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"Heroes of Our Time" is an exhibition of art paying tribute to healthcare workers and frontliners in Singapore's fight against COVID-19. Co-organised by the National Healthcare Group and Singapore Art Society, the exhibition captures diverse perspectives of the pandemic by featuring works of budding to professional artists of all ages, as well as migrant workers.

The 1.8m x 3m acrylic painting shown, created by 18 artists from Singapore Art Society, forms the central artwork. It was presented to the National Centre for Infectious Diseases, which has been at the forefront of Singapore's efforts to manage the pandemic.

Photo courtesy of the National Healthcare Group

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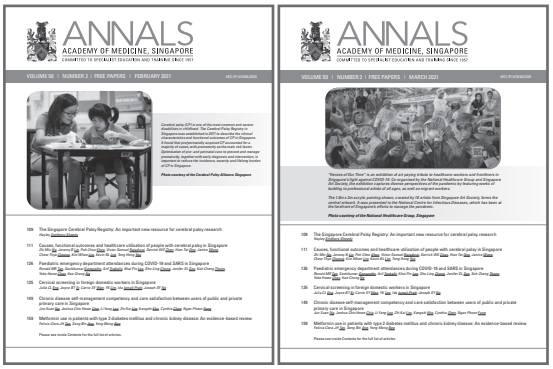

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EDITORIAL

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The impact of COVID-19 pandemic on global mental health: From the general public to healthcare workers

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The COVID-19 pandemic began in late 2019 and was declared a pandemic by the World Health Organization (WHO) on 11 March 2020. To decrease the spread of the virus and demand on the healthcare system, governments globally executed multiple public health measures including lockdown,[1] social distancing,[2] significant closure of the economy, as well as curbing domestic and international travel.

More than a year after the foregoing unprecedented interventions were implemented across countries around the world, tremendous uncertainty remains. This includes the availability of vaccinations and therapeutics, containment of the virus due to the emergence of variants, the return of the employment sector to pre-2020 levels, as well as the availability of unrestricted travel and social activities. Approximately two-thirds of households reported income loss due to the impact of the pandemic, which differentially affected specific sociodemographic groups (e.g. women, ethnic and racial minorities, individuals in unskilled labour positions).[2] During the lockdown, a surfeit of factors were identified that are associated with an increased level of depression, stress and anxiety, including but not limited to being female, single, younger age (i.e. <30 years), separated, widowed, impact of rumours, behavioural changes, losing jobs, and being in contact with potential COVID-19 patients.[2-4] The potential hazardous effects of COVID-19 on mental health have become an international public health priority.[5] Mental health research, which aims to identify risk and resiliency factors for mental health and mental disorders during this unprecedented crisis, is most likely to be achieved by international collaboration representing the disparate and global effect of COVID-19.

For middle-income countries in Asia, the risk factors for adverse mental health during the pandemic identified were age younger than 30 years, high education background, single status, and potential discrimination by people from other countries for spreading the COVID-19 virus.[6] In contrast, mental health protective factors include family support from cohabiting family members, employment, confidence in doctors, high perceived likelihood of survival, and spending less time on health information.[6] The foregoing finding of a link between less time on health information and mental health protection is in accordance with a separate observation that excess time on social media was associated with increased anxiety, stress and depression during COVID-19.[7]

The aforementioned studies also identified that being in physical contact with potential COVID-19 patients was a risk factor for poorer overall mental health. Compared with the general population, healthcare workers are expected to have higher exposure rates to patients who suffered from COVID-19 infection, and long working hours during the pandemic could lead to burnout.[8] A recent study involving healthcare workers from Asian countries found that non-medically trained personnel, the presence of physical symptoms, and prior medical conditions were all independent predictors for an increased likelihood of greater severity ratings on psychiatric scales.[9] Among healthcare workers from India, Indonesia, Malaysia, Singapore and Vietnam, Singaporean healthcare workers had a low prevalence of depression and anxiety.[9] Possible explanations could be due to the vast experience of Singaporean healthcare workers in handling previous pandemics such as the outbreak of severe acute respiratory syndrome (SARS) in 2003.

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Previous research on the mental health of Singaporean healthcare workers during the COVID-19 pandemic was conducted on healthcare workers who provided medical services for adults and elderly.[10] The latest study by Kirk et al. reported in this issue of the Annals assessed the psychological impact of the pandemic on paediatric healthcare workers in the middle of Phase I of the "circuit breaker"—the stay-at-home order and cordon sanitaire implemented as a preventive measure by the Singapore government.[11] This study found a relatively high prevalence of depression, anxiety and stress in paediatric healthcare workers at 39.1%, 47.7% and 24.7%, respectively. The foregoing prevalence rates are higher than the overall prevalence rates reported in other studies evaluating Asian healthcare workers (depression 4.5%, anxiety 5.2%, and stress 1%),[9] as well as a previous study on Singapore's healthcare workers (depression 8.9%, anxiety 14.5%, and stress 6.6%).[10] However, the findings by Kirk et al. are within the range of psychological response rates observed among healthcare workers during previous epidemics[12] and current COVID-19 pandemic,[13] based on recent reviews of a large number of extant studies. Kirk et al. had identified female gender, lack of choice on work scope/environment, insufficient physical activity, and stigma as key risk factors for poorer mental health outcomes in paediatric healthcare workers.

One interesting finding came out of the study. In contrast to the hypothesis that long working hours are associated with burnout and negative mental health, there was an inverse association between work hours per week and anxiety levels in paediatric healthcare workers. Kirk et al. proposed that those workers who volunteered to work longer were mentally more prepared for looking after COVID-19 patients.[11] The other possible explanation is that the long working hours made paediatric healthcare workers become desensitised to fear and anxiety associated with the pandemic.

Finally, this study found that organisational measures such as open, bidirectional communication with senior management, support from the hospital and family, and adequate personal protective equipment were associated with lower stress levels in healthcare workers. During the pandemic, online psychotherapy such as Internet-based cognitive behaviour therapy can reduce negative thoughts and behaviours by offering a safer alternative to face-to-face counselling.[14] Towards the aim of safeguarding the mental health of healthcare workers in Singapore, it is imperative to identify and modify risk factors, as well as embolden resiliency factors among this critical workforce.

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EDITORIAL

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Community-level interventions for out-of-hospital cardiac arrests in Singapore: Yay or nay?

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Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality and a significant public health problem globally. In Singapore, OHCA affected 11,061 adults between 2011 and 2016.[1] Despite multiple pre-hospital and hospital-based interventions, survival rates remain low. Initiation of time-sensitive cardiopulmonary resuscitation (CPR) while waiting for emergency services arrival is an essential key to survival in patients with OHCA.

Traditionally, improving bystander CPR (B-CPR) rates has been confined to public education campaigns with limited effectiveness. In a bid to increase rates, 2 community-level interventions in Singapore—dispatcher assisted-CPR (DA-CPR) and myResponder—were launched. DA-CPR refers to over-the-phone instructions on CPR by the dispatcher, enabling the lay rescuer to perform CPR with guidance. myResponder is a mobile application (app) that links potential rescuers to OHCA cases. Both interventions were designed to allow B-CPR to be commenced prior to the arrival of paramedics. Theoretically, this would decrease no-flow time and improve prognosis in these critically ill patients.

A study on the impact of 2 community-level interventions. This issue of the Annals features a retrospective before-and-after study by Wong et al.,[2] which examined if these community-led interventions would increase the odds of receiving B-CPR and its impact on survival outcomes. They included more than 10,000 cases of OHCA from 2010 to 2017. Three periods were studied: prior implementation of interventions; after DA-CPR implementation; and finally, a period where both DA-CPR and myResponder were instituted. The study revealed that implementation of DA-CPR and myResponder had a positive correlation with B-CPR rates, albeit an increasing but plateauing trend. Interestingly, there was no significant statistical increase in survival with both interventions.

Notwithstanding the inherent limitations of its retrospective nature, this study was methodologically robust. It included a national cohort consisting of a large sample size. The innovative segmented time-series design allowed temporal trends to be compared and understood. It should be noted that there were other ongoing initiatives to improve B-CPR rates concurrently such as Save-A-Life initiative and Dispatcher-Assisted first REesponder (DARE) programme. The overlap of these interventions limit conclusions drawn from this study.

