 (25.8)
II	21 (67.7)
III	2 (6.5)
Comorbidities, n (%)	
Diabetes	11 (35.5)
Hypertension	16 (51.6)
Ischaemic heart disease	4 (12.9)
Baseline ECOG performance status, n (%)	
0	7 (22.6)
1	19 (61.3)
2	5 (16.1)
SGA, n (%)	
A	5 (16.1)
B	16 (51.6)
C	10 (32.3)
Albumin, g/dL, mean ± SD	38.7 ± 4.5
TLC, mean ± SD	1.95 ± 0.7
Diagnosis, n (%)	
Stomach cancer	21 (67.8)
Cardio-oesophageal / oesophageal cancer	10 (32.3)
Cancer Stage, n (%)	
I	2 (6.4)
II	9 (29.0)
III	17 (54.9)
IV	3 (9.7)
Neoadjuvant therapy, n (%)	11 (35.5)
Types of surgery, n (%)	
Gastrectomy	21 (67.8)
Oesophagectomy	10 (32.2)
Length of stay (post-operative), days, median (IQR)	9 (6-21)
Gastrectomy	6 (5.5-22.5)
Oesophagectomy	13.5 (8.5-17.2)

SD: Standard deviation; IQR: interquartile range; BMI: body mass index; ASA: American Society of Anaesthesiologists physical status class; ECOG: Eastern Cooperative Oncology Group; SGA: Subjective Global Assessment; TLC: total lymphocyte count.

Table II: Comparison of baseline parameters and perioperative parameters outcome after one week of prehabilitation interventions (n=31)

Variables	Pre-intervention	Post-intervention	Improvement difference (%)	*p* value
PEFR, mean ± SD	322.2 (118.7)	394.5 (116.6)	72.3 (22.4)	<0.001[a]
Hand grip, mean ± SD	20.9 (6.7)	25.4 (6.8)	4.5 (20.9)	<0.001[a]
Calorie, mean ± SD	91.4 (18.6)	96.4 (6.4)	5.0 (5.4)	<0.001[a]
Protein, mean ± SD	89.7 (20.2)	97.4 (9.5)	7.7 (8.5)	0.004[a]
ECOG Performance, n (%)			NA	<0.001[b]
Grade 0	7 (22.6)	10 (32.3)		
Grade 1	19 (61.3)	20 (64.5)		
Grade 2	5 (16.1)	1 (3.2)		
Walking distance			NA	<0.001[b]
<3 meter	1 (3.2)	0 (0.0)		
< 10 meter	2 (3.2)	1 (3.2)		
>10 meter	29 (93.5)	20 (96.8)		
Incentive Spirometry (IS)			NA	<0.001[b]
Level 1	2 (6.5)	0 (0.0)		
Level 2	5 (16.1)	2 (9.7)		
Level 3	24 (77.4)	28 (90.3)		

[a]Wilcoxon Signed Ranks Test
[b]Chi-square Test

Table III: Comparison of baseline and perioperative parameter after two weeks of prehabilitation interventions (n=16)

Variables	Pre-intervention	Post-intervention	Improvement difference (%)	*p* value
PEFR, mean ± SD	304.3 (118.4)	419.3 (132.1)	115 (37.7)	<0.001[a]
Hand grip, mean ± SD	19.1 (7.0)	26.1 (6.3)	7 (36.6)	<0.001[a]
Calorie, mean ± SD	90.9 (22.6)	98.2 (3.5)	7.3 (8.0)	0.173[a]
Protein, mean ± SD	89.8 (23.6)	99.1 (9.8)	9.3 (10.3)	0.173[a]
ECOG Performance, n (%)			NA	0.072[b]
Grade 0	1 (6.3)	3 (18.8)		
Grade 1	11 (61.8)	13 (81.3)		
Grade 2	4 (25.0)	0 (0.0)		
Walking distance			NA	NA
< 10 meter	2 (12.6)	0 (0.0)		
>10 meter	14 (87.5)	16 (100.0)		
Incentive Spirometry (IS)			NA	<0.001[b]
Level 1	2 (12.5)	0 (0.0)		
Level 2	3 (18.8)	2 (12.5)		
Level 3	11 (68.8)	14 (87.5)		

[a]Wilcoxon Signed Ranks Test
[b]Fisher exact test

Table IV: The association between postoperative outcomes and the prehabilitation period

Variables	Prehabilitation weeks, n (%)		*p* value
	1 week	2 weeks	
Length of hospital stay			0.028[a]
< 8 days	11 (78.6)	3 (21.4)	
8 – 14 days	2 (28.6)	5 (71.4)	
15 – 21 days	1 (25.0)	3 (75.0)	
22 – 28 days	1 (50.0)	1 (50.0)	
>28 days	0 (0.0)	4 (100.0)	
Any complications			0.011[a]
Yes	5 (27.8)	13 (72.2)	
No	10 (76.9)	3 (23.1)	
Clavien-Dindo Classification			0.029[a]
No Complication	10 (76.9)	3 (23.1)	
Grade 1	2 (100.0)	0 (0.0)	
Grade 2	1 (14.3)	6 (85.7)	
Grade 3a	0 (0.0)	1 (100.0)	
Grade 3b	1 (33.3)	2 (66.7)	
Grade 4	1 (20.0)	4 (80.0)	
Grade 5	15 (48.4)	16 (51.6)	
Pneumonia			0.220
Yes	2 (25.0)	6 (75.0)	
No	13 (56.5)	10 (43.5)	
Wound infection			0.583
Yes	1 (33.3)	2 (66.7)	
No	14 (50.0)	14 (50.0)	
Anastomosis leak			0.226
Yes	0 (0.0)	3 (100.0)	
No	15 (53.6)	13 (46.4)	
Readmission within 30 days			0.484
Yes	0 (0.0)	2 (100.0)	
No	15 (51.7)	14 (48.3)	
Postoperative Mortality			0.516
Yes	0 (0.0)	1 (3.2)	
No	15 (100)	15 (96.8)	

[a] Chi-square Test

Eleven out of fifteen (73.3%) patients who required one week of prehabilitation interventions stayed in the hospital for less than 8 days of hospital postoperatively. While eight out of sixteen (50%) patients who require two weeks of prehabilitation interventions stayed over 14 days in the hospital. Furthermore, patients who need two weeks of rehabilitation interventions end up with 72.2% complications compared to those who required one week of rehabilitation interventions. In the meantime, post-operative outcomes have a significant association with prehabilitation interventions, especially on length of hospital stay (p=0.028), patient complications post-surgery (p=0.011), and Clavien-Dindo classification (p=0.029) (Table IV). Wound infection incidence was only evident in 9.7% of the sample studies. 90.3% of the participant did not reveal to have any form of wound dehiscence. Anastomotic leak incident was found to be 9.7%.

DISCUSSION

Patients with practice have directly shown improvement in the postoperative upper GI malignancy, experience progressive weight loss over time and usually present with moderate-to-severe malnutrition and impaired functional capacity.[13] In our study, most patients fall in the category of 5-10% weight loss with SGA B or more extreme SGA C and this explains how the initial presentation transforms constructively after the intervention prehabilitation. The aim of this is to determine the effectiveness of a basic bedside exercise programme entailed with a component of cardiorespiratory and muscle strengthening exercises, coupled with adequate nutritional loading in patients who are undergoing major upper GI surgery for esophagogastric cancer. Major abdominal surgeries are associated with significant morbidities despite recent improvements in perioperative care, including the ERAS concept.[20] Optimisation of a patient begins from the initial pre-operative stage itself.

The practice is alongside the growing literature base and with the given clinical recommendation of prehabilitation being increasingly adopted into clinical outcomes.[18,22] In this study, we concluded multimodal prehabilitation before major abdominal surgery improves the functional capacity, substantially reduce the post-operative length of hospital stay and significantly change postoperative complication. However, it does not significantly associate with 30 days of hospital readmissions or postoperative mortality. Nevertheless, this data needed to be delivered with caution, because of the substantial heterogeneity within and across the studies especially complications postoperatively. Based on this study, more than 70% of complications derived from patients required two weeks of prehabilitation. Caution prehabilitation assessment is needed especially for patients who may need longer prehabilitation duration for optimization prior to surgery.[33] Patient willingness to participate must also be considered when interpreting the findings, as consented participation was 100%. However, the compliance level is debatable and may vary from one to another. Improvement in surgical care, including the implementation of enhanced recovery after surgery (ERAS) pathway, has manifested and added complexity to interpreting the efficacy of prehabilitation interventions in the pre-operative period, intraoperative and particularly the postoperative period with early mobilisation and optimised pain management.

In this study, thirty-one patients who underwent gastrectomy and esophagectomy consented to partake in this study. We investigated the effect of short-term prehabilitation intervention has overall shown improvement within the period of two weeks. Prehabilitation usually starts two weeks before major upper GI surgery, which entails a component of cardiorespiratory exercise approximately every hour with deep breathing exercises and spirometry. In addition, muscle-resistant training approximately 3 times a day together with nutritional loading was provided during the hospital stay.[29] Parameters like handgrip assessment are expected to increase the muscle strength because of the other exercise load initiated by the patient ward e.g.: muscle strengthening exercises inward using Thera band, static bicycle in gym or dumbbells other fixed resistance used as a training tool.[9] Our group of patients are majorly the malnourished elderly, accustomed to sarcopenia and frailty. Overall, these patients also show a significant improvement in terms of muscle strength with maximal nutrient loading either via parenteral nutrition or full enteral nutrient inward despite the short prehabilitation intervention.

This study had a few limitations to be highlighted. First, this study has no control group to be compared with, which could be an excellent added value for the outcome of this study. Thus, we only compare patients based on the duration of prehabilitation. Second, this study did not directly reflect on the postoperative complications despite the improvement seen in their functional status before surgery. These outcomes should be evaluated by setting an intervention with a control group in major upper GI surgery. We intend to conduct future studies, including a postoperative outcome evaluation with a control group. However, in conclusion, although our study had limitations and a limited number of participants, it is confirmed with a short period of multimodal rehabilitation over one week significantly improved the patient's condition (functional capacity and nutrient loading) preoperatively and postoperatively.

It will have extraordinary potential if this study could be carried out in a prospective study. We have also intended to add another essential component, which is a psychological questionnaire among consented participants. This component of interventions is aimed at reducing preoperative anxiety as well as a motivational interview focusing on improving compliance with program elements which could be incorporated as part of multimodal prehabilitation programs within these included studies. A trained psychologist, a psychology-trained nurse, and a psychology-trained member of the research team should deliver interventions to reduce preoperative anxiety not reported. The motivational interview should be conducted by a specialised physiotherapist. Adherence to this concept will be beneficial and could give an overview of the whole and propel toward good post-surgical outcomes.

In a retrospective review of our practice, we will extend to prospective to recruit more patients to show any difference in terms of prehabilitation and outcome of surgery, length of stay, detailed complications, readmission and mortality postoperatively. On the other end of the spectrum, much prehabilitation research has widened its horizon and focuses on pre- and post-operative patients. Many still lack research on how these affect the intended oncologic (adjuvant) therapies and ongoing exercise behaviour. This will be great revenue for research in the future. More research and study can be developed on the prehabilitation effects.

CONCLUSION

Prehabilitation interventions significantly increase the functional capacity of cancer patients preoperatively, concurrently reducing hospital stays and complications postoperatively. However, certain cancer patients might require over two weeks of prehabilitation to improve the patient's functional capacity and reduce complications postoperatively.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: A Cancer Journal for Clinicians 2016; 66(1): 7-30.
2. Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and failure to rescue with high-risk surgery. Med Care 2011; 49(12): 1076-81.
3. Reames BN, Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and operative mortality in the modern era. Ann Surg 2014; 260(2): 244-51.
4. Ashok A, Niyogi D, Ranganathan P, Tandon S, Bhaskar M, Karimundackal G, et al. The enhanced recovery after surgery (ERAS) protocol to promote recovery following esophageal cancer resection. Surg Today 2020; 50(4): 323-34.
5. Lee L, Li C, Robert N, Latimer E, Carli F, Mulder DS, et al. Economic impact of an enhanced recovery pathway for oesophagectomy. Br J Surg 2013; 100(10): 1326-34.
6. Lee L, Schwartzman K, Carli F, Zavorsky GS, Li C, Charlebois P, et al. The association of the distance walked in 6 min with pre-operative peak oxygen consumption and complications 1 month after colorectal resection. Anaesthesia 2013; 68(8): 811-6.
7. Tanaka R, Lee SW, Kawai M, Tashiro K, Kawashima S, Kagota S, et al. Protocol for enhanced recovery after surgery improves short-term outcomes for patients with gastric cancer: a randomized clinical trial. Gastric Cancer 2017; 20(5): 861-71.
8. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010; 39(4): 412-23.
9. Mathiowetz V, Weber K, Volland G, Kashman N. Reliability and validity of grip and pinch strength evaluations. J Hand Surg Am 1984; 9(2): 222-6.
10. Jack S, West MA, Raw D, Marwood S, Ambler G, Cope TM, et al. The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery. Eur J Surg Oncol 2014; 40(10): 1313-20.
11. Hulzebos EH, Smit Y, Helders PP, van Meeteren NL. Preoperative physical therapy for elective cardiac surgery patients. Cochrane Database Syst Rev 2012; 11(11): Cd010118.
12. Hoogeboom TJ, Oosting E, Vriezekolk JE, Veenhof C, Siemonsma PC, de Bie RA, et al. Therapeutic Validity and Effectiveness of Preoperative Exercise on Functional Recovery after Joint Replacement: A Systematic Review and Meta-Analysis. PLoS One 2012; 7(5): e38031.
13. Ryan AM, Power DG, Daly L, Cushen SJ, Ní Bhuachalla Ē, Prado CM. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. Proc Nutr Soc 2016; 75(2): 199-211.
14. Doganay E, Moorthy K. Prehabilitation for esophagectomy. J Thorac Dis 2019; 11(Suppl 5): S632-s8.
15. Minnella EM, Awasthi R, Loiselle SE, Agnihotram RV, Ferri LE, Carli F. Effect of Exercise and Nutrition Prehabilitation on Functional Capacity in Esophagogastric Cancer Surgery: A Randomized Clinical Trial. JAMA Surg 2018; 153(12): 1081-9.
16. Banugo P, Amoako D. Prehabilitation. BJA Education 2017; 17(12): 401-5.
17. Santa Mina D, van Rooijen SJ, Minnella EM, Alibhai SMH, Brahmbhatt P, Dalton SO, et al. Multiphasic Prehabilitation Across the Cancer Continuum: A Narrative Review and Conceptual Framework. Front Oncol 2020; 10: 598425.
18. Tew GA, Ayyash R, Durrand J, Danjoux GR. Clinical guideline and recommendations on pre-operative exercise training in patients awaiting major non-cardiac surgery. Anaesthesia 2018; 73(6): 750-68.
19. Pouwels S, Stokmans RA, Willigendael EM, Nienhuijs SW, Rosman C, van Ramshorst B, et al. Preoperative exercise therapy for elective major abdominal surgery: a systematic review. Int J Surg 2014; 12(2): 134-40.
20. Hughes MJ, Hackney RJ, Lamb PJ, Wigmore SJ, Christopher Deans DA, Skipworth RJE. Prehabilitation Before Major Abdominal Surgery: A Systematic Review and Meta-analysis. World J Surg 2019; 43(7): 1661-8.
21. Santa Mina D, Clarke H, Ritvo P, Leung YW, Matthew AG, Katz J, et al. Effect of total-body prehabilitation on postoperative outcomes: a systematic review and meta-analysis. Physiotherapy 2014; 100(3): 196-207.
22. Minnella EM, Bousquet-Dion G, Awasthi R, Scheede-Bergdahl C, Carli F. Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience. Acta Oncol 2017; 56(2): 295-300.
23. Hara T, Kogure E, Kubo A, Kakuda W. Does pre-operative physical rehabilitation improve the functional outcomes of patients undergoing gastrointestinal cancer surgery? J Phys Ther Sci 2021; 33(3): 299-306.
24. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5(6): 649-55.
25. McCulloch P, Ward J, Tekkis PP. Mortality and morbidity in gastro-oesophageal cancer surgery: initial results of ASCOT multicentre prospective cohort study. Bmj 2003; 327(7425): 1192-7.
26. Papenfuss WA, Kukar M, Oxenberg J, Attwood K, Nurkin S, Malhotra U, et al. Morbidity and mortality associated with gastrectomy for gastric cancer. Ann Surg Oncol 2014; 21(9): 3008-14.
27. Low DE, Kuppusamy MK, Alderson D, Cecconello I, Chang AC, Darling G, et al. Benchmarking Complications Associated with Esophagectomy. Ann Surg 2019; 269(2): 291-8.
28. Blencowe NS, Strong S, McNair AG, Brookes ST, Crosby T, Griffin SM, et al. Reporting of short-term clinical outcomes after esophagectomy: a systematic review. Ann Surg 2012; 255(4): 658-66.
29. Jordan T, Mastnak DM, Palamar N, Kozjek NR. Nutritional Therapy for Patients with Esophageal Cancer. Nutr Cancer 2018; 70(1): 23-9.
30. Ryu SW, Kim IH. Comparison of different nutritional assessments in detecting malnutrition among gastric cancer patients. World J Gastroenterol 2010; 16(26): 3310-7.
31. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN practical guideline: Clinical Nutrition in cancer. Clinical Nutrition 2021; 40(5): 2898-913.
32. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009; 250(2): 187-96.
33. Faithfull S, Turner L, Poole K, Joy M, Manders R, Weprin J, et al. Prehabilitation for adults diagnosed with cancer: A systematic review of long-term physical function, nutrition and patient-reported outcomes. Eur J Cancer Care (Engl) 2019; 28(4): e13023.

ORIGINAL ARTICLE

Mapping cerebral atrophy and hypometabolism on ^{18}F-FDG PET/CT scans for detecting Alzheimer's disease in the Malaysian population using a Malaysian brain atlas template

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ABSTRACT

Introduction: Studies are lacking in evaluating brain atrophy patterns in the Malaysian population. This study aimed to compare the patterns of cerebral atrophy and impaired glucose metabolism on ^{18}F-FDG PET/CT imaging in various stages of AD in a Klang Valley population by using voxel-based morphometry in SPM12.

Materials and Methods: ^{18}F-FDG PET/CT images of 14 healthy control (HC) subjects (MoCA score > 26 (mean+SD~ 26.93+0.92) with no clinical evidence of cognitive deficits or neurological disease) and 16 AD patients (MoCA ≤22 (mean+SD~18.6+9.28)) were pre-processed in SPM12 while using our developed Malaysian healthy control brain template. The AD patients were assessed for disease severity using ADAS-Cog neuropsychological test. KNE96 template was used for registration-induced deformation in comparison with the ICBM templates. All deformation fields were corrected using the Malaysian healthy control template. The images were then nonlinearly modified by DARTEL to segment grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) to produce group-specific templates. Age, intracranial volume, MoCA score, and ADAS-Cog score were used as variables in two sample t test between groups. The inference of our brain analysis was based on a corrected threshold of p<0.001 using Z-score threshold of 2.0, with a positive value above it as hypometabolic. The relationship between regional atrophy in GM and WM atrophy were analysed by comparing the means of cortical thinning between normal control and three AD stages in 15 clusters of ROI based on Z-score less than 2.0 as atrophied.

Results: One-way ANOVA indicated that the means were equal for TIV, F(2,11) = 1.310, *p*=0.309, GMV, F(2,11) = 0.923, *p*=0.426, WMV, F(2,11) = 0.158, *p*=0.856 and CSF, F(2,11) = 1.495 *p*=0.266. Pearson correlations of GM, WM and CSF volume between HC and AD groups indicated the presence of brain atrophy in GM (*p*=-0.610, *p*<0.0001), WM (*p*=-0.178, *p*=0.034) and TIV (*p*=-0.374, p=0.042) but showed increased CSF volume (*p*=0.602, *p*<0.0001). Voxels analysis of the 18F-FDG PET template revealed that GM atrophy differs significantly between healthy control and AD (*p*<0.0001). Z-score comparisons in the region of GM & WM were shown to distinguish AD patients from healthy controls at the prefrontal cortex and parahippocampal gyrus. The atrophy rate within each ROI is significantly different between groups (c^2=35.9021, df=3, p<0.0001), Wilcoxon method test showed statistically significant differences were observed between Moderate vs. Mild AD (*p*<0.0001), Moderate AD vs. healthy control (p=0.0005), Mild AD vs. HC (*p*=0.0372) and Severe AD vs. Moderate AD (*p*<0.0001). The highest atrophy rate within each ROI between the median values ranked as follows severe AD vs. HC (*p*<0.0001) > mild AD vs. HC (*p*=0.0091) > severe AD vs. moderate AD (*p*=0.0143).

Conclusion: We recommend a reliable method in measuring the brain atrophy and locating the patterns of hypometabolism using a group-specific template registered to a quantitatively validated KNE96 group-specific template. The studied regions together with neuropsychological test approach is an effective method for the determination of AD severity in a Malaysian population.

KEYWORDS:
Statistical parametric mapping; image preprocessing; DARTEL; neuropsychological test; Malaysian population

INTRODUCTION

Atrophy and hypometabolism in specific grey matter (GM) regions in the brain have been correlated as features of AD. Several studies have been done on GM atrophy showing that early impairment affected the parahippocampal gyrus, precuneus, posterior cingulate, frontal lobe, insula and the cerebellum within a year prior to the diagnosis of AD.[1,2,3] Interestingly, structural neuroimaging had reported that the cerebellum is related to cognition and emotion and has interactions with the cerebral cortex which influences the cognitive deficits in AD patients.[4] The frontal lobes were typically impacted as AD progressed, with symmetrical alterations on both sides.[5] The preserved brain area is usually associated with the occipital and somatosensory cortex including deep cerebral nuclei.[6]

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Meguro et al.[7] had replicated the same method by Jobst et al.[8] to configure similar result by Yamaguchi et al.[5] that concluded by measuring the minimum thickness of both sides of the hippocampus denoted as the width of the hippocampus may be used as a benchmark for atrophy pattern in GM with AD. Damage to the medial temporal lobe can cause neurons to lose contact with each other. This may help explain the hypometabolism pattern, especially in the early stages.[9] However, studies are lacking in Asian brain, particularly in the development of Malaysian brain template, which is a pertinent issue that can be caused by potentially differing brain anatomy in terms of size and pattern of atrophy compared to Caucasian brains.[10]

Cortical thickness pattern from Magnetic resonance imaging (MRI) clustering methodology had assisted the determination of atrophy subtypes. This method is combined with ^{18}F-FDG PET/CT analysis to highlight the significant hypometabolism in different regions corresponding to the cortical thinning pattern. Atrophy occurs in the right superior, left inferior, and left middle occipital cortices in the parietal subtype, while in the medial temporal subtype, glucose hypometabolism occurs in the left hippocampus, left inferior orbital frontal, right superior medial frontal, and both caudate regions.[11] However, there is no significant change in the cerebrospinal fluid (CSF) volume in both subtypes of atrophy.[10]

Significant brain atrophy is greater at baseline and 1-year follow-up in Mild cognitive impairment (MCI) converters to Alzheimer's disease (AD), decline in gradient for MCI stable and healthy control, respectively. Continuation of this was the development of AD severity index that is associated with Mini-mental state examination (MMSE), Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog), Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) scale (global and a sum of boxes) and ApoE ε4 status.[12] A cross-sectional study between cognitive function and AD biomarkers had been done by Nathan et al. interpreting their association in the early stage of AD. Unfortunately, they failed to relate any potential moderating factors for instance, the ApoE ε4 status. The Cambridge Neuropsychological Test Automated Battery (CANTAB) method also leave inconclusive results as it was not tested in normal older adults and the volumetric study of the hippocampal was manually done on T1 images without any normalisation to the standard brain size in the population.[9]

Voxel-based morphometry (VBM) permits the evaluation of brain changes or group differences across the whole brain with great regional specificity, without needing an a priori determination of a region of interest (ROI).[13] It involves three basic pre-processing steps 1) tissue classification, 2) spatial normalisation and 3) spatial smoothing, later followed by statistical analysis (Figure 1).

Tissue.classification.segments.the.brain.into.grey.matter (GM), white matter (WM) and CSF. To guarantee voxel-wise comparability, it is necessary to spatially normalise either the individual brain or the native brain segmentation.[14] Aligning magnetic resonance (MR) images of the brain to a reference space is an essential pre-processing step for neuroimaging investigations that requires the use of spatial normalisation. All of the source images must be registered to a common reference image or "template image." Functional imaging investigations rely on the exact spatial placement of brain areas, which is made possible by the one-to-one connection between different brains.[15] The spatial transformation will likely face deformation fields that can be measured by the Jacobian determinant algorithm or DARTEL. The structural brain segments can be corrected by modulated segments (GM, WM and CSF). Lastly, spatial smoothing is applied to degrade the noise by applying a smoothing kernel at full-width-half-maximum (FWHM) between 4-16 mm.

There are currently no specific features in neuroimaging that can address the stages of AD from healthy normal aging. Evidence from previous literatures showed initial GM atrophy occur in the parahippocampal gyrus, precuneus, posterior cingulate, frontal lobe and insula while the National Institute on Aging-Alzheimer's Association workgroups had established guidelines on topographic atrophy of structural MRI in the region of medial, basal and lateral temporal lobes including the medial and lateral parietal cortices.[16] WM atrophy was significant in the corpus collasum, fornix, cingulate WM including the cingulum bundle and parahippocampal clusters.[17] Classical ^{18}F-FDG PET/CT study findings had shown hypometabolism in the lateral temporoparietal cortices, precuneus, posterior cingulate cortices, medial temporal lobes and bilateral hippocampi.[18] We implemented a direct measurement of atrophy and localisation of the patterns of glucose hypometabolism using a group-specific template registered to a quantitatively validated structural MRI KNE96 template to correct for the magnitude of brain deformations in term of the size of Malaysian brains compared with the ICBM 152 template which is used for Caucasians. This Malaysian group-specific template was derived from an optimised VBM method. The Statistical Parametric Mapping, Version 12 software (SPM) analysis with association to neuropsychological test approach was combined with the result from BAAD software (classification of AD using Support Vector Machine) that can predict the progression of AD. Presence of hypometabolism and atrophy on brain pattern analysis is assumed as an effective diagnostic method for AD detection. This study hypothesised that specific atrophy patterns in GM and WM with varying hypometabolism patterns can be used as the reference region for the explicit masking to be applied for an automated analysis. When combined ADAS-Cog scores, it will help in determining the stages of AD.[19]

The BAAD software was developed using VBM logarithmic analysis with the study on the region of interest (ROI) in the common area affected in AD patients. Additional information regarding this software is available from the following website: (http://www.shigamed.ac.jp/hqbioph/BAAD(English)/BAAD.html). This software is reliable due to the fact that it incorporates age as a covariate, which leads to age-corrected z-scores of the hippocampi that are more appropriate for the subject's age.[20]

MATERIALS AND METHODS

Participants

The subjects recruited in total (n=30), were 12 males and 18 females, consisting of 14 Malays, 10 Chinese and 6 Indians over 60 years of age (mean ± SD 9.95+2.73). There were 14

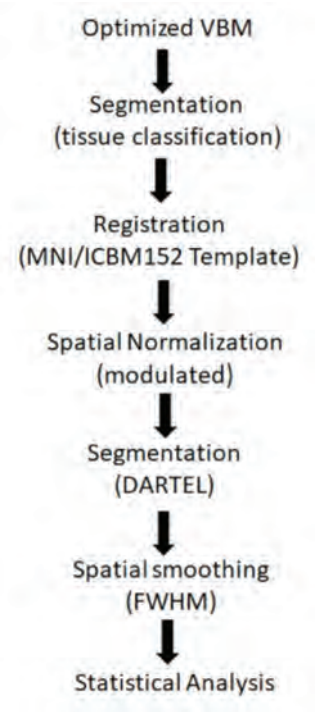

Fig. 1: Flow diagram of the pre-processing steps in an optimised VBM pipeline.

healthy control (HC) subjects and 16 AD subjects in this study. Enrolled HC subjects were volunteers from the same study site who came as escorts to patients or only visited the general clinic. They had no clinical evidence of cognitive deficit or neurological disease, having MoCA scores above 26 (mean±SD 26.93±0.92) and they underwent a standardised protocol of ^{18}F-FDG PET/CT brain scans that showed normal brain anatomy and glucose metabolism.

In brief, the inclusion criteria for AD patients who were recruited as subjects for this study include: (i) the presence of a subjective memory complaint that has been verified using the DSM-5; (ii) a MoCA score of less than 24; and (iii) a clinical diagnosis that sufficiently met the clinical National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD. Participants were not allowed to take part if they had a history of serious neurological or psychiatric illnesses, brain malformations, or other conditions that could make it hard for their bodies to break down ^{18}F-FDG. This included taking antidepressants with anticholinergic properties, which could cause problems. Ethical clearance was obtained from the Medical Research Ethics Committee, UPM (JKE-UPM), Human Research Ethics Committee, USM (JEPeM-USM) and Malaysia. The ethical principles conformed with the Helsinki Declaration and were consistent with Malaysian Good Clinical Practice.

The AD patients were screened using MoCA-BM to measure their cognitive deficits. Whereas the severity of the disease was determined using ADAS-Cog. The cut-off score for MoCA-BM was 22 (mean+SD~18.6+9.28) similar to studies conducted in other Asian countries such as Korea and Hong Kong.[15,21] The study also took into consideration of Malaysia's average lower level of educational attainment.[22] Based on the MoCA-BM cut-off scores, there were 3 mild AD subjects, 11 moderate AD subjects and 2 severe AD subjects classified from diagnosis by the clinical psychologists (mean+SD~43.65+12.65). The clinical characteristics of the participants are summarised in Table I.

^{18}F-FDG PET/CT brain analysis

Acquisitions of images were captured using Siemens Truepoint Biograph 64 PET/CT scanner from CDNI, UPM. Statistical analyses were applied using SPM12, whereas image preprocessing and image matrix calculations were done in MATLAB (MathWorks). As the reference brain, KNE96 template was used for registration-induced deformation because of its quantitatively validated Asian templates as opposed to the ICBM152 templates. It was developed by using 96 subjects (M/F=48/48) over 60 years of age (M=69.5±6.2 years old, F = 70.1±7.0 years old).

As there were more than 100% volume variances in the right hemisphere and in the left hemisphere, the use of the ICBM152 template as a reference atlas in Asian populations was unreliable.23 Our calculations also revealed that the differences in the total intracranial volume (TIV) based on Caucasian templates compared with our HC subjects' average brain size was approximately 12.8% and 5.2% larger, using ICBM152 and KNE96 templates, respectively. Therefore, we proceeded to correct all the deformation fields to develop a Malaysian healthy control template based on our 14 participants aged above 60 years old. The deformation field, D is defined by the displacement, d of each voxel point, p and is defined based on:

$$D\,(p) = p + d\,(p) \tag{1}$$

A local relative tissue volume change is measured throughout the brain by the Jacobian operator. It is determined by p as the Jacobian deformation field matrix determinant.[24]

$$Jac_p(D) = \begin{pmatrix} \frac{\partial D_x}{\partial_x} & \frac{\partial D_x}{\partial_y} & \frac{\partial D_x}{\partial_z} \\ \frac{\partial D_y}{\partial_x} & \frac{\partial D_y}{\partial_y} & \frac{\partial D_y}{\partial_z} \\ \frac{\partial D_z}{\partial_x} & \frac{\partial D_z}{\partial_y} & \frac{\partial D_z}{\partial_z} \end{pmatrix} \tag{2}$$

An elementary volume in the source image, denoted by δVsource, is related to its deformed counterpart volume, δVtarget in the target image, using the Jacobian operator.

$$\delta V_{target} = Jac_{\,p}\,(D)\;.\;\delta V_{source} \tag{3}$$

To construct a collection of group-specific templates, the new δV_{target} was nonlinearly modified by the DARTEL technique, and then segmented into GM, WM, and CSF. The images were then warped into the Montreal Neurological Institute (MNI) space using anatomical data from the International Consortium for Brain Mapping (ICBM152) and smoothed using an 8-mm FWHM kernel.

Table I: Clinical characteristics of the participants (n+?)

	Healthy control (N=14)	Alzheimer's disease (N=16)		
		Mild, Mean±SD (n=3)	Moderate, Mean ± SD (n=11)	Severe, Mean±SD (n=2)
Age, Mean±SD (max)	65.9 ± 3.5 (71)	73.7 ± 6.0 (73)	77 ± 6.9 (79)	77.5 ± 0.7 (78)
Education, mean±SD (max)	10.2 ± 2.6 (14)	9 ± 6 (9)	8.7 ± 7.1 (6)	10.5 ± 9.4 (11)
Women subjects (%)	65	67	45	100
MoCA score, mean±SD (max)	26.9 ± 0.9 (28)	20.0 ± 4.0 (24)	10.6 ± 4.8 (20)	5.0 ± 0(5)
ADAS-Cog score, mean±SD (max)	NIL	27.4 ± 2.7 (27)	42.5 ± 6.2 (39)	68.5±2.1 (69)
GMV, mean±SD (max)	1062.4 ± 43.7 (1143.8)	996.9 ± 36.7 (1026.3)	945.2 ± 0 (157.5)	766.1 ± 32.8 (789.3)
WMV, mean±SD (max)	180.4 ± 28.4 (242.6)	179.7 ± 54.4 (240.8)	156.6 ± 132.8 (544.3)	127.5 ± 54.5 (166.1)
CSF, mean±SD (max)	392.6 ± 80.7 (546.5)	468.6 ± 46.2 (521.9)	522.7 ± 36.7 (581.2)	444.1 ± 24.4 (461.33)
TIV, mean±SD (max)	1635.4 ± 83.0 (1804.8)	1645.3 ± 45.3 (1692.7)	1624.2 ± 101.2 (1756.09)	1337.5 ± 46.3 (1370.3)

Table II: Clusters of hypometabolism of subjects in this study (n=?)

Subject	Anatomical region	PFWE-corr	kE	Zscore	Coordinates		
					x	y	z
Healthy control	R superior frontal gyrus medial segment	0.905	516	4.37	9	61	22
	L medial frontal gyrus	0.531	1162	3.89	-35	51	19
	R medial frontal gyrus	0.739	815	3.65	44	44	2
	L cerebral WM	0.999	102	3.47	-36	30	-14
	L caudate	0.997	145	3.26	-18	20	4
	R lateral orbital gyrus	0.999	105	3.25	34	49	-12
Mild AD	L cerebral WM	0.652	169	6.70	-34	2	-14
	R cerebral WM	0.759	151	5.63	8	-54	54
	L fusiform gyrus	0.927	111	5.28	10	8	-12
	R parahippocampal gyrus	0.351	115	4.94	28	-86	42
	R precuneus	0.138	100	3.88	8	-86	34
Moderate AD	L medial temporal gyrus	0.992	140	6.24	-60	-46	-4
	R cerebral WM	0.976	228	5.83	44	-50	20
	RL posterior cingulate gyrus	0.976	228	3.40	-4	-42	26
	L lateral ventricle	0.992	116	3.36	-26	-50	20
	R medial temporal gyrus	0.998	119	3.19	52	-8	-18
	R lingual gyrus	0.998	103	3.16	12	-56	6
Severe AD	R/L cerebrum	0.999	435	7.31	-14	8	10
	R Superior temporal gyrus	0.992	316	6.75	-46	16	-14
	R Inferior temporal gyrus	0.872	212	5.23	6	12	-18
	L temporal lobe	0.992	286	5.73	-54	12	-6
	L cerebellum	0.766	197	5.44	12	18	-16
	R cerebellum	0.513	173	5.16	-28	-42	-24
	Middle occipital lobe	0.511	165	4.47	4	60	-18
	R fusiform gyrus	0.508	149	4.38	36	-49	-8

Comparisons of cerebral atrophy based on hypometabolic regions
Pre-processed images were further analysed using BAAD software for ROI-wise analysis using preset ROIs for automated anatomical labelling (AAL). Volume at the local level was modified, taking into account both TIV and chronological age. Since it was already known from experience that TIV cancelled out sex differences, we decided not to include sex as a covariate in our analysis. With age and TIV as confounders, BAAD used the 60+ age group in the IXI database as a reference to figure out z-scores.[20] In order to estimate the atrophy level for each AD group, z-score were calculated based on gray matter volume (GMV) and white matter volume (WMV) adjusted to the mean volume of healthy controls.

The z-score maps were displayed as an overlay on tomographic sections and surface renderings of the standardised 3D MRI brain in the software. Next, the volume loss was compared between mild AD, moderate AD and severe AD. Two-sample T-test analysis showed that covariates for factorial design were TIV and MoCA scores. ADAS-Cog scores were added for the AD group analysis. Significance for voxel was accepted at a corrected threshold of $p<0.001$ for GM, WM, and CSF comparisons versus healthy controls and an uncorrected threshold of $p<0.001$ for AD group comparisons. The Z-score map of 118 ROIs for GM and 23 ROIs of WM were compared between healthy control and the AD groups.

RESULTS

Voxel Analysis Using SPM
Based on Table II, the comparison with healthy control and AD patients showed a significant hypometabolic region at

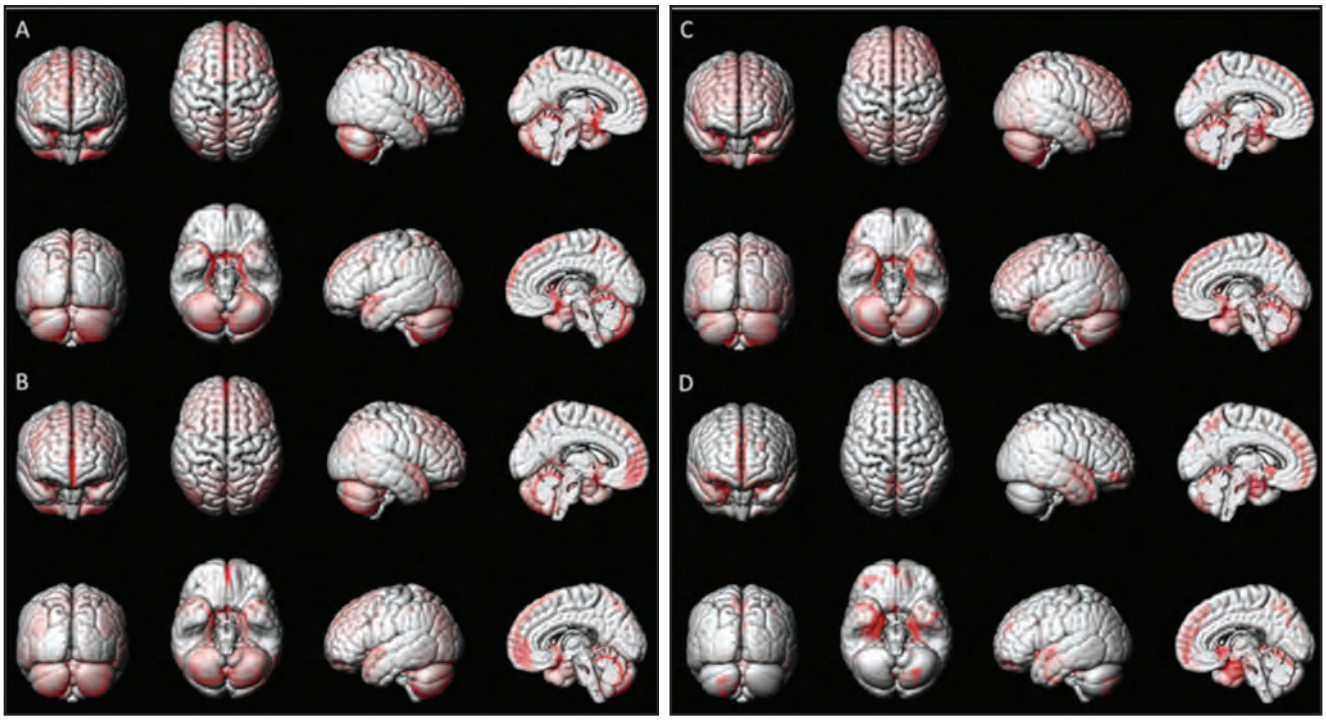

Fig. 2: Grey matter atrophy and white matter hyperintensities between all groups adjusted by total intracranial volume (TIV) and age; (A) Healthy control, (B) Mild AD, (C) Moderate AD, and (D) Severe AD. (Clusters of ROI are specified at 50 voxels with Z-score for voxel numbers (Z<=2.0) of ROI.)

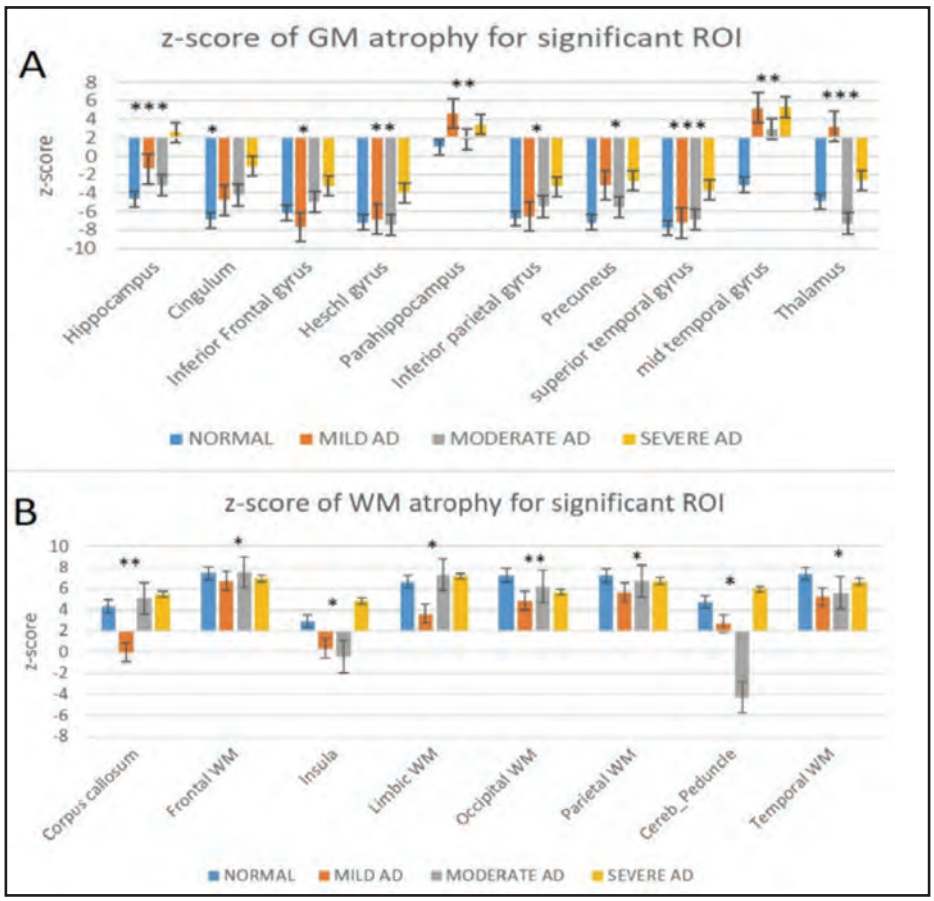

Fig. 3: Z-score of significant ROI showing atrophy in healthy control, mild AD, moderate AD and severe AD. Z-score of significant ROI showing atrophy in the GM (A). Z-score of significant ROI showing atrophy in the WM (B).
*Z score were compared using single-factor ANOVA. **When significance was ($p<0.05$), post hoc analysis was performed using Dunn All Paris for Joint Ranks (*$p<0.05$; **$p<0.005$;***$p<0.0001$).

the frontal, medio-temporal, hippocampal and parahippocampal gyrus. Comparisons within AD groups revealed a more widespread pattern of a hypometabolic region or distinct atrophy of GM and WM hyperintensity especially at the frontal, bilateral temporal, medio-temporal and parietal lobe.

Results based on one-way ANOVA indicated that the means were equal for TIV, $F(2,11) = 1.310$, p=0.309, GMV, $F(2,11) = 0.923$, p=0.426, WMV, $F(2,11) = 0.158$, p=0.856 and CSF, $F(2,11) = 1.495$ p=0.266. Therefore, we combined all of our healthy normal participants for the derivation of the Malaysian template. Comparisons between templates revealed different patterns were visualised between ICBM152, KNE96 and ^{18}F-FDG PET Malaysian template. Pearson correlations of GM, WM and CSF volume between healthy control and AD groups indicated that brain atrophy in GM (p=-0.610, p<0.0001), WM (p=-0.178, p=0.034) and TIV (ρ=-0.374, p=0.042) but the increased volume of CSF (ρ=0.602, p<0.0001).

One-way ANOVA between-group analysis was done selecting the TIV, MoCA-BM scores and ADAS-Cog scores as the covariates. Our results displayed in Table II were similar to previous works in locating the hypometabolic region of HC and AD brains.[2,4,25,26,27] The atrophy and WM hyperintensities between these groups were compared from the result of BAAD software, as shown in Figure 2.

Statistical Analyses

The relationship between regional atrophy in grey matter and white matter atrophy was analysed by comparing the means between normal control and three AD stages using all the criteria stated by Syaifullah et al.[20] The statistical analysis was run in SPSS version 26.0. As the sample size is small, the normality test using the Shapiro-Wilk test showed a significant difference between grey matter and white matter volume with the atrophy rate and atrophy weight in all the ROIs in AAL. To study the regional GM and WM atrophy effect on different groups of AD, analysis of means for Variances-Levene (ADM) were done on GM and WM regional volumes to select the region that falls outside the lower decision limit from the analysis of means charts. The GM clusters are the cingulum, hippocampus, inferior frontal gyrus, Heschl gyrus, parahippocampus, inferior parietal gyrus, medial temporal gyrus and thalamus. The WM clusters are corpus callosum, frontal, insula, limbic, occipital, parietal, peduncle and temporal region. Total GM and WM cluster to be considered are 15 clusters.

The correlations between variables were made using Spearman's ρ and Kendall's tau as the data showed a non-normal distribution. There was a strong, positive correlation between atrophy weight of ROI in a whole-brain with the atrophy rate within each ROI, (p=0.8025, p<0.0001), (τ_b =0.6242, p<0.0001) but less significant correlations between the reduced volumes of each ROI with the atrophy weight of ROI in a whole brain with the atrophy rate within each ROI. Consequently, there is a significant correlation between the z-score of each ROI and the atrophy rate within each ROI (p=0.5803, p<0.0001), (τb =0.4124, p<0.0001), whereas a negative strong correlation between the z-score of each ROI and the regional volume (p=-0.7011, p<0.0001), (τ_b =-0.5161, p<0.0001). Kruskal–Wallis H tests were conducted to examine the differences in the atrophy indicators among the three groups with healthy controls. Significant difference was found by chi-square approximation; consequently, the Wilcoxon method test was employed to generate a nonparametric pairwise comparison, and Dunn All-Patients for Joint Ranks was utilised to assess if the post hoc tests were significant.

The atrophy rate within each ROI is significantly different between groups from the chi-square approximation (c^2=35.9021, df=3, p<0.0001), Wilcoxon method test showed statistically significant differences were observed between Moderate vs. Mild AD (p<0.0001), Moderate AD vs. healthy control (p=0.0005), Mild AD vs. healthy control (p=0.0372) and Severe AD vs. Moderate AD (p<0.0001). The highest atrophy rate within each ROI between the median values ranked as follows severe AD vs. healthy control (p<0.0001) > mild AD vs. healthy control (p=0.0091) > severe AD vs. moderate AD is (p=0.0143). This result indicates that atrophy is the major indicator in the diagnosis of AD in grey matter and white matter shown in Figures 3A and 3B.

