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In June 2013, Southeast Asia was blanketed by thick clouds of haze arising from wildfires in Indonesia.

A Singapore study surveyed participants in a large residential district on their knowledge, perceived risk and behaviours during the haze crisis. The study found that knowledge of haze was associated with protective behaviours, while a lower education level and smokers were associated with lower knowledge. Wearing of N95 masks correlated with other protective behaviours and did not lead to a false sense of security. The insights gained to encourage adoption of protective behaviours may be applicable to urban populations facing haze problem and even infectious disease outbreaks like the COVID-19 pandemic.

Photo courtesy of NASA Earth Observatory image by Jeff Schmaltz, LANCE/EOSDIS Rapid Response

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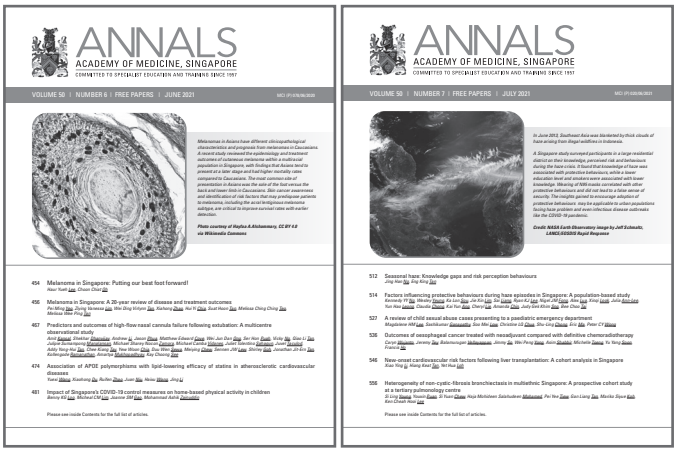

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EDITORIAL

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Seasonal haze: Knowledge gaps and risk perception behaviours

Jing Han Ng [1]*MBBS*, Eng King Tan [1,2]*MBBS*

The seasonal haze in Southeast Asia has been a recurrent concern whenever we enter the southwest monsoon season (June–September). This phenomenon, caused by agricultural fires, has vast effects on multiple countries in the region. Besides extensive socioeconomic impact, the seasonal haze poses a significant public health threat, as numerous studies had demonstrated harmful effects of air pollution and haze on human health. Epidemiological studies conducted in various countries consistently demonstrate an association between haze exposure and respiratory, cardiovascular, oncological and psychological morbidity.[1] Despite regional efforts, the Southeast Asian seasonal haze remains a persistent problem. It is thus imperative for people in this region to learn and practise personal protection against the haze.

In this issue of the Annals, Ng et al. sought to evaluate the knowledge and perceived risk of the seasonal haze in Singapore and the factors that affected protective behaviours taken by people during these haze episodes.[2] The investigators performed a cross-sectional study of approximately 700 individuals, who lived in Singapore during the 2013 Southeast Asian haze crisis that caused record levels of pollution in the region. They identified study participants by performing random sampling of households in a public residential district in Singapore, and obtained data to assess the knowledge, perceived risks and protective behaviours for haze. The analyses provided a few salient observations of the attitude and behaviour of people towards the seasonal haze.

Firstly, protective behaviour against the seasonal haze was positively related to the knowledge level and perceived risk of haze, consistent with the Health Belief Model, which states that health behaviours are influenced by the perceived susceptibility and severity of a health threat.[3] A different study in Southeast Asia also showed that greater knowledge and concern for the negative impact of haze on human health resulted in a higher likelihood for people to adopt protective measures.[4]

Secondly, basic knowledge and awareness of the seasonal haze and its negative impact on health were largely present in Singapore. However, while respondents generally demonstrated a basic understanding of the seasonal haze, crucial gaps in knowledge still existed. For example, a quarter of the study participants did not know that the Pollutant Standards Index (PSI) was used to measure haze severity and almost half thought that surgical masks would confer them protection against the haze.[5] This represents a significant knowledge gap despite public education efforts.

Thirdly, factors associated with knowledge and risk perception of the seasonal haze were identified in the survey by Ng et al. A recent study found that a higher education background and monthly household income was associated with better knowledge and protective behaviours.[6] Similarly, Ng et al. found that a lower education level and a habit of smoking were associated with poorer knowledge of the seasonal haze. This finding helps to highlight potential target groups for public health and haze education campaigns.

Ng et al. highlighted knowledge gaps of the seasonal haze within the Singapore population and drew attention to the frequently understated value of public education. Promoting protective behaviour by raising knowledge and risk perceptions of the seasonal haze can facilitate efforts to manage the consequences of the haze. It is interesting that higher education levels were linked to lower risk perception despite better knowledge of the haze situation. Higher monthly household income was also linked to fewer protective behaviours against the seasonal haze. This observation demonstrates the complex nature of human attitude and behaviour towards the haze, and highlights the need for a multidisciplinary and multifaceted approach to address some of the perceptions and behavioural responses. More studies are needed to further evaluate the relation between knowledge and perceived risk of haze, and the process for translation of awareness and knowledge into actual protective behaviours.

[1] National Neuroscience Institute, Singapore
[2] Duke-NUS Medical School, Singapore
Correspondence: Dr Eng King Tan, Department of Neurology, National Neuroscience Institute, Singapore General Hospital campus, Outram Road, Singapore 169608.
Email: gnrtek@sgh.com.sg

Several challenges and limitations exist in the translation of knowledge and perceived risk to actual protective behaviour against the seasonal haze. While the general public may be equipped with the knowledge that surgical masks are not entirely effective against the haze, the widespread use of N95 masks may not always be feasible. Elderly, young children, people with cardiorespiratory comorbidities, and pregnant women with reduced lung volumes may not be able to tolerate the use of N95 masks.[5] Yet, these are the individuals who are more vulnerable to the negative health effects of the haze. Likewise, those working in jobs with outdoor exposure may not have the luxury of choosing to stay indoors, despite knowledge and awareness of the importance in staying indoors during haze episodes. Clearly, an increase in knowledge and awareness of the haze alone is insufficient to promote individual protective behaviour. Government policies and organisational regulations can help to assist and facilitate personal protective behaviours. One example is the Workplace Safety and Health Act in Singapore that mandates employers to protect their employees' safety at work. On this premise, the Ministry of Manpower requires employers to identify vulnerable employees, reduce outdoor work, and provide employees who need to work outdoors with the appropriate N95 masks in situations of haze.[7] Some of these measures may result in work and business disruptions for employers and should be adequately supported to avoid forming barriers for employers trying to protect employee health. Employer education and grants may help employers develop contingency plans and working arrangements such that their core operations or the relevant workplace safety measures are not affected by the haze.

It is also noteworthy that evidence for protective behaviours against the haze remains limited. Of the 7 protective behaviours listed by Ng et al., only 4 are backed by evidence. The use of masks, portable air cleaners and limitation of outdoor physical activities had Grade C evidence, while the monitoring of air pollution levels had Grade D evidence, based on grading used by the Global Initiative for Asthma (GINA).[8] Further medical and scientific studies are required to validate protective behaviours and measures so that public education efforts may focus on the measures with proven effectiveness and robust evidence.

In addition, some lessons and observations from the current COVID-19 pandemic may be applicable to future haze crises. While the use of social media may facilitate quick dissemination of haze-related news, public health authorities need to manage misinformation and intervene swiftly when inaccurate or misleading information on the haze is disseminated. Mobile applications may help to provide real-time updates, alerts and advisories on the haze situation. The advancement and widespread use of telecommunication and videoconferencing platforms also provide a viable option for work, study and recreation during serious haze crises where physical and outdoor travel is not encouraged.

While the public health focus remains on COVID-19 in the current global pandemic, we should not lose sight of concurrent health threats. The Southeast Asian seasonal haze continues to be an important public health issue that should be studied and dealt with comprehensively.

Acknowledgment

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ORIGINAL ARTICLE

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Factors influencing protective behaviours during haze episodes in Singapore: A population-based study

Kennedy YY Ng *[1]MBBS, Wesley Yeung *[2]MBBS, Ka Lon Sou *[3]PhD, Jie Xin Lim *[4]PhD, Sai Liang [5]MBBS, Ryan KJ Lee [6]MBBS, Nigel JM Fong [7]MBBS, Alex Lua [8]MBBS, Xinqi Look [9]MBBS, Julia Ann-Lee [10]MBBS, Yun Hao Leong [11]MBBS, Claudia Chong [12]MBBS, Kai Yun Ang [13]MBBS, Cheryl Lie [14]MBBS, Amanda Chin [15]MBBS, Judy Gek Khim Sng [16]MBBS, Bee Choo Tai [16]PhD

ABSTRACT

Introduction: Haze is a recurrent problem in Southeast Asia. Exposure to haze is linked to ophthalmic, respiratory and cardiovascular diseases, and mortality. In this study, we investigated the role of demographic factors, knowledge and perceived risk in influencing protective behaviours during the 2013 haze in Singapore.

Methods: We evaluated 696 adults in a cross-sectional study. Participants were sampled via a 2-stage simple random sampling without replacement from a large residential district in Singapore in 2015. The questionnaire measured the participant's knowledge, perceived risk and behaviours during the Southeast Asian haze crisis in 2013. Reliability and validity of the questionnaire were assessed using comparative fit index (≥0.96) and root mean square error of approximation (≤0.05). We performed structural equation modelling to examine the relationship between the hypothesised factors and protective behaviours.

Results: More than 95% of the individuals engaged in at least 1 form of protective behaviour. Knowledge was strongly associated with protective behaviours via direct effect (β=0.45, 95% CI 0.19–0.69, *P*<0.001) and indirect effect through perceived risk (β=0.18, 95% CI 0.07–0.31, *P*=0.002). Perceived risk was associated with protective behaviours (β=0.28, 95% CI:0.11–0.44, *P*=0.002). A lower household income and ethnic minority were associated with protective behaviours. A lower education level and smokers were associated with lower knowledge of haze. A higher education and ethnic minority were associated with a lower perceived risk. Wearing of N95 masks was associated with other haze-related protective behaviours (β=0.24, 95% CI 0.08–0.37, *P*=0.001).

Conclusion: Knowledge was associated with protective behaviours, suggesting the importance of public education. Efforts should target those of lower education level and smokers. The wearing of N95 masks correlates with uptake of other protective behaviours.

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Keywords: Haze, knowledge, N95 mask, protective behaviour, risk perception

[1] Division of Medical Oncology, National Cancer Centre Singapore, Singapore
[2] University Medicine Cluster, National University Hospital, Singapore
[3] Singapore University of Technology and Design, Singapore
[4] Division of Psychology, School of Social Sciences, Nanyang Technological University, Singapore
[5] Department of Neurosurgery, National Neuroscience Institute, Singapore
[6] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[7] Division of Medicine, Singapore General Hospital, Singapore
[8] Department of Urology, Tan Tock Seng Hospital, Singapore
[9] Post-acute and Continuing Care, Outram Community Hospital, Singapore
[10] Division of Family Medicine, National University Hospital, Singapore
[11] Department of Anaesthesia, Singapore General Hospital, Singapore
[12] Department of Anaesthesia, Tan Tock Seng Hospital, Singapore
[13] Department of Anaesthesia, National University Hospital, Singapore
[14] Dermatology Service, KK Women's and Children's Hospital, Singapore
[15] Division of Neurology, Department of Medicine, National University Hospital, Singapore
[16] Saw Swee Hock School of Public Health, National University of Singapore, Singapore
Correspondence: Dr Kennedy Yao Yi Ng, Division of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Crescent, Singapore 169610.
Email: kennedy.ng.y.y@nccs.com.sg
* Joint first authors

CLINICAL IMPACT

What is New

- This study assesses factors influencing protective behaviours during haze episodes in Singapore.
- Knowledge of haze was associated with protective behaviours, while a lower education level and smokers were associated with lower knowledge.
- Wearing of N95 masks correlated with other protective behaviours and did not lead to a false sense of security.

Clinical Implications

- Public education remains an important public health strategy.
- Educational efforts should target those of lower education level and smokers.
- Encouraging the wearing of N95 masks can be part of a multipronged effort to minimise the impact of haze.

INTRODUCTION

Southeast Asia suffers from recurrent episodic air pollution from biomass smoke known as haze, which is mainly caused by human activities such as the extensive use of fire to clear land for agriculture,[1] or to settle disputes over land rights.[2] It is a major public health problem affecting an estimated 20–70 million people in the region.[3] These figures are expected to increase with population growth and an increasing frequency of haze events.[4]

In 2013, the 3-hour Pollutant Standards Index in Singapore peaked at a hazardous level of 401.[5] Exposure to micro-particulate matter (PM), the most consistent pollutant in biomass smoke,[6] is associated with adverse health effects, ranging from acute illnesses (e.g. conjunctivitis, upper respiratory tract infections)[7] to exacerbations of chronic respiratory diseases (e.g. asthma, chronic obstructive pulmonary disease).[8] Cardiovascular and respiratory mortality appears to increase in a concentration-dependent manner with PM exposure.[9] Mild physical and psychological distress are also common among otherwise healthy individuals.[10]

Despite the magnitude of the problem, there is a notable absence of literature on protective behaviours during acute haze episodes, such as seeking regular updates, wearing an N95 mask, staying indoor and conducting hygience practices.

In this study, we examined the knowledge and risk perception of Singapore residents towards haze, and the protective behaviours taken. We explored the underlying associated factors that could influence an individual's protective behaviours during haze.

METHODS

Study population

This study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. It was a substudy of a previously published paper. The sample size was calculated based on the primary endpoint of the main study.[11] We performed a cross-sectional study of a residential area in Singapore from 9 to 15 February 2015, based on a 2-stage simple random sampling without replacement. In the first stage, 120 blocks in a public housing estate were randomly selected from 166 blocks. Subsequently, 20% of the residential units were randomly selected within each apartment block. The first individual answering the door was screened for eligibility. Inclusion criteria were English-speaking or Mandarin-speaking Singapore citizens or permanent residents, age ≥21 years, residents in the estate since the 2013 haze, and the ability to wear an N95 mask independently. If that individual did not fulfil the criteria, the interviewer team would then randomly sample the next eligible resident in the household. Surveys were conducted in the evenings on weekdays and throughout the entire day on weekends. Verbal consent was obtained from all participants. An interviewer-administered questionnaire was used by the survey teams. Households with no response at the door were given a no-response notice and revisited on another occasion within the study duration. The institutional review board of the National University of Singapore granted ethical approval of the study (B-14-250).

Questionnaire

We collected demographic characteristics including age, sex, ethnicity, education, monthly household income, self-reported chronic diseases and tobacco use. Chronic disease was defined as the presence of asthma, chronic obstructive pulmonary disease or heart failure. These conditions were chosen based on the association of their exacerbations with air pollution exposure.[12-14]

At the time of this study, there were no existing measures developed for understanding the knowledge, perceived risk and behaviours towards haze. We developed and validated a questionnaire to assess the 3 domains of interest (Table 1). The knowledge domain

Table 1. Descriptive statistics of the items in knowledge, perceived risk and protective behaviours

Knowledge	**Correct[a] (%)**
k1: Haze is caused by forest fires in neighbouring countries	96.4
k2: PSI can measure severity of haze	75.3
k3: Health effects of haze depends on how long one has been exposed to it	88.2
k4: The main pollutant during haze is particulate matter (e.g. PM10, PM2.5)	39.1
k5: Individuals who spend a lot of time outdoors need to be protected	89.9
k6: Surgical masks provide protection from haze (reverse code)	51.6
Perceived risk	**High risk[b] (%)**
r1: I believe haze has a damaging effect on my health	84.9
r2: I am at risk of lung disease from haze	67.5
r3: I am at risk of heart disease from haze	48.7
r4: I am at risk of eye disease from haze	72.0
Protective behaviours	**Adequate[c] (%)**
p1: I sought updates about the severity of haze	82.9
p2: I wore an N95 mask	43.4
p3: I stayed indoors and avoided outdoor activities	76.3
p4: I cleaned my house more frequently than usual	57.2
p5: I used an air purifier	24.3
p6: I took showers more frequently than usual	40.9
p7: I kept myself hydrated more than usual	76.9

PSI: Pollutant Standards Index

[a] Original responses were dichotomised into incorrect (strongly disagree, disagree, neutral) and correct (agree, strongly agree). k6 was reversed coded prior to dichotomisation. A correct response indicates correct knowledge of the subject matter.

[b] Original responses were dichotomised into low risk (strongly disagree, disagree, neutral) and high risk (agree, strongly agree). A high-risk response indicates a belief in haze as having a damaging effect on health as opposed to being not concerned or being unaware of the health effects of haze.

[c] Original responses for p1 were dichotomised into "inadequate practice" (not at all, less than weekly, weekly) and "adequate practice" (once every few days, almost every day). Adequate practice indicates that individuals seek for updates at least once every few days. Original responses for p2 through p7 were dichotomised into "inadequate practice" (not at all) and "adequate practice" (less than weekly, weekly, once every few days, almost every day).

represents general knowledge of haze and was assessed by responses to 6 factual questions on haze (k1–k6).[4,9,15] Perceived risk represents one's perception of personal risk of harm from haze and was assessed by responses to 4 statements (r1–r4). Possible responses for these 2 domains were given on a 5-point scale, ranging from strongly disagree to strongly agree. Responses to the knowledge domain were dichotomised into correct and incorrect, and those to the perceived risk domain were dichotomised into low risk and high risk. Protective behaviours represent protective actions recommended by the National Environment Agency of Singapore that were taken during the 2013 haze and was assessed by 7 types of actions (p1–p7). A standardised visual aid with pictures of air purifiers, N95 masks and other protective behaviours was used in the interview. Possible responses were given on a 5-point scale, ranging from "not at all" to "almost every day". The responses were categorised as adequate or inadequate. The questionnaire was developed in English, translated into Chinese and back-translated to ensure semantic equivalence. Two public health experts from the Saw Swee Hock School of Public Health, National University of Singapore, verified the validity and accuracy of the questionnaire. A pilot study was conducted to test the questionnaire and survey protocols.

Statistical analyses

The analyses were performed in 2020. Demographics and survey responses were examined using frequencies

and percentages for categorical variables, and median and range for continuous variables. Structural validity of the measurements of knowledge on haze, perceived risk and protective behaviours was tested using factor analysis, and the reliability for each construct was estimated using the McDonald's omega coefficient.[16] The assessment of model goodness-of-fit followed the general criteria of Hu and Bentler[17] and the recommendations of Yu[18] for categorical outcomes (i.e. comparative fit index ≥0.96, root mean square error of approximation ≤0.05). The relationship between the demographic variables and the constructs were modelled using the structural equation modelling framework. Mplus version 8.4 (Muthén & Muthén, Los Angeles, US) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria), along with the R packages lavaan (version 0.6-61527)[19] and semTools (version 0.5-2.921)[20] were used for the analyses. All analyses were done using the weighted least square mean and variance-adjusted estimator with delta parameterisation. We obtained the bias-corrected and accelerated bootstrapped 95% confidence interval of the parameters, based on 1,000 replications. A 2-sided α=0.05 was used for evaluating statistical significance.

RESULTS

Participant characteristics

A total of 2,499 households were visited by the survey teams. Of these, 541 (21.6%) declined to be surveyed and 976 (39.1%) did not respond. Among households who consented to participate, 268 (10.7% of all households) did not meet the inclusion criteria and were excluded. Therefore, 714 individuals were interviewed, corresponding to a 32.0% response rate. Of these, 18 (2.5%) did not complete the survey questionnaire and were excluded from the analysis. Data from the remaining 696 individuals were analysed, and their demographic characteristics are presented in Table 2. The median age of our sample was 50 years (range 21–89 years). There were more female respondents (53.6%). Most participants were Chinese (71.8%). Participants with secondary school education constituted 30.3% of the sample. The most commonly reported monthly household income was USD3,500–8,400 (33.5%). The prevalence of chronic diseases was 7.5%.

Table 2. Demographics of 696 study participants

Characteristics	
Age, median (range), year	50 (21–89)
Sex, no. (%)	
Female	373 (53.6)
Male	323 (46.4)
Ethnicity, no. (%)	
Chinese	500 (71.8)
Malay	102 (14.7)
Indian	86 (12.4)
Other	8 (1.1)
Education level, no. (%)	
No qualification	31 (4.5)
Primary school	119 (17.1)
Secondary school	211 (30.3)
Tertiary school (polytechnic or junior college)	178 (25.6)
University	157 (22.6)
Monthly household income, no. (%)	
No income	139 (20.0)
Less than USD2100	100 (14.4)
USD2100–3500	166 (23.9)
USD3500–8400	233 (33.5)
USD8400 or more	58 (8.3)
Chronic disease, no. (%)	
Yes	52 (7.5)
No	644 (92.5)
Tobacco use, no. (%)	
Daily	93 (13.4)
Less than daily	29 (4.2)
Not at all	574 (82.5)

Descriptive statistics of knowledge, perceived risk and protective behaviours

A total of 690 participants (99.1%) answered at least 1 question correctly. For the knowledge measurements, the statement "Haze is caused by forest fires in neighbouring countries" had the highest proportion of correct responses (96.4%); while the statement "The main pollutant during haze is particulate matter (e.g. PM10, PM2.5)" had the lowest (39.1%). For the perceived risk measurements, most participants believed that haze had a damaging effect on their health (84.9%). More participants felt that they were at risk for eye diseases (72.0%) when compared with lung disease (67.5%) or heart disease (48.7%) (Table 1).

For the protective behaviour measurements, the most common protective behaviours taken during the 2013 haze were seeking updates about the severity of haze through the news, Internet or radio at least once every few days (82.9%), and staying at home and avoiding outdoor activities at least weekly (76.3%). Fewer participants took showers more frequently than usual (40.9%) or used air purifiers at least weekly (24.3%). Only 43.4% of the participants wore an N95 mask (Table 1). Overall, 97.1% of participants engaged in at least 1 protective behaviour.

Validation of questionnaire

To validate the constructed measurements, a confirmatory factor analysis was first used to test the data-model fit of the respective proposed factor structure. The constructs for knowledge and protective behaviours were hypothesised to be unidimensional, and fit indices suggested satisfactory data-model fit for both single factor models. The unidimensional factor model for perceived risk did not attain a satisfactory data-model fit. Based on subsequent exploratory and confirmatory factor analysis of the perceived risk measurements, an item was removed, which resulted in an analytic-driven unidimensional model. The final unidimensional factor models showed approximately satisfactory data-model fit for each of the 3 constructs (root mean square error of approximation ≤0.06; comparative fit index ≥0.94). Point estimates of the score reliability of the measurements were all ≥0.56.

Mediation model

The structural equation model is shown in Fig. 1. In general, perceived risk mediated the relationship between knowledge and protective behaviours. Protective behaviours were associated with both perceived risk (β=0.28, 95% confidence interval [CI] 0.11–0.44, P=0.002) and knowledge (β=0.45, 95% CI 0.19–0.69, P<0.001). Perceived risk was associated with knowledge (β=0.65, 95% CI 0.48–0.79, P<0.001). In addition to the direct effect from knowledge to protective behaviours, we also found a significant indirect effect from knowledge to protective behaviours (β=0.18, 95% CI 0.07–0.31, P=0.002). This indirect effect suggests that the effect of knowledge on protective behaviours is mediated by perceived risk.

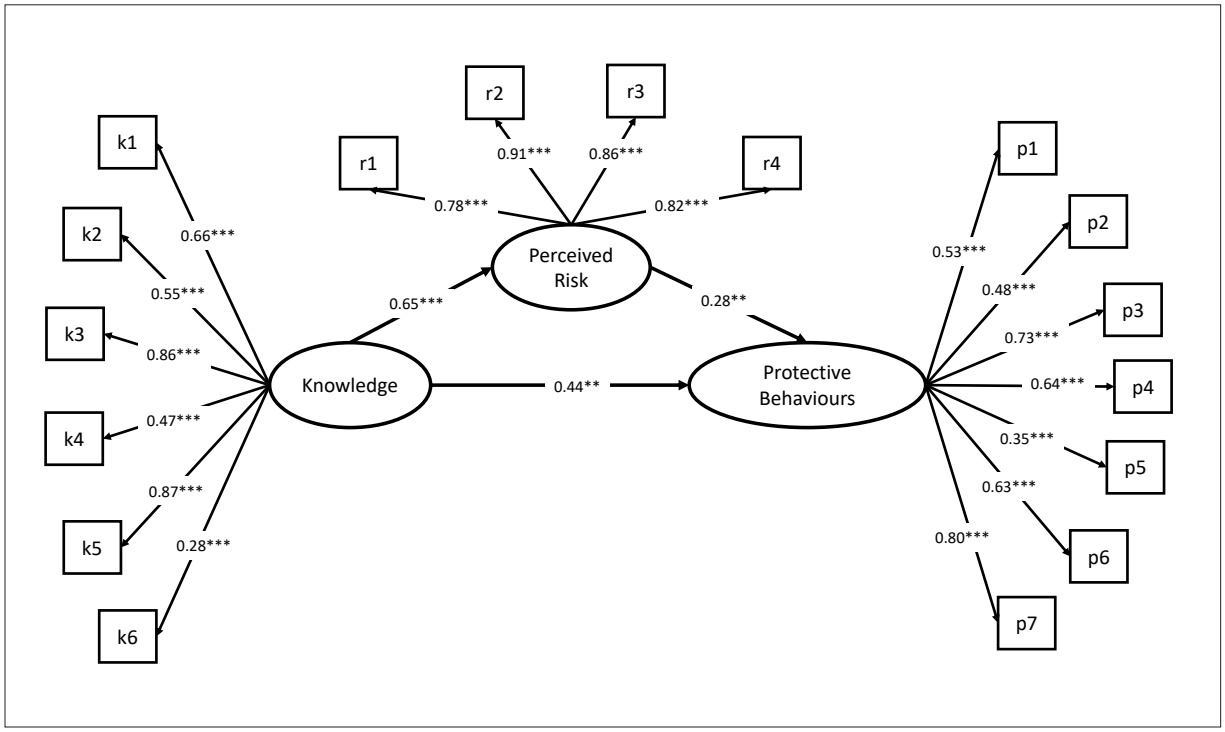

Fig. 1. Structural equation model showing the relationships among knowledge, perceived risk and protective behaviours.
The reported values are partially standardised parameter estimates (unit latent variable variance). Solid arrows indicate significant parameter estimates (e.g. from Knowledge to Perceived Risk). Control variables and demographics are omitted from the figure for brevity. Root mean square error of approximation was 0.04 and comparative fit index 0.88. R^2 estimates of knowledge, perceived risk and protective behaviours were 0.28, 0.36 and 0.40, respectively.
** P<0.01, *** P<0.001

A higher education level was associated with higher knowledge but a lower perceived risk. Smoking status was associated with lower knowledge. Malay and Indian ethnicity were associated with a lower perceived risk but higher protective behaviours. A higher household income was associated with fewer protective behaviours. Further details are described in Table 3. To examine the effect of ethnicity on the 3 constructs, we performed 2 exploratory analyses with 2 different groups (Malay and Chinese; Indian and Chinese). In both analyses, the models suggested the same underlying relationships among knowledge, perceived risk and protective behaviours.

We further classified protective behaviours as evidence-based (p1, p2, p3, p5)[21] and other general recommended protective behaviours (p4, p6, p7),[15] and modified the proposed mediation model. Evidence-based protective behaviours was associated with knowledge (β=0.76, 95% CI 0.28–0.81, $P<0.001$), while other protective behaviours was associated with perceived risk (β=0.65, 95% CI 0.13–0.51, $P<0.001$). Knowledge had an indirect effect on other protective behaviours mediated via perceived risk (β=0.21, 95% CI 0.09–0.36, $P=0.002$). Malay and Indian ethnicity was associated only with higher other protective behaviours. A higher household income was associated with fewer other protective behaviours. Further details are described in Fig. 2 and Table 4.

Association between N95 mask wearing and other protective behaviours

We also performed analyses to assess the relationship between mask wearing and other protective behaviours. We revised the structural equation modelling and separated the item p2 "I wore an N95 mask" from other protective behaviours. The other protective behaviours were used to form a new construct called "protective behaviours (mask-unrelated)" (Fig. 3). We found a positive relationship between p2 and mask-unrelated protective behaviours (β=0.24, 95% CI 0.08–0.37, $P=0.001$). This relationship suggests that subjects who wore masks during the haze period tended to engage in more protective behaviours. Furthermore, we observed that knowledge affected mask wearing behaviour differently from other protective behaviours. While mask-unrelated protective behaviours was affected by knowledge both directly (β=0.44, 95% CI 0.18–0.69, $P=0.001$) and indirectly (β=0.17, 95% CI 0.06–0.30, $P=0.006$), p2 was only affected by knowledge through the indirect pathway (via perceived risk; β=0.14, 95% CI 0.01–0.26, $P=0.034$) but not the direct pathway (β=0.20, 95% CI -0.07 to 0.43, $P=0.139$).

DISCUSSION

In our cross-sectional study that aimed to investigate the relationships among knowledge, perceived risk and protective behaviours in response to haze, we found that protective behaviours were associated with both perceived risk and knowledge. Perceived risk was associated with knowledge, and there was an indirect effect from knowledge to protective behaviours. This indirect effect suggests that the effect of knowledge on protective behaviours is mediated by perceived risk. In addition, we found that subjects who wore masks during the haze period tended to also engage in other protective behaviours. Participants wore masks only when they perceived the haze as hazardous to their health, regardless of their knowledge level.

Despite efforts by local health authorities to educate the public through its website and radio and television broadcast to provide information about the haze, its effects on health and protective measures that one could take,[15] approximately 50% of participants thought that surgical masks could provide protection and one-quarter did not know that the Pollutant Standards Index could be used to measure the severity of haze. Lower education level and smokers were associated with lower knowledge level of haze. This finding is congruent with studies demonstrating a positive association between education level and knowledge,[22,23] and lower health literacy among smokers.[24]

Our study showed that a higher number of participants felt that their health was at risk from the haze (84.9%), compared with a previous study on urban pollution in Los Angeles, US in the 1980s (72.5%).[25] Participants with higher education level, while associated with higher knowledge, had lower risk perceptions. While seemingly counterintuitive, numerous studies also found that a higher education level was associated with a lower perceived risk.[23,26] Individuals with lower education levels could have lower self-efficacy and hence higher perceived risk. However, we did not examine the construct of self-efficacy. Another explanation could be poor risk perception due to lower health literacy.[26] In addition, Malay and Indian ethnicity (both ethnic minorities in Singapore), compared with Chinese ethnicity, had lower risk perceptions, contrary to a previous study.[27]

More than 95% of our participants undertook at least 1 protective behaviour, compared with the <50%

Table 3. Structural equation model including knowledge on haze, perceived risk and protective behaviours[a]

	β	BCa 95% CI	*P* value
Protective behaviours predicted by			
Knowledge			
Direct effect	0.45	0.19, 0.69	<0.001
Indirect effect (through perceived risk)	0.18	0.07, 0.31	0.002
Perceived risk	0.28	0.11, 0.44	0.002
Control variables			
Age	-0.01	-0.02, 0.001	0.084
Sex	0.15	-0.06, 0.33	0.142
Education level	-0.12	-0.29, 0.02	0.109
Monthly household income	-0.10	-0.18, -0.02	0.019
Chronic disease	-0.04	-0.44, 0.31	0.869
Smoking habit during haze	0.02	-0.15, 0.19	0.856
Ethnicity			
Chinese	[Reference]	[Reference]	[Reference]
Malay	0.29	0.004, 0.56	0.043
Indian	0.58	0.26, 0.92	0.001
Others	0.27	-1.17, 2.18	0.735
Perceived risk predicted by			
Knowledge	0.65	0.48, 0.79	< 0.001
Control variables			
Age	0.01	-0.002, 0.02	0.108
Sex	-0.06	-0.27, 0.16	0.558
Education level	-0.16	-0.30, -0.04	0.025
Monthly household income	0.02	-0.06, 0.10	0.575
Chronic disease	-0.02	-0.57, 0.47	0.941
Smoking habit during haze	-0.05	-0.235, 0.10	0.557
Ethnicity			
Chinese	[Reference]	[Reference]	[Reference]
Malay	-0.32	-0.64, -0.002	0.052
Indian	-0.33	-0.67, -0.02	0.059
Others	0.23	-1.59, 1.71	0.778
Knowledge predicted by			
Age	0.001	-0.01, 0.01	0.818
Sex	-0.07	-0.26, 0.16	0.535
Education level	0.44	0.33, 0.56	<0.001
Monthly household income	0.03	-0.05, 0.11	0.410

Table 3. Structural equation model including knowledge on haze, perceived risk and protective behaviours[a] (Cont'd)

	β	BCa 95% CI	*P* value
Chronic disease	0.06	-0.45, 0.61	0.860
Smoking habit during haze	0.18	0.01, 0.36	0.046
Ethnicity			
Chinese	[Reference]	[Reference]	[Reference]
Malay	-0.13	-0.44, 0.20	0.425
Indian	0.03	-0.35, 0.51	0.891
Others	-1.03	-1.99, 1.44	0.324

BCa: bias-corrected and accelerated; CI: confidence interval

[a] β refers to partially standardised regression weights (unit latent variable variance). Root mean square error of approximation was 0.04 and comparative fit index 0.88. Wald test showed a significant overall effect of ethnicity on protective behaviours ($W_1(3)$=17.36, P<0.001) and perceived risk ($W_1(3)$=8.92, P=0.030), but not on knowledge ($W_1(3)$=4.56, P=0.207). Coding for variables: sex (0: male; 1: female), chronic disease (0: no; 1: yes) and smoking habit (1: daily; 2: less than daily; 3: not at all).