Groups in all time periods had varying baseline characteristics. While this should not have influenced the outcome of B-CPR rates, it would definitely have an impact on overall survival as well as Utstein survival. Patients in Periods II and III were older with more comorbidities, were more likely to have non-shockable initial rhythms, and had longer emergency medical service response times. In contrast, OHCAs in later periods were more likely to have been witnessed arrests, which would favour higher rates of B-CPR. Taken together, baseline variables favoured improvement in the primary outcome of B-CPR rates and worse survival outcomes. Consequently, Wong et al. were careful not to overstate the study's findings.

Unassisted bystander CPR vs dispatcher-assisted CPR: Same same or different? Two registry studies had shown that DA-CPR was associated with improved survival and favourable neurological outcome.[3,4] Consequently, we had hoped to see the higher rate of B-CPR translate to improved Utstein survival in Singapore. Interestingly, the adjusted odds ratio in this study did not show improved odds of Utstein survival despite the implementation of both interventions. There are 2 possible reasons.

Firstly, we assert that DA-CPR is likely to be of poorer quality than traditional, unassisted B-CPR, hence conferring less survival benefit. The authors allude to this in the paper but do not provide further metrics on the quality of DA-CPR administered.[2] In Singapore, given that most cardiac arrests occur in residential, non-public places, these bystanders could be the victim's elderly

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spouse or domestic helper, both of whom were unlikely to have received prior training. Inherently, the quality of CPR by a novice practitioner doing it for the first time with telephonic guidance would be poorer than a trained, confident bystander who volunteers to help. Impediments to good quality DA-CPR have been extensively documented in the literature. A Singapore study that analysed more than 1,000 audio recordings of DA-CPR showed that barriers were present in 37%, which led to lower proportion of CPR started and longer delay in CPR.[5] Unfamiliarity with what quality CPR is, fear of harming the patient, and uncertainty in the diagnosis of cardiac arrest in patients with agonal breathing could all lead to poorer depth, rate and recoil in performing chest compressions. CPR cards have been disbursed to the public that could aid in ascertaining the quality of B-CPR. Future research should be directed to shed more light on the relationship between the quality of DA-CPR and survival.

This does not mean that we should throw out DA-CPR. We believe that some CPR is better than no CPR at all. The words and positive attitudes of dispatchers can help to positively influence lay bystanders towards better quality CPR.[6] Prior exposure to CPR as well as formal CPR training for the public may further reduce barriers to DA-CPR.[5] With continued focus on dispatcher training and further public education on CPR, the quality of DA-CPR will improve.

Secondly, volunteers activated by the myResponder app may not be arriving earlier than paramedics. Studies[7,8] have shown that the time-to-first compression matters in improving survival. Unfortunately, this information was unavailable in the study by Wong et al. We will address myResponder further in the section below.

Mobile apps enable virtual volunteers to make in-person saves. Mobile CPR apps such as myResponder are not unique to Singapore. Other countries such as South Korea, Denmark and Sweden already have them in use. CPR apps represent a technological revolution in the way assistance is deployed to address and manage OHCA. A randomised controlled trial in Stockholm, Sweden showed that mobile app similar to myResponder was significantly associated with increased B-CPR rates.[9] Unlike DA-CPR bystanders, volunteers on such apps are motivated individuals and would likely be better trained and more highly skilled in providing good quality CPR.

The reported myResponder's activations seem low when compared to the overall proportion of patients receiving B-CPR. The authors postulate that this is unlikely to be true and is more likely to be due to under-reporting. There are two factors that support this. Registered number of users have been steadily increasing and average number of notifications sent by SCDF dispatch centre have been rising. The low uptake or reporting resulted in the authors using a segmented regression analysis to circumvent under-reporting.

To promote publicity and encourage use of myResponder, user-friendliness and various features can be addressed and updated, to promote its use and allow better data capture for future improvement. It will be beneficial to track time-to-first compression in myResponder and DA-CPR. We acknowledge the difficulties in collecting such information. CPR cards could be one way to overcome this challenge.

For existing volunteers, efforts should be directed at improving response times. As most OHCAs occur in high-rise residences, this could involve priming volunteers to the addresses of blocks in their vicinity as well as locations of elevators and automated external defibrillators (AEDs). An opportunity exists for gamification and augmented reality to train myResponder volunteers to arrive earlier.

Elevating the plateau in B-CPR. Both community-level interventions would have improved public awareness of CPR, which in turn would lead to more bystanders being willing to participate in the resuscitation process, forming a virtuous cycle. However, Wong et al. had observed that the B-CPR rates appeared to be plateauing. As the opportunity for gains decreases, this phenomenon is not unexpected. Elevating the CPR rates further would not come easy.

For more gains in CPR rates, one strategy would be to focus education efforts on unique population subgroups that would be more likely to perform CPR. These include carers of patients at risk of OHCA who would perform DA-CPR such as nursing home staff,[10] or groups likely to become myResponders such as tertiary students. Besides a mere increase in rates, education efforts to improve survival need to continue to emphasise good-quality CPR and encourage early usage of AEDs.

Singapore has come a long way from the time when B-CPR rates were at 23.1% in 2010, to 67.3% in 2017. Community-level interventions have undoubtedly played an important role in this massive improvement. Coupled with in-hospital advances in OHCA resuscitation such as the use of targeted temperature monitoring[11] and bedside ultrasound to guide resuscitation,[12] one is hopeful that OHCA survival rates can only improve.

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ORIGINAL ARTICLE

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Psychosocial impact of the COVID-19 pandemic on paediatric healthcare workers

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ABSTRACT

Introduction: Frontline healthcare workers (HCWs) exposed to coronavirus disease 2019 (COVID-19) are at risk of psychological distress. This study evaluates the psychological impact of COVID-19 pandemic on HCWs in a national paediatric referral centre.

Methods: This was a survey-based study that collected demographic, work environment and mental health data from paediatric HCWs in the emergency, intensive care and infectious disease units. Psychological impact was measured using the Depression, Anxiety, Stress Scale-21. Multivariate regression analysis was performed to identify risk factors associated with psychological distress.

Results: The survey achieved a response rate of 93.9% (430 of 458). Of the 430 respondents, symptoms of depression, anxiety and stress were reported in 168 (39.1%), 205 (47.7%) and 106 (24.7%), respectively. Depression was reported in the mild (47, 10.9%), moderate (76, 17.7%), severe (23, 5.3%) and extremely severe (22, 5.1%) categories. Anxiety (205, 47.7%) and stress (106, 24.7%) were reported in the mild category only. Collectively, regression analysis identified female sex, a perceived lack of choice in work scope/environment, lack of protection from COVID-19, lack of access to physical activities and rest, the need to perform additional tasks, and the experience of stigma from the community as risk factors for poor psychological outcome.

Conclusion: A high prevalence of depression, anxiety and stress was reported among frontline paediatric HCWs during the COVID-19 pandemic. Personal psychoneuroimmunity and organisational prevention measures can be implemented to lessen psychiatric symptoms. At the national level, involving mental health professionals to plan and coordinate psychological intervention for the country should be considered.

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Keywords: Anxiety, depression, healthcare worker, medical staff, psychological, stress

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in December 2019 and has since evolved into a global pandemic, infecting millions of people and causing more than 2.7 million deaths.[1,2] Early studies done in China during this COVID-19 pandemic have shown considerable mental health impact on healthcare workers (HCWs), especially those working on the frontline.[3,4] HCWs exposed directly to COVID-19 may be affected not only by fears of contracting the virus and spreading it to their loved ones, but also by work-related factors including the lack of manpower, increased working hours, inadequate personal protective equipment, difficult triage decisions and difficult isolation environments.[3,5,6] An international collaborative survey conducted in Asia Pacific, which was independent of the COVID-19 disease burden within the country, demonstrated varying levels of mental health burden among HCWs.[7] Moreover,

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CLINICAL IMPACT

What is New

- This survey showed a high prevalence of symptoms of depression, anxiety and stress among frontline paediatric healthcare workers during the COVID-19 pandemic.
- Modifiable risk factors included a perceived lack of choice of work, lack of protection from COVID-19, lack of access to physical activities and rest, the need to perform additional tasks, and the experience of stigma from the community.