DISCUSSION

Our objective was to characterise the atrophy patterns from statistical parametric testing and incorporate the information from MoCA-BM and ADAS-Cog in diagnosing the severity of AD among Malaysians. The neuropsychological test result of the ADAS-Cog results showed that the risk of AD is not covariate with age and formal education. Based on the three stages of severity of AD, our study showed that MoCA and ADAS-Cog was inversely correlated with increasing severity of AD.

Our study emphasised on categorising AD patients based on ADAS-Cog and the location of peak intensity signals on ^{18}F-FDG PET/CT from more than 100 voxels per cluster that had shown the correlation between these signals with the important cognitive functional parts in the brain.

We used the newly validated KNE96 template instead of the ICBM152 template to correct for all the global brain shapes and sizes of the Malaysian population as computational neuroimaging studies that interpret the anatomical features using an unsuitable template may lead to false study results.[28] The inference of our brain analysis was based on a corrected threshold of p<0.05 at Z-score threshold of 2.0 with a positive value above it as hypometabolic in agreement with a study done by Oshikubo et al. on his voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) combined with the Japanese version of the Neurobehavioral Cognitive Status Examination (COGNISTAT).[27] The threshold level was set higher than previous findings due to our age-specific ROIs with modulated VBM.[28] Healthy control showed a distinct hypometabolism pattern at the frontal part of the brain whilst the early stage of AD indicated that hypometabolic areas were concentrated at temporal, hippocampal and parahippocampal gyrus. It was also observed that healthy control and AD diagnostic group have similarities in the hypometabolic area detected in clusters of more than 100 voxels with reduced activity in multiple sites of the brain when neuropsychological test results were taken into account (Figure 2).

To the best of our knowledge, this ^{18}F-FDG PET/CT template was the first that was developed in a multi-ethnicity population pool. The small sample size collected degrades the co-registered brain images for each sample that does not correspond to the true shape of GM and WM as compared to the ICBM152 and KNE96 templates. Thus, hypometabolic regions appeared diffused to the deep brain from the 'real grey matter' region. Nonetheless, the incomplete registration to the reference template using the standard VBM was responsible for the differences in deep brain GM findings.[20] A study done by Bhalerao et al. on MRI brain of 15 Indian subjects to evaluate the registration accuracy differences between MNI, Chinese-56 and Indian templates had found out that the MNI-152 template was larger than that of both Chinese and Indian templates (p<0.001), whereas there were no significant differences between the Chinese template and MNI template (p=0.87). Global brain differences have demonstrated that the non-Caucasian subject spatial normalisation data were unsuitable using the MNI template.[10] However in this study, using the KNE96 template as the reference image, our Malay, Indian and Chinese healthy control participants' brain volume did not show a statistically significant difference.

Voxels analysis of the ^{18}F-FDG PET template revealed that GM atrophy with z-score of each ROI threshold at z<=2.0 differs significantly between healthy control and AD at the hippocampus, superior temporal gyrus and thalamus (p<0.0001). Z-score comparisons in the region of GM have been shown to distinguish mild AD patients from healthy control at the prefrontal cortex, parahippocampal gyrus, Heschl gyrus and medial temporal gyrus.[27,29] These region were the best discriminator in the preclinical stage of AD which supported a recent report pertaining entorhinal cortex and parahippocampus as the earliest region affected using texture analysis.[21] The medial temporal lobe atrophy associated with cognitive outcome is a consistent finding with earlier observations of patients with or without mild cognitive impairment.[30] The medial temporal gyrus comprising of hippocampus, entorhinal cortex, perirhinal cortex and parahippocampal cortex are the subregions critical for cognitive functions because they are the primary target of neurofibrillary tangles that are characteristics for the diagnosis of AD.[31]

Significant WM atrophy was observed in corpus callosum and insula in mild AD, while cerebral peduncle and insula were the significant WM atrophy region in worsened AD condition. These findings corroborate with results from a recent study that concludes amyloid beta plaque accumulation was associated with WM alterations mainly in corpus callosum, percuneus and insula.[32] Research into the WM changes in AD may clarify the pathophysiological mechanisms underlying neuropsychological and anatomical asymmetry. The effect of diffusivity of WM spreads bilaterally in the parahippocampal gyrus and temporal lobes.[21] Within the prefrontal cortex, the WM was particularly susceptible to age-related and cognitive decline in AD patients compared to the GM. It was also known that WM loss was selective as the volumetric measurements were less in older age AD, > 80 years compared to younger age AD, <70 years.[33] Another study also found that early indication of AD also includes WM atrophy was focused on cingulum bundle, parahippocampal clusters corresponding to the prefrontal and temporal WM clusters similar with our result in Figure 3(b).[26,34]

Acknowledgement of the atrophy pattern helps determine the advanced state of AD and can serve as biomarkers to forecast the future development of Alzheimer's disease-induced subjects. It should be noted that the clinical presentation and the actual level of glucose hypometabolism in the AD brain are still highly varied.

LIMITATIONS

The limitations of this study arise from firstly, the limited sample size. This single-centred study for the major population of Klang Valley with a convenience sampling method introduced sampling bias for representation of the Malaysian population. Therefore, multiple sites' involvement with larger sample sizes is suggested to understand the pattern of ^{18}F-FDG metabolism, for accurate co-registration of a standard brain for various ethnicity in Malaysia. Secondly, the spatial normalisation of our template does not match the reference MNI PET template which might introduce failure of exact morphological characteristics on an individual brain.

Our ^{18}F-FDG PET template suffers from non-rigid brain registration due to its low resolution and "spatial normalization" for each individual that failed to match the reference MNI PET template. The appearance of GM and WM volumes does not correspond to the true shape as registered to MRI T1-weighted image in ICBM152 and KNE96 template. This was due to the template used for SPM normalisation being based on oxygen-15-labelled water PET (15O-H20 PET) images that neither corresponds to the metabolic feature of ^{18}F-FDG brain scans nor the specific morphological characteristics of individual AD brain.[26]

For future studies, the development of brain templates of 18F-FDG PET/CT based on specific patient ethinicity for the development of a common stereotaxic space using DARTEL will help to improve automated image analysis, tissue classification and region of interest analysis.

CONCLUSION

Our study confirms the pattern of brain atrophy and hypometabolic regions of Alzheimer's disease subjects with reference to the ^{18}F-FDG PET/CT in a Malaysian brain template. It has an important diagnostic value and is a promising method with combination of MoCA and ADAS-Cog score as an effective method not only for the diagnosis but also in the assessment of the severity of disease in patients with AD in a multi-ethnicity Malaysian population. Our study has proven that the widespread of GM hypometabolism and distinct atrophy in the frontal, bilateral temporal, medio-temporal and parietal lobe are significant with WM atrophy of the insula region in all AD stages. This deciphered what has been the signature of AD severity marker compared with the healthy control. The correlation of z-score of each ROI with atrophy rate and brain regional volume is the major indicator in determining the AD severity.

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REFERENCES

1. Meguro K, LeMestric C, Landeau B, Desgranges B, Eustache F, Baron JC. Relations between hypometabolism in the posterior association neocortex and hippocampal atrophy in Alzheimer's disease: a PET/MRI correlative study.J Neurol Neurosurg Psychiatry 2001; 71(3): 315-21.
2. Spulber G, Niskanen E, Macdonald S, Kivipelto M, Padilla DF, Julkunen V, et al. Evolution of global and local grey matter atrophy on serial MRI scans during the progression from MCI to AD.Curr Alzheimer Res 2012; 9(4): 516-24.
3. Takahashi R, Ishii K, Miyamoto N, Yoshikawa T, Shimada K, Ohkawa S, et al. Measurement of gray and white matter atrophy in dementia with lewy bodies using diffeomorphic anatomic registration through exponentiated lie algebra: A comparison with conventional voxel-based morphometry.Am J Neuroradiol 2010; 31(10): 1873-8.
4. Jacobs HIL, Hopkins DA, Mayrhofer HC, Bruner E, van Leeuwen FW, Raaijmakers W, et al. The cerebellum in Alzheimer's disease: evaluating its role in cognitive decline.Brain 2018; 141(1): 37-47.
5. Yamaguchi S, Meguro K, Itoh M, Hayasaka C, Shimada M, Yamazaki H, et al. Decreased cortical glucose metabolism correlates with hippocampal atrophy in Alzheimer's disease as shown by MRI and PET.J Neurol Neurosurg Psychiatry 1997; 62(6): 596-600.
6. Silverman DHS. Brain 18 F-FDG PET in the Diagnosis of Neurodegenerative Dementias: Comparison with Perfusion SPECT and with Clinical Evaluations Lacking Nuclear Imaging*.J Nucl Med 2004; 45(4): 594-607.
7. Meguro K, Lemestric C, Landeau B, Desgranges B, Eustache F, Baron JC. Relations between hypometabolism in the posterior association neocortex and hippocampal atrophy in Alzheimer's disease: a PET/MRI correlative study. J Neurol Neurosurg Psychiatry 2001; 71: 315-21.
8. Jobst KA, Smith AD, Barker CS, Wear A, King EM, Smith A, et al. Association of atrophy of the medial temporal lobe with reduced blood flow in the posterior parietotemporal cortex in patients with a clinical and pathological diagnosis of Alzheimer's disease.J Neurol Neurosurg Psychiatry 1992; 55(3): 190-4.
9. Nathan PJ, Lim YY, Abbott R, Galluzzi S, Marizzoni M, Babiloni C, et al. Association between CSF biomarkers, hippocampal volume and cognitive function in patients with amnestic mild cognitive impairment (MCI). Neurobiol Aging 2017; 53: 1-10.
10. Bhalerao GV, Parlikar R, Agrawal R, Shivakumar V, Kalmady S V, Rao NP, et al. Construction of population-specific Indian MRI brain template: Morphometric comparison with Chinese and Caucasian templates.Asian J Psychiatr 2018; 35: 93-100.
11. Hwang J, Kim CM, Jeon S, Lee JM, Hong YJ, Roh JH, et al. Prediction of Alzheimer's disease pathophysiology based on cortical thickness patterns.Alzheimer's Dement Diagnosis, Assess Dis Monit 2015; 2: 58-67.
12. Hwang J, Kim CM, Jeon S, Lee JM, Hong YJ, Roh JH, et al. Prediction of Alzheimer's disease pathophysiology based on cortical thickness patterns.Alzheimer's Dement Diagnosis, Assess Dis Monit 2016; 2: 58-67.
13. Ashburner J, Friston KJ. Voxel-based morphometry - The methods.Neuroimage 2000; 11(6 I): 805-21.
14. Lee JY, Lee DW, Cho SJ, Na DL, Jeon HJ, Kim SK, et al. Brief screening for mild cognitive impairment in elderly outpatient clinic: validation of the Korean version of the Montreal Cognitive Assessment.J Geriatr Psychiatry Neurol 2008; 21(2): 104-10.
15. Chu LW, Ng KHY, Law ACK, Lee AM, Kwan F. Validity of the Cantonese Chinese Montreal Cognitive Assessment in Southern Chinese.Geriatr Gerontol Int 2015; 15(1): 96-103.
16. Jack CRJ, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.Alzheimers Dement 2011; 7(3): 257-62.
17. Villain N, Desgranges B, Viader F, de la Sayette V, Mézenge F, Landeau B, et al. Relationships between hippocampal atrophy, white matter disruption, and gray matter hypometabolism in Alzheimer's disease. J Neurosci 2008; 28(24): 6174-81.
18. Nasrallah IM, Wolk DA. Multimodality imaging of Alzheimer disease and other neurodegenerative dementias. J Nucl Med 2014; 55(12): 2003-11.
19. Zainal NH, Silva E, Lim LL, Kandiah N. Psychometric Properties of Alzheimer's Disease Assessment Scale-Cognitive Subscale for Mild Cognitive Impairment and Mild Alzheimer's Disease Patients in an Asian Context. Ann Acad Med Singapore 2016; 45: 273-83.
20. Syaifullah AH, Shiino A, Kitahara H, Ito R, Ishida M, Tanigaki K. Machine Learning for Diagnosis of AD and Prediction of MCI Progression From Brain MRI Using Brain Anatomical Analysis Using Diffeomorphic Deformation. Front Neurol 2021; 11: 1894.
21. Freitas S, Simões MR, Alves L, Santana I. Montreal Cognitive Assessment: validation study for mild cognitive impairment and Alzheimer disease. Alzheimer Dis Assoc Disord 2013; 27.
22. Aziz SAA, Saripan MI, Ibrahim N, Saad FFA, Suppiah S, Ismail SIF, et al. Combining ADAS-Cog Assessment with Hypometabolic Region of 18F-FDG PET/CT Brain Imaging for Alzheimer's Disease Detection. In: 2020 IEEE-EMBS Conference on Biomedical Engineering and Sciences (IECBES) 2021: 166-71.
23. Lee H, Yoo B Il, Han JW, Lee JJ, Oh SYW, Lee EY, et al. Construction and validation of brain MRI templates from a Korean normal elderly population. Psychiatry Investig 2016; 13(1): 135-45.
24. Shen S, Sterr A. Is DARTEL-based voxel-based morphometry affected by width of smoothing kernel and group size? A study using simulated atrophy. J Magn Reson Imaging 2013; 37(6): 1468-75.
25. Aziz SAA, Ling LJ, Saad FFA, Nordin AJ, Ibrahim N, Nuruddin A, et al. Voxel-wise analysis of 18F-fluorodeoxyglucose metabolism in correlation with variations in the presentation of Alzheimer's disease: a clinician's guide. Med J Indones 2019; 28(3 SE-Brief Communication).
26. Della Rosa PA, Cerami C, Gallivanone F, Prestia A, Caroli A, Castiglioni I, et al. A Standardized [^{18}F]-FDG-PET Template for Spatial Normalization in Statistical Parametric Mapping of Dementia.Neuroinformatics 2014; 12(4): 575–93.
27. Oshikubo G, Akahane A, Unno A, Watanabe Y, Ikebuchi E, Tochigi M, et al. Utility of VSRAD for diagnosing Alzheimer's disease in patients screened for dementia.J Int Med Res. 2020;
28. Matsunari I, Samuraki M, Chen WP, Yanase D, Takeda N, Ono K, et al. Comparison of 18F-FDG PET and Optimized Voxel-Based Morphometry for Detection of Alzheimer's Disease: Aging Effect on Diagnostic Performance. J Nucl Med 2007; 48(12): 1961-70.
29. Echávarri C, Aalten P, Uylings HBM, Jacobs HIL, Visser PJ, Gronenschild EHBM, et al. Atrophy in the parahippocampal gyrus as an early biomarker of Alzheimer's disease. Brain Struct Funct 2011; 215(3-4): 265-71.
30. Clerx L, van Rossum IA, Burns L, Knol DL, Scheltens P, Verhey F, et al. Measurements of medial temporal lobe atrophy for prediction of Alzheimer's disease in subjects with mild cognitive impairment. Neurobiol Aging 2013; 34(8): 2003-13.
31. Chauveau L, Kuhn E, Palix C, Felisatti F, Ourry V, de La Sayette V, et al. Medial Temporal Lobe Subregional Atrophy in Aging and Alzheimer's Disease: A Longitudinal Study. Front Aging Neurosci 2021; 13.
32. Phillips O, Joshi SH, Piras F, Orfei MD, Iorio M, Narr KL, et al. The Superficial White Matter in Alzheimer's Disease. Hum Brain Mapp 2016; 37(4): 1321-34.
33. Mahanand BS, Kumar AM. Analysis of Alzheimer's Disease Progression in Structural Magnetic Resonance Images. WSEAS Trans Comput 2009; 8(4, April): 579-88.
34. Serra L, Cercignani M, Mastropasqua C, Torso M, Spanò B, Makovac E, et al. Longitudinal Changes in Functional Brain Connectivity Predicts Conversion to Alzheimer's Disease. J Alzheimers Dis 2016; 51(2): 377-89.

ORIGINAL ARTICLE

End-stage kidney disease in Brunei Darussalam (2011-2020)

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ABSTRACT

Introduction: The Brunei Dialysis and Transplant Registry (BDTR) recorded data on patients with end-stage kidney disease (ESKD) from 2011 to 2020, mainly for planning of services and benchmarking of standards. We report the trends of epidemiologic and performance parameters, compare performances between modalities of Kidney Replacement Therapy and evaluate the survival of ESKD patients over the 10-year period.

Materials and Methods: Three groups of data were analysed from the BDTR over the 10-year period. Epidemiological data, blood parameters and dialysis are key performance indicators.

Results: There are increments in prevalence and incidence of treated ESKD patients in Brunei over 10 years, especially with haemodialysis (HD). The projected prevalence and incidence showed an anticipated annual increase of 42.2 per million population (pmp) and 9.9 pmp respectively. Diabetes mellitus (DM) (79%) was the main cause of ESKD. HD (86%), peritoneal dialysis (PD) (9%) and transplant (5%) were the main modalities of kidney replacement therapy in 2020. Cumulative results over the decade showed significant improvements in serum phosphate, peritonitis rates and HD blood flow rates. PD patients have better survival rates, lower systolic blood pressure and better adequacy. PD survival (patient survival of 91%, 73% and 56% at 1, 3 and 5 years respectively) was superior to HD survival (86% and 64% at 1 and 2 years, respectively), but patient demographics (age and DM status) were different. The 2020 dataset showed satisfactory anaemia management but mineral bone disease management was sub-optimal. Seventy percent of prevalent HD patients had arteriovenous fistula access. Thirty-two percent and fifty-two percent of HD and PD patients, respectively, achieved target dialysis adequacy. Peritonitis rate was 0.3 episodes per patient year.

Conclusion: Brunei has a high incidence and prevalence of treated ESKD in the last decade, especially DM-related ESKD. This study has identified many specific areas to be targeted for improvements and provided evidence for further proliferation of PD and transplant preference policy.

KEYWORDS:
Brunei; registry; dialysis; end-stage kidney disease; peritoneal dialysis; haemodialysis

INTRODUCTION

Brunei Darussalam is a small country in South East Asia with a reported total population of 453,600 in 2020.[1] The country has a relatively high Gross Domestic Product (GDP) per capita of around USD29,600 (BND39,989),[1] which ranks amongst the highest in the region.[2] Citizens and residents enjoy total government subsidies for healthcare, which includes dialysis treatment, transplant, medications and hospital admissions. Due to the small size of the country and free universal healthcare, kidney patients have attainable and equitable access to all the amenities of kidney replacement therapy (KRT). Data from the World Health Organization reported a high prevalence of diabetes (9%), obesity (19%) and hypertension (18%) in the country.[3] As a consequence of these adverse risk factors and open access to healthcare, there have been perpetual annual increments prevalence and incidence of end-stage kidney disease (ESKD) over the past few decades.[4]

The Brunei Dialysis and Transplant Registry (BDTR) was inaugurated in 2011 to describe the state of ESKD in the country and benchmark practice against other countries.[5] Results from the BDTR have influenced economic and fiscal policies employed by the local government, particularly in rationalizing decisions about the country's peritoneal dialysis (PD) preference policy[6] and kidney transplant program.[7] Previous local studies stemming from the BDTR have indicated that PD and transplant patients had a better quality of life and longer life expectancy,[8,9] which fueled momentum to propagate and proliferate the aforementioned policies. Despite the policy push, there has not been any major shift in penetration of PD and transplant in the last few years, likely as result of inadequate training and poor acceptance by patients.[10]

Benchmarking of standards with other countries is a major objective of any registry, as it enables assessment of progress and identification of major implementation goals. Brunei has been represented in the United States Renal Data System (USRDS), as a country with a high prevalence and incidence of kidney disease, particularly through diabetic kidney disease.[11] The decade-long journey of registry experience enables a more detailed and meaningful analysis with established registries, particularly through processes which can identify factors that can influence patients' outcomes and jeopardise the quality of services.

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The main objectives of the study are to report the trends of key performance indicators over a ten-year period, compare performances between different modalities of KRT and evaluate the survival of ESKD patients.

MATERIALS AND METHODS

Ethical committee permission was not sought for this research as data were collected through a national registry. Raw secondary data over a 10-year period was collected and collated from the Brunei Dialysis and Transplant Registry (BDTR), dating from 1st January 2011 and ending on 31st December 2020. Data on point prevalence (on the 31st December every year), annual incidence, percentage annual death rate and aetiology of kidney disease were collected at the end of every year. Blood results of patients [including haemoglobin (Hb), calcium (Ca), phosphate (Ph), parathyroid hormone (PTH), cholesterol, albumin and potassium] were collected at half-yearly intervals, where the average was taken as the patients' results for the year. Key performance indicators (including systolic blood pressure, diastolic blood pressure, PD peritonitis rates, PD weekly Kt/V and haemodialysis (HD) (urea reduction ratio) were also collected. Direct comparisons of blood parameters and key performance indicators between HD, PD and transplant patients were made with the appropriate statistical methods described below. For benchmarking purposes, whenever possible, comparisons were made with data from other similar regional registries (Singapore and Malaysia)[12,13] and established international registries; USRDS,[11] United Kingdom Renal Registry,[14] Australia and New Zealand Renal Registry[15] and European Renal Association and European Dialysis Transplant Association (ERA-EDTA) Registry.[16] References and recommendations from established international advisory and guideline working groups Kidney Disease Improving Global Outcomes (KDIGO), Kidney Disease Outcomes and Quality Initiatives (KDOQI) and International Society of Peritoneal Dialysis (ISPD) were used to benchmark dialysis parameters.[17-22] The benchmarking standards that were utilized include KDOQI for urea reduction ratio of 0.7 for HD patients, ISPD for Kt/V of 1.70 for PD patients. For blood parameters, KDOQI guidelines ranges for serum phosphate (1.13–1.78 mmol/l), PTH (16.5–33 pmol/l) and calcium (2.10–2.37 mmol) were used as reference points. For anaemia management, the target Hb was set at > 10 g/dl, through a hybrid of KDIGO and KDOQI benchmarks, and also to be consistent with reporting patterns of other registries.

The data were collated with Excel (version 2018) and analysed with R (ver.3.5) software (R core team, 2018) and Statistical Package for the Social Sciences software (version 18.0; SPSS Inc, Chicago, IL, USA) and R package. All data were expressed using measures of central tendency and dispersion (means and standard deviations) for quantitative variables. For statistical analyses, mean comparison was made using Student's t test for two groups and one-way ANOVA for multiple groups, with Scheffe's procedure for post hoc analysis. Pearson's Chi Square test was used to determine association between categorical or nominal variables. Pearson's correlation test was used to perform hypothesis testing to determine correlation between variables over the 10-year period. Correlation statistic runs from –1 to +1, utilizing the Munro grading for degree of significance (no, low, moderate, high, very high). Linear regression was also used to determine the relationship between the numerical variables with time for determination of regression coefficient to predict future outcome.

Kaplan–Meier method was used for patient survival and log-rank (Mantel-Cox) test to compare the curves. Primary end-point was defined as death. In patient survival analysis; patients who were lost to follow-up, who received kidney transplants or transferred to other modalities were censored. Survival analyses were performed for incident HD patients from 2018 to 2020 and incident PD patients from 2011 to 2020. Results were considered statistically significant if the *p*-value was less than 0.05.

RESULTS

The total number of treated KRT patients increased from 562 in 2011 to 881 in 2020. This is equivalent to a prevalence of 1430 per million population (pmp) in 2011 and 1944 pmp in 2020, after computation with official annual population census.[1] The incidence of KRT patients (defined as being on dialysis for greater than 3 months) fluctuated between 279 pmp and 479 pmp over the 10-year period. The calculated projected prevalence and incidence with simple linear regression showed an anticipated annual increase of 42.2 pmp and 9.9 pmp, respectively.

Table I compares data of HD, PD and transplant patients in 2020. There were 752, 81 and 48 patients on HD, PD and with transplant graft respectively on the 31st of December 2021. There was a significant age disparity between the three groups of KRT patients with younger patients on PD (49.57 ± 13.10 years) and transplant (38.61 ± 8.34). Prevalent PD and transplant patients were significantly less likely to die compared to HD patients in 2020. PD patients had lower systolic blood pressure, potassium levels and were more likely to achieve targeted adequacy levels.

Table II summarises the 10-year trend of the important ESKD parameters through simple linear regression. The results showed a 'very high' correlation for annual increment in prevalent ESKD patient numbers over all the KRT modalities, but incidence of ESKD only showed 'low' correlation without achieving statistical significance. There was a significant improvement in serum phosphate levels, peritonitis rates and HD blood flow rates but a reduction in PD adequacy over the decade.

Tables III compares epidemiological parameters and dialysis performance indicators of the BDTR against six other registries: Singapore, Malaysia, United States, United Kingdom, Australia and New Zealand. HD was the main modality of KRT (86%), followed by PD 9%) and transplant (5%). DM was the main cause of ESKD (79%). PD survival (patient survival of 91%, 73% and 56% at 1, 3 and 5 years, respectively) was superior to HD survival (86% and 64% at 1 and 2 years, respectively), with PD survival consistent with results from other registries. Targets for Hb (> 10g/dl), pH (1.13–1.78 mmol), PTH (16.3–33 pmol/l) and calcium (2.10–2.37) were achieved in 80%, 39%, 21% and 49% of patients, respectively. Thirty-two percent and 52% of HD and PD

Table I: Comparison of demographic and key performance indicators between HD, PD and Tx patients (n=?)

	HD (n= 752)	PD (n=81)	Tx (n=48)	*p* value
Age	55.22 ± 13.16	49.57 ± 13.10	38.61 ± 8.34	< 0.05*
Gender	381 /752 males	41/81 males	33/48 males	<0.05**
Mortality	131 / 883 died	7 / 88 died	1/ 39 died	< 0.05**
Haemoglobin	11.66 ± 2.01	10.81 ± 1.65		<0.05
Phosphate	1.87 ± 0.61	1.91 ± 0.61		0.35
Calcium	2.19 ± 0.24	2.23 ± 0.23		<0.05
PTH	68.2 ± 84.9	74.1 ± 70.3		0.43
Albumin	37.60 ± 5.15	34.75 ± 5.09		<0.05
Potassium	4.49 ± 0.74	3.90 ± 0.61		<0.05
Total Cholesterol	3.98 ± 1.14	4.04 ± 1.40		0.55
Systolic blood pressure	139 ± 15.20	136 ± 15.84		<0.05
Diastolic blood pressure	80 ± 7.80	84 ± 10.82		<0.05
Dialysis adequacy > target URR or Kt/V	240 out of 752 patients	42 out of 81 patients		< 0.05**

Note:
1. * Statistical analysis was done with One Way Anova and post-hoc analysis with Scheffe's procedure.
2. ** Statistical analysis was done with Chi-Square test
3. All other analysis was done with Student T-test
HD - haemodialysis, PD - peritoneal dialysis, Tx - transplant
PTH: Parathyroid Hormone
URR: urea reduction ratio

Table II: Pearson's correlation to assess trends over ten years (2011-2020)

	10 years mean	SD	Correlation	95% CI		*p*	t
All	721	93.87	0.97	0.89	0.99	<0.05	12.22
HD	612	78.48	0.95	0.8	0.99	<0.05	8.61
PD	68	13.56	0.86	0.5	0.96	<0.05	4.71
Tx	42	5.77	0.91	0.65	0.98	<0.05	6.19
Prevalence	1702.7	146.21	0.87	0.54	0.97	<0.05	5.08
Incidence	379.9	65.84	0.46	-0.24	0.84	0.18	1.45
Mortality	15.2	2.04	0.47	-0.23	0.84	0.17	1.49
Hb	11.1	0.38	-0.17	-0.71	0.51	0.65	-0.47
Ph	1.93	0.09	-0.67	-0.91	-0.07	<0.05	-2.53
PTH	42.9	9.72	0.38	-0.43	0.85	0.35	1.02
Ca	2.24	0.05	0.08	-0.57	0.67	0.82	0.23
SBP	144.2	3.94	-0.48	-0.85	0.22	0.17	-1.53
DBP	82.4	1.26	-0.2	-0.73	0.49	0.57	-0.59
HD URR	0.66	0.03	-0.22	-0.75	0.47	0.54	-0.64
PD kt/v	1.83	0.09	-0.99	-0.99	-0.93	<0.05	-15.62
Peritonitis	31.6	9.63	0.81	0.37	0.95	<0.05	3.92
HD flow	255.2	15.73	0.74	0.22	0.94	<0.05	3.15
HD % AVF usage	71.75	5.18	0.18	-0.61	0.78	0.67	0.44

patients achieved target adequacy levels, whilst 70% of prevalent HD patients had AVF.

Figure 1 shows the survival of HD patients through Kaplan–Meier analysis. From the shortlisted 538 HD patients between 2018 to 2020, 128 were excluded for failing to meet the inclusion criteria (patients who did not have enough baseline data or died within 3 months of dialysis). 410 patients were included in the final analysis with a total follow-up period of 1167 months. Kaplan–Meier survival plots showed an overall actuarial patient survival of 93%, 86%, 74% and 64% at 6, 12, 18 and 24 months.

Figure 2 shows the patient survival of PD patients through Kaplan–Meier analysis. From the shortlisted 187 PD patients between 2011 and 2020, 26 were excluded for acute kidney injury and being on dialysis for less than 3 months. Of the 158 eligible patients; there were 44 deaths, 46 transfer to HD (technique failure) and 6 transplants. Kaplan–Meier survival plots showed an overall patient survival of 91%, 73% and 56% at 1,3 and 5 years.

DISCUSSION

The decade-long registry journey has been important in facilitating emendatory changes to the services. There have been noticeable improvements in certain key performance indicators (serum phosphate, PD peritonitis, HD blood flow rate) over the 10-year period. On the other hand, certain performance parameters (PD and transplant national penetration, HD AVF usage rate, dialysis adequacy) remained steadfastly unaltered despite valiant efforts to improve these outcomes. Estimations from data over the last ten years showed an annual increment of 9.9 per million population (pmp) per year, which was lower than the rates achieved in neighbouring countries like Thailand (19.4 pmp/year) and Malaysia (13.4 pmp/year), but higher than many Western countries (USA 2.2 pmp/year, UK 1.0 pmp/year, Australia 0.9 pmp/year).11 Whilst we accept that continued progression of ESKD prevalence and incidence is a commonly observed worldwide phenomenon, we believe that more can be done to curb this progression at grassroot levels and especially, through collaboration with other allied specialties. Preventative strategies with general practitioners, endocrinologists, cardiologists and geriatricians to focus on

Table III: Comparison of epidemiological factors and dialysis key performance indicators between registries

	Brunei	Singapore	Malaysia	UK	Australia	New Zealand	USA
Year	2020	2020	2016	2020	2020	2020	2018
Incidence (pmp)	479	364	248 (does not include transplant)	139	124 (does not include transplant)	131 (does not include transplant)	390
Prevalence (pmp)	1944	2030	1286 (does not include transplant)	1290	1078 (does not include transplant)	1022 (does not include transplant)	2317
% DM in ESKD (incidence)	79	68	65	18	39	48	47
Modality (prevalence)	HD 86% PD 9% Tx 5%	HD 73% PD 11% Tx 16%	HD 86% PD 10% Tx 4%	HD 37% PD 6% Tx 57%	HD 43% PD 9% Tx 48%	HD 41% PD 16% Tx 42%	HD 64% PD 7% Tx 29%
Mortality (annual)	HD 15% PD 8% Overall 13%	HD 11% PD 16% Overall 12%	HD 13% PD 19% Overall 14%	NA NA NA	NA NA NA	NA NA NA	NA NA NA
Overall survival	NA	1 and 5 years- 91% and 56%	1, 3, 5 years- 88%, 67%, 52%	1 year survival- 90%	NA	NA	NA
HD Survival	1 and 2 years- 86% and 64%ç	1 and 5 years – 91% and 61%	1,3,5 years- 88%, 68% and 53%	NA	1,3,5 years- 87%,68%, 51%	1,3,5 years 90 %,71%, 54%	NA
PD Survival	Patient survival 1,3,5 years- 91% ,73%, 56%	Patient survival 1 year and 5 years – 90% and 41%	Patient survival 1,3, 5 years- 87%, 61% and 44%	NA	Patient Survival (PD) 1,3,5 years- 91%,71%, 51%	Patient Survival 1,3, 5 years- 90%,67% 42%	NA
Hb (mg/dl)	Mean – 11.57 Median- 11.50	NA	Median on ESA - 10.3 (HD), 10.2 (PD) Median without ESA- 11.8 (HD), 11.4 (PD)	Median 11.1 (HD and PD)	Median 11.0 (HD)	Median 11.1 (HD)	Incidence Hb 9.3 only 13% on ESA
	79% with Hb > 10	77% with Hb > 10 (HD)	62% with Hb > 10 (PD	59% Hb > 10 (on ESA and HD) 54% Hb > 10 (on ESA and PD)	58% between 10 and 12 (HD) 54% between 10 and 12 (PD)		
Ca (mmol/l)	Mean 2.19 Median 2.19 49% between 2.10 and 2.37	NA 74% < 2.37 (HD) 62% < 2.37 (HD)	Median 2.2 (HD), 2.3 (PD) 55% (HD and 49% (PD) between 2.1 to 2.37-	Median 2.3 79% between 2.2-2.5 (HD)	NA 62% between 2.1 to 2.4 (HD)	NA 58% between 2.1 to 2.4 (HD)	NA NA
Ph (mmol/l)	Mean and median - 1.87 and 1.83	NA	Mean and median 1.80 and 1.70 (HD) Mean and median 1.6 (PD)	NA	NA	NA	NA
	39% between 1.13 and 1.78	58% between 1.13-1.78 (HD) 52% between 1.13-1.78 (PD)	48% between 1.3-1.8 (HD) 51% between 1.3-1.8 (PD)	NA	45% between 0.8-1.6 (HD)	32% between 0.8 -1.6 (HD)	NA
PTH (pmol/l)	Mean and median- 69 and 43	NA	Mean and median 265 and 110 pg/ml (HD) Mean and median 288 and 195 pg/ml (PD)	NA	NA	NA	NA
	21% between 16.3 and 33 (KDOQI	30% between 16.3-33 (HD) 28% between 1 6.3-33 (PD) (KDOQI)	13% between 150-300 pg/ml (HD) 23% between 150-300 pg/ml (PD)	NA	NA	NA	NA
AVF usage (%)	Prevalent – 70% Incident- 20%	NA NA	Prevalent - 86% NA	Prevalent – 68% Incident – 36%	Prevalent- 83% Incident – 41%	Prevalent- 67% Incident- 22%	NA Incident- 20%

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Table III: Comparison of epidemiological factors and dialysis key performance indicators between registries

	Brunei	Singapore	Malaysia	UK	Australia	New Zealand	USA
HD adequacy (URR)	32% of patients > 0.7	97% of patients > 0.65	82% of patients > 0.65	85.6% of patients > 0.65	69.6% of patients > 0.7	54.6% of patients > 0.7	NA
PD adequacy (weekly Kt/V)	52% of patients > 1.7	41% of patients > 2	75% of patients > 1.7	NA	NA	NA	NA
Peritonitis	0.3 episodes per patient year	NA	1 in 42.3 patient months	0.38 episodes per patient year	0.26 episodes per patient year.	NA	NA

Note:
1. All blood result are prevalent data unless stated otherwise.
2. Adult registry data are utilized for comparisons, but some registries may not have specified the age range of the population they included in their registry data.

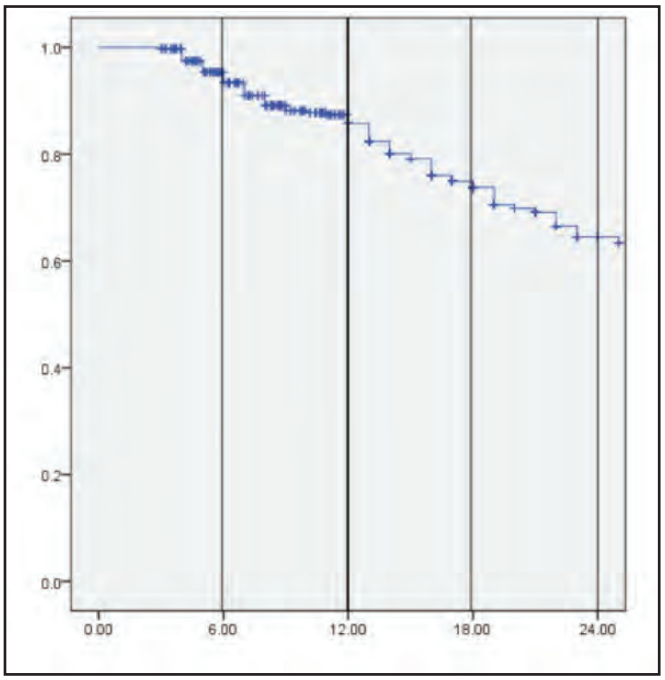

Fig. 1: Kaplan Meier Patient Survival for incident HD patients (2018-2020) (n=427); X-axis- months, Y axis – survival ratio

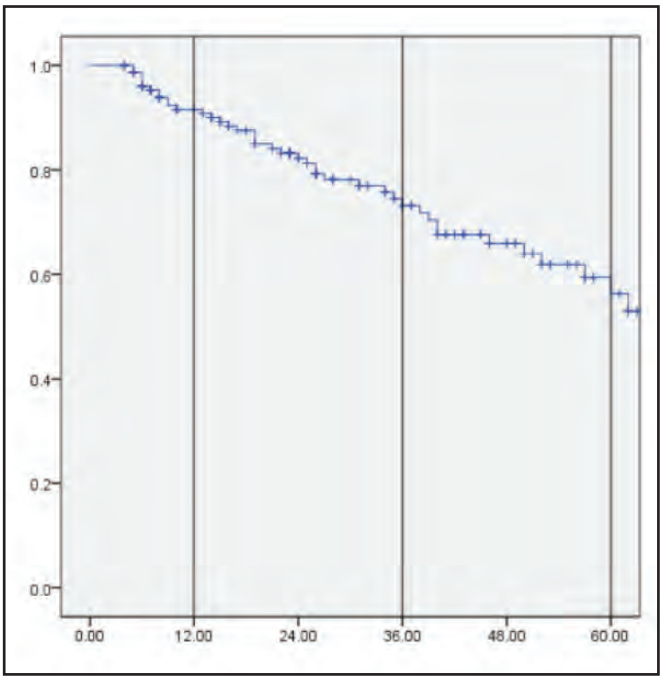

Fig. 2: Kaplan Meier Patient survival for incident PD patients (2011-2020) (n=158); X-axis- months, Y-axis- survival ratio

non-communicable diseases like diabetes mellitus and hypertension have been initiated at national level.

This study provided evidence that PD and transplant patients were not inferior to HD in certain aspects of their treatment outcomes. In fact, overall annual mortality of PD and transplant patients were significantly better than HD patients, although the latter group had a higher percentage of diabetes mellitus and were older (HD -55.22 ± 13.16 years vs PD-49.57 ± 13.10 years and transplant -38.61 ± 8.34 years). There were significant differences in haematological and biochemical parameters, but this could be related to differential implementation of guidelines, rather than being directly related to modality (eg. regular erythropoiesis-stimulating agent usage in HD patients affecting serum haemoglobin, pre-dialysis blood pressure measurements over HD, excessive PD effluent loss of potassium and albumin). Previous studies had also shown that local PD and Tx patients had a better quality of life8 and increased life expectancy.[23,24] Additionally, transplant has been shown to be provident and economical in cost effective exercises conducted by the Ministry of Health.[7] Plans are afoot to overhaul the infrastructure to provide less barriers for patients to take up PD; particularly through reducing waiting time for PD tube insertion, education of healthcare givers and increasing social support to patients. Transplant numbers are slowly increasing through the recent initiation of a local living-related kidney transplant program, but more time is needed for the program to mature and for the public to accept the concept of kidney donation. Additional furtherance activities have been initiated to pioneer a cadaveric and ABO-incompatible transplant program.

The 1- and 2- year patient survival of HD patients were 86% and 64% respectively. Projected 3-year survival of Brunei data through extension of the Kaplan–Meier analysis show a

likely actuarial survival of 57%. Correspondingly, these results were inferior compared to registry results from Singapore (1- and 5-year mortality of 91% and 56%) and Malaysia (1- and 3-year mortality of 88% and 67%) (12,13). Additionally, data from The Dialysis Outcomes and Practice Patterns Study (DOPPS) showed a 1-year HD survival rate of 93%, 84% and 78% in Japan, Europe and USA, respectively.[25] Australia and New Zealand reported similar first year survival (87% and 90%, respectively) but superior survival at 3 years (68% and 71%, respectively) (15). The poor local HD survival rate is likely to be a result of high proportion of incident diabetic HD patients compared to non-South East Asian cohorts, low arteriovenous fistula usage rate and high rates of catheter-related bloodstream infections. We also believe that our patients need more education on fluid and dietary compliance (complacency from free healthcare) and infection control. Contrastingly, the patient survival (91%, 73% and 56% at 1, 3 and 5 years) for PD patients were comparable to most countries like Singapore, Thailand and Hong Kong (83–91% and 40–54% at 1 and 5 years).[26]

DM-related ESKD (79%) and ESKD incidence rates are extremely high in Brunei, compared with the rest of the world. If these data were to be projected into the 2018 USRDS charts, Brunei would have ranked first for DM-related ESKD and second for ESKD incidence in the world. This pattern is similarly observed in neighbouring South East Asian countries, where DM-related ESKD accounted for 67% and 66% of incident ESKD patients in Malaysia and Singapore, respectively.[11] By contrast, only 12% of European ESKD population had reported diabetes mellitus as an aetiological cause,[20] with UK, USA and Australia registering at 18%, 47% and 39%, respectively.[11,14,15] Prevalence of DM in Brunei is similar to other developed countries,[27] indicating that there may strong local environmental and genetic factors that predispose diabetic patients to kidney failure.

Anaemia management, with a mean Hb of 11.57 g/dl and nearly 80% of the KRT population achieving a mean Hb level of > 10 g/dl, was higher compared to most countries, likely related to universal availability of erythropoietin. In terms of achieving the desired calcium, phosphate and PTH outcomes, only 49%, 39% and 21% of patients respectively achieved the pre-determined standards influenced by KDOQI and KDIGO.[19,20] This could be related to non-adherence to medication,[28] poor dietary compliance[28] and limited availability of non-calcium-based binders and calcimimetics.[29] AVF usage rate amongst HD patients (70% of prevalent patients) was similar to UK (68%) and New Zealand (67%), but inferior to Australia (83%) and Malaysia (86%).[13,14,15] Peritonitis rates in Brunei have been consistently below the ISPD recommended rate (0.4 episodes per patient year at risk), with the latest result being 1 in 40 patients-month or 0.3 episodes per patient year in 2020. This figure was comparable with Thailand (0.40), United Kingdom (0.38) and Australia and New Zealand (0.35).[30]

The registry results have allowed service introspection, which highlighted factors that were amenable to change. Restructuring of the education and training system for our staff and patients (through face-to-face encounters, seminars and workshops with dieticians, nurse educators, patient advocates and pharmacists) were done to improve delivery of messages to patients. The comparisons with other established practice have allowed us to establish norms in standard practice and learn from the experiences of others. It has also reaffirmed the justified preference for PD and transplant practices, which has led us to persuade the government to continue the emphasis of development of both practices ahead of HD. This includes public endorsement of these modalities, prioritisation in training of healthcare workers, enlisting professional support from overseas and investing in specialized infrastructure.

LIMITATIONS

The data collected were secondary data from the BDTR and there were missed data for some patients, particularly those who started dialysis near the annual cut-off date (31st December). The data for survival analyses for HD patients were only limited to 2018-2020, because there were many incomplete data before 2018 as the initial BDTR data were not collected with the intention for survival analysis. Nevertheless, typically more than 90% of data from patients were captured annually. Differences in methodologies and statistical analyses made certain international comparisons difficult; but as much as possible, these were presented in their unaltered formats to allow individual judgements and interpretations. As some registries do not update their data regularly, comparison can only be made with the last publicly available data.

CONCLUSION

Brunei had a high incidence and prevalence of treated ESKD in the last decade, likely related to the easy access of ESKD patients to KRT and free healthcare treatment. Diabetes mellitus, as a cause of ESKD, was disproportionately high compared to other countries in the world. PD outcomes (death rates, survival, dialysis adequacy) are superior to HD in the country, and on par with international targets, but factors like age and co-morbidities could have affected the outcomes. Mineral bone disease, HD adequacy, HD AVF rates and HD survival rates are areas that have been targeted for improvements. Concerted efforts have been initiated to improve the identified deficiencies, and to proliferate PD and transplant penetrance in the near future.

REFERENCES

1. Information from the Department of Economic Planning and Statistics, Brunei Darussalam [cited Nov 2022]. Available from: http://www.deps.gov.bn.
2. Information from the ASEAN Statistics Web Portal. Available from: https://www.aseanstats.org. [cited 18 Nov 2022].
3. Information from the World Health Organisation. Available from: http://www.who.int/diabetes/country-profiles/brn_en.pdf [cited 18 Nov 22].
4. Tan J, Zinna S, Ranganathan D, Chin S, Lock Syhe, Hart P. A history of renal services in Brunei Darussalam. Brunei Int Med J 2015; 11(1): 8-13.
5. Tan J. End stage disease in Brunei Darussalam- report from the first Brunei Dialysis Transplant Registry (BDTR). Ren Fail 2013; 35(8): 1101-4.
6. Tan J, Liew YP, Liew A. Peritoneal dialysis first policy in Brunei Darussalam. ISPD Asia-Pacific Newslett 2015; 13.