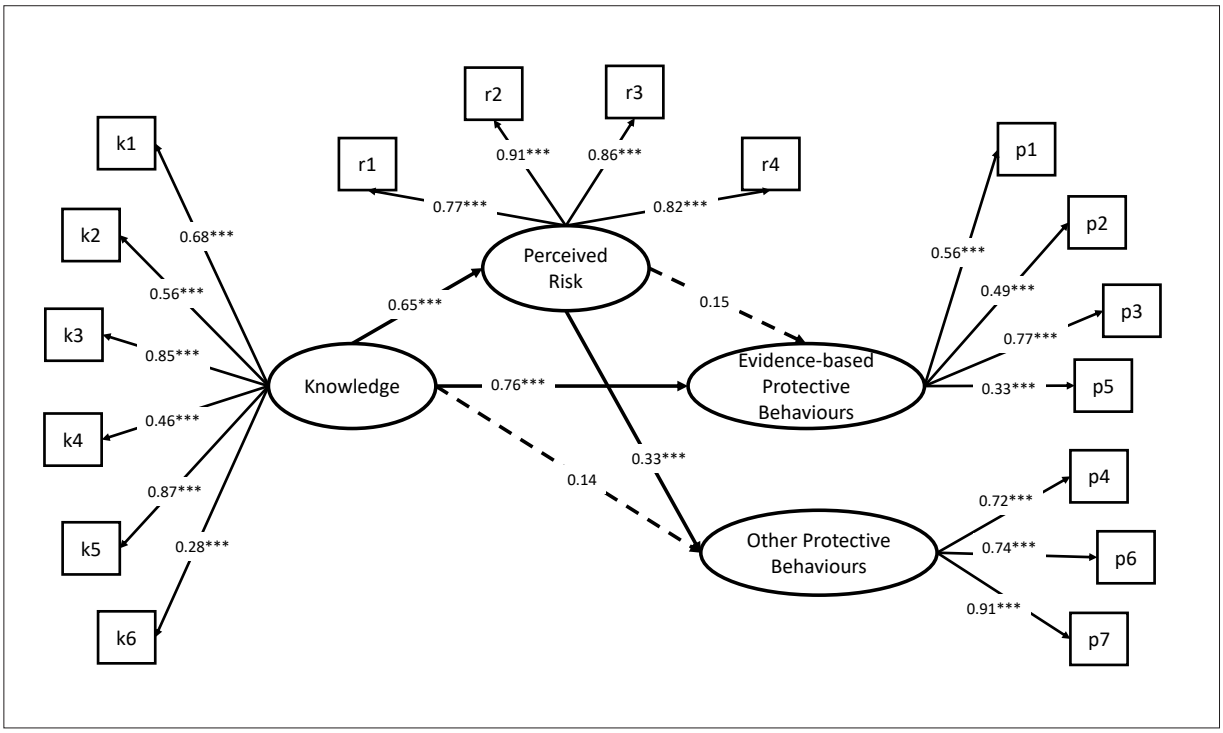

Fig. 2. Structural equation model showing the relationships among knowledge, perceived risk and evidence-based and other protective behaviours.

The reported values are partially standardised parameter estimates (unit latent variable variance). Solid arrows indicate significant parameter estimates (e.g. from Knowledge to Perceived Risk) whereas dashed arrows indicate non-significant parameter estimates (e.g. from Perceived Risk to Evidence-based Protective Behaviours). Control variables and demographics are omitted from the figure for brevity. Root mean square error of approximation was 0.04 and comparative fit index 0.92. R^2 estimates of knowledge, perceived risk, evidence-based protective behaviours and other protective behaviour were 0.28, 0.35, 0.64 and 0.24, respectively.

*** P<0.001

uptake of health advisory recommended measures against urban air pollution.[25,28] This finding may reflect the severity of the 2013 haze episode. Alternatively, it suggests a decline in the perceived risk and practice of personal protective behaviours as people grow accustomed to constant urban air pollution, compared with acute episodes of haze.[29] There is a strong association between knowledge and protective behaviours, similar to that observed in urban air pollution[25] and influenza.[27,30] While there was a

Table 4. Structural equation model including knowledge on haze, perceived risk, and evidence-based and other protective behaviours[a]

	β	BCa 95% CI	*P* value
Evidence-based protective behaviours predicted by			
Knowledge			
Direct effect	0.76	0.28, 0.81	<0.001
Indirect effect (through perceived risk)	0.10	-0.03, 0.15	0.179
Perceived risk	0.15	-0.07, 0.37	0.170
Control variables			
Age	-0.001	-0.01, 0.01	0.835
Sex	0.20	-0.04, 0.47	0.121
Education level	-0.12	-0.32, 0.05	0.197
Monthly household income	-0.06	-0.16, 0.03	0.214
Chronic disease	0.28	-0.27, 0.83	0.382
Smoking habit during haze	-0.01	-0.23, 0.18	0.901
Ethnicity			
Chinese	[Reference]	[Reference]	[Reference]
Malay	0.24	-0.15, 0.58	0.222
Indian	0.19	-0.19, 0.63	0.387
Others	0.33	-1.82, 2.72	0.750
Other protective behaviours predicted by			
Knowledge			
Direct effect	0.14	-0.14, 0.39	0.302
Indirect effect (through perceived risk)	0.21	0.09, 0.36	0.002
Perceived risk	0.65	0.13, 0.51	<0.001
Control Variables			
Age	-0.01	-0.02, -0.002	0.016
Sex	0.08	-0.12, 0.27	0.422
Education level	-0.10	-0.24, 0.07	0.234
Monthly household income	-0.10	-0.18, -0.02	0.010
Chronic disease	-0.22	-0.57, 0.12	0.228
Smoking habit during haze	0.04	-0.12, 0.21	0.654
Ethnicity			
Chinese	[Reference]	[Reference]	[Reference]
Malay	0.28	0.01, 0.57	0.044
Indian	0.77	0.48, 1.10	<0.001
Other	0.27	-0.94, 2.58	0.735
Perceived risk predicted by			
Knowledge	0.65	0.48, 0.79	<0.001

Table 4. Structural equation model including knowledge on haze, perceived risk, and evidence-based and other protective behaviours[a] (Cont'd)

	β	BCa 95% CI	*P* value
Control variables			
Age	0.01	-0.002, 0.02	0.104
Sex	-0.07	-0.28, 0.16	0.539
Education Level	-0.16	-0.30, -0.04	0.025
Monthly household income	0.02	-0.06, 0.10	0.583
Chronic disease	-0.02	-0.57, 0.47	0.942
Smoking habit during haze	-0.05	-0.25, 0.10	0.569
Ethnicity			
Chinese	[Reference]	[Reference]	[Reference]
Malay	-0.32	-0.64, -0.003	0.052
Indian	-0.33	-0.68, -0.02	0.060
Others	0.23	-1.56, 1.73	0.773
Knowledge predicted by			
Age	0.001	-0.01, 0.01	0.837
Sex	-0.06	-0.26, 0.16	0.566
Education level	0.44	0.33, 0.56	<0.001
Monthly household income	0.03	-0.05, 0.11	0.400
Chronic disease	0.06	-0.41, 0.62	0.862
Smoking habit during haze	0.18	0.01, 0.37	0.049
Ethnicity			
Chinese	[Reference]	[Reference]	[Reference]
Malay	-0.13	-0.44, 0.21	0.437
Indian	0.03	-0.35, 0.51	0.884
Other	-1.04	-2.08, 1.34	0.321

BCa: bias-corrected and accelerated; CI: confidence interval

[a] β refers to partially-standardised regression weights (unit latent variable variance). Root mean square error of approximation was 0.04 and comparative fit index 0.92. Coding for variables: sex (0: male; 1: female), chronic disease (0: no; 1: yes) and smoking habit (1: daily; 2: less than daily; 3: not at all).

direct effect between knowledge and evidence-based protective behaviours, the association between knowledge and other protective behaviours was fully mediated by perceived risk. Perceived risk was associated with the overall protective behaviours. This provides partial empirical evidence for the health belief model, which proposes that a higher perceived risk will result in a higher likelihood of protective behaviour.[31]

In our study, we also found that household income levels were inversely associated with other protective behaviours, while there was no association between household income and evidence-based protective behaviours. These results have not been found in previous studies in urban air pollution[32] or influenza,[27] and run contrary to the well demonstrated inverse relationship between socioeconomic status and unhealthy behaviours.[33] A possible explanation might be that individuals of lower socioeconomic status are more likely to take public transport and be involved in non-office-based occupations, and be more exposed to the negative effects of haze. Hence, they may see a greater need for protective behaviours. In addition, the negative effect of income disparity could have been mitigated by the targeted effort by the Singapore government and multiple voluntary welfare organisation

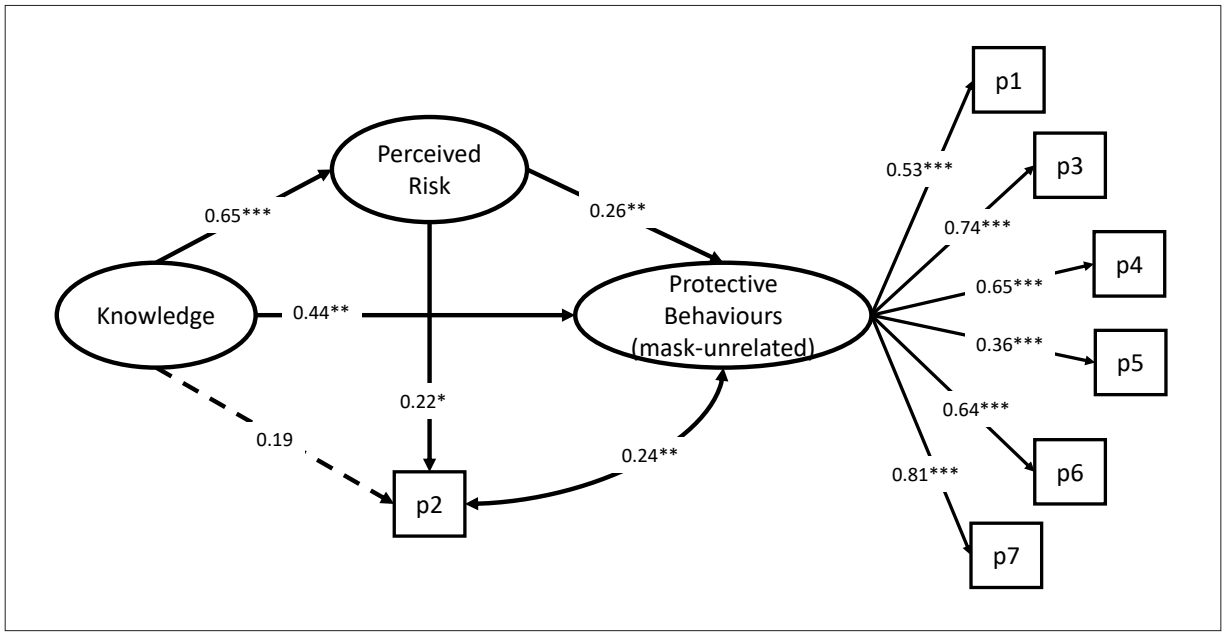

Fig. 3. Structural equation model showing the relationships among knowledge, perceived risk, mask-unrelated protective behaviours and p2 ("I wore an N95 mask").
The reported values are partially standardised parameter estimates (unit latent variable variance). Solid arrows indicate significant parameter estimates (e.g. from Knowledge to Perceived Risk) whereas dashed arrows indicate non-significant parameter estimates (e.g. from Knowledge to p2). Unidirectional arrows (e.g. from Knowledge to Perceived Risk) indicates that Perceived Risk was regressed on Knowledge, whereas the bidirectional arrow indicates correlational relationship between constructs (e.g. between error variances of Protective Behaviours (mask-unrelated) and p2). Control variables and indicators of Knowledge and Perceived Risk are omitted from the figure. Root mean square error of approximation was 0.04 and comparative fit index 0.89.
* $P<0.05$, ** $P<0.01$, *** $P<0.001$

that distributed N95 masks and household essentials to residents with lower household income.[34]

In addition, ethnic minorities were more likely to adopt other protective behaviours. A previous study suggested a shared perceived vulnerability.[27] However, our study showed that perceived risks were also lower in these groups as well, despite a higher frequency of other protective behaviours. Exploratory analyses with each ethnic group suggested the same underlying relationships among knowledge, perceived risk and protective behaviours, suggesting that reasons beyond the existing constructs may explain the seemingly contradictory relationships. More research will need to be conducted to elucidate the relationship between ethnicity and protective behaviours.

Together, our results suggest the importance of increasing knowledge of haze, as a higher knowledge level was associated with greater frequency of protective behaviours. While the public education efforts by the Singapore government were commendable, there can be significant room for improvement as there were significant knowledge gaps among the participants. Educational effort should be directed at smokers and those with a lower educational level.

While N95 masks are an effective means of reducing exposure to PM, only 43.4% of participants reported using them during the haze. In addition, their efficacy was dependent on proper fitting. A previous study found that only 12.6% of participants in the community could don the N95 mask proficiently.[11] There were concerns that poorly fitted N95 mask may create a false sense of security and lead to lower adoption of other protective behaviours (e.g. staying indoors). In our analysis, we found that wearing of the N95 mask was associated with other mask-unrelated protective behaviours and there was no evidence of poor adoption of other protective behaviours.

The strength of this study was the relatively large sample size. The use of a structural equation modelling allowed us to elucidate complex interactions among demographic characteristics, knowledge, perceived risk and protective behaviours. In addition, good fit indices and good internal consistencies of our subscales improved the credibility of our findings.

Our study, however, had several limitations. This was a cross-sectional study and the temporal relationship between the constructs could not be assessed. The response rate of 32.0% might have introduced non-

response bias. Also, there could be recall bias. We examined the relationship between the knowledge at the time of survey and protective behaviours during the haze. It was possible that participants had become more knowledgeable after experiencing the severe 2013 haze episode. This study was conducted in a public housing estate and omitted the high-income earners, possibly explaining the contradictory finding of the inverse relationship between income and other protective behaviours. However, the majority of Singapore citizens and permanent residents (>80%) live in public housing and the study would be generalisable to them. The questionnaire was administered in only English and Chinese. This limitation might have excluded ethnic minority participants who were non-native speakers of the 2 languages. However, the ethnic composition of our participants was largely consistent with the Singapore Census data in 2015 (Chinese 74.3%, Malay 13.3%, Indian 9.1% and others 3.2%), which suggested that ethnic minorities were not underrepresented in our study.[35] Another limitation was the significant time interval between data collection and analysis (5-year gap). However, insights gained in this study to encourage the adoption of protective behaviours are likely to be applicable to other urban populations facing the issue of haze and perhaps even infectious disease outbreaks (e.g. COVID-19 pandemic), given the many similarities between these 2 issues and the protective behaviours required. The COVID-19 pandemic demonstrated the importance of public education to counter disinformation and to increase uptake of protective behaviours.

The nature of the haze in Southeast Asia and its associated health consequences present a unique and recurrent public health problem. The link between haze and acute adverse health outcomes has been well studied;[7,8,36] hence, encouraging protective behaviours is a logical solution. Our findings suggest that knowledge about the haze is directly associated with the practice of protective behaviours, the association of which is also mediated via perceived risk. Interventions that increase knowledge, like public education, remain a pertinent public health strategy. In addition, the wearing of N95 masks correlates with uptake of other protective behaviours and can be part of the multipronged effort to minimise the impact of haze, provided proper fitting and training are performed.

Disclosure

Dr Bee Choo Tai reported receiving personal fees from Boehringer Ingelheim and Wiley-Blackwell outside the submitted work.

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ORIGINAL ARTICLE

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A review of child sexual abuse cases presenting to a paediatric emergency department

Magdalene HM Lee [1]*MMed (EM)*, Sashikumar Ganapathy [1,2]*MRCPCH (UK)*, Soo Mei Low [3]*BSW*, Christine LQ Chua [3]*MSc*, Shu-Ling Chong [1,2]*MPH*, Eric Ma [1]*MBBS*, Peter CY Wong [1,2]*MMed (Paeds)*

ABSTRACT

Introduction: Child sexual abuse (CSA) adversely affects a child's growth and well-being. This study aimed to describe the profile of children presenting to a tertiary paediatric emergency department (ED) with CSA.

Methods: Children 0–16 years old presenting to KK Women's and Children's Hospital ED from June 2016 to August 2020 with sexual abuse were retrospectively reviewed. We performed a secondary analysis on girls and stratified them by age <13 and ≥13 years old.

Results: There were 790 patients who made 833 visits for CSA. Victims were predominantly girls (747, 94.8%) and perpetrators were predominantly men (763, 96.6%). The abuse first occurred before the age of 13 years in 315 victims (39.9%). For 468 (59.2%), more than one incident occurred before presentation. Compared to girls ≥13 years old, girls <13 years old were more frequently abused by a family member (47.7% versus 8.0%, $P<0.001$) and abused in their own home (55.7% vs 21.0%, $P<0.001$). Among all children, parental divorce and the absence of one or both biological parents in the household were prevalent, with 287/783 (36.7%) having divorced parents, and only 374/784 (47.8%) residing with both biological parents.

Conclusion: The findings highlight common characteristics of CSA cases, and can aid the future identification and protection of vulnerable children. The fact that most children presented after more than one incident suggests the need to more closely monitor and protect potentially at-risk children.

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Keywords: Child abuse, child sexual abuse, child welfare, sexual abuse

INTRODUCTION

Child sexual abuse (CSA) is a global public health issue with adverse short- and long-term repercussions. Formal definitions of CSA and the age for defining children differ around the world. In Singapore, CSA refers to any act where a child or young person below 16 years old is used for sexual pleasure or taken advantage of sexually.[1]

CSA has multiple consequences, many of which last into adulthood. Physical effects include sexually transmitted diseases such as human immunodeficiency virus infection[2] and somatic complaints such as gastrointestinal disorders, chronic pain and psychogenic seizures.[3] Many psychiatric consequences have been described, including post-traumatic stress disorder, sleep disorders, anxiety, depression, eating disorders, conversion disorder, borderline personality disorder, decreased self-esteem, decreased life satisfaction and suicide attempts.[4-7] Behavioural outcomes include an increased risk of smoking, alcohol dependence, illicit drug use,[8] delinquency, criminal behaviour[9] and risky sexual behaviour.[10] There are suggestions of increased risks of future marital problems[11] and dependence on welfare.[7] Subsequent generations are also affected, with children of victims of CSA at greater risk of being born preterm, having a single mother, or being involved in protective services.[12]

In Singapore, the Child Protective Service (CPS) oversees the investigation of child abuse allegations and the protection of children. The number of CSA cases

[1] Department of Emergency Medicine, KK Women's and Children's Hospital, Singapore
[2] Duke-NUS Medical School, Singapore
[3] Medical Social Work Department, KK Women's and Children's Hospital, Singapore
Correspondence: Dr Magdalene HM Lee, Department of Emergency Medicine, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: magdalene.lee2@mohh.com.sg

CLINICAL IMPACT

What is New

- This is likely the first study describing the profile of child sexual abuse in Singapore.
- It is of great concern that girls <13 years old were frequently abused in their own home by a family member, and many children presented only after more than one incident of abuse had occurred.
- Girls <13 more often had parent- or family-related potential risk factors, while girls ≥13 years old more often had psychiatric or behavioural issues.

Clinical Implications

- These findings can aid the future identification and protection of vulnerable children.

investigated by CPS increased from an average of 63.2 per year in 2010–2014 to an average of 165.6 per year in 2015–2019.[13] A previous study described the profile of children hospitalised for child maltreatment, which included physical abuse, sexual abuse, emotional abuse and neglect.[14] This study only included hospitalised children, whereas most children who present to the emergency department (ED) for sexual abuse are not admitted to hospital. Another study described the profile of children presenting to an ED for physical abuse only.[15] There are no previous studies describing the profile of CSA cases in Singapore.

This study aimed to describe the profile of children 0–16 years old presenting with CSA to a paediatric ED in Singapore. With this information, we hope to aid future efforts to identify children potentially at risk of CSA and facilitate future development of preventive measures.

METHODS

We performed a retrospective chart review of electronic medical records. We included all patients aged 0–16 years old who presented to the ED of KK Women's and Children's Hospital (KKH) with sexual abuse from 17 June 2016 to 31 August 2020. KKH ED is the larger of 2 tertiary paediatric EDs in Singapore, and sees about 150,000 patients a year. The patients either presented of their own accord, with or without parents or guardians, for sexual abuse, or were accompanied by the police as part of the protocol for police investigations of CSA in Singapore, which includes a mandatory paediatric ED consultation for the purpose of safe disposition and referral to Gynaecology. A referral to a multidisciplinary team, including a medical social worker (MSW), was subsequently made, either by the attending ED doctor if the patient was discharged, or by the inpatient team if the patient was admitted. For patients who presented more than once for CSA, only their first ED presentation was included.

Patients were identified using ED diagnosis codes of "sexual abuse", "child sexual abuse" and "sexual assault". The diagnosis code of "child abuse" was also screened but did not yield any CSA cases. Data were extracted from ED records, follow-up outpatient specialist clinic records and MSW records. A structured data extraction form was used to extract information on the child's demographics, details of the sexual abuse, perpetrator characteristics, the presence of pregnancy or sexually transmitted infections, the child's background (e.g. psychiatric or behavioural issues, substance use, previous encounters with social service agencies), the child's family structure, and potential associated family characteristics (e.g. history of parental incarceration or illicit drug use). Each case was assigned a unique case identifier, and patient identifiers were not entered into the dataset. Our definition of CSA, and thus our study population, included cases where the victim was aged below 16 years, the legal age of consent for sexual activity, and voluntarily participated in the sexual activity. In our study, we referred to these cases of voluntary participation as "consensual" as opposed to "non-consensual".

We described categorical data using frequencies and percentages, and continuous data using mean and standard deviation (SD). We performed a secondary analysis on girls, stratifying them by age <13 and ≥13 years, and compared the 2 groups for differences in abuse characteristics and risk factors. Boys were not included in this analysis due to their small number in the study, and characteristics between female and male victims of CSA are known to be different.[16] We differentiated between these 2 age groups because children typically progress from primary to secondary school education at age 13 and may have an associated increase in autonomy. Categorical variables were analysed using chi-square tests and continuous variables were analysed using Student's t-test. Data were analysed using SPSS Statistics software version 23 (IBM Corp, Armonk, US).

The study was approved by the SingHealth Centralised Institutional Review Board (2020/2761). The requirement for informed consent was waived due to the minimal risks of the study, the low feasibility

of retrospectively obtaining consent from a large number of patients, and the risk of inflicting psychological damage on patients by contacting them regarding a potentially traumatic past event.

RESULTS

Epidemiology

There were 790 patients who made 833 visits to the ED for CSA. Of these, 38 patients presented more than once for CSA, and only their first visit was included in the study. From 2016 to 2019, a mean of 16.2 patients per month were seen (Table 1). Fewer patients were seen in 2020 (mean of 13.0 per month) due to a fall in attendances by about half from April to July 2020, compared to the same period in the preceding years. This coincided with COVID-19 movement restrictions imposed nation-wide from 2 April to 1 June 2020, and subsequent phased reopening measures. The majority (747, 94.6%) of patients were girls, and 261 (33.0%) patients presented at <13 years old. Ethnic distribution is as shown in Table 1.

Abuse characteristics

Abuse characteristics are described in Table 2. The first abuse occurred at <13 years old for 315 (39.9%) of patients. The majority (468, 59.2%) had more than one alleged event of CSA prior to presentation. The perpetrators were predominantly male for both female (721/747, 96.5%) and male (42/43, 97.7%) victims. A small proportion of victims was subjected to concurrent physical abuse (19, 2.4%).

The abuse involved non-consensual acts in 432 victims (54.7%). The abuse was non-consensual for most male victims (36/43, 83.7%), and for more than half of female victims (396/747, 53.0%). Among girls <13 years old compared to those ≥13 years old, the abuse was more frequently non-consensual (210/237, 88.6% versus 186/510, 36.5%, $P<0.001$) and intrafamilial (113, 47.7% vs 41, 8.0%, $P<0.001$). In contrast, the perpetrator was most commonly a friend (452, 88.6%) for girls ≥13 years old. For girls <13 years old, the perpetrator more frequently lived in the same household (116, 48.9% vs 34, 6.7%, $P<0.001$), and the perpetrators were generally older (mean 30.5, SD 15.7 vs mean 19.1, SD 8.4, $P<0.001$). For girls <13 years old, the abuse occurred most frequently in the patient's residence (132, 55.7%, $P<0.001$), whereas for girls ≥13 years old, the abuse occurred most commonly in the perpetrator's residence (205, 40.2%), followed by the patient's residence (107, 21.0%).

Girls ≥13 years old were more likely to have been involved in more intrusive abuses, with higher rates of penile-vaginal intercourse (390, 76.5% vs 56, 23.6%, $P<0.001$) and penile-oral or oral-vaginal intercourse (15.4, 30.2% vs 38, 16.0%, $P<0.001$). In contrast, girls <13 years old were more likely to have been fondled with no penetration (88, 37.1% vs 18, 3.5%, $P<0.001$).

Disclosure

Eight children were preverbal. Of the 782 children who could communicate verbally, 454/740 (61.4%) had

Table 1. Year-on-year demographics between 2016 and 2020

Year	2016[a]	2017	2018	2019	2020[b]	Total
Total no. of cases	115	185	189	197	104	790
Mean no. of cases per month	17.8	15.4	15.8	16.4	13.0	15.7
Girls, no. (%)	100 (87.0)	174 (94.1)	179 (94.7)	194 (98.5)	100 (96.2)	747 (94.6)
Age <13, no. (%)	45 (39.1)	73 (39.5)	64 (33.9)	60 (30.5)	19 (18.3)	261 (33.0)
Girls aged <13, no. (%)[c]	37 (37.0)	67 (38.5)	59 (33.0)	58 (29.9)	16 (16.0)	237 (31.7)
Ethnicity, no. (%)						
Chinese	55 (47.8)	88 (47.6)	82 (43.4)	92 (46.7)	45 (43.3)	362 (45.8)
Malay	37 (32.2)	75 (40.5)	75 (39.7)	82 (41.6)	51 (49.0)	320 (40.5)
Indian	15 (13.0)	13 (7.0)	23 (12.2)	13 (6.6)	2 (1.9)	66 (8.4)
Others	8 (7.0)	9 (4.9)	9 (4.8)	10 (5.1)	6 (5.8)	42 (5.3)

[a] From 17 June 2016 to 31 December 2016 (6.47 months)
[b] From 1 January 2020 to 31 August 2020 (8 months)
[c] Percentage out of number of girls presenting in that year

Table 2. Abuse characteristics

Characteristic	Total (N=790)	Girls			
		All (n=747)	<13 (n=237)	≥13 (n=510)	*P* value[a]
Age <13 at first incident, no. (%)	315 (39.9)	289 (38.7)	–	–	–
>1 incident of sexual abuse prior to presentation, no. (%)	468 (59.2)	445 (59.6)	129 (54.4)	316 (62.0)	0.051
Non-consensual, no. (%)	432 (54.7)	396 (53.0)	210 (88.6)	186 (36.5)	<0.001
Perpetrator male, no. (%)	763 (96.6)	721 (96.5)	214 (90.3)	507 (99.4)	<0.001
Perpetrator age (mean±SD)	23.3±12.9	22.7±12.4	30.5±15.7	19.1±8.4	<0.001
Intrafamilial, no. (%)	171 (21.6)	154 (20.6)	113 (47.7)	41 (8.0)	<0.001
Relationship of perpetrator to child, no. (%)					
Friend	524 (66.3)	510 (68.3)	58 (24.5)	452 (88.6)	–
Biological father	77 (9.7)	68 (9.1)	53 (22.4)	15 (2.9)	–
Mother's partner	34 (4.3)	34 (4.6)	19 (8.0)	15 (2.9)	–
Other relative	60 (7.6)	52 (7.0)	41 (17.3)	11 (2.2)	–
Helper	16 (2.0)	15 (2.0)	15 (6.3)	0 (0.0)	–
Teacher	16 (2.0)	14 (1.9)	11 (4.6)	3 (0.6)	–
Others	63 (8.0)	54 (7.2)	40 (16.9)	14 (2.7)	–
Perpetrator in same household as child, no. (%)	171 (21.6)	150 (20.1)	116 (48.9)	34 (6.7)	<0.001
Location of most recent incident, no. (%)					<0.001
Patient's residence	260 (32.9)	239 (32.0)	132 (55.7)	107 (21.0)	
Perpetrator's residence	244 (30.9)	236 (31.6)	31 (13.1)	205 (40.2)	
Public areas of housing estates e.g. staircases, void decks	100 (12.7)	100 (13.4)	20 (8.4)	80 (15.7)	
Others	186 (23.5)	172 (23.0)	54 (22.8)	118 (23.1)	
Type of sexual abuse, no. (%)					
Penile-vaginal	446 (56.5)	446 (59.7)	56 (23.6)	390 (76.5)	<0.001
Penile-oral/Oral-vaginal	206 (26.1)	192 (25.7)	38 (16.0)	154 (30.2)	<0.001
Digital penetration	303 (38.4)	296 (39.6)	98 (41.4)	198 (38.8)	0.511
Penile-anal	50 (6.3)	32 (4.3)	8 (3.4)	24 (4.7)	0.403
Foreign object penetration	13 (1.6)	10 (1.3)	9 (3.8)	1 (0.2)	<0.001
Fondling with no penetration	118 (14.9)	106 (14.2)	88 (37.1)	18 (3.5)	<0.001
Voluntary disclosure, no. (%)[b]	490/782 (62.7)	454/740 (61.4)	188/230 (81.7)	266/510 (52.2)	<0.001
If voluntarily disclosed, person to whom child disclosed, no. (%)					
Parent/Guardian	220/490 (44.9)	201/454 (44.3)	129/188 (68.6)	72/266 (27.1)	–
Other relative	34/490 (6.9)	34/454 (7.5)	17/188 (9.0)	17/266 (6.4)	–
Teacher/Counsellor/Youth worker	125/490 (25.5)	112/454 (24.7)	25/188 (13.3)	87/266 (32.7)	–
Friend	60/490 (12.2)	59/454 (13.0)	8/188 (4.3)	51/266 (19.2)	–
Other	51/490 (10.4)	48/454 (10.6)	9/188 (4.8)	39/266 (14.7)	–

[a] Comparing girls aged <13 and ≥13
[b] Not including preverbal children

voluntarily disclosed the abuse to another person prior to presentation. Girls <13 years old more often voluntarily disclosed compared to girls ≥13 years old (188/230, 81.7% vs 266/510, 52.2%, *P*<0.001). Among those who voluntarily disclosed, girls <13 years old most commonly disclosed to parents or guardians (129/188, 68.6%), whereas girls ≥13 years old disclosed to teachers, counsellors or youth workers (87/266, 32.7%), parents or guardians (72, 27.1%), or friends (51, 19.2%). Those who had not voluntarily disclosed were typically brought to medical attention because of suspicions on the part of parents or other adults.

When comparing consensual and non-consensual acts, children involved in non-consensual acts were significantly more likely to voluntarily disclose the abuse (350/422, 82.9% vs 140/358, 39.1%, *P*<0.001), and were more likely to disclose the abuse to parents or guardians (183/350, 52.3% vs 37/140, 26.4%, *P*<0.001). On subgroup analysis of girls ≥13 years old, a similar pattern of voluntary disclosure (non-consensual 140/184, 76.1% vs consensual 126/324, 38.9%, *P*<0.001) was observed. However, in this subgroup, there was no significant difference in rates of disclosure to parents or guardians between those involved in non-consensual and consensual acts (40/140, 28.6% vs 32/126, 25.4%, *P*=0.561).

Consequences

Table 3 shows consequences resulting from sexual abuse. Girls <13 years old were more likely to be admitted to hospital compared to those ≥13 years old (42, 17.7% vs 25, 4.9%, *P*<0.001). This was likely for child protection reasons, given the higher rates of intrafamilial sexual abuse in the younger age group.

Psychiatric, behavioural and familial characteristics

Psychiatric, behavioural and familial characteristics for CSA are shown in Table 4. Just over half of the patients had parents who were married to each other (411/783, 52.5%). The others had parents who were divorced, never married, or deceased. Less than half (374/784, 47.7%) lived in the same home as both biological parents. The majority lived with a single parent (including cases where the other parent was incarcerated), step-parent, other relative, or in a foster home or institution.

Among girls, those <13 years old more commonly had parent- or family-related potential risk factors, such as a parental history of illicit drug use (19/201, 9.5% vs 21/461, 4.6%, *P*=0.015) or a parental history of incarceration (28/233, 12.0% vs 28/498, 5.6%, *P*=0.002). In contrast, those ≥13 years old more commonly had child-related potential risk factors, such as a history of psychiatric or behavioural issues (230/510, 45.1% vs 27/237, 11.4%, *P*<0.001), a history of smoking (161/347, 46.4% vs 15/211, 7.1%, *P*<0.001), a history of alcohol use (75/333, 22.5% vs 6/209, 2.9%, *P*<0.001) or a history of illicit drug use (23/333, 6.9% vs 2/209, 1.0%, *P*=0.001).

Three in 8 (294/790, 37.2%) patients were previously known to CPS, a MSW, a counsellor, or other social service organisations. One in 8 (98/790, 12.4%) had either a previous ED visit or hospital admission for maltreatment, or a subsequent one during the study period.

DISCUSSION

Our study showed that CSA is a major problem in Singapore, with 39.9% of the victims in our study having been abused before they were 13 years old.