Clinical Implications

- This study indicates that the psychological impact on high-risk healthcare workers in paediatric hospitals was substantial, despite the relatively mild clinical impact of COVID-19 on the paediatric population.
- Data from this study may guide future efforts to improve personal psychoneuroimmunity, organisational prevention and interventional measures to lessen psychiatric symptoms during crises.

physical symptoms including headache, lethargy and insomnia have also been reported in a considerable proportion of HCWs and were associated with their psychological states.[8]

Reports on the psychological impact on HCWs from paediatric hospitals, however, are relatively scarce. This lack of study may be due to the relatively lower prevalence and generally milder disease severity of paediatric COVID-19 compared to adults,[9] resulting in greater focus being diverted to adult hospitals. Nevertheless, the psychological impact may be independent of disease burden.[7] An early multicentre study among paediatric medical staff in China highlighted that paediatric HCWs are also vulnerable to adverse psychological impact.[10]

Singapore reported its first imported case of COVID-19 on 23 January 2020, and our first paediatric COVID-19 case was reported on 4 February 2020.[11] To date, approximately 60,000 COVID-19 cases have been confirmed in Singapore.[12] Of note, all paediatric COVID-19 patients from our hospital survived, none required ICU admission and all were discharged without complication. Although the clinical impact of COVID-19 on the paediatric population is mild, we hypothesised that the psychological impact on high-risk HCWs in paediatric hospitals would be substantial. In this study, we aimed to evaluate the psychological impact of the COVID-19 pandemic on HCWs in a national paediatric referral centre.

METHODS

This study was an electronic survey administered by email invitation to eligible participants. All data collected were completed in an anonymised and voluntary fashion. Reminders were sent via mass e-mail and token reward vouchers were given as an incentive to increase the response rate. Reporting was in accordance with the Checklist for Reporting Results of Internet E-Surveys guidelines.[13] This study received exemption from the ethics board review.

Participating sites and target population

This study was conducted at KK Women's and Children's Hospital, which is a standalone children's hospital and the main referral centre for paediatric COVID-19 cases in Singapore. The target population was high-risk HCWs comprising medical and nursing professionals who were part of the paediatric intensive care unit (ICU), children's emergency (CE) and infectious disease (ID) teams in direct contact with confirmed or suspected COVID-19 cases, as these cases were considered at greatest risk of developing adverse psychological outcomes.[14] Since January 2020, the hospital has made changes to the workflows and protocols in preparation for the COVID-19 outbreak. The isolation facilities were boosted in numbers and equipped with critical care paraphernalia, in anticipation of admitting COVID-19 patients requiring intermediate care or ICU management.[15,16] ICU staff deployment had to be doubled to cope with routine care as well as anticipate a surge in COVID-19 admissions.[15] Concurrent changes in our CE department included the building of a temporary, pre-triage screening facility and alterations of staffing schedules into modular teams in 12-hour shifts to prevent cross-exposure and hospital transmission.[17] ID physicians led the hospital on COVID-19 preparedness, planned workflows, responded to clinical queries relating to COVID-19, and managed the care of suspected or confirmed COVID-19 cases. ICU, CE and ID HCWs were surveyed from 28 April 2020 to 5 May 2020. The survey period was midway (3 weeks) through a nationwide lockdown period (6 weeks).[18,19]

Self-analysis questionnaire

The Depression, Anxiety, Stress Scale (DASS) is a self-reported inventory to measure the negative emotional states of depression, anxiety and stress.[20] The original 42-item scale was abbreviated to a 21-item short version (DASS-21),[21] which received further validation in clinical cohorts, including Asian cohorts during the COVID-19 pandemic.[10,22,23] In addition to DASS-21, subjects were surveyed on sociodemographic factors, work environment and daily lifestyle. Both closed-ended and open-ended questions were used to collect information on work environment and lifestyle factors. All closed-ended questions were mandatory, whereas optional open-ended questions were used to solicit additional opinions or comments. Instructions were included in the survey and participants were reminded to submit only 1 response.

Statistical analyses

Sociodemographic characteristics and work environment factors were described for the medical and nursing cohorts in the ICU, CE and ID teams. Categorical variables are presented as counts and percentages, and continuous variables as median and interquartile range. The median DASS-21 scores and prevalence of depression, anxiety and psychological stress of the medical cohort were compared with those of the nursing cohort of the frontline HCWs. These comparisons were repeated among the ICU, CE and ID teams. The main outcomes were the prevalence of depression, anxiety and stress among frontline HCWs and were treated as binary data. Depression, anxiety or stress was considered present if scores exceeded the normal cut-off, and was categorised as mild, moderate, severe and extremely severe based on published cut-offs.[24] The Kruskal-Wallis and chi-square tests were used to compare continuous and categorical variables, respectively.

Univariate and multivariable logistic regression models were used to quantify the association of demographic and work-environment risk factors with the primary outcome. The association was described using odds ratio (OR) with 95% confidence intervals (CI). Variables with P value <0.2 in the univariate model were selected for the multivariable model. Union of the variables selected in the forward, backward and stepwise methods were then used to finalise the variables list in the multivariable model with entry criteria and stay criteria of 0.2 and 0.05, respectively. Separate univariate and multivariable models were also fitted for secondary outcomes, that is, anxiety and stress. All tests were 2-tailed and P value <0.05 was accepted as statistically significant. Analyses were performed using Stata software version 15.1 (StataCorp, College Station, US) and SAS software version 9.3 (SAS Institute, Cary, US).

RESULTS

This survey achieved a response rate of 93.9% (430 of 458). Of the 430 respondents, 175 (40.7%) were medical staff and the remainder were nursing staff. The sociodemographic profile and work environment characteristics of the HCWs are described in Tables 1 and 2, respectively.

The majority of participants had come into contact with suspected or confirmed cases of COVID-19 at the time of this study. Sixty-nine of 430 respondents (16.0%) were required to perform tasks in addition to their usual work routine (e.g. infection control, administrative and training tasks in various settings, and housekeeping tasks in the isolation wards). However, only 35 (8.1%) felt uncomfortable with these additional tasks. Eighty-seven respondents (20.2%) perceived a lack of choice with regard to the tasks they were required to perform, and the highest incidence of this perception were from the ICU nursing cohort (23 of 67 [34.3%]); they reported a perceived lack of choice in nursing suspected or confirmed critical cases of COVID-19. Majority of frontline HCWs felt protected from contracting the virus and had access to basic needs like rest, healthy food or beverages, and exercise. However, of the 430 respondents, 129 (30.0%) perceived a lack of time and access to stay in contact with friends and family, and 100 (23.3%) perceived avoidance by family members or their community owing to stigma and fear of contracting COVID-19 from them (e.g. avoidance from family members, friends, neighbours and taxi drivers). Participants expressed that the closure of sports facilities, lack of time and insufficient rest had contributed to the lack of access to and time for physical activities. With the nationwide lockdown, the mandate for social distancing and travel prohibition for returning to overseas family members had prevented them from staying in contact with family and friends during this pandemic.