7. Tan J, Mabood Khalil MA, Ahmed D, Pisharam J, Lim CY, Chua HB, et al. The Living-Related Kidney Transplant Program in Brunei Darussalam: Lessons Learnt from a Nascent National Program in a Small, Muslim, and Asian Country. J Transplant 2021; 8828145
8. KY Hon, S Alam, J Tan. Quality of life comparison between patients on renal replacement therapy in Brunei Darussalam. Transplantation 2012; 94 (10S): 806-7.
9. Tan J, Khalil MA, Tan SY, Khalil M, Ahmed D, Zinna S, et al. Outcomes of renal transplantation in Brunei Darussalam over a twenty year period (1993-2012). J Transplant 2014: 784805
10. Farah SS, Alhaji MM, Ahmed D, Tan J, Johan N, Alam S, et al. Barriers to kidney transplantation as a choice of renal replacement therapy. Transplant Proc 2018; 50(10): 3165–71
11. United States Renal Data System. Available from: http://www.usrds.org [cited 16 Nov 22].
12. Singapore Renal Registry. Available from: Chronic Kidney Failure Registry - National Registry Of Diseases Office (nrdo.gov.sg). [cited 16 Nov 22].
13. Malaysian Dialysis and Transplant Registry. Available from: MDTR - Malaysian Dialysis and Transplant Registry (msn.org.my) [cited 16Nov 22].
14. UK renal Registry. [cited 16 Nov 2]. Available from: https://renal.org/audit-research/annual-report.
15. Australia and New Zealand Renal Registry [cited 16 Nov 2]. Available from: https://www.anzdata.org.au/anzdata/.
16. European Renal Association and European Dialysis Transplant Association (ERA-EDTA) 2018 Registry. [cited 16 Nov 22]. Available from: www.era-edta.org.
17. KDIGO Clinical Practice Guideline for Anaemia in Chronic Kidney Disease. [cited 16Nov 22]. Available from KI_SuppCover_2.4.indd (kdigo.org).
18. KDIGO Updated CKD-MBD Guideline. [cited 16 Nov 22]. Available from KISU_v7_i1_COVER.indd (kdigo.org).
19. NKF KDOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. [cited 16 Nov 2022]. Available from: Bone Metabolism in CKD | National Kidney Foundation.
20. NKF KDOQI Clinical Practice Guidelines for Haemodialysis Adequacy: 2015 update. [cited 16 Nov 2022]. Available from: KDOQI Clinical Practice Guideline for Hemodialysis: 2015 Update | National Kidney Foundation.
21. NKF KDOQI Clinical Practice Guidelines for Peritoneal Dialysis Adequacy: 2006 Update. [cited 16 Nov 2022]. Available from: Peritoneal Dialysis Adequacy | National Kidney Foundation.
22. International Society of Peritoneal Dialysis [cited 16 Nov 22]. Available from: https://ispd.org/guidelines .
23. Othman E, Tan J. Patient and technique survival on peritoneal dialysis in Brunei. Unpublished paper.
24. Tan J, Khalil MA, Tan SY, Khalil M, Ahmed D, Zinna S, et al. Outcomes of Renal Transplantation in Brunei Darussalam over a Twenty-Year Period (1993-2012). J Transplant 2014; 784805
25. Goodkin D. Association of comorbid conditions and mortality in haemodialysis patients in Europe, Japan and the United States: The Dialysis Outcomes and Practice Patterns Study (DOPPS). J Am Soc Nephrol 2003; 14(12): 3270.
26. Liu FX, Gao X, Inglese G, Chuengsaman P, Pecoits-Filho R, Yu A. A global overview of the impact of peritoneal dialysis first or favored policies: an opinion. Peritoneal Dialysis Int 2015. 35: 406-20.
27. Data from International Diabetes Federation. Available from: https:www.indexmundi.com/facts/indicators/SH.STA.DIAB.ZS/rankings
28. Liew YP, Ang SK, Tan J. Medication compliance and understanding in pre-end stage renal disease. Nephrology 2010; 15: 33.
29. Alam S, Hussain H, Tan J. Clinical efficacy of sevelamer hydrochloride in patients with end-stage renal disease: a retrospective study. Singapore Med J 2013; 54(5): 263-6.
30. Perl J, Fuller D, Bieber B, Boudville N, Kanjanabuch T, Ito Y et al. Peritoneal dialysis-related infection rates and outcomes: results from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS). Am J Kidney Dis 2020; 76(1): 42-53.

Team-based self-directed learning enhanced students' learning experience in undergraduate surgical teaching

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ABSTRACT

Introduction:To evaluate the effectiveness of team-based self-directed learning (SDL) in the teaching of the undergraduate Year 5 surgical posting.

Materials and Methods: A quasi-experimental study was conducted to develop and administer a team-based SDL versus a conventional SDL to teach undergraduate surgical topics. One hundred and seventy-four medical students who underwent the Year 5 surgical posting were recruited. They were assigned to two groups receiving either the team-based SDL or the conventional SDL. Pre- and post-SDL assessments were conducted to determine students' understanding of selected surgical topics. A self-administered questionnaire was used to collect student feedback on the team-based SDL.

Results: The team-based SDL group scored significantly higher than the conventional SDL group in the post-SDL assessment (74.70 ± 6.81 vs. 63.77 ± 4.18, t = −12.72, p < 0.01). The students agreed that the team-based SDL method facilitated their learning process.

Conclusion: The study demonstrated that the use of a team-based SDL is an effective learning strategy for teaching the Year 5 surgical posting. This method encouraged peer discussion and promoted teamwork in completing task assignments to achieve the learning objectives.

KEYWORDS:
Self-directed learning; team-based learning; undergraduate; surgical training

INTRODUCTION

Self-directed learning (SDL) is a learning process in which students take the initiative, with or without guidance from others, to formulate their own learning goals, select resources for learning, implement learning strategies and evaluate the outcomes achieved.[1] The learners are primarily responsible for identifying their learning needs and formulating learning objectives.[2] SDL encourages in-depth learning and thinking, prepares students for lifelong learning and improves knowledge retention more than traditional courses.[3,4] In medical education, this allows students to keep abreast of the latest advancements in the world of medicine and helps them become better doctors.

However, despite the proven advantages of SDL over conventional teaching in medical education, the introduction of SDL into undergraduate medical curricula has faced many challenges. Many have found it difficult to precisely define SDL and implement SDL modules within the existing framework of medical education.[5] The indiscriminate application of SDL principles and poorly prepared lecturers and/or students have at times led to resentment at the introduction of SDL rather than welcome.

The Universiti Malaysia Sarawak (UNIMAS) medical programme (Doctor of Medicine, M.D.) is a five-year undergraduate program. This program has adopted a fully integrated curriculum for the first two pre-clinical years that includes both problem-based learning (PBL) and SDL. In the subsequent three clinical years, the students undergo clinical rotations in multiple disciplines. SDL has also been introduced to the clinical postings for many years, including the surgical posting.

Students are exposed to a basic surgical posting in Year 3 and a final surgical posting in Year 5. The learning objectives of both surgical postings are clearly defined and well-structured according to Bloom's taxonomy and matched to the medical programme learning outcomes. The teaching and learning activities in surgical postings (Years 3 and 5) include both teacher- and student-centred learning strategies—for example, didactic lecture, bedside teaching, seminars (prepared and presented by students) and SDL. The essential topics in the surgical logbook are selected for SDL, but the students might not have the chance to observe all these procedures in operation theatres or wards due to tight posting schedules and the dynamic hospital environment.

Over time, it was noticed that most students were unable to appreciate the concept of SDL and, thus, performed unsatisfactorily on certain surgical topics in the end-of-posting exam. Thus, the current SDL activities may not enhance the learning process or fully achieve the learning objectives of surgical postings as stated in the course plan. Given the inadequacy of existing SDL offerings, the Department of Surgery has planned to adopt a team-based approach in the SDL sessions.

Team-based learning (TBL) is an instructional method that promotes problem-solving and teamwork.[6] It involves teaching and learning in small groups and does not require large numbers of tutors. This learning strategy allows

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medical educators to provide students with a resource-effective, authentic experience of working in teams to solve real-life clinical problems.[7] In this study, we implemented a structured team-based SDL in the Year 5 surgical posting and evaluated its efficacy in achieving the learning objectives.

MATERIALS AND METHODS

We conducted a quasi-experimental study from December 2020 to February 2022 at the UNIMAS Faculty of Medicine and Health Sciences. The study was approved by the Ethics Committee of the UNIMAS Faculty of Medicine and Health Sciences (Ethics Reference Number: FME/20/07).

Participants were recruited through convenience sampling. All students enrolled in Year 5 surgical postings were recruited (four rotations from Academic Years 2020/2021 and 2021/2022). Students from Rotations 1 and 2 were allocated to the Control group (conventional SDL), and the subsequent Rotations 3 and 4 were allocated to the Intervention group (team-based SDL). A total of 174 students participated in the study (86 in the Control group and 88 in the Intervention group). All students gave written informed consent before participating in the study.

All students enrolled in Year 5 surgical posting (four rotations) were eligible for inclusion except for those repeating the Year 5 surgical posting.

Both Control and Intervention groups sat for a pre- (first week of surgical posting) and post-SDL (last week of surgical posting) assessment. A list of reading resources was provided to both groups. Additional materials (selected reading materials and videos, team assignment for each SDL topic, short-answer questions) were provided only to the Intervention group.

One SDL topic was assigned for each week during the surgical posting for a total of seven topics:

Week 1: Laparotomy and Wound Closure (Indications, Complications, Procedural Steps, Anatomy of Abdominal Wall)

Week 2: Open and Laparoscopic Appendectomy (Indications, Complications, Procedural Steps, Types of Incision)

Week 3: Inguinal Hernia Repair (Indications, Complications, Procedural Steps, Anatomy of Inguinal Canal and Hesselbach's Triangle)

Week 4: Open and Laparoscopic Cholecystectomy (Indications, Complications, Procedural Steps, Fundamental Knowledge on Endoscopic Surgery)

Week 5: Endoscopic Retrograde Cholangiopancreatography (Indications, Complications, Procedural Steps, Methods of Stone Removal)

Week 6: Emergency Oesophagogastroduodenoscopy (Indications, Complications, Test for Helicobacter Pylori, Anatomy of Stomach Blood Supply)

Week 7: Local Anaesthesia (Indications, Complications, Procedural Steps, Anatomy of Abdominal Wall)

This study was designed according to the four essential principles of TBL outlined by Michaelsen et al.[8]: 1) The group of students must be properly formed and managed, 2) students must be made accountable for their individual and group work, 3) group assignments must promote both learning and team development and 4) students must have frequent and timely feedback. The study protocol is shown in Figure 1. During the first week of the Year 5 surgical posting, a pre-SDL assessment was conducted consisting of 35 best-answer questions. The lists of SDL topics and resources were then distributed to all the students. The learning objectives of each SDL topic were explained by the Posting Coordinator.

Students in the Control group (Rotations 1 and 2) used the conventional SDL. Specific SDL sessions were allocated in the posting time table. The students were allowed to complete the SDL activities either individually or in small groups and based on their own schedule planning. Students were intended to take the initiative to find the resources on the provided list or other resources in the library. Students were free to approach the lecturers at any time for clarification should they have any doubt about the topics.

In the Intervention group (Rotations 3 and 4), the students were divided into smaller sub-groups consisting of 5–6 participants (mixing strong and average students). The students were required to follow the SDL topic as assigned for each week. For each topic, the lecturers carefully selected a few educational materials (journal article, book chapter, or video) to be provided one week ahead through the eLearning platform with a set of assignments (short-answer questions related to the weekly topic). The students were required to read or view the materials first and then to meet up in a team (sub-group) to discuss the assignment.

The role of the assignment task in each SDL session was to enhance the learning process and apply reasoning and critical thinking. The discussion included only students; no lecturer was present. If there was any doubt, the students would approach the lecturer via WhatsApp message for clarification. Following the discussion, the students would submit the assignment, and the lecturer would check the answers and provide feedback. In the eighth week of the surgical posting, a post-SDL assessment was conducted. These were the same 35 best-answer questions as in pre-SDL assessment but were rearranged in a different sequence. At the end of this study, the scores on the pre- and post-SDL assessments were collected and compared between the conventional and team-based SDL groups.

A self-administered questionnaire was distributed to the students from the Intervention group to collect feedback regarding their learning experience with team-based SDL. The questionnaire was adapted from a previous study by Burgess et al.[9] and included closed (using a 5-point Likert scale with 1 being 'strongly disagree' and 5 being 'strongly agree') and open-ended questions.

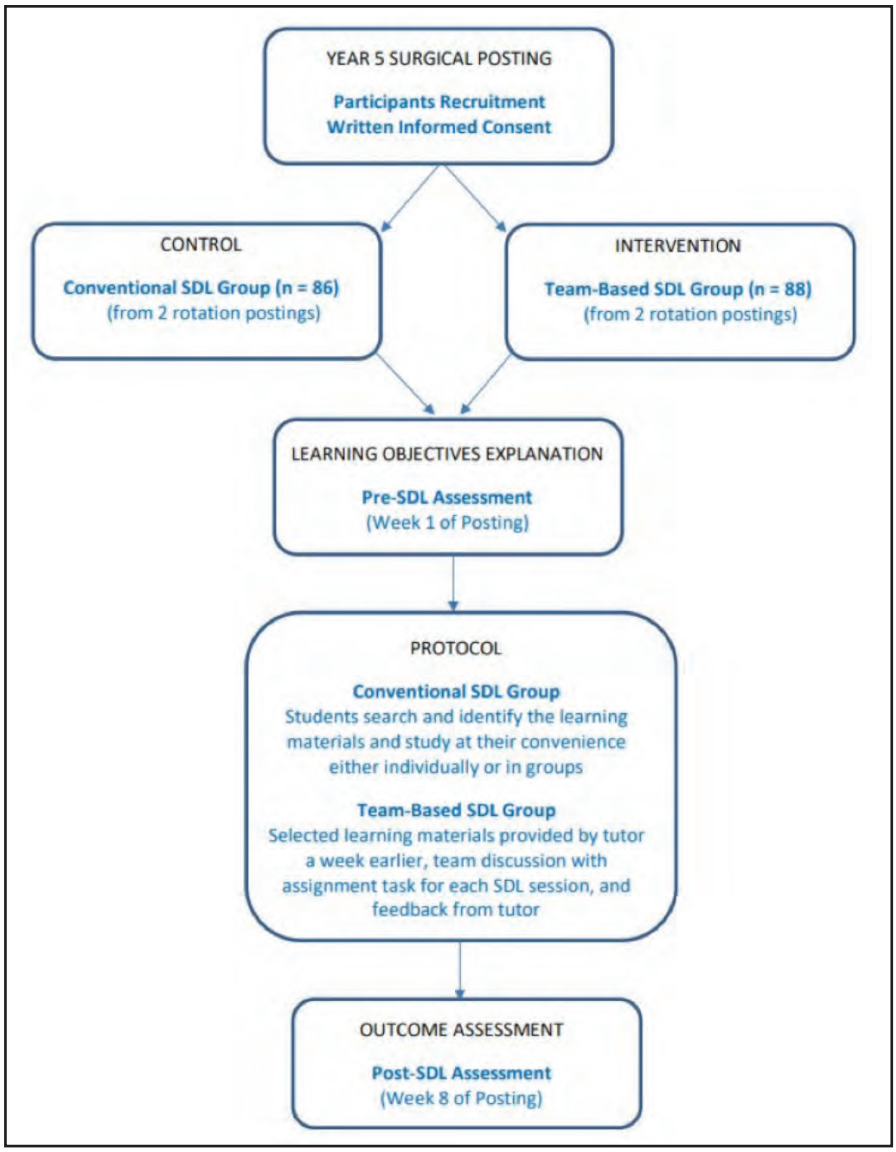

Fig. 1: The study protocol. SDL = self-directed learning

Statistical Analysis

The collected data were analysed using SPSS statistical software for Windows (v 22.0; IBM, Armonk, NY, USA). Quantitative data were analysed using descriptive statistics. Paired t-test was used to compare the mean pre- and post-SDL assessment scores in the study groups. An independent t-test was used to compare the mean post-SDL assessment scores between the Control and Intervention groups.

RESULTS

A total of 174 students participated in this study (Control group: 86 students; Intervention group: 88 students). There were no significant differences among students from any study groups in the mean pre-SDL assessment scores. After 8 weeks of posting, the mean post-SDL assessment scores were significantly higher than the pre-SDL scores in both conventional (63.77±4.18 vs. 46.56±6.05, t=–26.73, p<0.01) and team-based SDL (74.70 ± 6.81 vs. 46.93 ± 4.93, t=–33.69, p<0.01) groups (Figure 2). This means that both conventional and team-based SDL strategies improved students' understanding of the selected surgical topics.

However, when comparing the effectiveness between the conventional and team-based SDL, the latter showed a significantly higher mean post-SDL assessment score than the SDL group (74.70±6.81 vs. 63.77±4.18, t=–12.72, p<0.01) (Figure 3); the team-based SDL group improved learning by 59.2% while the Control group improved learning by 37.0%. These results demonstrate that team-based SDL is a better learning strategy than conventional SDL.

Results from the self-administered questionnaire revealed that most students were satisfied with team-based SDL (Figure 4); all responses were 3 and above on the 5-point Likert scale.

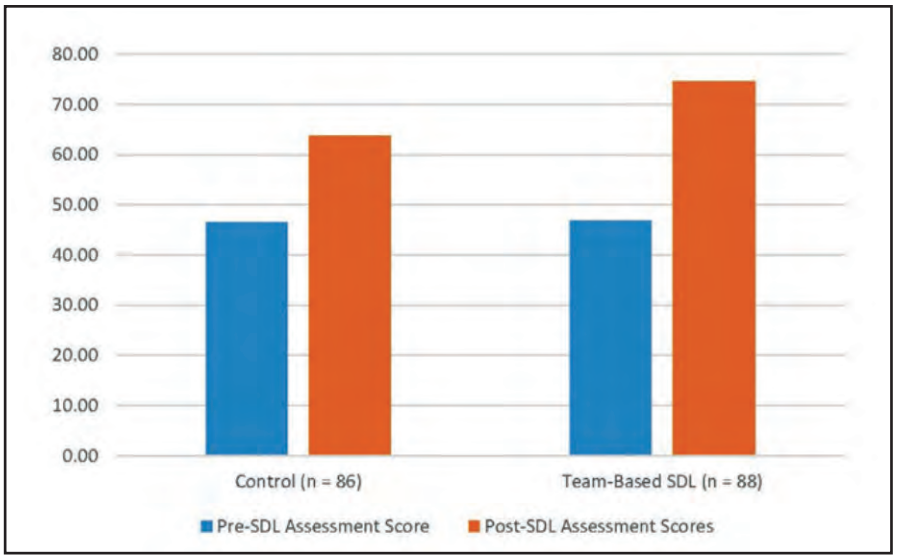

Fig. 2: Mean pre- and post-learning assessment scores in Control and Intervention groups. SDL = self-directed learning

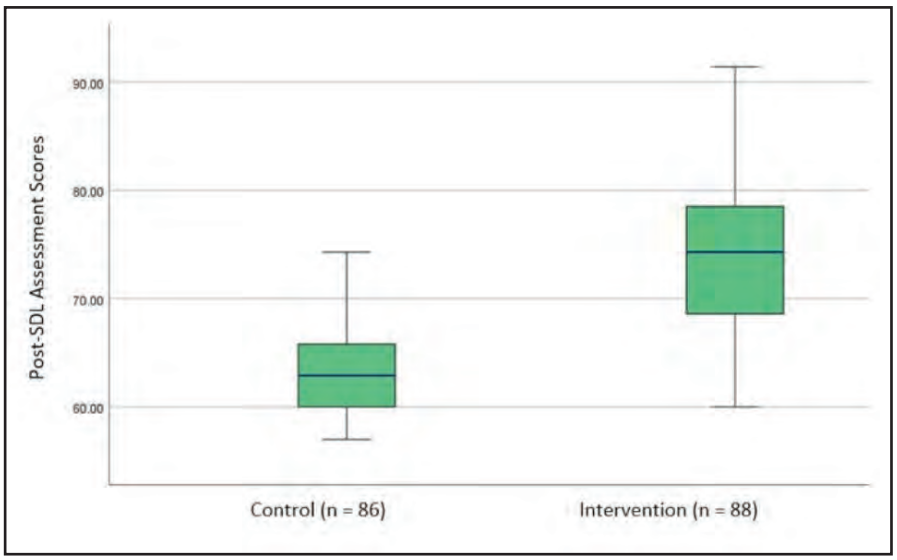

Fig. 3: Comparison of mean post-learning assessment scores between control and intervention groups. SDL = self-directed learning

DISCUSSION

The UNIMAS medical programme includes 9 weeks of study in one rotation of the Year 5 surgical posting with 40 student learning hours per week as required by the Malaysian Medical Council. Thus, the schedule for the undergraduate surgical posting is packed with various teaching and learning activities. One of these learning activities is SDL, and there are a total of seven SDL sessions in one rotation (average of one SDL session per week).

SDL is an important tool for transforming medical students into lifelong learners so that they are competent to identify their learning needs, allocate resources, and evaluate the learning process throughout their career.[1] The SDL approach is effective if the objectives are realistic and accomplishable, ensuring that learners can apply SDL modalities to situations in which they are required to learn by themselves.[3] However, the success of SDL relies on self-discipline, independence, self-evaluation and reflection. The readiness of the lecturers, the facilities available, and the types of learning subjects could also affect the success of SDL.

Several studies have demonstrated the value and effectiveness of SDL in pre-clinical teaching years—for example, in learning biochemistry, physiology and anatomy.[2,4] However, the efficacy of SDL in some clinical courses is debated.[5] Furthermore, without monitoring, students may lose interest in searching for correct and adequate information in their studies.

The UNIMAS Year 5 surgical posting has been adopting SDL for many years. The topics selected for SDL are the essential topics in daily surgical practice for their future internship. Successful SDL requires self-discipline and active involvement of the students in the learning process. Probably due to lack of motivation and inadequate search for information, the

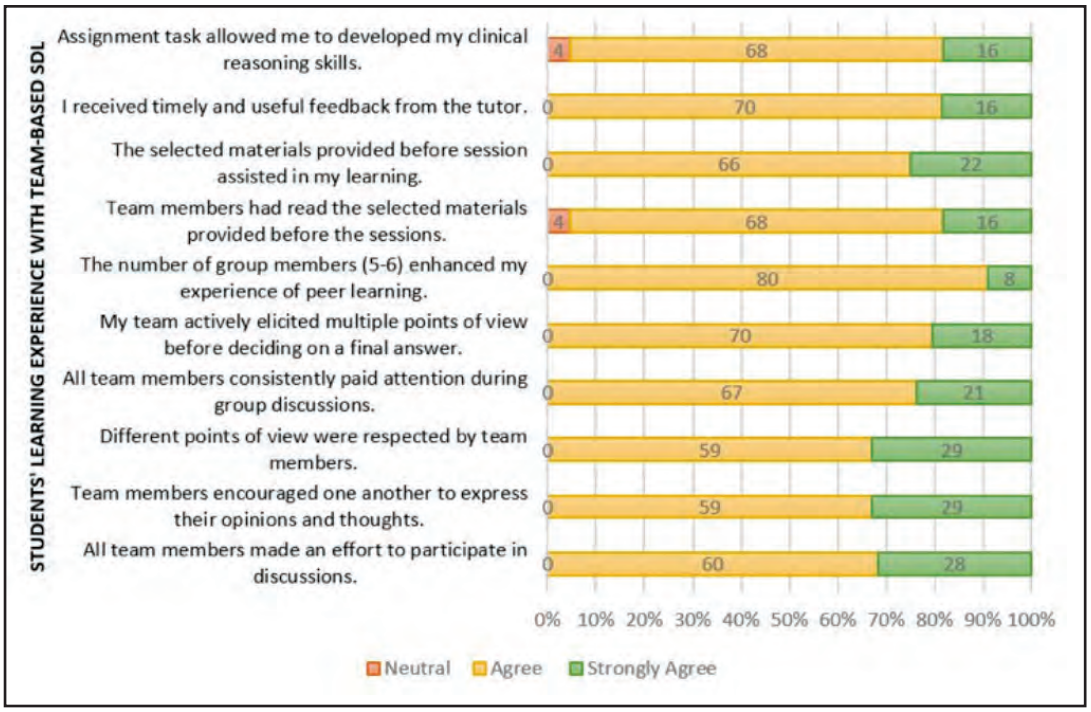

Fig. 4: Students' feedback on learning experience with team-based self-directed learning (SDL)

Table I: Comparison of the main characteristics of SDL, PBL and TBL

SDL	PBL	TBL
• It prepares the students to be lifelong learners. • Based on clear learning objectives, students identify their learning needs, search for information resources and self-evaluate the learning process. • Facilitators may or may not be needed in the learning process. • Self-discipline and active involvement of the students in the learning process are needed.	• It promotes problem-solving and interpersonal skills. • A problem scenario is given to a group of students, and students must recall the existing knowledge to find new knowledge to solve the given problem for two or more sessions. There is usually no evaluation of the learning process. • Facilitators are required in each small group, and the facilitators may not necessarily be content experts. • Teamwork is needed to gather existing and new knowledge to solve the problem.	• It promotes problem-solving and interpersonal skills. • Pre- and post-learning assessments are used. Pre-discussion materials and tasks are provided. Individual students will prepare the pre-discussion work, meet in a group for discussion and complete the tasks. • Fewer facilitators are required. One facilitator can handle multiple groups and may not need to be physically present during the discussion. Peer evaluation is emphasised. Facilitators with knowledge in the learning topics are preferred. • Peer monitoring motivates the learning process.

SDL = self-directed learning, PBL = problem-based learning, TBL = team-based learning

students in the existing SDL program were found to perform poorly on the end-of-posting exam with regard to these topics. To ensure that students can benefit from SDL and achieve the course learning outcomes, some modifications are needed.

In this study, we introduced the TBL approach into SDL. Based on the TBL pedagogy,[8,10] there are certain important elements that must be applied for the successful conduct of team-based SDL: i) clear learning objectives, ii) well-selected learning resources (journal articles, book chapters and videos), iii) discussion in a small group with tasks to enhance the learning experience, iv) feedback from lecturer for improvement and v) implementation of pre- and post-SDL assessment for SDL sessions to assess the learning outcomes.

TBL is relatively new in medical education, although it has been implemented in other educational curricula since 1970. It was first introduced by Professor Larry K. Michaelsen from the University of Oklahoma.[8] In this learning approach, students are encouraged to develop higher-level group cohesiveness, which, in turn, increases their intellectual abilities in a particular subject. Like conventional SDL, TBL also has a different approach from PBL. According to Burgess et al.,[9] TBL maintains the advantages of small-group teaching and learning, but, in contrast to PBL, it does not

require large numbers of tutors. Furthermore, the structure and format of the TBL sessions are more conducive to learning, engagement and participation than PBL sessions as pre-review of content is encouraged in TBL.

The advantage of TBL compared to the traditional modality of competitive and individualistic learning is that the small-group learning environment allows a greater sense of accomplishment, learning and application of reasoning and critical thinking among students.[11] The TBL approach motivates students to actively participate in their learning activities, providing social support for weaker students and improves their communication and interpersonal skills. Table I summarises and compares the main characteristics of SDL, PBL and TBL.

The recommended team size in the TBL approach is about 5–7 members. This is because the team must be large enough to maximise their intellectual resources and as heterogeneous as possible but also not so large as to prevent full participation by all team members. For this reason, we reviewed the academic results of the students in their pre-clinical years and previous clinical postings. We then identified the students with a cumulative grade point average (CGPA) above and below 3.0. The students were then randomly divided into smaller groups consisting of 5–6 students (depending on the number of students per rotation) with a mixture of students with high and average CGPAs. The intention of this arrangement was to encourage fruitful discussion, hoping that the students with high CGPAs would guide the average students in their study.

Our study demonstrated that team-based SDL improved the students' learning process and enhanced their understanding of the topics given better than conventional SDL. The students in the team-based SDL group scored 59.2% higher in their post-SDL assessment compared with 37.0% for the students in the conventional SDL group. One of the main advantages of team-based SDL over conventional SDL is peer support, which motivates and encourages students in active learning.

Previous studies have suggested that students taking initiative in the learning process and engaging in group discussions under the guidance of teachers to promote the students' self-motivated learning and teamwork are the key steps to success in the TBL approach.[12,13] However, in our adoption, the lecturers did not attend the students' discussion. Based on our past experience, we suspected students might be afraid of offering ideas and would not actively participate in the discussion when the tutors were around. In our study, the students were allowed to form their discussions at their own convenience as agreed by the team members. The students were able to contact the lecturer-in-charge if they encountered any problems in their discussions by means of WhatsApp. Following the team discussion and completion of the assignment task, the students would then meet up with the lecturer-in-charge for a two-way feedback session. Most of the students found that this team-based SDL facilitated their learning process.

This study implies that the team-based SDL model is an implementable and more effective learning strategy in the teaching of undergraduate Year 5 surgical posting through peer motivation compared to SDL alone. This model is also a practical approach in the institutions with small numbers of teaching staff, since it does not require the presence of tutors during the students' discussion. In future, it can be introduced into the teaching of Year 3 surgical posting, as well as the teaching of other clinical postings.

In addition, this model may be applicable in teaching the local postgraduate clinical master programme. The local postgraduate clinical master programme is a 4-year residency clinical specialist training programme. The trainee must perform supervised specialist clinical work, conduct research and explore the latest information on the relevant speciality. Owing to the tight working schedule, a traditional teacher-centred teaching method may not be practical. Thus, team-based SDL may help the trainees by equipping them with updated medical knowledge through team discussion and allowing them to monitor each other's learning process without compromising their clinical services and research.

LIMITATIONS

There were a few limitations to the study. First, this was a single-centre study with the team-based SDL strategy applied only in the Year 5 surgical posting. Second, the content area covered was limited to seven SDL topics of a 9-week posting. Third, the intervention group was formed through convenience sampling with no randomisation. In view of these limitations, further studies are required to validate the findings of this study with crossover methodology and in other clinical postings.

CONCLUSION

Lack of motivation could impede the learning process in SDL. A structured team-based SDL that includes clear learning objectives, adequate and correct resources, peer discussion with assignment tasks and feedback from the lecturers could enhance the learning experience and improve the learning outcomes.

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REFERENCES

1. Charokar K, Dulloo P. Self-directed learning theory to practice: A footstep towards the path of being a life-long learner. J Adv Med Educ Prof 2022; 10(3): 135-44.
2. Hill M, Peters M, Salvaggio M, Vinnedge J, Darden A. Implementation and evaluation of a self-directed learning activity for first-year medical students. Med Educ Online 2020; 25(1): 1717780.
3. Atta IS, Alghamdi AH. The efficacy of self-directed learning versus problem-based learning for teaching and learning ophthalmology: A comparative study. Adv Med Educ Pract 2018; 9: 623-30.

4. Pai KM, Rao KR, Punja D, Kamath A. The effectiveness of self-directed learning (SDL) for teaching physiology to first-year medical students. Australas Med J 2014; 7(11): 448-53.
5. Premkumar K, Pahwa P, Banerjee A, Baptiste K, Bhatt H, Lim HJ. Does medical training promote or deter self-directed learning? A longitudinal mixed-methods study. Acad Med 2013; 88(11): 1754–64.
6. Parmelee D, Michaelsen LK, Cook S, Hudes PD. Team-based learning: a practical guide: AMEE guide no. 65. Med Teach 2012; 34(5): e275-87.
7. Rotgans JI, Rajalingam P, Ferenczi MA, Low-Beer N. A students' model of team-based learning. Health Prof Educ 2019; 5(4): 294-302. -
8. Michaelsen LK, Knight AB, Fink LD. 2002. Team-based learning: a transformative use of small groups in college teaching. Stylus Publishing.
9. Burgess A, Bleasel J, Haq I, Roberts C, Garsia R, Robertson T, et al. Team-based learning (TBL) in the medical curriculum: Better than PBL? BMC Med Educ 2017; 17(1): 243.
10. Burgess AW, McGregor DM, Mellis CM. Applying established guidelines to team-based learning programs in medical schools: A systematic review. Acad Med 2014; 89(4): 678-88.
11. Park HR, Kim CJ, Park JW, Park E. Effects of team-based learning on perceived teamwork and academic performance in a health assessment subject. Collegian 2015; 22(3): 299-305.
12. Sakamoto SR, Dell'Acqua M, Abbade L, Caldeira SM, Fusco S, Avila M. Team-based learning: A randomized clinical trial in undergraduate nursing. Rev Bras Enferm 2020; 73(2): e20180621.
13. Tsai MF, Jao JC. Evaluation of the effectiveness of student learning and teacher instruction on team-based learning during quality control of diagnostic imaging. Med Educ Online 2020; 25(1): 1732159.

ORIGINAL ARTICLE

Fetoscopic laser ablation for twin-to-twin transfusion syndrome in Malaysia: A 15-month retrospective cohort review from an emerging centre in South East Asia

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ABSTRACT

Introduction: The authors aim to review the early outcomes of fetostopic laser ablation (FLA) to improve outcomes for twin-to-twin transfusion syndrome (TTTS) in an emerging national centre in Malaysia.

Materials and Methods: This is a retrospective cohort study of 17 monochorionic diamniotic (MCDA) twin pregnancies with severe TTTS treated by FLA over 15 months in a single centre by a single operator after performing simulations.

Result: The overall survival rate at day 28 after birth for at least one twin was 76% while the dual-twin survival was 64%. The survival rates at day 28 after birth for at least one twin for stages II, III and IV were 90% vs 40% vs 100% (p=0.054) while dual survival rates were 80% vs 0% vs 100% (p=0.05), respectively. The rate of miscarriage was higher with anterior placentation compared to posterior placentation (33% vs 18%, p=0.660). There was one case of recurrent TTTS and no twin anaemia-polycythaemia sequence post-FLA. The fetal medicine unit in Ipoh is the national centre in Malaysia which covers the whole country, including the western coast of the Borneo Island (Sabah, Sarawak and Labuan) accessible only by air travel. All three cases from Borneo Island had resolved TTTS after FLA and dual neonatal survival at day 28 after birth.

Conclusion: This data from an emerging new fetoscopic laser centre in Malaysia indicates results consistent with the published international learning curve and within the limits of good clinical governance.

KEYWORDS:
Solomon technique; fetoscopic laser ablation; placenta vascular anastomoses; twin-to-twin transfusion syndrome; fetoscopic laser ablation simulation; Malaysia

INTRODUCTION

The incidence of multiple pregnancies, particularly twins, in Malaysia is increasing with the universal use of assisted reproductive therapy in healthcare systems and increased maternal age at conception, because of delayed fecundity.[1] Monochorionicity is present in approximately 20% of all twin pregnancies and results from the cleavage of a single zygote, with subsequent sharing of the placenta between the fetuses.[2,3] Twin-to-twin transfusion syndrome (TTTS), selective fetal growth restriction (sFGR), twin reversed arterial perfusion sequence (TRAPs) and twin anaemia-polycythaemia sequence (TAPS) are some examples of complications specific to monochorionic (MC) pregnancies.

TTTS specifically is the consequence of "unbalanced" net flow of blood between the two fetuses through placental vascular anastomoses (arterioarterial, venovenous and arteriovenous) as well as unequal sharing of placental territory between these fetuses.[4,5] Djaafri et al.[6] and Berghella et al.[7] reported that TTTS complicates up to 15% of MC pregnancies and has a fetal mortality rate of up to 90% without treatment.

Fetoscopic laser ablation (FLA) of shared placental vascular anastomoses has been demonstrated to improve survival outcomes in TTTS.[8,9] The single and dual twin survival rates for TTTS following FLA have been quoted to be as high as 91% and 61%, respectively, and is superior therapy in comparison with other treatment options such as serial amniodrainage, septostomy or selective fetal reduction.[10,11] Neurodevelopmental outcomes of infants with TTTS are more favourable after FLA compared to amniodrainage, for both short-term (3-16% vs 5-38% for cerebral injury, respectively) and long-term outcomes (3–12% cerebral palsy (CP) and 7–18% neurodevelopmental impairment (NDI) vs 5-23% CP and 14-26% NDI, respectively).[12,13]

The current fetal medicine team in Raja Permaisuri Bainun Hospital (HRPB), Ipoh is the national centre in Malaysia providing FLA services since the beginning of 2019. This is a retrospective cohort study to present the outcomes of FLA in the first consecutive 17 MC pregnancies complicated by severe TTTS between March 2019 until May 2020. The authors aim to review the early outcomes of FLA in this emerging national centre in which FLA service was started

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after performing simulations and offered to all TTTS patients nationwide including the states of Sabah and Sarawak on Borneo Island, accessible only by air travel.

MATERIALS AND METHODS

Study Population

The authors retrospectively reviewed the prenatal and neonatal outcomes (up to 28 days) in all monochorionic diamniotic (MCDA) twin pregnancies in which FLA was performed over a 15-month period. The prospective ultrasound diagnosis of TTTS was made using accepted international criteria and staged using the Quintero staging system.[14] TAPS was diagnosed antenatally based on discrepancies of middle cerebral artery peak systolic velocity (MCA-PSV) measurement using a Multiple of Median (MoM) (delta MCA-PSV of more than 0.5). FLA was performed on all MCDA cases with TTTS Quintero stages II, III and IV between gestational ages ranging from 17^{+0} to 27^{+6}, within 48 hours of diagnosis.

Procedure

Prior to performing FLA on the first patient with TTTS, the team (a surgeon, a senior medical assistant and a nursing sister) underwent simulated training to replicate the actual clinical scenario to improve the performance of FLA in real patients.[15] Actual postpartum monochorionic placentas were fixed onto the floor of a container and submerged in water. The container was subsequently covered and fetoscope was inserted through a hole made in the lid of the container, following which FLA was performed on the placental vascular anastomoses. The placentas were examined post-procedure to evaluate the completeness of laser ablation using color dye injection. All human cases of FLA were performed by a single operator (one of the authors, LNT), who had undergone a 1-year clinical fellowship at Birmingham Women's Foundation trust (observed and participated in FLA for TTTS with more than 60 cases per annum).

In cases of monochorionic twin pregnancies complicated by TTTS, transabdominal ultrasound scan including placental site documentation with the mapping of umbilical cord insertions was performed by the operating team prior to surgery, and written consent was obtained from all subjects. All patients received a single dose of pre-operative intravenous Cefuroxime 1.5 grams, 6 hours before operation. All surgeries were performed in the operation theatre, using a 'minimal touch technique' with local analgesia only (10 ml 2% lignocaine hydrochloride and 10 ml 0.5% Marcaine of the skin, subcutaneous tissues and uterine muscle of the portal entry site), with additional maternal sedation with intravenous midazolam and fentanyl if required.

A vascular access trocar (Terumo Radifocus) and cannula were inserted under ultrasound guidance into the amniotic sac of the recipient twin, followed by insertion of a straight-forward (2mm, 0o, Karl Storz) fetoscope.[16,17] In cases with anterior placentation, the subjects were positioned in either lithotomy or lateral positions to improve visualisation and ablation of placental vascular anastomoses. In all cases, direct visualisation and mapping of the placental vascular anastomoses were performed, followed by FLA of the anastomoses (30W, diode laser, Dornier Medilas D Multibeam) using a selective, sequential technique and then the "Solomon modification".[9,18] Amnioreduction was performed after FLA to achieve a deepest vertical amniotic pool depth of between 6 and 8 cm, and in cases where there were still significantly high amniotic fluid volume despite amnioreduction of between 2 and 3 litres, amnioreduction was performed only until the uterus was less distended and the mother felt comfortable lying supine. If the cervical length prior to delivery was less than 25mm from transvaginal scan, a cervical cerclage (McDonald) was inserted after FLA and amnioreduction.

Clinical assessment of all women and fetuses was performed immediately after surgery and they were reviewed again at 24 hours post-surgery for fetal viability, MCA-PSV Doppler measurements and sonographic evidence of inadvertent septostomy. Cases were subsequently followed up by weekly ultrasound scans in their respective referral centers and delivery outcomes were collected through telephone communication with both doctors and patients.

Outcome Measures

Intra-operative, immediate (within 24 hours) and post-operative outcomes, along with live birth rate and neonatal survival at day 28 were analysed. The primary outcomes were survival of the fetuses at day 28 after birth, intraoperative and immediate (within 48 hours) complications. Intraoperative outcomes included non-completion of surgery, bleeding, uterine rupture and escalation of analgesia, whereas immediate post-operative outcomes included miscarriage (loss of pregnancy at less than 24 weeks' gestation), preterm pre-labour rupture of membranes PPROM), preterm labour, placental abruption, in-utero fetal demise and septostomy. Secondary outcomes were diagnoses during antenatal follow-up and at delivery, such as TAPS, resolution or recurrence of TTTS, PPROM, interval from procedure to delivery and survival of baby at birth.

Statistical Analysis

Statistical analysis was conducted with the SPSS software (IBM SPSS Statistics, version 25 MacOS) and qualitative data were compared using χ^2 test or Fisher exact test as appropriate. Continuous variables were tested for normality. Mann–Whitney U test was used to compare between groups for the continuous variables and Kaplan–Meier test for survival. A probability value of less than 0.05 was considered statistically significant. Interquartile range calculation was used in this study to account for extreme outliers in this dataset.

RESULTS

Over the period of 15 months, there was a total of 18 cases of FLA done for severe TTTS identified from the hospital records. Of these cases, 17 (94%) were MCDA and 1 (6%) dichorionic triamniotic which was excluded from this study. During the study period, none of the patients diagnosed with TTTS referred to HRPB declined FLA or opted for other treatment options. The subjects were all Malaysians with the exception of one Thailand national residing in Malaysia, and the ethnic origins were 10 Malays, 3 Chinese, 1 Indian, 1 Dayak and 1 Kadazandusun.

Table I: Background and case characteristics (n=?)

	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17
Quintero staging	II	IIID	II	II	IV	III	II	II	II	IIIR	IIIR	II	IIID	IV	II	II	II
Gestation at diagnosis	26	25	21	19	25	21	22	25	21	19	22	24	17	23	18	24	20
Growth discrepancy	36%	30%	19%	40%	47%	64%	9%	7%	4%	19%	38%	41%	53%	21%	25%	39%	35%
Placental location	Pos	Ant	Ant	Pos	Pos	Ant	Pos	Pos	Pos	Pos	Ant	Pos	Pos	Pos	Pos	Ant	Ant

C: case; D: donor; R: recipient; Ant: anterior; Pos: posterior

Table II: Duration of surgery, intra-operative, immediate post-operative and pregnancy outcomes (n=?)

Outcomes	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17
Intra-operative																	
Duration of surgery min)	64	80	50	58	50	60	50	51	32	50	50	68	48	55	35	60	60
Non completion	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Bleeding	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Uterine rupture	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Escalation of analgesia	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Immediate post-operative																	
Miscarriage	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N
PPROM	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	N	N	N
Preterm labour	N	N	N	N	N	-	N	N	N	N	N	N	N	N	N	N	N
Placental abruption	N	N	N	N	N	-	N	N	N	N	N	N	N	N	N	N	N
IUFD	N	N	N	N	N	-	N	N	N	N	N	N	N	N	N	N	N
Septostomy	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pregnancy Outcomes																	
TAPS	N	N	N	N	N	-	-	N	N	N	-	N	-	N	N	N	N
Resolved TTTS	Y	N	Y	Y	Y	-	-	Y	Y	Y	-	Y	-	Y	Y	Y	Y
Recurrent TTTS	N	Y	N	N	N	-	-	N	N	N	-	N	-	N	N	N	N
PPROM (w, d)	N	N	N	N	N	Y (d1)	N	N	Y (d5)	Y (d1)	N	N	Y (w4)	N	N	N	N
Donor survival in-utero	Y	Y	Y	Y	Y	-	-	Y	Y	Y	-	Y	-	Y	Y	Y	Y
Recipient survival in-utero	Y	Y	Y	Y	Y	-	-	Y	Y	Y	-	Y	-	Y	Y	Y	Y
Donor survival and weight at birth (g)	Y, 1800	N, 600	Y, 1500	Y, 750	Y, 900	N, N/A	N, 350	Y, 1450	Y, 1980	Y, 580	N, 570	Y, 1295	N/A	Y, 1510	Y, 1500	N, 800	Y, 1500
Recipient survival and weight at birth (g)	Y, 1800	Y, 900	Y, 1700	Y, 900	Y, 1000	N, N/A	N, 380	Y, 2100	Y, 2500	Y, 580	N, 590	Y, 1320	N/A	Y, 1715	Y, 1700	Y, 1100	Y, 1700
Donor neonatal survival (d28)	Y	N	Y	Y	Y	-	-	Y	Y	N	-	Y	-	Y	Y	N	Y
Recipient neonatal survival (d28)	Y	Y	Y	Y	Y	-	-	Y	Y	Y	-	Y	-	Y	Y	Y	Y
Gestation at delivery (w)	37	28	35	27	29	21	23	34	33	25	23	31	22	33	33	26	33
Procedure to delivery interval (w)	11	3	14	8	4	0	1	9	12	6	1	7	5	10	15	2	13
Mode of delivery	C-sec	C-sec	Vag	C-sec	Vag	Vag	Vag	C-sec	C-sec	Vag	Vag	C-sec	Vag	C-sec	C-sec	Vag	C-sec

C: case; N: No; Y: Yes; PPROM: preterm pre-labour rupture of membrane; IUFD: intrauterine fetal demise of either one or both twins; TAPS: twin anaemia-polycythaemia sequence; TTTS: twin-to-twin transfusion syndrome; PPROM: preterm prelabour rupture of membrane; w: week; d: day; g: gram; FLA: fetoscopic laser ablation; C-sec: caesarean section; Vag: vaginal delivery

Table III: Perinatal data for TTTS post-FLA (n=?)

	Quintero stage n(%)			
Median (IQR)	Overall	II	III	IV
Gestational age at procedure (weeks) - Median (IQR)	22 (5)	21.5 (4)	21 (5.5)	24 (2)
Gestational age at delivery (weeks) - Median (IQR)	29 (9)	33 (7)	23 (5)	31 (4)
Procedure to delivery interval (weeks) - Median (IQR)	7 (9)	10 (6)	3 (5)	7 (6)
At least 1 survivor	13/17 (76)	9/10 (90)	2/5 (40)	2/2 (100)
1 survivor	2/17 (11)	1/10 (10)	2/5 (40)	0/2
2 survivors	11/17 (64)	8/10 (80)	0/5 (0)	2/2 (100)
Donor death (in-utero)	0/17 (0)	0	0	0
Recipient death (in-utero)	0/17 (0)	0	0	0
Donor neonatal survivor	11/17 (64)	8/10 (80)	0/5 (0)	2/2 (100)
Recipient neonatal survivor	13/17 (76)	9/10 (90)	2/5 (40)	2/2 (100)

IQR: interquartile range; Survivor: measured up to 28 days of life

Table I shows the characteristics of the cases at the time of diagnosis, with 10 cases diagnosed with Quintero stage II, 5 stage III, and 2 stage IV TTTS. The median gestation at diagnosis was 22 weeks (IQR: 5 weeks). None of the cases had concurrent TAPs prior to FLA. The growth discrepancy ranged from 4% to 64% with a median of 35% (IQR: 21.5%). Anteriorly located placenta was diagnosed in 6 out of 17 (35%) cases while the remaining 11 (65%) had posterior placentation.

The median surgery time was 50 minutes (IQR: 10 minutes). Table II demonstrates the intra-operative and immediate post-operative outcomes of FLA. There were no intraoperative complications (intra-abdominal bleeding or uterine rupture) and all cases were performed to completion; however, 1 case required escalation of analgesia (Case 3) with intravenous midazolam and fentanyl from initially only having local analgesia. In the immediate post-operative period, case 6 had amniorrhexis and miscarried 6 hours after FLA. There were three other cases with amniorrhexis; case 9 had preterm prelabour rupture of membrane (PPROM) 5 days after FLA and delivered 12 weeks later with dual twin survival; case 10 had amniorrhexis at 1 hour after FLA and induction of labour was commenced for chorioamnionitis 6 weeks later with single baby survival; case 13 had PPROM at week 4 and miscarried 1 week after. All fetuses were viable in-utero after FLA and there were no cases with placental abruption or septostomy. All cases required amnioreduction from the recipient sac and one case (case 7) had cervical cerclage for cervical length of 13 mm diagnosed pre procedure.

Table II also shows the outcomes during pregnancy and after delivery. For pregnancies with anteriorly located placenta, two out of six cases ended with miscarriage, whereas the rate was lower in cases with posteriorly located placenta (2 out of 11 cases) (33% vs. 18%, p=0.660). Case 2 had recurrent TTTS and had amnioreduction subsequently. There was no TAPS after FLA in this study. Of the 13 cases who did not miscarry, 4 (30%) delivered vaginally while 9 cases (64%) underwent caesarean section.

The perinatal outcomes of severe TTTS post-FLA are summarised in Table III. The overall survival rate for at least one twin was 76% while dual twin survival was 64% at day 28 after birth. The survival rates at day 28 after birth for at least one twin for stages II, III and IV were 90% vs 40% vs 100% (p=0.054), respectively, and dual twin survival for stages II, III and IV were 80% vs 0% vs 100% (p=0.005), respectively. The median procedure-to-delivery time was 7 weeks (IQR: 9 weeks).