Table 3. Consequences of sexual abuse

Consequence	Total (N=790)	Girls			
		All (n=747)	<13 (n=237)	≥13 (n=510)	*P* value[a]
Pregnant, no. (%)	–	39 (5.2)	1 (0.4)	38 (7.5)	<0.001
Sexually transmitted infections, no. (%)	49 (6.2)	47 (6.3)	4 (1.7)	43 (8.4)	<0.001
Gonorrhoea	7 (0.9)	6 (0.8)	1 (0.4)	5 (1.0)	0.426
Chlamydia	44 (5.6)	43 (5.8)	3 (1.3)	40 (7.8)	<0.001
Pelvic inflammatory disease	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.2)	0.495
Presence of injuries, no. (%)	34 (4.3)	30 (4.0)	21 (8.9)	9 (1.8)	<0.001
Admitted to hospital, no. (%)	82 (10.4)	67 (9.0)	42 (17.7)	25 (4.9)	<0.001

[a] Comparing girls aged <13 and ≥13

Table 4. Psychiatric, behavioural and familial characteristics

Characteristic	Total	Girls			
		All	<13	≥13	*P* value[a]
Child-related characteristics					
History of psychiatric or behavioural issues, no. (%)	265/790 (33.5)	257/747 (34.4)	27/237 (11.4)	230/510 (45.1)	<0.001
Special needs/Developmental delay, no. (%)	53/790 (6.7)	45/747 (6.0)	22/237 (9.3)	23/510 (4.5)	0.011
History of smoking, no. (%)	181/586 (30.9)	176/558 (31.5)	15/211 (7.1)	161/347 (46.4)	<0.001
History of alcohol use, no. (%)	82/569 (14.4)	81/542 (14.9)	6/209 (2.9)	75/333 (22.5)	<0.001
History of illicit drug use, no. (%)	26/569 (4.6)	25/542 (4.6)	2/209 (1.0)	23/333 (6.9)	0.001
History of institutionalisation, no. (%)	57/790 (7.2)	53/747 (7.1)	11/237 (4.6)	42/510 (8.2)	0.075
Previously known to social services, no. (%)	294/790 (37.2)	276/747 (36.9)	65/237 (27.4)	211/510 (41.4)	<0.001
Child Protective Service, no. (%)	87/790 (11.0)	83/747 (11.1)	34/237 (14.3)	49/510 (9.6)	0.055
Medical social worker, no. (%)	122/790 (15.4)	115/747 (15.4)	38/237 (16.0)	77/510 (15.1)	0.742
Counsellor/Others, no. (%)	266/790 (33.7)	251/747 (33.6)	54/237 (22.8)	197/510 (38.6)	<0.001
Parent- or family-related characteristics					
Marital status of parents, no. (%)[b]					
Married	411/783 (52.5)	384/741 (51.8)	118/236 (50.0)	266/505 (52.7)	0.497
Divorced	287/783 (36.7)	275/741 (37.1)	101/236 (42.8)	174/505 (34.5)	–
Never married	52/783 (6.6)	49/741 (6.6)	10/236 (4.2)	39/505 (7.7)	–
One or both deceased	33/783 (4.2)	33/741 (4.5)	7/236 (3.0)	26/505 (5.1)	–
Child living with, no. (%)					
Both biological parents	374/784 (47.7)	352/741 (47.5)	108/236 (45.8)	244/505 (48.3)	0.517
Single biological parent	114/784 (14.5)	108/741 (14.6)	42/236 (17.8)	66/505 (13.1)	–
Biological parent + Step-parent	118/784 (15.1)	113/741 (15.2)	28/236 (11.9)	85/505 (16.8)	–
Biological parent + Other relative	64/784 (8.2)	59/741 (8.0)	28/236 (11.9)	31/505 (6.1)	–
Other relative	50/784 (6.4)	48/741 (6.5)	14/236 (5.9)	34/505 (6.7)	–
Non-relative, e.g. adopted or foster parent	23/784 (2.9)	23/741 (3.1)	7/236 (3.0)	16/505 (3.2)	–
Institutionalised	41/784 (5.2)	38/741 (5.1)	9/236 (3.8)	29/505 (5.7)	–
Mother employed, no. (%)	518/769 (67.4)	495/729 (67.9)	160/232 (69.0)	335/497 (67.4)	0.674
History of illicit drug use in parents, no. (%)	46/699 (6.6)	40/662 (6.0)	19/201 (9.5)	21/461 (4.6)	0.015
History of incarceration of parents, no. (%)	60/769 (7.8)	56/731 (7.7)	28/233 (12.0)	28/498 (5.6)	0.002
History of domestic violence in family, no. (%)	109/774 (14.1)	103/734 (14.0)	43/234 (18.4)	60/500 (12.0)	0.020

[a] Comparing girls aged <13 and ≥13
[b] The discrepancy between 783 and 784 is due to missing data of 1 child about the marital status of the parents.

Similar to worldwide studies,[16–18] most of the victims were girls and most of the perpetrators were men. However, the proportion of victims who were boys (43, 5.4%) in our study was lower than global reports,[16,17] even in comparison to other Asian countries such as South Korea,[19] China[20] and Taiwan.[21] There are reports that boys are more reluctant to disclose CSA.[22-24] Reasons that have been postulated include boys fearing not being recognised as a victim, being perceived as less masculine, or being labelled

homosexual.[22,25] It is unclear whether the low proportion of boys in our study is due to a true lower prevalence or a lower rate of disclosure.

The Singapore ethnic composition in 2020 was 74.3% Chinese, 13.5% Malay, 9.0% Indian and 3.2% others.[26] Comparing the ethnic composition of victims to national statistics, there were proportionately fewer Chinese (362, 45.8%) and more Malay (320, 40.5%) victims. Further research is needed to understand the reasons for the ethnic distribution of patients who presented to the ED, and the extent to which this distribution reflects differences in the prevalence and disclosure rates of CSA between ethnic groups.

Certain differences in characteristics of the abuse between girls aged <13 and ≥13 years old were similar to differences found in studies conducted in other countries. Those aged <13 years old were more likely to be involved in non-consensual and intrafamilial abuses, whereas those aged ≥13 years old were more likely to be involved in consensual and extrafamilial underaged sexual activity. This was similar to previous studies that showed that younger children are more likely to be victimised by a parent or relative, whereas older children are more likely to be victimised by extrafamilial perpetrators.[27-29] Those ≥13 years old were also more likely to have penetrative abuse, especially penile-vaginal and penile-anal penetration, which was consistent with previous findings.[27]

Interestingly, potential risk factors were different for girls aged <13 and ≥13 years old. Previous studies have demonstrated that risk factors for CSA can be grouped into child-, parent- and family-related domains.[30] In our study, we found that child-related potential risk factors such as a history of psychiatric or behavioural issues, smoking, alcohol use and illicit drug use were more common in the ≥13 age group, whereas parent- and family-related potential risk factors such as a parental history of illicit drug use or incarceration were more common in the <13 age group. It should be noted that child behavioural issues such as smoking, alcohol use and illicit drug use are generally more common in the ≥13 age group, and it was not within the scope of our study to conclude whether they were more common in CSA victims than in the general paediatric population. The interplay of factors contributing to CSA is complex and causality relationships may be difficult to determine. However, the differing characteristics between the <13 and ≥13 age groups indicate that existing strategies to identify and prevent CSA could be specifically targeted at different age groups. For example, we suggest that for at-risk families with younger children, schools, prisons, courts, hospitals and community agencies could work more closely with individuals or family groups to identify possible threats to child safety, including those created by prolonged parental absence resulting from parental divorce or incarceration. For teenagers in whom curiosity and peer influence may contribute to risk-taking behaviours, more emphasis could be placed on equipping parents and teachers to handle issues relating to teenage sexuality and to educate teenagers on managing situations that may lead to sexual abuse.

In children of both sexes and age groups, parental divorce was prevalent. The parental divorce rate of 36.7% in the study is in contrast to national statistics that show 21.1% of marriages are dissolved by the 15th year of marriage.[31] The majority of children lived in a household that did not include both biological parents. It is reported that children from non-nuclear families are at higher risk for CSA victimisation,[30,32] and they form an important group for schools, courts and social service agencies to target in efforts to detect and reduce CSA.

While the majority of children voluntarily disclosed the abuse, this was more common among girls <13 compared to those ≥13 years old. Moreover, while most girls <13 years old disclosed to their parents or guardians, those ≥13 years old disclosed to a wider variety of people including teachers, counsellors, youth workers and friends, with only a quarter disclosing to their parents or guardians. In addition, although those involved in non-consensual acts, compared to those involved in consensual acts, were more likely to disclose to parents or guardians, this difference was not seen when analysing girls ≥13 years old. This was consistent with previous studies that have found that adolescents are less likely to disclose to parents compared to younger children.[27] It has been proposed that this may be because adolescents may feel that family members will react more negatively to a disclosure, especially when the perpetrator is known to the family.[33]

We found a worrying trend that the majority of children experienced recurring incidents of CSA before presenting to the ED, suggesting a delay in disclosure. Previous studies exploring why children may be reluctant to disclose CSA have found that barriers to disclosure include emotions of guilt and shame, not considering themselves to be abused, a perceived lack of understanding and limited support from adults, the fear of parental sanctions, and the fear of negative consequences for the offender and the child's own family.[34-36] Further investigations need to be carried out to identify barriers to disclosure in

Singapore's cultural context. We believe that efforts should be taken to encourage prompt disclosure before recurrent events occur. This could include training parents and teachers on effective questioning of children about possible CSA,[35] providing more opportunities for children to disclose, and providing avenues for friends of victims, particularly adolescent victims, to disclose.[33,37]

It is notable that 37.2% of the children were previously known to social services prior to their ED visit. In Singapore, the child protection system involves statutory interventions via CPS, specialised community-based interventions via child protection specialist centres, and community-based services via community agencies such as family service centres and school-based services[38]. These offer a wide range of targeted services at the legal, educational, community and healthcare levels. In the acute hospital setting, CSA cases are referred to MSWs, and the type of support offered depends on the patient's age and whether the event was consensual. For children aged ≥13 years who engage in consensual acts, MSWs typically offer education on sexuality, handling peer relationships and contraception. For children of all ages involved in non-consensual acts, MSWs typically focus on screening for trauma symptoms, providing emotional support and counselling, and educating children on recognising and avoiding potentially dangerous situations.

The occurrence of CSA in the group of children already known to social services suggests that more can be done for primary and secondary prevention of CSA. For young children, previous research has found that education programmes are more effective when based on concrete concepts, such as appropriate touch and what is forbidden, rather than abstract concepts such as rights and feelings.[39] We suggest that schools and community organisations work together with parents and caregivers to equip young children with the knowledge of recognising inappropriate sexual behaviour and developing preventive skills. For teenagers, there is evidence that programmes that increase attachment to school or reduce school dropout are effective in delaying sexual activity and reducing teenage pregnancy, even when the programmes do not directly address sexuality. Besides providing sexual education, schools offer opportunities for youths to succeed, and help them to develop plans for higher education and careers.[40] We suggest that programmes focus on keeping teenagers engaged in schools, including giving pregnant youths the opportunity to continue their studies.

The study was limited by its retrospective nature. There may be inaccuracies in self-reported data obtained from interviews with children and their caregivers, especially regarding sensitive information such as the children's history of substance use and their parents' history of illicit drug use or incarceration. The history was also limited in young, and especially preverbal, children. In addition, we were only able to include cases that were brought to medical attention, and were unable to account for cases that were unreported. In particular, the low proportion of boys in our study suggests the possibility of under-reporting of male victims. The fall in reported cases in 2020 during the period of national COVID-19 movement restrictions also suggests that the true rate of CSA may have been under-represented during this period. The characteristics of unreported cases may differ from reported cases, and further studies are required to investigate the prevalence of under-reporting of CSA in Singapore and the nature of unreported cases. Finally, we were unable to determine if families utilised community resources and sought help through existing helplines prior to or after the ED attendance. We were therefore unable to fully evaluate the utility and effectiveness of existing community resources.

CONCLUSION

Our study highlights that CSA is an important problem in Singapore and found that girls <13 years old were frequently abused in their own home by a family member. Parental divorce and not living with both biological parents were frequent in the population. Girls ≥13 years old more frequently had psychiatric and behavioural issues, and a history of smoking and/or alcohol use. Understanding the characteristics associated with CSA will enable vulnerable groups of children to be identified and protected, for example by training them to recognise and avoid situations that may lead to sexual abuse. We found that many children presented after more than one incident of abuse, suggesting that potentially at-risk children require closer surveillance by parents, schools and support organisations, and that they should be provided with more opportunities for disclosure.

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ORIGINAL ARTICLE

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Outcomes of oesophageal cancer treated with neoadjuvant compared with definitive chemoradiotherapy

Caryn Wujanto [1]*MRCP*, Jeremy Tey [1]*FRANCZR*, Balamurugan Vellayappan [1]*FRANCZR*, Jimmy So [2]*FRCS*, Wei Peng Yong [3]*MRCP*, Asim Shabbir [2]*FRCS*, Michelle Tseng [1]*FRANCZR*, Yu Yang Soon [1]*FRANCZR*, Francis Ho [1]*FRANCZR*

ABSTRACT

Introduction: We report outcomes of patients with oesophageal cancer treated with neoadjuvant chemoradiotherapy (NACRT) plus surgery or definitive chemoradiotherapy (chemoRT) at our institution.

Methods: We retrospectively reviewed patients who underwent chemoRT from 2005 to 2017. The primary outcome was overall survival (OS). Secondary outcomes were disease-free survival (DFS) and toxicities.

Results: We identified 96 patients with median age of 64 years and squamous cell carcinoma in 82.3%. Twenty-nine patients (30.2%) received NACRT plus surgery, 67 patients (69.8%) received definitive chemoRT. Median follow-up was 13.5 months. The 3/5-year OS were 26.4%/13.4%, and 59.6%/51.6% in the definitive chemoRT and NACRT plus surgery groups, respectively. The 3/5-year DFS were 19.3%/12.3%, and 55.7%/37.2% in the definitive chemoRT and NACRT plus surgery groups, respectively. NACRT plus surgery significantly improved OS (hazard ratio [HR] 0.40, 95% confidence interval [CI] 0.22–0.72, $P<0.01$) and DFS (subhazard ratio [SHR] 5.21, 95 CI 1.20–22.7, $P=0.03$). Multivariable analysis for OS in the definitive chemoRT group indicated stage (1–2 vs 3–4a; HR 2.17, 95% CI 1.15–4.11, $P=0.02$) and feeding tube (no tube versus tube; HR 1.85, 95% CI 1.00–3.43, $P=0.05$) as significantly associated with OS. The cumulative incidence of local recurrence was significantly higher in the definitive chemoRT group (SHR 5.21, 95 CI 1.2022.7, $P=0.03$). Nineteen patients (65.5%) had postoperative complications.

Conclusion: NACRT plus surgery improved OS and DFS. However, in view of treatment-related complications, careful selection of patients is warranted. With the predominant histology of our cohort being squamous cell carcinoma (SCC), our results may be more relevant for those with SCC.

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Keywords: Neoadjuvant chemoradiotherapy, oesophageal cancer, surgery

INTRODUCTION

Oesophageal cancer is the 7th most common cancer in the world, with 572,034 new cases diagnosed in 2018,[1] and is the 6th most common cause of cancer-related mortality worldwide.[2] Oesophageal squamous cell carcinoma (SCC) is the predominant histological subtype. However, the incidence of adenocarcinoma has risen among the Western population due to the rising prevalence of central obesity and gastro-oesophageal reflux disease.[3-5]

Studies have reported high recurrence and mortality rates from oesophageal cancer, hence the use of multimodality treatment to improve survival.[6-8] The ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) randomised controlled trial reported long-term survival benefit with neoadjuvant chemoradiotherapy (NACRT) plus surgery in resectable locally advanced oesophageal SCC/adenocarcinoma when compared to surgery alone.[9] However, other studies showed comparable survival with definitive

[1] Department of Radiation Oncology, National University Cancer Institute, Singapore
[2] Division of Surgical Oncology, National University Cancer Institute, Singapore
[3] Department of Haematology-Oncology, National University Cancer Institute, Singapore
Correspondence: Dr Jeremy Tey, Department of Radiation Oncology, 1E Kent Ridge Road, Level 7, NUHS Tower Block, Singapore 119228.
Email: jeremy_tey@nuhs.edu.sg

CLINICAL IMPACT

What is New

- This study provides outcomes of patients with oesophageal cancer treated with neoadjuvant chemoradiotherapy followed by surgery or definitive chemoradiotherapy at an academic medical centre in Singapore.
- Patients treated with neoadjuvant chemoradiotherapy plus surgery had improved overall survival and disease-free survival.

Clinical Implications

- This study supports the use of neoadjuvant chemoradiotherapy followed by surgery for patients with localised oesophageal cancer. However, careful selection of patients is warranted.

chemoradiotherapy (chemoRT) alone, particularly in SCC.[10,11]

For locally advanced SCC and adenocarcinoma (cT1b-cT2 N+ or cT3-cT4aN), the latest National Comprehensive Cancer Network (NCCN) guideline recommends NACRT in surgically fit patients with non-cervical oesophageal SCC or definitive chemoRT for cervical oesophageal SCC.[12] For those with cT2N0 SCC or adenocarcinoma, NCCN recommends oesophagectomy for low-risk lesions (<3cm, well differentiated) and NACRT or definitive chemoRT for those with high-risk lesions (lymphovascular invasion, ≥3cm, poorly differentiated).[12]

In this study, we evaluate the outcome of patients in our institution treated with NACRT plus surgery versus definitive chemoRT for locally advanced oesophageal SCC and adenocarcinoma.

METHODS

This study at the National University Cancer Institute, Singapore was approved by the National Healthcare Group Domain Specific Review Board Domain B.

Patients

We conducted a retrospective review of patients with histologically confirmed oesophageal carcinoma who underwent curative intent chemoRT +/- surgery at our institution from 2005 to 2017. Tumour staging was based on the American Joint Cancer Committee 8th edition Cancer Staging Manual.[13] Patients who received prior definitive, neoadjuvant or palliative intent RT were excluded.

Treatment

Radiotherapy

All patients received radiotherapy (RT) with 3-dimensional conformal or intensity modulated RT (IMRT). RT was delivered in 1.8Gy daily fractions (50.4Gy in 28 fractions for definitive RT, 41.4–50.4Gy in 23–28 fractions as per the CROSS trial for neoadjuvant RT[9]) with 10MV photon beams, 5 days/week. As per our department protocol, the clinical target volume (CTV) included the gross tumour volume (GTV) with 3cm margin superiorly/inferiorly, 0.5icm margin in the axial dimension. The planning target volume (PTV) included the CTV with 1cm margin. Elective nodal coverage includes bilateral supraclavicular nodes for tumours above the carina and celiac axis coverage for distal oesophageal tumours (32–40cm from incisors). Lung dose is limited to V20Gy <35%/mean lung dose <18Gy, heart dose V40Gy <30%/mean heart dose <26Gy, spinal cord <45Gy max dose.

Chemotherapy

Chemotherapy regimens include paclitaxel/carboplatin or fluorouracil/oxaliplatin for neoadjuvant or definitive chemoRT with the alternative of fluorouracil/cisplatin for definitive regimen. As per NCCN guideline: intravenous paclitaxel 50mg/m^2, intravenous carboplatin area under curve (AUC) 2, given on day 1 and weekly thereafter for 5 weeks. Intravenous oxaliplatin 85mg/m^2, leucovorin 400mg/m^2, intravenous fluorouracil 400mg/m^2 push, fluorouracil 800mg/m^2 continuous infusion on days 1 and 2, are given every 2 weeks for a total of 3 cycles concurrently with RT.[12]

Surgery

Suitability for surgery and type of resection depends on the tumour location, anatomy and surgeons' preference. Surgical approaches include Ivor Lewis oesophago-gastrectomy (laparotomy + right thoracotomy), McKeown oesophago-gastrectomy (right thoracotomy + laparotomy + cervical anastomosis) and transhiatal oesophago-gastrectomy (laparotomy + cervicalanastomosis).[12]

Data collection

Data obtained from our institution's medical records and RT databases include clinical diagnosis, RT technique/dose, chemotherapy, treatment break/completion, surgical procedures, and complications.

Follow-up data were obtained from patients' medical record up until the time of death or most recent review.

Performance status, comorbidities and overall health status

Performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) grading.[14] The extent of comorbid conditions was evaluated using the Charlson Comorbidity Index.[15] The International Society of Geriatric Oncology (SIOG) score was used for patients ≥65 years to assess their functional status, and pre-existing comorbidities.[16]

Follow-up

Clinical examination (with endoscopy and imaging if clinically indicated) was scheduled 3–6 monthly for the first 2 years, 6–12 monthly for the 3rd to 5th year, and annually thereafter.[12]

Outcomes

Overall survival (OS) was defined as the time from the first treatment to death due to any cause. Disease-free survival (DFS) was defined as the time from the first treatment to the time of first recurrence (local or distant) as detected by endoscopy or imaging. Local recurrence was defined as the time from the first treatment to the time of local recurrence detected by endoscopy or imaging.

Toxicity

Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[17]

Statistical analysis

OS and DFS were estimated using the Kaplan-Meier method. Survival differences were compared using the log rank test. Univariable and multivariable cox proportional hazard regression models were performed to identify independent factors with significant impact on survival. Factors analysed include: age group (<64 vs ≥65), sex (men vs women), stage (stage 1/2 vs 3/4a), weight loss (no vs yes), surgery (no vs yes), feeding tube (no vs yes), T-stage, histology (SCC vs adenocarcinoma), RT (IMRT vs 3DCRT), RT break (no vs yes), chemotherapy break (no vs yes), Charlson score, SIOG score and ECOG grading. Factors with a P value of ≤0.2 on univariable analyses were entered into the multivariable model. Competing risk regression with death as a competing risk was performed to compare local recurrence rates between the NACRT plus surgery versus definitive chemoRT groups.

Chi-square test was used to compare baseline characteristics between the NACRT plus surgery and definitive chemoRT groups.

Statistical analysis was performed using STATA version 14 (StataCorp LLC, College Station, US). A P value of ≤0.05 was considered to indicate statistical significance.

RESULTS

Patient characteristics

Ninety-six patients underwent curative RT for oesophageal carcinoma at our institution (Table 1). Majority were men (87.5%). Median age was 64 years (range 30–88 years).

Tumour characteristics

All had histological diagnosis of oesophageal carcinoma (82.3% SCC). Majority of tumours were within the thoracic oesophageal region (58.3%), mostly stages 2 and 3 (45.8% and 36.5%, respectively). The predominate depth of tumour invasion as detected on CT scan was T3 (51 patient, 53.1%) and most patients had no nodal involvement (45.8%) while 41 patients (42.7%) had N1 disease (Table 1).

Treatment

Radiotherapy

All patients received RT; 67 patients (69.8%) received definitive RT and 29 patients (30.2%) received NACRT. Most received 50.4Gy/28 fractions for definitive RT (74.6%). As for NACRT, 48.3% received 41.4Gy/23 fractions, 48.3% received 50.4Gy in 28 fractions.

RT break (i.e. number of days that a patient did not have RT) ranged from 1–12 days and was recorded in 31 patients (32.3%), mostly within the definitive chemoRT group (Table 2). Reasons include fever, mucositis, diarrhoea, dehydration, stent insertion, bleeding, fatigue, stroke, fall and machine repair. Majority (93 patients, 96.9%) completed RT.

Chemotherapy

Eighty-four patients (87.5%) received concurrent chemotherapy with intravenous paclitaxel/carboplatin in 38 patients (45.2%) and intravenous fluorouracil with leucovorin plus platinum-based chemotherapy (cisplatin or oxaliplatin) in 20 patients (23.8%). Other regimens include oral capecitabine (625mg/m^2 twice a day on days 1–5 every week for 5 weeks) plus intravenous

Table 1. Patients and tumour characteristics

	All (N=96) No. (%)	No surgery (67) No. (%)	Surgery (29) No. (%)	χ^2 *P* value
Sex				
Male	84 (87.5)	59 (88.1)	25 (86.2)	
Female	12 (12.5)	8 (11.9)	4 (13.8)	0.80
Age				
< 64	54 (56.3)	34 (50.7)	20 (69.0)	
≥ 65	42 (43.8)	33 (49.3)	9 (31.0)	0.10
Ethnicity				
Chinese	79 (82.3)	56 (83.6)	23 (79.3)	
Indian	6 (6.3)	4 (6.0)	2 (6.9)	
Malay	4 (4.2)	2 (3.0)	2 (6.9)	
Others	7 (7.3)	5 (7.5)	2 (6.9)	0.84
ECOG				
0	22 (22.9)	8 (11.9)	14 (48.3)	
1	68 (70.8)	55 (82.1)	13 (44.8)	
2	5 (5.2)	3 (4.5)	2 (6.9)	**<0.01**
3	1 (1.0)	1 (1.5)	0	
Charlson score				
0-1	69 (71.9)	48 (71.6)	21 (72.4)	
2-3	22 (22.9)	16 (23.9)	6 (20.7)	
4-6	5 (5.2)	3 (4.5)	2 (6.9)	0.85
SIOG Group				
1	69 (71.9)	47 (70.1)	22 (75.9)	
2	13 (13.5)	10 (14.9)	3 (4.5)	
3	2 (2.1)	2 (3.0)	0	0.53
CT staging				
T1	2 (2.1)	0	2 (6.9)	
T2	28 (29.2)	22 (32.8)	6 (20.7)	
T3	51 (53.1)	33 (49.3)	18 (62.1)	
T4	15 (15.6)	12 (17.9)	3 (10.3)	0.31
N0	44 (45.8)	36 (53.7)	8 (27.6)	
N1	41 (42.7)	29 (43.3)	12 (41.4)	
N2	10 (10.4)	2 (3.0)	8 (27.6)	**<0.01**
Nx	1 (1.0)	0	1 (3.4)	

oxaliplatin (85mg/m^2 on days 1, 15 and 29 for 3 doses). Twenty-six patients (31%) required chemotherapy break (range 1–14 days) due to neutropenic fever, thrombocytopenia, pneumonia, dehydration and haematemesis. Fifty-one patients (60.7%) completed all planned cycles of chemotherapy.

Table 1. Patients and tumour characteristics (Cont'd)

	All (N=96) No. (%)	No surgery (67) No. (%)	Surgery (29) No. (%)	χ^2 *P* value
Stage				
1	2 (2.1)	0	2 (6.9)	
2	44 (45.8)	36 (53.7)	8 (27.6)	
3	35 (36.5)	19 (28.4)	16 (55.2)	
4a	15 (15.6)	12 (17.9)	3 (10.3)	**0.02**
Location				
Cervical	12 (12.5)	12 (17.9)	0	
Thoracic	56 (58.3)	39 (58.2)	17 (58.6)	
Lower/abdominal	26 (27.1)	14 (20.9)	12 (41.4)	0.16
Not recorded	2 (2.1)	2 (3.0)	0	
Histology				
SCC	79 (82.3)	58 (86.6)	21 (72.4)	
Adenocarcinoma	14 (14.6)	6 (9.0)	8 (27.6)	**0.02**
Others	2 (2.1)	2 (3.0)	0	
Not specified	1 (1.0)	1 (1.5)	0	

CT: computed tomography; ECOG: Eastern Cooperative Oncology Group; SIOG: International Society of Geriatric Oncology: SCC: squamous cell carcinoma
P values in bold are significant

Surgery

Twenty-nine patients (30.2%) had surgery. Median time between completion of RT to surgery was 50 days (range 17–109). Twenty-three patients underwent Ivor-Lewis oesophagogastrectomy, 1 patient underwent transhiatal oesophagogastrectomy, and 5 had various approaches (McKeown oesophagogastrectomy, oesophagectomy with jejunal transposition, total oesophagectomy, total gastrectomy, and Ivor Lewis oesophagogastrectomy with total cholecystectomy). One patient (3.4%) had a positive proximal margin (radial/distal margins clear). Pathologic complete response was achieved in 9 patients (31.0%). Downstaging of the tumour (T) stage was achieved in 18 patients (62.1%), and downstaging of the lymph node (N) stage was achieved in 11 patients (37.9%) (Table 3).

Cause of death

Fifty-four patients (56.3%) died during the period. Out of 37 patients with recorded cause of death, 24 patients died of advanced oesophageal cancer. Twelve patients died of pneumonia and 1 died of acute myocardial infarction. Two patients died of postoperative complications and referred to the coroners.

Outcomes and subgroup analyses

Overall Survival

Median follow-up was 13.5 months (range 1–132). Median OS for all patients was 18 months. Median OS was 71 months (range 3–114) and 13 months (range 1–132) for the NACRT plus surgery, and definitive chemoRT groups, respectively. The 3- and 5-year OS were 26.4% and 13.4%, respectively, in patients who underwent definitive chemoRT, and 59.6% and 51.6%, respectively, in patients who underwent NACRT plus surgery (Table 2). Patients treated with NACRT plus surgery had significantly improved OS compared to patients treated with definitive chemoRT (hazard ratio [HR] 0.40, 95% confidence interval [CI] 0.22–0.72, $P<0.01$). There was no significant difference in OS between tumours located within the cervical region and other locations (HR0.99, 95% CI 0.47–2.09, $P<0.985$) (Fig. 1).

In the 29 patients who had NACRT plus surgery, higher radiation dose improved survival. Fourteen patients who received 50.4Gy/28 fractions due to borderline resectable tumours had significantly improved survival compared to 14 patients who

Table 2. Treatment characteristics, comparison of overall survival, overall survival by stage and disease-free survival between patients with and without surgery

	All (N=96) No. (%)	No surgery (67) No. (%)	Surgery (29) No. (%)	χ^2 *P* value
Feeding tube				
Nasogastric	12 (12.5)	9 (13.4)	3 (10.3)	
Nasojejunal	15 (15.6)	11 (16.4)	4 (13.8)	
PEG	8 (8.3)	7 (10.4)	1 (3.4)	
None	61 (63.5)	40 (59.7)	21 (72.4)	0.58
Stenting				
Yes	11 (11.5)	10 (14.9)	1 (3.4)	
No	85 (88.5)	57 (85.1)	28 (96.6)	0.11
RT technique				
3DCRT	33 (34.4)	27 (40.3)	6 (20.7)	
IMRT	63 (65.6)	40 (59.7)	23 (79.3)	0.06
RT dose				
41.4Gy/23#	15 (15.6)	1 (1.5)	14 (48.3)	
41.7Gy/25#	1 (1.0)	1 (1.5)	0	
45Gy/25#	1 (1.0)	1 (1.5)	0	
48Gy/24#	1 (1.0)	1 (1.5)	0	
50Gy/25#	3 (3.1)	2 (3.0)	1	
50.4Gy/28#	64 (66.7)	50 (74.6)	14 (48.3)	<0.01
54Gy/30#	2 (2.1)	2 (3.0)	0	
56Gy/28#	1 (1.0)	1 (1.5)	0	
66Gy/33#	2 (2.1)	2 (3.0)	0	
66.6Gy/37#	1 (1.0)	1 (1.5)	0	
RT break				
Yes	31 (32.3)	22 (32.8)	9 (3.1)	
No	58 (60.4)	38 (56.7)	20 (69.0)	0.60
Not recorded	7 (7.3)	0	7 (2.4)	
Concurrent chemo				
Yes	84 (87.5)	55 (82.1)	29 (43.3)	
No	4 (4.2)	4 (6.0)	0	
Not recorded	8 (8.3)	8 (11.9)	0	
Type of surgery				
Ivor-Lewis	23	0	23 (79.3)	
Transhiatal	1	0	1 (3.4)	
Others	5	0	5 (17.2)	

Table 2. Treatment characteristics, comparison of overall survival, overall survival by stage and disease-free survival between patients with and without surgery (Cont'd)

	All (N=96)	No surgery (67)	Surgery (29)	χ^2 *P* value
Overall survival				
Median, months	18	13		71
Range, months	1–132	1–132		3–114
1 yr (%)		50.6		75.0
3 yr (%)		26.4		59.6
5 yr (%)		13.4		51.6
Overall survival by stage				
Stage 2				
1 yr (%)		58.8		100
3 yr (%)		45.7		85.7
5 yr (%)		23.2		57.1
Stage 3				
1 yr (%)		45.1		60.0
3 yr (%)		5.6		45.7
5 yr (%)		5.6		45.7
Stage 4				
1 yr (%)		35.2		66.7
3 yr (%)		11.7		33.3
5 yr (%)		11.7		33.3
Disease-free survival				
1 yr (%)		35.1		71.4
3 yr (%)		19.3		55.7
5 yr (%)		12.3		37.2

3DCRT: 3-dimensional radiotherapy; IMRT: intensity modulated radiotherapy; PEG: percutaneous endoscopic gastrostomy; RT: radiotherapy

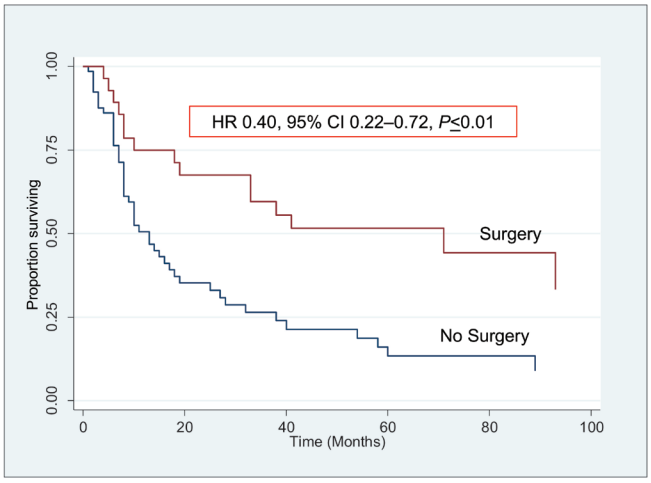

Fig. 1. Kaplan Meier survival curves of patients who had surgery versus no surgery.
HR: hazard ratio; CI: confidence interval

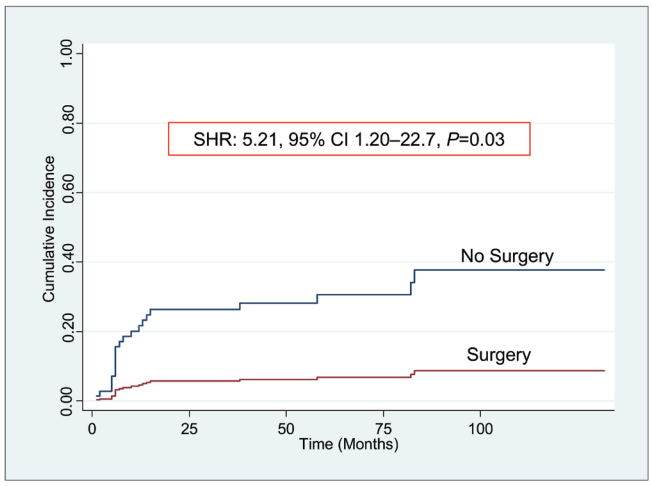

Fig. 2. Cumulative incidence of local recurrence (surgery versus no surgery).
SHR: subhazard ratio; CI: confidence interval

Table 3. Pre- and postoperative TNM staging of patients (n=29)

Preoperative TNM stage	No. (%)	Postoperative TNM stage	No. (%)
T1	2 (6.9)	T0	2 (100)
		T1	0 (0)
		T2	0 (0)
		T3	0 (0)
		T4	0 (0)
T2	6 (20.7)	T0	1 (16.7)
		T1	3 (50)
		T2	0 (0)
		T3	0 (0)
		T4	0 (0)
		Unknown	2 (33.3)
T3	18 (62.1)	T0	1 (5.6)
		T1	4 (22.2)
		T2	2 (11.1)
		T3	8 (44.4)
		T4	0 (0)
		unknown	3 (16.7)
T4	3 (10.3)	T0	1 (33.3)
		T1	0 (0)
		T2	0 (0)
		T3	2 (66.7)
		T4	0 (0)
N0	8 (27.6)	N0	5 (62.5)
		N1	1 (12.5)
		N2	0 (0)
		unknown	2 (25)
N1	12 (41.4)	N0	4 (33.3)
		N1	5 (41.7)
		N2	2 (16.7)
		unknown	1 (8.3)
N2	8 (27.6)	N0	4 (50)
		N1	2 (25)
		N2	1 (12.5)
		unknown	1 (12.5)
Nx	1 (3.4)	N0	1 (100)

TNM: tumour, node, metastasis

received lower dose RT with 41.4Gy/23 fractions (HR 5.36, 95% CI 1.46–19.75, $P<0.012$).