Among the 430 respondents, the prevalence of mild, moderate, severe and extremely severe depression based on the DASS-21 categories were 10.9% (n=47), 17.7% (n=76), 5.3% (n=23) and 5.1% (n=22), respectively. There were no differences in the median depression factor scores (interquartile range) between the medical

Table 1. Sociodemographic characteristics of survey respondents from intensive care units, children's emergency and infectious disease units

Characteristics	Total (N=430)	ICU, no. (%)		CE, no. (%)		ID, no. (%)	
		Medical (n=11)	Nursing (n=67)	Medical (n=84)	Nursing (n=110)	Medical (n=80)	Nursing (n=78)
Age, years							
≤30	157 (36.5)	0 (0.0)	22 (32.8)	24 (28.6)	41 (37.3)	31 (38.8)	39 (50.0)
31–40	193 (44.9)	6 (54.5)	31 (46.3)	34 (40.5)	49 (44.5)	44 (55.0)	29 (37.2)
41–50	54 (12.6)	4 (36.4)	5 (7.5)	22 (26.2)	14 (12.7)	4 (5.0)	5 (6.4)
≥51	26 (6.0)	1 (9.1)	9 (13.4)	4 (4.8)	6 (5.5)	1 (1.3)	5 (6.4)
Female sex	369 (85.8)	7 (63.6)	64 (95.5)	52 (61.9)	108 (98.2)	61 (76.3)	77 (98.7)
Married	236 (54.9)	10 (90.9)	36 (53.7)	49 (58.3)	63 (57.3)	48 (60.0)	30 (38.5)
With children	186 (43.3)	5 (45.5)	33 (49.3)	38 (45.2)	56 (50.9)	25 (31.3)	2 (37.2)
Healthcare work experience, years							
<5	118 (27.4)	0 (0.0)	18 (26.9)	23 (27.4)	31 (28.2)	26 (32.5)	20 (25.6)
5–10	153 (35.6)	2 (18.2)	16 (23.9)	19 (22.6)	38 (34.5)	45 (56.3)	33 (42.3)
11–20	125 (29.1)	7 (63.6)	24 (35.8)	35 (41.7)	32 (29.1)	7 (8.8)	20 (25.6)
≥21	34 (7.9)	2 (18.2)	9 (13.4)	7 (8.3)	9 (8.2)	2 (2.5)	5 (6.4)

CE: children's emergency; ICU: intensive care unit; ID: infectious disease

Table 2. Work environment characteristics of survey respondents from intensive care units, children's emergency and infectious disease units

Characteristics	ICU, no. (%)			CE, no. (%)		ID, no. (%)	
	Total (N=430)	Medical (n=11)	Nursing (n=67)	Medical (n=84)	Nursing (n=110)	Medical (n=80)	Nursing (n=78)
Weekly work duration, hours							
< 40	58 (13.5)	0 (0.0)	7 (10.5)	17 (20.2)	24 (21.8)	0 (0.0)	10 (12.8)
40–50	275 (64.0)	4 (36.4)	56 (83.6)	60 (71.4)	86 (78.2)	7 (8.8)	62 (79.5)
51–60	50 (11.6)	7 (63.6)	4 (6.0)	5 (6.0)	0 (0.0)	29 (36.3)	5 (6.4)
61–70	24 (5.6)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	22 (27.5)	1 (1.3)
≥71	23 (5.3)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	22 (27.5)	0 (0.0)

Table 2. Work environment characteristics of survey respondents from intensive care units, children's emergency and infectious disease units (Cont'd)

Characteristics	ICU, no. (%)			CE, no. (%)		ID, no. (%)	
	Total (N=430)	Medical (n=11)	Nursing (n=67)	Medical (n=84)	Nursing (n=110)	Medical (n=80)	Nursing (n=78)
Direct contact with COVID-19 cases	344 (80.0)	9 (81.8)	39 (58.2)	66 (78.6)	95 (86.4)	64 (80)	71 (91.0)
Required to perform additional tasks	69 (16.0)	2 (18.2)	9 (13.4)	11 (13.1)	13 (11.8)	17 (21.3)	17 (21.8)
Required to perform tasks outside of comfort zone	35 (8.1)	0 (0.0)	11 (16.4)	6 (7.1)	7 (6.4)	5 (6.3)	6 (7.7)
Perceives a lack of choice in work scope or environment	87 (20.2)	1 (9.1)	23 (34.3)	16 (31.0)	12 (10.9)	21 (26.3)	14 (17.9)
Perceives a lack of protection from COVID-19	46 (11.0)	0 (0.0)	1(25.4)	7 (8.3)	11 (10.0)	3 (3.8)	8 (10.3)
Perceives a lack of sufficient rest	43 (10.0)	1 (9.1)	9 (13.4)	7 (8.3)	7 (6.4)	12 (15.0)	7 (9.0)
Perceives a lack of access to healthy food or drink	43 (10.0)	0 (0.0)	9 (13.4)	4 (4.8)	9 (8.2)	5 (6.3)	16 (20.5)
Perceives a lack of access to physical activities	122 (28.4)	2 (18.2)	19 (28.4)	19 (22.6)	23 (20.9)	34 (42.5)	25 (32.1)
Perceives inability to contact family or friends	129 (30.0)	2 (18.2)	19 (28.4)	21(25.0)	30 (27.3)	34 (42.5)	23 (29.5)
Experiences stigma from community	100 (23.3)	4 (36.4)	17 (25.4)	14 (16.7)	24 (21.8)	19 (23.8)	22 (28.2)

CE: children's emergency; ICU: intensive care unit; ID: infectious disease

Table 3. Depression, Anxiety, Stress Scale-21 (DASS-21) domain scores and prevalence of depression, anxiety and stress in frontline medical and nursing staff

	Overall (N=430)	Medical (n=175)	Nursing (n=255)	*P* value
DASS-21 domain score, median (interquartile range)				
Depression	6 (2–14)	6 (2–14)	6 (2–14)	0.985
Anxiety	6 (2–12)	4 (2–10)	8 (2–14)	<0.001
Stress	8 (2–14)	8 (4–16)	8 (2–14)	0.137
Prevalence, no. (%)				
Depression	168 (39.1)	70 (40.0)	98 (38.4)	0.763
Anxiety	205 (47.7)	64 (36.6)	141 (55.3)	<0.001
Stress	106 (24.7)	48 (27.4)	58 (22.8)	0.306

and nursing cohorts (Table 3) or among the ICU, CE and ID teams (5 [2–12], 6 [2–14] and 6 [2–14], respectively; *P*=0.547). Anxiety was found in the mild category only, and its prevalence was 47.7% (205 of 430). The median anxiety factor score was higher in the nursing cohort than that in the medical cohort (Table 3), but the median score (interquartile range) was not significantly different among the ICU, CE and ID teams (8 [2–12], 6 [2–14] and 6 [2–10], respectively; *P*=0.320). Lastly, psychological stress was also only found in the mild category, and its prevalence was 24.7% (106 of 430). There were no differences in the median stress factor scores (interquartile range) between the medical and nursing cohorts (Table 3) or among the ICU, CE and ID teams (8 [2–16], 8 [2–16] and 8 [2–14], respectively; *P*=0.975). Respondents cited clear communication from hospital leaders; availability of adequate personal protective equipment; and support from the hospital administration, colleagues, family and religious observances as helping to relieve stress during this pandemic. Uncertainty, fear of contracting the virus, frequent changes in workflow and staff deployment added stress to the participants.

In the multivariable model, predominantly work environment–related factors were associated with depression, anxiety and stress (Table 4). The only sociodemographic factors associated with psychological outcome in our study were female sex, which was associated with an increased risk of anxiety (adjusted OR 2.92, 95% CI 1.49–5.72), and being married, which was associated with a decreased risk of anxiety (adjusted OR 0.63, 95% CI 0.42–0.96).

DISCUSSION

Our survey of frontline HCWs, performed midway through a nationwide lockdown in Singapore, revealed a high prevalence of depression (39.1%), anxiety (47.7%) and stress (24.7%). Our study also highlights that despite the mild clinical impact on paediatric patients, the psychological impact on their healthcare providers was substantial. Factors associated with negative psychological impact were largely modifiable and included the requirement to perform additional tasks, lack of choice in work scope or environment, a perceived lack of protection from COVID-19, lack of access to physical activities, and experience of stigma from the community. Female sex was also associated with a higher risk of anxiety, whereas being married and working in the ≥71-hour work week bracket seemed to be protective.