DISCUSSION

The 15-month review of the outcomes for FLA cases performed has shown a positive trend with overall survival rates of 76% and 64% for at least one infant survival and dual infant survival, respectively, which is comparable with internationally published success rates. This study reveals a low rate of intra- and post-operative complications, which further supports the safety of timely intervention with FLA for the treatment of TTTS to improve the outcomes of these pregnancies. The outcomes of FLA were least favourable in stage III TTTS, with only 40% survival of at least one twin, and 0% dual survival at day 28 after delivery. Although the survival rates in this study were best for cases with stage IV at diagnosis, there were only two cases in this group and the result did not reach statistical significance. Until further studies are done to confirm these findings, the authors would recommend early detection of TTTS to improve FLA outcomes in these patients.

In this series, three cases had miscarriage within 2 weeks of FLA. Case 6 had amniorrhexis after FLA was completed and delivered 6 hours after procedure. Case 7 had cervical shortening prior to FLA, and cervical cerclage was inserted vaginally (McDonald cerclage) after FLA and amnioreduction. However, she had contractions a week later and the cervical suture was removed when the contractions failed to subside despite tocolysis. The third case (case 11) is described below. The proportion of concomitant sFGR of growth discrepancy of more than 25% with TTTS in this study is consistent with that published by Van Winden et al (2015) at 67%.19 There were no cases of in-utero fetal demise in our cohort, although in the literature this ranges between 10 and 30%.[20-22]

Anterior placentation has been associated with additional technical challenges in visualising and ablating all vessels successfully with a higher rate of miscarriage. One particularly challenging case faced in the early phase of performing FLA was case 2, which took 80 minutes to complete due to difficulty in ablating a vessel located anteriorly. Follow-up ultrasonography revealed recurrent TTTS with worsening polyhydramnios in the recipient, with amnioreduction done once. The patient delivered at 28 weeks with single baby survival (recipient) at day 28 after birth.

Case 11 was referred at 22 weeks' gestation with stage III TTTS and severe polyhydramnios with deepest vertical pool (DVP) measuring 20 cm. Despite amnioreduction of 3 litres after FLA, the DVP measured 15 cm; however, no further amnioreduction was done because the patient's abdomen was soft and sudden massive amnioreduction might increase the risk of preterm labour or placental abruption. She miscarried 5 days after the procedure.

This study supports the use of only straight-forward scope for all FLA regardless of placental localisation instead of using different scopes (curved/angulated) for anterior placentation, which may result in lower overall cost of equipment. The technical difficulties of ablating vessel anastomoses in these subjects can be overcome with several measures. If vessels could not be visualised clearly due to placental 'folding' when polyhydramnios was not profound, amnioinfusion was performed to stretch and flatten the placenta surface to aid visualisation of vessel anastomoses. On the other hand, for cases with severe polyhydramnios and the length of scope was not enough to reach the placental surface, amnioreduction was performed. Cloudy amniotic fluid was resolved by performing amnio-exchange using warm normal saline infusion. Excess amniotic fluid was drained after completion of FLA to achieve a DVP of between 6 and 8 cm. Access for subjects with anterior placentation was improved by tilting patients on lateral positions and performing meticulous sonography by utilising both grey-scale and colour Doppler scans prior to trochar insertion to minimise the risk of bleeding and viscus injuries. This data also shows that most women tolerate the procedure well under local analgesia, which potentially results in lower risks associated with regional/general anaesthesia as well as encouraging earlier mobilisation post-procedure.

The strength of our team is that as the national referral centre for FLA, all cases are performed by the same dedicated team members. Each additional case enhanced the learning curve exponentially when team members worked increasingly in tandem. The learning experience is further reinforced by a comprehensive pre-operative planning for each case as well as a post-procedural discussion involving the whole team in spite of the relatively lower volume. Studies by Peeters et al. (2014) and Morris et al. (2010) regarding the learning curve for fetoscopic laser surgery have shown that operators reach a level of competence after at least 25 cases and outcomes are improved after about 61 cases and 3.4 years of experience.[15,23] Although more cases are required before we reach this number, the initiation of FLA services was deemed to be of priority to improve outcomes of TTTS in the country. However, due to the high cost of training for the whole team at an established training centres, repeated simulations were done locally instead to increase familiarity and improve troubleshooting amongst team members. After performing five simulations as a team, the first case of FLA was done in March 2019. Although the simulation model was not as realistic as an advanced simulator, the cost of our simulator was low and easy to assemble.

Another interesting point to note in this study is the safety of patient transfer using flights to access FLA treatment. Cases 4 (stage II), 5 (stage IV) and 17 (stage II) travelled 2 hours from Sabah and Sarawak via commercial flights and then 4 hours on land to reach HRPB. All mothers travelled home within 1 week after the procedure with 1 to 2 weekly follow-ups by the maternal–fetal medicine consultants at their primary care centres. All three had resolution of TTTS after FLA with live babies at day 28 after birth. To our knowledge, at the time of writing, the fetal medicine unit in HRPB which is located in the northern region of Peninsular Malaysia, is the single national referral centre for treatment of severe TTTS with FLA. Malaysia is formed by Peninsular Malaysia and East Malaysia (Sabah, Sarawak and Labuan on Borneo island), which is 132, 091 km^2 and 198,444 km^2, respectively.[24] Geographically, East Malaysia is separated from Peninsular Malaysia by the South China Sea, and the only mode of transport is by air travel. The major safety concerns arising from these transfers are the risks of preterm delivery, PPROM, miscarriage and antepartum haemorrhage during the journey, which may deter referrals for FLA and deprive patients of life-saving procedure. The findings offer reassurance that distance should not be a reason to dismiss FLA as a treatment option for TTTS to patients from remote areas, after careful assessment of risks such as the presence of contractions and cervical shortening. This service can also be expanded to Malaysia's neighbouring countries in South East Asia where FLA is not available locally yet by increasing awareness about TTTS and the use of laser coagulation as the preferred treatment.[26]

The main limitation of this study is the small number of subjects resulting in non-statistically significant findings. The other limitation is the lack of direct placental evidence to demonstrate the completeness of occlusion of vessel anastomoses. Most patients travelled back to their respective hospitals for post-operative reviews and delivery, and due to financial constraints and distance, majority could not travel to HRPB for follow-up after the primary surgery. Most hospitals did not have expertise to perform complex ultrasound surveillance of placenta in the antenatal period to support regression of TTTS and postpartum examination of placenta using color dye injection was not done in most cases. The 'success' of FLA therefore relied mainly on simpler and less specialised sonographic measurements indicating resolution of TTTS during the antenatal period which are easier to perform, including normalisation of liquor volume, presence of urine in bladder and improvement in Doppler studies and fetal hydrops. In this region where subspecialised care by Fetal Medicine Consultants is not widely available, further training of obstetricians in future should incorporate the evaluation of placenta both sonographically as well as by colour dye injection after birth to improve the accuracy of diagnosis.

Further studies looking into larger numbers and long-term outcomes, including single and dual survival outcomes and morbidities for our cases treated with FLA, are required. It is also important to note that the survival of fetuses above the threshold of viability in Malaysia is also influenced by post-delivery care, taking into consideration the resources and availability of neonatology care in different delivery centres where the babies are born. Decision regarding mode of delivery is made at the time of delivery by individual obstetricians caring for these women post-FLA, although the majority of cases were delivered via caesarean section.

CONCLUSION

In summary, the early outcomes of FLA done in the emerging national centre in Malaysia are encouraging and are consistent with the internationally published learning curve within the limits of good clinical governance. Early diagnosis and timely intervention are crucial to improve outcomes for cases of monochorionic pregnancies complicated by TTTS. Long-term follow-up of these babies are required to establish the sequealae as well as delayed morbidity. It is also vital to have a dedicated core team who are adequately trained to perform FLA in order to achieve optimal results with minimal complications. Distance from treatment centre and air travel should not discourage referrals for FLA as a life-saving measure to treat severe TTTS.

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REFERENCES

1. Soon R, Lim CKK, Hoong MFW, Zolkepali NA, Soelar SA. Multiple pregnancies: A risky affair for mothers and babies. National Obstetric Registry (NOR) and Clinical Research Centre (CRC). 26-28th September 2012. Accessed from: http://www.acrm.org.my/nor/doc/poster/Multiple_pregnancy_NOR_poster.pdf.
2. National Institute for Health and Clinical Excellence. Multiple pregnancy: Antenatal Care for Twin and Triplet Pregnancies. Clinical Guideline (CG129). 4th September 2019.
3. Cameron AH, Edwards JH, Derom R, Thiery M, Boelaert R. The value of twin surveys in the study of malformations. Eur J Obstetr Gynecol Reprod Biol 1983; 14: 347-56.
4. Lewi L, Cannie M, Blickstein I, Jani J, Huber A, Hecher K, et al. Placental sharing, birthweight discordance and vascular anastomoses in monochorionic diamniotic twin placentas. Am J Obstetr Gynecol 2007; 197(6): 587.e1-8.
5. Denbow ML, Cox P, Taylor M, Hammal DM, Fisk NM. Placental angioarchitecture in monochorionic twin pregnancies: relationship to fetal growth, fetofetal transfusion syndrome, and pregnancy outcome. Am J Obstetr Gynecol 2000; 182(2): 417-26.
6. Djaafri F, Stirnemann J, Mediouni I, Colmant C, Ville Y. Twin-twin transfusion syndrome – what we have learned from clinical trials. Seminars Fetal Neonatal Med 2017; 22(6): 367-75.
7. Berghella V, Kaufmann M. Natural history of twin-twin transfusion syndrome. J Reprod Med 2001; 46(5): 480-4.
8. Roberts D, Neilson JP, Kilby M, Gates S. Interventions for the treatment of twin-twin transfusion syndrome (a cochrane review). Ultrasound Obstetr Gynecol 2008; 31(6): 701-11.
9. Slaghekke F, Lopriore E, Lewi L, Middeldorp JM, van Zwet EW, Weingertner AS, et al. Fetoscopic laser coagulation of the vascular equator versus selective coagulation for twin-to-twin transfusion syndrome: an open-label randomised controlled trial. The Lancet 2014; 383(9935): 2144-51.
10. Kontopoulos EV, Quintero RA. Treatment of twin-twin transfusion syndrome: an evidence-based analysis. In: Quintero RA, Editor. Twin-twin transfusion syndrome. London: Informa, 2007.
11. Chmait RH, Kontopoulos EV, Korst LM, Llanes A, Petisco I, et al. Stage-based outcomes of 682 consecutive cases of twin-twin transfusion syndrome treated with laser surgery: the USFetus experience. Am J Obstetr Gynecol 2011; 204: 393.e1-6.
12. van Klink JMM, Koopman HM, Steggerda SJ, Oepkes D, Rijken M, Lopriore E. Cerebral injury and neurodevelopmental outcome in twin-twin transfusion syndrome. Curr Obstetr Gynecol Reports 2013; 2: 240-48.
13. Salomon LJ, Ortqvist L, Aegerter P, Bussieres L, Staracci S, Stirnemann J, et al. Long-term developmental follow-up of infants who participated in a randomised clinical trial of amniocentesis vs laser photocoagulation for the treatment of twin-to-twin transfusion syndrome. Am J Obstetr Gynecol 2010; 203: 444,e1-7.
14. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kurger M. Staging of twin-twin transfusion syndrome. J Perinatol 1999; 19(8Pt 1): 550-55.
15. Peeters SHP, Akkermans J, Slaghekke F, Bustraan J, Lopriore E, Haak MC, et al. Simulator training in fetoscopic laser surgery for twin-twin transfusion syndrome: a pilot randomized controlled trial. Ultrasound Obstetr Gynecolol 2015; 46: 319-26.
16. Sago H, Ishii K, Sugibayashi R, Ozawa K, Sumie M, Wada S. Fetoscopic laser photocoagulation for twin-twin transfusion syndrome. J Obstetr Gynaecol Res 2018; 44(5): 831-9.
17. Thia E, Thain S, Yeo GSH. Fetoscopic laser photocoagulation in twin-to-twin transufsion syndrome from a single institution. Singapore Med J 2017; 58(6): 321-26.
18. Slaghekke F, Zhao D, Middeldorp J, Klumper F, Haak M, Opekes D, et al. Antenatal management of twin-twin transfusion syndrome and twin anemia-polycythemia sequence. Expert Rev Hematol 2016; 9(8): 815-20.
19. Van Winden KR, Quintero RA, Kontopoulos EV, Korst LM, Llanes A, Chmait RH, 2015. Perinatal survival in cases of twin-twin transfusion syndrome complicated by selective intrauterine growth restriction. J Maternal-Fetal Neonatal Med 2015; 28(13): 1549-53.
20. Society for Maternal-Fetal Medicine, Simpson L. Twin-twin transfusion syndrome. Am J Obstetr Gynecol 2013; 208(1): 3-18.
21. Badr DA, Bevilacqua E, Carlin A, Gajewska K, Done E, Sanchez TC, et al. Antenatal management and neonatal outcomes of monochorionic twin pregnancies in a tertiary teaching hospital: a 10-year review. J Obstetr Gynaecol 2021; 41(8): 1199-204.
22. Snowise S, Moise K, Johnson A, Bebbington M, Papanna R. Donor death after selective fetoscopic laser surgery for twin-twin transfusion syndrome. Obstetr Gynecol 2015; 126(1): 74-80.
23. Morris RK, Selman TJ, Harbidge A, Martin WI, Kilby MD. Fetoscopic Laser coagulation for severe twin-to-twin transfusion syndrome: factors influencing perinatal outcome, learning curve of the procedure and lessons for new centers. BJOG 2010; 117(11): 1350-7.
24. Land and Survey Malaysia. [Cited November 2021] Accessed from: https://www.data.gov.my/data/ms_MY/dataset/keluasan-malaysia/resource/f9c7dc6f-dd9d-4ea3-8eb3-f722e75d1de0.
25. Akkermans J, Peeters SH, Middeldorp JM, Klumper FJ, Lopriore E, Ryan G, et al. A worldwide survey of laser surgery for twin-twin transfusion syndrome. Ultrasound Obstetr Gynecol 2015; 45(2): 168-74.

ORIGINAL ARTICLE

Descemet stripping endothelial keratoplasty versus penetrating keratoplasty in bullous keratopathy: A 2-year analysis of graft survival and outcomes in a tertiary eye centre in Kuala Lumpur

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ABSTRACT

Introduction: This study aims to compare the 2-year graft survival and outcomes of descemet stripping endothelial keratoplasty (DSEK) and penetrating keratoplasty (PK) for the treatment of bullous keratopathy (BK) among multiethnic Malaysia populations treated at a Tertiary Eye Centre in Kuala Lumpur, Malaysia.

Materials and Methods: This was a retrospective study of BK or Fuchs endothelial dystrophy (FED) patients who underwent DSEK or PK from 2015 to 2019 in Kuala Lumpur Hospital with a minimal post-operative follow-up of 2 years. Outcome measures included best-corrected visual acuity (BCVA), graft survival and complications. A total of 26 DSEK cases and 32 PK cases were included.

Results: At 2 years, graft survival rates were quite similar in two groups (DSEK 80.8% vs PK 75%, *p*=0.765). The mean follow-up period was 35.2 months in DSEK and 31.4 months for PK (*p*=0.465). The cumulative survival rates were slightly higher in the DSEK group (DSEK 73.1% vs PK 53.1%, *p*=0.119), but the result was not statistically significant. Post-operative complications were associated with higher graft failure in both groups (*p*=0.019). DSEK group has better post-operative BCVA (LogMAR DSEK 0.42 vs PK 0.83, *p*=0.003).

Conclusion: Similar graft survival rates were observed with both corneal transplant techniques for 2 years among Malaysian patients with BK. Post-operative complications can cause a higher risk of graft failure. DSEK produced better post-operative BCVA compared to PK.

KEYWORDS:
Bullous keratopathy; penetrating keratoplasty; descemet stripping endothelial keratoplasty

INTRODUCTION

Bullous keratopathy (BK) is characterised by corneal endothelial decompensation associated with irreversible corneal oedema. Aetiologies include Fuchs endothelial dystrophy (FED), iridocorneal endothelial syndrome (ICE), congenital hereditary endothelial dystrophy (CHED) and endothelial injury caused by intraocular surgeries such as phacoemulsification or glaucoma surgeries.

Descemet stripping endothelial keratoplasty (DSEK) and penetrating keratoplasty (PK) are safe surgical procedures to treat BK.[1] PK involved full-thickness corneal transplant, while DSEK only involved posterior stroma, Descemet membrane and endothelial of the cornea.

Complications of PK and DSEK include infection, wound dehiscence, and most importantly graft failure. Several risk factors are associated with a higher risk of graft failures, such as young patient, graft for corneal ulcer, large graft size, suture-related inflammation and ABO incompatibility.[2,3]

The most important outcome is the graft survival rate. Few articles have been published on this topic, especially in Western countries and Eastern Oriental countries (mostly the Chinese population).[4-7] Data on other ethnicities in South East Asia such as Malay, Indian and Natives population are not reported.

Even with all the reported results, there is no conclusive result and unified recommendation. United Kingdom National Transplant Registry reported a higher graft failure in the endothelial keratoplasty (EK) group than the PK group in FED at 2 years.[8] Similarly, Hong Kong researchers noticed DSEK has poorer survival in 2 years than the PK group. However, in Taiwan and Singapore, studies with predominantly Chinese patients reported better graft survival in the EK group than PK for BK at 100-days and 5 years, respectively.[5,7] Otherwise, a Cochrane review and a few studies from Western and Eastern countries with mostly Oriental patients have no statistical difference between the DSEK and PK groups in terms of graft survival.[9-11]

The present study aimed to report the graft survival and outcomes of both PK and DSEK in BK patients among multiethnic Malaysia populations treated in a tertiary referral center in Kuala Lumpur, Malaysia.

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MATERIALS AND METHODS

This retrospective study was conducted in Kuala Lumpur Hospital, following the tenets of the Declaration of Helsinki and ethics approval obtained from our local institutional review board (Medical Research & Ethics Committee, Ministry of Health; NMRR ID-21-02147-JF6). BK patients who underwent corneal transplantation from 2015 to 2019 in Hospital Kuala Lumpur were included. Their identities were extracted from the corneal transplant logbook recorded in the Ophthalmology Department of Kuala Lumpur Hospital. All corneal transplantation surgeries were conducted by three corneal consultants and three fellows in Kuala Lumpur Hospital. All surgeries were using the standard surgical techniques of DSEK and PK. Most of the corneal grafts were imported from the United States with only a few of them being local donors. A minimum follow-up of 2 years post-operative is required to be included in this study. All patients were transplant-virgin. We excluded patients that underwent repeated corneal transplants

The basic demographic was extracted. Factors of interest include age, race, gender, diagnosis, laterality, corneal transplantation operation date, type of operation, donor source, graft size, pre-operative best-corrected visual acuity (BCVA), co-morbidities, ocular co-morbidities, post-operative BCVA, survival periods and complications.

Study outcome measures were compared between DSEK and PK groups. Graft survivability between both groups will be compared over a 2 years and cumulative period and look for any statistical significance. The definition of graft failure was based on the definition used in the collaborative corneal transplantation studies, which were an irreversible loss of optical clarity sufficient to compromise vision for a minimum of consecutive 3 months.[12]

Statistical Analysis

All the data analysis will be analysed by using the SPSS version 25. Descriptive data will be done to describe the demographic of the population. Categorical data will be expressed in frequency and percentage, numerical data will be expressed in terms of mean and standard deviation (if normally distributed), and median with interquartile range (if abnormally distributed). For inferential analysis, all the categorical data will be analysed with chi-square test while numerical data will be analysed with Independent t-test. Mann–Whitney U tests were used for the skewed data. Fisher-exact test was used if the criteria for chi-square test were not met. Kaplan–Meier survival curve will be conducted to determine the 2-year and cumulative survival probabilities of DSEK and PK groups. Cox regression was used to assess the association between any factors and graft failure. A p value <0.05 will be considered statistically significant.

RESULTS

Among a total of 58 patients (33 males and 25 females) with BK, 32 cases of PK and 26 DSEK operations were done in a multiethnic Malaysia population in Kuala Lumpur Hospital. Basic demographic and surgical outcomes of patients who underwent PK or DSEK procedures were summarised in Table I.

Totally eight patients underwent combined surgery. Most of the combined surgery were triple procedure (62.5%). PK group has a higher proportion of combined surgery; however, there was no statistical difference between two groups.

Graft survival at 2 years in DSEK was 80.8% vs 75.0% in PK (p=0.765). Cummulative graft survival showed no statistic difference between DSEK and PK (DSEK 73.1% vs PK 53.1%, p=0.119) (Figures 1 and 2).

Cox analysis revealed that ethnicity, gender, age, graft size, ocular co-morbidities, combined surgery and presence of glaucoma drainage devices showed no significant effects on the graft survival rates. Eyes with post-operative complications were more likely to fail compared with eyes without complication (HR, 5.47; 95% CI, 1.44-60.71; p=0.019).

DISCUSSION

There are only limited articles provide result of DSEK vs PK in a South-East Asian populations. Most of the reported data are mainly from Western countries (Caucasian) and East Asian (Chinese & Korean).[4-6] Singapore who had quite a similar population with Malaysia conducted similar study reported 76.6% of their patients are Chinese.[7] To our best knowledge, there is no article comparing the outcome of DSEK and PK among BK patients in a balanced multiethnic South-East Asian population. Our study comprised 39.6% of Malay ethnicity, 10.3% Indian and 5.2% of natives originating from Sabah or Sarawak (Borneo island).

It has been a long debate on whether DSEK or PK will have a greater graft survival rate in BK or FED patients. Data from different regions of the world showed a different result. Most of the studies have no statistical difference between DSEK and PK. Singapore reported DSEK has a superior graft survival rates compared to PK.[7] Taiwan and UK studies revealed a higher graft survival rate in PK groups.[5,8]

Our 2-year survival for DSEK and PK is 80.8% and 75%, respectively, with DSEK marginally survived longer than PK. Our DSEK survival rate is comparable with other studies at 2 years periods (70–81% in UK and 81% in Hong Kong).[2,4] In contrast, our PK survival rate is relatively lower compared to UK (79–94%) and Hong Kong (88%) at 2 years period.[2,4] The lower PK graft survival rate in this study was similar to the finding from Korea and Singapore, and this has contributed to the difference in our result from the UK and Hong Kong.[2,4,6,7] However, the difference is not statistically significant in our population.

Cumulative graft survival analysis showed a further discrepancy between DSEK and PK graft survival (73.1% vs 53.1%). Our mean follow-up periods for both groups were around 31.4 and 35.2 months. Even though our follow-up period was not up to 5 years, our cumulative result resembles two Singapore 5-year studies.[7,13] In the South-East Asian population, DSEK graft survived better than PK albeit our result is not statistically significant. Similarly, our PK survival rate was poorer than UK and Dutch registry study.[2,14]

Table I: Data comparison between DSEK and PK groups (n=?)

	DSEK	PK	*p* value
No of cases (n)	26	32	
Age (year)	68.8	60.7	0.081#
Gender:			0.136
Male (n, %)	12, (46)	21, (66)	
Female (n, %)	14, (54)	11, (34)	
Ethnicity:			0.380
Malay (n, %)	8, (31)	15, (47)	
Chinese (n, %)	15, (58)	11, (34)	
Indian (n, %)	2, (8)	4, (13)	
Others (n, %)	1, (3)	2, (6)	
Mean follow-up period (months)	35.2	31.4	0.465
Pre-operative BCVA (LogMAR)	1.49	1.77	0.051
Ocular co-morbidities (n, %)	10 (38)	18 (56)	0.178
Operation duration (minutes)	83.6	83.8	0.981
Combined surgery (%)	3.8	21.9	0.063*
Post-operative complication rate (%)	11.5	31.3	0.073
Post-operative BVCA (LogMAR)	0.42	0.83	0.002#
Graft survival at 2 years (%)	80.8	75.0	0.765
Cumulative graft survival (%)	73.1	53.1	0.119

*Fisher-exact test was used.
#Mann–Whitney test was used.
best-corrected visual acuity (BCVA),
LogMAR: Logarithm of the Minimum Angle of Resolution

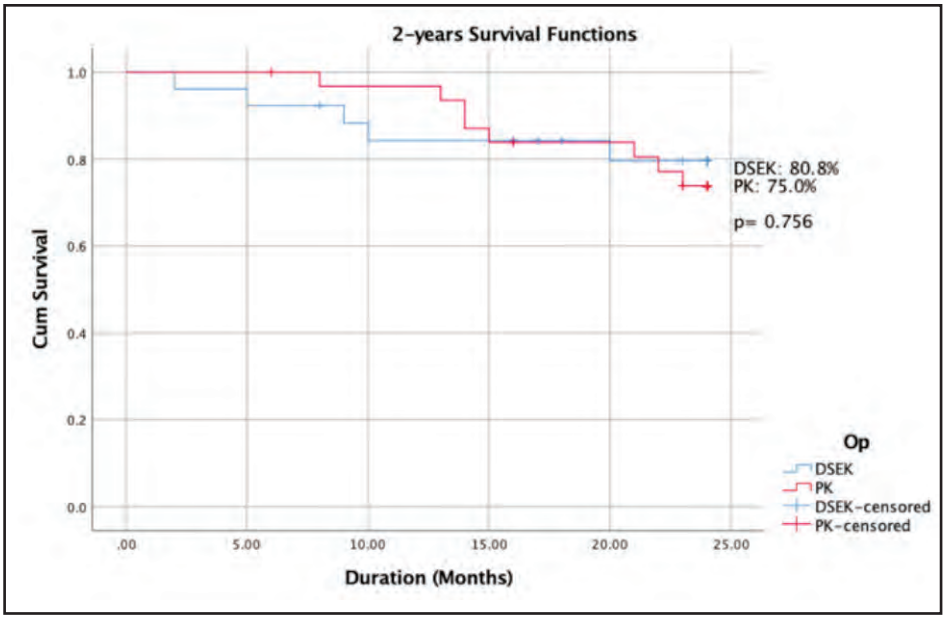

Fig. 1: 2-years survival analysis between DSEK and PK using Kaplan–Meier graft survival curve

In this study, the pre-operative BCVA results were similar for both PK and DSEK groups. Post-operative BCVA was significantly better in the DSEK group (p=0.002), this result was consistent with other studies.[2,6] DSEK has a better advantage in terms of refraction stability and shorter visual rehabilitation compared to PK.

Cox analysis of graft failure, we noticed eyes with complications had higher graft failure with a hazard ratio of 5.47. The most common complication from our study was raised intraocular pressure and glaucoma. Topical pressure-lowering medications are known risk factors for graft failure.[15] It has been reported that topical glaucoma medications can increase leukocyte and fibroblast accumulation in conjunctival and limbal tissue.[16] These pro-inflammatory cells could trigger immunologic recognition of donor tissue leading to graft rejection and failure if did not treat promptly.[15]

Other complications included infective keratitis. Two of our patients experienced infective keratitis (bacterial keratitis and HZO keratitis) after PK and DSEK procedure. Graft infection is a bane for all corneal surgeons and likely will lead to graft failure.[17] Despite given medical therapy, both of the grafts failed and the visual outcome were very poor. Vajaypee et al.[18] reported visual prognosis in eyes with post-keratoplasty graft infection is guarded despite optimal therapy.

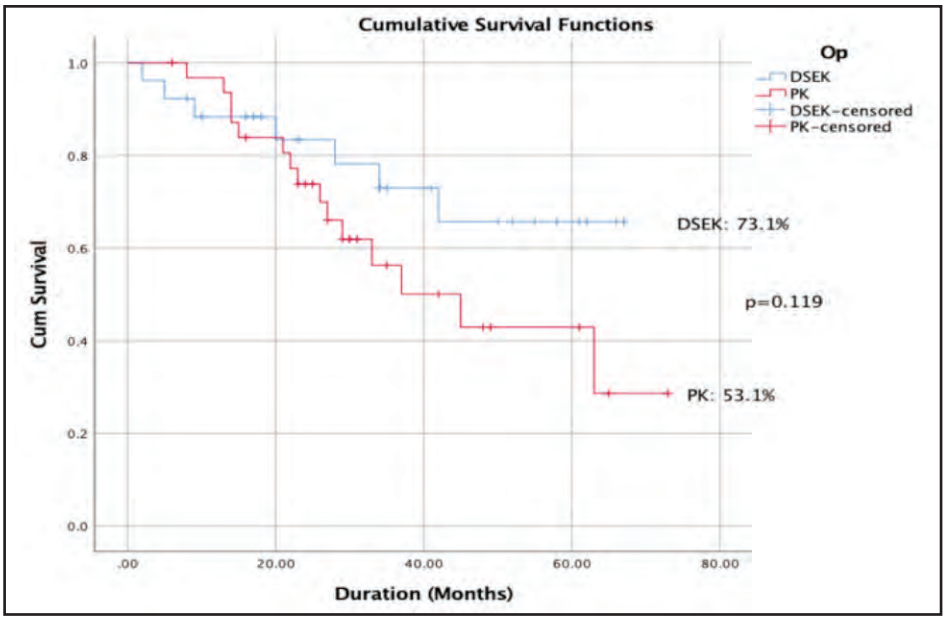

Fig. 2: Cumulative Kaplan–Meier graft survival curve comparing overall DSEK and PK in the overall study period

There are few limitations in this study, which include the small sample size and relatively short follow-up. Ideally, 5 years or longer follow-up and a larger sample will yield more valuable data. Besides that, we were not able to perform endothelial cell count measurement due to the limitation of our resources. This study provides post-keratoplasty outcomes in a multiethnic South-East Asian population from Kuala Lumpur, Malaysia.

CONCLUSION

In conclusion, DSEK and PK have similar graft survival rates for 2 years among Malaysian patients with BK. Eye which underwent DSEK had significantly better post-operative BCVA compared to PK. Future studies comparing long-term survival and outcomes of DSEK and PK will undoubtedly further our knowledge of each technique's advantages.

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REFERENCES

1. Lee WB, Jacobs DS, Musch DC, Kaufman SC, Reinhart WJ, Shtein RM. Descemet's stripping endothelial keratoplasty: safety and outcomes. A report by the American Academy of Ophthalmology. Ophthalmology 2009; 116(9): 1818-30.
2. Keane MC, Galettis RA, Mills RAD, Coster DJ, Williams KA. A comparison of endothelial and penetrating keratoplasty outcomes following failed penetrating keratoplasty: A registry study. Br J Ophthalmol 2016; 100(11): 1569-75.
3. Sellami D, Abid S, Bouaouaja G, Ben Amor S, Kammoun B, Masmoudi M, et al. Epidemiology and risk factors for corneal graft rejection. Transplant Proc 2007; 39(8): 2609-11.
4. Wah LAL, Wai KRP, Kam KW, Young AL. A 5-year analysis of endothelial vs penetrating keratoplasty graft survival in Chinese patients. Int J Ophthalmol 2020; 13(9): 1374-7.
5. Hsiao FC, Chen PY, Meir YJJ, Tan HY, Hsiao CH, Lin HC, et al. Clinical outcomes of penetrating keratoplasty and descemet stripping automated endothelial keratoplasty in asian population with American corneas. Int J Environ Res Public Health 2019; 16(22): 1-12.
6. Kim SE, Lim SA, Byun YS, Joo CK. Comparison of long-term clinical outcomes between descemet's stripping automated endothelial keratoplasty and penetrating keratoplasty in patients with bullous keratopathy. Korean J Ophthalmol 2016; 30(6): 443-50.
7. Ang M, Soh Y, Htoon HM, Mehta JS, Tan D. Five-year graft survival comparing descemet stripping automated endothelial keratoplasty and penetrating keratoplasty. Ophthalmology 2016; 123(8): 1646–52.
8. Greenrod EB, Jones MNA, Kaye S, Larkin DFP. Center and surgeon effect on outcomes of endothelial keratoplasty versus penetrating keratoplasty in the United Kingdom. Am J Ophthalmol 2014; 158(5): 957-66.e1.
9. Nanavaty MA, Wang X, Shortt AJ. Endothelial keratoplasty versus penetrating keratoplasty for Fuchs endothelial dystrophy CONTRIBUTIONS OF AUTHORS Conceiving the review: MN, AS Designing the review: MN, AS Coordinating the review: MN Data collection for review Designing electronic. 2014; Available from: www.controlled-trials.com
10. Nam KY, Lee JE, Lee JE, Jeung WJ, Park JM, Park JM, et al. Clinical features of infectious endophthalmitis in South Korea: a five-year multicenter study. BMC Infect Dis 2015; 15: 177. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4399575&tool=pmcentrez&rendertype=abstract
11. Anshu A, Price MO, Price FW. Risk of corneal transplant rejection significantly reduced with Descemet's membrane endothelial keratoplasty. Ophthalmology 2012; 119(3): 536-40.
12. The collaborative corneal transplantation studies (CCTS). Effectiveness of histocompatibility matching in high-risk corneal transplantation. The Collaborative Corneal Transplantation Studies Research Group. Arch Ophthalmol 1992; 110(10): 1392-403.

13. Woo JH, Ang M, Htoon HM, Tan D. Descemet membrane endothelial keratoplasty versus descemet stripping automated endothelial keratoplasty and penetrating keratoplasty. Am J Ophthalmol 2019; 207: 288-303.
14. Dickman MM, Peeters JMPWU, van den Biggelaar FJHM, Ambergen TAW, van Dongen MCJM, Kruit PJ, et al. Changing practice patterns and long-term outcomes of endothelial versus penetrating keratoplasty: a Prospective Dutch Registry Study. Am J Ophthalmol 2016; 170: 133-42.
15. Price MO, Thompson RW, Price FW. Risk factors for various causes of failure in initial corneal grafts. Arch Ophthalmol 2003; 121(8): 1087-92.
16. Sherwood MB, Grierson I, Millar L, Hitchings RA. Long-term morphologic effects of antiglaucoma drugs on the conjunctiva and Tenon's capsule in glaucomatous patients. Ophthalmology 1989; 96(3): 327-35.
17. Varley GA, Meisler DM. Complications of penetrating keratoplasty: graft infections. Refract Corneal Surg 1991; 7(1): 62-6.
18. Vajpayee RB, Sharma N, Sinha R, Agarwal T, Singhvi A. Infectious keratitis following keratoplasty. Surv Ophthalmol 2007; 52(1): 1-12.

ORIGINAL ARTICLE

Prevalence of COVID-19 among healthcare workers in the paediatric department: Estimates from a multicenter cross-sectional survey in Negeri Sembilan

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ABSTRACT

Introduction: The COVID-19 pandemic has reached a phase where many have been infected at least once. Healthcare workers were not spared from being infected. This study aimed to determine the period prevalence of COVID-19 among the paediatric healthcare workers in Negeri Sembilan as the country transitioned into an endemic phase of the pandemic. Additionally, we investigate potential sociodemographic and occupational characteristics associated with SARS-CoV-2 infection among healthcare workers.

Materials and Methods: A cross-sectional study was conducted among the healthcare workers in the paediatric department at three public specialist hospitals in Negeri Sembilan between 15 and 21 April 2022. Data were collected through a self-administered questionnaire.

Results: Out of the 504 eligible healthcare workers, 493 participated in this study (response rate 97.8%). The overall prevalence of COVID-19 (11 March 2020–15 April 2022) among healthcare workers was 50.9%. The majority (80.1%) were infected during the Omicron wave two months before the survey. Household contacts accounted for 35.9% of infection sources. The proportion of non-doctors in the COVID-19-infected group was significantly higher compared to the non-infected group (74.1% vs 64.0%, *p*=0.016). The COVID-19-infected group had a higher proportion of school-going children (44.6% vs 30.6%, *p*=0.001) and children who attended pre-school/sent to the babysitter (49.0% vs 24.4%, *p*<0.001). There were no significant differences between infection rates among the healthcare workers working in the tertiary hospital and the district hospitals. There were also no significant differences in the proportion of COVID-19-infected doctors and nurses when analysed by seniority.

Conclusion: Our study provided an estimate on the prevalence of COVID-19 among paediatric healthcare workers in Negeri Sembilan and the factors associated with infection, which captures the extent and magnitude of this pandemic on the state's paediatric department. Most infections resulted from household contact, with a higher proportion of infected healthcare workers having young children.

KEYWORDS:
COVID-19; SARS-CoV-2; healthcare workers; prevalence

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been an unprecedented global crisis since being officially declared a pandemic by the World Health Organization (WHO) on 11 March 2020.[1] The pandemic has placed immense pressure on the healthcare systems in many countries worldwide.

Healthcare workers are at high risk of contracting the disease in the course of their duties as front-line responders in the pandemic. Risk factors for nosocomial transmission of COVID-19 include frequent exposure to infected patients, work overload, poor infection control practices and pre-existing medical conditions.[2,3] Furthermore, healthcare workers could be exposed to infected colleagues, family members or contacts during social events such as weddings or religious gatherings.

The Ministry of Health Malaysia reported almost 9,000 infected healthcare workers in just the first 6 weeks of 2022.[4] The numbers more than doubled during the peak of the Omicron wave in the country.[5] The pandemic has exerted significant physical and psychological impact on healthcare workers, highlighting the need for appropriate psychological and emotional support.[6,7]

The epidemiology of COVID-19 has been studied locally among the general population and healthcare workers before the emergence of the Omicron variant.[8-10] There are no studies on the prevalence of COVID-19 among healthcare workers following Omicron, which drove a massive surge of cases in the country.[11] Malaysia transitioned into an endemic phase on 1 April 2022, more than 2 years after the outbreak of COVID-19.[12] As we recover from the pandemic, it would be

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informative to know the proportion of healthcare workers who have been infected with COVID-19. In this study, we report the period prevalence, symptoms and clinical outcomes of COVID-19 among healthcare workers in the paediatric department in Negeri Sembilan. Additionally, we investigate potential socio-demographic characteristics associated with SARS-CoV-2 infection.

MATERIALS AND METHODS

Study Design and Setting

We conducted a cross-sectional study among the paediatric department staff at the three public specialist hospitals in Negeri Sembilan from 15 to 21 April 2022, in the third week following the country's transition to the endemic phase of COVID-19. Hospital Tuanku Ja'afar (HTJ) Seremban served as the sole tertiary referral centre for both COVID-19 and non-COVID-19 cases, whereas Hospital Tuanku Ampuan Najihah (HTAN) Kuala Pilah and Hospital Port Dickson (HPD) served as non-COVID-19 district hospitals with specialists. During this period, the total cumulative cases of COVID-19 had exceeded 200,000 in the state of Negeri Sembilan.[13] The study was conducted when booster COVID-19 vaccination was already widely available to the general population.[14]

The study population comprised doctors, nurses, healthcare assistants, medical assistants and office clerks. All healthcare workers in the paediatric department were included in the study, even those on quarantine or leave. We excluded those who had left the department at the time of the survey, as well as those who declined to participate. Healthcare workers working in the paediatric department of other district hospitals in the state were excluded as these district hospitals were fully converted to COVID-19 hospitals during the study period. A liaison officer at each study site was appointed. The liaison officer recruited participants from the department based on a list of healthcare workers obtained from the paediatric office.

Participants were invited to participate in the survey using a self-administered online questionnaire. The link to the online questionnaire was disclosed through WhatsApp by the appointed liaison officer at each study site. Upon clicking the link to the questionnaire, the participants would be directed to a webpage containing the participant information sheet. Permission to participate in the study was obtained by the "I agree" checkbox, signifying implied consent from the participants. Participants who selected "I disagree" would be allowed to withdraw from the study. The participants were given a week to respond to the survey. The questionnaire took approximately 10 minutes to complete.

The questionnaire comprised three main sections and was conducted in Bahasa Malaysia. Section A contained socio-demographic information such as age, gender, job position, comorbidities and vaccination status. Section B contained information about the household members, such as the number of people in the household, and children in school or kindergarten. Section C included details of COVID-19 infection such as the number of times infected, symptoms and outcomes.

The primary outcome measures were the period prevalence of COVID-19 among healthcare workers in the paediatric department (11 March 2020–15 April 2022). Secondarily, we described the symptoms of COVID-19 among healthcare workers and compared the socio-demographic differences between healthcare workers who had COVID-19 with those who have not.

Study Definitions

Healthcare workers who were COVID-19-infected were defined as those who had a laboratory-proven diagnosis of COVID-19 at any point since the start of the pandemic (either by reverse transcriptase polymerase chain reaction or antigen detection tests using nasopharyngeal swabs or saliva samples). Prevalence in this study refers to the period prevalence of COVID-19 between 11 March 2020 (the start of the pandemic) and 15 April 2022 (the start of the study period), calculated by the proportion of healthcare workers who were COVID-19 infected at any point during the period mentioned above. Healthcare workers were considered to have completed COVID-19 booster vaccination if they had received the COVID-19 booster dose for more than 14 days following the vaccination. The period of 1 February 2022 onwards was considered the Omicron wave, with more than 95% of samples tested in the country being Omicron, which corresponded to Omicron dominance elsewhere around the world.[15] The source of infection was identifiable only when there was significant face-to-face contact within 1 meter for more than 15 minutes with a confirmed COVID-19 case in the preceding two weeks prior to the onset of the healthcare worker's diagnosis. The household attack rate was defined as the number of infected household members (excluding the healthcare worker) divided by the total number of household members.

Statistical Analysis

Categorical variables were expressed as frequencies (%). Continuous variables were expressed as means and standard deviation of the mean (SD) or as medians and interquartile ranges (IQR) when appropriate. Data were assessed for conformance to the normal distribution using the Shapiro–Wilk test. Independent t-test was used to compare means if the data distribution was normal, and Mann–Whitney U test was used if the data were not distributed normally. Categorical variables were compared using Chi-squared or Fisher's exact tests. Logistic regression was used to calculate odds ratio (OR) and its 95% confidence interval (95% CI). A p-value <0.05 was considered statistically significant. Data analysis was performed using SPSS Version 26.0 (IBM Corp., Armonk, NY, USA).

Ethical Consideration

The study was reviewed and approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia [NMRR-22-01170-VKK(2)]. The survey was anonymous, and confidentiality of the respondent's information was ensured. No personal or identifiable data were collected during the conduct of the study. There was no patient or public involvement in the study design.

Table I: Baseline characteristics of the study population (n=?)

Baseline Characteristics of patients	Total n (%)
Age in years, mean ± SD	35.4 (7.2)
Sex	
• Male	59 (12.0)
• Female	434 (88.0)
Post	
• Specialist	23 (4.7)
• Medical officer	64 (13.0)
• House officer	65 (13.2)
• Matron/ nursing sister	23 (4.7)
• Staff nurse	222 (45.0)
• Community nurse	44 (8.9)
• Health care assistant	46 (9.3)
• Others	6 (1.2)
Hospital	
• Hospital Tuanku Ja'afar Seremban	342 (69.4)
• Hospital Tuanku Ampuan Najihah Kuala Pilah	103 (20.9)
• Hospital Port Dickson	48 (9.7)
Completed booster COVID-19 vaccination	455 (92.3)
Comorbidities[a]	
• None	419 (85.0)
• Obesity	29 (5.9)
• Hypertension	28 (5.7)
• Respiratory	20 (4.1)
• Diabetes mellitus	16 (3.2)
• Others	23 (4.7)
COVID-infected healthcare workers	
• Yes	251 (50.9%)
• No	242 (49.1%)

SD Standard deviation

[a]A patient may have more than one comorbidity

RESULTS

A total of 493 out of the 504 eligible healthcare workers participated in this study, which corresponded to a participation rate of 97.8%. The characteristics of the study participants are described in Table I. The mean age of the participants was 35.4 years (SD 7.2) with a male: female ratio of 1:7. The doctors made up less than a third of the respondents, while more than two-thirds were nursing staff members. Most participants (69.4%) were from HTJ Seremban, the state's sole hospital with specialists managing COVID-19 cases. These baseline data reflected the demographics of the paediatric department workforce in Negeri Sembilan. At least one comorbidity was identified in 74 participants (15%), with obesity being the most commonly reported comorbidity (5.9%). The prevalence of COVID-19-infected healthcare workers was 50.9% (251/493).

The mean age of those infected was 35.0 years (SD 6.5) and 25 (10%) were males. The characteristics of the COVID-19-infected healthcare workers are further described in Table II. The proportion of COVID-19-infected healthcare workers in the paediatric department of HTJ Seremban was 50.3% (172/342), while the proportion of COVID-19 infected healthcare workers in the non-COVID-19 hospitals was 52.3% (79/151). The vast majority (80.1%) were infected during the Omicron wave, which occurred two months before the survey. Only 8 (3.2%) were infected more than once. The source of the COVID-19 infection was unknown to most of the respondents (41.8%). Household contacts accounted for 35.9% of infection sources, while contacts from the work circle accounted for 17.1% of cases. Most healthcare workers had completed their COVID-19 vaccination or had been boosted at the time of infection. Only 11 (4.4%) required hospitalisation. The overall proportion of household attack rate (excluding the healthcare workers) was 54.7% (488/892).

The clinical characteristics and outcomes during the Omicron wave and previous waves were compared in Table III. Healthcare workers infected during the Omicron wave were significantly older than the previous waves, with a mean age difference of 2.3 years (p=0.03). During the Omicron wave, asymptomatic infection was less common (OR 0.39, 95% CI 0.17–0.92). Symptoms such as fever (OR 2.73, 95% CI 1.33–5.61), cough (OR 4.94, 95% CI 2.34 – 10.44), sore throat (OR 5.18, 95% CI 2.33–11.49), lethargy (OR 2.29, 95% CI 1.14–4.58) and headache (OR 2.11, 95% CI 1.05–4.20) were significantly more common during the Omicron wave. On the other hand, anosmia and ageusia were significantly less common during the Omicron wave (OR 0.18, 95% CI 0.09–0.39 and OR 0.16, 95% CI 0.08–0.33, respectively). The proportion of healthcare workers requiring hospitalisation was significantly higher during previous waves than during the Omicron wave (15.0% vs 2.7%, p=0.004).

We compared the socio-demographic characteristics of the COVID-19-infected and non-infected healthcare workers to identify parameters associated with infection (Table IV). The mean age, sex, comorbidities and the proportion of healthcare workers who received booster vaccination did not significantly differ between both groups (p>0.05). There were no significant differences between the proportion of infected healthcare workers working in the tertiary and district

Table II: Characteristics of healthcare workers who had been COVID-infected Include (n=?)

Characteristics of healthcare workers	Total n (%)
COVID-infected, by hospital[a]	
• Hospital Tuanku Ja'afar Seremban (n=342)	172 (50.3)
• Hospital Tuanku Ampuan Najihah Kuala Pilah (n=103)	50 (48.5)
• Hospital Port Dickson (n=48)	29 (60.4)
COVID-infected, by profession[a]	
• Specialist (n=23)	9 (39.1)
• Medical officer (n=64)	33 (51.6)
• House officer (n=65)	23 (35.4)
• Matron/ nursing sister (n=23)	11 (47.8)
• Staff nurse (n=222)	122 (55.0)
• Community nurse (n=44)	24 (54.5)
• Health care assistant (n=46)	25 (54.3)
• Others (n=6)	4 (66.7)
COVID-infected, by date	
• Pre-Feb 2022	50 (19.9)
• Post-Feb 2022	201 (80.1)
Number of times COVID-infected	
• Once	243 (96.8)
• More than once	8 (3.2)
Source of COVID-19 infection	
• Household	90 (35.9)
• Workplace	43 (17.1)
• Social activities	13 (5.2)
• Unknown	105 (41.8)
COVID-19 vaccination status while infected	
• Not vaccinated	8 (3.2)
• Completed 1 dose COVID-19 vaccine	4 (1.6)
• Completed 2 doses COVID-19 vaccine	53 (21.1)
• Completed booster dose of COVID-19 vaccine	186 (74.1)
Outcome	
• Not hospitalised	240 (95.6)
• Hospitalised	11 (4.4)
Symptoms lasting for more than 2 weeks	85 (33.9)
Household attack rate	54.7 (95% CI 51.4 – 57.9)

CI confidence interval.
[a]Percentages reflected the proportion by row instead of column

Table III: Comparison of clinical characteristics and outcomes during the Omicron wave and previous waves (n=?)