Multivariable analysis for OS in the definitive chemoRT group showed that stage (1–2 vs 3–4a; HR 2.40, 95% CI 1.30–4.44, $P<0.01$) was the only significant variable and in the NACRT group, stage (1–2 vs 3–4a; HR 4.26, 95% CI 1.19–15.22, $P=0.03$) and RT dose (41.4 Gy vs >50.4Gy; HR 4.63, 95% CI 0.97–22.0, $P=0.05$) were significant (Table 4).

Disease-free survival

The 3- and 5-year DFS were 19.3% and 12.3%, respectively, in patients who underwent definitive chemoRT, and 55.7% and 37.2% in patients who underwent NACRT plus surgery.

Multivariable analysis for DFS in patients treated with definitive chemoRT showed that age group (<64 vs ≥65 years; HR 0.66, 95% CI 0.37–1.17, $P=0.16$), stage (1–2 vs 3–4a; HR 1.92, 95% CI 1.07–3.43, $P=0.03$), feeding tube (no tube vs tube; HR 2.36, 95% CI 1.29–4.32, $P<0.01$), histology (SCC vs adenocarcinoma/others; HR 0.66, 95% CI 0.37–1.17, $P=0.16$) were significant and in patients treated with NACRT, RT break (no break vs break; HR 4.00, 95% CI 1.26–12.70, $P=0.02$) was the only significant variable associated with DFS.

Local recurrence

Twenty-two patients (22.9%) had local recurrence, of which 2 patients had NACRT plus surgery and 20 patients had definitive chemoRT. Ten were detected following clinical presentation, 5 were detected through computed tomography (CT) scan, 4 through positron emission tomography-CT scan, and 3 through upper gastrointestinal endoscopy. Local recurrence occurred within the high dose RT region in all 20 cases, with 1 case also having a recurrence within the marginal region. The cumulative incidence of local recurrence was significantly higher in patients treated with definitive chemoRT compared to NACRT plus surgery (subhazard ratio [SHR] 5.21, 95 CI 1.20–22.7, $P=0.03$) (Fig. 2).

Distant recurrence

Thirty-seven patients (38.5%) had distant recurrence, of which 11 patients had NACRT plus surgery, 26 patients only had definitive chemoRT. The most common sites were in the lung (12 patients), lymph nodes (7 patients), brain (6 patients), bone (3 patients) and liver (3 patients).

Table 4. Univariable and multivariable analysis for overall survival in definitive and preoperative chemoradiotherapy

Definitive ChemoRT – Univariable analysis for overall survival			
Variable	**HR**	**95% CI**	***P***
Age group <64 (ref) vs ≥65	0.55	0.31–0.99	**0.049**
Sex Male (ref) vs female	1.11	0.44–2.83	0.82
ECOG	1.20	0.71–2.02	0.51
Stage Stage 1–2 (ref) vs 3–4a	2.17	1.20–3.91	**0.01**
Weight loss No (ref) vs yes	1.17	0.85–1.61	0.33
Feeding tube No (ref) vs yes	1.91	1.06–3.46	**0.03**
Histology SCC (ref) vs adeno/others	1.61	0.75–3.44	0.22
T-stage	1.27	0.80–2.03	0.31
RT dose ≥50.4Gy vs <50.4Gy (ref)	1.20	0.47–3.08	0.70
RT technique IMRT (ref) vs 3DCRT	1.35	0.75–2.44	0.31
RT break Yes (ref) vs No	0.85	0.45–1.59	0.61
Charlson comorbidity score	1.08	0.82–1.27	0.87
SIOG score	0.91	0.52–1.61	0.76
Multivariable (include univariable with cut-off at 0.2)			
Variable	**HR**	**95% CI**	***P***
Age group <64 (ref) vs ≥65	0.57	0.31–1.06	0.08
Stage Stage 1–2 (ref) vs 3–4a	2.40	1.30–4.44	**<0.01**
Feeding tube No (ref) vs yes	1.76	0.96–3.24	0.07
Neoadjuvant ChemoRT – Univariable analysis for overall survival			
Variable	**HR**	**95% CI**	***P***
Age group <64 (ref) vs ≥65	1.35	0.46–3.98	0.59
Gender Male (ref) vs female	0.36	0.48–2.78	0.33
ECOG	1.44	0.69–2.97	0.33
Stage Stage 1–2 (ref) vs 3–4a	2.27	0.72–7.17	**0.16**
Weight loss No (ref) vs yes	0.81	0.38–1.71	0.58
Feeding tube No (ref) vs yes	0.88	0.24–3.19	0.84
Histology SCC (ref) vs adeno/others	1.86	0.62–5.57	0.27

Table 4. Univariable and multivariable analysis for overall survival in definitive and preoperative chemoradiotherapy (Cont'd)

Neoadjuvant ChemoRT – Univariable analysis for overall survival			
Variable	**HR**	**95% CI**	***P***
T stage	1.31	0.68–2.54	0.42
RT dose 41.4Gy vs ≥50.4Gy (ref)	5.92	1.60–21.90	**0.01**
RT technique IMRT (ref) vs 3DCRT	0.16	0.02–1.35	**.09**
RT break Yes (ref) vs No	0.25	0.09–0.74	**0.01**
Charlson score	0.85	0.26–2.77	0.78
SIOG score	0.79	0.10–6.17	0.82
Multivariable (include univariable with cut-off at 0.2)			
Variable	**HR**	**95% CI**	***P***
Stage Stage 1–2 (ref) vs 3–4a	4.26	1.19–15.22	**0.03**
RT break Yes (ref) vs No	0.34	0.09–1.26	0.09
RT dose 41.4 Gy vs ≥50.4Gy	4.63	0.97–22.0	**0.05**
RT technique IMRT (ref) vs 3DCRT	0.68	0.06–7.84	0.76

3DCRT: 3-dimensional radiotherapy; adeno: adenocarcinoma; CI: confidence interval; HR: hazard ratio; IMRT: intensity modulated radiotherapy; RT: radiotherapy; SCC: squamous cell carcinoma; SIOG: International Society of Geriatric Oncology
P values in bold are significant

Toxicity

Acute toxicity of definitive chemoRT

Most patients tolerated the treatment. Five patients experienced at least grade 3 toxicity (3 cases of tracheoesophageal fistula, 1 case of grade 3 mucositis with resulting percutaneous endoscopic gastrostomy tube insertion, 1 case of grade 3 dermatitis). One out of 5 patients with grade 3 toxicity did not complete chemoRT due to tracheoesophageal fistula and stopped treatment after 34Gy/17 fractions and 2 cycles of chemotherapy.

One patient developed sealed perforation of the gastro-oesophageal junction tumour 10 days after chemoRT and had septic shock. He recovered, underwent total gastrectomy, developed post-op intra-abdominal sepsis secondary to anastomotic leak requiring a laparotomy. He died 41 days after the initial surgery.

Late toxicity of definitive chemoRT

One patient developed radiation pneumonitis and recovered. Two patients developed oesophageal stricture, with one requiring multiple dilatations and the other a nasogastric tube insertion.

Postoperative complications

Nineteen patients (65.5%) developed postoperative complications which included: anastomotic leak (6 patients), pneumonia (6 patients), pneumothorax (5 patients), pleural effusion (4 patients), sepsis (3 patients), fistula (2 patients), wound infection (1 patient), and perforation (1 patient).

DISCUSSION

In our study of 96 patients with oesophageal carcinoma, we found that patients who underwent NACRT plus surgery had significantly improved OS compared to

definitive chemoRT alone. The NACRT plus surgery group had more patients with ECOG 0 compared to the definitive group (48.3% vs 11.9%). Interestingly, although there were 2 patients with stage 1 disease in the NACRT plus surgery group, there were fewer patients with stage 2 disease and more patients with stage 3 disease in the NACRT plus surgery group, compared to the definitive chemoRT group (stage 2: 27.6% vs 53.7%; stage 3: 55.2% vs 28.4%). Among those who had surgery, higher dose of RT (50.4Gy/28 fractions) significantly improved survival compared to lower dose of RT (41.4Gy/23 fractions). DFS was also better in the NACRT plus surgery compared to definitive chemoRT alone group. Our study showed that RT break was significantly associated with DFS. As RT break prolongs the total duration of RT, this results in less favourable outcome due to accelerated repopulation of tumour cells.[18] In our cohort, significantly higher proportion of patients with adenocarcinoma underwent surgery compared to SCC. This may be due to previous randomised controlled trials on patients with predominantly oesophageal SCC reporting limited or no survival benefit with surgery.[10,11]

Our findings are consistent with studies reporting improved survival with NACRT plus surgery. A retrospective study on 298 patients from the Asian population with oesophageal SCC comparing neoadjuvant versus definitive chemoRT reported improved outcome with NACRT plus esophagectomy (HR of death 0.56, 95% CI 0.42–0.75, $P<0.001$).[19] In another retrospective study on Asian patients, Wong et al. reported an estimated median survival of 24.2 months vs 12.7 months ($P=0.047$) in 46 patients from the "CROSS eligible" group and 42 patients in the "CROSS ineligible" group, respectively.[20] We reported a median OS of 71 months and 13 months for the NACRT plus surgery group and definitive chemoRT group, respectively. Our data are more similar to the CROSS trial that reported a median survival of 81.6 months in the NACRT plus surgery group.[9] Hofstetter et al. reported significant improvement in OS with NACRT (3-year OS 56% with NACRT vs 34% with no NACRT, $P=0.003$) with higher likelihood of a complete resection being achieved.[21]

In our study, patients who had NACRT plus surgery had significantly lower local recurrence compared to definitive chemoRT alone. Hofstetter et al. showed that those receiving NACRT plus surgery also had significantly fewer locoregional recurrence compared to those who did not (17% vs 25%, $P=0.01$).[21] These results are consistent with a Cochrane systematic review that showed a reduction in local recurrence with the addition of surgery to chemoRT.[22]

However, not all studies have reported benefit in OS with NACRT plus surgery. The abovementioned Cochrane systematic review reported that the addition of esophagectomy only provided little or no difference in OS (HR 0.99, 95% CI 0.79–1.24, $P=0.92$, $I^2=0\%$, 2 trials) and may even be associated with higher treatment-related mortality.[22] One of the studies included in the review was a randomised controlled trial comparing neoadjuvant vs definitive chemoRT in 444 patients with thoracic oesophageal SCC. There was no survival benefit with surgery (2-year OS 34% in NACRT vs 40% in definitive chemoRT only; HR 0.90, $P=0.44$).[11] The other study in the review found that the addition of surgery improved local control but not OS in patients with SCC treated with chemoradiotherapy.[10] For oesophageal adenocarcinoma, a sequential prospective non-randomised phase II studies on 35 patients also reported comparable outcome between NACRT and definitive chemoRT.[23]

On multivariable analysis for OS, we found that there was no significant difference for OS in SCC compared to adenocarcinoma. This is in keeping with other studies who have also not found significant difference in outcome based on histology. Interestingly, one study noted a shift in the predominant histology of oesophageal cancer among the Western population during their study period from SCC to adenocarcinoma (29% adenocarcinoma in 1970–1985; 83% adenocarcinoma in 1997–2001), which was also accompanied by a shift in the location of the tumour from the upper/mid-oesophageal region to the lower/gastro-oesophageal junction.[20] A retrospective study by Tustumi et al. reported no significant difference in OS between SCC and adenocarcinoma. They reported a 5-year OS of 22.8% in patients with SCC vs 20.2% in patients with adenocarcinoma. In their cohort of patients treated with curative intent surgical resection, 5-year OS was 56.6% in SCC and 28% in adenocarcinoma.[24] Eloubeidi et al. reported age at diagnosis, race, lower oesophageal tumour, and increasing depth of invasion as factors associated with increased mortality risk in oesophageal carcinoma and tumour length, number, as well as proportion of lymph nodes as important prognostic factors in oesophageal carcinoma.[25]

The strengths of our study are that patients were treated using a standardised treatment with quality

assurance for RT performed within a week of commencing treatment. Limitations include its retrospective nature and the relatively small patient numbers, most of whom had SCC. Selection bias might have occurred in that surgery were offered to fitter patients; there could be further selection bias for those who received a higher dose of RT (≥50Gy) and that good responders had subsequent surgery. In addition, as this was a non-randomised comparison, there may have been confounders that were not accounted for and reviewer bias may have led to under-reporting of treatment toxicities.

CONCLUSION

In this study, we report outcomes comparable to internationally published data. Our results suggest that NACRT plus surgery reduced local recurrences and improved OS; however, careful selection of patient is warranted to minimise perioperative risks. With the predominant histology of our cohort being SCC, results from our study may be more relevant for SCCs within the Asian population.

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ORIGINAL ARTICLE

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New-onset cardiovascular risk factors following liver transplantation: A cohort analysis in Singapore

Xiao Ying Li [1] *MNutrDiet*, Hiang Keat Tan [2] *MRCP (UK)*, Yet Hua Loh [1] *PhD*

ABSTRACT

Introduction: The aims of this study were to establish weight change, incidence of non-alcoholic fatty liver disease (NAFLD) and cardiovascular risk factors (CvRF) in liver transplant recipients (LTRs).

Methods: Eighty-three patients whose mean (standard deviation [SD]) age was 55.6 (8.4) years (median follow-up 73 months) and who underwent their first liver transplantation (LT) at Singapore General Hospital between February 2006 and March 2017 were included in the study. Anthropometric, clinical and demographic data were collected retrospectively from patients' medical records. Diabetes mellitus (DM), hyperlipidaemia and hypertension were regarded as CvRF.

Results: Compared to baseline, mean (SD) body weight decreased significantly at 1 month post-LT (60.8kg [11.9] versus 64.3kg [13.7], $P<0.001$). There was a gradual recovery of body weight thereafter, increasing significantly at year 2 (64.3kg [12.3] vs 61.5kg [13.7], $P<0.001$) until year 5 (66.9kg [12.4] vs 62.2kg [13.9], $P<0.001$), respectively. The prevalence of CvRF was significantly higher post-LT. NAFLD occurred in 25.3% of LTRs and it was significantly associated with post-LT DM and hyperlipidaemia.

Conclusion: CvRF increased significantly post-LT, and NAFLD occurred in 25.3% of LTRs. Body weight dropped drastically within the first month post-LT, which then returned to baseline level just before the end of first year. This novel finding suggests that nutritional intervention needs to be tailored and individualised, based on events and time from transplant. Although long-term obesity is a significant problem, aggressive oral or enteral nutritional supplements take precedence in the early and immediate post-LT period, while interventions targeted at metabolic syndrome become necessary after the first year.

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Keywords: Cardiovascular risk factors, liver transplantation, non-alcoholic fatty liver disease, obesity, weight change

INTRODUCTION

Malnutrition is well described in liver cirrhosis. The hyperdynamic circulation and altered metabolism in cirrhosis result in a hypercatabolic state which accelerates tissue breakdown.[1] Ascites and gastrointestinal dysmotility in advanced cirrhosis, compounded by the need for dietary restrictions, often result in early satiety and anorexia.[2] Inevitably, liver transplant wait-list patients eat poorly, leading to a diet grossly deficient in calories, protein and nutrients, culminating in muscle wasting and weight loss.[2]

Liver transplantation (LT) is the only curative treatment for end-stage liver failure.[3] After LT, patients regain a sense of well-being and a more liberalised diet contribute to improved appetite.[4] A higher caloric intake, the effect of tacrolimus associated with hypometabolism,[4] increased adiposity and decreased lean muscle mass predispose liver transplant recipients (LTRs) to developing metabolic syndrome (MetS).[5] More than half of long-term LT survivors will eventually develop 1 or more metabolic diseases, including obesity, impaired glucose tolerance and hypertension.[3,6,7] It is therefore not surprising that non-alcoholic fatty liver disease (NAFLD), a hepatic manifestation of MetS, is common following LT.[8] A recent study by National University Hospital in Singapore showed that MetS increased significantly post-LT with a prevalence of 35.6%.[9] However, for Singapore LTRs,

[1] Department of Dietetics, Singapore General Hospital, Singapore
[2] Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore
Correspondence: Ms Xiao Ying Li, Department of Dietetics, Singapore General Hospital, Level 10, SingHealth Tower, 10 Hospital Blvd, Singapore 168582.
Email: cherrylxy2010@gmail.com

CLINICAL IMPACT

What is New

- Our study reported 3-monthly body weight trends in liver transplant recipients for the first year. Weight reduced significantly by 5.5% in the first month and increased to baseline level before the end of 1 year.
- The recipients were followed up for a median period of 73 months. Metabolic complications increased significantly post-liver transplant and non-alcoholic fatty liver disease occurred in 25.3% of recipients.

Clinical Implications

- Oral or enteral nutritional supplements take precedence in the early post-transplant period, while interventions targeted at metabolic syndrome are necessary after the first year.

the evolution of body weight (BW) and the development of NAFLD post-LT remain unclear. We aimed to establish weight change, prevalence of NAFLD and cardiovascular risk factors (CvRF) in stable LTRs in Singapore.

METHODS

This was a retrospective study of adult patients who underwent LT at Singapore General Hospital between February 2006 and March 2017. The study, approved by the Institutional Review Board, included patients older than 21 years of age at the time of their transplantation, and with at least 1 year of post-LT follow-up. Exclusion criteria were multiorgan transplantation and re-transplantation. A retrospective chart review was conducted for eligible study participants. Demographic, anthropometric, clinical and biochemical data were collected. Demographic characteristics included age, sex and ethnicity. Clinical data included pre-LT Child-Pugh scores, Model for End-stage Liver Disease (MELD) scores and indications for LT, pre-LT and post-LT comorbidities. Weight, height and body mass index (BMI) were recorded at the time of transplant, 1 month post-LT, and at 3-monthly intervals, until 1 year post-LT and then annually thereafter. For patients with fluid overload at LT, dry weight was estimated according to Mendenhall et al.[10] For those with mild, moderate and severe ascites, BW was subtracted by 2.2kg, 6.0kg and 14.0kg, respectively. In the case of mild, moderate and severe oedema, BW was adjusted by subtracting 1.0kg, 5.0kg and 10.0kg, respectively. The primary outcomes of the study were post-LT weight trends and obesity prevalence. Secondary outcomes were the incidence of NAFLD and CvRF, defined by hypertension, hyperlipidaemia and diabetes mellitus (DM).

The following definitions were used in the study:

(1) Hypertension: systolic or diastolic blood pressure >140 or 90mmHg; or patient on at least 1 antihypertensive drug for more than 3 months post-LT;[11]

(2) Hyperlipidaemia: low-density lipoprotein (LDL) >2.6mmol/L or triglyceride (TG) >1.7mmol/L; or patient on statin or fibrate for more than 3 months post-LT;[11]

(3) DM: persistent fasting or random blood glucose level ≥7.0mmol/L or ≥11.1mmol/L, respectively; or patient on antidiabetic drug after the first 3 months post-LT;[11]

(4) Post-LT NAFLD diagnosis was based on ultrasound or computerised tomography (CT) scan of the liver.[12] In our centre, ultrasound surveillance on the liver graft is routinely performed 3-monthly for the first 12 months post-LT, then annually for patients without pre-LT hepatocellular carcinoma; whereas patients with hepatocellular carcinoma prior to LT are monitored with CT scan 3-monthly for the first 24 months, followed by alternating CT and ultrasound thereafter;

(5) Obesity: BMI >27.5kg/m^2, based on World Health Organization (WHO) recommendations for Asians.[13]

Post-transplant care

Our multidisciplinary LTR care involves transplant surgeons, hepatologists, endocrinologists, pharmacists, specialty nurses, dietitians and physiotherapists. We practise triple immunosuppression with corticosteroid, a calcineurin inhibitor (CNI)—preferably tacrolimus—and mycophenolate mofetil. Tacrolimus dose is titrated to a trough of 7–10ng/mL in the first 3 months, 5–7ng/mL in months 4–6, and thereafter 4–6ng/mL. Corticosteroid dose is gradually tapered and stopped after 3 months. In patients with pre-existing renal impairment, additional induction with basiliximab is considered to delay exposure to CNI at reduced dose. Lipid profile and glycated haemoglobin (HbA1c) are monitored every 3–6 months. Pharmacological therapies are initiated for suboptimal levels by endocrinologists.

Statistical analysis

Statistical analysis was performed using SPSS Statistics software version 25 (IBM Corp, Armonk, US). Continuous variables were expressed as mean and standard deviation (SD) and categorical variables as frequencies and percentages (%). Statistical significance of mean difference between continuous variables was determined by paired-samples t test. Chi-square test was performed for categorical variables. Prevalence of CvRF pre- and post-LT were compared by McNemar's test. The statistical significance level was set at $P<0.05$.

RESULTS

From February 2006 to March 2017, 99 patients underwent LT. Included in our study were 83 LTRs, as 16 LTRs were excluded due to early death (n=15) and re-transplantation (n=1). Table 1 shows the baseline characteristics of the study population. The mean (SD) age was 55.6 (8.4) years and the majority were Chinese (83.1%). The median duration of post-LT follow-up was 73 (interquartile range [IQR] 34–109) months. The most common indication for LT was hepatitis B (44.6%). The mean (SD) MELD score at LT was 18 (8) and a majority were of Child-Pugh class C (43.4%). Most of the LTRs (90.4%) received tacrolimus for immunosuppression.

Obesity and body weight change

Post-LT obesity prevalence was 24.1%, which was higher than pre-LT (18.1%, $P<0.05$). Post-LT obesity was associated with pre-LT obesity ($P<0.0001$), with 66.7% of patients with pre-existing obesity remaining obese post-LT. There were 10 LTRs (14.7%) who developed de novo obesity post-LT, at a median (IQR) of 17 (9–45) months. Fig. 1 shows post-LT BW trend. Compared to baseline, mean (SD) BW decreased significantly at 1 month post-LT (60.8kg [11.9] versus 64.3kg [13.7], $P<0.001$). This was followed by a gradual recovery of BW which eventually reached pre-LT level at 9 months post-LT. Mean (SD) weight gain continued until the fifth year (66.9kg [12.4] vs 62.2kg [13.9], $P<0.001$).

Cardiovascular risk factors

At last follow-up in March 2018, the rate of new-onset DM, hypertension and hyperlipidaemia was 29.3%, 44.5% and 46.4%, respectively (Fig. 2). A higher prevalence for DM (68.9% vs 57.8%, $P<0.005$), hypertension (62.7% vs 33.7%, $P<0.0001$), and hyperlipidaemia (57.8% vs 28.9%, $P<0.0001$) was observed post-LT. There was no significant difference for HbA1c between baseline and any time point post-LT, while total cholesterol (T-CHOL), high-density lipoprotein (HDL), TG and LDL increased significantly 3 months post-LT (Fig. 3). However, the mean values of T-CHOL, HDL and TG were all within healthy range at all time points. LDL levels were slightly above the desirable level of 2.6mmol/L at 3 months, 6 months and 3 years.

Table 1. Baseline characteristics of liver transplant recipients

Characteristics	n=83
Age, mean (SD), years	55.6 (8.4)
Male, no. (%)	57 (68.7)
Female, no. (%)	26 (31.3)
Ethnicity, no. (%)	
Chinese	69 (83.1)
Malay	5 (6.0)
Indian	4 (4.8)
Others[a]	5 (6.0)
Time from transplant	
Mean (SD), months	74.5 (38.9)
Median (IQR), months	73.0 (34.0–109.0)
Aetiologies of liver diseases, no. (%)[b]	
HBV	37 (44.6)
NASH/cryptogenic cirrhosis	15 (18.1)
PBC, PSC, AIH	14 (16.9)
ALD	8 (9.6)
HCV	5 (6.0)
Others	11 (13.3)
MELD score, mean (SD)	18 (8)
Child-Pugh score, no. (%)	
A	15 (18.0)
B	32 (38.6)
C	36 (43.4)

AIH: autoimmune hepatitis; ALD: alcoholic liver disease; HBV: hepatitis B virus; HCV: hepatitis C virus; MELD: Model for End-stage Liver Disease; NASH: non-alcoholic steatohepatitis; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; SD: standard deviation

[a] Other aetiologies included acute liver failure (6 cases), familial amyloid polyneuropathy (2 cases), type 2 citrullinemia (2 cases) and Caroli disease (1 case)

[b] The total adds up to more than 100% as some patients had more than 1 aetiologies for chronic liver disease or indications for liver transplantation

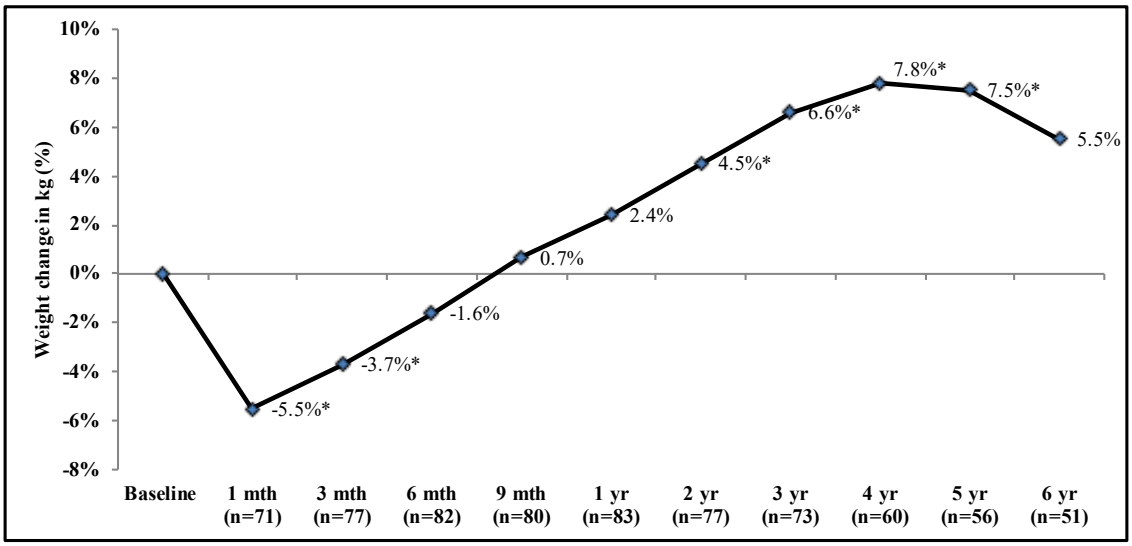

Fig. 1. Body weight change in liver transplant recipients post-liver transplantation.
*P<0.01

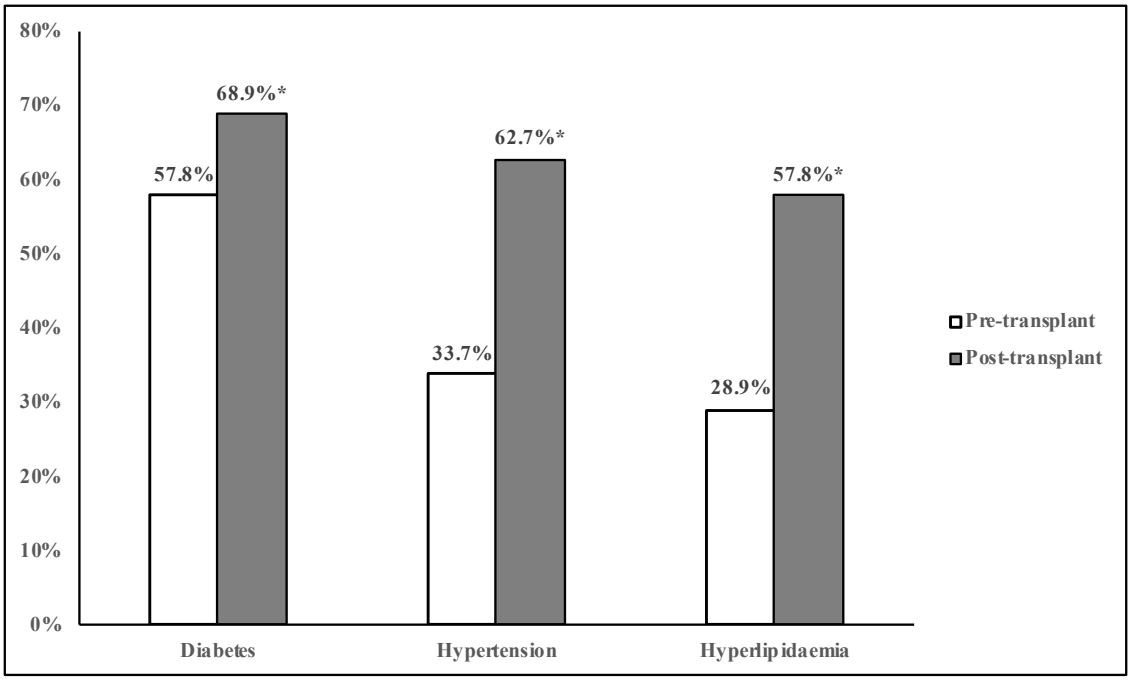

Fig. 2. Prevalence of cardiovascular risk factors pre- and post-transplantation.
*P<0.001

NAFLD occurred in 21 patients (25.3%), at a median (IQR) of 16 (10–37) months post-LT. Approximately 21% developed de novo NAFLD post-LT. Interestingly, almost half (46.7%) of the patients with a history of cryptogenic or non-alcoholic steatohepatitis (NASH) cirrhosis developed post-LT NAFLD. Overall, post-LT NAFLD was associated with DM (91.4% patients, P<0.01) and hyperlipidaemia (85.3% patients, P<0.005). Although 33.2% post-LT NAFLD patients were obese, we did not find any statistically significant association between post-LT NAFLD and obesity.

DISCUSSION

Our study showed that BW and the prevalence of CvRF increased significantly in LTRs, including the occurrence of NAFLD. This suggests that the burden of obesity and MetS is high among LTRs in Asia. The consequence of MetS is significant and our study

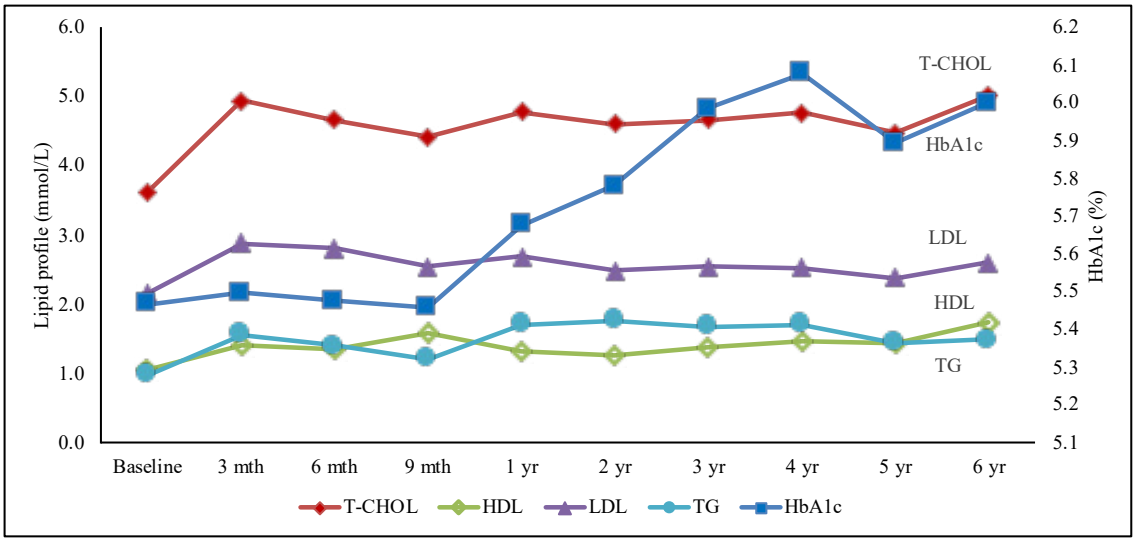

Fig. 3. Trends of HbA1c and lipid profile post-liver transplantation.
HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride; T-CHOL: total cholesterol

highlights the multiple cardiovascular risks in this population.

We collected BW data at multiple time points post-LT and reviewed patients for more than 6 years. To the best of our knowledge, this is the first study reporting detailed BW change in the early post-LT period at close intervals, with the longest follow-up duration. Other studies reported weight trends with either less frequent intervals or shorter follow-up duration.[6,14] The weight trend in our study offers fresh insights into the dynamic weight change of LTRs, especially during the early and intermediate post-LT period where early post-surgery catabolism frequently necessitates oral nutritional supplements or tube feeding to prevent weight loss. Later excessive weight gain from effects of immunosuppression and improved appetite requires timely nutritional intervention to curb obesity and prevent metabolic complications in the longer term.

A majority of studies in the literature did not report weight change at 1 month post-LT.[6,14,15] A significant weight loss at 1 month after transplantation has been reported, due in part to a reduced fluid overload.[16] Another major factor contributing to the weight loss is the hypercatabolic state in the immediate post-LT period, resulting in increased muscle breakdown and loss. A longitudinal study showed that resting energy expenditure increased significantly post-surgery to as high as 42% above predicted value, peaking at day 10, and that hypermetabolism persisted for 6 months only to resolve at 1 year post-LT.[17] Furthermore, patients were typically fasted in the immediate postoperative period until they were able to pass flatus. By the time a full diet was allowed, a few days would have typically passed. This would represent missed opportunities for early postoperative tube feeding within 12 hours, which has been shown to be beneficial in reducing length of stay in intensive care and in lowering infection rates.[18] Additionally, intermittent fasting is often necessary for post-surgery protocol ultrasound scans (for early detection of hepatic artery thrombosis) and other advanced imaging procedures (in patients suspected of having biliary leaks or strictures).[19,20] These frequent interruptions in the delivery of nutrition to LTRs in the early postoperative period pose a major challenge to maintaining a delicate balance between fasting for investigations and provision of adequate calories and protein to an already malnourished population.