The baseline prevalence of major depressive disorder and generalised anxiety disorder in Singapore, based on the World Health Organization World Mental Health Composite International Diagnostic Interview criteria, was reportedly 5.8% and 0.9%, respectively.[25] In the early phase of the COVID-19 pandemic and prior to the nationwide lockdown, the prevalence of depression, anxiety and stress among HCWs was reported in a previous study to be 8.1%, 10.8% and 6.4%, respectively.[22] Our study indicates a sharp rise in prevalence of depression (39.1%), anxiety (47.7%) and stress (24.7%) over the course of this pandemic. There were some differences between the prior study and ours; the former included subjects from adult-based hospitals and it is unclear if the participants worked in high-risk areas. It was also conducted approximately 2 months before our study when there were no reported COVID-19 deaths compared with 14 deaths by the time of our study.[2] Hence, these results have to be interpreted in the context of the COVID-19 trajectory and the nationwide mitigation measures implemented in Singapore.[18,19] During the lockdown period, a surge in the number of calls to the local national mental health hotline was reported, indicating that the prolonged mitigation measures could have an impact on mental health, and particularly depression.[26] A Singapore report during the COVID-19 pandemic cited that the morale of HCWs was negatively affected by increased workload, uncertainty over the effectiveness of personal protective equipment, concerns of well-being of family members and stigmatisation from the public.[15]

Our study also highlights that paediatric HCWs are not exempt from the psychological stressors incurred during the COVID-19 pandemic. Despite the mild clinical impact on paediatric patients, the psychological impact on their healthcare providers was shown to be substantial. Firstly, being a frontline HCW itself may confer a higher risk of psychological impact compared with HCWs not working in high-risk areas. A multicentre study (n=1,257) conducted in China, which used the 9-item Patient Health Questionnaire, showed that frontline HCWs directly engaged in the diagnosis, treatment and care of patients with COVID-19 had 1.5-fold increased odds of experiencing depression and anxiety.[3] Secondly, the exposure to varying healthcare occupational hazards among paediatric HCWs (especially nursing staff) is known to be high, possibly associated with strained doctor–patient–caregiver relationships during stressful situations.[27] A recent study examining the psychological impact on paediatric HCWs in China reported rates of depression, anxiety and stress of 15%, 18% and 10%, respectively.[10] It is concerning that our study reported rates that were greater than double the rates of the report: depression,

Table 4. Risk factors for depression, anxiety and stress identified by multivariate analysis

Characteristics	Adjusted odds ratio (95% confidence interval)	*P* value
Depression		
Perceives a lack of choice in work scope or environment		
Yes	1.84 (1.10–3.10)	0.021
No	1 [Reference]	
Perceives a lack of access to physical activities		
Yes	2.81 (1.78–4.42)	<0.001
No	1 [Reference]	
Experiences stigma from community		
Yes	2.51 (1.54–4.08)	<0.001
No	1 [Reference]	
Anxiety		
Sex		
Female	2.92 (1.49–5.72)	0.002
Male	1 [Reference]	
Married		
Yes	0.63 (0.42–0.96)	0.033
No	1 [Reference]	
Weekly work duration (hours)		0.035[a]
<40	1 [Reference]	
40–50	0.80 (0.44–1.47)	0.471
51–60	0.56 (0.25–1.28)	0.172
61–70	0.36 (0.12–1.06)	0.064
≥71	0.19 (0.06–0.64)	0.007
Perceives a lack of choice in work scope or environment		
Yes	2.01 (1.16–3.50)	0.013
No	1 [Reference]	
Perceives a lack of sufficient rest		
Yes	3.02 (1.37–6.67)	0.006
No	1 [Reference]	
Experiences stigma from community		
Yes	2.77 (1.66–4.64)	<0.001
No	1 [Reference]	
Stress		
Required to perform additional tasks		
Yes	1.84 (1.04–3.27)	0.036
No	1 [Reference]	
Perceives a lack of protection from COVID-19		
Yes	2.22 (1.15–4.29)	0.018
No	1 [Reference]	
Perceives a lack of access to physical activities		
Yes	2.88 (1.79–4.64)	<0.001
No	1 [Reference]	

[a] Type 3 *P* value

39.1%; anxiety, 47.7%; and stress, 24.7%. However, this discrepancy may be due to differences in study design; the earlier study only included medical professionals and utilised the social media platform that may have significantly biased the population surveyed.[10]

Symptoms of anxiety were reported in 25.5–44.6% of HCWs in China during the COVID-19 pandemic, which was comparable to results of our survey.[3,4] Consistent with these studies, the female sex was associated with risk of anxiety.[3] A concern is that the majority of medical and nursing staff in our centre were female (369 of 430, 85.8%). Similarly, a Singapore study reported that 35.8% of antenatal women were screened positive for anxiety during the COVID-19 pandemic.[28] Further research to identify actual anxiety disorders may be necessary as a next step to diagnose and support our staff. In our cohort, being married and working in the ≥71-hour work week bracket seemed to be associated with a reduced risk of anxiety. The latter seems counterintuitive, but on examining the multivariable model, there was a consistent trend of decreased risk of anxiety with increased work hours per week. More investigation is needed to explore the association between working hours and psychological impact during a pandemic. A study performed during the severe acute respiratory syndrome (SARS) epidemic in Hong Kong alluded to a similar phenomenon; it reported that HCWs who were less willing to work in SARS units were at a higher risk for psychological morbidity, whereas those who volunteered to do so were more psychologically prepared and had better "reserves" to cope with the epidemic.[29] Hence, we observed that participants who perceived a lack of choice in work scope or environment may be less psychologically resilient to challenges and were more vulnerable to psychological impact.

The prevalence of stress reported in our study was lower than that of other research involving HCWs or the general public during COVID-19 outbreak.[3,6] Respondents reported that clear communication from hospital leaders, availability of adequate personal protective equipment, support from the hospital administration, colleagues, family and religious observances helped relieve stress during this pandemic. As initially described in the SARS study in Hong Kong, our report confirms that psychological support from employers has a protective effect against stress in the workplace.[29] The perception of a lack of protective gear influenced the risk of stress in HCWs (adjusted relative risk 2.22, 95% CI 1.15–4.29, P=0.0177). The reassurance of personal safety and availability of adequate personal protective equipment during the COVID-19 pandemic are factors that encourage medical staff to continue working during the pandemic.[4,30] It is known that COVID-19 is highly infectious; therefore, reassurance from clear infectious control guidelines is important to ensure the psychological well-being of HCWs.

This study adds to the existing but limited literature on the psychological impact of the COVID-19 pandemic on paediatric HCWs. Our study has several limitations. As with every self-reporting questionnaire, responses elicited may be biased in favour of finding a certain outcome rather than representing what the participants truly believe.[31] Measures were taken to minimise this bias; for example, the questionnaires were administered in an anonymous manner and a high response rate minimised selection bias. Secondly, symptoms of depression, anxiety and stress identified in the DASS-21 are not equivalent to a formal psychiatric assessment and do not constitute a diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders.[32] Thirdly, this survey sampled participants from a single site and therefore has limited generalisability. Lastly, this cross-sectional study lacks baseline and longitudinal comparison. Nevertheless, our study provides preliminary data that future research is necessary to track progression or resolution of mental health symptoms of HCWs as the COVID-19 pandemic situation changes, and to evaluate the effects of any therapeutic intervention.

CONCLUSION

After 3 months into the COVID-19 pandemic and midway into a nationwide lockdown, approximately 40% of high-risk paediatric HCWs reported symptoms of depression and anxiety. It is necessary to track progression or resolution of mental health symptoms in this cohort as the COVID-19 pandemic situation evolves, and for hospitals to consider interventions to support the mental wellness of HCWs. Personal psychoneuroimmunity prevention measures, including hand hygiene and wearing of face masks, as well as organisational measures including stepping-up of workplace hygiene measures and support from the hospital management, can be implemented to lessen psychiatric symptoms. At the national level, involving mental health professionals to plan and coordinate psychological intervention for the country should be considered. This is especially pertinent, given that the pandemic is likely to be long drawn out and affecting many facets of healthcare.

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ORIGINAL ARTICLE

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Impact of dispatcher-assisted cardiopulmonary resuscitation and myResponder mobile app on bystander resuscitation

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ABSTRACT

Introduction: Bystander cardiopulmonary resuscitation (B-CPR) is associated with improved out-of-hospital cardiac arrest survival. Community-level interventions including dispatcher-assisted CPR (DA-CPR) and myResponder were implemented to increase B-CPR. We sought to assess whether these interventions increased B-CPR.