	Total (n=/) (%)	Previous waves (n=/) (%)	Omicron wave (n=/) (%)	*p* value	Odds ratio (95% CI)[a]
Age in years, mean ± SD	35.0 (6.5)	33.2 (6.1)	35.5 (6.5)	0.030	1.06 (1.01 – 1.12)
Sex, male	25 (10.0)	6 (12.0)	19 (9.5)	0.591	0.77 (0.29 – 2.03)
Asymptomatic	28 (11.2)	10 (20.0)	18 (9.0)	0.031	0.39 (0.17 – 0.92)
Fever	167 (66.5)	23 (46.0)	144 (71.6)	0.006	2.73 (1.33 – 5.61)
Cough	179 (71.3)	22 (44.0)	157 (78.1)	<0.001	4.94 (2.34 – 10.44)
Rhinorrhea	164 (65.3)	29 (58.0)	135 (67.2)	0.869	1.07 (0.50 – 2.30)
Sore throat	189 (75.3)	25 (50.0)	164 (81.6)	<0.001	5.18 (2.33 – 11.49)
Shortness of breath	21 (8.4)	3 (6.0)	18 (8.9)	0.648	1.35 (0.38 – 4.81)
Anosmia	83 (33.1)	28 (56.0)	55 (27.4)	<0.001	0.18 (0.09 – 0.39)
Ageusia	72 (28.7)	27 (54.0)	45 (22.4)	<0.001	0.16 (0.08 – 0.33)
Lethargy	132 (52.6)	17 (34.0)	115 (57.2)	0.020	2.29 (1.14 – 4.59)
Headache	139 (55.4)	19 (38.0)	120 (60.0)	0.035	2.11 (1.05 – 4.20)
Myalgia	145 (57.8)	24 (48.0)	121 (60.1)	0.463	1.30 (0.64 – 2.63)
Loss of appetite	69 (27.5)	10 (20.0)	59 (29.3)	0.371	1.43 (0.65 – 3.11)
Vomiting/diarrhoea	172 (68.5)	34 (68.0)	138 (68.7)	0.196	0.54 (0.21 – 1.37)
Hospitalised	11 (4.4)	6 (12.0)	5 (2.5)	0.004	0.16 (0.05 – 0.55)

CI confidence interval
[a]Using the previous waves as the reference group

Table IV: Comparison of characteristics of COVID-19-infected and non-infected group of healthcare workers

	COVID-19 infected (n=/) (%)	Non-infected (n=/) (%)	*p* value
Age in years, mean ± SD	35.0 (6.5)	35.7 (8.0)	0.317
Sex			
• Male	25 (10.0)	34 (14.0)	0.162
• Female	226 (90.0)	208 (86.0)	
Presence of comorbidity	45 (17.9)	29 (12.0)	0.065
Completed booster vaccination	227 (90.4)	228 (94.2)	0.116
Hospital			
• HTJS (tertiary)	172 (68.5)	170 (70.2)	0.678
• HTAN/HPD (non-tertiary)	79 (31.5)	72 (29.8)	
Profession			
• Doctors	65 (25.9)	87 (36.0)	0.016
• Non-doctors	186 (74.1)	155 (64.0)	
Doctors, by seniority[a]			
• Specialist	9 (13.8)	14 (16.1)	0.702
• MO/ HO	56 (86.2)	73 (83.9)	
Nurses, by seniority[b]			
• Sister/Matron	11 (7.0)	12 (9.1)	0.514
• SN/ JM	146 (93.0)	120 (90.9)	
Number of household, median (IQR)	4 (2-5)	3 (2-4)	0.135
Partner/spouse working as healthcare worker	63 (25.1)	44 (18.2)	0.063
Child in primary school/secondary school	112 (44.6)	74 (30.6)	0.001
Child in kindergarten/baby sitter	123 (49.0)	59 (24.4)	<0.001

[a]The calculated percentages were based on a total of 65 doctors in the COVID-19-infected group and 87 doctors in the non-infected group, respectively.
[b]The calculated percentages were based on a total of 157 nurses in the COVID-19-infected group and 132 nurses in the non-infected group, respectively.
HO: House officer, MO: Medical officer, SN: staff nurse and JM: jururawat masyarakat (community nurse).

Table V: Subgroup analysis of healthcare workers who had children attending primary/secondary school or kindergarten/babysitter

	Doctors (n=/) (%)	Non-doctors (n=/) (%)	*p* value
Child in primary school/ secondary school	22 (14.5)	164 (48.1)	<0.001
Child in kindergarten/ baby sitter	31 (20.4)	151 (44.3)	<0.001
Number of household, median ± IQR	3 (2 -5)	3 (2 -5)	0.228

hospitals (p=0.678). However, the proportion of non-doctors in the COVID-19-infected group was significantly higher compared to the non-infected group (74.1% vs 64.0%, p=0.016). We observed no significant differences between both groups when the doctors and nurses were analysed separately by seniority.

The household characteristics of both groups were examined, and no significant differences were found between the median number of household members and the proportion of participants who had a partner/spouse who worked in healthcare (p>0.05). However, the COVID-19-infected group had a higher proportion of school-going children (44.6% vs 30.6%, p=0.001) and children who attended pre-school/sent to the babysitter (49.0% vs 24.4%, p<0.001). A subgroup analysis between the doctors and non-doctors in Table V revealed a higher proportion of non-doctors who had school-going children (48.1% vs 14.5%, p<0.001) and children who attended pre-school/sent to babysitter (44.3% vs 20.4%, p<0.001).

DISCUSSION

A high prevalence of COVID-19 was found in this multicentre cross-sectional study of healthcare workers working in the paediatric department in Negeri Sembilan. More than half of the 493 healthcare workers surveyed have been infected with COVID-19 at least once since the pandemic began. Seroprevalence studies among healthcare workers generally reported lower prevalence.[16-20] However, these studies were conducted much earlier in the pandemic, before COVID-19 was widely prevalent in the community. On the contrary, seroprevalence studies from community-based studies carried out in a comparable period in the pandemic ranged from 57.7% to 66.0%.[21-23] The significant increase in seropositivity rates was driven by the large number of infections during the Omicron wave. These findings were reflected in our study, whereby a vast majority (80.1%) of our healthcare workers were infected during the Omicron wave.

There were observable differences in the clinical manifestations of COVID-19 during the Omicron wave compared to the previous waves. Our findings of lower rates of anosmia/ageusia during the Omicron wave were consistent with existing literature.[24-26] On the other hand, sore throat was more common during the Omicron wave, which was similarly observed elsewhere.[24,26] Fever and cough were found to be more common during Omicron predominance in our study, in contrast to the previous reports.[25,27] Hospitalisation rates were significantly lower during the Omicron wave. This could be attributed to various factors, including Omicron's milder clinical course[28] and

comprehensive COVID-19 vaccine coverage was already achieved during the Omicron wave. Additionally, mandatory hospitalisation as part of containment measures was no longer necessary during the Omicron wave.

Most healthcare workers had no identifiable source of infection, which was not unusual at this stage of the pandemic when contact tracing activities were no longer carried out routinely. Household exposure was the most common among those with a known source of infection. Workplace exposure accounted for less than half that of household exposure. There were no significant differences between the infection rates among healthcare workers working in the tertiary hospital caring for COVID-19 patients and the district hospitals that do not manage COVID-19 cases. Our findings suggest that nosocomial transmission was not the primary source of infection, which concurred with existing literature that healthcare workers were not at an increased risk of infection.[17,29,30] This was likely due to the widespread use of personal protective equipment and stringent enforcement of infection control practices within the workplace.

We observed variations in infection rates by profession. The proportion of doctors who had been infected with COVID-19 was lower than the non-doctors. However, there were no significant differences in the proportion of COVID-19-infected doctors and nurses when analysed by seniority. This suggested that most infections originated from out-of-the-hospital sources since the junior staffs tend to have more patient contact than the senior ones.

We observed a significantly higher proportion of COVID-19-infected healthcare workers with school-aged children or children who attended kindergarten/sent to the babysitter, which further implied that household contacts were the primary source of infection. A subgroup analysis revealed a higher proportion of non-doctors who had school-aged children and children who attended pre-school/sent to the babysitter, thereby explaining the differences in the infection rates by profession earlier. Although children were less likely to be the vector for SARS-CoV-2 transmission within household settings, their transmissibility appeared to have increased with the Omicron variant.[31] Additionally, the reopening of schools and communities during the Omicron wave likely altered transmission dynamics. Young children tend to be less compliant with masking and social distancing and are more likely to be exposed and become a foci for viral transmission within the household. The overall household attack rate in our study was 54.7%, which was comparable to a previously published study locally.[32]

Despite a high prevalence of COVID-19 infection among healthcare workers, the outcomes were largely favourable, with only a small proportion requiring hospitalisation. The good prognosis can be attributed to our healthcare workers' high uptake of COVID-19 vaccination. Almost all (95.2%) healthcare workers had completed two doses of COVID-19 vaccination or their booster vaccination at the time of infection. However, a substantial proportion of healthcare workers reported symptoms that persisted for more than 2 weeks, raising the possibility that some might progress to develop long COVID.

Our study has certain limitations. First, this study on the prevalence of COVID-19 infection used a self-reported questionnaire rather than serological prevalence using SARS-CoV-2 immunoglobulin G (IgG) detection. The prevalence of COVID-19 infection could have been higher as some healthcare workers could have had a subclinical or asymptomatic infection and were not tested. The data obtained from the self-administered questionnaire could also be predisposed to underreporting bias, although participation in this study was voluntary with a declaration of non-disclosure of identity and confidentiality. Nevertheless, our findings on the prevalence of COVID-19 infection matched the gross figures of quarantine leaves obtained from official office records. Second, we acknowledge the possibility of recall bias when the healthcare workers report their symptoms, which could overestimate or underestimate their symptoms of COVID-19. Lastly, our study was not designed to test transmission dynamics within the household. Therefore, some participants may have misidentified their exposure source. However, this bias was minimised by defining a definite source only when the chronological and epidemiological link matched the natural history of COVID-19. Healthcare workers were given an option for an unidentified source if they could not identify their COVID-19 source of infection. A larger-scale study conducted nationwide addressing those limitations would provide more wholesome data.

CONCLUSION

In conclusion, our study provided an estimate on the prevalence of COVID-19 among healthcare workers in the paediatric department of hospitals in Negeri Sembilan and the factors associated with infection. This study would serve as a formal record for future generations of medical professionals on the magnitude of this once-in-a-lifetime pandemic on the state's paediatric department, where more than half of the healthcare workers had contracted the illness by the time the pandemic reached an endemic phase. The high prevalence of infection resulted in periods of shortages in staff due to the significant cumulative absent days from work. Additionally, a substantial proportion of healthcare workers reported symptoms that persisted for more than 2 weeks. Our study highlights the need for further research on the prevalence of long-COVID among healthcare workers, which may impact their work performances and psychological well-being.

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REFERENCES

1. World Health Organization, Geneva. 2020. Director-General's opening remarks at the media briefing on COVID-19 - March 11, 2020 [cited September 2022]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19--11-march-2020.
2. Mhango M, Dzobo M, Chitungo I, Dzinamarira T. COVID-19 risk factors among health workers: a rapid review. Saf Health Work 2020; 11(3): 262-5.
3. Ran L, Chen X, Wang Y, Wu W, Zhang L, Tan X. Risk factors of healthcare workers with coronavirus disease 2019: a retrospective cohort study in a designated hospital of Wuhan in China. Clin Infect Dis 2020; 71(16): 2218-21.
4. Ying TP. Nearly 9,000 healthcare workers contracted COVID-19 this year: New Straits Times Malaysia; [cited September 2022]. Available from: https://www.nst.com.my/news/nation/2022/02/772307/nearly-9000-healthcare-workers-contracted-covid-19-year.
5. Hisamudin HA. Over 18,000 healthcare workers down with COVID-19, says KJ: Free Malaysia Today; [cited September 2022]. Available from: https://www.freemalaysiatoday.com/category/nation/2022/03/24/over-18000-healthcare-workers-down-with-covid-19-says-kj/.
6. Shreffler J, Petrey J, Huecker M. The impact of COVID-19 on healthcare worker wellness: a scoping review. West J Emerg Med 2020; 21(5): 1059-66.
7. De Kock JH, Latham HA, Leslie SJ, Grindle M, Munoz SA, Ellis L, et al. A rapid review of the impact of COVID-19 on the mental health of healthcare workers: implications for supporting psychological well-being. BMC Public Health 2021; 21(1): 104.
8. Supramanian RK, Sivaratnam L, Rahim AA, Abidin N, Richai O, Zakiman Z, et al. Descriptive epidemiology of the first wave of COVID-19 in Petaling District, Malaysia: Focus on asymptomatic transmission. Western Pac Surveill Response J. 2021; 12(2): 82–8.
9. Jayaraj VJ, Rampal S, Ng CW, Chong DWQ. The Epidemiology of COVID-19 in Malaysia. Lancet Reg Health West Pac 2021; 17: 100295.
10. Ramli NS, Fauzi MFM, Moktar NMA, Hajib N, Nawi AM. Prevalence, characteristics, and predictors of healthcare workers with COVID-19 infection in an urban district in Malaysia. Pan Afr Med J 2022; 41: 243.
11. Shirodkar R. Malaysia hits new daily Covid record as Omicron surge continues: Bloomberg News; [cited September 2022]. Available from: https://www.bloomberg.com/news/articles/2022-02-16/malaysia-hits-new-daily-covid-record-as-omicron-surge-continues?leadSource=uverify%20wall.
12. Kaos J. PM : M'sia will transition into endemic phase from April 1: The Star Malaysia; [cited September 2022]. Available from: https://www.thestar.com.my/news/nation/2022/03/08/pm-msia-will-enter-endemic-phase-from-april-1.
13. Crisis Prepardness and Response Center, Ministry of Health Malaysia. Situasi Terkini COVID-19 Negeri Sembilan, 24 April 2022; [cited September 2022]. Available from: https://covid-19.moh.gov.my/terkini-negeri/2022/04/kemaskini-negeri-covid-19-di-malaysia-24042022.
14. Krishnan DB. More than 15 million Malaysians have taken booter shots against COVID-19: New Straits Times Malaysia; [cited September 2022]. Available from: https://www.nst.com.my/news/nation/2022/03/782420/more-15-million-malaysians-have-taken-booster-shots-against-covid-19.
15. Hodcroft EB. CoVariants: SARS-CoV-2 mutations and variants of interest [cited September 2022]. Available from: https://covariants.org/per-country.
16. Wiggen TD, Bohn B, Ulrich AK, Stovitz SD, Strickland AJ, Naumchik BM, et al. SARS-CoV-2 seroprevalence among healthcare workers. PLoS One 2022; 17(4): e0266410.
17. Weber S, Didelot A, Agrinier N, Peyrin-Biroulet L, Schvoerer E, Rabaud C, et al. SARS-CoV-2 seroprevalence in healthcare workers and risk factors. Infect Dis Health 2022; 27(4): 203-10.
18. Yoshihara T, Ito K, Zaitsu M, Chung E, Aoyagi I, Kaji Y, et al. SARS-CoV-2 Seroprevalence among healthcare workers in general hospitals and clinics in Japan. Int J Environ Res Public Health 2021; 18(7): 3786.
19. Varona JF, Madurga R, Penalver F, Abarca E, Almirall C, Cruz M, et al. Seroprevalence of SARS-CoV-2 antibodies in over 6000 healthcare workers in Spain. Int J Epidemiol 2021; 50(2): 400-9.
20. Neumann M, Aigner A, Rossow E, Schwarz D, Marschallek M, Steinmann J, et al. Low SARS-CoV-2 seroprevalence but high perception of risk among healthcare workers at children's hospital before second pandemic wave in Germany. World J Pediatr 2021; 17(5): 484-94.
21. Clarke KEN, Jones JM, Deng Y, Nycz E, Lee A, Iachan R, et al. Seroprevalence of Infection-Induced SARS-CoV-2 Antibodies - United States, September 2021-February 2022. MMWR Morb Mortal Wkly Rep 2022; 71(17): 606-8.
22. Castilla J, Lecea O, Martin Salas C, Quilez D, Miqueleiz A, Trobajo-Sanmartin C, et al. Seroprevalence of antibodies against SARS-CoV-2 and risk of COVID-19 in Navarre, Spain, May to July 2022. Euro Surveill 2022; 27(33): 2200619.
23. Erikstrup C, Laksafoss AD, Gladov J, Kaspersen KA, Mikkelsen S, Hindhede L, et al. Seroprevalence and infection fatality rate of the SARS-CoV-2 Omicron variant in Denmark: A nationwide serosurveillance study. Lancet Reg Health Eur 2022; 21: 100479.
24. Vihta KD, Pouwels KB, Peto TE, Pritchard E, House T, Studley R, et al. Omicron-associated changes in SARS-CoV-2 symptoms in the United Kingdom. Clin Infect Dis 2022; ciac613 (online ahead of print).
25. Bouzid D, Visseaux B, Kassasseya C, Daoud A, Femy F, Hermand C, et al. Comparison of patients infected with delta versus omicron COVID-19 variants presenting to paris emergency departments : a retrospective cohort study. Ann Intern Med 2022; 175(6): 831-7.
26. Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, Nogal A, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. Lancet 2022; 399(10335): 1618-24.
27. Yang W, Yang S, Wang L, Zhou Y, Xin Y, Li H, et al. Clinical characteristics of 310 SARS-CoV-2 Omicron variant patients and comparison with Delta and Beta variant patients in China. Virol Sin 2022; 37(5): 704-15.
28. Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and Outcomes of Hospitalized Patients in South Africa During the COVID-19 Omicron Wave Compared With Previous Waves. JAMA 2022; 327(6): 583-4.
29. Bouwman M, van Osch F, Crijns F, Trienekens T, Mehagnoul-Schipper J, van den Bergh JP, et al. SARS-CoV-2 seroprevalence in healthcare workers of a teaching hospital in a highly endemic region in the Netherlands after the first wave: a cross-sectional study. BMJ Open 2021; 11(10): e051573.
30. Lau JS, Buntine P, Price M, Darzins P, Newnham E, Connell A, et al. SARS-CoV-2 seroprevalence in healthcare workers in a tertiary healthcare network in Victoria, Australia. Infect Dis Health 2021; 26(3): 208-13.
31. Chen F, Tian Y, Zhang L, Shi Y. The role of children in household transmission of COVID-19: a systematic review and meta-analysis. Int J Infect Dis 2022; 122: 266-75.
32. Ng DC, Tan KK, Chin L, Cheng XL, Vijayakulasingam T, Liew DWX, et al. Risk factors associated with household transmission of SARS-CoV-2 in Negeri Sembilan, Malaysia. J Paediatr Child Health 2022; 58(5): 769-73.

ORIGINAL ARTICLE

Serum vitamin D levels among immunoglobulin A nephropathy patients and the associated parameters

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ABSTRACT

Introduction: Low serum 25-hydroxyvitamin D is associated with chronic kidney disease progression, and there are limited data on the vitamin D levels in patients with Immunoglobulin A nephropathy. This study was conducted to determine the level of 25-hydroxyvitamin D in a stable immunoglobulin A nephropathy patient and its association with other parameters.

Materials and Methods: We performed a cross-sectional study involving 70 patients with biopsy-proven immunoglobulin A nephropathy with a stable estimated glomerular filtration rate and urinary albuminuria. Their demographic profiles were documented, and blood samples were taken for serum 25-hydroxyvitamin D, highly sensitive C-reactive protein, urine albuminuria and other routine blood tests.

Results: We found nine patients (12.9%) had sufficient 25-hydroxyvitamin D [25(OH)D] levels of more than 30ng/mL and the rest of the patients; 61 (87.1%) had serum 25(OH)D levels below 30 ng/ml. Amongst those with low vitamin D, 38 (62.3%) had serum 25(OH)D between 15–30 ng/mL (insufficient), and the remaining 23 (37.7%) had serum 25(OH)D below 15 ng/ml (deficient). Their mean level of serum 25(OH)D was 19.92 ± 9.04 ng/mL with a serum creatinine of 106.23 ± 38.56 µmol/L and mean estimated glomerular filtration rate (eGFR) at 68.11± 27.65 mL/min/1.73 m^2. There was no association between urinary albuminuria, highly sensitive C-reactive protein, estimated glomerular filtration rate or systolic blood pressure with serum 25(OH)D level.

Conclusion: Low vitamin D (insufficiency and deficiency) are indeed prevalent in stable immunoglobulin A nephropathy patients. We found no correlation between the vitamin D levels with albuminuria, renal function and highly sensitive C-reactive.

KEYWORDS:
25-hydroxyvitamin D; vitamin D insufficiency; vitamin D deficiency; immunoglobulin A nephropathy; urine albumin creatinine ratio

INTRODUCTION

IgA nephropathy (IgAN) was first described in 1969 and is one of the most common forms of glomerulonephritis in many countries. In Asia, it accounts for approximately 30–40% of patients undergoing renal biopsy compared to 15–20% in Europe, and 5–10% in North America.[1] In Malaysia, the report from 6th Malaysian Registry of Renal Biopsy 2017 showed that IgAN is the third commonest primary glomerulonephritis at 23.3% after minimal change disease and focal segmental glomerulosclerosis, which contributed about 29.2% and 29.8%, respectively.[2] IgAN is defined histologically by the presence of glomerular immunoglobulin A (IgA) deposits accompanied by a variety of histopathology lesions.

Therefore, the pathogenesis of IgAN appears to be due to mesangial deposition of IgA, causing activation of the mesangial cells. In human, IgA is produced in two forms, IgA1 and IgA2, and is secreted from different mucosal surfaces. There is emerging evidence showing a molecular abnormality in IgAN patients that involves defects in glycosylation of the IgA1 hinge region. Bindings of IgA to mesangial cells are associated with mesangial cells expansion, apoptosis and increased synthesis of extracellular matrix components that can further potentiate glomerular injury. It does also activate complement to enhance the inflammatory cascade and potentiate further glomerular injury in IgA nephropathy.

Vitamin D has been shown to express non-calcaemic effects which are beyond the regulation of calcium and phosphorus. These effects are mediated by the vitamin D receptor (VDR), which includes the regulation of kidney and cardiovascular functions as well as immune systems. Studies have shown that low level of serum 25-hydroxy-vitamin level [25(OH)D] has been significantly associated with a severe decrease in estimated glomerular filtration rate (eGFR) in chronic kidney diseases (CKD).[3,4] Indeed, Framingham study also showed vitamin D deficiency is associated with cardiovascular diseases, and it has consistently shown that vitamin D deficiency increases the risk of myocardial infarction, and independent of classical risk factors such as diabetes and hypertension.[5] Nutrition Examination Survey (NHANES III) cohort showed that individuals with serum 25(OH)D levels lower than 15 ng/ml had a higher risk for all-cause mortality despite adjustments for potential confounders.[6]

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An interesting finding is that vitamin D also has a role in protecting the podocytes in the kidney glomerular and downregulate the renin-angiotensin-aldosterone-system (RAAS).[7] Podocytes were found to express VDR, and experimental animal studies showed that vitamin D has a renoprotective function in the podocytes.[8] These findings can potentially bring the therapeutic value of vitamin D therapy in IgAN, focussing on podocytes and mesangial cell regulation. Clinical studies by Szeto and Liu have shown that supplementation of calcitriol, a vitamin D analogue have been proven beneficial in reducing proteinuria in IgAN.[9,10] With this understanding, it would be interesting to explore the vitamin D levels in IgAN patients and potentially to understand the effect of 25(OH)D therapy in these group of patients. To date, limited studies are exploring issues as mentioned earlier. Therefore, we embarked in this study to evaluate vitamin D levels in a stable IgAN and to correlate the findings with other clinical parameters.

MATERIALS AND METHODS

Biopsy-proven IgAN patients were recruited from the Nephrology Clinic at Hospital Canselor Tuanku Muhriz (HCTM), Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The Research and Ethics Committee, UKMMC approved the study with Research Grant (FF-2018-361). We included patients aged between 18 and 75 years with eGFR more than 30 ml/kg/1.73m^2, whom on a stable dose of immunosuppression and anti-proteinuric medications. Their urinary albumin creatinine ratio (UACR) is between 3 and 300 mg/mmol. We excluded those with active IgAN with nephrotic or nephritic syndrome, acute renal failure, chronic liver disease, malabsorption syndromes, uncontrolled diabetes with glycosylated haemoglobin (HbA1C) > 7.5%, granulomatous disease, pregnant or lactating women and patients who were on medications known to affect vitamin D absorption or metabolism.

The equation of CKD Epidemiology Collaboration (CKD EPI) 4 variables was used to measure eGFR during the study period. Ten millilitres of fasting venous blood were collected for measurement 25(OH)D, highly sensitive C-reactive protein (hs-CRP), and other routine blood tests. Urine was collected for urine dipstick, microscopy, and UACR.

Urinary Albuminuria Measurement and Definition

UACR is a ratio between urine albumin and urine creatinine. UACR was measured using Abbott Architect c8000 analyzer available in UKMMC pathology laboratory according to the manufacturer's protocol as described below. It is classified based on KDIGO CKD guideline 2012; normal to mildly increased (< 3 mg/mmol); moderately increased (3–30 mg/mmol) and severely increased (> 30 mg/mmol).

Serum 25-Hydroxyvitamin D Measurement and Definition

25(OH)D was measured using an electro-chemiluminescent immunoassay (ECLIA) with an Elecsys® Vitamin D total system (Roche Diagnosis Elecsys) according to the manufacturer's protocol. For analysis, 25(OH)D concentration was categorised based on current Kidney Disease Outcomes Quality Initiative guidelines (K/DOQI guidelines, 2003) as; sufficiency (> 30ng/mL); insufficiency (15–30ng/mL) and the deficiency (< 15 ng/mL).

Serum hs-CRP Measurement

Serum hs-CRP value was analysed using immune-turbidometry methods with hsCRP ELISA kits (EU59151) from Hamburg Germany by IBL International Gmb-H company according to the manufacturer's protocol.

Statistical Analysis

Data were analysed using the Statistical Package for Social Science (SPSS) software version 25. Continuous variables were reported as mean ± standard deviation. Categorical variables were reported as frequencies and percentages. To determine the difference between groups, the Pearson Chi-Square test was used for all categorical data. For continuous data, Independent t-test and paired t-test were used. Pearson correlation was used for correlation analysis. Multivariate analyses were performed using binary logistic regression. All statistical tests were two-sided, and an unadjusted p-value of <0.05 was considered significant.

RESULTS

Seventy patients were enrolled in our study, and their baseline demographic data were summarised in Table I. Nearly 88% of our patients were already on RAAS blockade as their treatment which concurred with the current guideline to use this agent as part of IgAN treatment. We found only 9 (12.9%) had sufficient 25(OH)D levels of more than 30ng/mL and the rest of the patients; 61 (87.1%) had serum 25(OH)D levels ≤ 30 ng/mL. Amongst those with low vitamin D (n=61), 38 (62.3%) of them had serum 25(OH)D between 15 and 30 ng/mL (insufficient) and the remaining 23 (37.7%) had serum 25(OH)vitamin D below 15 ng/mL. The mean level of 25(OH)D in this study was 19.92 ± 9.04 ng/mL.

The correlation between serum 25(OH)D and other parameters

In our study, we grouped patients according to the levels of 25(OH) D; > 30 ng/mL (sufficient), 15–30 ng/mL (insufficient) and < 15 ng/mL (deficient). We summarised the relationship between these three groups with their clinical parameters in Table II. There was no difference in their UACR, renal function, blood pressure and hs-CRP (Table II) in the various levels of serum 25(OH)D. Figure 1 illustrates those patients with sufficient 25(OH)D levels has lower UACR compared to those with low serum 25(OH)D levels (insufficient and deficient), but it was statistically not significant (p=0.25). Further analysis on the percentage of those with severely increased UACR (> 30 mg/mmol), there were no differences if we stratified them according to the degree of vitamin D levels (Figure 2). Fifty-six (80%) of our patients has hs-CRP above ≥1mg/ml that would indicate moderate to high risk of inflammation.

Serum 25(OH)D levels did not show any correlation with UACR, eGFR and hs-CRP, but interestingly it has a weak positive correlation with serum creatinine. Meanwhile, only systolic blood pressure (SBP) correlates with eGFR, serum creatinine and hs-CRP (Table III).

DISCUSSION

Vitamin D deficiency is highly prevalent among CKD patients. The prevalence of serum 25(OH)D deficiency in IgA nephropathy was less studied. Our study in this group of

Table I: Baseline characteristics of IgA nephropathy patients (n=?)

Age (years)	49.31 ±12.90
Sex (n, %)	
• Male	23 (32.9)
• Female	47 (67.1)
Race (n, %)	
• Malay	42 (60.0)
• Chinese	24 (34.3)
• Indian	4 (5.7)
Serum 25(OH)D (ng/mL)	19.92 ± 9.04
25-OHD (ng/mL), (n, %)	
-Sufficiency (>30 ng/mL)	9 (12.9)
-Insufficiency (15–30 ng/mL)	38 (54.3)
-Deficiency (<15 ng/mL)	23 (32.8)
UACR (mg/mmol)	74.30 ± 93.98
Albuminuria (n, %)	
-Moderately increased (3–30 mg/mmol)	27 (38.6)
-Severely increased (>30 mg/mmol)	43 (61.4)
Creatinine (µmol/l)	106.23 ± 38.56
eGFR (ml/min/1.73 m2)	68.11± 27.65
Serum albumin (mg/dl)	39.23 ± 3.31
Serum calcium(mmol/l)	2.37 ± 0.01
Serum hs-CRP (mg/ml), n (%)	3.41 ± 4.15
< 1	14 (20.0)
1–3	37 (52.9)
> 3	19 (27.1)
Treatment (n, %)	
• RAAS blockers	62(88.6)
• Immunosuppressant	28(40)

Data are presented as mean ± SD. UACR= urine albumin creatinine ratio, eGFR; estimated glomerular filtration rate; IgAN; IgA nephropathy; RAAS; renin–angiotensin–aldosterone system

Table II: The association between 25(OH)D level and other parameters

Variables	Serum 25-hydroxyvitamin (ng/mL)			*p* value
	>30 (n=9)	15-30 (n=38)	<15 n=23)	
Age (years)	59.00 ±15.19	48.39 ± 11.21	47.04 ± 13.46	0.13
Race (n, %)				
Malay	2(22.2)	24(63.2)	16(69.6)	
Chinese	7(77.8)	13(34.2)	4(17.4)	0.013
Indian	0 (0)	1(2.6)	3(13.0)	
Sex (n, %)				
Male	4(44.4)	13(34.2)	6(26.1)	0.59
Female	5 (55.6)	25(65.8)	17(73.9)	
UACR (mg/mmol)	67.81 ± 64.99	69.97 ± 74.45	90.59 ± 128.18	0.36
Serum albumin (mg/dl)	38.67 ± 2.29	39.68 ± 3.35	38.70 ± 3.59	0.27
Creatinine(µmol/l)	114.60 ± 30.09	111.46 ± 42.22	94.30 ± 33.23	0.41
Mean eGFR (ml/min/1.73 m^2)	57.11 ± 25.05	65.92 ± 26.64	76.04 ± 29.20	0.35
eGFR (n, %)				
CKD stage 1	2(22.2)	12(31.6)	11(47.8)	
CKD stage 2	1(11.1)	7(18.4)	4(17.4)	0.51
CKD stage 3	1(11.1)	7(18.4)	4(17.4)	
CKD stage 4	5(55.6)	12(31.6)	4(17.4)	
hs-CRP (mg/ml)	1.78± 1.84	3.56 ± 4.32	3.80 ± 4.49	0.38
hs-CRP (n, %)				
<1	4(44.5)	6(15.8)	4(17.4)	
1-3	2(22.2)	22(57.9)	13(56.5)	0.28
>3	3(33.3)	10(26.3)	6(26.1)	

UACR= urine albumin creatinine ratio, eGFR = estimated glomerular filtration rate, CKD= chronic kidney disease, hs-CRP= highly sensitive C-Reactive protein.

patients showed 87.1% of our IgAN patients had vitamin D levels ≤ 30ng/ml and only 12.9% were sufficient. This raised the concern of the possibility that low vitamin D is genuinely prevalent in our healthy population. Rozita et al. conducted a study in our institution to explore vitamin D levels among CKD patient compared to a healthy population, and she found 100% of the study participants including the healthy individuals had low serum 25(OH)D (< 30mg/dl).[11]

Nonetheless, Khor et al. who also studied the prevalence of vitamin D deficiency among Malaysians population demonstrated the prevalence of vitamin D insufficiency was

Table III: Pearson correlation coefficients between various parameters in IgAN patients

	25(OH)D	hs-CRP	SBP	DBP
UACR	r = -0.12; p=0.29	r = 0.25; p=0.83	r = 0.34; p=0.05	r = 0.14; p=0.24
eGFR	r = -0.28; p=0.18	r = -0.171; p=0.16	r = - 0.26; p=0.03	r = 0.10; p=0.40
Creatinine	r = 0.31; p=0.01	r = 0.17; p=0.16	r = 0.28; p=0.02	r = 0.23; p=0.85
hs-CRP	r = -0.15; p=0.22	-	r = 0.34; p=0.01	r = 0.14; p=0.24
25(OH)D	-	r = -0.15; p=0.22	r = -0.95; p=0.44	r = -0.83; p=0.49

UACR= urinary albumin creatinine ratio, eGFR= estimated glomerular filtration rate, hs-CRP= highly sensitive C-reactive protein, SBP- systolic blood pressure, DBP – diastolic blood pressure

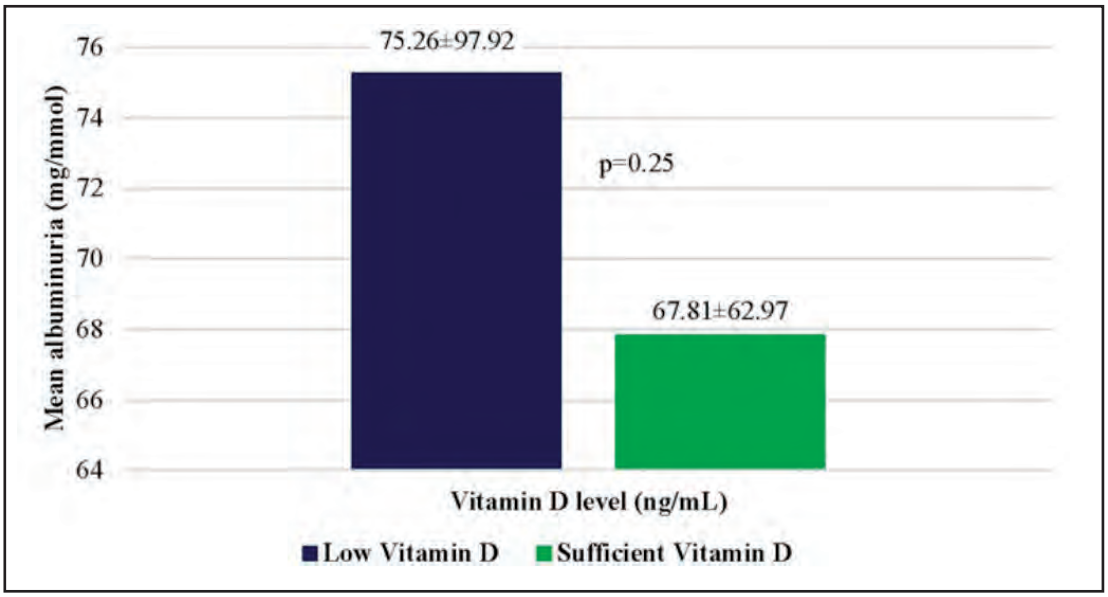

Fig. 1: Albuminuria levels between low vitamin D (< 30 ng/mL) and sufficient vitamin D (> 30 ng/mL)

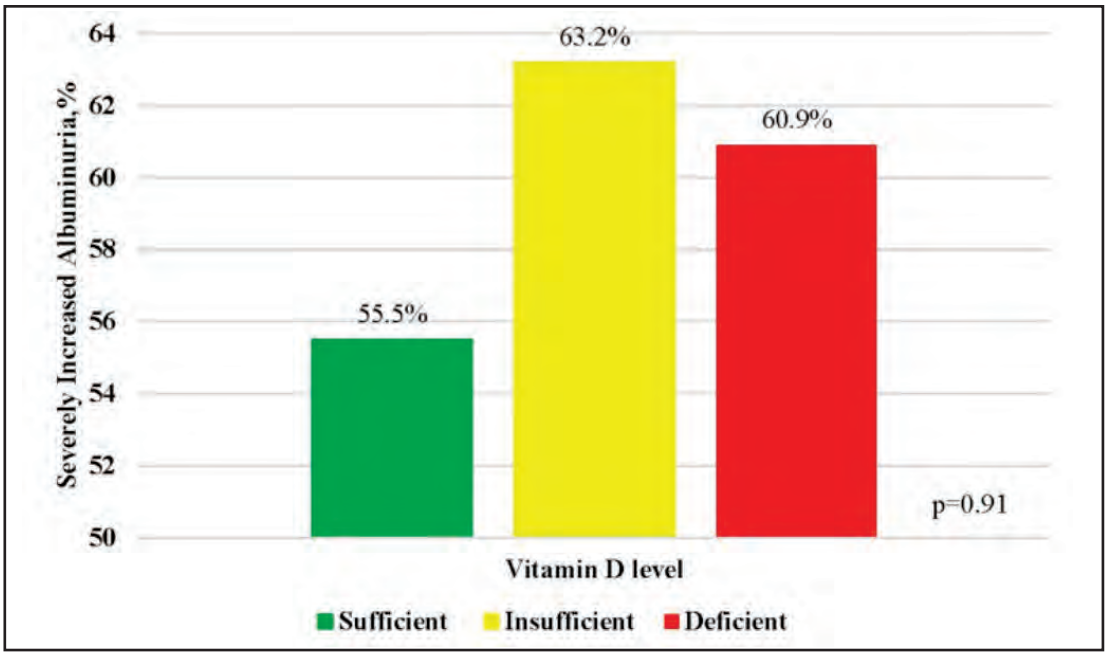

Fig. 2: Percentage of severely increased albuminuria amongst various groups of vitamin D levels

73% among obese primary school children aged 7–12 years old, whereas, Rahman et al. found in post-menopausal women aged 50 to 65 years showed significantly lower in the post-menopausal Malay women (71%) compared to Chinese (11%).[12,13] These are alarming evidence that the prevalence of low vitamin D is high in the general population. As expected, those with CKD also will be at risk, including those with IgAN.

Among the patients with different 25(OH)D levels, we found no significant differences in the severely increased albuminuria. This result is contrary to the previous study by Li et al. 2016, which showed there is an inverse correlation between vitamin D level and albuminuria.[14] Interesting to note in our study that those with low vitamin D (<30 ng/ml) compared to those with sufficient vitamin D levels (>30 ng/ml) showed no significant difference in the mean albuminuria levels; 75.26 ± 97.92 vs 67.81 ± 62.97 mg/mmol (p=0.25). This finding may suggest that the degree of vitamin D levels does not have any effects on the UACR in stable IgA nephropathy patients. Nonetheless, a study with a larger sample size would be needed.

Highly sensitive C-reactive protein (hs-CRP) serves as a marker for systemic inflammation, and it has emerged as the leading inflammatory marker in predictive ability importantly in coronary syndromes. Similarly, Want et al. showed that vitamin D deficiency is associated with incident cardiovascular disease.5 Several studies have also proposed vitamin D receptor (VDR) activation inhibits renal inflammation by promoting VDR-mediated sequestration of nuclear factor κB signalling.[15,16] There were studies which utilised hs-CRP as a marker of inflammation in IgAN; however, their results were inconsistent. Nelson et al. and Kaartinen showed increased hs-CRP levels in early IgAN, and it is a marker of kidney disease progression, but Baek et al. showed that hs-CRP was not elevated in IgAN.[17-19] In this study, we also measured hs-CRP as a biomarker of inflammation, and we found that 80% of our patients had hs-CRP of more than 1 mg/ml. Our result on hs-CRP concurred with Kaartinen at al. and Nelson et al.[17,18] Overall, the result indicates that generally, IgAN patients have increased systemic inflammation even though in our study population, their disease is in a stable state. These findings concurred with the notion that IgAN is an auto-immune disease and potentially also has an increased cardiovascular risk. Chronic inflammatory state in CKD patients is a topic of interest amongst many researchers. Mustafar et al.[20] also found raised hs-CRP in 70% of CKD patients with low serum 25(OHD). However, in this study population with IgAN, we did not find any significant association or serum 25(OH)D with the hs-CRP level.

Low level of serum vitamin D was consistently prevalent in CKD patients due to the reduced eGFR. However, in this study amongst the IgAN patients with mean eGFR > 60ml/min/1.73m^2, we found 87.1% had low serum 25(OH)D as well. A study by Li et al. suggested that the plasma 25(OH)D level at the time of initial diagnosis is a possible independent inverse-predictor of IgAN progression.[14] Another study also found that baseline level of 25(OH)D was significantly correlated with eGFR and showed an inverse correlation between the 25(OH)D level and proteinuria.[4] Additional to that, blood pressure showed an inverse relationship with 25(OH)D level in several epidemiological studies.[6,21] Our observation failed to show such correlations. We found there was no correlation among baseline eGFR, UACR, blood pressure, hs-CRP and 25(OH)D level. This could be due to our small sample size. SBP has shown a positive correlation with UACR, creatinine and hs-CRP. It showed a negative correlation with eGFR. These are the classical association that has been demonstrated by several kidney studies.

CONCLUSION

Our study has clearly shown the high proportion of low vitamin D in IgA nephropathy patients; however, we are not able to describe any significant correlation between the vitamin D levels with other parameters especially the albuminuria in this stable patient. The significance of low vitamin D in our patients may explain the chronic inflammatory state, and as shown in our result, 80% had serum hs-CRP of more or equal to 1mg/ml. It will be interesting to evaluate the effect of correcting low vitamin D levels in these patients' cohort and observing the improvement of disease progression indices. Given such a high prevalence of low vitamin D levels in our study population, our findings needed to be confirmed by another more extensive study. The effects of vitamin D replacement in reducing proteinuria will be interesting to explore, and it is beyond the scope of this paper.

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REFERENCES

1. Huang HD, Lin FJ, Li XJ, Wang LR, Jiang GR. Genetic polymorphisms of the renin-angiotensin-aldosterone system in Chinese patients with end-stage renal disease secondary to IgA nephropathy. Chin Med J (Engl) 2010; 123(22): 3238-42.
2. Rosnawati Yahya, Anita Bhajan Manocha, Yee S Y, Rizna A C, Thong K M, Lee M L, et al. 6th Report of the Malaysian Registry of Renal Biopsy (MRRB). 2019(0300–5283 (Print)).
3. Ravani P, Malberti F, Tripepi G, Pecchini P, Cutrupi S, Pizzini P, et al.Vitamin D levels and patient outcome in chronic kidney disease. Kidney Int 2009; 75(1): 88-95.
4. Satirapoj B, Limwannata P, Chaiprasert A ,Supasyndh O,Choovichian P. Vitamin D insufficiency and deficiency with stages of chronic kidney disease in an Asian population. BMC Nephrol 14, 206 (2013).
5. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008; 117(4): 503-11
6. Scragg R, Sowers MF, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the third national health and nutrition examination survey. Am J Hypertens 2007; 20(7): 713-19.

7. Vaidya A, Williams JS. The relationship between vitamin D and the renin-angiotensin system in the pathophysiology of hypertension, kidney disease, and diabetes. Metabol Clin Exp 2012; 61(4): 450-58.
8. Matsui I, Hamano T, Tomida K, Inoue K, Takabatake Y, Nagasawa Y, et al. Active vitamin D and its analogue, 22-oxacalcitriol, ameliorate puromycin aminonucleoside-induced nephrosis in rats. Nephrol Dial Transplant 2009; 24(8): 2354-61.
9. Szeto CC, Chow KM, Kwan BC, Chung KY, Leung CB, Li PK. Oral calcitriol for the treatment of persistent proteinuria in immunoglobulin A nephropathy: an uncontrolled trial. Am J Kidney Dis 2008; 51(5): 724-31.
10. Liu LJ, Lv JC, Shi SF, Chen YQ, Zhang H, Wang HY. Oral calcitriol for reduction of proteinuria in patients with IgA nephropathy: a randomized controlled trial. Am J Kidney Dis 2012;59(1):67-74.
11. Rozita M, Noorul Afidza M, Ruslinda M, Cader R, Halim AG, Kong CT, et al. Serum Vitamin D levels in patients with chronic kidney disease. EXCLI J 2013; 12: 511-20.
12. Khor GL, Chee WS, Shariff ZM, Poh BK, Arumugam M, Rahman JA, et al. High prevalence of vitamin D insufficiency and its association with BMI-for-age among primary school children in Kuala Lumpur, Malaysia. BMC Public Health 2011; 11: 95.
13. Rahman SA, Chee WS, Yassin Z, Chan SP. Vitamin D status among postmenopausal Malaysian women. Asia Pac J Clin Nutr 2004; 13(3): 255-60.
14. Li XH, Huang XP, Pan L, Wang CY, Qin J, Nong FW,et al. Vitamin D deficiency may predict a poorer outcome of IgA nephropathy. BMC Nephrol 17, 164 (2016).
15. Penfold RS, Prendecki M, McAdoo S, Tam FW. Primary IgA nephropathy: current challenges and future prospects. Int J Nephrol Renovasc Dis 2018; 11: 137-148.
16. Tan XY, Wen XY, Liu YH. Paricalcitol inhibits renal inflammation by promoting vitamin D receptor-mediated sequestration of NF-kappa B signaling. J Am Soc Nephrol 2008; 19(9): 1741-52.
17. Nelson CL, Karschimkus CS, Dragicevic G, Packham DK, Wilson AM, O'Neal D, et al. Systemic and vascular inflammation is elevated in early IgA and type 1 diabetic nephropathies and relates to vascular disease risk factors and renal function. Nephrol Dial Transplant 2005; 20(11): 2420-6.
18. Kaartinen K, Syrjänen J, Pörsti I, Hurme M, Harmoinen A, Pasternack A, et al. Inflammatory markers and the progression of IgA glomerulonephritis. Nephrol Dial Transplant 2008; 23(4): 1285-90.
19. Baek JE, Chang JW, Min WK, Cho YM, Park JS, Kim SB. Serum high-sensitivity C-reactive protein is not increased in patients with IgA nephropathy. Nephron Clin Pract 2008; 108(1): c35-40
20. Mustafar RB, Mohd R, Miswan NA, Bain A, Cader R, Gafor AH, et al. The effects of calcitriol with calcium carbonate supplementation on inflammatory biomarkers in chronic kidney disease patients' with low vitamin D. Cent Eur J Immunol 2014; 39(2): 236-42
21. Hintzpeter B, Mensink GB, Thierfelder W, Müller MJ, Scheidt-Nave C. Vitamin D status and health correlates among German adults. Eur J Clin Nutr 2008; 62(9): 1079-89.

ORIGINAL ARTICLE

Terbutaline for acute tocolysis prior to emergency caesarean delivery for suspected foetal compromise

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ABSTRACT

Introduction: Terbutaline has been used as a foetal resuscitation measure to improve the intrapartum foetal heart rate abnormalities and neonatal outcome for suspected foetal compromise. Unfortunately, till date, the available data are limited to draw any recommendation.