After the initial decrease in the first month, the weight of our LTRs gradually increased. This was partially due to the hypermetabolic state slowly regressing to normal, resulting in a lower energy expenditure compared to the period immediately post-LT.[17] The disappearance of ascites after LT leads to a marked improvement in patients' appetite and food intake.[21] Richardson et al. reported that mean (SD) calorie intake in post-LT patients increased significantly at 2,227kcal/d (41) compared with consumption at 1,542kcal/d (124) during the pre-transplant period.[21] Our study showed that BW eventually returned to pre-LT level around 9 months post-LT. Weight gain continued to progress, reaching a peak in the fourth year. Two large-scale studies by Everharts et al. and

Richards et al. showed that the most rapid weight gain occurred within the first year after LT, but the initial drastic weight loss seen in our study at 1 month was not reported in the studies due to a lack of data in the early postoperative period.[6,14]

Similar to the study by Tan et al.,[9] nearly a quarter (24.1%) of our LTRs was found to have obesity after a median follow-up of 73 months. This was comparatively lower than the prevalence of 30% reported by the aforementioned 2 studies.[6,14] This discrepancy could possibly be due to the difference in the trajectory of BW change during the first year post-LT. While our patients suffered from significant weight loss in the first month before a gradual recovery in BW to baseline level, the other 2 studies reported rapid weight gain of 5–6kg at 1 year post-LT. Of note, we defined obesity at BMI cut-off of 27.5kg/m^2 based on WHO recommendations,[13] as opposed to BMI of 30.0 kg/m^2 in many Western studies.[6,14] In spite of differences in definition, we believe that our study reflects the true health risks of our LTRs as it is well established that Asians have significantly higher risks for type 2 DM and cardiovascular diseases at a lower BMI compared to their Caucasian counterparts.[13] Similar to most Western studies,[6,14,22] our centre's post-LT obesity prevalence is significantly higher than the general local population. Based on recent data from the Ministry of Health, Singapore, obesity prevalence was 8.7% in local adult residents.[23] Newly developed obesity was 14.7% in our LTRs, compared with 15.5–40.7% reported in other studies.[6,24]

In our study, the prevalence of DM, hypertension and hyperlipidaemia was 68.9%, 62.7% and 57.8%, respectively. Other centres reported 61%,[22] 62%[22] and 27–71%,[25] respectively, in comparison with Tan et al.[9] who reported 51.1%, 60.0% and 46.7%, respectively. The incidence of new-onset DM, hypertension and hyperlipidaemia in our study was 29.3%, 44.5% and 46.4%, respectively and this was comparable with other studies,[26-28] where post-LT prevalence was much higher than pre-LT figures. It is widely believed that immunosuppressive drugs play a crucial role in the onset of metabolic complications post-LT. Steroid increases insulin resistance and reduces beta cell function; influencing glucose homeostasis and contributing to the development of DM.[27] It also increases vascular resistance and cardiac contractility, leading to hypertension.[27] Steroids induce hyperlipidaemia via the stimulation of enzyme activity involved in cholesterol metabolism and fatty acid synthesis.[29] New onset diabetes may also be induced by CNI reducing insulin secretion.[30] Furthermore, the vasoconstrictive effect of CNI on renal arteriole induces sodium and water reabsorption with a consequence of volume expansion, contributing to blood pressure increase.[31] Lastly, CNI reduces cholesterol excretion through the biliary system and blocks LDL-cholesterol receptors, resulting in elevated blood cholesterol levels.[32]

Although the prevalence of CvRF was high in our cohort, control of hyperlipidaemia and DM was excellent. One of the current leading causes of mortality among long-term transplant survivors is cardiovascular diseases.[33] Mean values of T-CHOL, HDL and TG were all well within healthy ranges at all time points. The highest mean HbA1c (SD) recorded was 6.1% (1.3) at 4 years post-LT, while mean (SD) LDL was 2.7mol/L (0.9) at 1 year post-LT. This was likely due to the intensive surveillance and management of metabolic diseases in our centre. Due to the alarmingly high prevalence of post-LT obesity, it is of paramount importance to prevent and manage obesity to improve long-term survival. As such, long-term care of our LTRs is provided for by a dedicated transplant endocrinologist and dietitian.

NAFLD, a hepatic manifestation of MetS, occurred in 25.3% of our patients. Post-transplant NAFLD recurred in almost half of patients whose indication for transplant was cryptogenic or NASH cirrhosis. In the literature, the reported recurrence ranged from 25–100%, up to 5 years post-LT.[34-37] De novo post-LT NAFLD was found in 20.6% of our patients. This is comparable to the incidence rate of 18% at 28 months post-LT that was reported by Seo et al.[38] for 68 patients with liver biopsy. However, 2 other larger studies by Dumortier et al. and Galvin et al. reported more than 30% de novo biopsy-proven NAFLD at 3 years post-LT.[39,40] The varying rates are likely due to the different diagnostic criteria among the studies. Seo et al. defined de novo NAFLD as >33% increase in hepatic steatosis compared to their respective donor biopsies,[38] while Dumortier et al. and Galvin et al. adopted the more conventional diagnostic criteria of steatosis >5% on liver biopsy.[39,40] In our centre, routine protocol biopsy is not carried out except when there is a clinical suspicion of graft rejection. Although ultrasound is not sensitive enough for the detection of mild steatosis,[12] it is the only practical means for the diagnosis of NAFLD. It is not surprising then that our study detected a much lower rate of de novo NAFLD compared to the literature. Reported NAFLD risk factors included increased BMI, metabolic complications, weight gain post-LT, immunosuppressant and donor liver steatosis, and use of angiotensin-converting enzyme inhibitors.[38-40]

In our study, de novo NAFLD was significantly a ssociated with post-LT DM and HLD. Data on long-term prognosis of de novo NAFLD are scarce. Galvin et al. reported that almost 40% of LTRs with de novo NAFLD had biopsies indicating significant fibrosis and 5% cirrhosis.[40] Dureja et al. showed that patients with recurrent NAFLD post-LT were at a higher risk of cardiovascular diseases and death in the long term.[36] We were unable to examine cardiovascular mortality rate due to our small sample size and short follow-up duration.

The current study has limitations. The retrospective nature of the study would invariably introduce biases. Firstly, the actual BW in some of our pre-LT patients would have been masked by the presence of oedema/ascites. Although we made the best effort to adjust weight based on the method described by Mendenhall et al.,[10] discrepancies between the estimated and actual BW may still exist. Secondly, we lacked complete data on all patients at all follow-up time points, except at 1 year post-LT. Thirdly, the diagnosis of NAFLD in our LTR cohort based on ultrasound was likely an underestimate, as ultrasound is only reliable when there is at least moderate hepatic steatosis.[12] Last but not least, dietary and lifestyle interventions may have impacted the weight of our patients. Post-LT routine care included diet education and counselling from dietitians but may not routinely involve a physiotherapist, especially after hospital discharge. Physical activity data were unavailable to us to analyse the impact of an exercise regime in the evolution of BW post-LT. Based on the limited data, we cannot comment on the impact of our nutritional intervention on the lesser degree of weight gain in our LTRs compared to other centres. Although we reported similarly high incidences of DM, hypertension and hyperlipidaemia, we were unable to further examine the risk factors for the development of metabolic complications post-LT due to our limited study sample size.

CONCLUSION

CvRF increased significantly post-LT and NAFLD occurred in 25.3% of our LTRs. We observed a drastic decrease in weight within the first month post-LT, which then returned to baseline before the end of 1 year. This novel finding suggests that nutritional intervention needs to be tailored and individualised, based on events and time from LT. Although long-term obesity is a significant problem, aggressive oral or enteral nutritional supplements take precedence in the early and immediate post-LT period, while interventions targeted at MetS are necessary after the first year.

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ORIGINAL ARTICLE

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Heterogeneity of non-cystic-fibrosis bronchiectasis in multiethnic Singapore: A prospective cohort study at a tertiary pulmonology centre

Si Ling Young [1]*MRCP*, Youxin Puan [1]*MRCP*, Si Yuan Chew [1]*MRCP*, Haja Mohideen Salahudeen Mohamed [2]*FRCR*, Pei Yee Tiew [1]*MRCP*, Gan Liang Tan [3]*MRCP*, Mariko Siyue Koh [1]*MRCP*, Ken Cheah Hooi Lee [1]*MRCP*

ABSTRACT

Introduction: Non-cystic fibrosis bronchiectasis (NCFB) is a highly heterogenous disease. We describe the clinical characteristics of NCFB patients and evaluate the performance of Bronchiectasis Severity Index (BSI) in predicting mortality.

Methods: Patients attending the bronchiectasis clinic between August 2015 and April 2020 with radiologically proven bronchiectasis on computed tomography were recruited. Clinical characteristics, spirometry, radiology, microbiology and clinical course over a median period of 2.4 years is presented.

Results: A total of 168 patients were enrolled in this prospective cohort study. They were predominantly women (67.8%), Chinese (87.5%) and never-smokers (76.9%). Median age of diagnosis was 64 years (interquartile range 56–71) and the most common aetiology was "idiopathic" bronchiectasis (44.6%). Thirty-nine percent had normal spirometries. Compared to female patients, there were more smokers among the male patients (53.8% versus 8.5%, $P<0.001$) and a significantly larger proportion with post-tuberculous bronchiectasis (37.0% vs 15.8%, $P=0.002$). Fifty-five percent of our cohort had a history of haemoptysis. Lower body mass index, presence of chronic obstructive pulmonary disease, ever-smoker status, modified Reiff score, radiological severity and history of exacerbations were risk factors for mortality. Survival was significantly shorter in patients with severe bronchiectasis (BSI≥9) compared to those with mild or moderate disease (BSI<9). The hazard ratio for severe disease (BSI≥9) compared to mild disease (BSI 0–4) was 14.8 (confidence interval 1.929–114.235, $P=0.01$).

Conclusion: The NCFB cohort in Singapore has unique characteristics with sex differences. Over half the patients had a history of haemoptysis. The BSI score is a useful predictor of mortality in our population.

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Keywords: Bronchiectasis, exacerbations, gender, haemoptysis, mortality, Reiff score, sex

INTRODUCTION

Bronchiectasis is a chronic lung disease of significant morbidity and mortality. The pathological hallmarks of the disease are abnormal dilatation of airways resulting from recurrent inflammation, airway obstruction and mucous plugging.[1] The past 2 decades have seen a significant increase in its prevalence, exceeding the threshold of 5 per 10,000 persons for the definition of an "orphan disease".[2-7] In the UK, a rising incidence and prevalence was reported across nearly all age groups between 2004 and 2013, most notably among women above 70 years of age.[2] A similar growing trend is reported in the US.[3] There is less epidemiologic data on non-cystic fibrosis bronchiectasis (NCFB) in Asian countries. A cross-sectional survey from China reported a 1.2% prevalence of bronchiectasis among those aged 40 years and older.[6] More recently, Choi et al. reported a prevalence of 464 patients per 100,000 person-years with NCFB in South Korea, with a mean age of 63.8±13.1 years.[7] These observations suggest that unlike cystic fibrosis that predominantly affects Caucasians, NCFB occurs commonly in both Caucasians and Asians, especially in the older age groups.

[1] Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore
[2] Department of Diagnostic Radiology, Singapore General Hospital, Singapore
[3] Department of Respiratory and Critical Care Medicine, Sengkang General Hospital, Singapore
Correspondence: Dr Si Ling Young, Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Outram Road, Singapore 169608.
Email: siling.young@mohh.com.sg

CLINICAL IMPACT

What is New

- This is one of the first studies describing the characteristics of non-cystic fibrosis bronchiectasis (NCFB) patients in Singapore, highlighting key features such as a high incidence of haemoptysis among these patients.
- The Bronchiectasis Severity Index (BSI) is a useful prognostic marker in our NCFB population.

Clinical Implications

- This study highlights the heterogeneity of NCFB and importance of further research to identify phenotypes that may help guide future management.
- The BSI can aid clinicians in their communication with NCFB patients regarding the prognosis of their disease.

Geographic variation in the aetiology and microbiology of NCFB has been described, such as the higher prevalence of idiopathic and post-infectious NCFB patients reported in European and Asian countries,[8] compared to the US where NCFB was frequently associated with immune dysregulation.[9] For microbiology, the rates of *Pseudomonas aeruginosa* and *Hemophilus influenzae* colonisation vary across the US, Europe and Asia Pacific region. Non-tuberculous mycobacterium (NTM) colonisation was found in 63% of NCFB patients in the US bronchiectasis research registry,[10] but much lower rates were reported in Chinese studies.[9] Other organisms like *Klebsiella pneumoniae* were significantly prevalent in NCFB patients in Thailand and South Korea.[11,12]

The heterogeneity of NCFB is further reflected in its diversity in clinical presentation, radiologic involvement, spirometry patterns and prognosis as reported by the various global registries on patients with NCFB.[10,13-17] Such heterogeneity has led to a keen interest to identify phenotypes and endotypes with the aim of individualising treatment to improve outcomes.[18] To date, information about the NCFB population in Singapore remains scarce. In this study, we describe the characteristics of NCFB patients in Singapore and evaluated the performance of Bronchiectasis Severity Index (BSI) in predicting mortality.

METHODS

Consecutive subjects (aged ≥21 years) with diagnosis of bronchiectasis based on computed tomography (CT), and attending the bronchiectasis clinic in Singapore General Hospital, a tertiary hospital in Singapore, were recruited into this prospective cohort study from 2017. The patients underwent a systematic evaluation of potential underlying aetiologies with a thorough assessment of disease symptoms, past history of sino-pulmonary infections including tuberculosis, ear infections, gastro-oesophageal reflux, subfertility, autoimmune disease and inflammatory bowel disease. Serum immunoglobulins and full blood count were performed for all patients, in accordance with the British Thoracic Society and European Respiratory Society guidelines.[19,20] Other investigations such as autoimmune markers, alpha-1-antitrypsin level, and genetic testing for cystic fibrosis were performed if relevant clinical features were present. The aetiology of bronchiectasis was determined on the basis of the aforementioned investigations by the treating physician via a clinical-radiological approach. Spirometry results, respiratory microbiology and exacerbation history from time of diagnosis were also collected. Interpretation of spirometry was in accordance with the 2005 American Thoracic Society interpretative strategies for lung function tests.[21] Bacterial colonisation was defined by the growth of the same bacteria on 2 or more occasions at least 3 months apart on either sputum or broncheo-alveolar lavage specimens.

The CT images were independently reviewed by an experienced thoracic radiologist, and the morphological characteristics and severity of bronchiectasis were determined. The modified Reiff score was used to assess the number of lobes involved and degree of dilatation.[22,23] The left lingula was considered a separate lobe. The extent of bronchiectasis within each lobe was also graded with a score of 1, 2 or 3, according to the proportion of airways involved: <25%, 25–50% and >50%, respectively. A radiology severity score was obtained by a summation of scores for all the lobes.

Exacerbation was defined as a deterioration in 3 or more of the following symptoms for at least 48 hours—cough, sputum volume or consistency, sputum purulence, breathlessness or exercise tolerance, fatigue and haemoptysis—associated with a requirement for treatment with antibiotics, which is modified from the original definition by Hill et al.[24] A history of haemoptysis was defined as the patient having reported any amount of haemoptysis before in their lifetime that is attributed to bronchiectasis. Clinically significant haemoptysis referred to haemoptysis requiring bronchoscopy, intubation, bronchial artery embolisation or surgery. The BSI score was first derived and validated by Chalmers et al. and provided an easily

Table 1. Clinical characteristics of patients with NCFB in Singapore and mortality subgroup analysis

Characteristic	Baseline characteristics (N=168)	Mortality group (n=18)	Survival group (n=150)	*P* value
Age at diagnosis, median (IQR), years	64 (56–71)	56 (54–60)	64 (57–71)	0.693
BMI, median (IQR)	19.3 (17.3–21.8)	18.5 (18.1–21.5)	19.3 (17.3–21.7)	**0.003**
Female, no. (%)	114 (67.8)	11 (61.1)	103 (68.7)	0.517
Smoking status, no. (%)				
Never	123 (76.9)	8 (53.3)	113 (78.5)	**0.030**
Active	4 (2.5)	0 (0.0)	4 (2.8)	0.513
Ever	33 (20.6)	7 (46.7)	26 (18.1)	**0.009**
Asthma, no. (%)	15 (8.9)	0 (0.0)	15 (10.0)	0.160
COPD, no. (%)	9 (5.3)	3 (16.7)	6 (4.0)	**0.024**
Aetiology, no. (%)				
Idiopathic	75 (44.6)	5 (27.8)	70 (46.7)	0.128
Post-TB	42 (25.0)	6 (33.3)	32 (21.3)	0.250
Post-infectious	38 (22.6)	5 (27.8)	37 (24.7)	0.773
FEV1 % predicted (baseline), median (IQR)	79 (63–95)	70 (51–84)	80 (65–95)	0.138
Spirometry pattern, no. (%)				
Normal	52 (39.0)	3 (25.0)	49 (40.5)	0.294
Restrictive	29 (21.8)	5 (41.7)	24 (19.8)	0.081
Obstructive	15 (11.2)	1 (8.3)	14 (11.6)	0.735
Non-specific	13 (9.7)	1 (8.3)	12 (9.9)	0.860
Microbiology, no. (%)				
Pseudomonas aeruginosa	35 (22.3)	6 (33.3)	29 (20.9)	0.232
Pseudomonas aeruginosa colonisation	24 (15.2)	5 (29.4)	19 (14.4)	0.113
Klebsiella pneumoniae	16 (10.2)	1 (5.6)	15 (10.8)	0.490
Hemophilus influenzae	6 (3.8)	1 (5.6)	5 (3.6)	0.683
Staphylococcus aureus	10 (6.4)	3 (16.7)	7 (5.0)	0.057
NTM	74 (46.3)	12 (66.7)	62 (43.7)	0.065
Radiology, no. (%)				
Upper lobes	103 (61.3)	14 (77.8)	89 (59.3)	0.129
Middle lobes	146 (86.9)	17 (94.4)	129 (86.0)	0.316
Lower lobes	129 (76.7)	14 (77.8)	115 (76.7)	0.916
Lobes involved, median (IQR)	3 (2–4)	4 (3–4)	3 (2–4)	**0.004**
Radiology severity score, median (IQR)	6 (4–9)	7 (4–9)	6 (5–6)	**0.007**
Modified Reiff score, median (IQR)	4 (3–5)	4 (3–4)	4 (3–5)	**0.015**
Radiology pattern, no. (%)				
Cylindrical	132 (78.5)	12 (66.7)	120 (80.0)	0.193
Cystic	22 (13.0)	5 (27.8)	17 (11.3)	0.051
Varicose	14 (8.3)	1 (5.6)	13 (8.7)	0.652
Exacerbations in the past year, no. (%)	45 (25.7)	10 (55.6)	35 (23.3)	**0.004**
Haemoptysis ever, no. (%)	92 (54.7)	8 (44.4)	84 (56.0)	0.352
Significant haemoptysis, no. (%)	36 (21.4)	3 (16.7)	33 (22.0)	0.602
BSI score, median (IQR)	6 (5–8)	8 (6–9)	6 (5–8)	**<0.001**
CAT score, median (IQR)	12.5 (8.0–19.0)	18.0 (17.5–22.5)	12.0 (8.0–19.0)	0.081
Aetiology of death in mortality group, no (%)				
Pneumonia			4 (22.2)	
Bronchiectasis			1 (5.6)	
Colorectal cancer			1 (5.6)	
Coroner's case or unknown			12 (66.7)	

BMI: body mass index; BSI: Bronchiectasis Severity Index; CAT: COPD assessment test; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; NCFB: non-cystic fibrosis bronchiectasis; NTM: non-tuberculous mycobacteria; TB: tuberculosis
P values in bold are significant

accessible clinical score to aid in prognostication of patients with NCFB, which can influence clinical decision making and management.[23] This was a composite score of clinical variables used to classify bronchiectasis severity, and prospectively validated to predict 1- and 4-year morbidity and mortality. The BSI scores, as well as chronic obstructive pulmonary disease (COPD) assessment test scores were obtained.[23,25] Mortality outcome was defined in this study as the point of death from any cause. In calculating the clinical scores, missing data for variables were assumed to be normal. All data were entered into a secure digital platform (Research Electronic Data Capture).

Statistical analyses were done using SPSS Statistics software version 23.0 (IBM Corp, Armonk, US). Chi-square test and Mann-Whitney U test were applied in the comparison of categorical and continuous data, respectively. Data were expressed as median (interquartile range) for non-normally distributed continuous variables. Kaplan-Meier survival curves were plotted to determine the relationship between BSI severity grades and mortality, and hazard ratios were obtained using Cox proportional hazard regression models. Statistical significance was defined as a *P* value less than or equal to 0.05.

RESULTS

A total of 168 subjects were recruited. The clinical characteristics are presented in Table 1. There was preponderance of women (67.8%) and Chinese ethnicity (87.5%). The median age at diagnosis was 64 years (56–71). Most subjects were never-smokers (76.9%). Nearly half the subjects had idiopathic bronchiectasis (44.6%). Those with known aetiologies included 37 post-tuberculosis (TB) (33.3%), 42 post-infectious (25.0%), 8 autoimmune-related (4.8%), 2 cilia dysmotility (1.2%) and 2 immunoglobulin deficiency (1.2%). One subject had alpha-1-antitrypsin level measured, which was normal. None underwent genetic testing for cystic fibrosis. The median follow-up period was 2.4 years (1.3–3.4).

Spirometry

A normal spirometry was most commonly observed (39.0%). Eleven percent of subjects had an obstructive pattern, and 21.8% showed restriction. The median *forced expiratory volume* in the first second (FEV1) predicted was 79% (63–95).

Microbiology

Thirty-five (22.3%) subjects had at least 1 growth of *Pseudomonas aeruginosa* from a respiratory specimen. Sixteen (10.2%) subjects had *Klebsiella pneumoniae* and 6 (3.8%) had *Hemophilus influenzae*. Seventy-four subjects (46.3%) had sputum positive for NTM. The most common NTM isolated was *Mycobacterium abscessus* (41.9%), followed by *M. fortuitum* (25.7%), *M. avium* complex (20.3%), and *M. kansasii* (8.1%). Eighteen (24.3%) subjects were initiated on NTM treatment, of whom 14 completed the course of treatment. Two patients did not complete treatment due to intolerable side effects, and 2 were still undergoing treatment at the time of this writing. The median treatment duration was 12 months (10–18).

Radiology

The median number of lobes involved was 3 (2–4). The median modified Reiff score was 4 (3–5), and median radiology severity score was 6 (4–9). Majority had middle lobe involvement (86.9%). The most common radiological pattern observed was a cylindrical pattern (78.5%), followed by cystic pattern (13.0%).

Clinical history

Fifty-seven subjects (33.9%) had no history of exacerbations. Eight subjects (4.8%) had 3 or more exacerbations per year in their lifetime. Seventy-two subjects (60.0%) had a COPD assessment test score of 10 and above. Eighteen subjects (10.7%) had demised during the period of follow-up. Ninety-two (54.7%) subjects had a history of haemoptysis, of which 36 (21.4%) were clinically significant.

Sex differences

There were more smokers (51.8% vs 7.9%, $P<0.001$) and subjects with obstructive spirometry patterns (20.8% vs 5.9%, $P=0.009$) observed among men (Table 2). Men were also more likely to have post-TB as the aetiology for bronchiectasis (37.0% vs 15.8%, $P=0.002$) and upper lobe disease (75.9% vs 54.4%, $P=0.007$). Women had a higher prevalence of NTM (55.0% vs 27.5%, $P=0.001$).

Comparison of patients with and without a history of haemoptysis

Ninety-two subjects (54.7%) had a history of haemoptysis (Table 3). Subjects with haemoptysis tend to have a normal spirometry (48.6% vs 27.9%, $P=0.015$) with higher baseline FEV1 (84L [67–100] vs 72L [63–87], $P=0.004$), as compared to subjects without haemoptysis, who tend to have a restrictive pattern (29.5% vs 15.3%, $P=0.048$). More subjects without haemoptysis had asthma (14.5% vs 4.3%, $P=0.022$). The use of anticoagulation or antiplatelets was not associated with the development of haemoptysis.

Table 2. Comparison of female and male NCFB patients in Singapore

Characteristics	Female (n=113)	Male (n=54)	*P* value
Age, median (IQR), years	62 (56–69)	69 (60–74)	0.115
BMI, median (IQR)	19.3 (17.4–21.2)	19.1 (17.0–26.2)	0.658
Smoking status, no. (%)			
Active	0 (0)	4 (7.4)	**0.004**
Previous	9 (7.9)	24 (44.4)	**<0.001**
Never	97 (85.8)	24 (44.4)	**<0.001**
Aetiology, no. (%)			
Idiopathic	55 (48.2)	20 (37.0)	0.172
Post-infectious	31 (27.2)	11 (20.4)	0.340
Post-TB	18 (15.8)	20 (37.0)	**0.002**
Comorbidities, no. (%)			
Asthma	11 (9.6)	4 (7.4)	0.634
COPD	3 (2.6)	6 (11.1)	**0.023**
Spirometry, no. (%)			
Normal	40 (47.1)	12 (25.0)	**0.012**
Restrictive	19 (22.4)	10 (20.8)	0.838
Obstructive	5 (5.9)	10 (20.8)	**0.009**
Non-specific	7 (8.2)	6 (12.5)	0.426
FEV1 % predicted (baseline), median (IQR)	83 (68–98)	69 (61–94)	**0.004**
Sputum cultures, no. (%)			
Pseudomonas aeruginosa	26 (24.3)	9 (18.0)	0.377
Klebsiella pneumoniae	8 (7.5)	8 (16.0)	0.100
Hemophilus influenzae	5 (4.7)	1 (2.0)	0.416
Staphylococcus aureus	7 (6.5)	3 (6.0)	0.897
NTM	60 (55.0)	14 (27.5)	**0.001**
Radiology, no. (%)			
Cylindrical	90 (78.9)	42 (77.8)	0.863
Cystic	14 (12.3)	8 (14.8)	0.649
Varicose	10 (8.8)	4 (7.4)	0.765
Involvement, no. (%)			
Upper lobes	62 (54.4)	41 (75.9)	**0.007**
Middle lobes	102 (89.5)	44 (81.5)	0.152
Lower lobes	88 (77.2)	41 (75.9)	0.856
Lobes involved, median (IQR)	3 (2–4)	4 (2–5)	0.358
Radiology severity score, median (IQR)	6 (4–8)	8 (5–12)	0.107
Modified Reiff score, median (IQR)	4 (2–5)	4 (3–6)	0.263
Haemoptysis, no. (%)	64 (56.1)	28 (51.9)	0.602
Significant haemoptysis, no. (%)	29 (25.4)	7 (13.0)	0.066
BSI score, median (IQR)	6 (4–8)	7 (6–9)	**0.022**
CAT score, median (IQR)	13 (8–20)	13 (7–18)	0.394

BMI: body mass index; BSI: Bronchiectasis Severity Index; CAT: COPD assessment test; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; NCFB: non-cystic fibrosis bronchiectasis; NTM: non-tuberculous mycobacteria; TB: tuberculosis
P values in bold are significant

Mortality outcomes

Causes of death are shown in Table 1. The most common aetiology of death was pneumonia (4, 22.2%). The cause of death was not available in 12 patients who died outside our institution. Our national policy on patient data confidentiality does not allow investigators to obtain information from national records for the purpose of research. Lower BMI, concomitant COPD, modified Reiff score, radiological severity, exacerbations and BSI scores correlated with mortality. Growth or colonisation of *Pseudomonas aeruginosa* was not associated with mortality. The hazard ratio for moderate grade BSI (BSI 5–8) compared to mild grade BSI (BSI 0–4) was 1.6 (confidence interval [CI] 0.188–15.053, *P*=0.642), and for severe grade BSI (BSI≥9) compared to mild grade BSI was 14.8 (CI 1.929–114.235, *P*=0.01) (Table 4). The Kaplan-Meier survival curve

Table 3. Comparison of NCFB patients with and without a history of haemoptysis

Characteristics	Haemoptysis (n=92)	No haemoptysis (n=76)	*P* value
Age, median (IQR), years	65 (56–71)	63 (56–73)	0.554
BMI, median (IQR)	19.0 (16.9–21.1)	20.2 (17.9–23.4)	0.247
Female gender, no. (%)	64 (69.6)	50 (65.8)	0.602
Smoking status, no. (%)			
Active	3 (3.4)	1 (1.4)	0.438
Previous	21 (23.6)	12 (17.1)	0.319
Never	64 (71.9)	57 (81.4)	0.162
Aetiology, no. (%)			
Idiopathic	41 (44.6)	34 (44.7)	0.982
Post-infectious	21 (22.8)	21 (27.6)	0.474
Post-TB	25 (27.2)	13 (17.1)	0.121
Asthma, no. (%)	4 (4.3)	11 (14.5)	**0.022**
COPD, no. (%)	6 (6.5)	3 (3.9)	0.461
Spirometry, no. (%)			
Normal	35 (48.6)	17 (27.9)	**0.015**
Restrictive	11 (15.3)	18 (29.5)	**0.048**
Obstructive	7 (9.7)	8 (13.1)	0.538
Non-specific	7 (9.7)	6 (9.8)	0.982
FEV1 % predicted (baseline)	84 (67–100)	72 (63–87)	**0.004**
Sputum cultures, no. (%)			
Pseudomonas aeruginosa	22 (24.7)	13 (19.1)	0.403
Klebsiella pneumoniae	8 (9.0)	8 (11.8)	0.569
Hemophilus influenzae	3 (3.4)	3 (5.9)	0.736
Staphylococcus aureus	8 (9.0)	2 (2.9)	0.124
NTM	44 (48.9)	30 (42.9)	0.448
Radiology pattern, no. (%)			
Cylindrical	73 (79.3)	59 (77.6)	0.787
Cystic	8 (8.7)	14 (18.4)	0.063
Varicose	11 (12.0)	3 (3.9)	0.062
Involvement, no. (%)			
Upper lobes	53 (51.5)	50 (48.5)	0.305
Middle lobes	81 (55.5)	65 (44.5)	0.488
Lower lobes	71 (55.0)	58 (45.0)	0.544
Lobes involved, median (IQR)	3 (2–4)	4 (2–5)	0.080
Radiology severity score, median (IQR)	6 (4–9)	7 (5–10)	0.326
Modified Reiff score, median (IQR)	4 (2–5)	4 (3–6)	0.073
Use of antiplatelets or anticoagulation, no. (%)	11 (12.1)	12 (15.8)	0.489
BSI score, median (IQR)	7 (5–9)	6 (4–8)	0.398
CAT score, median (IQR)	12 (5–19)	15 (8–20)	0.433

BMI: body mass index; BSI: Bronchiectasis Severity Index; CAT: COPD assessment test; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; NCFB: non-cystic fibrosis bronchiectasis; NTM: non-tuberculous mycobacteria; TB: tuberculosis
P values in bold are significant

Table 4. Hazard ratios of Bronchiectasis Severity Index (BSI) severity grades

BSI	Hazard ratios	95% confidence interval	*P* value
Grade 1: Mild	Reference	Reference	Reference
Grade 2: Moderate	1.682	0.188–15.052	0.642
Grade 3: Severe	14.844	1.929–114.235	0.01

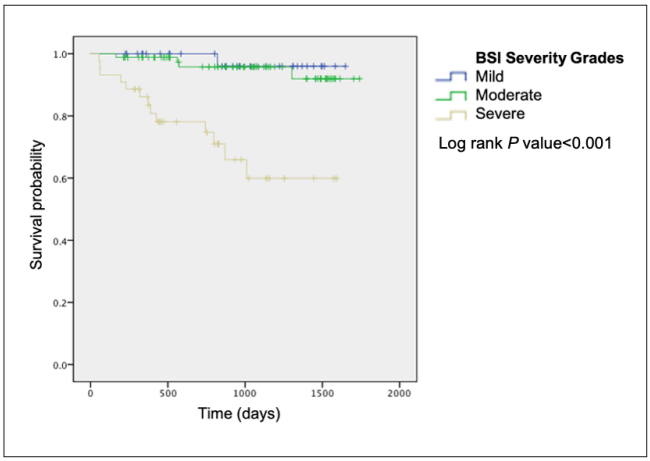

Fig. 1. Kaplan-Meier survival curves according to Bronchiectasis Severity Index (BSI) severity grades.

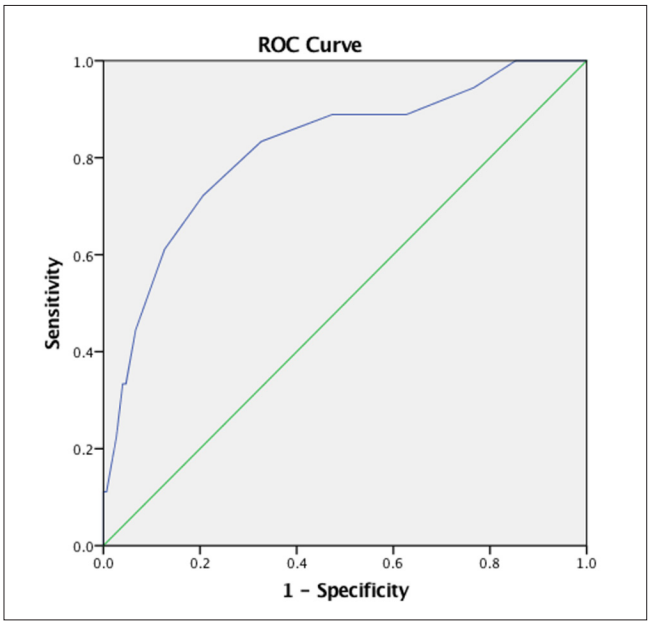

Fig. 2. Receiver operating characteristic curve for mortality according to Bronchiectasis Severity Index score.
ROC: receiver operating characteristic

demonstrated a lower survival at the median overall follow-up period of 2.4 years for subjects with severe BSI grade as compared to those with mild or moderate grades (P<0.001) (Fig. 1). The receiver operating characteristic curve for mortality according to BSI score demonstrates an area under the curve of 0.818 (Fig. 2).

DISCUSSION

We observed a disproportionate Chinese majority and female predominance in our study, which is one of the first reports describing characteristics of NCFB patients in a multiethnic Southeast Asian population. Most patients had normal spirometry patterns, and fewer than 2 exacerbations per year. There was a high prevalence of NTM, *P. aeruginosa* and *K. pneumonia* infection. Over half the patients had a history of haemoptysis, and approximately one-fifth of the patients had clinically significant haemoptysis. There is a higher proportion of NCFB among Chinese (87.5%) compared to other races and this is out of proportion to Singapore's ethnic distribution (74.3% Chinese, 13.5% Malays and 9.0% Indians, according to Singapore Department of Statistics' 2020 figures). The reason for this is unknown but postulated to be due to differences in disease aetiology and sputum microbiology.[26] We are unable to confirm these findings due to the small number of non-Chinese patients in our cohort.