Methods: The Singapore out-of-hospital cardiac arrest registry captured cases that occurred between 2010 and 2017. Outcomes occurring in 3 time periods (Baseline, DA-CPR, and DA-CPR plus myResponder) were compared. Segmented regression of time-series data was conducted to investigate our intervention impact on the temporal changes in B-CPR.

Results: A total of 13,829 out-of-hospital cardiac arrest cases were included from April 2010 to December 2017. Higher B-CPR rates (24.8% versus 50.8% vs 64.4%) were observed across the 3 time periods. B-CPR rates showed an increasing but plateauing trend. DA-CPR implementation was significantly associated with an increased B-CPR (level odds ratio [OR] 2.26, 95% confidence interval [CI] 1.79–2.88; trend OR 1.03, 95% CI 1.01–1.04), while no positive change was detected with myResponder (level OR 0.95, 95% CI 0.82–1.11; trend OR 0.99, 95% CI 0.98–1.00).

Conclusion: B-CPR rates in Singapore have been increasing alongside the implementation of community-level interventions such as DA-CPR and myResponder. DA-CPR was associated with improved odds of receiving B-CPR over time while the impact of myResponder was less clear.

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Keywords: Bystander CPR, community responders, out-of-hospital cardiac arrest, pre-hospital care

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality worldwide, with a global incidence of 62 cases per 100,000 person-years.[1] In addition, there are variations in the reported survival-to-hospital discharge rates among different regions in the world. In Singapore, OHCA incidence rate was 27.2 per 100,000 person-years, with an overall survival rate of 5.3% in 2015.[2] In contrast, some cities had reported higher survival rates, with King County, Seattle in the US reporting a rate of 16%,[1] suggesting that more could be done in Singapore to improve OHCA survival.

Key to the treatment of OHCA is the "chain of survival", which comprises early recognition, early cardiopulmonary resuscitation (CPR), early defibrillation, basic and advanced emergency medical

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CLINICAL IMPACT

What is New

- Singapore's cardiac arrest registry study showed that dispatcher-assisted cardiopulmonary resuscitation (CPR) increased odds of bystander CPR (B-CPR). myResponder mobile app did not achieve the same effect.
- An increasing but plateauing trend in B-CPR rates was also noted.

Clinical Implications

- Our study suggests that dispatcher-assisted CPR has been effective in improving B-CPR rates over time, and supports its continued implementation.
- A plateauing trend in B-CPR rates underscores the need to investigate the optimisation of existing interventions such as myResponder or implementation of other novel interventions.

services (EMS) treatment, and post-resuscitation care.[3] Survival decreases by 7–10% per minute without treatment.[4] CPR carried out by bystanders (B-CPR) has been shown to at least double the chance of survival from OHCA[5] and has been recommended to be a global priority.[6]

In Singapore, several new initiatives were introduced in recent years to improve B-CPR rates. In July 2012, dispatcher-assisted CPR (DA-CPR) was implemented at the Singapore Civil Defence Force (SCDF) Operations centre to enable a trained dispatcher to recognise a cardiac arrest over the phone and provide timely instructions to the caller to commence compression-only CPR. In April 2015, the SCDF launched the myResponder mobile application (app) to recruit and dispatch registered volunteers to potential OHCA cases if they are within a 400-meter radius of the victim. The app also highlights the locations of the nearest public access automated external defibrillators (AEDs) for retrieval by the responders.

The main aim of this study was to assess whether our community-level interventions, including DA-CPR and myResponder, increased the odds of receiving B-CPR compared to baseline prior to their implementation. Secondary aims of the study were to assess the interventions' effect on improving survival outcomes after OHCA. It was hypothesised that our interventions will increase B-CPR rates and improve patient survival outcomes.

METHODS

Setting

Singapore is a high-density city-state 724.2 km^2 in size, with a total population of 5.7 million and a population density of 7,866 per km^2.[7] Emergency calls are received by the SCDF, which operates a centralised "995" dispatch centre for the country's EMS. A total of 65 ambulances were available for dispatch in 2017.[8]

DA-CPR

The DA-CPR intervention relies on a standardised dispatch protocol to guide trained dispatch personnel to rapidly and accurately recognise suspected cardiac arrest patients through a systematic "no-no-go" process by posing 2 key questions to callers: Is the patient conscious? Is the patient breathing normally?[9] Once identified, the protocol also guides the dispatcher on how to instruct the caller to commence CPR. Dispatch instruction is limited to chest compression only, which is associated with better long-term survival compared to traditional CPR that includes ventilation.[10] Dispatch audio recordings are subsequently reviewed for quality improvement purposes.[11]

myResponder mobile phone application

myResponder uses the global positioning system (GPS) within mobile phones to locate registered volunteers geographically. Volunteers will need to download the app (available on both Android and iOS platforms), register their names in the system and consent to sharing their GPS location before they can be activated.

When the 995 dispatch centre receives a call for a suspected OHCA, an ambulance (comprising 1 paramedic, 1 emergency medical technician (EMT) and 1 driver) is dispatched to the scene. A fire-biker may also be dispatched when conditions (e.g. availability, weather and traffic) allow. In addition, a 4-man fire vehicle manned by trained EMTs has been dispatched alongside the ambulance since April 2019, as part of a pilot project to introduce a high-performance CPR team. Since the launch of myResponder in April 2015, alerts are also sent out by the dispatch centre to volunteers with an active myResponder app within a 400-metre radius of an OHCA, with the address of the case and the locations of the nearest AEDs. The workflow for the mobile application is illustrated in Fig. 1. Both the number of registered users and the average number of notifications sent for each OHCA case have been steadily increasing since myResponder's implementation in April 2015.

Fig 1. myResponder mobile application workflow.

PAROS registry and myResponder database

The Pan-Asian Resuscitation Outcome Study (PAROS) is an Asia-Pacific cardiac arrest registry set up in 2009 to understand OHCA and improve survival in Asia.[12] It includes Singapore records of all OHCA attended by the SCDF EMS, including those sent to public hospitals, patient characteristics, incident location information, EMS dispatch information, as well as pre-hospital and emergency department resuscitation information. In this study, de-identified PAROS records from Singapore between April 2010 and December 2017 were used.

The myResponder database contains app-related records of all suspected OHCA in which the app was activated, including "activation", "alerts", "response", and "arrival" information. Although myResponder was implemented in April 2015, records of cases were only available from January 2016. For this study, de-identified records between January 2016 and December 2017 were used.

Study design and outcomes

This retrospective cohort study examined OHCA cases and outcomes in Singapore from 1 April 2010 to 31 December 2017. In this study, Period I corresponds to the baseline period from 1 April 2010 to 30 June 2012, where there were no significant interventions implemented to increase B-CPR. Period II corresponds to the period after implementation of DA-CPR (1 July 2012 to 31 March 2015), while Period III corresponds to the period with both DA-CPR and myResponder (1 April 2015 to 31 December 2017).

The primary exposure was the implementation of the respective interventions in each period. The primary outcome was B-CPR rate. B-CPR is defined as CPR initiated by any individual including passers-by, family members or off-duty healthcare professionals; it excludes on-duty EMS first responders, on-duty law enforcement officers and on-duty medical staff.

The secondary outcomes were survival-to-hospital discharge, and Utstein survival. Survival-to-hospital discharge in this study is defined as being discharged alive from hospital or remaining alive in hospital 30 days post-arrest. Utstein survival is a standardised format that facilitates reporting of OHCA resuscitation outcomes for comparison with other studies and represents cases where there are opportunities for intervention to improve survival outcomes. It is thus a consensus measurement of EMS system efficacy. To determine Utstein survival, only cases that are bystander-witnessed and presented with a shockable rhythm were included in the analysis[13].

Inclusion criteria

Both adult and paediatric cases were included in this study. Cases with no prehospital resuscitation attempted, not attended to by the EMS, or that were EMS-witnessed, were excluded from the study. Cases with missing data for any study variable were also excluded.

Ethics approval

SingHealth Centralised Institutional Review Board and National Healthcare Group Domain Specific Review Board granted approval with waiver of patient's informed consent for this study.