Material and Methods: This was a double-blind, placebo-controlled trial conducted among women planned for emergent caesarean delivery for suspected foetal compromise where 100 were randomised to receive subcutaneous terbutaline or placebo. The primary outcomes were the neonatal acid–base status, while the 5-minute Apgar score, admission to the intensive care unit and the maternal outcomes were recorded as secondary outcomes.

Results: Data from a total of 96 women were analysed and showed a lower incidence of neonatal acidemia (4.4% vs 10.4%) and fewer neonates born with umbilical artery pH of less than 7.20 (12.5% vs 27.1%) and 7.10 (4.2% vs 6.2%) after terbutaline injection. However, the difference in the incidence of neonatal acidaemia, mean cord pH and base excess, Apgar score or admission to the intensive care unit did not differ significantly. No difference was seen in the maternal mean arterial pressure, estimated blood loss or haematocrit after the surgery between the study groups. The only significant maternal effect was tachycardia which was more common after terbutaline injection (54.2% vs 25.0 %, p=0.003).

Conclusion: The study shows that acute tocolysis with subcutaneous terbutaline prior to caesarean delivery has the potential to improve the neonatal outcome in suspected intrauterine foetal compromise and should be further investigated.

KEYWORDS:
Foetal resuscitation; acute tocolysis; foetal compromise; terbutaline; caesarean section

INTRODUCTION

The National Institute for Clinical and Health Excellence (NICE) has recommended that emergency caesarean section should be completed within 30–75 minutes of decision depending on the risk assessed.[1] These targets may not be achieved for various reasons, including the unavailability of the operation theatre. In such a situation, intervention(s) that can increase the oxygen delivery to the placenta and umbilical blood flow, alleviating the insult(s) and improving the outcome of the neonate would be of tremendous value. One of these is acute tocolysis which by relaxing the myometrium could reduce the ischaemic effect of contraction on the uteroplacental blood flow.[2] Numerous medications had been investigated, such as terbutaline, atosiban, hexoprenaline, sildenafil, fenoterol bromhydrate, ritodrine, magnesium sulphate and nitroglycerine but the outcome varies.[3-9]

Improvement in the cardiotocography (CTG) patterns and neonatal umbilical artery pH had been demonstrated after subcutaneous terbutaline injection in a small randomised trial.[4] Similar results were also demonstrated in a retrospective cohort study comparing intravenous terbutaline and no intervention, where significantly fewer neonates with low Apgar score and higher umbilical cord pH were seen in the intervention group.[10] In another trial, acute tocolysis with subcutaneous terbutaline was associated higher percentage of abnormal cardiotocography resolution and fewer babies with umbilical cord pH of less than 7.20, compared with intravenous magnesium sulphate.[11] However, these studies were limited by the small sample sizes, retrospective study design and/or non-placebo controlled.[12] Here, we present results of a double-blind, placebo-controlled, randomised trial using subcutaneous terbutaline as a form of intrauterine resuscitation for cases of suspected foetal compromise.

MATERIALS AND METHODS

Between January and December 2017, all women with a singleton pregnancy at term admitted in the active phase of labour in our hospital were invited to participate in a placebo-controlled, randomised trial. Once the diagnosis of suspected foetal compromised in first stage of labour was made based on the abnormal foetal heart rate monitoring (cardiotocography) according to NICE 2014 guideline and the delivery via caesarean section was planned, the participants were randomised to receive either subcutaneous terbutaline or equivalent volume of placebo.[13]

The women were excluded if they have cardiomyopathy, hyperthyroidism, abruptio placentae or other placental accidents, hypertensive disease of pregnancy, hyperstimulation with oxytocin, multiple gestation, abnormal foetus planned for conservative management,

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evidence of intrauterine growth restriction or on medication that will interact with terbutaline (tricyclic antidepressants, beta-blockers, diuretics and sympathomimetic medicine).

Consented women in the intervention group received 0.25 mg subcutaneous terbutaline while the control group was injected an equivalent volume (0.5 mls) of placebo by a nurse who prepared the solutions in a treatment room, separated from the labour suites. The obstetricians who ordered the intervention, the surgeons who performed the caesarean section, the anaesthetists, the neonatologists and the patients themselves were blinded to the injection given.

The primary objective was to determine if the pre-caesarean delivery tocolysis can reduce the incidence of acidosis in the neonatal umbilical artery. Acidosis in the umbilical artery is defined as pH level 7.00 or less and a base excess (BE) < –8 mmol/L.[14] The mean pH value, base excess, low Apgar score (less than 7) at 5 minutes of life and the need for admission to the neonatal intensive care unit (NICU) or special care nursey (SCN) were recorded as secondary outcomes. Other investigated outcomes were the maternal effects related to the interventional drug, which are the changes in mean arterial pressure and heart rate (before and 10 minutes after the drug or placebo injection), the estimated blood loss and the changes in the haematocrit level before and after the surgery. Maternal characteristics such as age, parity and gestational age were also recorded, together with induction and augmentation of labour. The neonatal birthweight, the colour of the amniotic liquor and interval between the decision for caesarean delivery, subcutaneous injection and the delivery of the neonate were also analysed. This trial methodology was based on the Consolidated Standards of Reporting Trials statement (http://www.consortstatement.org/consort-statement/).

Reported incidence of neonatal umbilical artery acidosis varies, depending on the level of cord pH and/ base excess used in the definition, ranging from 1.4% to 20%.[15,16] Taking the estimated neonatal acidaemia in cases of suspected foetal distress as 18%, samples required to show 50% reduction with the intervention, were calculated to be 247 in each arm (with 80% power and at 95% confidence) and was estimated to take more than 2 years to complete in our centre. Compromising on these, we had decided to include 110 women in each arm to achieve the study power of 50% and the recruitment was expected to be completed within a year. However, the Medical Research and Ethics Committee only approved 100 participants in total. The randomisation sequence was in random blocks of ten with a 1:1 ratio, generated by using a computerised random generator (www.random.org) and the blinding was secured using sealed opaque envelopes containing a random number and instruction for active drug or placebo administration. Mean and standard deviation were calculated for the qualitative variables and analysed using Student t test while the qualitative data were reported as percentage and analysed using chi-square test or Fisher exact test when necessary. Data handling and analysis were performed using Statistical Package for Social Science (SPSS) version 22 (SPSS Inc, Chicago, IL, USA) software with p-value of less than 0.05 considered to indicate statistical significance.

The study is registered with National Medical Research Register, Ministry of Health Malaysia (NMRR-16-1985-33115 (IIR)) and had received the approval of Medical Research & Ethic Committee, Ministry of Health Malaysia on 20th February 2017 (((23) KKM/NIHSEC/ P16-1613). The protocol was registered in Clinical Trail Registry (NCT05326269) and the study complies with the Declaration of Helsinki.

RESULTS

In 2017, there were 4063 deliveries in our centre where 136 (from a total of 649) were caesarean section for foetal distress in 1st stage of labour. Of the 100 women randomised in this trial, one in the control group delivered vaginally in the operation theatre and three others (one from the control and two from the intervention group) had incomplete data, hence were excluded from the analysis. The women's characteristics and delivery progress are depicted in Table I, where no significant differences were seen between these two groups. More women in the terbutaline group had received labour induction and augmentation but the differences were not significant. It is to note that the average interval between the injections and delivery of the babies was 39 minutes in both groups while the mean decision to delivery time was 50 minutes in the terbutaline group and 48 minutes in the control group (p=0.755).

Neonates delivered in both groups had a similar mean birthweight, although more babies in the terbutaline group were small for gestational age (p=0.140). The incidence of neonatal acidosis was 4.2% and 10.4% in the terbutaline and placebo group, respectively; however, this difference was not statistically significant. The mean umbilical cord pH and base excess also did not differ between the groups (Table II). Two neonates had an umbilical cord pH of 7.00 or less at delivery (one in each group) and 25 had a base excess of less than -8.0 (thirteen in the terbutaline group). Even though there was no difference in mean cord pH and base excess, there were less babies in the intervention cohort that had the cord pH of less than 7.20 and 7.10 (Table III).

All 96 neonates had Apgar score of at least 7 at 5 minutes of life, and there was no significant difference in mean score between the groups. There was no perinatal death recorded in this study and no difference in the percentage of babies requiring admission to the NICU and SCN (Table II). Majority of these admissions were for respiratory-related issues such as suspected congenital pneumonia, meconium aspiration syndrome and transient tachypnoea of newborn.

Table IV shows the maternal outcomes related to the use of subcutaneous terbutaline or placebo. We found that significantly more women had tachycardia in the intervention group but the mean pulse rate and arterial pressure after the injections did not differ. Five women who were given terbutaline and four receiving the placebo had the estimated blood loss of more than 1000 ml, with highest blood lost recorded in both groups was 2 L. Despite so, no differences in the mean estimated blood loss and haematocrit changes after the surgery were noted.

Table I: Maternal demographic and labour characteristics

	Terbutaline (n=48)	Placebo (n=48)	*p* value
Maternal age (years), mean (SD)	27.4 (5.6)	28.8 (5.8)	0.444
Gravidity, mean (SD)	2.3 (1.7)	2.1 (1.1)	0.559
Nulliparous, n (%)	24 (50.0)	22 (45.8)	0.683*
Gestational age at delivery (weeks), mean (SD),	39.1 (1.1)	39.4 (1.1)	0.598
Duration of first stage of labour (minutes), mean (SD)	239.2 (117.4)	239.0 (186.2)	0.059
Induction of labour, n (%)	20 (41.7)	15 (31.3)	0.298*
Oxytocic augmentation, n (%)	34 (70.8)	27 (56.2)	0.138*
Interval of injection to delivery (minutes), mean (SD)	39.4 (13.2)	39.5 (14.2)	0.880
Interval of decision to delivery (minutes), mean (SD)	50.0 (16.1)	48.7 (14.8)	0.755
Decision to delivery 30 minutes or less, n (%)	4 (8.3)	2 (4.2)	0.399*
Meconium-stained amniotic liquor, n (%)	9 (18.7)	10 (20.8)	0.798*
Atypical variable deceleration, n (%)	30 (62.5)	26 (54.2)	0.408*

Analysed with t-test unless stated; *Chi-square test.

Table II: Neonatal outcomes

	Terbutaline (n=48)	Placebo (n=48)	*p* value
Birth weight (gm), mean (SD)	2922 (436)	3039 (335)	0.970
Small for gestational age, n (%)	4 (8.3)	2 (4.1)	0.140*
Acidosis, n (%)	2 (4.2)	5 (10.4)	0.435**
Umbilical cord pH, mean (SD)	7.25 (0.80)	7.23 (0.12)	0.269
Umbilical cord base excess, mean (SD)	-6.42 (3.74)	-6.11 (3.50)	0.673
Neonatal Apgar score at 5 minutes of life, mean (SD)	9.8 (0.7)	9.7 (0.8)	0.580
Number of NICU admission, n (%)	27 (56.2)	28 (58.3)	0.837*
Admission for respiratory problem, n (%)	24 (50.0)	25 (52.1)	0.838*

Analysed with t-test unless stated; *Chi-square test; ** Fisher exact test.

Table III: Neonatal umbilical artery parameters

	Terbutaline (n=48)	Placebo (n=48)	*p* value
Umbilical cord pH			
< 7.2	12.5%	27.1%	0.073*
<7.1	4.2%	6.3%	0.500**
<7.0	2.1%	2.1%	-
Umbilical cord base excess			
<-12.0	8.3%	4.2%	0.677**
<-10.0	12.5%	14.6%	0.765*
<-8.0	27.1%	25.0%	0.816*

*Chi-square test; ** Fisher exact test.

Table IV: Maternal outcomes

	Terbutaline (n=48)	Placebo (n=48)	*p* value
Maternal mean arterial pressure (mmHg), mean (SD)¥	95.6 (15.3)	96.2 (12.2)	0.228
Maternal heart rate (bpm), mean (interquartile range)¥	100 (90-108)	90 (80-99)	0.425
Maternal tachycardia, n (%)¥	26 (54.2)	12 (25.0)	0.003*
Additional uterotonic, n (%)	6 (12.5)	7 (14.6)	0.765*
Estimated blood loss (mL), mean (interquartile range),	597.9 (325-800)	584.4 (300-600)	0.693
Postpartum hemorrhage > 1 L, n (%)	5 (10.4)	4 (8.3)	0.726*
Maternal haematocrit difference (%), mean (SD)	4.8 (3.8)	4.3 (3.2)	0.923

Analysed with t-test unless stated. bpm, beat per minute; ¥ At 10 minutes after injection; *Chi-square test.; Significant p value indicated in bold.

DISCUSSION

The study was conceived to investigate the use of acute tocolysis to improve the neonatal outcome in cases of suspected intrapartum foetal compromise, as it was one of the most common indications for caesarean delivery. In 2016-17, more than one-third of the caesarean sections in Malaysia was performed for this indication.[17] A positive result would tremendously help the management of intrapartum foetal distress especially in hospitals without dedicated obstetric operation theatre such as ours. During the trial, the mean decision to delivery time was 49 minutes, and only 6.3% of the deliveries were completed within 30 minutes. Effective intrapartum resuscitation would also benefit cases from non-specialist hospitals that need to be transferred to other facilities for operative deliveries.

Terbutaline was chosen as it had been shown to be effective in reducing uterine tone in low-dose subcutaneous administration, of which the effect can be seen within 2 minutes of the injection.[10] Furthermore, studies have shown that a single subcutaneous dose is also associated with minimal side effects.[10,18] Our results support the safety of subcutaneous administration with no significant maternal effects except for tachycardia, which did not cause a significant prolonged effect.

Earlier evidence had shown that terbutaline was associated with improvement or resolution of abnormal CTG patterns in more than 70% of intrapartum foetal distress.[8,10] Our study was designed to look a step further, that is, the neonatal outcomes, where the number of neonates with umbilical cord acidosis in the intervention group was less than half of the placebo group. Even though the difference is not statistically significant, the finding did show the possible positive effect of an intrauterine intervention.

The mean umbilical cord pH and base excess, however, are not statistically different. Similar findings were also seen in a recent prospective audit report from Sydney.[19] Buckley et al investigated the neonatal outcomes after the introduction of a practice of administrating subcutaneous terbutaline prior to emergent caesarean delivery. The authors reported no difference in neonatal cord pH and base excess before and after the policy implementation. However, the study was not a randomised trial and only about 60% of the caesarean deliveries were performed for foetal distress; hence, drawing a definite conclusion is not possible.

Previous workers had demonstrated that acute tocolysis with terbutaline prior to caesarean delivery could reduce the incidence of low neonatal Apgar score at 5 minutes of life (from 14% to 6.8%).[5] In contrary, none of the neonates born within our trial had low Apgar score and no difference was seen in the mean 5 minutes Apgar score and NICU/ SCN admission. A larger study population could, however, give a different picture.

Despite these findings, the strength of this study lies in its design, of which to date, is the only published double-blind, placebo-controlled randomised trial investigating subcutaneous terbutaline for acute tocolysis prior to emergency delivery. It was, unfortunately, limited by the small sample size allowed by the ethic committee and the lower-than-expected incidence of neonatal acidosis (7.3%). In fact, if a lower base excess value is used for the definition of neonatal acidosis (pH < 7.00 and base deficit >12 mmol/l), the incidence would be much lower at 2.1%.[20]

Yet, it is not all lost concerning acute tocolysis for suspected foetal distress. Data from other investigators did show significantly higher mean neonatal umbilical cord pH in groups receiving terbutaline for foetal compromised diagnosed with foetal scalp pH, especially when the pH is less than 7.25.[4,11] Other than the lower incidence of neonatal acidosis, our data demonstrated that fewer babies were born with cord pH of less than 7.10 and 7.20 in the terbutaline group. These findings suggest that further research with larger samples could shed some light on this promising intervention. We hope these findings could motivate other researchers to pursue this subject.

CONCLUSION

Acute tocolysis with subcutaneous terbutaline prior to caesarean section is a safe intervention and has the potential to improve the acid–base status of suspected compromised foetuses. Even though our data could not confidently support this postulation, further trials with refined protocols and bigger sample sizes may give a different result.

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REFERENCES

1. National Institute for Health and Clinical Excellence. Caesarean section (update). (Clinical guideline 132). 2011. Available from: http://guidance.nice.org.uk/CG132.
2. Mendez-Bauer C, Shekarloo A, Cook V, Freese U. Treatment of acute intrapartum fetal distress by beta 2-sympathomimetics. Am J Obstet Gynecol 1987; 156: 638-42.
3. Gerris J, Thiery M, Bogaert M, De Schaepdryver A. Randomized trial of two beta-mimetic drugs (ritodrine and fenoterol) in acute intra-partum tocolysis. Eur J Clin Pharmacol 1980; 18: 443-8.
4. Patriarco MS, Viechnicki BM, Hutchinson TA, Klasko SK, Yeh SY. A study on intrauterine fetal resuscitation with terbutaline. Am J Obstet Gynecol 1987;157(2): 384-7.
5. Vigil-De Gracia P, Simiti E, Lora Y. Intrapartum fetal distress and magnesium sulfate. Int J Gynecol Obstetr 2000; 68(1): 3-6.
6. Afschar P, Scholl W, BaderA, Bauer M, Winter R. A prospective randomised trial of atosiban versus hexoprenaline for acute tocolysis and intrauterine resuscitation. BJOG 2004; 111(4): 316-8.
7. Briozzo L, Martinez A, Nozar M, Fiol V, Pons J, Alonso J. Tocolysis and delayed delivery versus emergency delivery in cases of non-reassuring fetal status during labor. J Obstet Gynaecol Res 2007; 33(3): 266–73.
8. Pullen KM, Riley ET, Waller SA, Taylor L, Caughey AB, Druzin ML, et al. Randomized comparison of intravenous terbutaline vs nitroglycerin for acute intrapartum fetal resuscitation. Am J Obstetr Gynecol 2007; 197(4): 414.e1–.e6.
9. Dunn L, Flenady V, Kumar S. Reducing the risk of foetal distress with sildenafil study (RIDSTRESS): a double-blind randomised control trial. J Transl Med 2016; 14(1): 15.

10. Magann EF, Cleveland RS, Dockery JR, Chauhan SP, Martin JN, Morrison JC. Acute tocolysis for fetal distress: terbutaline vs magnesium sulphate. Australian and New Zealand J Obstetr Gynaecol 1993; 33: 362-4.
11. Cook VD, Spinnato JA. Terbutaline tocolysis prior to cesarean section for fetal distress. J Matern Fetal Med 1994; 3: 219-26.
12. Leathersich SJ, Vogel JP, Tran TS, Hofmeyr GJ. Acute tocolysis for uterine tachysystole or suspected fetal distress. Cochrane Database Syst Rev 2018; CD009770.
13. National Institute for Health and Clinical Excellence. Intrapartum care: care of healthy women and their babies during childbirth. (Clinical guideline 190). 2014. Available from: http://guidance.nice.org.uk/CG190.
14. Cahill AG, Roehl KA, Odibo AO, Macones GA. Association and prediction of neonatal acidemia. Am J Obstet Gynecol 2012; 207(3): 206.e1–8.
15. Gilstrap 3rd LC, Hauth JC, Hankins GD, Beck AW. Second-stage fetal heart rate abnormalities and type of neonatal acidemia. Obstet Gynecol 1987; 70(2): 191-5.
16. Sabol BA, Caughey AB. Acidemia in neonates with a 5-minute Apgar score of 7 or greater - What are the outcomes? Am J Obstet Gynecol 2016; 215(4): 486.e1-6.
17. Ravichandran J, Shamala DK. Report of National Obstetrics Registry, 2011-2012. National Obstetrics Registry. 2015. Available from: http://www.acrm.org.my/nor/doc/reports/5th_NOR_Report.pdf
18. El-Sayed YY, Pullen K, Riley ET, Lyell D, Druzin ML, Cohen SE, et al. Randomized comparison of intravenous nitroglycerin and subcutaneous terbutaline for external cephalic version under tocolysis. Am J Obstet Gynecol 2004; 191(6): 2051-5.
19. Buckley VA, Wu J, De Vries B. Outcomes following acute tocolysis prior to emergency caesarean section. Aust N Z J Obstet Gynaecol 2020; 60(6): 884-89.
20. MacLennan A. A template for defining a causal relationship between acute intrapartum events and cerebral palsy: International consensus statement. Int Cerebral Palsy Task Force. Aust N Z J Obstet Gynaecol 2000; 40(1): 13-21.

Natural fixatives alternative to formalin in histopathology: A systematic review

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ABSTRACT

Introduction: Since constant long-term exposure to formaldehyde endangers the health of laboratory personnel, sugar-based natural products have become interesting alternative fixatives to formaldehyde because of their preservative and antibacterial properties. However, there are controversial findings on the fixative effects of natural fixatives. This study systematically reviews the evidence comparing natural fixatives' types, dilutions, fixative properties and staining quality in normal tissues and histopathological specimens.

Materials and methods: A comprehensive search was performed for studies comparing the natural fixatives- and formaldehyde-fixed tissues using databases from inception to January 2022: PubMed, Ovid Medline and Google Scholar. Two independent reviewers did data extraction. The data were pooled for the type of natural fixatives, their concentrations and fixative qualities compared to formaldehyde.

Results: Fifteen studies were included in this systematic review. Nine studies used one natural fixative with different dilutions, while six used several natural fixatives to compare their fixative properties with formaldehyde. The most used natural fixative was honey (n = 12) followed by jaggery (n = 8), sugar (n = 3) and others (n = 1). Honey showed the most promising results in fixation and staining, which are compatible with formalin. Jaggery and sugar also showed the possibility of replacing formaldehyde in tissue fixation and staining in smaller tissue samples.

Conclusion: Natural fixatives showed promising results in tissue fixation. However, optimising the concentrations and conditions of natural fixatives is difficult because of the different chemical constituents and production steps. More comprehensive studies are necessary for application.

KEYWORDS:
Natural fixatives; sugar-based fixatives; honey fixatives; histopathological practice

INTRODUCTION

Fixation is a crucial step in any histopathology setting. Fixation allows tissue sections to be studied microscopically by preserving tissues and preventing bacterial putrefaction or autolysis.[1] Discovered in the 18th century, formaldehyde is used as a gold standard fixative in routine histopathology, with excellent preservative properties. Antiseptic and antiperspirant features were also observed in formalin, encouraging its use in anatomical and histological settings.[2] As formalin is cost-effective and highly efficient, there is hardly a need to seek an alternative to the 'gold-standard' fixative.[3] Despite its benefits, formalin has been known for many years as a potent irritant of the skin and nasal cavity, and it is cytotoxic at high doses. It is considered a carcinogen for nasopharyngeal,[4] and lymphatic and haematopoietic cancers, including leukaemia.[5] Due to its hazardous nature, numerous natural fixatives have been studied to seek an alternative to formalin fixatives. The Occupational Safety and Health Administration (OSHA) has greatly encouraged ongoing research to look for a safer and eco-friendly replacement to formalin fixatives.[6]

Natural products such as honey, sugar and jaggery have preservative properties.[7] Natural fixatives are low-cost, non-toxic and eco-friendly, making them suitable for routine laboratory usage.[6,8] Honey has antibacterial and dehydrating properties.[9-11] Anti-autolysis and tissue hardening qualities were also highlighted in the use of honey.[9] In addition, scientific studies have proven that natural fixatives can preserve tissue morphology similarly to formalin with no interferences to routine processing and staining.[6]

As theorised based on the study made by Patil et al., fructose present in natural fixatives creates a low pH environment which would result in a breakdown process to form aldehydes which then cross-link with tissue amino acids present for tissue fixation to occur. This possible fixation mechanism is similar to the action of formaldehyde, providing evidence that natural fixatives can be used as an alternative to formalin.[7,12]

A study conducted by Chittemsetti et al. compared the fixative ability of both khandsari and jaggery, sugar cane derivatives. Their results showed that tissue sections fixed in khandsari provided promising results regarding cytoplasmic staining, nuclear details and staining quality. This demonstrates that natural fixatives can replace the use of formalin.[13] There are several studies regarding alternative fixatives, and some of them showed promising results.

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However, formaldehyde is still used in daily clinical practice because most studies' results are obscure and conflicting and need robust research.

In modern health care, systematic reviews are used to appraise evidence, and information policy, construct guidelines and assess the cost-effectiveness of interventions.[14] This systematic review aims to elucidate the spectrum of natural fixatives and their efficacy in tissue preservation. With scientific evidence, this study can establish safer, eco-friendly natural fixatives alternatives to formaldehyde.

MATERIALS AND METHODS

Literature Search

The search strategy followed the Cochrane guidelines, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), for systematic review.[14] The articles included in this review were extracted from PubMed, Ovid Medline and Google scholar databases, and backreferences of the articles till 31st March 2021. The internet search was also done to enhance the inclusion of the relevant articles. The studies which assessed and compared the efficacy of natural fixatives, such as honey, sugar, cane and khandsari, were included in this study. The titles and abstracts of articles were systematically screened by two independent researchers at all stages and identified eligible studies. The search included terms ('natural fixatives' OR 'sugar fixatives' OR 'honey fixatives' OR 'Jaggery fixative' OR 'sugar cane fixatives' OR 'khandsari fixatives') AND ('tissue morphology') AND ('nucleic acid' OR 'DNA' OR 'RNA') AND ('protein'). In addition, an internet search was also done using the above-mentioned keywords.

Study Selection

Studies were included if: (1) they were original studies that evaluated the use of natural fixatives in tissue samples (both human and animal) as an alternative to formaldehyde; (2) they were published in English. Studies were excluded if (1) they were review articles, case reports, case series, conference abstracts, editorials, letters to the editor and commentaries; (2) they were published in languages other than English.

Two independent authors (AYWL and PSO) screened titles and abstracts of all collected articles and then evaluated the full text of studies that met inclusion criteria. A third author (SNA) resolved disagreements at both screening stages. Eligible articles were included based on the pre-specified criteria, and references were screened to retrieve additional studies.

Quality Assessment of Included Articles

All studies were evaluated for quality assessment with NHLBI Study Quality Assessment Tools. The credibility of the knowledge produced, and the product's usefulness determined the quality of the evidence recorded.

Data Extraction

Extracted data included the name of the first author, publication year, country of the study, tissue type, fixative type, morphological analysis and protein and nucleic acid (DNA/RNA) level. One reviewer (AYWL) extracted the data and confirmed it by an independent reviewer (PSO).

RESULTS

Study Selection Process

Initially, 468 studies were recovered from three databases (PubMed: 295, Ovid Medline: 83, google scholar: 90). A total of 450 articles were excluded based on the exclusion criteria by screening the title and abstract. A total of 18 relevant articles were collected after excluding the duplication. Three articles were added from the google search. After reviewing full articles, six were excluded, as formaldehyde was not used as a control experiment, lacked histological analysis, deviated from standard tissue processing, or had incomplete result interpretation. Fifteen articles were finalised to review; data were collected and tabulated from each article, and results were verified and interpreted (Figure 1).

Study Characteristics

The present review included the studies published between 2008 and 2021. Based on geographical location, nine studies were from India, two from Oman and one from Nepal, Nigeria, Thailand and Turkey. All articles described the results of cross-sectional studies (Table I, Figure 2).

Nine studies (60%) tested the natural fixatives in human samples, while 6 (40%) studies used animal samples. Human tissue samples included oral mucosa, gingiva, lymphoid, salivary gland, fat, muscle, skin, endometrium, breast, placenta, uterus, omentum, suprarenal gland, stomach, lung, etc. Animal samples included the liver, kidney, brain, lung, heart, intestines, stomach, spleen, tongue, buccal mucosa, and brain. Sample sizes are from n = 5 to n = 90. One study did not mention the sample size. Eleven studies tested the fixation for up to 24 hours; two studies tested 24 to 72 hours, and two studies tested for a duration of stability of up to 6 months. Thirteen studies were conducted at room temperature except for milk, but two papers did not mention the temperature. Table I illustrates the studies' (n = 15) characteristics.

Natural Fixatives Used in Studies

Six out of 15 studies used more than one natural fixative in each study,[7,13,15-18] while nine used one fixative with different concentrations or diluted in different solutions.[6,8,12,19-24] The natural fixatives used in the studies were honey, jaggery, sugar and khandsari sugar, and their fixative efficacy excelled compared to formalin-fixed control specimens. Milk and ice were used as transport media as well. Twelve out of 15 studies included honey as a natural fixative alternative to formalin. The second most studied natural fixative was jaggery (n = 8) which is followed by sugar (n = 4) and other fixatives like milk or ice (n = 1) (Figure 3).

Different grades of commercial honey were used in the studies and were prepared with distilled water (DW), neutral buffer and ethanol. Dilutions from 1% to 100% were used in the studies.

Natural Fixatives in Tissue Fixation

Five out of 15 studies described gross fixation or changes during tissue microtoming (Table II). Chittemsetti et al. described the tissue folding and difficulty in preparing the sections,[13] but other studies revealed the brownish discolouration of fixed tissues by jaggery without interfering with histological findings.[6,7] For longer fixation time, Inyang

and Udonkang described that 20% and 50% of honey showed poor fixation after 72 hours, while 70%, 90% and 100% revealed good preservation for up to 6 months.[21]

Honey as an Alternative Fixative in Histopathology

Eleven out of 15 studies examined the histological features of tissues by Haematoxylin and Eosin (H&E) staining alone (Figure 3). One study examined the histological features of tissue by special stains[19,] and three studies used both H&E and special stains.[18,20,23]

Four studies used 10% honey to determine the histological analysis by H&E staining in rat tissues (liver, kidney and stomach) and human tissues (oral mucosa, endometrium, breast, placenta, uterus, omentum, suprarenal, stomach and lung).[8,12,20,23] The nuclear and cytoplasmic staining by H&E revealed a similar demonstration to that of formalin-fixed tissues. However, Lalwani et al. revealed more artefacts in processed and unprocessed honey-fixed tissues compared to formalin-fixed tissue samples. Out-of-focus areas and hyalinised tissues were reported in Lalwani's and Srii's studies[8,12] (Table II).

Six studies used 20% honey to demonstrate the histological feature by H&E staining. 20% honey-fixed tissues revealed good nuclear details and staining quality after 24 hours of fixation. However, after 6 months of fixation, cellular and nuclear clarity were decreased in 20% honey-fixed tissues compared to 10% formalin-fixed tissues. Cellular and nuclear shrinkage was also observed in H&E staining. The connective tissue staining by PAS and Mason Trichrome stains also revealed adequate but not optimal.18 Even though other researchers stated that a higher concentration of honey caused tissue shrinkage, a higher concentration of honey (50%-100%) was used in two studies. The nuclear and cytoplasmic staining revealed similar staining qualities of formalin-fixed tissues.[21,24] Sabarinath et al.[24] reported connective tissue homogenisation and background staining in honey-fixed tissues (Table II).

In the case of tissue fixation, Udongkang (2018) reported that 20% and 50% of honey revealed poor fixation after 72 hours, although nuclear and cellular staining revealed promising results. However, after 6 months, 70%, 90% and 100% honey demonstrated good tissue preservation (Table II).[21] The overall findings suggested that honey was a promising fixative for histological examination in routine histopathological practice.

Jaggery as an Alternative Fixative in Gross and Histological Examination

Eight out of 15 studies (53%) used jaggery as an alternative fixative and compared the tissue fixation efficiency and histological interpretation using H&E and special stains (Figure 3). One study used 20% jaggery diluted in DW,[16] and the remaining seven used 30% jaggery in human specimens and goat buccal mucosa tissues.[6,7,13,15,17,18,22] Patil (2013), Kuriachan (2017) and Sinha (2017) revealed that 30% of jaggery-fixed tissues demonstrated similar or superior results in H&E staining compared with that of formalin after 24 to 48 hours of fixation. 30% of jaggery-fixed tissues revealed good overall morphology with good nuclear and cellular outlines.[6,7,16] In shorter durations (1, 6 and 12 hours), 30% of jaggery-fixed tissues demonstrated superior to formalin-fixed tissues in histological examination.[17] However, other researchers revealed contrasting results on the fixation efficiency of jaggery in 20% or 30% in DW compared to formalin-fixed tissues. Chittemsetti et al.[13] revealed that 30% of jaggery-fixed tissues demonstrated significant differences in cellular outline, cytoplasmic and nuclear details, staining quality and overall morphology compared with that of formalin-fixed tissues. Imran et al.[15] also revealed that 30% of jaggery demonstrated cellular swelling and tissue autolysis after 24-hour fixation. Lam-ubol et al.[22] revealed that 30% of jaggery-fixed tissues demonstrated satisfactory stroma staining after 24-hour fixation, while there was mild nuclear condensation in inflammatory cells and separation of epithelial cells from each other and underlying connective tissues. 72-hour fixation with 30% jaggery revealed fibrous stroma hyalinisation. The staining integrity was reduced after a 6-month fixation with 30% jaggery with cellular and nuclear shrinkage. The connective tissue staining was not optimised with PAS and mason trichrome stain.[18] The fixative efficacy of jaggery was controversial in the studies (Table II).

Sugar as an Alternative Fixative in Histological Examination

The study's third most used alternative fixative (n = 4) was sugar. One study used 30% khandsari sugar, which is unrefined cane sugar,[13] while the other three studies used 20% sugar syrup in DW.[7,15,16] Human oral tissue specimens and goat buccal mucosa specimens were fixed with 20%–30% sugar solutions for 24 hours, and histological examination was done with H&E staining. Chitttemsetti et al.[13] revealed that 30% khandsari sugar-fixed tissues revealed promising staining quality except for cellular outline compared with formalin-fixed tissues. A similar result was reported with 20% sugar syrup as a fixative.[15] Patil et al. and Kuriachan et al. demonstrated controversial results with 20% sugar syrup. In those studies, sugar-fixed tissues revealed poor overall staining with a lack of cellular outline clarity and uneven staining.[7,16] Additionally, tissue folds and difficulty in preparing sections were reported in khandsari-fixed tissues[13] and in 20% sugar-fixed tissues7 (Table II).

Other Natural Fixatives

Milk and ice were also used as instant transport media for soft tissue biopsy, and the diagnostic value of tissues was assessed with H&E staining. Milk was kept at 5°C, and fixation was done at the same temperature. Fixation with milk and ice was done for 1, 6, 12 and 24 h, followed by 10% buffered formalin for 24 h. Milk-fixed tissues revealed poor tissue structures after 1 h fixation, while ice-fixed tissued revealed deterioration and loss of morphological details after 12 h fixation.[17]

Natural Fixatives with Special Stains in Histopathology

Four studies used special stains to demonstrate the extracellular matrix staining in natural fixatives fixed tissue. Al-Maaini and Bryant revealed that 1% honey demonstrated poorly stained collagen, reticulin, elastin and keratin, while 5%, 10% and 20% honey demonstrated a compatible staining quality with 10% formalin.[19] Alwahaibi et al.[20] also demonstrated similar results with 10% honey diluted for connective tissues; however, reticulin staining intensity with

Table I: Demographic characteristics of sexual assault victims

	Study ID	Natural Fixatives	Sample size	Type of sample	Parameter analysis	Duration	T°	pH	Gross Morphology	Outcomes compared to formaldehyde		
										Histology (H&E)	Histochemistry	Immunohistochemistry
1	Al-Maaini, 2008, Oman	Honey	Not mentioned	Animal	liver, kidney, brain, lung, heart, bowel, stomach, spleen and tongue	24 hr	RT	Not mentioned	Not mentioned	Not done	1% honey → satisfactory result in MT 5%, 10% and 20% honey → satisfactory in VVG, GS, MT and Miller's elastic stain	Not done
2	Alwahaibi, 2021, Oman	Sumer honey Date honey	N = 81	Animal	liver, kidney & stomach	24 hr	RT	10% Sumer honey 3.56 10% Date honey 5.15 10% Netural buffer 7.25, 7.27 10% Alcoholic honey 5.1, 5.8	Satisfactory	Satisfactory	Satisfactory result with JMS, PAS and GS	Satisfactory (Vimentin)
3	Chittemsetti, 2018, India	Jaggery Khandsari	N = 90	Human	Oral surgical specimens	24 hr	RT	Not mentioned	Difficulty in in microtone	Satisfactory Khandsari> Jaggery	Not done	Not done
4	Imran, 2020, India	Honey Sugar Jaggery syrup	N = 40	Human	Human Oral tissues	24 hr	RT	4.5 – 5.5	Not mentioned	Satisfactory Formalin> sugar> honey> jaggery	Not done	Not done
5	Kuriachan, 2017, India	Honey Jaggery Sugar	N = 40	Human	human gingival tissue	24 hr	RT	Not mentioned	Not mentioned	Satisfactory Honey> Jaggery> formalin> sugar	Not done	Not done
6	Lalwani, 2015, India	Unprocessed honey Processed honey	N = 36	Human	oral epithelium, lymphoid, salivary gland, fat, muscle and skin	24 hr	RT	10% unprocess honey 3.6 10% process honey 5.05	Not mentioned	Satisfactory Processed honey> unprocessed honey	Not done	Not done
7	Lam-ubol, 2018, Thailand	Jaggery	N = 40	Human	Oral tissues	24 hr & 72 hr	RT	Not mentioned	Not mentioned	Satisfactory	Not done	Not done
8	Özkan, 2011, Turkey	Pine honey	N = 21	Human	endometrium, breast, placenta, uterus, omentum, suprarenal, stomach and lung	24 hr	RT	4.8 – 5.0	Not mentioned	Satisfactory trichrome)	Satisfactory (Gomori's	Satistifactory (Ki-67, Vimentin)
9	Patil, 2013, India	Honey Sugar syrup Jaggery syrup	N = 5	Animal	buccal mucosa	24 hr	RT	Not mentioned	Brownish colour in jaggery solution	Satisfactory	Not done	Not done

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Table I: Demographic characteristics of sexual assault victims

	Study ID	Natural Fixatives	Sample size	Type of sample	Parameter analysis	Duration	T°	pH	Outcomes compared to formaldehyde			
									Gross Morphology	Histology (H&E)	Histochemistry	Immunohistochemistry
10	Patil & Rao, 2015, India	Honey Jaggery Milk Ice	n = 80	Animal	buccal mucosa	1, 6, 12, 12, 24 hr	RT	Not mentioned	Not mentioned	Satisfactory	Not done	Not done
11	Patil, 2015, India	Jaggery Honey	n = 42	Animal	Fresh goat meat (buccal mucosa)	48hr – 6 months	Not mentioned	Not mentioned	Not mentioned	Satisfactory	Satisfactory (PAS, MT)	Not done
12	Sabarinath, 2014, India	Honey	n = 30	Human	Human Oral çissues (pericornitis, percoronal abscess)	24 hr	Not mentioned	Not mentioned	Not mentioned	Satisfactory	Not done	Not done
13	Sinha, 2017, India	Jaggery solution	n = 65	Human	Human pathologica specimens	24 - 48 hr	RT	4.5 – 5.5	Not mentioned	Satisfactory	Not done	Not done
14	Srii, 2016, Nepal	Bee honey	n = 60	Human	gingiva and pericoronal region	24 hr	RT	4.5 - 5	Brown tint tint in jaggery solution	Satisfactory	Not done	Not done
15	Udongkang, 2018, Nigeria	Honey	n = 10	Animal	heart, intestine, lungs, kidneys, and brain	48 hr, 1 week, 2 weeks, 1 month, 3 months 6 month	RT (27'C)	4	20% and 50% honey → poor fixation after 72 hours 70%, 90% and 100% honey → good preservation after 6 months	Satisfactory	Not done	Not done

Footnote RT = Room temperature, MT = Masson trichrome stain, VVG = Van Gieson Stain, GS = Gordon & Sweet's reticulin stain, JMS = Jones Methenamine silver stain, PAS = Periodic acid–Schiff stain

Table II: Findings of natural fixatives-fixed tissues compared to formalin

	Study ID	Natural Fixatives	Type of tissues	Type of stain used	Findings		
					Tissue sectioning	Histology	Artefacts in alternative fixatives-fixed tissues
1	Al-Maaini, 2008, Oman	Honey	liver, kidney, brain, lung, bowel, stomach, spleen and tongue	1) VVG 2) Miller's elastin 3) GS 4) MT	Not mentioned	- Excellent connective tissue staining in honey-fixed tissues comparable to formalin-fixed control tissues	Not mention
2	Alwahaibi, 2021, Oman	Sumer honey Date honey	liver, kidney & stomach	1) H&E 2) JMS 3) GS 4) PAS 5) IHC	Not mentioned	- Satisfactory overall quality of staining in honey-fixed tissues - Inadequate cytoplasmic staining in neutral buffered honey and 10% honey compared - Weak reticulin fibres staining with Gordon and Sweets method in all honey groups	Absence of red blood cell staining
3	Chittemsetti, 2018, India	Jaggery Khandsari	Oral surgical specimens	1) H&E	Tissue folds and difficulty in preparing sections	- Formalin is superior to Khandsari sugar and jaggery in histological staining. - Khandsari sugar is superior to jaggery in histological staining.	Homogenization of tissues, loss of structure differentiation in jaggery
4	Imran, 2020, India	Honey Sugar Jaggery syrup	Human Oral tissues	1) H&E	Not mentioned	- Good staining quality in sugar and honey-fixed - Cellular swelling and tissue autolysis in jaggery-fixed tissues	Not mentioned
5	Kuriachan, 2017, India	Honey Jaggery Sugar	human gingival tissue	1) H&E	Brittleness of tissues fixed in sugar	- Superior tissue staining in honey and jagger-fixed tissues - Poor overall staining and a lack of clarity of cell outline in sugar-fixed tissues	Not mentioned
6	Lalwani, 2015, India	Unprocessed honey Processed honey	oral epithelium, lymphoid, salivary gland, fat, muscle and skin	1) H&E	Not mentioned	- Adequate tissue morphology and staining for diagnosis in honey-fixed tissues - Processed honey demonstrated better results than unprocessed honey.	Out-of-focus area and slit-like spaces in epithelial tissues and hyalinized collagen fibres
7	Lam-ubol, 2018, Thailand	Jaggery	Oral tissues	1) H&E	Not mentioned	- Satisfactory tissue morphology and staining quality in Jaggery-fixed and formalin-fixed tissues. - Mild chromatin condensation of inflammatory cells, hyalinization of fibrous stroma in jaggery-fixed tissues.	Epithelial separation from each other (acanthosis) and underlying connective tissue.
8	Özkan, 2011, Turkey	Pine honey	Endometrium, breast, placenta, uterus, omentum, suprarenal, stomach and lung	1) H&E 2) GT	Not mentioned	- Weak nuclear and cytoplasmic details in endometrial tissues - Well-preserved cell morphology, cytoplasm and nuclear antigen preservation and staining in other types of tissues	Not mention
9	Patil, 2013, India	Honey Sugar syrup Jaggery syrup	Buccal mucosa	1) H&E	Sugar syrup - difficulty in sectioning	- Satisfactory staining with H&E in all types of fixatives - Uneven staining in honey- and jaggery-fixed tissues	Sugar syrup - tissue folds

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Table II: Findings of natural fixatives-fixed tissues compared to formalin

	Study ID	Natural Fixatives	Type of tissues	Type of stain used	Findings		
					Tissue sectioning	Histology	Artefacts in alternative fixatives-fixed tissues
10	Patil & Rao, 2015, India	Honey Jaggery Milk Ice	buccal mucosa	1) H&E	Not mentioned	- High-quality preservation of tissue morphology and staining quality in 30% jaggery	Not mentioned
11	Patil, 2015, India	Jaggery Honey	Fresh goat meat (buccal mucosa)	1) H&E 2) PAS 3) MT	Honey and Jaggery fixed tissues - fragile and need attention in sectioning	- Cellular and nuclear shrinkage after six months of fixation in jaggery and honey - Satisfactory overall histomorphology with H&E stain in all fixatives - Adequate connective tissue staining in jaggery and honey-fixed tissues	Not mentioned
12	Sabarinath, 2014, India	Honey	Human Oral tissues (pericornitis, percoronal abscess)	1) H&E	Not mentioned	- Satisfactory morphology and staining with H&E in honey	Homogenization of collagen fibres in honey-fixed tissues
13	Sinha, 2017, India	Jaggery solution	Human pathological specimens	1) H&E	Difficulty during sectioning because of hard tissues in jaggery-fixed tissues.	- Satisfactory and comparable morphology and staining quality in jaggery and formalin-fixed tissues - Better nuclear details in jaggery-fixed tissues.	Not mentioned
14	Srii, 2016, Nepal	Bee honey	Gingiva and pericoronal region	1) H&E	Not mentioned	- No nuclear and cytoplasmic size change between honey- and formalin-fixed tissues	Hyalinization of collagen fibres in honey-fixed tissues
15	Udongkang, 2018, Nigeria	Honey	Heart, intestine, lungs, kidneys, and brain	1) H&E		- Good histological staining and cellular structures of tissues in higher concentrations of honey beyond 48 hours.	Not mentioned

Footnote: H&E= Haematoxylin and eosin, MT = Masson trichrome stain, VVG = Van Gieson collagen Stain, GS = Gordon & Sweet's reticulin stain, JMS = Jones Methenamine silver stain, PAS = Periodic acid–Schiff stain, IHC = Immunohisochemistry, GT = Gomori's trichrome muscle and collagen stain

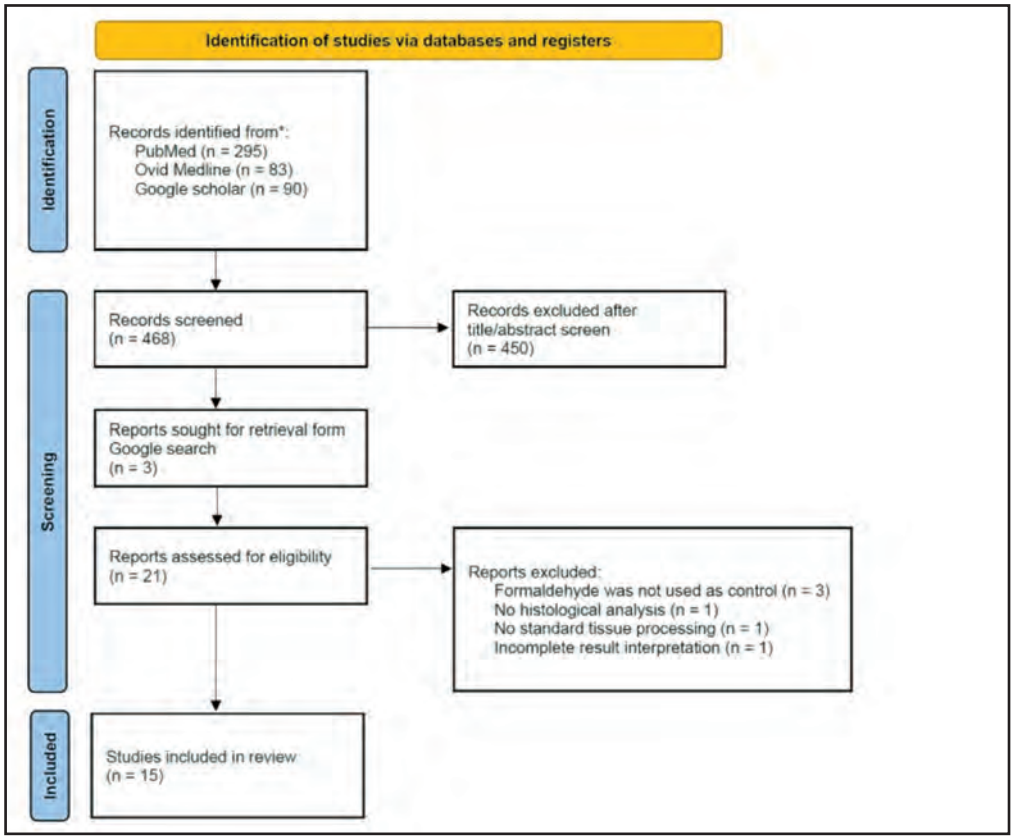

Fig. 1: PRISMA flow diagram for included studies

Gordon and Sweets method. However, Özkan et al. and Patil et al. revealed that 10% honey, 20% honey and 30% jaggery syrup demonstrated weak collagen and reticulin staining intensity compared to that of 10% formalin[18,23] (Table II).