Female preponderance of NCFB has been widely described in various global registries including the UK, US and Australia.[10,13,18] Reasons postulated for this sex distribution include the smaller conducting airways in females, as well as the effects of oestrogen and progesterone on mucociliary clearance.[27] However, the sex ratio is reversed in TB-endemic countries like China, India and Pakistan.[6,14,16] In these countries, TB is a significant cause of NCFB and is more common among men.[28] NCFB patients in India and Pakistan are also younger—83.1% of Pakistani patients are younger than 60, and the mean age of diagnosis in India was 56 (41–66)—compared to the European cohort with mean age of 67 (57–74).[14,16] Factors such as the incidence of childhood pulmonary infections (including TB) and poor access to healthcare may contribute to the earlier onset, higher burden and increased severity of the disease.[29,30] Southeast Asia accounts for over 40% of the global TB incidence.[31] Despite a high incidence of TB in Singapore (47 per 100,000 population), the overall mean age of diagnosis of NCFB remains comparable to the UK and US.[10,18] In the current study, 40% of the NCFB patients with known aetiology were due to previous TB infection. Idiopathic and post-TB bronchiectasis were equally common as aetiology of NCFB among male patients. On the other hand, the proportion of female patients with idiopathic bronchiectasis was thrice that of post-TB bronchiectasis. The higher frequency of male patients with post-TB bronchiectasis is likely due to a significantly higher TB prevalence among the men in Singapore (70.7% vs 29.3%).[32]

Other significant sex differences observed were smoking status and sputum microbiology. Most female NCFB patients were never-smokers (90.7%), compared to 46.2% in males (P<0.001). This sex difference

in smoking habits is similarly reflected in the larger proportion of COPD (11.1% vs 2.6%, *P*=0.023), and obstructive spirometry (20.8% vs 5.9%, *P*=0.009) seen in the male NCFB patients. The frequency of positive microbiology for NTM was significantly higher among females (55.0% vs 27.5%, *P*=0.001).

The spirometry findings of the present study contradict previous reports that NCFB patients often have an obstructive lung pattern.[33] Proposed mechanisms for the airway obstruction include collapse of the major airways during expiration, bronchial wall thickening, presence of endobronchial secretions and obliterative bronchitis.[34] However, a high proportion of smokers in some older studies might have contributed to the high frequency of airway obstruction observed. Other studies assessing lung function in NCFB patients have reported that obstructive and restrictive spirometry were both associated with increased disease severity and hospitalisation rate.[33] The high proportion of patients with normal spirometry and fairly preserved FEV1 may signal better clinical outcomes in our NCFB population.

Nearly half the NCFB patients (46.3%) in our study had positive NTM culture, which is higher than the NTM prevalence (11.2%) reported in China.[6] Our NTM prevalence is more comparable to that of the US, which was 63% with a predominance of *M. avium* complex (37%).[10] In our population, *M. abscessus* was the most common mycobacterium species isolated (18.6%). The most common bacterium isolated in our population is *P. aeruginosa* (22.3%), which is comparable to other NCFB registries.[10,14-16] Notably, *K. pneumoniae* is not widely reported in the microbiological characteristics of patients in US or European registries, and its overall incidence appears to be low. In our study, we observed an incidence of 10.2%, comparable to the Thai (14%) and Korean (22.4%) cohorts.[11,12] *K. pneumoniae* is associated with less mortality, exacerbations and hospitalisation rates than *P. aeruginosa*.[35-37] The lung microbiome composition appears to affect response to anti-inflammatory therapy. In the erythromycin group in the Bronchiectasis and Low-dose Erythromycin Study (BLESS), patients with a *Haemophilus*-dominated microbiome had fewer exacerbations compared to those with *Pseudomonas*-dominated microbiome.[38] There may be a geographical or racial predisposition that affects colonisation and further research into the bronchiectasis microbiome is imperative.

Interestingly, more than half of our patients (54.7%) had a history of haemoptysis, 40% of whom were clinically significant. This is significantly higher than the prevalence of 20.9% and 23% that were reported in studies from Pakistan and the US, respectively.[10,16] In bronchiectasis, chronic airway inflammation causes hypertrophy and tortuosity of the vessels accompanying the airways.[39,40] Haemoptysis occurs due to the rupture of these vessels, usually in the setting of an acute infection or exacerbation. Despite our understanding of the pathophysiology, it remains uncertain why haemoptysis occurs more frequently in some patients but not others. We did not find an association between haemoptysis and the presence of hypertrophied bronchial arteries on computed tomography imaging in our population, which may suggest the presence of other factors affecting the development of haemoptysis. Other factors associated with haemoptysis in NCFB include the use of inhaled anticholinergics and short-acting beta agonists,[41] presence of cystic pattern of on CT[42] and post-TB aetiology.[37] However, these findings were not replicated in our study.

Lower BMI, smoking status, history of exacerbations, modified Reiff scores and radiological severity were associated with mortality in our study, which is in keeping with results from previous studies.[23,43] BSI scores were calculated and showed to be a good predictor of mortality, with an area under the curve (AUC) value of 0.818 that was similar to the derivation and validation cohorts of the original study (AUC of 0.80 and 0.81–0.84, respectively). The Kaplan-Meier survival curve and hazard ratios showed a significant difference in mortality when comparing patients with mild (BSI 0–4) and severe (BSI>9) bronchiectasis. Our results validate the use of BSI as a prognostic indicator in our local population. The inclusion of further markers of radiological severity such as a composite of lobar severity grades as we have done in our study may further refine the accuracy and utility of such clinical scores.

The limitations of this study include the relatively small cohort of patients, the potential selection bias due to recruitment of participants from a single study centre, and incomplete data, as in most real-world clinical studies. A multicentre study would likely provide more comprehensive information about characteristics of the NCFB population in Singapore. Causal inference between the variables analysed should also be made with caution given the relatively short follow-up period. The labels of post-infectious and post-TB aetiologies are based on self-reported histories of pulmonary infections or TB, and may have an element of recall bias. However, as far as possible,

objective evidence of previous pulmonary TB infection was documented. Similarly, there was a degree of reliance on self-reporting of bronchiectasis exacerbations and haemoptysis. We were unable to perform analysis for respiratory-specific mortality as the cause of death was not available for a significant proportion of the non-survivors. There may be interpretation bias introduced as the radiological assessment was performed by a sole radiologist. The strengths of the study include its prospective nature, and a broad inclusion criteria to reflect real-world clinical practice.

CONCLUSIONS

The NCFB population in Singapore has a female and Chinese predominance. Sex differences were found and haemoptysis was common. The BSI score is a useful predictor of mortality in our population. Future research and longitudinal data should focus on better understanding of the Asian bronchiectasis microbiome and cause of haemoptysis in NCFB.

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COMMENTARY

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Transthyretin amyloid cardiomyopathy: The emerging role of cardiac amyloid imaging

Sarah Ming Li Tan [1]*MD*, Yoke Ching Lim [2,3]*MRCP*, Ping Chai [2,3]*MRCP*, Lenith Tai Jit Cheng [4]*MRCP*, Ching Hui Sia [2,3]*MRCP*, Raymond Ching Chiew Wong [2,3]*MRCP*, Hoi Yin Loi [4,5]*FRCR*, Weiqin Lin [2,3]*MRCP*

Transthyretin amyloidosis (or ATTR amyloidosis) is an under-recognised multisystemic disorder, arising from misfolding of transthyretin proteins into insoluble amyloid fibrils. As amyloid fibrils deposit into various tissues and organs, the process invariably leads to organ dysfunction. Deposition of amyloid fibrils into the heart results in cardiac amyloidosis (CA). Manifestations include restrictive cardiomyopathy, heart failure, conduction abnormalities and arrhythmias.[1] Early and accurate recognition of cardiac involvement is important, as it is a leading cause of morbidity and mortality in ATTR amyloidosis, and emerging therapies may delay disease progression.[2]

Definitive diagnosis of transthyretin amyloid cardiomyopathy (ATTR-CM) has conventionally relied on endomyocardial biopsy.[3] Over the last decade, however, advancements in imaging modalities, particularly radionuclide scintigraphy, have enabled non-invasive diagnosis of ATTR-CM.[4,5] We present the case of a patient who was non-invasively diagnosed, and discuss the evidence, as well as the latest recommendations behind non-invasive diagnosis of ATTR-CM.

A 72-year-old Chinese man was admitted to the cardiology ward with a history of exertional dyspnoea and abnormal electrocardiogram (ECG) findings in routine outpatient primary care review. ECG showed sinus rhythm with poor R-wave progression and anteroseptal ST-segment elevations, without dynamic changes. There was no chest pain, dizziness or palpitations. He had a background of hypertension, hyperlipidaemia and diabetes, but no personal or family history of cardiac conditions. Vital signs and cardiorespiratory examination were unremarkable.

Further workup revealed elevated serum high-sensitivity troponin I levels (serial 36–38ng/mL; normal <14ng/mL). Transthoracic echocardiogram (TTE) demonstrated left ventricular ejection fraction (LVEF) of 60% and concentric left ventricular hypertrophy (LVH), without regional wall motion abnormalities. Subsequent myocardial perfusion imaging revealed normal myocardial perfusion and dilated left ventricle, suggesting myopathic disease. Contrast-enhanced cardiovascular magnetic resonance (CMR) confirmed concentric LVH, dilated atria, LVEF of 58% and right ventricular ejection fraction of 57%. Left ventricular myocardial signal intensities were increased on T2-weighted fat suppressed turbo inversion recovery magnitude imaging. Diffuse subendocardial and mid-myocardial patterns of late gadolinium enhancement were present, together with gadolinium enhancement of atrial walls and atrial septum and rapid clearance of gadolinium from the blood pool, raising suspicion for CA (Fig. 1). Endomyocardial biopsy was then recommended to our patient for diagnosing CA. Given its invasive nature, he declined and subsequently failed to attend follow-up cardiology clinic appointments.

Over the next 2 years, the patient was readmitted twice for heart failure with volume overload, manifesting as worsening exertional dyspnoea and exercise intolerance, orthopnoea and lower limb swelling in the preceding few months. Notably, repeat TTE demonstrated a LVEF decline to 40%. The patient remained reluctant to undergo endomyocardial biopsy. In the latter admission, he underwent ^{99m}technetium-pyrophosphate (^{99m}Tc-PYP) scintigraphy, as a scintigraphy scan service for diagnosing ATTR-CM had become available since his last admission. The ^{99m}Tc-PYP scan performed with planar imaging at 1 hour showed a heart-to-contralateral lung ratio of 1.5 (Fig. 2). Combined with single-photon emission computed tomography (SPECT) imaging demonstrating increased myocardial radiotracer uptake equalling rib radiotracer uptake (grade 2), the findings suggested ATTR-CM. Light

[1] School of Medicine, University of New South Wales Sydney, Australia
[2] Department of Cardiology, National University Heart Centre, Singapore
[3] Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[4] Department of Diagnostic Imaging, National University Hospital, Singapore
[5] Department of Diagnostic Radiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
Correspondence: Dr Weiqin Lin, Department of Cardiology, National University Heart Centre, Singapore, 1E Kent Ridge Road, NUHS Tower Block Level 9, Singapore 119228.
Email: weiqin_lin@nuhs.edu.sg

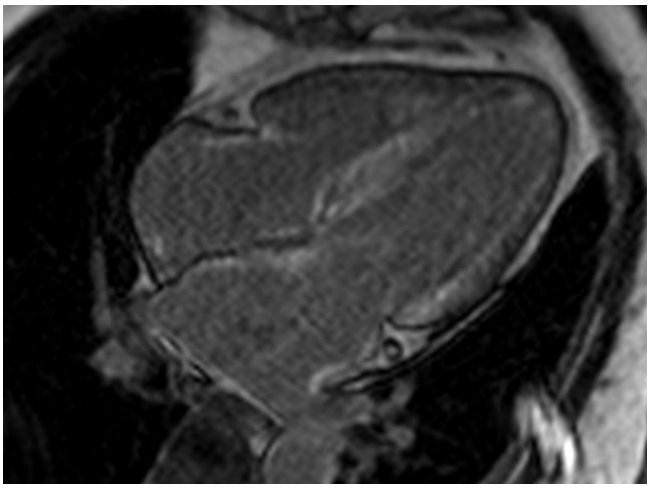

Fig. 1. Cardiac magnetic resonance imaging showing late gadolinium enhancement of the subendocardium and mid-myocardium of the left ventricle, atrial walls and atrial septum.

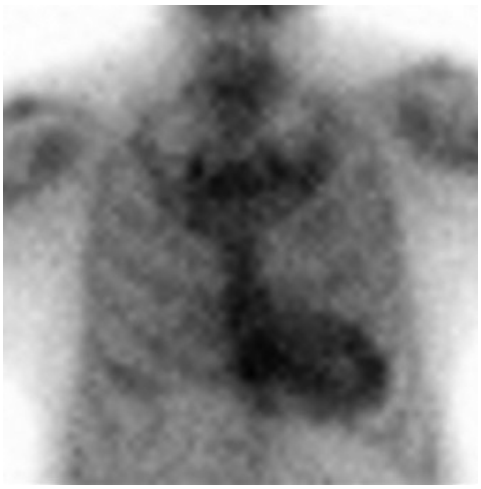

Fig. 2. ^{99m}Technetium-pyrophosphate cardiac amyloid imaging scan showing grade 2 myocardial tracer uptake with heart-to-contralateral ratio of 1.5008.

chain amyloid cardiomyopathy (AL-CM) remained an important differential diagnosis, which was excluded given the normal serum free light chain (sFLC) ratio (0.97; normal 0.26–1.65), and negative serum and urine immunofixation. In view of the patient's clinical history, strongly positive scintigraphy scan and negative monoclonal screen, he was therefore diagnosed with ATTR-CM, non-invasively.

In following up with the patient in our heart failure clinic, retrospective questioning revealed a 6-year history of bilateral carpal tunnel syndrome and lumbar spinal stenosis, both likely being associated with ATTR amyloidosis. Doxycycline/ursodeoxycholic acid, an off-label fibril-disruptor therapy for ATTR-CM was then commenced. Tafamidis, a transthyretin stabiliser and the only agent licensed for treating ATTR-CM was a less feasible option given its prohibitively high costs. The patient was counselled and offered transthyretin genetic (*TTR* gene) testing to differentiate hereditary ATTR amyloidosis (hATTR) from wild-type ATTR amyloidosis (wtATTR), for which he has requested for more time to discuss the test with his family. Patient remained otherwise well in follow-up clinics.

Cardiac involvement is the most important prognostic factor in amyloidosis, and is associated with poor life expectancy and quality of life.[6] Amyloidosis can be classified based on misfolded precursor proteins, which form amyloid fibrils that deposit in the myocardium.[2] Over 30 proteins are known to form amyloid fibrils, including immunoglobulin light chain, transthyretin, amyloid A and β2-microglobulin. However, immunoglobulin light chain (AL) amyloidosis and ATTR amyloidosis are the most common types, accounting for more than 95% of cases.[2,3] AL amyloidosis arises from the overproduction of misfolded immunoglobulin light chains by clonal plasma cells. In contrast, ATTR amyloidosis results from misfolding of transthyretin, a tetrameric transporter protein produced by the liver. Distinguishing between AL and ATTR amyloidosis is important, given their different manifestations, prognosis and management.[7]

ATTR amyloidosis can be further classified as hATTR, due to *TTR* gene mutations, or wtATTR associated with ageing and misfolded genetically normal transthyretin protein.[2] Previously, ATTR amyloidosis was thought to be rare and untreatable. However, autopsy studies have demonstrated wtATTR cardiomyopathy to be relatively prevalent in older adults, in around 25% of patients 80 years old and above.[8,9] Recent advancements in diagnostic imaging modalities have also improved ATTR-CM detection, allowing it to become an increasingly recognised cause of heart failure with preserved ejection fraction (HFpEF). With new disease-modifying therapies available for ATTR-CM, timely diagnosis has becoming increasingly crucial.[10]

Diagnosis of ATTR-CM is challenging because of its heterogenous presentation, perceived rarity, and limited awareness within the medical community.[1] Given the clinical overlaps with common disorders and frequent comorbidities, ATTR-CM is often misdiagnosed as hypertrophic cardiomyopathy, aortic stenosis, undifferentiated HFpEF or hypertensive heart disease.[1] Non-specific early symptoms and multisystemic manifestations (neurologic, orthopaedic,

gastrointestinal) further confound diagnosis.[3] Carpal tunnel syndrome is prevalent in ATTR-CM (15–60% of cases), often preceding cardiac involvement by 5–9 years, as demonstrated in our patient. Hence, recognition of this association may promote earlier diagnosis of subclinical ATTR-CM.[11]

Non-invasive diagnosis of ATTR-CM. Endomyocardial biopsy has been considered the gold standard for diagnosing ATTR-CM. However, it is invasive and carries a small but significant risk of complication. Consequently, many older patients are unwilling to undergo the procedure, potentially delaying diagnosis as seen in our patient. Furthermore, it is often limited to experienced specialised centres and not widely available. Following diagnosis, endomyocardial biopsy does not estimate cardiac amyloid burden and is impractical for monitoring disease progression.[7] Conventional investigation modalities including ECG, TTE and CMR are useful adjuncts, as typical findings collectively raise suspicion for CA (Table 1). However, typical findings are not always present, and clinicians are unable to definitively diagnose nor distinguish between amyloid subtypes.[12]

In recent years, technetium-labelled cardiac amyloid imaging has emerged as a reliable method for non-invasive diagnosis of ATTR-CM. The advantages include its ease of access, relatively lower costs, repeatability for assessing treatment response, and being non-invasive. It can be used in centres without endomyocardial biopsy access, or in patients who refuse, or are poor candidates for biopsy.[12] The main technetium-labelled radiotracers are ^{99m}Tc-PYP, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), and ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP). These tracers preferentially bind to myocardial transthyretin amyloid fibrils, and are visualised using planar and SPECT imaging at 1 or 3 hours.[5] With planar imaging, myocardial uptake can be graded using 2 scoring systems: semi-quantitatively by visual grading of myocardial uptake relative to rib bone uptake (grade 0: no myocardial uptake; grade 1: myocardial uptake less than rib bone uptake; grade 2: equal uptake; grade 3: myocardial uptake greater than rib bone uptake), and quantitatively using heart-to-contralateral lung (H/CL) ratio. SPECT imaging is necessary to confirm myocardial uptake, as the left ventricle blood pool can cause false-positive results on planar imaging alone.[7]

Technetium-labelled cardiac amyloid imaging has shown high diagnostic accuracy for ATTR-CM.[10] In a large multicentre study by Gillmore et al., radiotracer uptake was >99% sensitive and 86% specific for biopsy-proven ATTR-CM, with false positives largely attributed to radiotracer uptake in AL-CM. Notably, when grades ≥2 radiotracer uptake was combined with negative monoclonal protein testing, ^{99m}Tc-PYP scintigraphy had 100% specificity and positive predictive value for ATTR-CM.[4] In another smaller study, Perugini et al. similarly demonstrated high sensitivity and accuracy of scintigraphy for differentiating ATTR-CM from AL-CM.[13] Subsequently, Bokhari et al. showed that H/CL>1.5 had 97% sensitivity and 100% specificity for detecting ATTR-CM.[5] These findings were later confirmed by another multicentre study, which additionally found H/CL≥1.6 to be associated with poorer survival in ATTR-CM.[14]

Current recommendations for the diagnosis of ATTR-CM. Multisocietal guidelines support technetium-labelled cardiac amyloid imaging for diagnosing ATTR-CM.[7,15] In the diagnostic algorithm, patients with suspected CA, either clinically or through typical ECG, TTE and/or CMR findings, should undergo monoclonal protein testing (sFLC and serum/urine immunofixation) and technetium-labelled cardiac amyloid imaging (Fig. 3).[7] Endomyocardial biopsy has become reserved for cases with equivocal or conflicting clinical and imaging findings, or unavailable scintigraphy.[12] Definitive diagnosis of ATTR-CM can be made non-invasively, provided that clinical (eg. unexplained heart failure or clinical red flags with TTE and/or CMR findings suggestive of CA), laboratory (absent monoclonal proteins) and imaging criteria (positive scintigraphy with SPECT imaging; grades ≥2 myocardial uptake) are fulfilled.[15] Following diagnosis of ATTR-CM, genetic counselling and testing should be offered to patients and families to differentiate hATTR from wtATTR.[2]

Importantly, AL-CM is a differential diagnosis that must be excluded. Positive scintigraphy cannot exclude AL-CM, as radiotracer uptake (grades ≥2) is seen in approximately 22% of biopsy-proven AL-CM.[4,15] Consequently, monoclonal protein testing should always accompany scintigraphy.[7] In the absence of monoclonal proteins, positive scintigraphy is diagnostic of ATTR-CM. When monoclonal proteins are present, positive scintigraphy cannot diagnose ATTR-CM. Endomyocardial biopsy with amyloid typing is hence required to assess for AL-CM.[15] Finally, positive monoclonal proteins may not necessarily indicate AL-CM, as monoclonal gammopathy of undetermined significance is relatively common and can coexist with ATTR-CM, especially in older patients with wtATTR.[13]

Table 1. Typical findings of conventional cardiac investigation modalities in cardiac amyloidosis[a]

Modality	Findings	Strengths	Limitations
ECG	Pseudo-infarct pattern[17]	Widely available investigation[1]	Low voltage has poor sensitivity with various causes (eg. pericardial or pleural effusions, obesity, chronic obstructive lung disease)[18]
	Low QRS complex voltage (limb leads ≤0.5mV and praecordial leads ≤1mV; or Sokolow-Lyon index: S in V1 + R in V5/V6≤1.5mV)[18]	Pseudo-infarct pattern is relatively common, seen in 47–74% cases[17]	Low voltage is often a relatively late finding, hence not useful for early identification of CA[18]
	Conduction abnormalities		
	Arrhythmia (eg. atrial fibrillation, atrial flutter, ventricular tachycardia)[17]		
TTE	Two-dimensional imaging[7] - Increased LV wall thickness (>1.2cm) - Biatrial enlargement - Impaired diastolic and systolic function in early and advanced stages, respectively - Small pericardial effusion	Widely available, cost-effective and quick to perform by bedside[1]	Lacks specificity for CA, especially in early stages[12]
	Strain imaging[12] - Relative apical-sparing pattern of global LS (apical LS/average of combined mid and basal LS>1.0)	Relative apical sparing of LS has good sensitivity (82%) and specificity (93%) for CA[19]	Typical features only most prominent in advanced disease[12]
		Longitudinal LV strain imaging can distinguish CA from other causes of LVH (eg. hypertension, HCM)[10]	Cannot definitively diagnose, nor distinguish between CA subtypes[12]
CMR	Increased LV wall thickness[7]	High-resolution structural and functional assessment[7]	CMR cannot definitively diagnose, nor distinguish between CA subtypes[12]
	LGE - Diffuse subendocardial or transmural LGE pattern[7]	Can differentiate CA from other causes of LVH[7]	LGE - Not easily quantifiable and unreliable for tracking disease progression[12]
	Parametric mapping[7,12] - Native T1 mapping (pre-contrast): increased values - ECV mapping: increased values, with ECV>0.40 highly suggestive - T2 mapping: increased values	LGE - Enables tissue characterisation through LGE, which has high sensitivity (80%) and specificity (94%) for CA[7,20] - LGE is a significant predictor of prognosis and mortality in CA[7,12]	Limitations regarding gadolinium contrast use in severe renal impairment[7]
		Native T1 mapping[7,12] - High diagnostic accuracy, with 92% sensitivity and 91% specificity for CA - Quantitative measure and indicator of amyloid infiltration, which correlates with markers of systolic and diastolic dysfunction - Useful when contrast administration is contraindicated	Parametric mapping[7,12] - Lack of reproducibility when different scanners or magnetic field strengths used - Heterogeneity in reported reference ranges - T2 more variable than native T1 measures, and less extensively studied in CA compared to native T1 and ECV
		ECV mapping[12] - Surrogate marker of amyloid infiltration, and strong predictor of outcomes - Can potentially detect early disease (before LGE findings present), and track disease progression and treatment response	
		T2 mapping - Specific marker for myocardial oedema, which is present in CA[12]	

CA: cardiac amyloidosis; CMR: cardiac magnetic resonance; ECG: electrocardiogram; ECV: extracellular volume; HCM: hypertrophic cardiomyopathy; LGE: late gadolinium enhancement; LS: longitudinal strain; LV: left ventricle; LVH: left ventricular hypertrophy; TTE: transthoracic echocardiogram.
[a] Superscript numbers: Refer to reference numbers in REFERENCES

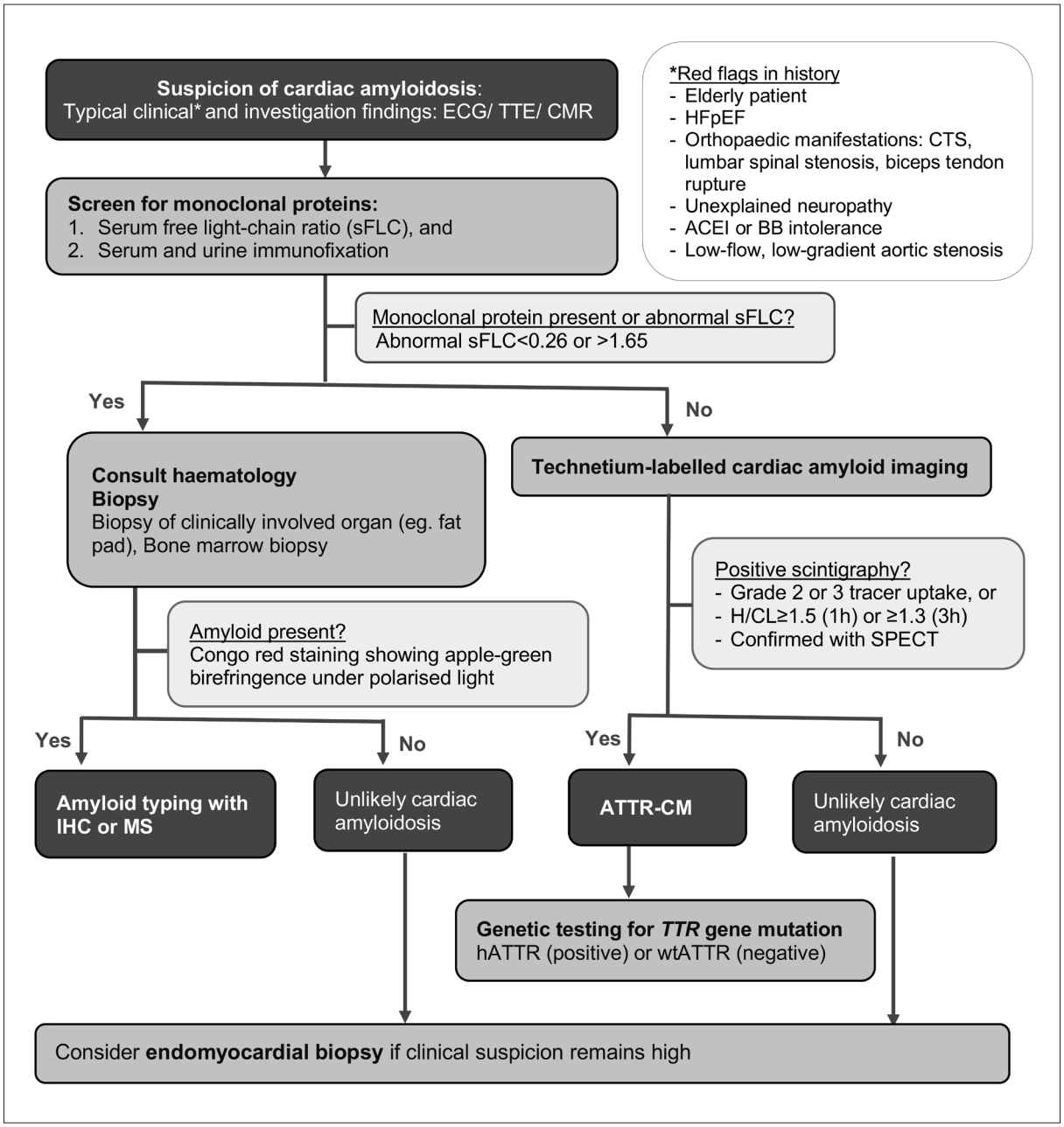

Fig. 3. Diagnostic algorithm for cardiac amyloidosis based on recent multisocietal guidelines. Definitive diagnosis of ATTR-CM can be established with a combination of positive ^{99m}Tc-PYP scintigraphy scan and negative monoclonal protein testing (adapted from Maurer et al.,[1] Hanna et al.,[15] Dorbala et al.[7]).

ACEI: angiotensin-converting enzyme inhibitor; ATTR-CM: transthyretin amyloid cardiomyopathy; BB: beta blocker; CMR: cardiac magnetic resonance; CTS: carpal tunnel syndrome; ECG: electrocardiogram; hATTR: hereditary transthyretin amyloidosis; H/CL: heart-to-contralateral lung ratio; HFpEF: heart failure with preserved ejection fraction; IHC: immunohistochemistry; MS: mass spectrometry; sFLC: serum free light chain ratio; SPECT: single-photon emission computed tomography; TTE: transthoracic echocardiogram; TTR: transthyretin; wtATTR: wild-type transthyretin amyloidosis.

Future directions. The ^{99m}Tc-PYP scintigraphy service in Singapore for diagnosing ATTR-CM has shown potential for diagnosing ATTR-CM in patients with TTE and/or CMR findings suggesting CA. Scintigraphy and diagnostic recommendations have allowed our patient to be diagnosed with ATTR-CM non-invasively. With the recent establishment of a ATTR amyloidosis registry in Singapore to characterise epidemiology and disease course; response to treatment approaches; and factors contributing to delayed diagnoses, clinicians will gain a better understanding of ATTR amyloidosis to optimise diagnostic and

therapeutic strategies in ATTR-CM.[16] Positive scintigraphy can definitively diagnose ATTR-CM, following AL-CM exclusion. Diagnosing CA requires a high index of clinical suspicion and combined multimodality imaging and multidisciplinary approach, involving cardiologists, neurologists, haematologists, nuclear radiologists, pathologists and geneticists. With clearer diagnostic guidelines and non-invasive diagnostic modalities now available, early detection of ATTR-CM has become increasingly possible and may translate into improved patient outcomes.

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COMMENTARY

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Merits of a harmonised system to classify drug-related problems in Singapore

Tat Ming Ng [1 PharmD], Wee Chuan Hing [2 MSc (Pharm)], Tsing Yi Koh [2 PharmD], Wei Terk Chang [3 MClin (Pharm)], Grace SW Chang [4 PharmD], Jian Wei Heng [4 PharmD], Isnarti Bte Abuaman [4], Beng Yi Sia [1 MSc (Pharm)], Yik Chuen Saw [3 MClin (Pharm)], Daphne Chan [5 B Pharm], Chwee Huat Tan [5 MSc (Pharm)], Wei Shan Fan [6 MClin (Pharm)], Franky Franky [6 BCGP], Poh Ching Tan [7 MClin (Pharm)], Cheryl WY Tan [7 PharmD], Joanne HL Sng [8 PharmD], Chun Wei Yap [9 PhD], Shanti Uma Devi d/o Gnanamani [10 Bsc (Pharm)], Doreen SY Tan [4,11 PharmD]

A drug-related problem (DRP) is commonly defined as an event or circumstance involving drug treatment that actually or potentially interferes with the optimal outcome of a patient's medical care. It broadly includes events related to errors, adverse effects or adherence issues.[1] DRPs are associated with increased healthcare costs and hospital admissions, prolonged hospital stays, reduced quality of life and increased mortality.[2,3] Patients with multiple comorbidities and polypharmacy are at risk of DRPs, present during or immediately after discharge.[4] Polypharmacy and DRPs are also associated with readmissions in Singapore.[5]

Healthcare professionals and primarily pharmacists help to identify and resolve DRPs daily in their course of work in different settings such as hospitals, nursing homes, polyclinics, community pharmacies and other community-based care facilities.[6-10] In many pharmacy departments, data on DRPs and their resolution have also been collected as part of medication safety surveillance as well as to facilitate quality and safety improvements and education initiatives. In addition, such data may also be used to estimate pharmacy workload as DRPs can lead to reworking of prescriptions. A recently conducted cross-sectional study of DRPs detected 38.3% of 379 hospitalisations with one or more DRPs. Over 90% of these DRPs were preventable, with an estimated median admission cost of SGD1,424 and interquartile range of SGD1,068–2,678.[11] The detection and resolution of DRPs optimises medication use, maximises the utility of medication costs and potentially reduces healthcare costs in Singapore's healthcare system.[12]

Currently, there is no harmonised classification system across Singapore institutions. Different methods of classifications result in difficulties interpreting reports of DRP prevalence rates and causes.[13] To tackle these DRPs as a healthcare system, it is important that institutions share similar classifications. This will enable development and research on pharmaceutical care practices. It is also important as a way to communicate to other healthcare professionals effectively.[14]

Development of the harmonised DRP classification system. In February 2019, a workgroup consisting the following 7 Singapore healthcare institutions was convened: Tan Tock Seng Hospital, Khoo Teck Puat Hospital, Institute of Mental Health, National Skin Centre, NHG Pharmacy, National University Hospital and Ng Teng Fong General Hospital. DRP definitions that each institution adopted were obtained for reference to develop a harmonised classification system. The system aims to capture data on identification, causes and resolution of DRP across settings, including inpatient and outpatient acute care hospitals, community hospitals, polyclinics, nursing homes and home-based care. We took a broader definition of DRPs involving medication errors from prescribing and drug administration, as well as operational issues, such as missing instructions or signature in prescriptions, and expired medications.