Statistical methods

Data analysis was carried out using software R version 3.6.1 for all statistical analysis. There were no missing data for any of the primary and secondary outcomes, as well as other relevant variables included in the analysis.

Univariate analyses were performed to compare the characteristics and survival outcomes of OHCA cases in the 3 periods. Chi-square test was used for categorical variables, and one-way ANOVA for continuous variables.

B-CPR rates from 1 April 2010 to 31 December 2017 were plotted as a time-series to visualise the differences in B-CPR rates over time. The primary and secondary hypotheses of increased B-CPR, survival-to-hospital discharge, and Utstein survival after the implementation of DA-CPR and myResponder, were tested using a segmented regression analysis of time series data. This analysis allows us to determine the impact each intervention has on B-CPR rates immediately and cumulatively over time, while accounting for baseline trends.[14,15] It also allows us to circumvent the limitation of possible underreporting of B-CPR contributed by myResponder as the database relies on volunteers reporting their arrival, which may be inaccurate. By comparing all cases before and after myResponder intervention, we can determine myResponder's impact on our outcomes over time without requiring arrival information for each case. We recoded 5 variables on a month-on-month basis for 2 interventions (namely, DA-CPR and myResponder) to accommodate the segmented regression framework. The framework comprises baseline trend (a continuous variable representing time since the beginning of the observation period); immediate or "level" effect of each intervention (coded 0 before the intervention and 1 after the intervention); and rate of increase or "trend" effect of each intervention (coded 0 before the start of the intervention and coded as a continuous variable after the intervention). Multivariable logistic regression was performed with these variables included, adjusted for predictors that were significant at P value of <0.20 based on a univariate analysis. Statistical significance was set at $P<0.05$.

RESULTS

A total of 15,355 OHCA cases occurred from April 2010 to December 2017, with 13,829 cases included in our analysis after excluding cases with no prehospital resuscitation, not EMS-attended, and EMS-witnessed. A small number (n=6) with incomplete hospital outcomes were also excluded (Fig. 2). We compared the characteristics and outcomes of OHCA cases that occurred during the 3 periods (Table 1). Mean age of patients increased across the 3 time periods (63.6 versus 65.7 vs 67.1, $P<0.001$). A greater proportion of cases were witnessed by bystanders (53.7% vs 56.2% vs 59.9%, $P<0.001$) and occurred in residential locations over time (72.9% vs 73.9% vs 75.6%, $P<0.001$). Proportion of cases with shockable rhythm (19.2% vs 17.5% vs 16.1%, $P<0.001$) and a presumed cardiac aetiology (75.5% vs 69.3% vs 66.6%, $P<0.001$) decreased over time. There was an increase in the proportion of cases with B-CPR (24.8% vs 50.8% vs 64.4%, $P<0.001$), with bystander AED (1.8% vs 3.3% vs 5.5%, $P<0.001$), survival-to-hospital discharge (2.6% vs 3.7% vs 4.8%, $P<0.001$), and Utstein survival (12.4% vs 16.0% vs 21.6%, $P<0.001$) over time.

We plotted the trendline for yearly B-CPR rates from January 2010 to December 2017 (Fig. 3**)**. B-CPR rates are shown in this diagram to account for the increasing number of OHCA cases over time; yearly B-CPR rates were calculated by dividing the number of cases recorded to have received B-CPR over the total number of OHCA cases that occurred in that year. We noted an increase in B-CPR rates in 2012 after DA-CPR was introduced, followed by a gradual increase in B-CPR rates that appear to be plateauing over time. In addition, both the absolute number of OHCA cases and proportion of cases with B-CPR over the years have increased, in keeping with Singapore's ageing population. Similarly, cases associated with DA-CPR and myResponder have also increased over the years since their respective year of implementation.

Table 2 shows the segmented regression analysis for B-CPR, survival-to-hospital discharge, and Utstein survival after adjusting for underlying survival trends and other known predictors. Period II was significantly associated with an increase in odds of receiving B-CPR both immediately after the implementation of DA-CPR (level odds ratio [OR] 2.26, 95% confidence interval [CI] 1.79–2.88, $P<0.001$) and in the month-to-month trend (trend OR 1.03, 95% CI: 1.01–1.04, $P=0.006$). No level change was detected in Period III (OR 0.95, 95% CI 0.82–1.11, $P=0.52$), while a slight reduction in rate of increase was noted, in line with our observed trend of positive but plateauing B-CPR rates (OR 0.99, 95% CI 0.98–1.00, $P=0.04$). On the other hand, there were no changes in the adjusted

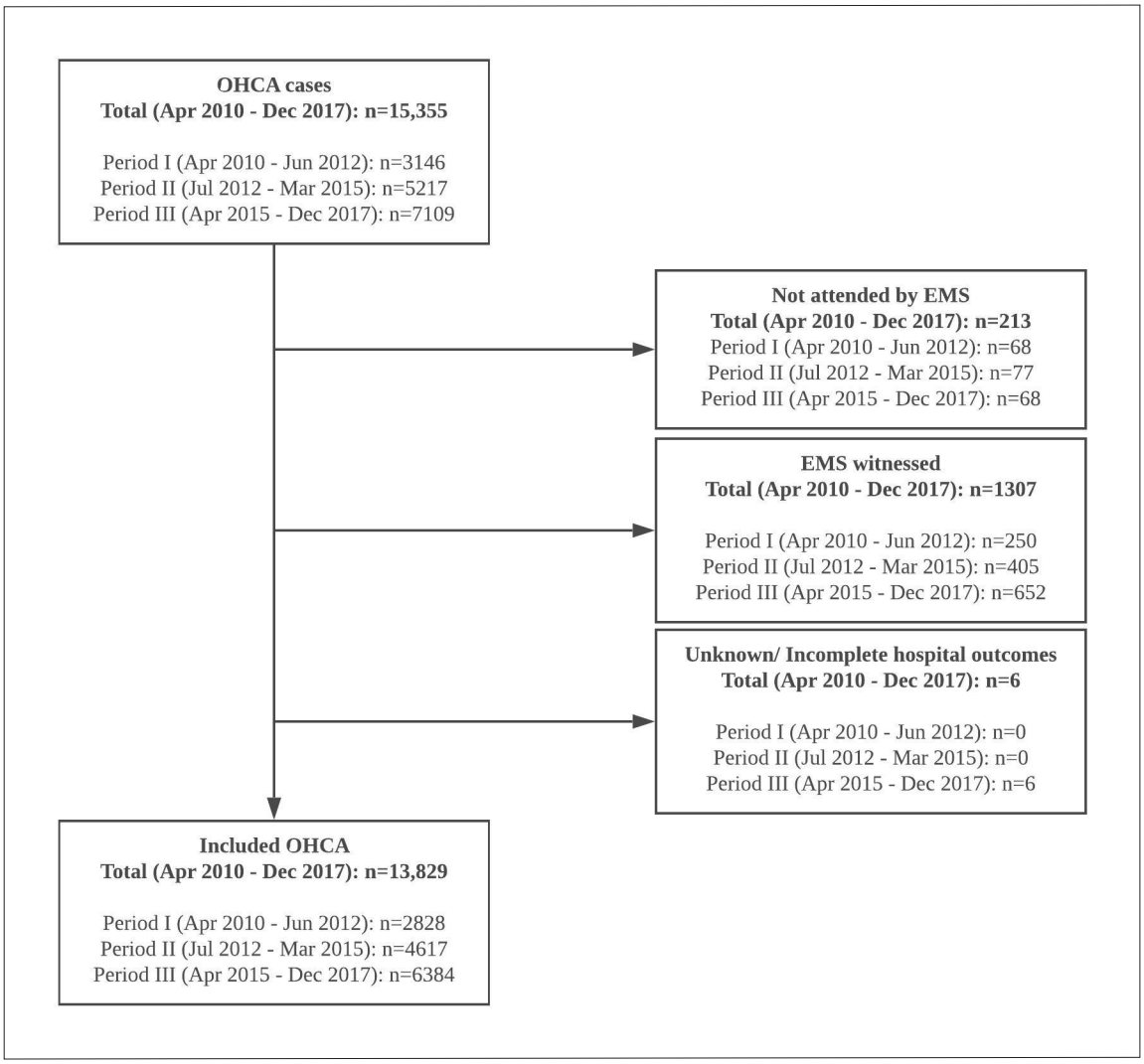

Fig 2. Inclusion criteria.
EMS: emergency medical service; OHCA: out-of-hospital cardiac arrest

odds of survival-to-hospital discharge in both Period II (level OR 0.85, 95% CI 0.46–1.62, *P*=0.61; trend OR 0.98, 95% CI 0.93–1.03, *P*=0.47) and Period III (level OR 1.21, 95% CI 0.82–1.40, *P*=0.34; trend OR 0.99, 95% CI 0.97–1.01, *P*=0.30). Similarly, for Utstein survival, adjusted odds ratio showed no significant level and trend change in both Period II (level OR 1.03, 95% CI 0.30–4.33, *P*=0.96; trend OR 0.87, 95% CI 0.74–1.01, *P*=0.08) and III (level OR 1.76, 95% CI 0.85–3.76, *P*=0.13; trend OR 1.00, 95% CI 0.96–1.04, *P*=0.94).