Natural Fixatives in Immunohistochemistry

Two studies reported the vimentin and Ki-67 staining by immunohistochemistry in honey-fixed tissues showing similar findings to that of 10% neutral buffered formalin.[20,23]

Natural Fixatives and Artefacts

Seven studies addressed the artefacts in natural fixatives-fixed tissues compared to 10% formalin (Table II). Honey-fixed tissues failed to demonstrate red blood cell staining in liver and kidney samples.20 Out-of-focus area in epithelial tissues, slit-like spaces at the epithelium basement membrane[8] and homogenisation of collagen fibres[8,12,24] were found in honey-fixed tissues compared to 10% formalin-fixed tissues. In contrast with the findings of Patil et al., three studies addressed the artefacts in jaggery-fixed tissues; homogenisation of tissues, loss of tissue structure differentiation,[13] and epithelial separation from each other (acanthosis) and underlying connective tissues.[22] One study described tissue fold artefacts in sugar srup-fixed tissues[7] (Table II).

DISCUSSION

This is the first study to evaluate the natural fixatives as an alternative to formalin in a systematic review to the best of our knowledge. Fixation is a critical step in tissue processing for histopathological examination and archival preservation by preserving the cellular architecture and composition of cells in the tissues. Fixation also preserves proteins, carbohydrates and other bio-active components in their relationship to cells.[25] An ideal fixative should be able to harden the tissue components and prevent decomposition, bacterial putrefaction and autolysis. Routinely used 10% formalin contains 3.7% formaldehyde in water with 1% methanol. When the tissues are immersed in formalin, methanol initially causes dehydration, hardening the tissues and membrane, followed by a cross-linking phase with protein, mediated by aldehyde.[26] Formalin is the most widely used fixative in histopathological practice worldwide because of its convenience in handling, accuracy, adaptability and cost-effectiveness. However, as formalin is considered a toxic and carcinogenic substance to humans, many questions have been raised to seek an alternative fixative to replace formalin in histopathological practice.

Natural fixatives act by various mechanisms to best preserve the tissues. A higher level of fructose composition in honey, jaggery and sugar suggested the possible fixation mechanism by breaking down fructose into aldehyde and developing the cross-link with tissue amino acid.[7] Moreover, honey's antibacterial, acidic and dehydrating properties, whilst the cytoprotective and antioxidant activity of jaggery, supported the potential fixating properties of natural fixatives.[6]

Honey was the most frequently used alternative fixative to replace formalin because of its antibacterial effects. Bacteria

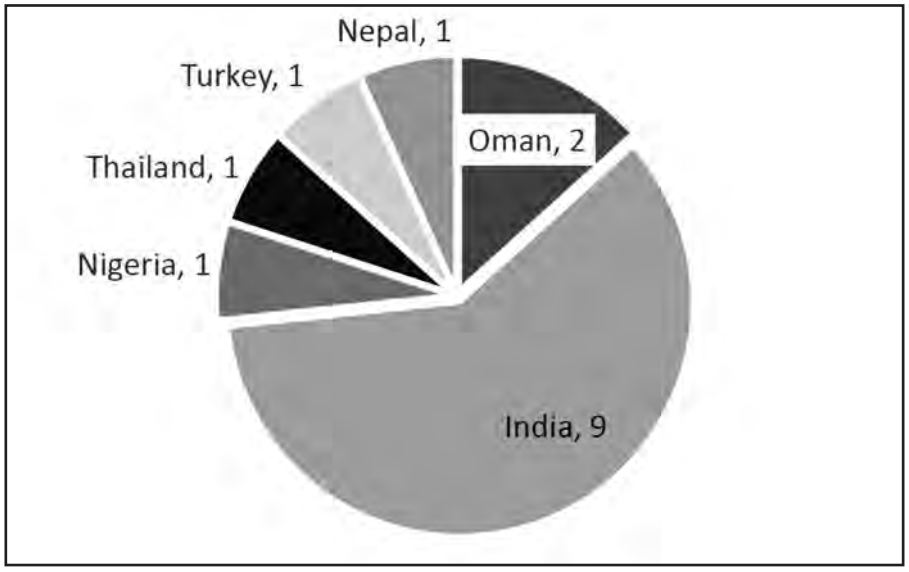

Fig. 2: Geographic distribution of studies included in the systematic review

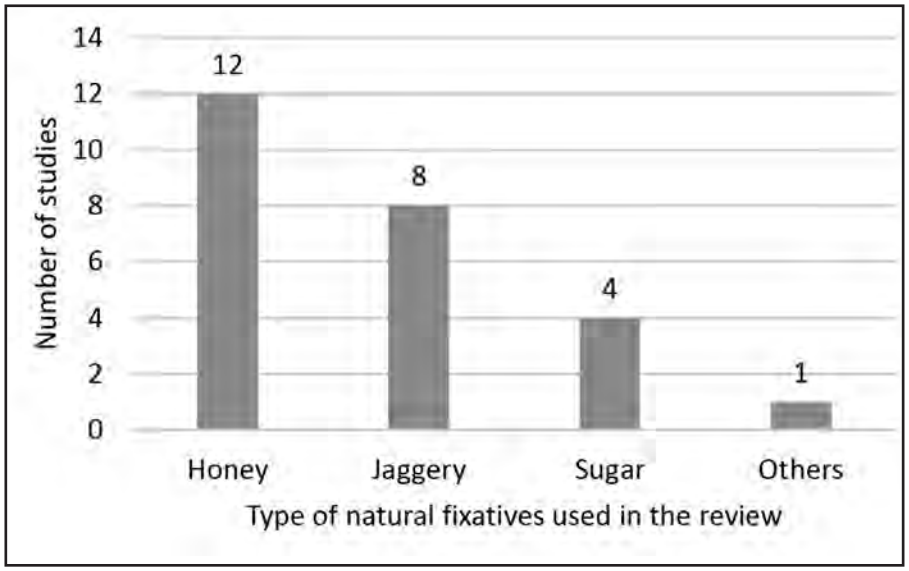

Fig. 3: Natural fixatives used in the systematic review

cannot survive in honey because of acidic pH and high sugar content, which dry out the bacteria with an osmotic effect.[27] Moreover, glucose peroxidase is released in diluted honey and oxidises glucose to produce hydrogen peroxide, inhibiting certain bacteria's growth.[27]

Eleven studies showed that honey provided the proper tissue fixation and compatible staining intensity with formalin in H&E stain, special stains and immunohistochemistry staining.[7,8,12,15-19,21,23,24] However, the concentration of honey was inconsistent in the studies. The argument may be due to the different chemical compositions of honey depending on the botanical and geographical origin.[27] Honey was diluted in distilled water, neutral buffer and alcohol from 1% to 90%. The studies agreed the lower concentration of honey gave better antiseptic actions because of the slow-release hydrogen peroxide at low concentrations. Honey also showed inhibitory effects on gram-positive and gram-negative bacteria, with a minimum concentration of 0.5% to a maximum concentration of 40%, depending on the type and production of honey.[28] The fermentation process was produced in diluted honey at room temperature. However, mould development was found on paraffin block and in diluted honey solution at room temperature.[19] Thus, more studies are required to optimise the honey concentration for tissue fixation based on kill kinetics against microorganisms in honey or keep the process in cold storage.

Fixation is a complex series of chemical events and differs for the different groups of chemical substances found in tissues.[29] The fixation speed depends on the rate of diffusion of the fixative into the tissue and the rate of chemical reaction with

various components. In practice, it is estimated that the fixation process requires at least 1 hour/mm of tissue thickness; however, the tissues are routinely fixed for 24–48 hours.[1] All included studies used the small piece of tissue samples (5 mm) in their studies with a 1:10 ratio of tissue and fixatives for 24–48 hours. It provided that natural fixatives could penetrate the small tissues and complete the fixation process. However, larger tissue samples were not pointed out. Piątek-Koziej et al.[30] revealed that 10% honey in DW was unsuitable for fixing large tissue samples like whole swine hearts, but 10% honey in absolute alcohol gave satisfactory fixation with tissue shrinkage. These findings suggested that an alcohol-based honey solution would provide a more promising result, but optimal alcohol dilution needs to be figured out.

Jaggery and sugar are mainly composed of sucrose. It was hypothesised that jaggery and sugar might preserve the tissue by breaking down sucrose at low pH, producing aldehydes and cross-linking with tissue amino acids.[7] This hypothesis explains why sugar and jaggery are best to fix at low pH (3.6–5.8) while formalin is best to fix at neutral pH.[6,15] The studies revealed promising results in tissue fixation with 20% or 30% jaggery or sugar diluted in DW.[6,7,13,15-18,22] 30% of jaggery fixatives showed superior cellular and nuclear staining compared to formalin or other natural fixatives.[6,7,16-18,22] Still, their findings were not aligned with Chittemsetti et al. and Imran et al., who showed cellular swelling and tissue autolysis in jaggery-fixed tissues.[13,15] It may be due to the different techniques used in cane processing to remove colour and impurities, which affect the number of polyphenols in sugar and jaggery.[31]

With natural fixatives, the authors focussed mainly on tissue fixative and histological staining. Only two studies tested the protein expressions by immunohistochemistry,[20,23] but protein levels and nucleic acid levels were not tested. Although six studies were conducted with human tissue biopsies, only histomorphological examinations were demonstrated. Specific disease and diagnostic variation were not evaluated between formalin-fixed and alternative fixatives-fixed tissues.

All the natural substances, honey, sugar, jaggery and khandsari sugar, gave promising results in small tissue fixation. Pricewise, honey is more expensive than formalin, but jaggery is cheaper and costs 1/6th of honey. Because of economic reasons, jaggery is more favourable than honey even though its chemical composition on antibacterial effects is limitedly known.[6,7,13,15,16,22]

CONCLUSION

Natural substitutes like honey, jaggery and sugar are boons when the health hazards of formalin are considered. Those natural fixatives provided promising results in small tissue fixation and histological staining. More studies should be done to explore the optimal dilutant and dilution for locally available natural fixatives. There are no studies regarding nucleic acid and protein levels in natural fixatives-fixed tissues, and these areas need further exploration. The penetrating power of the natural fixatives in different tissues also needs to be examined, and larger tissue samples should be tested for fixation. No disease tissue or diagnostic interpretation was made for alternative fixatives-fixed tissues. Future studies should be done in disease tissues to determine whether alternative fixatives can overcome the formalin pigments and artefacts or not. The authors of this article are currently working on an ongoing project that evaluates the effect of natural fixatives in histochemical staining as an alternative to formalin. By using natural fixatives, we aim to derive a safe and pleasant working environment for healthcare professionals.

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CONFLICT OF INTEREST

There is no actual or potential conflict of interest in relation to this article.

REFERENCES

1. Srinivasan M, Sedmak D, Jewell S. Effect of fixatives and tissue processing on the content and integrity of nucleic acids. Am J Pathol 2002; 161(6): 1961-71.
2. Musiał A, Gryglewski RW, Kielczewski S, Loukas M, Wajda J. Formalin use in anatomical and histological science in the 19th and 20th centuries. Folia Med Cracov 2016; 56(3): 31-40.
3. Shetty JK, Babu HF, Hosapatna Laxminarayana KP. Histomorphological assessment of formalin versus nonformalin fixatives in diagnostic surgical pathology. J Lab Phys 2020; 12(4): 271-5.
4. Cogliano VJ, Grosse Y, Baan RA, Straif K, Secretan MB, Ghissassi FE, et al. Meeting report: summary of IARC Monographs on formaldehyde, 2-butoxyethanol, and 1- tert -butoxy-2-propanol. Environ Health Perspect 2005; 113(9): 1205-8.
5. Mundt KA, Gentry PR, Dell LD, Rodricks JV, Boffetta P. Six years after the NRC review of EPA's draft IRIS toxicological review of formaldehyde : regulatory implications of new science in evaluating formaldehyde leukemogenicity. Regulat Toxicol Pharmacol 2018; 92: 472-90.
6. Sinha N, Nayak M, Sunitha J, Dawar G, Rallan N, Gupta S. Comparitive efficacies of a natural fixative with a conventional fixative. J Oral Maxillofac Pathol 2017; 21(3): 458.
7. Patil S, Premalatha B, Rao RS, Ganavi B. Revelation in the field of tissue preservation - a preliminary study on natural formalin substitutes. J Int Oral Health 2013; 5(1): 31-8.
8. Lalwani V, Surekha R, Vanishree M, Koneru A, Hunasgi S, Ravikumar S. Honey as an alternative fixative for oral tissue: an evaluation of processed and unprocessed honey. J Oral Maxillofac Pathol 2015; 19(3): 342.
9. Muddana K, Muppala JNK, Dorankula SPR, Maloth AK, Kulkarni PG, Thadudari D. Honey and olive oil as bio-friendly substitutes for formalin and xylene in routine histopathology. Indian J Dental Res 2017; 28(3): 286.
10. Wijesinghe M, Weatherall M, Perrin K, Beasley R. Honey in the treatment of burns: a systematic review and meta-analysis of its efficacy. N Z Med J 2009; 122(1295): 47-60.
11. Zainol MI, Mohd Yusoff K, Mohd Yusof MY. Antibacterial activity of selected Malaysian honey. BMC Complement Altern Med 2013; 13(1): 129.
12. Srii R, Marla V. BEE honey as a locum for routine formalin fixative. Int. J. Sci. Res 2016; 5(10): 2277-8179.

13. Chittemsetti S, Nallamala S, Sravya T, Guttikonda VR, Manchikatla PK, Kondamari S. Natural substitutes for formalin: A boon to histopathology!! J Oral Maxillofac Pathol 2018; 22(1): 143.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339(jul21 1): b2535-b2535.
15. Imran M, Kumar D.R. S, Ahmed SA, Tanveer S. Eco-friendly natural fixatives - a substitute for formalin? Health Sci 2020; 12(06): 11906-9.
16. Kuriachan D, Suresh R, Janardhanan M, Savithri V, Aravind T, Thampy LM. Analysis of fixative properties of three eco-friendly substances: a comparison with formalin. Oral Maxillofac Pathol J 2017; 8(2): 79-84.
17. Patil S, Rao RS, Agarwal A, Raj AT. Instant transport media for biopsied soft tissue specimens: a comparative study. Scientifica 2015; 2015: 1-5.
18. Patil S, Rao R, Ganavi B, Majumdar B. Natural sweeteners as fixatives in histopathology: a longitudinal study. J Nat Sc Biol Med 2015; 6(1): 67.
19. Al-Maaini R, Bryant P. Honey as an alternative to formalin in the demonstration of connective tissue components. J Histotechnol 2008; 31(2): 67-72.
20. Alwahaibi N, Al Dhahli BS, Al Issaei H, Al Wahaibi L, Al Sinawi S. Efficiency of neutral honey as a tissue fixative in histopathology. bioRxiv [Preprint]. 2021.04.27.437988.
21. Inyang I, Udonkang M. Honey as fixative and safer substitute for formalin in histology. Int J Med Lab Res 2018; 3(3): 11-7.
22. Lam-ubol A, Kitrueangphatchara K, Putthanuparp T, Arayakhun R, Kwanthong R, Choonhawarakorn K. Nonformalin fixative agents: a comparative study of fixative efficacy and histomorphology. Int J Surg Pathol 2018; 26(8): 701-6.
23. Özkan N, Şalva E, Çakalağaoğlu F, Tüzüner B. Honey as a substitute for formalin? Biotechnic Histochem 2012; 87(2): 148-53.
24. Sabarinath B, Sivapathasundharam B, Sathyakumar M. Fixative properties of honey in comparison with formalin. J Histotechnol 2014; 37(1): 21-5.
25. Thavarajah R, Mudimbaimannar V, Rao U, Ranganathan K, Elizabeth J. Chemical and physical basics of routine formaldehyde fixation. J Oral Maxillofac Pathol 2012; 16(3): 400.
26. Kiernan JA. Formaldehyde, formalin, paraformaldehyde and glutaraldehyde: what they are and what they do. Micros Today. 2000; 8(1): 8-13.
27. White, JW, Jr., Landis W. Doner. Physical characteristics of honey. In: Crane, E, editor. Honey: a comprehensive survey. London: Heinemann; 1980. p. 157-206.
28. Mandal MD, Mandal S. Honey: its medicinal property and antibacterial activity. Asian Pacif J Trop Biomed 2011; 1(2): 154-60.
29. Suvarna SK, Layton C, Bancroft JD. Bancroft's theory and practice of histological techniques. In: Bacnroft's theory and practice of histological techniques. 7th ed. Oxford: Elsevier; 2019. p. 105-24.
30. Piątek-Koziej K, Hołda J, Koziej M, Tyrak K, Jasińska KA, Bonczar A, et al. Fixative properties of honey solutions as a formaldehyde substitute in cardiac tissue preservation. Folia Med Cracov 2019; 59(1): 101-14.
31. Harish Nayaka MA, Sathisha UV, Manohar MP, Chandrashekar KB, Dharmesh SM. Cytoprotective and antioxidant activity studies of jaggery sugar. Food Chem 2009; 115(1): 113-8.

SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Factors associated with the spatial accessibility of healthcare services measured by the floating catchment area (FCA)-based method: A scoping review

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ABSTRACT

Introduction: The floating catchment area (FCA) method has emerged as the most comprehensive and accurate method for quantifying the spatial accessibility of health care services. There were variants of the FCA-based method that was continuously improvised by the researchers to suit specific local contexts and the different nature of healthcare service delivery. This scoping review identifies factors associated with the spatial accessibility of healthcare services that were specifically measured using the FCA-based method.

Materials and Methods: This scoping review was performed through electronic databases (PubMed and ScienceDirect) using keywords: 'spatial accessibility', 'floating catchment area' and 'factors'. Google Scholar and Mendeley Network were also used as additional sources to obtain relevant studies.

Results: A total of 32 articles were included in this review. Factors identified can be distinguished into two broad categories, which are spatial and non-spatial factors. Spatial factors were remoteness or distance from the urban centre, areas in close proximity to main roads, and some specific geographical characteristics such as mountainous and deltaic regions, whereas non-spatial factors were the degree of urbanisation, population density and various demographic profiles of the population such as socio-economic status, health need, and minority ethnic composition.

Conclusion: This study adds to the body of literature pertinent to the factors associated with spatial accessibility to healthcare services. These findings could give insight for researchers to consider and incorporate those additional variables to further improve the FCA-based method calculations.

KEYWORDS:
spatial accessibility; healthcare services; floating catchment area; factors

INTRODUCTION

Accessibility is a huge concept, which comprises four main elements: geographical accessibility, availability, affordability and acceptability.[1] Spatial accessibility encompasses geographic accessibility and availability due to its association with geographical location and is influenced by the spatial impedance between the service and the user, subject to the availability of the services in a specified location. Measuring the spatial accessibility contributes to evidence-based health policies and planning for a better understanding of the performance of the healthcare delivery system.[2] There were several methods for measuring spatial accessibility, such as nearest distance, provider-to-population ratio and the number of services within a specific threshold distance from the population.[3] Besides that, due to advancements in geographical information systems (GIS) and its application in health-related fields, the floating catchment area (FCA)-based method has emerged since the last decade[4,5] and is now widely used to measure the spatial accessibility.

In short, the FCA-based method is basically a two-step process as it considers the: (i) service catchment area and (ii) population catchment area. The first step is assigning an initial supply–demand ratio for each service location; this is calculated by dividing the number of services, with the number of people that reside within the service catchment area. The second step is the summation of all services that were located within the population catchment area (the threshold distance of the population to travel to seek care). The summation will result in a numerical score, which is the spatial accessibility score, where a higher score indicates better access. Details of the calculation were described elsewhere by Wang and his associates.[5-7] There were various FCA-based methods that existed, which were the evolution and originated from the two-step FCA (2SFCA) method by Wang & Luo circa 2004.[5] The variants were mainly due to the improvements made to the original 2SFCA as well as modifications made specifically to cater to their health care and local context,[3,7,8] such as integrating other components into the formula, the use of multiple modes of transport, variable catchment size, depending on data availabilityand

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are still constantly being improvised to suit specific local contexts and/or healthcare services.

In the theoretical framework of access, various external factors from the population characteristics and macroenvironments were often associated with the accessibility of healthcare services in general.[1,9] However, there is still a lack of knowledge in relation to the factors associated specifically with the spatial component of accessibility. By incorporating those factors in the calculation of the method, a better understanding of the association of the external factors could contribute to establishing a more comprehensive and accurate quantification of the spatial accessibility than available FCA-based methods. Thus, this scoping review was conducted with the intention to summarise existing literature, using a scoping review framework to identify factors associated with the spatial accessibility of healthcare services that were specifically measured using the FCA-based method, as well as exploring what factors can be incorporated into the current available FCA-based method to provide a better measure of spatial accessibility.

MATERIALS AND METHODS

The scoping review was performed according to the five-stage Arksey and O'Malley framework of a scoping review: (i) identifying the research question; (ii) identifying relevant studies; (iii) study selection; (iv) charting the data and (v) collating, summarising and reporting the results.[10]

Stage One: the Research Question

The review was guided by the following research questions: (i) to what extent has the FCA-based method been used to quantify the spatial accessibility to various healthcare services?; (ii) what are the factors and how is it associated with the spatial accessibility to the specific health care services? and (iii) how those factors can be incorporated into the FCA-based calculation to further improve the method?.

Stage Two: Identifying Relevant Studies

The three-step method by the Joanna Briggs Institute (JBI)[11] was applied. In the first step, the articles were identified through searching the public domain PubMed and ScienceDirect bibliographic electronic databases. The searches were performed on 25th January 2022. The keywords for the searches include: (spatial accessibility) AND (floating catchment area) AND (factors), based on the title or abstract. Searches only include full-text articles published from 2000 onwards, in English, and related to the healthcare field. In second step, articles were screened using search term 'health' through the text, title and abstract in the included databases, to the ensure the relevance for eligibility of the selected articles only resolve around factors associated with the spatial accessibility to health care services as the primary outcome of interest. Screening was done by two investigators (JAH and MHJ) independently and any discrepancies that arose were resolved by consensus. In the third step, reference list of the identified articles was also searched to identify additional papers. In addition, related documents were also examined and identified through Google Scholar searches and the Mendeley network to supplement the searches through electronic databases.

Stage Three: Study Selection

Articles or studies that did not deliberate on factors associated with the spatial accessibility score or when the spatial accessibility score for the specific health services was not the main outcome (as the dependent variable) of the study were excluded. Only studies with an ecological cross-sectional design were included. Studies on any types of healthcare services (primary care, inpatient care, and any specialised care) and any types of users were included. The full-text screening was conducted by two investigators (JAH and MHJ) and discrepancies were resolved by consensus. Figure 1 depicts the study selection process and additional details on excluded studies.

Stage Four: Charting the Data

Data were extracted by JAH and MHJ, including authors, title, year of publication, location (including country), types of health care services, outcomes on reported significant factors associated with the spatial accessibility score to the specified health services, the study design (with level of spatial aggregation), population (basically is the potential user of the services) as well as the grant involved in the respective study. Information for each of the included study is charted in Table I.

Stage Five: Collating, Summarising and Reporting the Results

Studies were then grouped based on types of health care services, tabulated against identified factors (which were organised thematically according to similar characteristics; which are either spatial or non-spatial factors) as shown in Table II, summarising findings addressing the first two research questions. The third research question was discussed accordingly after collating all the findings from the included studies.

RESULTS

Of the 53 records obtained, a total of 21 were excluded, where 5 were excluded upon screening at the title and abstract level and 16 records were further excluded after assessing the full text of the articles due to being outside the focus of this study. This was illustrated in the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews)[12] flowchart of the literature included in the study (Figure 1).

A total of 32 articles were reviewed, where notable findings on identified factors associated with the respective studied healthcare services are listed in Table I. The FCA-based method has also been widely used across several healthcare services, such as primary care (14 articles),[5,7,8,13–23] in-patient care (8 articles),[2,24–30] maternal care (2 articles),[31,32] elderly care (2 articles)[33,34] and other specialised services (6 articles).[35–40] Factors associated with those studies can be identified based on the general spatial pattern of the calculated accessibility score across the map, often visualised using choropleth maps, supplemented by geostatistical analysis such as Moran's I index or Getis-ord-Gi* or using regression analysis.

The distribution of accessibility scores was generally unequally distributed across the study areas of the included studies. Several factors were reported to be associated with spatial accessibility scores (calculated using the FCA-based

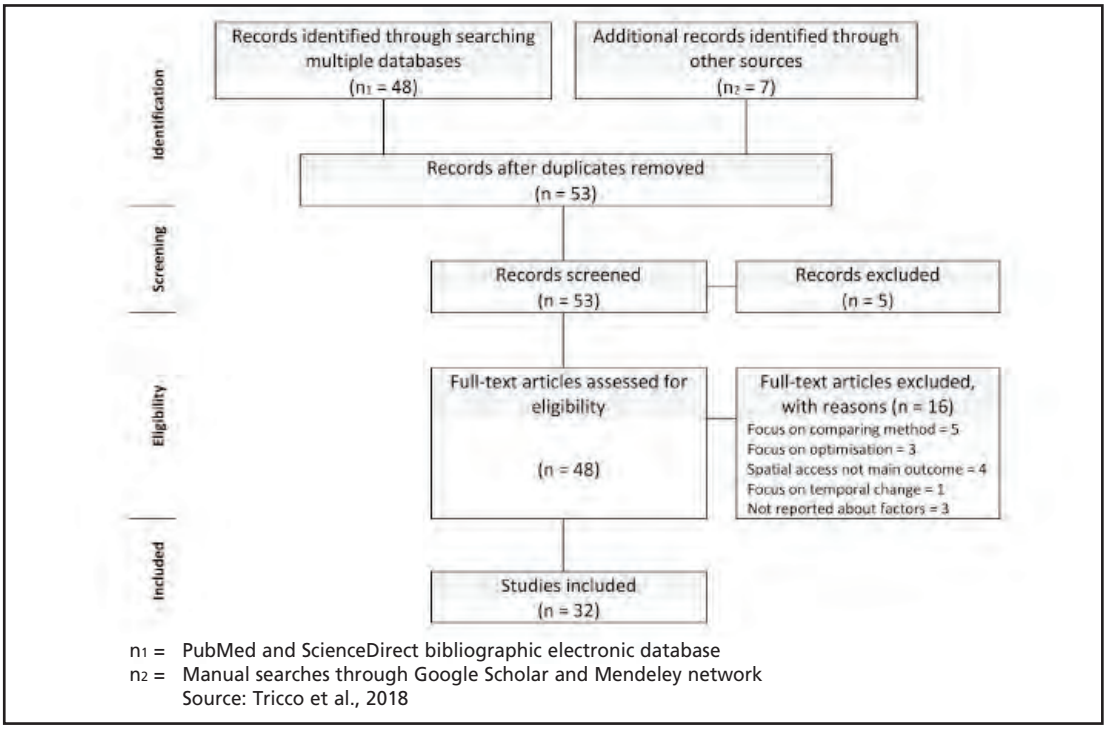

Fig. 1: PRISMA-ScR flowchart for eligible articles included

method) for healthcare services. In summary, the associated factors that contribute to the variation of spatial accessibility can be either spatial or non-spatial factors. Spatial factors are often related to the remoteness or distance from the main urban centre or some specific geographical locations (such as mountainous regions). Non-spatial factors, such as degree of urbanisation, socio-economic demographic profiles, health needs and socio-cultural factors were also reported by those studies. Table II shows the factors associated with the spatial accessibility scores for studied healthcare services.

Spatial Factors

High spatial accessibility scores for healthcare services often occur at the main city or urban centre, as well as its surrounding areas,[7,13–16,21,26,29,30,33] while lower accessibility scores are often seen in the periphery region, inclined outwards or further from the urban centre.[2,7,14,15,30,33] Remote areas are often associated with lower accessibility scores,[14,15,21,29,32,39] but one study[22] found otherwise. The study found that spatial accessibility to Family Medicine Specialist (FMS) in particular was better in the remote areas due to the fewer potential users (patients) in the area, as remote areas are mostly inhabited by the elderly population, hence fewer health needs specifically for the FMS, while the FMS were fairly distributed.[22] The accessibility score was also often reported to be higher in areas with higher road density and for those populations who live nearby or along the main roads.[15,23,34] In terms of specific geographical characteristics, deltaic[32] and mountainous[39] regions also reported low accessibility scores.

Non-Spatial Factors

The spatial accessibility score to health care services can also be associated with non-spatial factors. Urban areas or areas with a higher degree of urbanisation were mostly reported to be positively associated with higher accessibility scores.[5,13,17,19–21,25,26,27,31,33,35,37,38] In addition to that, denser populated areas are also commonly reported to be positively associated with higher accessibility scores.[18,23,25,27,37]

Some studies found that a high accessibility score is associated with a population with higher socio-economic status (SES) and its related parameters such as education and household income[5,7,14,23,32,36–38,40] although Wang & Roisman (2011)[17] found no correlation between the accessibility score and socio-economic variables. Theoretically, SES (such as income, house ownership, vehicle ownership, education level) could be positively associated with spatial accessibility as it relates to the capability or affordability of the individual to access health care (such as cost of services or travel). Those with disadvantaged SES (e.g. lower income and lack of education) generally had lower spatial accessibility scores.[2,32]

Studies have found that areas with higher healthcare needs, such as a higher percentage of elderly population, are associated with low accessibility scores.[5,14,40] Lower accessibility scores were also associated with socio-culture disadvantages, such as social deprivation[13] or higher proportion of non-natives, ethnic minorities, aborigines or immigrants.[14,23,25,38,40] Table II summarises our findings on commonly reported factors associated with the spatial accessibility score for specific healthcare services.

DISCUSSION

This scoping review has mapped out several factors that are commonly associated with the spatial accessibility of various healthcare services, which could be further divided into spatial or non-spatial-related factors as aforementioned. Of

Table I: Articles included in scoping review (n = 32)

	Author, year	Location	Health care services	Findings/factors associated with spatial accessibility to healthcare services
1.	Bauer et al., 2018[13]	England	Primary care services	• Positively associated: areas surrounding major cities; higher degree of urbanisation • Negatively associated: higher social deprivation • Design: ecological cross-sectional (aggregated at Office for National Statistics boundary classification) • Population/participant: all population • Grant: none stated
2.	Bozorgi et al., 2021[38]	South Carolina, USA	Opioid treatment programs (OTP)	• Positively associated: metropolitan areas; areas with low social vulnerability index (calculated based on socio-economic status, household composition and disability, minority status and language, housing and transportation) • Design: Ecological cross-sectional (aggregated at census block group level) • Population/participant: all population • Grant: Open Access Fund from University Libraries, University of South Carolina
3.	Cao et al., 2019[37]	New Hampshire, USA	Opioid use disorder treatment	• Positively associated: higher population density areas; higher degree of urbanisation; areas with higher SES related variables (higher proportion of full-time employed population, higher median household income and higher proportion of adult population with tertiary education) • Design: ecological cross-sectional (aggregated at county subdivision/town level) • Population/participant: all population • Grant: National Institute on Drug Abuse of the National Institute of Health
4.	Cheng et al., 2012[33]	Beijing, China	Residential care services for elderly aged above 60	• Positively associated: city centre; degree of urbanisation • Negatively associated: outwards to periphery of city centre • Design: ecological cross-sectional (aggregated at census subdistrict level) • Population/participant: population aged 60 and above • Grant: Ministry of Education, China
5.	Delameter, 201328	Michigan, USA	Acute care (hospital)	• Positively associated: higher degree of urbanisation • Design: ecological cross-sectional (aggregated at census tract/zip code level) • Population/participant: all population • Grant: Michigan Department of Community Health
6.	Dewulf et al., 2013[20]	Belgium	General physician (doctors)	• Positively associated: degree of urbanisation • Design: ecological cross-sectional (aggregated at census tract level) • Population/participant: all population • Grant: none stated
7.	Eberth et al., 2014[35]	14 selected states in south region of United States (USA)	Mammography services	• Positively associated: urban areas • Design: ecological cross-sectional (aggregated at census block group level) • Population/participant: women aged 40 and above • Grant: National Cancer Institute and National Institute of Health US
8.	Gao et al., 2016[31]	France	health professional for general practitioner, maternal health services)	• Positively associated: urban area • Design: ecological cross-sectional (aggregated at census block level) • Population/participant: all pregnant women population • Grant: none stated
9.	Hu et al., 2013[15]	Donghai, China	Primary care (clinics)	• Positively associated: city centre; areas along highway • Negatively associated: edge/periphery of city centre; rural areas; remote areas • Design: ecological cross-sectional (aggregated at administrative village level) • Population/participant: all population • Grant: National Science and Technical Basic Research Key Project of China
10.	Izumi et al., 2016[26]	Japan	Hospital bed for Tuberculosis (TB)	• Positively associated: areas surrounding major cities; higher degree of urbanisation • Design: ecological cross-sectional (aggregated at Japan's medical administrative unit level) • Population/participant: all newly diagnosed TB patients • Grant: Japan Agency for Medical Research
11.	Jamtsho et al., 2015[18]	Bhutan	Primary care services, health personnel (doctors and health assistant)	• Positively associated: higher population density areas • Design: ecological cross-sectional (aggregated at town enumeration block level) • Population/participant: all population • Grant: none stated

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Table I: Articles included in scoping review (n = 32)

	Author, year	Location	Health care services	Findings/factors associated with spatial accessibility to healthcare services
12.	Jin et al., 2019[29]	Shenzhen, China	Public hospitals (3 tiers; community, town-level, municipal)	• Positively associated: main districts (accessibility to municipal hospitals) • Negatively associated: rural • Other findings: Town and community hospitals had better distribution across study area. • Design: ecological cross-sectional (aggregated at population statistics' community scale level) • Population/participant: all population • Grant: National Natural Science Foundation of China
13.	Lin et al, 2016[39]	Kaohsiung City, Taiwan	Out-of-hospital cardiac arrest (OHCA) services	• Negatively associated: rural areas, mountainous areas • Design: ecological cross-sectional (aggregated at Statistics Department's basic statistical area level) • Population/participant: out-of-hospital cardiac arrest patients • Grant: Academia Sinica
14.	Luo & Qi, 2009[7]	Northern Illionis, USA	Primary care services	• Positively associated: city centre • Negatively associated: periphery to city centre; rural areas; areas with lower population income • Design: ecological cross-sectional (aggregated at census latitude-longitude quadrilateral grid) • Population/participant: all population • Grant: none stated
15.	Luo et al., 2018[34]	Wuhan, China	Elderly services (total bed and number of doctors)	• Positively associated: higher road density areas • Design: ecological cross-sectional (aggregated at urban-rural autonomous unit level) • Population/participant: population aged 65 and above • Grant: National Natural Science Foundation of China
16.	Ma et al., 2018[30]	Wuhan, China	Hospitals (3 tiers)	• Positively associated: centre of the main city • Negatively associated: further distance to main city • Design: ecological cross-sectional (aggregated at geometry centres of buildings) • Population/participant: all population • Grant: National Key R&D Program of China
17.	McGrail & Humpreys 2009[8]	Victoria, Australia	Primary care services	• Positively associated: high population density areas • Design: ecological cross-sectional (aggregated at census collection district level) • Population/participant: all rural population • Grant: Monash University
18.	Naylor et al., 2019[22]	USA	Primary care (physicians, family medicine specialist, nurse practitioner)	• Positively associated: urban areas; areas with higher level of poverty, rural and isolated areas (Family Medicine Specialist) • Design: ecological cross-sectional (aggregated at census block level) • Population/participant: all population • Grant: National Center for Complementary & Integrative Health
19.	Ngui & Apparicio 2011[16]	Montreal, Canada	Primary care services (medical clinics)	• Positively associated: centre of the island • Design: ecological cross-sectional (aggregated at census dissemination area level) • Population/participant: all population • Grant: none stated
20.	Pan et al., 2015[27]	Sichuan, China	General inpatient care (number of doctors, staff and bed)	• Positively associated: higher population density areas • Design: ecological cross-sectional (aggregated at 2 km * 2 km grid) • Population/participant: all population • Grant: National Natural Science Foundation of China
21.	Pan et al., 2016[25]	Sichuan, China	General inpatient care	• Positively associated: higher population density areas • Other finding: government health expenditure has no association with spatial accessibility • Design: ecological cross-sectional (aggregated at country level) • Population/participant: all population • Grant: National Natural Science Foundation of China
22.	Ranga et al., 2014[2]	Selected rural area in northern India	Inpatient care	• Negatively associated: further distance to main urban areas • Design: ecological cross-sectional (aggregated at village level) • Population/participant: all rural population • Grant: European Union's FP7 programme

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Table I: Articles included in scoping review (n = 32)

	Author, year	Location	Health care services	Findings/factors associated with spatial accessibility to healthcare services
23.	Shah et al., 2016[14]	14 selected urban areas in Canada	Remote health care services (outpatient)	• Positively associated: city centre • Negatively associated: areas at the edge / periphery of the city centre; rural and remote areas; areas with higher following population characteristics: elderly population, without tertiary education, aborigine population, lower socio-economic statuses, recent immigrants • Design: ecological cross-sectional (aggregated at census metropolitan area level) • Population/participant: all urban population • Grant: University of Saskatchewan
24.	Shah et al., 2017[40]	Saskatchewan, Canada	Physiotherapies & family physician	• Negatively associated: higher proportion of elderly aged >65; low income population; areas with higher proportion of recent immigrant and/or aborigine • Design: ecological cross-sectional (aggregated at Canada's census subdivisions level) • Population/participant: all population • Grant: University of Saskatchewan
25.	Subal et al., 2021[21]	Swabia and city of Augsburg, Germany	General practitioner	• Positively associated: urban areas; surrounding main city • Negatively associated: rural areas • Design: ecological cross-sectional (aggregated at one-hectare grid) • Population/participant: all population • Grant: Projekt DEAL, Germany
26.	Vadrevu & Kanjilal, 2016[32]	India	Maternal health services	• Negatively associated: deltaic region and remote areas, which resides by population with lower socio-economics status (SES) • Other finding: proxy variables for SES include: percentage (%) of female population, % illiterate adults, % non-working age, % minority ethnic, % adult working status, household size, % house ownership, household income • Design: ecological cross-sectional (aggregated at village level) • Population/participant: all population • Grant: UK Department of International Development for 'Future Health System Research Consortium'
27.	Wan et al., 2012[19]	Texas, USA	Primary care services	• Positively associated: higher degree of urbanisation • Design: ecological cross-sectional (aggregated at census tract and census block level) • Population/participant: all population • Grant: Freedom Explore Program of Central South University, Beijing China
28.	Wang & Luo, 2005[5]	Illionis, USA	Primary care services	• Positively associated: urban areas • Design: ecological cross-sectional (aggregated at census tract level) • Population/participant: all population • Grant: US Department of Health and Human Services, Agency for Healthcare Research and Quality
29.	Wang & Pan, 2016[24]	Sichuan, China	General inpatient care (public and private)	• Negatively associated: higher percentage of ethnic minority • Design: Ecological cross-sectional (aggregated at 2 km * 2 km grid) • Population/participant: all population • Grants: National Natural Science Foundation of China, the China Postdoctoral Science Foundation, Sichuan University, Health and Family Planning Commission of Sichuan Province, and China Medical Board
30.	Wang & Roisman, 2011[17]	Toronto, Canada	Primary care clinics (with Chinese doctor)	• Positively associated: higher degree of urbanisation • Negatively associated: suburban areas • Other finding: SES indicators (income, tertiary education, proficiency of language) did not associated with accessibility scores • Design: ecological cross-sectional (aggregated at census tract level) • Population/participant: Mainland Chinese immigrant population • Grants: Social Sciences and Humanities Research Council, Canada

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Table I: Articles included in scoping review (n = 32)

	Author, year	Location	Health care services	Findings/factors associated with spatial accessibility to healthcare services
31.	Wang et al., 2018[23]	Sichuan, China	Primary care services	• Positively associated: flat land region; productive plains and well-developed region (higher gross domestic product, GDP); areas with less minority ethnic; areas with higher population density; areas with higher highway road density; areas with higher proportion of non-agriculture population • Negatively associated: mountainous region; underdeveloped region; areas with low proportion of adults with tertiary education level • Design: ecological cross-sectional (aggregated at 2 km * 2 km grid) • Population/participant: all population • Grants: none stated
32.	Zahnd et al., 2019[36]	Mississippi delta region, USA	Mammography	• Positively associated: areas with higher poverty level • Other findings: no difference in accessibility between delta region and non-deltaic region, across racial composition and urban–rural differences • Design: ecological cross-sectional (aggregated at census tract level) • Population/participant: women aged 45–74 years population • Grants: none stated

Table II: Spatial and non-spatial factors associated with the spatial accessibility scores

	Spatial factors						Non-spatial factors				
Health care services	City centre/ nearby	Further distance to urban/city centre	Remote/ rural areas	Higher road density	Mountainous region	Deltaic region	Higher degree of urbanisation	Higher population density	Higher socio-economic status*	Higher proportion of elder population	Higher proportion of minority / immigrants
Primary care services	+[7,13–16,21]	-[7,14,15]	+[22] -[14,15,21]	+[15,23]	-[23]		+[5,13,17,19–21]	+[8,18,23]	+[7,13,23] -[22]	-[5,14]	-[14,23]
Inpatient care services	+[26,29,30]	-[2,30]	-[29]				+[25,26,28]	+[25,27]			-[24]
Maternal health services			-[32]			-[32]	+[31]		+[32]		
Elderly care	+[33]	-[33]		+[34]			+[33]				
Other specialised services			-[39]		-[39]		+[35,37,38]	+[37]	+[36–38,40]	-[40]	-[38,40]

Notes:
* Refers to all socio-economic related variables such as household income, poverty level, proportion of working population, proportion of population with tertiary education
Plus (+) sign indicates positive association, while negative (-) sign indicates negative association, as reported by the study(ies) in superscript.

the 32 studies included in this review, most of the studies were conducted in high-income and developed nation settings, such as Americas[5,7,14,16,17,19,22,28,35–38,40] and European countries,[13,20,21,31] as well as from China.[15,23–25,27,30,33,34] Most studies have shown similar associations among the studied factors, although only a few contradictory results were found. This review not only includes studies that were conducted primarily to search for the associated factors or affirm their findings through statistical significance. The association between factors could also be indirectly reported based on the spatial pattern observed when mapped (such as surrounding the city center and mountainous areas).

Most studies have reported a positive association or a higher spatial accessibility score of various health care services in the city centre and its surroundings. This is also directly related to the higher degree of urbanisation. This is because the health facilities and services are commonly concentrated in the urban areas and city centres.[4,23,29] This also could be the reason for higher population density positively associated with accessibility score, because urban areas are often classified based on areas with higher population density as compared to rural areas. Rural areas are also often associated with inferior availability of a wide range of infrastructures and build environments,[32] and a lack of these can serve as barriers to accessing health care. For example, road density was also positively associated with spatial accessibility to healthcare services, as demonstrated by a few published studies,[15,23,34] indicating that areas with scarce road networks had lower spatial accessibility scores.

Geographical characteristics certainly play a role in affecting spatial accessibility. Disadvantageous features such as non-flat areas or ground, mountainous and deltaic areas often had negative associations with the spatial accessibility score. This could be attributed to the nature of scarce resources and less productive plains for population economic activities and suitability for development.[23] Remote areas are typically negatively associated with the accessibility score. However, in some instances, the spatial accessibility score in remote areas is even better for certain healthcare services. This is commonly due to the demand–supply imbalance of the population and services. Having a decent distribution of resources, coupled with low demand for that specific health care area, results in a higher accessibility due to a lack of competition and congestion.[22,29]

Non-spatial-related factors refer to population characteristics. This study found that SES-related variables of the population were frequently reported to be associated with spatial accessibility. Populations with certain characteristics, such as low income, lack of education or ethnic minority, frequently had negative associations. Although it might not be the direct cause of having a low spatial accessibility score to the services, the consequences could be detrimental to those vulnerable populations.

Considering the fact that ensuring equitable access according to health needs is the ultimate goal towards universal health coverage, it is fairly important to know how the health needs of the population can be quantified and incorporated into the calculation of the spatial accessibility score.[31] The health needs of the population can be quantified using proxy variables such as age, proportion of the elderly population, children and female population.[5] Later studies followed similar attempts to incorporate the health need into the calculation of the FCA-based method[8,31] with the basis that areas with higher population health needs would have reduced access due to competition as the consequence of higher service utilisation. The SES of the population could also be incorporated into the FCA-based method with the basis that those with SES disadvantageous theoretically have some sort of financial barrier (affordability) to access health care, particularly for those fees-for-services. Such findings could provide the researchers with a basis for further improvement of the FCA-based method by incorporating non-spatial factors.[19]

This study has summarised the factors associated and their relationships, specifically for spatial accessibility to several healthcare services, from the existing literature. The limitation of this study is that most of the studies included in this review originated from high-income countries, and the scenario could differ in middle- and low-income countries (LMIC), as the accessibility could be very context-specific. Nonetheless, a few LMIC studies in this review did show similar findings in high-income countries. Another limitation is that this study only looks at studies that use FCA-based methods to measure spatial accessibility. In fact, the spatial accessibility could also be measured using other methods, such as using the nearest distance to services[3] or population coverage. The FCA-based method is the most accurate method for measuring spatial accessibility (compared to other methods aforementioned) because of its comprehensiveness and closer to real-world setting.[4,20,27,40]

CONCLUSION

The spatial accessibility to healthcare services was best determined using the FCA-based method, and the method has continuously evolved and enriched since it was last introduced, with growing interest among the researchers. This study collates and identifies factors that are specifically associated with the spatial component of accessibility to healthcare services, which can be distinguished from spatial or non-spatial-related factors. Some of these factors can be quantified and incorporated into the current available FCA-based method to provide a better measure of spatial accessibility of health care services.

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REFERENCES

1. Peters DH, Garg A, Bloom G, Walker DG, Brieger WR, Hafizur Rahman M. Poverty and access to health care in developing countries. Ann N Y Acad Sci 2008; 1136: 161-71.
2. Ranga V, Panda P. Spatial access to in-patient health care in northern rural India. Geospat Health 2014; 8(2): 545-56.