Published DRP classification systems were reviewed. A widely used classification system recommends that DRPs be broadly categorised as "indication", "adherence", "safety" and "effectiveness" (Table 1).[15] These systems are multi-focused, and usually have a "problem" and "intervention" sections.[16] Many of these

[1] Division of Pharmacy, Tan Tock Seng Hospital, Singapore
[2] Department of Pharmacy, National University Hospital, Singapore
[3] Department of Pharmacy, Ng Teng Fong General Hospital, Singapore
[4] Department of Pharmacy, Khoo Teck Puat Hospital, Singapore
[5] Department of Pharmacy, Alexandra Hospital, Singapore
[6] Department of Pharmacy, Woodlands Health Campus, Singapore
[7] NHG Pharmacy, National Healthcare Group, Singapore
[8] Institute of Mental Health, Singapore
[9] Singapore Health Services and Outcomes Research, National Healthcare Group, Singapore
[10] Pharmacy Transformation Office, National Healthcare Group Pharmacy, Singapore
[11] Department of Pharmacy, Faculty of Science, National University Singapore
Correspondence: Dr Tat Ming Ng, Division of Pharmacy, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: tat_ming_ng@ttsh.com.sg

Table 1. Tasks taken in identifying and resolving broad categories of a drug-related problem (DRP)

Broad categories of DRP	Tasks
Indication (appropriateness)	Eliminate unnecessary medications. Initiate medicines for untreated indication.
Adherence	Increase patient's willingness to adhere to medication regimen through different methods, which include motivational interviewing and shared decision making.
Safety	Eliminate toxicities. Identify and/or pre-empt adverse reactions.
Effectiveness	Identify most effective medication in a specific patient. Increase dosages to effective levels.

systems are modified based on an existing classification system or newly developed.[13] The DOCUMENT system[1] comprehensively classifies a DRP and interventions into the type of DRP, action undertaken to investigate it, recommendations made to resolve it, outcome of the actions undertaken and perceived clinical significance of the DRP. We also reviewed the Pharmaceutical Care Network Europe (PCNE) classification system, which is structured similar to the DOCUMENT system. However, these systems may not contain the specific descriptors of DRPs which we are tracking. In the PCNE system, if a wrong diluent was used, the closest "causes" category will be "drug form", thus defining and classifying the cause of the DRP as related to the selection of the drug form. If a need for therapeutic drug monitoring was identified to ensure treatment safety, it will be classified as "others".[17] The workgroup members felt strongly that explicit categories to describe DRPs of interest in Singapore, needs to be developed. Hence, we adapted and modified both systems for the Singapore context to ensure that the new classification system is able to provide data that ensures continuity in the quality and safety surveillance system of each institution.

The new classification was then tested and refined from May to July 2019. The following additional institutions took part in the testing phase: Alexandra Hospital, Woodlands Health Campus, St Luke's Hospital, Yishun Community Hospital and Jurong Community Hospital. The classification system was tested by pharmacists and pharmacy technicians on a total of 864 DRPs, using data from every participating institutions (data unpublished). Feedback on the DRP categories and their definitions were received, and changes were made to the system collectively.

A hierarchical approach to classify DRPs was developed. The system allows classification of the different aspects of a DRP and the actions taken to resolve it. The system consisted of (1) DRP categories, (2) actions taken to address "indication", "adherence", "safety" and "efficacy" (IASE), (3) process-related causes of the DRP, (4) types of medication errors (adapted from the US National Coordinating Council for Medication Error Reporting and Prevention [NCC MERP] classification) and (5) assessment and recommendations (documentation).[14] Table 2 describes the relationships of the DRP categories, actions taken and process-related causes. The user first selects the DRP category deemed most appropriate. This is followed by the identification of the action taken to address the "indication", "adherence", "safety" and/or "efficacy" associated with the DRP. After which, the cause of the DRP associated with the action taken can be selected. Each DRP is then subcategorised as either a medication error (4) or a recommendation to optimise drug therapy. This is followed by a clear and concise documentation of the assessment and recommendation using the SBAR format: situation, background, assessment and recommendation.[18] The descriptors (1) to (4) can be modified to fit the local electronic medical record systems, such as the Epic electronic medical record system (Epic Systems Corp, Verona, US), while keeping the definition as described in this document

DRP categories. To ensure appropriate classification of each DRP category and actions taken to address the DRP, the team elected to follow a thought process. The verbatim transcriptions for each DRP category are as follows:

A. Drug selection: I started, stopped or changed a drug to….
B. Dosage regimen: I changed dosing regimen by…
C. Preparation and administration: I changed route/site/diluent/container for….
D. Monitoring: I suggested monitoring or tests because of potential…
E. Adherence and education: I engaged patient/client/caregiver to….

Table 2 describes each DRP and the corresponding actions taken to resolve it based on broad DRP categories. DRPs categorised as "operational" describes the role of pharmacists as well as pharmacy technicians in addressing routine operational aspects of medication use, and hence do not require the reporter to document actions taken under IASE.

Actions taken to address DRPs and process-related causes of DRPs. Prior to developing the harmonised categorisation system, DPR definitions in some institutions were based on process-related causes of the DRP. For example, a wrong medical history taken by the prescriber resulting in a higher dose prescribed was classified as "wrong medical history" rather than "dose and regimen". These processes-related causes of DRPs are routinely reported and tracked by quality and improvement committees of these institutions. In contrast, a DRP can also be caused by "risk of treatment continuation outweighs benefits". There can be a multitude of descriptions for these "clinical causes". DRP can also be caused by patient-related causes (e.g. lack of insight into disease, forgetfulness, etc). In the new categorisation, only process-related causes are defined. Hence, the "cause of DRP (process-related)" category was added following actions taken to address IASE in this hierarchical system.

However, operational DRPs will not be linked to "actions taken" and "process-related causes" as they refer to problems that are related to routine operational aspects of medication use, and are mainly used for estimation of workload or to drive process improvements. As we had to ensure continuity in the quality and safety surveillance system of each institution, these specific categories were placed under operational DRPs (Table 2).

Defining DRPs that are regarded as medication errors, and documenting assessment and recommendations. A DRP is commonly defined as an event or circumstance involving drug treatment that actually or potentially interferes with the optimal outcome of a patient's medical care. It broadly includes events related to errors, adverse effects or adherence issues.[1] DRPs can be preventable or unpreventable; and can potentially or actually be caused by an error, intentional or unintentional deviation from accepted drug use, or an unpredictable reaction to an appropriate drug.[19]

We adopted the definition that a medication error is defined as any preventable event in the medication use process that may cause or lead to patient harm while the medication is in the control of the healthcare professional, patient, or consumer.[20] In an attempt to provide focus and definitions to medication errors, the workgroup developed 2 consensus decisions: (1) as the primary focus is to identify medication errors by healthcare professionals, medication errors caused by the patient or consumers will need to be explicitly stated, and (2) DRPs that can be defined as medication errors will be additionally classified.

The types of medication errors were adapted from NCC MERP and defined:

A. Hazards/Risks (events that have capacity to cause error/harm)
B. Near-misses (error occurred but did not reach patient)
C. Actual Error (reached patient but no harm)
D. Actual Error (reached patient and require monitoring/intervention to confirm no harm)
E. Actual Error (caused temporary patient harm requiring intervention)
F. Actual Error (caused temporary patient harm requiring initial/prolonged hospitalisation)
G. Actual Error (caused permanent patient harm)

Due to varying reporting needs, some of these medication errors, particularly categories E to G, may be reported only in the incident reporting systems of the respective institutions.

We adopted a pragmatic approach in the design and testing of the classification system, and acknowledge that inter-rater reliability and external validity could be evaluated for future research. This DRP classification system will be incorporated in the Next Generation Electronic Medical Record system, which will be progressively deployed across the National Healthcare Group and National University Health System. Further work and improvements to this classification may be needed for other public and private healthcare institutions to adopt the new DRP categorisation system. The harmonisation will allow institutions to build a common framework to identify gaps for innovative care and to characterise the value of pharmacy.

Over time, the collection of large quantities of DRP data with harmonised categorisation, together with natural language processing and machine learning, will form the foundation to establish an accurate algorithm and automate the classification of DRPs by analysing the SBAR documentation. With a better understanding of the DRPs across the Singapore healthcare system, decision support systems based on machine learning can be designed to prevent the occurrence of DRPs at the point of prescribing.

Table 2. Drug-related problem (DRP) categories, actions taken to address "indication", "adherence", "safety" and "efficacy", and process-related causes of DRP

DRP categories	**Actions taken (in bold)** Process-related causes (non-bold)							
Drug selection (dosage form, strength, better or safer choice)	**Stopped drug – No indication**	**Restarted drug for untreated indication – Indication**	**Changed drug or dosage form or strength – Efficacy**	**Changed drug or dosage form or strength – Safety**	**Stopped drug because of duplicate therapy – Safety**	**Changed drug or dosage form because of ADR/allergy or contraindication/ precaution or interaction – Safety**	**Changed drug or dosage form or strength for cost savings – Adherence**	**Changed drug or dosage form or strength because unavailable – Operational**
	Transcribing error	Transcribing error	Transcribing error	Transcribing error	Transcribing error	Transcribing error	Transcribing error	Not in formulary
	Inaccurate medication history	Inaccurate medication history	Inaccurate medication history	Inaccurate medication history	Inaccurate medication history	Inaccurate medication history	Inaccurate medication history	Out of stock
	Wrong patient	Wrong patient	Other slips and lapses	Other slips and lapses	Wrong patient	Other slips and lapses	Other slips and lapses	
	Other slips and lapses	Labs/cultures not noted			Other slips and lapses		Affordability	
		Other slips and lapses						
Dosage regimen (frequency, timing, rate, quantity, duration, add "once order")	**Dose/frequency increased – Efficacy**	**Rate of infusion increased – Efficacy**	**Duration or quantity increased – Efficacy**	**Dose or frequency reduced – Safety**	**Rate of infusion reduced – Safety**	**Duration or quantity reduced – Safety**	**Dose or frequency changed – Adherence**	**Dose or frequency changed for cost savings – Adherence**
	Transcribing error	Transcribing error	Transcribing error	Transcribing error	Transcribing error	Transcribing error	Transcribing error	
	Inaccurate medication history	Inaccurate medication history	Inaccurate medication history	Inaccurate medication history	Other slips and lapses	Inaccurate medication history	Inaccurate medication history	
	Other slips and lapses	Other slips and lapses	TCU mismatch	Other slips and lapses		Other slips and lapses	Other slips and lapses	
			Other slips and lapses					

Table 2. Drug-related problem (DRP) categories, actions taken to address "indication", "adherence", "safety" and "efficacy", and process-related causes of DRP (Cont'd)

DRP categories	**Actions taken (in bold)** Process-related causes (non-bold)						
Preparation and administration (route, site, diluent, container, dilution)	**Route or site of administration changed – Efficacy**	**Diluent or dilution or container changed – Efficacy**	**Route or site of administration changed – Safety**	**Diluent or dilution or container changed – Safety**	**Route or site of administration changed – Adherence**		
	Transcribing error	Incompatibility	Transcribing error	Incompatibility			
	Inaccurate medication history	Drug concentration	Inaccurate medication history	Drug concentration			
	Other slips and lapses	Other slips and lapses	Other slips and lapses	Other slips and lapses			
Monitoring	**Adverse drug reaction or allergy monitoring – Safety**	**Drug interactions or precautions – Safety**	**Test added to see therapeutic response – Efficacy**	**Test added for undiagnosed condition – Indication**	**Remove unnecessary test – Operational**	**Remove wrong lab test – Operational**	
					Other slips and lapses	Other slips and lapses	
Adherence and education	**Drug administration instructions reinforced – Adherence**	**Provide compliance aids or tools – Adherence**	**Improve health literacy – Adherence**	**Shared decision-making goals made – Adherence**	**Provide specialised counselling – Adherence**	**Provide information – Adherence**	
Operational[a]	No original prescription	Missing or incomplete dosage regimen or signature	Request by patient	Documentation of ADR into system	Referral or update to HCP	Illegible handwriting	Removed expired/ unnecessary medications
	Inappropriate storage conditions	Routine specialised counselling					

ADR: adverse drug reaction; HCP: healthcare professional; TCU: "to see you" for an appointment between patient and prescriber following mis-match of prescription duration and next visit date
In bold: descriptors describe each action taken. Non-bold: descriptors describe process-related causes.
[a] Operational DRPs will not be linked to "actions taken" and "process-related causes". The 9 sub-categories are described in the table.

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Impact of true fetal mosaicism on prenatal screening and diagnosis

Dear Editor,

Over the past decade, the non-invasive prenatal test (NIPT) has increasingly been used as a method for prenatal screening for trisomy 21 (T21) and other aneuploidies, complementing the traditional approach of first trimester screening (FTS). FTS comprises ultrasound of the nuchal thickness and blood test to measure the levels of maternal serum free-β-human chorionic gonadotropin and pregnancy-associated plasma protein-A (PAPP-A). FTS has been quoted to produce a sensitivity of 0.998 and 0.977 for T21 and T18, respectively, with a sensitivity of 0.900 for T13 in high-risk populations.[1] False positive rate was <1%[2] and false negative rate ranges between 0.02% and 0.26%.[3] Comparatively, the FTS test has a sensitivity of 90% at a false positive rate of 5%.[4]

We recently encountered a patient with a high-risk FTS and a low-risk NIPT who underwent chorionic villus sampling (CVS), which confirmed trisomy of the long arm and monosomy of the short arm of chromosome 18. This resulted in a mid-trimester termination of pregnancy.

This is a rare case of a false negative NIPT result. The basis of NIPT lies in the extraction of cell-free fetal DNA (cffDNA) circulating in the maternal serum, derived from placenta cytotrophoblast cells. In order to achieve adequate sequencing and analysis, the cell fetal fraction (FF), defined as the amount of cffDNA divided by the amount of total cell-free DNA, must be more than 4%. Factors affecting the FF include maternal weight and gestation age at time of test with a lower FF in higher maternal weight and lower gestational age.[2]

The theoretical explanation for false negative and false positive results lies in the fact that cffDNA is mainly derived from the apoptosis of the placenta cytotrophoblast and syncytiotrophoblast cells, which may be discordant with the true fetal karyotype due to mosaicism.[2,5] This cytotrophoblast layer is derived from the trophoblast of the blastocyst, whereas cells of the mesenchymal core and fetus are derived from the epiblast of the inner cell mass.

General mosaicism occurs when the aneuploidy occurs in the first days of embryonic development prior to any cellular differentiation (i.e. in a preimplantation embryo). Early embryos have a mosaicism rate of 65–70%.[6] However, not all abnormal cell lines continue to propagate during development because euploid cells proliferate more quickly than aneuploidy cells. Confined placental mosaicism (CPM) is a phenomenon when the chromosomally abnormal cell line is confined within the cytotrophoblast and the mesenchymal core of the chorionic villus, while the fetus itself has a normal karyotype.[3]

False positive NIPT results may arise due to CPM Type 1 or Type 3,[3,5] where the fetus has a normal karyotype but the cytotrophoblast cells are abnormal (Table 1). The chance of obtaining a false positive NIPT result due to CPM increases with higher percentage of mosaicism, greater fetal fraction and method of performing NIPT (counting or single-nucleotide polymorphism-based methods).[7] False negative NIPT results due to mosaicism are largely due to true fetal mosaicism (TFM) type 5,[5] where the cytotrophoblast layer has a normal karyotype while the mesenchymal core and fetus have an abnormal karyotype (Table 1).

The consensus statement released by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) in 2014 recommended that all women should be offered a first trimester ultrasound scan, regardless of their intention to undergo NIPT.[8] The use of NIPT can either be performed as a first line screening test or as an alternative to invasive testing following an abnormal or "intermediate risk" result on combined screening test. However, it recommended the cautious use of NIPT as most guidelines endorse NIPT only for high-risk populations, and usage of NIPT in lower-risk populations may result in lower positive predictive values.[8] The ISUOG also recommended that the use of NIPT should not replace invasive diagnostic tests in patients with trisomy risk of more than 1 in 10 on FTS as only 70% of chromosomal abnormalities in this group of patients are trisomy 21, 18 or 13. In our case, if we had taken NIPT alone without FTS, we may not have picked up the abnormality until the fetal anomaly scan usually performed around 20 weeks of gestation.

All abnormal results from NIPT should hence be confirmed with diagnostic testing. This can either be in the form of a chorionic villus sampling or an amniocentesis, depending on the involved chromosomal aberration. Chorionic villus sampling involves analysis

Table 1. Summary of the effects of various types of CPM and TFM on NIPT results[a]

Types of mosaicism		Cytotrophoblast (direct preparation or short-term culture)	Mesenchyme (long-term culture)	Amniocytes	Expected NIPT result
CPM	I	Abnormal	Normal	Normal	False positive
	II	Normal	Abnormal	Normal	True negative
	III	Abnormal	Abnormal	Normal	False positive
TFM	IV	Abnormal	Normal	Abnormal	True positive
	V	Normal	Abnormal	Abnormal	False negative
	VI	Abnormal	Abnormal	Abnormal	True positive

CPM: confined placental mosaicism; NIPT: non-invasive prenatal test; TFM: true fetal mosaicism
[a] Grati FR. Chromosomal Mosaicism in Human Feto-Placental Development: Implications for Prenatal Diagnosis. J Clin Med 2014;3:809-37.

of both the cytotrophoblast and mesenchymal core, while amniocentesis involves sampling amniocytes. If the NIPT is high risk for trisomy 13, 18 or 21, then CVS is a reasonable option as the result is representative of the fetal karyotype in around 97% of cases.[9] Patients should however be counselled of the 3% risk of receiving a mosaic result that would need further confirmatory testing with amniocentesis. If NIPT is high risk for sex chromosome aneuploidy, then amniocentesis is recommended over CVS as the chance of CPM is higher.[9]

Our case illustrates the importance of pre-test counselling emphasising the limitations of prenatal screening test and alternative options. Patients should be aware of the possibility of a false negative screening test and the implications on the management of the pregnancy. Fetal anomaly screening scans and regular antenatal follow-up scans remain as a second line of assessment for these patients in detecting fetal anomalies that may trigger further invasive diagnostic testing. A delayed detection of fetal chromosomal abnormalities poses significant distress to parents deciding on late termination of pregnancy, and care issues for parents where abnormalities are only detected at birth. Parental karyotyping for assessment of recurrence risks should also be offered for post-pregnancy counselling. Lastly, clinicians should understand the basis of NIPT and its limitations such as in this scenario of TFM so as to allow appropriate counselling.

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Poh Ting Lim [1]*MBBS*, Liying Yang [1]*MRCOG*,
Wei Ching Tan [1]*MRCOG*

[1] Department of Obstetrics and Gynaecology, Singapore General Hospital, Singapore

Correspondence: Dr Poh Ting Lim, Department of Obstetrics and Gynaecology, Singapore General Hospital, Outram Road, Singapore 169608.
Email: pohting.lim@mohh.com.sg

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Prevalence of vitamin D deficiency and insufficiency in Malaysian infants

Dear Editor,

Vitamin D deficiency, a worldwide health problem, is also prevalent in tropical countries.[1] It is estimated that 15% of the world's population are either vitamin D deficient or insufficient.[1] In a study on the state of Kelantan in Malaysia (2010–2012), 60% of pregnant women were vitamin D deficient.[2] Maternal vitamin D deficiency predisposes infants to vitamin D deficiency especially if they are exclusively breastfed. The prevalence of vitamin D deficiency in Malaysian infants is unknown. We conducted a cross-sectional study to ascertain the prevalence and risk factors predisposing to vitamin D deficiency in Malaysian neonates.

We recruited term neonates (gestational age ≥37 weeks; aged 2 to 4 weeks) followed up for neonatal jaundice in a well-baby clinic from December 2016 to December 2017. Written informed consent was obtained from parents. Ethical approval was obtained (Ethics Number: 20161115-4600). No blood samples were obtained purely for the purpose of the study. We excluded neonates with the following: prematurity (gestational age <37 weeks), neonatal cholestasis (conjugated bilirubin >17mmol/L if total bilirubin <85mmol/L, or conjugated bilirubin >20% if total bilirubin >85mmol/L), infants who were on diuretics or vitamin D supplements, and infants with feeding difficulties. Infants whose mothers had renal, liver, thyroid and gastrointestinal disorders or taking anti-epileptic medications were excluded.

We collected data on age, gender, ethnicity, gestational and feeding history. Daily sun exposure of the infants was determined via a set of sunshine exposure behaviour in a questionnaire adapted from Barger and Heaney.[3] Blood was collected for liver function, serum 25-hydroxy vitamin D (25(OH)D) and bone profile tests. Serum 25(OH)D level was assayed using Siemens Advia Centaur Analyser, which has a within-run precision coefficient of variation (CV) of ≤8% and a total CV of ≤12%. Maternal vitamin D level was not assayed. We defined vitamin D status of the infants according to Munns et al.[4]—25(OH)D >50nmol/L as sufficient, 25(OH)D 30.0–50.0nmol/L as insufficient, and 25(OH)D<30.0nmol/L as deficient.

T-test and Mann-Whitney U test were used to compare the mean quantitative variables while the differences between mean qualitative variables were analysed with Pearson's chi-square or Fisher's exact test. A *P* value of <0.05 was considered statistically significant. For the ease of statistical analysis, infants with vitamin D insufficiency and sufficiency (non-deficient) were grouped together.

Of the 110 term neonates (mean age: 2.5 [±0.9] weeks; 60.0% males; Malay 70.0%, Chinese 20.9%, Indian 8.2%, other ethnicities 0.9%), 79.1% (n=87) were exclusively breastfed, including 80.5% (62/77) of the Malays and 75.8% (25/33) of the non-Malays (*P*=0.574). None of the 110 neonates had a serum vitamin D level of <20nmol/L; 47 (42.7%) were 20.1–30.0nmol/L, 33 (30.0%) 30.1–40.0nmol/L, and 11 (10.0%) 40.1–50.0nmol/L. Only 17.3% (n=19) were vitamin D sufficient. The overall mean (SD) serum vitamin D level of all neonates was 36.9 (±15.3) nmol/L. No correlation between serum calcium level and degree of vitamin D deficiency was observed. None of the neonates had clinical symptoms or signs of vitamin D deficiency.

On univariate analysis, the only factor significantly associated with vitamin D deficiency was a shorter duration of sunlight exposure (mean [±SD] duration of exposure, hour/week; deficient versus non-deficient: 2.00 [±1.40] vs 2.60 [±1.63], *P*=0.043).

Our results showing vitamin D deficiency and insufficiency is common in Malaysian neonates are consistent with studies from other tropical countries.[5] We did not find any correlation between exclusive breastfeeding and vitamin D deficiency, possibly due to the small number of study subjects and a high exclusive breastfeeding rate in the present cohort. Other authors have observed that exclusive breastfeeding without adequate sunlight exposure and vitamin D supplementation were risk factors for vitamin D deficiency in neonates.[6] It is likely that changes in lifestyle related to urbanisation, increased indoor activities and use of sunscreen have increased the prevalence of hypovitaminosis D in tropical countries, including pregnant mothers.

We found that the only significant risk factor for vitamin D deficiency was a shorter duration of sunlight exposure. A possible effective strategy to improve vitamin D level in the newborn is having adequate sunlight exposure. A study from India showed

Table 1. Factors associated with vitamin D deficiency in 110 Malaysian neonates

Factors	Total N=110	Vitamin D deficient (<30nmol/L) n=41	Vitamin D non-deficient (≥30nmol/L) n=69	*P* value
Sex, no. (%)				
Male	66 (60.0)	21 (51.2)	45 (65.2)	0.147
Female	44 (40.0)	20 (48.8)	24 (34.8)	
Ethnicity, no. (%)				
Malay	77 (70.0)	29 (70.7)	48 (69.6)	0.897
Non-Malay	33 (30.0)	12 (29.3)	21 (30.4)	
Gestational age, median (IQR), weeks	38.0 (0)	38.0 (0)	38.0 (2.0)	0.715
Birth weight, mean (SD), g	2920 (456)	2940 (467)	2907 (451)	0.715
Birth weight <2500g, no. (%)	17 (15.5)	6 (14.6)	11 (15.9)	0.854
Feeding method, no. (%)				
Exclusive breastfeeding	87 (79.1)	35 (85.4)	52 (75.4)	0.212
Non-exclusive breastfeeding	23 (20.9)	6 (14.6)	17 (24.6)	
Feeding frequency per day, median (IQR)	8.0 (3.0)	8.0 (4.0)	8.0 (3.0)	0.832
Current weight, median (IQR), g (N=107)	3420 (715)	3390 (820)	3430 (639)	0.873
Weight gain from day 14, median (IQR), g/day (N=107)	73 (83)	66 (90)	92 (96)	0.136
Laboratory parameters, median (IQR)				
ALP, mean (SD), U/L	287.00 (100.14)	289.15 (113.06)	285.72 (92.47)	0.863
Intact parathyroid hormone, pmol/L (n=109)	2.4 (2.6)	2.4 (3.8)	2.3 (2.2)	0.610
Calcium, mmol/L	2.57 (0.16)	2.54 (0.18)	2.58 (0.15)	0.178
Phosphate, mmol/L	2.25 (0.38)	2.23 (0.21)	2.25 (0.43)	0.757
Child sun exposure, mean (SD), hours/week	2.38 (1.57)	2.00 (1.40)	2.60 (1.63)	0.043[a]

ALP: alkaline phosphatase; IQR: interquartile range; SD: standard deviation
[a] $P<0.05$

that a minimum of 30 minutes weekly sunlight exposure in the afternoon between 10am and 3pm, over 40% of the body area with the infant clothed in diapers in prone position for at least 16 weeks, was all that was required to achieve sufficient vitamin D levels by 6 months of age.[7] In the present study, the mean duration of sunlight exposure for the whole cohort was 2.38 hours/week, but the 19 neonates who had sufficient vitamin D (>50nmol/L) had a mean duration of 3.21 (1.39) hours/week of sunlight exposure. Unfortunately data on the body area and the timing of day the neonates were exposed to sunlight were unavailable.

Other possible strategies to prevent neonatal vitamin D deficiency include supplementing high-dose vitamin D (4,000 or 6,400IU/day) to lactating mothers with limited sunlight exposure,[8] or supplementing vitamin D to all newborn babies irrespective of their breastfeeding status. Selective supplementation of vitamin D to breastfed infants,[9] however, should be avoided as it is associated with concerns that lactating mothers would switch to infant formula due to the potential negative perception with breastfeeding.[10]

Drawbacks of the present study include a lack of maternal vitamin D level and the small sample size. Data on breastfeeding jaundice, caused by inadequate breastmilk leading to inadequate vitamin D intake in the first few days of life, were also not collected. Finally, data on phototherapy for neonatal jaundice, which may increase the level of vitamin D in babies with low levels of vitamin D, were unavailable.

In summary, in this cohort of Malaysian neonates, we found a very high prevalence of vitamin D deficiency and insufficiency. Supplementing pregnant and lactating mothers, and all newborn infants with vitamin D as well as ensuring adequate sunlight exposure a few months after birth are possible strategies to prevent neonatal vitamin D deficiency.

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Way Seah Lee [1]*FRCPCH*, Sean Yee Wong [1]*MBBS (Malaya)*, Shin Yee Wong [1]*PhD*, Zhong Ling Koay [1]*MBBS (Malaya)*, Nong Sofea Ku Safuan [2]*MBBS (Malaya)*, Zhi Heng Sam [2]*MPaeds (Malaya)*, Muhammad Yaziud Jalaludin [1]*MPaeds (Malaya)*, Choong Yi Fong [1]*FRCPCH*, Lucy CS Lum [1]*MRCP (UK)*

[1] Department of Paediatrics, Faculty of Medicine, University of Malaya, Malaysia
[2] Department of Paediatrics, University Malaya Medical Centre, Malaysia

Correspondence: Prof Way Seah Lee, Department of Paediatrics, Faculty of Medicine, University of Malaya, 59100 Kuala Lumpur, Malaysia.
Email: leews@um.edu.my

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The "Jeff Cut": A simple innovation to minimise up-riding sleeves of protective gown

Dear Editor,

Personal protective equipment (PPE) including the N95 mask, face shield, cap, splash-resistant gown and gloves are worn by frontline healthcare workers for various duties in the care of patients with communicable diseases like COVID-19.[1,2] PPE is also worn by ancillary staff such as security personnel, porters, medical transport crew and cleaning staff who come into direct contact with infectious patients.

For protection to be optimal, the equipment has to fit properly. Otherwise, there will be breaches in protection leading to potentially serious consequences. For example, all personnel undergo a rigorous N95 mask fitting exercise before they are deployed to care for potentially infectious individuals.

The protective gowns that healthcare and other support workers in Singapore don during the COVID-19 pandemic[3] may not be well-fitted to all individuals as the gown comes in 1 standard size. Cuffs that are too loose coupled with ill-fitting non-sterile gloves will result in up-riding of sleeves, leading to exposure of bare skin over the wrist, as exemplified in Fig. 1A.

Our medical team was deployed to a foreign worker dormitory from 12 April to 20 July 2020 under the National Healthcare Group's support of the dormitory medical operations during the COVID-19 outbreak in Singapore.[4] This deployment was part of the nationwide effort to provide adequate care to the huge number of infected foreign workers.[5] At the end of the deployment period for our medical team on 21 July 2020, there was a cumulative total of 45,260 dormitory residents out of a total of 48,035 people who were reported as positive for COVID-19 in Singapore.[7]

A doctor from our team shared a technique to overcome this up-riding of the sleeve—a technique that was inspired by the design of commercially available arm sleeves for sports such as riding, which features a slot for the thumb. We term it the "Jeff Cut", and outline the following steps to achieve it.

Step 1. Before the gown is worn, cut a 1cm slit at the midpoint of the non-seam side of the white cuff (Fig. 2).

Step 2. Don the splash-resistant gown and the non-sterile glove. The white cuff should cover the inner glove and the thumb should go through the slit (Figs. 3A and B). The first glove can be worn before or after donning the gown, depending on personal preference.

Step 3. Don the second glove to cover the junction (Figs. 3C and D).

The up-riding of the sleeve is now prevented by the grip of the cuff anchored at the base of the thumb as

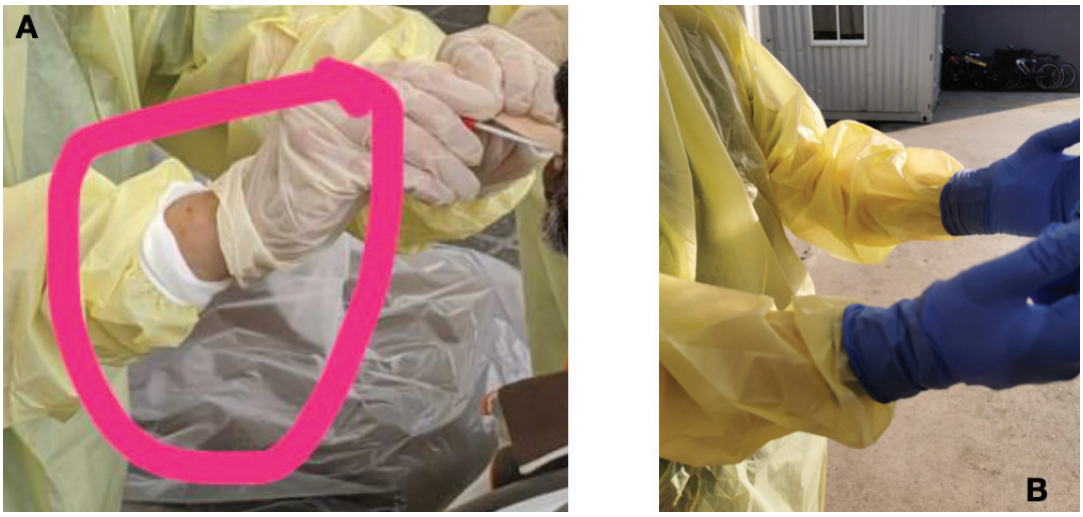

Fig. 1. (A) Up-riding of gown sleeve during a swabbing procedure. (B) Prevention of up-riding of sleeve suitable for any work posture.

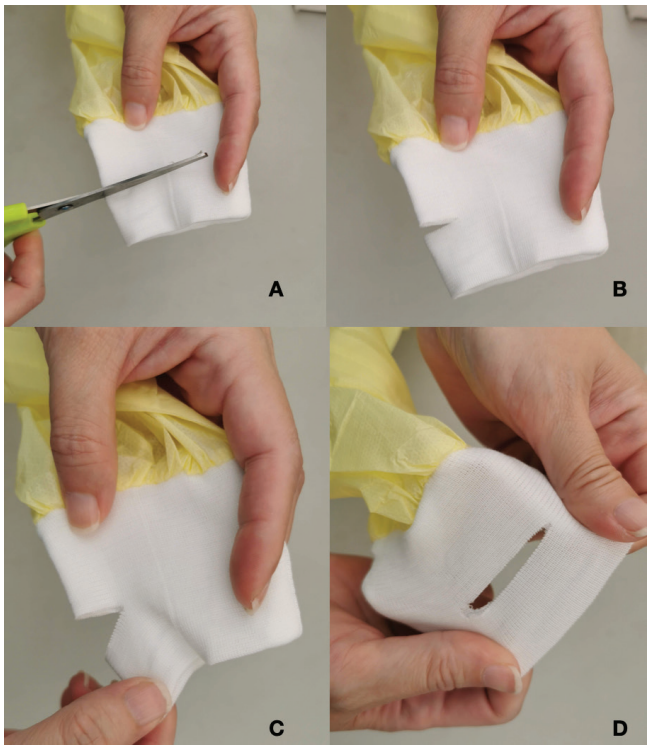

Fig. 2. Step 1 for the "Jeff Cut".

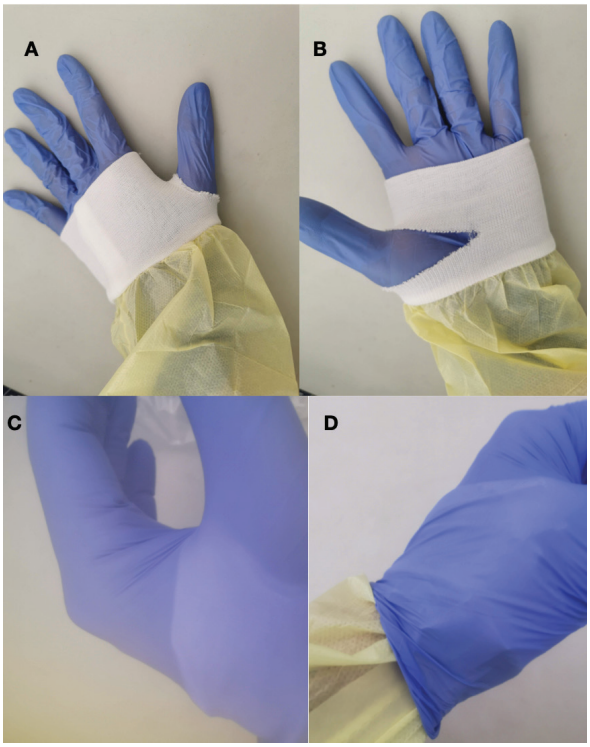

Fig. 3. Steps 2 and 3 for the "Jeff Cut".

it emerges through the created slit (Fig. 1B), thus preventing a breach in the protective barrier.