3. Apparicio P, Gelb J, Dubé AS, Kingham S, Gauvin L, Robitaille É. The approaches to measuring the potential spatial access to urban health services revisited: Distance types and aggregation-error issues. Int J Health Geogr 2017; 16(1): 1-24.
4. Mcgrail MR. Spatial accessibility of primary health care utilising the two step floating catchment area method: an assessment of recent improvements. Int J Health Geogr 2012; 11(1): 1-12.
5. Wang F, Luo W. Assessing spatial and nonspatial factors for healthcare access: Towards an integrated approach to defining health professional shortage areas. Heal Place 2005; 11(2): 131-46.
6. Luo W, Wang F. Measures of spatial accessibility to health care in a GIS environment: Synthesis and a case study in the Chicago region. Environ Plan B Plan Des 2003; 30(6): 865-84.
7. Luo W, Qi Y. An enhanced two-step floating catchment area (E2SFCA) method for measuring spatial accessibility to primary care physicians. Health Place 2009; 15(4): 1100-7.
8. McGrail MR, Humphreys JS. Measuring spatial accessibility to primary care in rural areas: Improving the effectiveness of the two-step floating catchment area method. Appl Geogr 2009; 29(4): 533-41.
9. Derose KP, Gresenz CR, Ringel JS. Understanding disparities in health care access—and reducing them—through a focus on public health. Health Aff 2011; 30(10): 1844-51.
10. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. Int J Soc Res Methodol Theory Pract 2005; 8(1): 19-32.
11. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc 2015; 13(3): 141-6.
12. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. Ann Intern Med 2018; 169(7): 467-73.
13. Bauer J, Müller R, Brüggmann D, Groneberg DA. Spatial accessibility of primary care in england: A cross-sectional study using a floating catchment area method. Health Serv Res 2018; 53(3): 1957-78.
14. Shah TI, Bell S, Wilson K. Spatial accessibility to health care services: Identifying under-serviced neighbourhoods in canadian urban areas. PLoS One 2016; 11(12): e0168208.
15. Hu R, Dong S, Zhao Y, Hu H, Li Z. Assessing potential spatial accessibility of health services in rural China : a case study of Donghai county. Int J Equity Health 2013; 12(35): 1-11.
16. Ngui AN, Apparicio P. Optimizing the two-step floating catchment area method for measuring spatial accessibility to medical clinics in Montreal. BMC Health Serv Res 2011; 11(166): 1-12.
17. Wang L, Roisman D. Modeling spatial accessibility of immigrants to culturally diverse family physicians. Prof Geogr. 2011; 63(1): 73-91.
18. Jamtsho S, Corner R, Dewan A. Spatio-temporal analysis of spatial accessibility to primary health care in Bhutan. ISPRS Int J Geo-Information 2015; 4: 1584-604.
19. Wan N, Zou B, Sternberg T. A three-step floating catchment area method for analyzing spatial access to health services. Int J Geogr Inf Sci 2012; 26(6): 1073-89.
20. Dewulf B, Neutens T, De Weerdt Y, Van De Weghe N. Accessibility to primary health care in Belgium: An evaluation of policies awarding financial assistance in shortage areas. BMC Fam Pract 2013; 14(1): 1-13.
21. Subal J, Paal P, Krisp JM. Quantifying spatial accessibility of general practitioners by applying a modified huff three-step floating catchment area (MH3SFCA) method. Int J Health Geogr 2021; 20(1): 1-14.
22. Naylor KB, Tootoo J, Yakusheva O, Shipman SA, Bynum JPW, Davis MA. Geographic variation in spatial accessibility of U.S. Healthcare providers. PLoS One 2019; 14(4): 1-15.
23. Wang, Yang H, Duan Z, Pan J. Spatial accessibility of primary health care in China: A case study in Sichuan Province. Soc Sci Med 2018; 209: 14-24.
24. Wang X, Pan J. Assessing the disparity in spatial access to hospital care in ethnic minority region in Sichuan Province, China. BMC Health Serv Res 2016; 16(1): 1-11.
25. Pan J, Zhao H, Wang X, Shi X. Assessing spatial access to public and private hospitals in Sichuan, China: The influence of the private sector on the healthcare geography in China. Soc Sci Med 2016; 170: 35-45.
26. Izumi K, Kawatsu L, Ohkado A, Uchimura K, Kato S. Evaluating the impact of health resource reconstruction on improving spatial accessibility of tuberculosis care 2016; 20: 1501-8.
27. Pan J, Liu H, Wang X, Xie H, Delamater PL. Assessing the spatial accessibility of hospital care in Sichuan Province, China. Geospat Health 2015; 10(2): 261-70.
28. Delamater PL. Spatial accessibility in suboptimally configured health care systems: A modified two-step floating catchment area (M2SFCA) metric. Heal Place 2013; 24: 30-43.
29. Jin M, Liu L, Tong D, Gong Y, Liu Y. Evaluating the spatial accessibility and distribution balance of multi-level medical service facilities. Int J Environ Res Public Health 2019; 16(7): 1150.
30. Ma L, Luo N, Wan T, Hu C, Peng M. An improved healthcare accessibility measure considering the temporal dimension and population demand of different ages. Int J Environ Res Public Health 2018; 15(11): 2421.
31. Gao F, Kihal W, Le Meur N, Souris M, Deguen S. Assessment of the spatial accessibility to health professionals at French census block level. Int J Equity Health 2016; 15(1): 1-14.
32. Vadrevu L, Kanjilal B. Measuring spatial equity and access to maternal health services using enhanced two step floating catchment area method (E2SFCA) - A case study of the Indian Sundarbans. Int J Equity Health 2016; 15(1): 1-12.
33. Cheng Y, Wang J, Rosenberg MW. Spatial access to residential care resources in Beijing, China. Int J Health Geogr 2012; 11(1): 32.
34. Luo J, Chen G, Li C, Xia B, Sun X, Chen S. Use of an E2SFCA method to measure and analyse spatial accessibility to medical services for elderly people in wuhan, China. Int J Environ Res Public Health. 2018; 15(7): 1503.
35. Eberth JM, Eschbach K, Morris JS, Nguyen HT, Hossain MM, Elting LS. Geographic disparities in mammography capacity in the south: A longitudinal assessment of supply and demand. Health Serv Res 2014; 49(1): 171-85.
36. Zahnd WE, McLafferty SL, Sherman RL, Klonoff-Cohen H, Farner S, Rosenblatt KA. Spatial Accessibility to Mammography Services in the Lower Mississippi Delta Region States. J Rural Heal 2019; 35(4): 550-9.
37. Cao Y, Stewart K, Wish E, Artigiani E, Sorg M. Determining spatial access to opioid use disorder treatment and emergency medical services in New Hampshire. J Subst Abus Treat 2019; 101: 55-66.
38. Bozorgi P, Eberth J, Eidson J, Porter D. Facility attractiveness and social vulnerability impacts on spatial accessibility to opioid treatment programs in Sough Carolina. Int J Environ Res Public Health 2021; 18: 4246.
39. Lin BC, Chen CW, Chen CC, Kuo CL, Fan I chun, Ho CK, et al. Spatial decision on allocating automated external defibrillators (AED) in communities by multi-criterion two-step floating catchment area (MC2SFCA). Int J Health Geogr 2016; 15(1): 1-14.
40. Shah TI, Milosavljevic S, Bath B. Measuring geographical accessibility to rural and remote health care services: Challenges and Considerations. Spat Spatiotemporal Epidemiol 2017; 21: 87-96.

Healthcare service quality measurement in Malaysia: A scoping review

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ABSTRACT

Introduction: Although healthcare service industry has been thriving in Malaysia, the types of healthcare service quality models used in past research as well as their key messages had not been explored. A scoping review was performed to determine the validated healthcare service quality models, the key messages of these past studies and potential research gaps that should be addressed in future studies.

Materials and Methods: Relevant, peer-reviewed, English-language articles on healthcare service quality in Malaysia were independently searched by the authors using the SCOPUS and EMERALD databases. Articles that do not directly address healthcare service quality within the Malaysian setting were excluded. Additional articles were identified from the reference lists of the selected articles and from Google search engine. A total of 43 out of 2,749 articles were selected.

Results: Most of these studies (28 out of the 43 articles, 65.1%) in this scoping review used either the original or a modified version of SERVQUAL instrument to measure healthcare service quality. Significant positive relationships between tangibles, assurance and empathy with patient satisfaction were identified. As SERVQUAL primarily measures the functional dimension of service quality, this suggests that past studies on Malaysian healthcare services emphasised heavily on the functional dimension of healthcare service quality. Functional dimension refers to the expressive performance on how the healthcare service is rendered whereas technical dimension refers to the types of services rendered as well as its safety and efficacy.

Conclusion: A pertinent research gap identified in this review is the lack of studies that measure both technical and functional dimensions comprehensively. Future research should adopt a more holistic (incorporating both technical dimension and functional dimension) measurement of healthcare service quality.

KEYWORDS:
Service quality; SERVQUAL; healthcare; Malaysia

INTRODUCTION

According to Endeshaw[1], there are five major generic models of healthcare service quality. These are (1) the Donabedian's model[2] (2) SERVQUAL instrument[3] (3) HEALTHQUAL instrument[4] (4) PubHosQual instrument[5] and (5) HospitalQual instrument[6] (see Table I for the detailed descriptions on these models). Interestingly, Endeshaw[1] also commented that as the majority of these models (i.e., Donabedian's, SERVQUAL and HEALTHQUAL) were developed in the Western countries, they may not be suitable to be used in developing countries. Furthermore, service quality perception can be highly culturally centric.[7] As a result, healthcare models conceptualised in a Western setting may not be able to fully capture a patient's personal health beliefs in a non-Western setting. These personal beliefs, however, can be an important force in shaping how patients consume healthcare services. Hence, whilst past literature[1-7] can shed light on the dimensions of healthcare service quality commonly measured in developed countries, the dimensions of healthcare service quality commonly measured in developing countries, including in Malaysia, are less well known.

A service product does not take place in a vacuum. Rather, it involves the interactions between the service provider and the customer. Hence, the totality of a service quality rendered to a customer is not just dependent on what the customer receives, but how the customer receives it. As explained by Grönroos[8], service quality is broadly divided into two dimensions: (1) the technical dimension and (2) the functional dimension. Technical dimension refers to the instrumental performance of a service product delivered to and consumed by the consumer (e.g., the types of treatment or surgery received by the patient) whereas functional dimension refers to the expressive performance of a service product (e.g., the conditions of the ward or operation suite where the treatment or surgery is carried out). Basically, the technical dimension answers the question of "what" the customer receives whereas the functional dimension answers the question of "how" the customer receives the services.[8]

To the best of our knowledge, although healthcare service industry has been a thriving industry in Malaysia, the types of healthcare service quality models used in past research as well as their key messages or metanarrative had not been explored. To address these overarching questions, we conducted a scoping review to answer three questions: (1) What were the common validated models or instruments that had been used to measure Malaysian healthcare service quality in past studies? Are these models primarily reflect the technical dimension or the functional dimension of service quality or a combination of both? (2) What were the key

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messages emerged from these past studies? (3) What are the potential research gaps in the Malaysian healthcare service quality that should be addressed in future studies?

MATERIALS AND METHODS

Procedure

Scoping review is a type of literature review aimed "to map rapidly the key concepts underpinning a research area, its main sources as well as the types of evidence available in the body of literature".[9] This scoping review was conducted using the 5-step methodological framework by Arksey & O'Malley.[9] These five steps are: (1) identifying research objectives or research questions; (2) identifying relevant studies; (3) selecting studies to be included based on the inclusion and exclusion criteria; (4) charting and interpreting data and (5) collating, summarising, synthesising and reporting the results.[9]

Eligibility Criteria

Only peer-reviewed academic articles that specifically address healthcare service quality in Malaysia were included in our scoping review. General review articles on service quality, articles that do not specifically describe the application of a service quality model within the Malaysian healthcare context as well as anecdotal reports were excluded. Only English-language articles were included. No specific publication time period was imposed as part of our search criteria.

Literature search was conducted using the search strategy described by Aromataris and Riitano.[10] The keywords and Boolean operators used for our search on titles and article abstracts were: (1) service qualit* AND Malaysi* AND hospital*, (2) service qualit* AND Malaysi* AND healthcare, (3) service qualit* AND Malaysi* AND health care, (4) service qualit* AND Malaysi* AND clinic* as well as (5) service qualit* AND Malaysi* AND medical.

The search was conducted on Scopus, Emerald and Google Scholar databases. Reporting of these studies was performed based on the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guideline.[11] Following the initial identification of records generated in the selected databases, a preliminary screening of the texts in titles and abstracts was conducted to look for eligible articles. Two of the authors (KSC and KLS) independently screened for articles eligibility. If there was any disagreement between the authors, discussions were held together with the other two authors (SSLW and RAB) to resolve the disagreement through consensus. Additional articles were then manually searched by authors KSC and KLS from the reference lists of the articles identified for review as well as from google search engine. The eligible articles were then charted using the PRISMA flow diagram for scoping review process.

Quantitative and qualitative synthesis of the studies were then conducted. For quantitative synthesis, the authors' names, the year of publication, the objectives of the study, the settings where the study took place (i.e., whether in public healthcare system or private healthcare system or both) and the types of service quality models were recorded. For qualitative synthesis, the full texts of the identified articles were first iteratively read by the two authors. Open coding via NVivo software was first performed using thematic content analysis. After the initial open coding, a second axial coding was performed by re-analysing these open codes to look for key trends or key findings on Malaysian healthcare service quality reported in these studies. Finally, focus group discussions were held among all authors to specifically answer research questions no. 2 and no. 3.

RESULTS

From our initial search, a total of 1662 articles were identified from the Scopus, Emerald and Google Scholar databases. An additional 1087 potentially relevant articles were found by manual searching for citations within the reference sections of the identified articles as well as from google search engine. Out of these 1662 articles identified from databases, 949 articles were initially removed due to duplicates. A total of 1718 articles were then excluded or not retrieved as these articles were considered irrelevant, abstract-only articles or articles written in languages other than the English language. Out of these remaining 82 articles, another 39 articles were further excluded from our analysis. This is because albeit the fact that these articles describe some aspects of healthcare service quality, they did not specifically describe the application of any specific service quality instruments within the Malaysian healthcare context. Eventually, 43 full-text articles were identified to be included in this scoping review (see Figure 1 for the PRISMA diagram). Most of these included papers were published in the recent decade, i.e., 13 papers (30.2%) were from the period of 2011–2015 and another 24 papers (55.8%) from the period of 2016–2020.

With regards to the first research question, SERVQUAL (or a modified form of SERVQUAL) was found to be the only validated generic model (out of the five described by Endeshaw[1]) used in studies identified in this review. SERVQUAL was used in 28 out of the 43 (65.1%) studies identified. In all other studies, the authors defined their own dimensions of service quality. Interestingly, only 18 studies (41.9%) were conducted solely in private healthcare settings, another 20 studies (46.5%) were conducted solely in public healthcare settings (e.g., in public hospitals, community health clinics, armed forces medical centers and public university healthcare services) and another 5 studies (11.6%) were conducted in both private and public healthcare settings (Table II). Hence, as most of the papers identified in this scoping review used SERVQUAL instrument to measure healthcare service quality, this suggests that research on healthcare service measurement in Malaysia thus far leaned heavily on the functional dimension.[8]

With regards to the second research question, a key message gleaned from these past studies is the existence of a clear positive relationship between healthcare service quality and patient satisfaction.[12-24] Greater patient satisfaction, in turn, leads to positive behavioral intention.[14-16,18-20] The dimensions of service quality most commonly found to have significant relationships with patient satisfaction and behavioral intentions were tangibles, assurance and empathy.[12;17-19] (see Figure 2 of the word cloud generated from NVivo).

Table I: Description of five major models or instruments of healthcare service quality

Healthcare Service Quality Model/Instrument	Description
Donabedian Model[2]	According to Donabedian, there are three inter-related components that determine healthcare quality. These three components are structure, process and outcome.[2] "Structure" refers to tangibles such as buildings, qualifications and competencies of the healthcare staff and the equipment. "Process" refers to all interactions (e.g., diagnostic processes, treatment and intervention, patient education) that occur within the "structure" of a healthcare organisation and "outcome" refers to the result of a "process" that has happened within the "structure" of a healthcare organisation.
SERVQUAL model[3]	A commonly used service quality instrument in many different types of industries including healthcare services by Parasuraman et al.[3] This model addresses five dimensions of a customer's overall perceptions of quality.[4] These five dimensions are (1) R = reliability, (2) A = assurance, (3) T = tangibles, (4) E = empathy and (5) R = responsiveness (hence, the acronym, RATER). "Reliability" refers to the capability of a healthcare organisation to provide services in a consistent and timely manner as promised. "Assurance" refers to the competency of the healthcare staff to deliver healthcare services in a manner that can inspire trust and confidence. "Tangibles" refer to the physical aspects (the environment, the building, etc.) where the healthcare services are delivered. "Empathy" refers to the healthcare staff's ability to build positive relationships with compassion and understanding of a patient's needs and "responsiveness" refers to the ability of the healthcare organisation to respond to the patient's needs in a prompt manner.
HEALTHQUAL[4]	This is an integrated model aimed to measure healthcare service quality from both the perspectives of patients as well as the hospital. The five components measured using this instrument are empathy, tangibles, safety, efficiency and improvement of care services.
PubHosQual[5]	This instrument measures five dimensions of service quality, i.e., (1) admission, (2) medical service, (3) overall service, (4) discharge and (5) social responsibility, in a public hospital setting in India.
HospitalQual[6]	This instrument was developed for the purpose of monitoring, controlling and improving the quality of inpatient healthcare services.

Table II: Characteristics of studies included in this scoping review

Variables		Number (%)
Publication years		
	2001–2005	1 (2.3)
	2006–2010	5 (11.7)
	2011–2015	13 (30.2)
	2016–2020	24 (55.8)
Types of healthcare studied		
	Private healthcare services	18 (41.9)
	Public healthcare services	20 (46.5)
	Both	5 (11.6)
Types of service quality instruments used		
	SERVQUAL or modified versions of SERVQUAL	28 (65.1)
	Others	15 (34.9)

With regards to the third research question, as much fewer studies had included the technical dimension of service quality (4.6%) compared to functional dimension, a pertinent research gap identified is the lack of studies measuring both technical and functional dimensions comprehensively.

DISCUSSION

The findings from this scoping review suggest that past studies on healthcare service quality measurement in Malaysia are customer-centric and gravitates toward the functional dimension of service quality. As explained by Andaleb[25], measuring customer-centric service quality is important as patient satisfaction is pivotal for long-term sustainability and profitability of healthcare services, particularly private healthcare services. A dissatisfied patient leads to a number of negative behaviors including switching healthcare service providers as well as spreading and influencing others with the news of their unpleasant experiences.[26] A satisfied customer, on the other hand, is more likely to continue using the services rendered and to spread the positive news to others.[27] In fact, Petersen[28] went as far as to say that "it really does not matter if the patient is right or wrong. What counts is how the patient felt even though the caregiver's perception of reality may be quite different." As patients become more and more educated, coupled with the easy availability of information from the

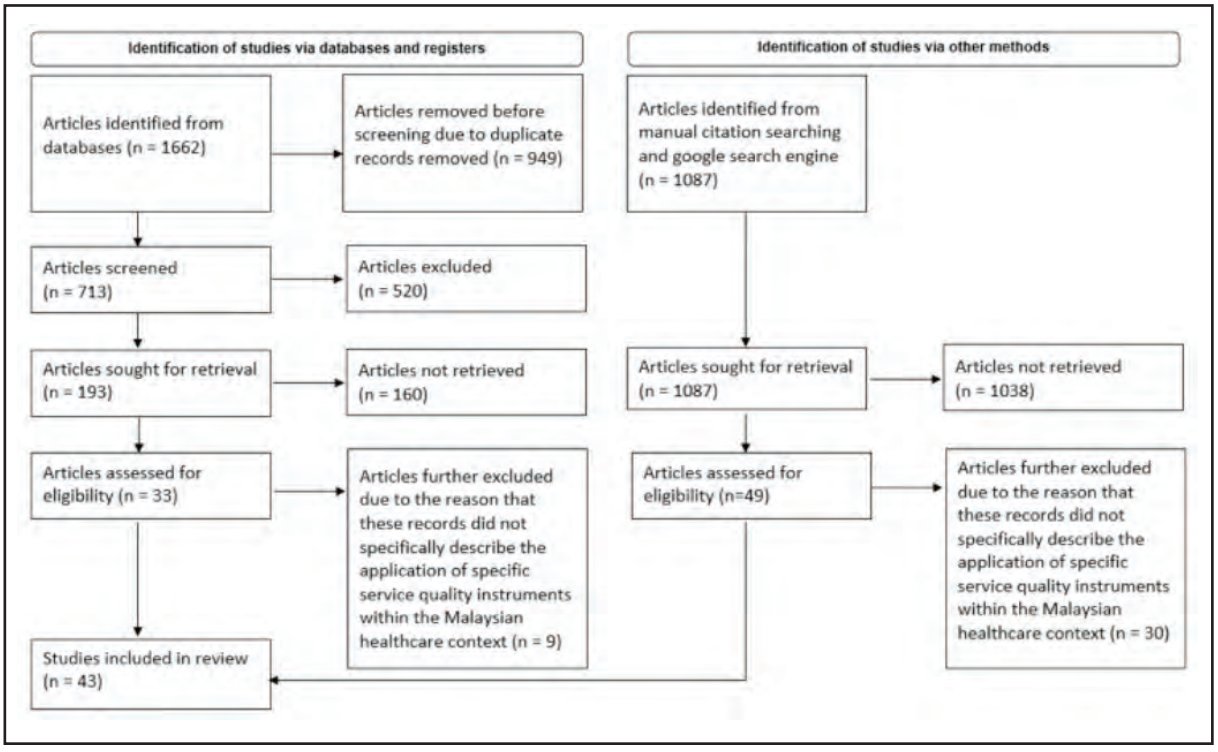

Fig. 1: Preferred reporting items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram

Fig. 2: Word cloud of relative importance of keywords identified in the study

internet, these patients can become even more critical of the quality of services that they receive as well as becoming more aware of the various options available to them.[29]

However, due to the complexity of healthcare services,[30] the patient, as a customer, is often not the best judge of healthcare service quality, particularly the technical dimension of healthcare service quality.[30-31] A patient often lacks the necessary knowledge to provide a valid assessment of the technical dimension of healthcare service quality.[31] For example, the patient may not be able to fully comprehend and evaluate the surgeon's skills or the appropriateness of a suggested diagnostic tool (i.e., the sensitivity, specificity, negative and positive predictive values of plain radiography in detecting intracranial tumor).[31,32] This inability to assess the technical dimension inadvertently causes the patient to place relatively more emphasis on the functional dimension of healthcare service quality (e.g., the personal hygiene or demeanor of the paramedic, the cleanliness of the toilet or the aesthetics of the ward).[33]

A service product (or good), where a customer is not able to fully evaluate the quality of a product due to the lack of technical knowledge is known as "credence good".[34] In the context of healthcare service, due to the credence nature of the healthcare service, the patient, as a customer, often has to depend on other "signals" or "cues" from the functional dimension (the brand of the hospital, the cleanliness of the ward, the dress code of the staff, the quality of hospital food, etc.) to gauge its quality.

On the other hand, the Institute of Medicine in United States defines healthcare service quality very differently in these six domains: (1) safety (i.e., minimising risk of harm to patients); (2) effectiveness i.e., (providing healthcare services based on scientific knowledge that would benefit and refraining from services that would not benefit the patients); (3) patient-centeredness (i.e., providing care that is respectful of and responsive to the patient's preferences, needs and values); (4) timeliness (i.e., reducing waits and sometimes harmful delays to the patients); (5) efficiency (i.e., avoiding waste and redundancy of resources) and (6) equitability (i.e., ensuring that the services rendered does not vary in quality because of personal characteristics and socioeconomic status of the patients).[35]

Therefore, as fewer studies had included the technical dimension of service quality (4.6%) compared to the functional dimension (100%), a pertinent research gap identified in this review is the lack of studies that measure a combination of both technical and functional dimensions comprehensively. While customer-centric measurement ("what the patient think are important as a customer") remains an integral part of any research on Malaysian healthcare service quality, it is incomplete if it is not accompanied by the measurement of technical dimension of service quality ("what are actually important for the customer as a patient").

CONCLUSION

In summary, we found that (1) SERVQUAL or a modified version SERVQUAL was the only validated generic instrument used in past studies on healthcare service quality measurement in Malaysia; (2) there were positive relationships between healthcare service quality (notably from the dimensions of tangibles, assurance and empathy) with patient satisfaction and (3) as most of these studies adopted a very customer-centric approach to primarily measure the functional dimension of service quality, future studies should include measurement on the technical dimension as well to ensure that a holistic healthcare service quality is measured.

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REFERENCES

1. Endeshaw B. Healthcare service quality-measurement models: a review. J Health Res 2021; 35(2): 106-17.
2. Donabedian A. Evaluating the quality of medical care. 1966. Milbank Q 2005; 83(4): 691-729.
3. Parasuraman A, Zeithaml VA, Berry LL. A conceptual model of service quality and its implications for future research. J Market 1985; 49(4): 41-50.
4. Lee D. HEALTHQUAL: a multi-item scale for assessing healthcare service quality. Service Business 2017; 11(3): 491-516.
5. Aagja JP, Garg R. Measuring Perceived Service Quality for Public Hospitals (Pubhosqual) in the Indian Context. Int J Pharm Healthcare Market. 2010; 4(1): 60-83.
6. Itumalla R, Acharyulu G, Shekhar BR. Development of HospitalQual: a service quality scale for measuring in-patient services in hospital. Operations Supply Chain Manag 2014; 7(2): 54-63.
7. Fatima I, Humayun A, Iqbal U, Shafiq M. Dimensions of service quality in healthcare: a systematic review of literature. Int J Qual Health Care 2019; 31(1): 11-29.
8. Grönroos C. A Service quality model and its marketing implications. Eur J Market 1984; 18(4): 36-44.
9. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005; 8(1): 19-32.
10. Aromataris E, Riitano D. Constructing a search strategy and searching for evidence. A guide to the literature search for a systematic review. Am J Nurs 2014; 114(5): 49-56.
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372: n71.
12. Hayati IN, Azimatun N, Rozita H, Ezat W, Rizal A. In-patient's satisfaction in the medical and surgical wards-A comparison between accreditted and non accreditated hospital in the state of Selangor. J Commun Health 2010; 16(1): 60-8.
13. Rad NF, Som APM, Zainuddin Y. Service quality and patients' satisfaction in medical tourism. World Appl Sci J 2010; 10(1): 24-30.
14. Aliman NK, Mohamad WN. Perceptions of service quality and behavioral intentions: a mediation effect of patient satisfaction in the private health care in Malaysia. Int J Market Stud 2013; 5(4): 15-29.
15. Amin M, Nasharuddin SZ. Hospital service quality and its effects on patient satisfaction and behavioural intention. Clin Govern 2013; 18(3): 238-54.

16. Mohamed B, Azizan NA. Perceived service quality's effect on patient satisfaction and behavioural compliance. Int J Health Care Quality Assurance 2015; 28(3): 300-14.
17. Aliman NK, Mohamad WN. Linking service quality, patients' satisfaction and behavioral intentions: an investigation on private healthcare in Malaysia. Procedia - Social Behav Sci 2016; 224: 141-8.
18. Ismail A, Yunan YM. Service quality as a predictor of customer satisfaction and customer loyalty. Logforum 2016; 12(4): 269–83.
19. Ismail A, Rose IR, Tudin R, Dawi NM. Relationship between service quality and behavioral intentions: The mediating effect of customer satisfaction. Etikonomi 2017; 16(2): 125-44.
20. Ismail A, Zaki HO, Rose IR. Interlinkages between service quality, customer satisfaction and customer loyalty in Malaysia: a case study of Armed Forces Medical Organizations. Geografia 2017; 12(7): 47-59.
21. Aljaberi MA, Juni MH, Al-Maqtari RA, Lye MS, Saeed MA, Al-Dubai SAR, et al. Relationships among perceived quality of healthcare services, satisfaction and behavioural intentions of international students in Kuala Lumpur, Malaysia: a cross-sectional study. BMJ Open 2018; 8(9): e021180.
22. Asnawi A, Awang Z, Afthanorhan A, Mohamad M, Karim F. The influence of hospital image and service quality on patients' satisfaction and loyalty. Manag Sci Lett 2019; 9(6): 911-20.
23. Tan CNL, Ojo AO, Cheah JH, Ramayah T. Measuring the Influence of Service Quality on Patient Satisfaction in Malaysia. Qual Manag J 2019; 26(3): 129-43.
24. Idris S, Choong FK, Sulong RS, Dausin O. Perceived service quality, customer satisfaction and behavioural intentions towards hospital in Sabah. Int J Supply Chain Oper Manag Logis 2020; 1(2): 21-35.
25. Andaleeb SS. Determinants of customer satisfaction with hospitals: a managerial model. Int J Health Care Quality Assurance 1998; 11(6): 181-7.
26. Bendall-Lyon D, Powers TL. The impact of gender differences on change in satisfaction over time. J Consumer Market 2002; 19(1): 12-23.
27. Zeithaml VA, Bitner MJ. Services marketing: integrating customer focus across the firm. 7th ed. New York: McGraw-Hill Education; 2017.
28. Petersen MBH. Measuring patient satisfaction: collecting useful data. J Nurs Care Qual 1988; 2(3): 25-35.
29. Lim PC, Tang NK. A study of patients' expectations and satisfaction in Singapore hospitals. Int J Health Care Quality Assurance 2000; 13(7): 290-99.
30. Eiriz V, Figueiredo JA. Quality evaluation in health care services based on customer-provider relationships. Int J Health Care Qual Assur 2005; 18(6): 404-12.
31. Wong JCH. Service quality measurement in a medical imaging department. Int J Health Care Qual Assur 2002; 15(5): 206-12.
32. Butt MM, de Run EC. Private healthcare quality: applying a SERVQUAL model. Int J Health Care Qual Assur 2010; 23(7): 658-73.
33. Ramsaran-Fowdar RR. The relative importance of service dimensions in a healthcare setting. Int J Health Care Qual Assur 2008; 21(1): 104-24.
34. Bloom PN, Reve T. Transmitting signals to consumers for competitive advantage. Business Horizons. 1990; 33(4): 58-66.
35. Institute of Medicine (IOM). Crossing the quality chasm: a new health system for the 21st Century. Washington, DC: The National Academies Press; 2001.

Making the case for the Malaysian Medical Association-Junior Doctors Network (MMA-JDN): A report and memorandum of the 2022 MMA-JDN International Conference

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ABSTRACT

The Malaysian Medical Association-Junior Doctors Network (MMA-JDN) was recently formed via constitutional amendments during the 62nd Annual General Meeting of the Malaysian Medical Association held in 2022. MMA-JDN subsequently went on to organise its first international conference held from 4th to 6th November 2022. This paper documents the rationale behind the establishment of this new section in MMA and the timeline of its formation, reports on the aforementioned conference, as well as lays down the future direction of MMA-JDN.

INTRODUCTION

Junior doctors refer to those within 10 years of their medical graduation and/or currently undergoing postgraduate training. The Junior Doctors Network (JDN) is a branch under the World Medical Association that strives to empower young doctors to work together towards a healthier world through advocacy, education and international collaboration.[1]

HISTORY OF JUNIOR DOCTORS NETWORK IN MALAYSIA

Locally in Malaysia, the Section Concerning House Officers, Medical Officers and Specialists (SCHOMOS) in the Malaysian Medical Association (MMA) has been the main body supporting and representing junior doctors since the year 1971. The Malaysian Chapter of JDN was subsequently formed in 2016 under the auspices of SCHOMOS, and its first milestone was the 2018 Penang Declaration Against Workplace Bullying and Harassment.[2] More recently, further steps were undertaken in the 2022 MMA Annual General Meeting to formalise and recognise JDN as an important bloc within the Association itself. The Malaysian Medical Association-Junior Doctors Network (MMA-JDN) was established through constitutional amendments, with a seat guaranteed for an MMA-JDN representative at the National Working Committee (NWC) of SCHOMOS.[3] Further constitutional amendments are planned to replicate these arrangements within the Private Practioners' Section (PPS) in the MMA.

JUSTIFYING THE NEED FOR MMA-JDN

The formalisation of MMA-JDN was done in recognition that junior doctors in Malaysia face unique and unusual circumstances, especially with the introduction of contract hiring in the government sector over the past 5 years. This has led to the scenario of an increasing number of junior doctors exiting government service into the private sector.[3,4] Now that a significant proportion of junior doctors are employed in both the government and private sectors (which are separately represented by SCHOMOS and PPS, respectively), there is a need for one common uniting platform for junior doctors to meet and discuss their concerns. These concerns may then be brought forward during NWC meetings for further input from senior doctors and subsequent action. All in all, the establishment of MMA-JDN through constitutional amendments is a strong demonstration of MMA's continued support for junior doctors.

MMA-JDN INTERNATIONAL CONFERENCE 2022

As its first official event, an international MMA-JDN conference was held in conjunction with the 26th Commonwealth Medical Association Triennial Conference and Council Meeting from 4th to 6th November 2022. The theme of the conference was "Empowering Junior Doctors: The Future of Malaysian Healthcare Providers". It saw an attendance of 133 delegates from 14 countries with good representation across the Asian, African, European, Caribbean and North American regions.

After the opening address by the outgoing President of the Commonwealth Medical Association and incumbent President of the World Medical Association, Dr Osahon Enabulele, the conference proceedings were kickstarted with a presentation on the history of SCHOMOS in Malaysia and its ongoing efforts to support junior doctors.[4] This was followed by educational and informative talks about private general practice, pathways to specialisation, research and career progression, in addition to a forum on Best Country Practices in conjunction with our international delegates.

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Before the conference officially drew to a close, a memorandum was presented to commemorate this significant milestone in MMA-JDN's history. It was promptly ratified without amendment by all delegates present.

2022 MMA-JDN MEMORANDUM

The participants of the 2022 Malaysian Medical Association-Junior Doctors Network (MMA-JDN) Conference gathered in Kuala Lumpur, Malaysia, made a declaration on 5th November 2022 that:

1) Junior doctors are an important bloc within the medical fraternity in their own right, and consequently should be represented adequately in their respective National Medical Associations.
2) The vulnerability of junior doctors in the fledging phase of their careers should not be exploited. Instead, they should be treated fairly with proper remuneration and sufficient opportunities for career advancement, without neglecting the importance of self-care and work-life balance.
3) Junior doctors themselves must realise that they have a huge role to play in shaping the future of their national healthcare landscape, especially if they are to influence it to reflect their generational values and aspirations. All junior doctors should therefore be actively involved in JDN activities for their collective voices to be heard.
4) Likewise, senior doctors have a duty to safeguard the future of their profession by supporting the next generation of junior doctors and inculcating the right values in them.
5) All National Medical Associations should nurture Junior Doctor Bodies in their respective countries (with representation at the Junior Doctors Network) to empower them and facilitate advocacy, education and collaboration concerning issues of junior doctors.

THE FUTURE OF MMA-JDN

Exchanges during this conference revealed that junior doctors across the world continue to share similar issues and pain points of less-than-desirable working hours and environments, unsatisfactory remuneration, and workplace bullying.[1] On the international front, MMA-JDN will actively participate in these ongoing discussions and seek to transcribe best practices found overseas into the Malaysian setting. Locally, MMA-JDN will complement SCHOMOS and value add via activities to support the professional development of our junior doctors.

In addition to implementing such programmes, MMA-JDN will also seek to evaluate ongoing trends in the operational aspects of the practice of medicine in Malaysia, such as manpower mobility and availability, brain drain, workforce allocations and workplace culture. It is hoped that the data generated will serve to produce evidence-based, well-informed policymaking. Given that the practice of medicine is invariably tied to the quality and quantity of human resources,[5,6] its non-academic aspects cannot be overlooked. MMA-JDN will strive to contribute to the advancement of our medical fraternity via a holistic and inclusive approach.

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REFERENCES

1. Mishima C, Abe K. A report on the Junior Doctors Network (JDN) meeting: the JDN's challenges and future prospects. Japan Med Assoc J 2014; 57: 104-6.
2. Malaysian Medical Association. Junior Doctors Network-SCHOMOS MMA Penang Declaration 2018 [cited Dec 2022]. Available from: https://mma.org.my/web/wp-content/uploads/JDn-Declaration-Penang-2018-1.pdf.
3. Malaysian Medical Association, Kuala Lumpur. Minutes of the 62nd Annual General Meeting (hybrid). 2022; 42-6.
4. Goh ZNL, Wong AC, Thum SCC, Muhammad Ridzuan Tan NA, Cheng TTJ, Ganasan V. The ethics of a work strike. Med J Malaysia 2022; 77: 90-1.
5. Fujii Y, Hirota K, Muranishi K, Mori Y, Kambara K, Nishikawa Y, et al. Clinical impact of physician staffing transition in intensive care units: a retrospective observational study. BMC Anesthesiol 2022; 22: 362.
6. Li H, Yang Y, Xiao LD, Wiley JA, Chen H, Liao L, et al. Quality of care in Hunan Province nursing homes: relationship to staffing and organizational climate. Geriatr Nurs 2021; 42: 427-32.

Combating chlorhexidine allergy in perioperative setting

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ABSTRACT

Chlorhexidine is labelled as hidden allergen as the health care professionals (HCPs) are unaware of the wide range of products containing chlorhexidine. Adverse events from chlorhexidine allergy can be reduced by appropriate perioperative management especially heeding on positive history during preoperative assessment, awareness regarding this hidden allergen, and educating HCPs on possible chlorhexidine-containing products. The regulatory agencies all over the world have issued recommendations regarding safety and risk of hypersensitivity reactions with chlorhexidine-containing products. The onus lies on HCPs to disseminate this knowledge to the stakeholders. We present a brief update to combat chlorhexidine allergy in perioperative setting.

INTRODUCTION

Chlorhexidine, an antiseptic with antibacterial, some antiviral, and antifungal activity is a synthetic bisbiguanide, binding well with cutaneous proteins accounting for its prolonged antiseptic effects.[1] It is widely used in health care setting worldwide and has become ubiquitous in the perioperative setting. It is found in surgical skin preparation solutions, skin wipes, lubricant gels for urethral catheterisation, vaginal and rectal examination. It has also been impregnated into central venous catheters (CVCs) and other medical devices in wound dressings, throat gargles/mouthwashes, toothpastes, contact lens solutions and cosmetics.[2] Malaysia alone has 47 products containing chlorhexidine registered with the Drug Control Authority (DCA) in various dosage forms, such as creams, lotions, gels, scrubs, solutions, mouthwashes and lozenges.[3]

Due to its widespread use, the incidence of allergic reactions is on the rise though the true prevalence of chlorhexidine allergy remains unknown. It has been labelled as the "hidden allergen" in health care setting.[4]

Adverse reactions to chlorhexidine range from mild cutaneous reactions to anaphylaxis and involve both immediate and non-immediate hypersensitivity. The most common allergic reactions, T cell-mediated, type IV hypersensitivity reactions, described are delayed. Contact dermatitis is the most frequent manifestation after topical use. Immediate IgE-mediated and type I hypersensitivity reactions have also been reported though less frequently. The symptoms range from urticaria to anaphylaxis with cardiorespiratory arrest and death.[2,4]

The National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health, Malaysia, reported 55 adverse events and 29 reports suspected to be related to chlorhexidine-containing products, majority of which involved rash, pruritis and skin irritation and four cases developed anaphylaxis/anaphylactic shock. The NPRA has issued a safety directive concerning chlorhexidine that all local package inserts and labels of products containing chlorhexidine be updated with information on risk of hypersensitivity reactions.[3] Various other international regulatory bodies have issued warnings for chlorhexidine-containing products and devices.[5]

The anesthesiologists widely use chlorhexidine in the perioperative setting for the skin preparation for central and peripheral blocks and venous canulation, central venous lines impregnated with chlorhexidine and local anesthetic and lubricant jelly. The international guidelines recommend that chlorhexidine in alcohol should be used for skin antisepsis before performing central neuraxial blockade (CNB) and peripheral nerve blocks.[6]

In the largest UK study of anaesthetic hypersensitivity reactions, the 6th National Audit Project (NAP6), chlorhexidine accounted for 9% of cases and third most prevalent cause of anaphylaxis after antibiotics and neuromuscular-blocking agents, the overall estimated incidence being 0.78 per 100,000 exposures. One case of chlorhexidine-induced anaphylaxis was fatal. Three cases were potentially avoidable by heeding a relevant history.[7] The routes of exposure of chlorhexidine included skin preparation for peripheral cannulation, neuraxial block or surgery, coated CVC and urethral gel. Majority of cases had two to three routes of exposure. None had exposure via skin preparation for peripheral venous cannulation only.[7]

Life-threatening anaphylaxis is commonly associated with mucosal and parenteral exposure and less often through intact skin.[6,8,9] Severe anaphylactic reactions are usually preceded by milder non-specific reactions, often dismissed by patients as well as doctors.[9,10]

We present ways to prevent chlorhexidine-induced morbidity and mortality during perioperative management.[6,7,9]

PREOPERATIVE MANAGEMENT

A detailed history pertaining to allergy status during preoperative assessment is essential. History of localised reactions post-exposure may indicate possibility of severe

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systemic reactions on subsequent exposures. Studies have shown that most patients diagnosed with chlorhexidine allergy had already reported a possible chlorhexidine allergy that could have been confirmed prior to the adverse event. Thus, perioperative morbidity and mortality can be reduced by thorough history taking and evaluation.[7]

The specific history should include allergy-type symptoms during previous medical or dental procedures or when using hygiene products at home or at work especially history of itch, rash or redness following preoperative antiseptic body wash, cannulation or venesection. If the previous reaction is not investigated, patient should be referred to allergy clinic for further investigation.

Preoperative assessment for chlorhexidine allergy are not yet standardised. Testing includes skin prick test, intradermal tests and blood tests for allergen-specific IgE and basophil activation performed within 6 months of exposure due to a decrease in IgE levels subsequently with time. Due to unclear reasons, patients with chlorhexidine allergy show positive allergy tests to neuromuscular blocking agents, latex, opioids and beta-lactam antibiotics.[7]

A high index of suspicion with a positive history of allergy is vital. Prevention is better than cure. The allergens should be avoided with the use of readily available alternatives. For instance, using povidone-iodine for skin preparation and alcohol-based swabs for venepuncture.

For CNB, 0.5% chlorhexidine solution in alcohol is preferred to 2% chlorhexidine solution due to the lack of convincing evidence of the antimicrobial superiority of 2% solution and clear evidence of its neurotoxicity. Meticulous measures should be taken to prevent chlorhexidine from reaching cerebrospinal fluid. Chlorhexidine should be kept away from drugs and not be poured into containers on or near the same surface as CNB equipment. The operator should check for contamination of his gloves and equipment. The solution should be allowed to dry before skin puncture.[6]

INTRAOPERATIVE MANAGEMENT

During the intraoperative period, continuous vigilant monitoring of the patient can detect early signs, and timely management can prevent untoward consequences. The clinical features include hypotension, tachycardia, non-urticarial and urticarial rash, desaturation, bronchospasm, unwell feeling, angioedema, nausea/vomiting, bradycardia, laryngeal edema and cardiac arrest. Management includes discontinuation of exposure with standard resuscitative measures and anaphylaxis management. Resuscitation drugs such as adrenaline, hydrocortisone and antihistamines have been reported in cases with successful treatment.[9]

POSTOPERATIVE MANAGEMENT

Postoperatively, the patient should be kept under observation and thoroughly investigated for possible allergens. During hospital stay, "allergy alert" sign should be attached to the front door and charts of the patient. Any patient with possible warning features should be referred to allergy clinic for further investigation.

The patient should be issued a wristband or pocket card as an allergy alert upon discharge. They should be educated on allergy and possible allergens together with the family members. List of easily available alternatives should be provided.

We suggest educating HCPs about this hidden allergen and creating awareness among HCPs and public on chlorhexidine allergy.

REFERENCES

1. Gilbert P, Moore LE. Cationic antiseptics: diversity of action under a common epithet. J Appl Microbiol 2005; 99(4): 703–15.
2. Sharp G, Green S, Rose M. Chlorhexidine-induced anaphylaxis in surgical patients: a review of the literature. ANZ J Surg 2016; 86(4): 237-43.
3. Seng NC. Chlorhexidine preparations: Risk of hypersensitivity reactions. Malaysian Adverse Drug Reactions Advisory Committee MADRAC Newsletter vol. 23,02 (2017). [cited 2022 December 24] Available from: https://www.npra.gov.my/images/Publications/Newsletter_MADRAC_Bulletin/2017/MADRACBulletin22017.pdf
4. Fernandes M, Lourenço T, Lopes A, Spínola Santos A, Pereira Santos MC, Pereira Barbosa M. Chlorhexidine: a hidden life-threatening allergen. Asia Pac Allergy 2019; 9(4): e29.
5. Chiewchalermsri C, Sompornrattanaphan M, Wongsa C, Thongngarm T. Chlorhexidine allergy: current challenges and future prospects. J Asthma Allergy 2020; 13: 127-33.
6. Association of Anaesthetists of Great Britain and Ireland, Obstetric Anaesthetists' Association, Regional Anaesthesia UK, Association of Paediatric Anaesthetists of Great Britain and Ireland, Campbell JP, Plaat F, et al. Safety guideline: skin antisepsis for central neuraxial blockade. Anaesthesia 2014; 69(11): 1279-86.
7. Tomaz Garcez. Chlorhexidine. In: National Audit Projects, NAP6 Report. Anaesthesia, Surgery and Life-Threatening Allergic Reactions. Report and findings of the Royal College of Anaesthetists' 6th National Audit Project. [cited 2022 December 24] Available from: https://www.nationalauditprojects.org.uk/downloads/NAP6%20Chapter%2017%20-%20Chlorhexidine.pdf
8. Ebo DG, Bridts CH, Stevens WJ. IgE-mediated anaphylaxis from chlorhexidine: diagnostic possibilities. Contact Dermatitis 2006; 55(5): 301-2.
9. Kow R, Low C, Ruben J, Zaharul-Azri M, Ng M. Life-threatening chlorhexidine anaphylaxis: a case report. Malays Orthop J 2017; 11(2): 72-4.
10. Garvey LH, Roed-Petersen J, Husum B. Anaphylactic reactions in anaesthetised patients - four cases of chlorhexidine allergy. Acta Anaesthesiol Scand 2001; 45(10): 1290-4.

Erratum

Correction to: Does knowledge and attitude of healthcare professionals working in critical care areas affect their willingness to offer the option of organ donation? Results of a tertiary hospital survey

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Following publication of the original article[1], the author Jea Sheng Ong identified an error of the Table IV: association between brain death attitudes and willingness to offer the option of organ donation to families of potential organ donors.

REFERENCES

1. Ong JS, James Foong W, Oo WL, Vallapil MK, Hossain MM, Hossain H, et al. Does knowledge and attitude of healthcare professionals working in critical care areas affect their willingness to offer the option of organ donation? results of a tertiary hospital survey. Med J Malaysia. 2022 May; 77(3): 347-56.

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Table IV: Association between brain death attitudesand willingness to offer the option of organ donation to families of potential organ donors

	Willingness to Offer*							
	Yes (312)	No/Unsure (99)	Univariable Analysis			Multivariable Analysis		
	n (%)	n (%)	cOR†	95% CI§	*p*-Value	aOR‡	95% CI§	*p*-Value
How convinced are you of the existence of a clinical state called brain death?								
Yes	284 (79.1)	75 (20.9)	2.98	(1.61– 5.50)	< 0.001	1.22	0.59– 2.49	0.592
No / Unsure	28 (56.0)	22 (44.0)	1	-	-	1	-	-
No answer	0	2	-	-	-	-	-	-
Do you feel confident to explain what brain death is to a patient's family member?								
Yes	288 (78.7)	78 (21.3)	5.87	(3.61 – 9.55)	< 0.001	5.04	3.02 – 8.43	<0.001
No / Unsure	24 (53.3)	21 (46.7)	1	-	-	1	-	
In your opinion, can doctors reliably diagnose brain death?								
Yes	245 (86.6)	38 (13.4)	3.23	(1.71 – 6.11)	< 0.001	2.34	1.13 – 4.82	0.022
No / Unsure	67 (52.3)	61 (47.7)	1	-	-	1	-	-

*One participant did not respond to the question on willingness to offer, total = 411
†cOR, crude odds ratio;
‡aOR, adjusted odds ratio
§95% CI, 95% confidence interval

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