In our experience, as the cuff was made of an elastic material, it did not tear easily—as long as the slit was made away from the seams—and we did not encounter any inadvertent exposure.

This method is simple and quick to execute. It utilises and enhances the safety of preexisting equipment and we recommend it to personnel who are required to don this in the course of their work.

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Jeffrey Kah Leong Lum [1] *MBBS (S'pore)*,
Qi Wei Fong [2] *MBBS (S'pore)*, Shipei Law [2] *MD*,
Erik Sze Wee Ang [3] *FRCS (Glasg)*

[1] OMF International, Singapore
[2] National Healthcare Group Polyclinics (Geylang Polyclinic), Singapore
[3] Yap & Ang Surgical Associates, Farrer Park Medical Centre, Singapore

Correspondence: Dr Erik Sze Wee Ang, Yap & Ang Surgical Associates, 1 Farrer Park Station Road, #09-09 Farrer Park Medical Centre, Singapore 217562.
Email: angplasticsurgery@gmail.com

LETTER TO THE EDITOR

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Health professions education in pandemics and epidemics: A proposed framework for educators

Dear Editor,

The COVID-19 pandemic has disrupted healthcare systems and health professions education (HPE). There are few frameworks to help educators manage HPE before, during and after pandemics and epidemics. We developed a crisis management framework which draws from diverse theories to emphasise preparedness, leadership, stakeholder perceptions and organisational learning to provide guidance.[1] Bundy et al. define crisis management in 3 stages: before, during and after a crisis. This allows detailed response planning.[1] We adapted it to derive a framework for HPE in pandemics and epidemics (HPEPE). This framework is relevant as it reminds educators to not only focus on the present pandemic, but also the steps to take before and after the crisis to learn and prepare further for the future.

We performed a systematic literature review and identified 208 publications relevant to HPEPE. We distilled the key points, grouped them into 6 elements, reaffirmed representativeness, then mapped them back to the crisis management framework.[1] We describe 6 elements, comprising 6 Cs—curriculum, continuing professional development (CPD), communications, courage, communities and continuity—and demonstrate their relevance to HPEPE and crisis management stages. Table 1 illustrates how our proposed framework was applied during the COVID-19 pandemic in the Singapore context.

Curriculum. Swift curriculum adaptation is essential in HPEPE.[2-4] Hybrid models, combining remote and on-site teaching and training could be adopted. Similarly, to minimise risk of exposure, alternatives could be used for assessments, such as electronic proctoring for written examinations, or use of simulated patients and videoconferencing for clinical assessments. Virtual selection interviews and even graduation ceremonies could be conducted online. Investing in technology resources (high-speed Internet access, video-production facilities, videoconferencing software and learning management systems[5]) and upskilling faculty to thoughtfully use technology[5] are crucial for HPEPE. While technological innovations are welcome, educational principles should guide design and implementation,[5] with emphasis placed on programme evaluation. Context must be considered during implementation. Uptake of technology varies depending on resource settings,[3] and increased technology use may exacerbate resource disparities between learners, regions or countries, leading to disenfranchised learners. Education systems should thus provide additional resources as appropriate.

During pandemics, important but less visible curriculum elements (including leadership skills, ethics, decision-making in uncertainty, resource management, adaptability and professionalism) may be opportunistically and authentically taught using case discussions, reflection and role modelling.[6,7] Post-pandemic, schools should re-examine the teaching and integration of public health, epidemiology and infection control preparedness[6,7] in their curricula during curricular review.

CPD. During pandemics, adapting CPD for healthcare professionals is vital for just-in-time learning and up-to-date practice as pandemic-related medical knowledge evolves rapidly.[3] Frontline healthcare professionals should educate themselves through trustworthy CPD resources and international resources (e.g. online resources by the US Centers for Disease Control and Prevention and the World Health Organization) for accessible and up-to-date information. Post-pandemic CPD might embrace a wider range of pandemic-related topics such as communications, technology-enhanced learning, disaster medicine, or psychological effects of the pandemic on individuals or societies.

Communications. Good communications applies equally to crisis management[1] and HPEPE. Communications is important in all stages of HPEPE, but particularly critical during the pandemic for internal and external stakeholders.[6,8] Two-way communications for internal stakeholders (learners, faculty and administrators) serve to provide information, receive feedback, offer reassurance and maintain morale; technology can extend the reach of these communications. Communications allow engagement, build trust and may mitigate the sense of isolation. For external stakeholders (healthcare institutions or government/regulatory bodies), communications allow for effective coordination of student/resident placements, planning of curricular changes and crafting of education-related policies. Before the next pandemic, planning for defined communications protocols and teams can be done.[2]

Table 1. Application of the framework for health professions education in pandemics and epidemics (HPEPE) at institutional and national levels during the COVID-19 pandemic

	Institutional level activities and outcomes	National level activities and outcomes
Curriculum	1. Creation of new neurology e-lecture series for students from 3 medical schools, blueprinted to national curriculum 2. Use of teleconferencing (Zoom) for neurology residents for: a. Teaching b. Assessments: case-based discussions and assessments of entrustment in entrusted professional activities 3. Survey of neurology residents to assess impact of COVID-19 pandemic on their teaching, training and supervision 4. Upgrading of Internet routers, purchase of software licences and laptops for digital education	1. Several Ministry of Health advisories were issued on training for all health professions that provided guidance for curriculum, especially in learning and assessment (formative or summative), aiming to balance workforce competency, student safety and sustainability 2. Advisory from Ministry of Health covering principles and conduct of summative examinations during COVID-19 3. Review of coverage of infection control in curriculum of all health professions (medical, nursing, allied health) 4. Modified objective structured clinical examination (OSCE) for Singapore neurology exit examination, which was conducted in accordance to advisories above
Continuing professional development (CPD)	(Creation of national level CPD resources)	1. Creation of national level CPD resources: a. Ministry of Health (https://www.moh.gov.sg/covid-19/faqs) b. Saw Swee Hock School of Public Health, National University of Singapore (https://sph.nus.edu.sg/covid-19/webcasts/) c. Academy of Medicine, Singapore (https://www.ams.edu.sg/policy-advocacy/covid-19-resource-page)
Communications	1. Frequent communications to faculty by institute's Education Director during COVID-19 pandemic (initially sent weekly, later monthly) covering education-related issues relevant to the pandemic 2. Meetings by Programme Directors with neurology and neurosurgery residents to update residents, address concerns and co-create solutions 3. Care packages given to all staff, with signed note from institutional Medical Director	1. Regular communications by Ministry of Health with multiple stakeholders: a. Medical, nursing, allied health schools' leadership b. Students from schools above c. Postgraduate training programmes and Designated Institutional Officers Policies adjusted based on stakeholder feedback 2. Message from Health Minister to all healthcare workers in Singapore (https://www.moh.gov.sg/hpp/all-healthcare-professionals/news/NewsArticleDetails/minister-s-message-to-healthcare-workers)
Courage	1. Healthcare staff volunteered for patient care in COVID-19 wards and community care facilities 2. Faculty trialed new educational methods, such as Zoom-based teaching and assessments, and Zoom-based team-based learning	1. Ministry of Health made difficult but necessary decisions, balancing safety with learning to: a. Allow students back to clinical areas for focused clinical learning with appropriate precautions b. Continue summative examinations with precautions, and allow newly graduated doctors to start work earlier c. Set boundaries and reject calls from some faculty asking for students to be posted to areas with higher risk of COVID-19 infection to ensure student safety 2. Postgraduate clinical examinations reviewed by Ministry of Health and conducted using teleconferencing and other safe-distancing precautions
Communities	1. Staff support hotline 2. Continuation of existing faculty development programme, "Fireside Chat", using Zoom teleconferencing to build community of practice 3. Academic conference in October 2020 on medical humanities during COVID-19 pandemic	1. Faculty development webinar on technology-enhanced learning held via Zoom in April 2020 by the Academy of Medicine, Singapore, bringing health professions education community together 2. Singapore government's initiative to highlight voices from Singaporeans speaking about the pandemic (https://www.singaporetogether.gov.sg/reflect/stories)
Continuity	1. Continuation of funding support for conferences (both scientific and educational) 2. Ongoing revision of institutional continuity plan, including educational aspects 3. Ongoing revision of neurology residency curriculum and structure to be more pandemic-resilient	1. Ministry of Health's existing standards for medical schools revised to include need for education continuity 2. Archiving documents and decisions made during the pandemic by government 3. Plans for post-pandemic review and planning a whole-of-government response to the next pandemic

Courage. This is important in all stages of a pandemic. Courageous behaviours take many forms and can be displayed by both individuals and organisations.[7] As individuals, faculty members become role models by courageously staying true to their ethical duty to provide care. Such behaviours reinforce professional values for junior learners and facilitate the formation of professional identity. In bravely embracing lifelong learning, faculty can learn new technology skills, while students/residents can adopt new roles and responsibilities by becoming peer teachers or preparing CPD updates.

As organisations, schools and training programmes need to restructure curricular components and make difficult curricular decisions during pandemics. Courageous leadership is needed to make necessary sacrifices. Schools may need to graduate students earlier to supplement the workforce.[6] This requires strong leadership to address student/parental concerns, while making the necessary curricular adaptations to ensure that critical competencies are achieved before graduation. Post-pandemic reviews are also important to courageously acknowledge failures and also celebrate successes. Key learning points should be documented.

Communities. During and after pandemics, our learners experience fear and isolation. Healthcare communities can provide much-needed emotional support to learners.[7] The educator community can also support learners using a variety of approaches to encourage self-care, constructivist growth and professional development.[9] Our learners, as fledgling members of a healthcare community of practice,[4] can assist in clinical care during pandemics. This facilitates acculturation into the community of practice via legitimate peripheral participation that forms their professional identity.

Continuity. The crisis management literature emphasises the utility of business continuity plans. As an example, higher education maintains analogous academic continuity plans that can be adopted and developed for HPE systems.[8,10] A coordinating taskforce should be formed once the crisis is recognised to ensure continuity of the education mission, which is contingent upon the first 5 elements in our framework. If additional resources are needed to support these preceding elements, organisations should acquire them as a demonstrated commitment to education continuity. Post-pandemic, the continuity plans should be refined after review, and can be also stress-tested and strengthened via simulation.

Our proposed HPEPE framework emphasises principles and critical influences. As it is new, it has yet to be successfully implemented in full throughout all stages of a pandemic. We also acknowledge that the framework has only been used in a healthcare system in Singapore. Therefore, context needs to be considered in implementation. Future studies on application of this framework will help with validation and refinement.

Epidemics and pandemics will undoubtedly recur. A framework will help educators manage these crises, and plan responses to current and future crises. In this way, HPE becomes an active enabler of learning and resilience for students, faculty, and the health and education systems.

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Nigel Choon Kiat Tan [1]*FRCP*,
Mabel Anne Mei Poh Yap [2]*PhD*, Kevin Tan [1]*MRCP*

[1] Office of Neurological Education, Department of Neurology, National Neuroscience Institute, Singapore
[2] Professional Training and Assessment Standards Division, Ministry of Health, Singapore

Correspondence: A/Prof Kevin Tan, Office of Neurological Education, Department of Neurology, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: kevin.tan@singhealth.com.sg

LETTER TO THE EDITOR

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Permanent visual impairment in dengue fever following platelet transfusion: A series of 5 cases

Dear Editor,

Dengue fever (DF) is endemic in India and Singapore, and also causes frequent epidemics. Dengue virus belongs to the *Flavivirus* genus of the family *Flaviviridae* and its members include the 4 antigenically related serotypes of dengue virus (DENV 1–4). It is transmitted to humans through the bite of infected female *Aedes aegypti* mosquitoes, and is characterised by an acute onset of fever associated with symptoms of malaise, headache, muscle aches, retro-orbital pain, joint pain, abdominal discomfort, rash and bleeding diathesis.

Thrombocytopaenia, a major feature of DF, results from decreased platelet production from bone marrow suppression or increased platelet destruction. Prophylactic platelet transfusion is a common practice to prevent clinical bleeding in adults with dengue and thrombocytopaenia. However, transfusion of blood products may be detrimental to patients given the risks of fluid overload, transmission of infectious diseases and transfusion reactions.

Ocular findings associated with DF are subconjunctival haemorrhage, vitreous haemorrhage, retinal haemorrhage, cotton wool spots, central and branch retinal artery occlusion, central scotoma, papilloedema, optic neuropathy, retinal vasculitis, retinitis, retinal pigment epithelium mottling, foveolitis, choroidal effusion, exudative retinal detachment, anterior uveitis, endogenous endophthalmitis and panophthalmitis.[1]

Panophthalmitis is a rare complication, with only 7 cases reported following platelet transfusion in DF in the literature.[2-7] We report 5 cases of unusual complication of DF causing panophthalmitis, leading to rapidly progressive and painful visual loss shortly after receiving platelet transfusion. These 5 cases were referred from 5 different centres to our tertiary eye centre for ocular evaluation. As we are not aware of the prevailing practices in those centres, we are unable to comment on the rationale for platelet transfusion. These 5 cases occurred over a 6-month period from July to December 2019. Table 1 summarises these 5 cases.

Platelets are vulnerable to bacterial growth as they are stored at room temperature for up to 5 days, whereas other blood components are refrigerated or frozen. Gram-positive bacteria (e.g. *Staphylococcus* sp.) found on the skin are the most frequent contaminants of platelet units. Gram-negative bacteria (e.g. *Serratia, Enterobacter* or *Salmonella* sp.) account for more severe and fatal infections, and are attributed to donor bacteremia or contamination during product processing.[8] Kuehnert et al. estimated that the rate of transfusion-transmitted bacteremia (in events/million units) was 9.98 for single-donor platelets, 10.64 for pooled platelets and 0.21 for red blood cell units.[8] The US Food and Drug Administration requires only fatal complications of blood collection or transfusion to be reported. Antimicrobials and anti inflammatory agents in transfused populations may account for the partial masking of symptoms that are normally associated with sepsis.[8]

A study by Lee et al. on adult dengue patients in Singapore found that the occurrence of internal bleeding after platelet transfusion was slightly more common albeit statistically insignificant.[9] More mucosal bleeding after platelet transfusion in transfused patients (18.5%) versus non-transfused patients (9.3%) was reported. In the transfused patients, platelet count increased significantly more the next day after platelet transfusion than in the non-transfused patients followed by a slow increase over the few days. Among the transfused patients, liver enzyme levels (aspartate aminotransferase and alanine aminotransferase) were found to be higher, 2 patients developed liver failure and 1 patient developed renal failure.[9]

Studies in India showed that acute respiratory distress syndrome, fever, longer duration of fever, longer duration of hospitalisation and slower recovery of platelets were more common in transfused patients compared to the control group.[10]

Approaches to reduce the incidence of transfusion-transmitted bacterial infection include expansion of donor screening, improved donor skin antisepsis, discarding an initial aliquot of donated blood to reduce skin contaminants, limitation of component storage time or lowering storage temperature, diagnostic screening of components and photochemical decontamination.[8]

Frequency of blood component bacterial contamination associated with transfusion reaction (the BaCon Study)[8] was initiated to better estimate their occurrence. Results showed no significant

Table 1. Summary of our 5 cases

Case no.	Age/sex	Symptoms	Systemic treatment	Interval between fever and ocular symptoms	Ocular symptoms	Ocular signs at presentation	Systemic investigations	Ocular imaging (B-scan)	CT/MRI findings	Treatment
1	26/male	Fever (5 days), bleeding from gums	Platelet transfusion, IV methylprednisolone	5 days	Sudden decrease in vision in BE associated with pain	BE: NPL, severe proptosis, subconjunctival haemorrhage, corneal blood staining, total hyphaema, high digital IOP, restricted ocular motility	Dengue NS1 positive, platelet count of 16,000/mm^3	Vitreous debris, thickening of the scleral coats, with fluid in Sub Tenon's space	CT of orbit: vitreous haemorrhage with mild thickening of ocular coats. RE: a focal thinning of ocular coat on nasal aspect with impending rupture was visible	Intravenous antibiotics and anti-glaucoma agents
2	30/male	Fever (4 days)	Platelet transfusion (3 units)	4 days	Pain and sudden loss of vision in RE	RE: NPL, severe proptosis, subconjunctival haemorrhage, adherent leucoma, total hyphaema, high digital IOP, restricted ocular motility. LE: WNL	Dengue NS1 positive, platelet count of 12,000/mm^3	Thickening of the scleral coats, with fluid in Sub Tenon's space in RE	MRI of orbit: deformed globe with deformed anterior chamber. Lens was subluxated thickened globe wall. Vitreous haemorrhage was present. Peribulbar inflammatory soft tissue was present with thinning of the globe wall on temporal aspect with epibulbar/episcleral abscess collection with impending rupture/ ruptured globe	Intravenous antibiotics and anti-glaucoma agents
3	55/female	Fever, nausea, abdominal pain, generalised weakness	Platelet transfusion, IV antibiotics, PPI, anti-emetics, steroids and other supportive measures	2 weeks	Sudden onset pain, swelling and decrease in vision in RE	RE: PL, eyelid oedema, orbital swelling, hazy cornea, organised hyphaema, very shallow AC, ocular motility restricted. LE: WNL	Dengue NS1 positive	Multiple hyperdense dot echoes in vitreous cavity, severe choroidal thickening, positive T-sign	MRI of brain and orbit with contrast: right-sided proptosis with inflammatory changes in retro-orbital soft tissues. Associated preseptal oedema. Thickening of RE globe wall. Periscleral inflammatory changes present	Tapering oral steroids

Table 1 Summary of our 5 cases (Cont'd)

Case no.	Age/sex	Symptoms	Systemic treatment	Interval between fever and ocular symptoms	Ocular symptoms	Ocular signs at presentation	Systemic investigations	Ocular imaging (B-scan)	CT/MRI findings	Treatment
4	45/male	Fever, generalised weakness	Platelet transfusion, IV fluids	5 days	Sudden onset pain and redness in BE	RE: NPL, LE: PL, BE: dilated episcleral vessels, conjunctival congestion, opaque cornea, IOP RE: 28mmHg, LE: 20mmHg	Dengue NS1 positive	RE: subretinal moderate to high reflective echoes, suprachoroidal echoes, LE: thickening of the scleral coats, with fluid in Sub Tenon's space	MRI: bilateral chorioretinitis with retro-orbital oedema	BE lensectomy and vitrectomy, antibiotics, steroids
5	15/male	Fever (1 week), vomiting, giddiness	Platelet transfusion, IV antibiotics, IV fluids	6 days	Sudden onset pain and swelling in RE	RE: NPL, RE: proptosis, lid oedema, conjunctival congestion, corneal blood staining, hyphaema, hypotonous	Dengue NS1 positive, eye swab and blood culture (no growth)	RE: deformed globe, posterior wall thickening and oedematous periorbital soft tissue swelling, subtle internal echoes in posterosuperior aspect of globe suggesting abscess	MRI: RE with thickened ocular coats, abscess in orbit, thickening in preseptal and periorbital soft tissues indicating panophthalmitis of RE	Intravitreal antibiotics, topical steroids, RE evisceration

AC: anterior chamber; BE: both eyes; CECT: contrast enhanced computed tomography; CT: computed tomography; IOP: intraocular pressure; IV: intravenous; LE: left eye; MRI: magnetic resonance imaging; NPL: no perception of light; NS1: nonstructural protein 1; PPI: proton pump inhibitor; PL: perception of light; RE: right eye; VH: vitreous haemorrhage; WNL: within normal limits

difference between the rates of transfusion-transmitted bacterial infection associated with single donor platelets and those associated with pooled platelets.[11]

Most DF-related ocular involvements are limited to the posterior segment, and manifest in the form of retinal vasculitis, retinitis, macular oedema or optic neuropathy. Endogenous endophthalmitis have been reported in DF and following platelet transfusion.[5] Panophthalmitis associated with DF has been rarely reported.[1]

Panophthalmitis, a rare complication of DF, is an acute inflammation of all the coats of eyeball including intraocular structures. In normal circumstances, the blood ocular barrier provides a natural resistance against invading organisms. Panophthalmitis/endophthalmitis may result in secondary to inflammatory or immune response to dengue virus; it may also lead to microorganisms crossing the blood ocular barrier to cause septic foci in the retina, which then spreads to the vitreous and anterior segments. Disintegration of the endothelial cells caused by antibodies against nonstructural protein 1 (NS1) antigen facilitates direct entry of the bacteria into the uveal and retinal circulation, causing septic foci and secondary endophthalmitis.

Five of the previous 7 published cases of dengue panophthalmitis had history of platelet transfusion. Five cases had unilateral involvement and 2 had bilateral involvement. The vision could not be salvaged in any of the affected eyes. Microorganisms isolated from the eye swab included gram-positive cocci with no growth, and *Bacillus cereus* was isolated from the eviscerated sample of the eye.[4,5]

In our series of 5 cases, the patients developed panophthalmitis shortly after receiving platelet transfusion and were referred to our tertiary eye centre. Average onset duration of complication was 5.5 days after transfusion (range of 4–7 days). Three cases had unilateral and 2 bilateral involvements respectively.

In 2 of our cases the presentation of panophthalmitis was initially atypical, hence an initial diagnosis of retrobulbar haemorrhage was made before referring to our centre. Both patients on ultrasound B scan had vitreous debris and thickening of the scleral coats, with fluid in Sub Tenon's space in the affected eyes and were blind. All the patients had undergone blood culture before referral to us with no reported growth of pathological organisms. At our tertiary eye centre, Gram's stain and potassium hydroxide mount and culture of the conjunctival swab did not show any microorganisms in all the 5 cases. Cases 4 and 5 underwent vitreous sampling and no growth of pathological organism was detected.

The crux in the management of dengue patients is maintaining good hydration, monitoring for any overt bleeding, alongside periodic checking on peripheral pulses and blood pressure with serial estimation of haematocrit and platelet counts.[12] Supportive care consists of bed rest, fluid therapy and fever and pain relief medications.

The risk of transfusion-related adverse effects such as anaphylaxis, transmission of blood-borne infections and acute lung injury always exists with transfusion of blood products, including platelets. Prophylactic platelet transfusion has no added advantage over supportive care. The lack of efficacy of prophylactic platelet transfusion, combined with higher risk of adverse events, leads us to discourage the practice of routine prophylactic platelet transfusion in adult dengue.

Clinicians and ophthalmologists should be aware of this vision-threatening complication of DF for early recognition and prompt treatment. Vision could not be salvaged in any of the affected eyes in our 5 cases. Therefore, caution should be exercised while considering prophylactic platelet therapy in patients with DF.

Ophthalmological examination should be routinely done in all patients with DF. Patients with dengue who present with endophthalmitis or panophthalmitis should be aggressively managed, and samples (aqueous/vitreous or eviscerated material) should be subjected to standard microbiological tests to investigate for offending organisms to tailor the therapy accordingly.

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Srinivasan Sanjay [1]*MRCS (Edin)*, Sameeksha Agrawal [1]*MS (Oph)*, Pooja Jain [2]*MS (Oph)*, Padmamalini Mahendradas [1]*DNB (Oph)*, Ankush Kawali [1]*DNB (Oph)*, Naren Shetty [3]*MS (Oph)*

[1] Department of Uveitis and Ocular Immunology, Narayana Nethralaya, Bengaluru, India
[2] Department of Cornea, Narayana Nethralaya, Bengaluru, India
[3] Department of Cataract and Refractive Lens Services, Narayana Nethralaya, Bengaluru, India

Correspondence: Dr Srinivasan Sanjay, Department of Uveitis and Ocular Immunology, Narayana Nethralaya, 121/C Chord Road, Rajajinagar 1st R block, Bengaluru 560010, Karnataka, India.
Email: sanjaygroup24@gmail.com

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Bradycardia in a patient with lung cancer

A 70-year-old man presented with fatigue and dyspnea. He denied any chest pain, orthopnea, pedal oedema, dizziness and syncope. He had a history of hypertension, hyperlipidaemia and minor coronary artery disease identified on coronary angiography performed a year ago. He also had metastatic squamous cell lung carcinoma and last received carboplatin, paclitaxel and a second cycle of pembrolizumab a month before presenting. His blood pressure was 115/55mmHg, pulse rate was 38 beats/min and oxygen saturation was 96% on room air. He was afebrile. Laboratory results revealed markedly raised troponin I of 18,266ng/L (normal <17.4ng/L), N-terminal pro-brain natriuretic peptide (NT-proBNP) of 8140pg/mL (normal <241pg/mL) and creatine kinase of 4789U/L (normal 30–350U/L). An electrocardiogram (ECG) was obtained (Fig. 1).

The ECG demonstrates complete heart block with a ventricular escape rate of 31 beats/min. There are irregular PR intervals with constant P-P and R-R intervals consistent with atrioventricular dissociation. The broad QRS complexes suggest an infra-Hisian escape rhythm with the level of block below the bundle of His. The patient's baseline ECG showed normal sinus rhythm with narrow QRS complexes.

What is the most likely cause of this patient's complete heart block given his medical history and clinical presentation?

A. Acute myocardial infarction
B. Beta blocker therapy
C. Myocarditis
D. Lyme disease
E. Degeneration of conduction system

Clinical course. The absence of symptoms of myocardial ischaemia and/or ST segment changes on the ECG makes option A unlikely. A careful review of the patient's medication list did not reveal atrioventricular nodal blocking agents, ruling out option B as an aetiology. Travel history was negative for Lyme disease-endemic areas, and in the absence of typical systemic symptoms and physical signs, option D is highly unlikely. Option E is possible given the patient's age; however, given his past medical history, other reversible aetiologies need to be evaluated for in this clinical context.

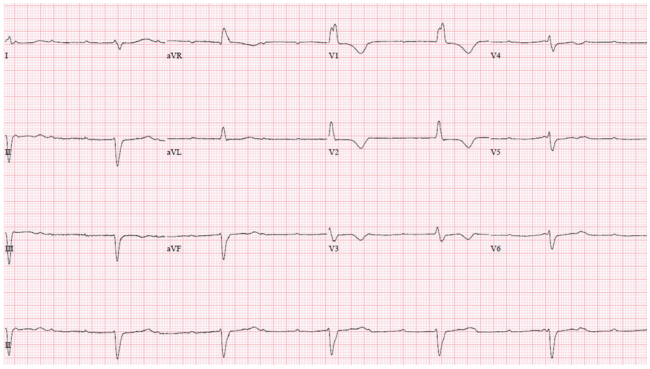

Fig. 1. Twelve-lead electrocardiogram (ECG) at presentation.

The patient was transferred to the coronary care unit for insertion of a temporary pacing wire. Transthoracic echocardiogram (TTE) revealed global left ventricular hypokinesia with a left ventricular ejection fraction of 42%. This was a drop from 60% demonstrated on a TTE performed prior to the start of chemotherapy treatment. Serum aldolase was raised at 71.3U/L (normal <7.6U/L). The cardio-oncology team was consulted and the diagnosis was refined to immune-related adverse events (irAEs) from pembrolizumab, an immune checkpoint inhibitor (ICI), resulting in complete heart block secondary to myocarditis (option C). There was also concurrent ICI-mediated myositis. The patient underwent an endomyocardial biopsy and was treated with empirical high-dose intravenous methylprednisolone 1gram/day for 5 days before conversion to oral prednisolone. Serum cardiac biomarkers and muscle enzyme levels significantly reduced with steroid therapy. The patient experienced an episode of mild fluid overload that improved with oral diuretics. However, he required a permanent pacemaker implantation as he remained pacing dependent despite a week of steroid treatment. Endomyocardial biopsy showed inflammatory cell infiltration and myocardial necrosis with increased programmed cell death-ligand 1 (PD-L1) immunoexpression, confirming the diagnosis of ICI-mediated myocarditis (Fig. 2). The patient improved after pacemaker implantation and was discharged stable.

Discussion. ICI-mediated myocarditis is a rare but notable cause of complete heart block which may be misdiagnosed. Common causes of complete heart block include degeneration of the conduction system, acute myocardial infarction and atrioventricular nodal

Answer: C

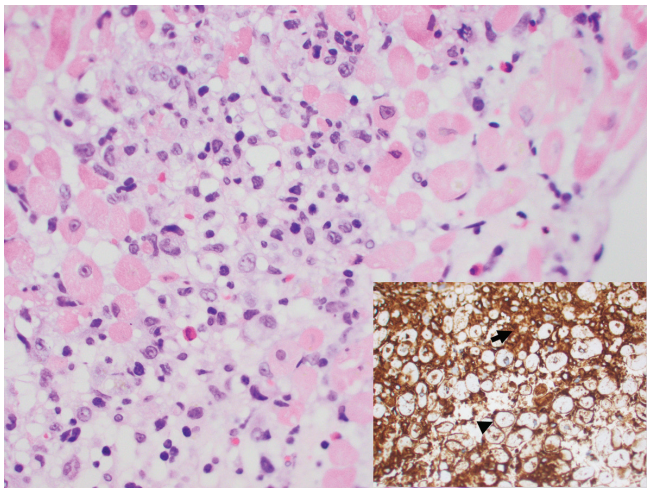

Fig. 2. Photomicrograph of endomyocardial biopsy showing area of myocardial necrosis with inflammatory infiltrate comprising histiocytes, lymphocytes and eosinophils. Inset: Positive immunoexpression of PD-L1 in inflammatory cells (arrow) and cardiomyocytes (arrowhead). (Main image: haematoxylin and eosin stain. Inset: immunoperoxidase stain. Both images: magnification x400.)
PD-L1: programmed cell death-ligand 1

blocking agents. Management involves addressing the underlying cause and supportive treatment via advanced cardiac life support algorithms.

ICIs are an emerging class of cancer therapy agents used in the treatment of solid and haematological malignancies. One example of an ICI is pembrolizumab, which is a programmed cell death protein 1 (PD-1) inhibitor. Multiple unique irAEs from ICI therapy have been described. They typically occur after 2–3 cycles of ICI therapy, and most commonly involve the skin and gastrointestinal system.[1] Although cardiac irAEs are rare with an incidence of approximately 1%,, they are associated with high mortality of 25–50%.[2] Cardiac irAEs include myocarditis, atrioventricular block, ventricular dysrhythmias, heart failure and pericarditis.[2] The diagnosis of ICI-mediated myocarditis is supported by elevated troponins, conduction abnormalities or ischaemic changes on ECG, left ventricular dysfunction or wall motion abnormalities on TTE, and myocardial oedema or late gadolinium enhancement on cardiac magnetic resonance imaging (MRI).[3] Endomyocardial biopsy is the gold standard for diagnosis, and findings include inflammatory cell infiltration and myocardial necrosis. Up-regulation and positive immunostaining of PD-L1 have been described in ICI-mediated myocarditis.[3] Clinicians should be aware of the triad of myocarditis, myositis and myasthenia gravis as it is associated with poorer outcomes.[4] Risk factors for irAEs include dual ICI therapy and pre-existing cardiovascular or autoimmune disease.[2]

The American Society of Clinical Oncology (ASCO) Clinical Practice Guideline[5] recommends baseline ECG and troponins especially for patients treated with combination immunotherapies, and further testing upon the development of signs and symptoms. Additional testing may include TTE, chest X-ray, stress testing and cardiac MRI as guided by cardio-oncology. ASCO also recommends permanent discontinuation of ICI in the event of grade 1 cardiovascular toxicity (defined by abnormal cardiac biomarker levels and/or ECG). The cardio-oncology unit at the Vanderbilt University Medical Center, US recommends weekly surveillance of troponin levels for 6 weeks after initiation of ICI.[6] Patients with raised troponins prior to the initiation of ICI are assumed to have injury unrelated to ICI treatment, while those with troponin elevation on surveillance should be referred to cardio-oncology for evaluation of myocarditis and concomitant myositis.

Patients with irAEs often present with non-specific symptoms and may mimic common conditions such as acute myocardial infarction or sepsis. Emergency medicine and internal medicine physicians are usually on the front line of these acute presentations. Hence, a high level of suspicion and early recognition is crucial to institute prompt and appropriate treatment.[1] Management of cardiac irAEs includes discontinuation of ICI therapy and early consultation with the cardio-oncology team. Treatment of ICI-mediated myocarditis involves early high-dose intravenous methylprednisolone until the patient is clinically stable, followed by oral prednisolone tapered over weeks.[7] Second-line agents include mycophenolate mofetil or infliximab. Atrioventricular block may improve with discontinuation of ICI and institution of steroid treatment, although permanent pacemaker insertions have been required.[3]

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Zhe Yan Ng [1]*MRCP (UK)*, Chieh Yang Koo [1,2]*MRCP (UK)*, Kong Bing Tan [2,3]*FRCPath*, Weiqin Lin [1,2]*MRCP (UK)*, Matilda Lee [4]*MRCP (UK)*, Li Ling Tan [1,2]*MRCP (UK)*

[1] Department of Cardiology, National University Heart Centre Singapore, Singapore
[2] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[3] Department of Pathology, National University Hospital, Singapore
[4] Department of Haematology-Oncology, National University Cancer Institute, Singapore

Correspondence: Dr Zhe Yan Ng, Department of Cardiology, National University Heart Centre, Singapore, 1E Kent Ridge Road, NUHS Tower Block, Level 9, Singapore 119228.
Email: zhe_yan_ng@nuhs.edu.sg

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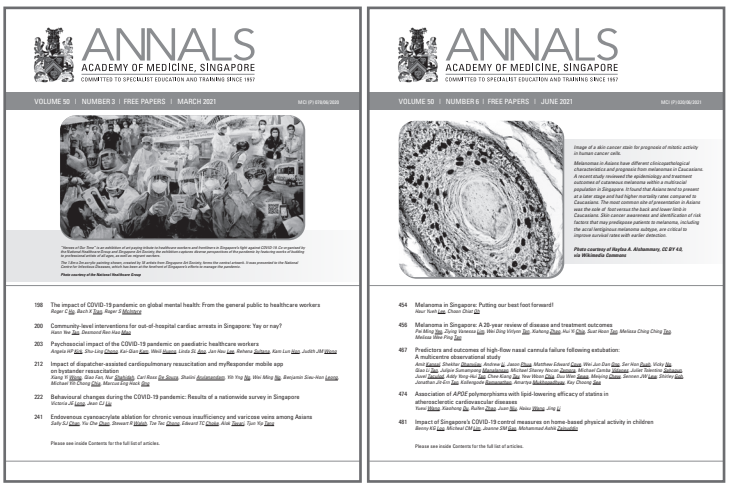

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