DISCUSSION

This retrospective cohort study was designed to examine the effect of 2 community-level interventions on B-CPR and survival over time.

Our study showed that B-CPR rates had improved over the 3 time periods, from 23.1% in 2010 to 67.3% in 2017. A visual inspection of yearly B-CPR rates showed an increasing but plateauing trend. Up-to-date literature trending B-CPR rates elsewhere is limited. In the US, a rising trend is similarly noted, reaching up to 43.6% in 2015.[16] In Sweden, B-CPR rates increased from 46% to 73% from 1990 to 2009.[17] In a previous study comparing OHCA outcomes from 7 countries under the PAROS network, B-CPR rate varied from 10.5% to 40.9% in the period between 2009 and 2012.[18] These suggest that good progress has been made in improving B-CPR rates in Singapore over the years.

Specifically, we noted that the implementation of DA-CPR correlated with a positive level and trend change in the odds of receiving B-CPR, while no change

Table 1. Comparison of clinical characteristics of OHCA cases

Characteristics	Period I	Period II	Period III	
	Baseline	DA-CPR implementation	DA-CPR + myR implementation	
	Apr 2010–Jun 2012	Jul 2012–Mar 2015	April 2015–Dec 2017	*P* value
	n=2828	n=4617	n=6384	
Age, mean (SD), years	63.6 (17.9)	65.7 (17.9)	67.1 (18.4)	<0.001
Sex, no. (%)				
Female	945 (33.4)	1616 (35.0)	2349 (36.8)	0.005
Male	1883 (66.6)	3001 (65.0)	4035 (63.2)	
Arrest witnessed by, no. (%)				
Bystander	1515 (53.6)	2596 (56.2)	3822 (59.9)	<0.001
Not witnessed	1313 (46.4)	2021 (43.8)	2562 (40.1)	
First arrest rhythm, no. (%)				
Shockable	543 (19.2)	809 (17.5)	1029 (16.1)	0.001
Unshockable	2285 (80.8)	3808 (82.5)	5355 (83.9)	
Location type, no. (%)				
Residential	2062 (72.9)	3412 (73.9)	4827 (75.6)	0.01
Non-residential	766 (27.1)	1205 (26.1)	1557 (24.4)	
EMS response time interval (RTI), min				
Median (IQR)	07:56 (05:59–10:17)	08:35 (06:37–11:05)	08:20 (06:39–10:25)	<0.001
0–4 min, no. (%)	388 (13.7)	397 (8.6)	430 (6.7)	<0.001
5–7 min, no. (%)	1046 (37.0)	1547 (33.5)	2438 (38.2)	
≥ 8 min, no. (%)	1394 (49.3)	2673 (57.9)	3516 (55.1)	
Medical history, no. (%)				
Heart disease	1027 (36.3)	1678 (36.3)	2284 (35.8)	0.79
Diabetes mellitus	815 (28.8)	1525 (33.0)	2096 (32.8)	<0.001
Hypertension	1346 (47.6)	2529 (54.8%)	3524 (55.2)	<0.001
Cause of cardiac arrest, no. (%)				
Presumed cardiac	2136 (75.5)	3198 (69.3)	4251 (66.6)	<0.001
Non-cardiac	692 (24.5)	1419 (30.7)	2133 (33.4)	
Outcomes, no. (%)				
Bystander CPR	701 (24.8)	2346 (50.8)	4112 (64.4)	<0.001
Bystander AED	50 (1.8)	153 (3.3)	351 (5.5)	<0.001
Pre-hospital ROSC	777 (27.5)	1445 (31.0)	1956 (30.6)	0.001
Survival to admission	351 (12.4)	844 (18.3)	1164 (18.2)	<0.001
Survival to hospital discharge	74 (2.6)	169 (3.7)	309 (4.8)	<0.001
Utstein survival	42 (12.4)	93 (16.0)	162 (21.6)	<0.001

AED: automated external defibrillator; DA-CPR: dispatcher-assisted cardiopulmonary resuscitation; myR: myResponder; ROSC: return of spontaneous circulation

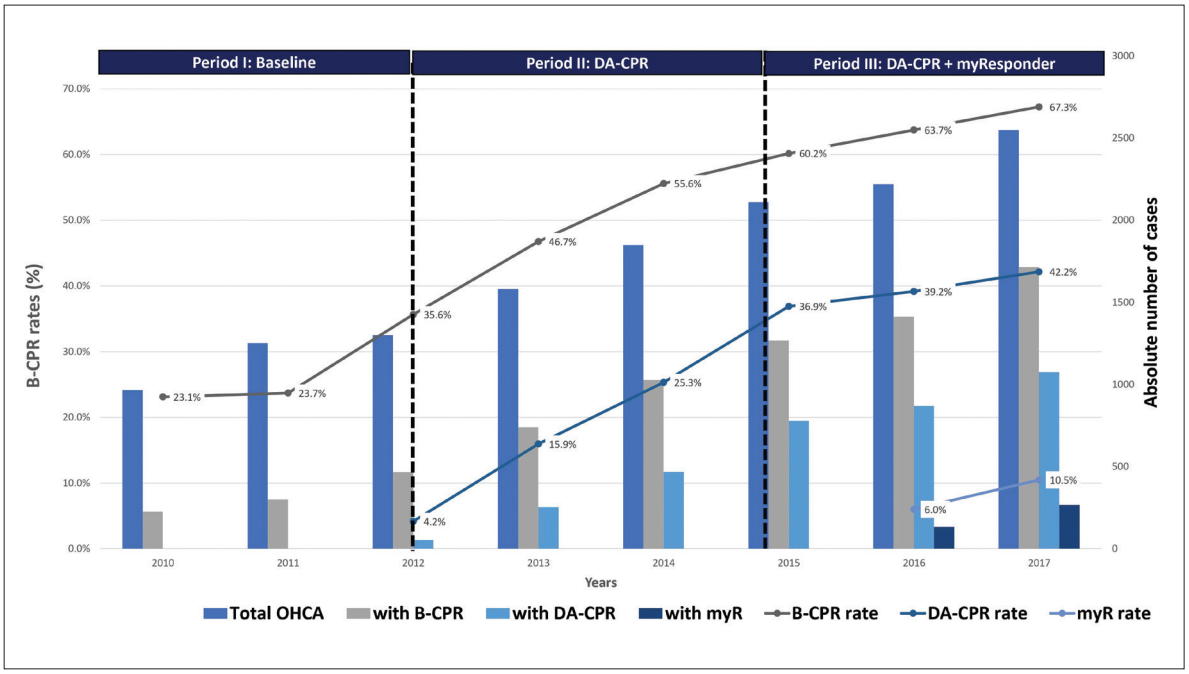

Fig 3. Time series of bystander CPR (B-CPR) rates from 2010 to 2017.
Time series of bystander CPR rates are indicated by solid black line. Also shown are the percentages of OHCA cases with interventions reported (DA-CPR rate and myR rate). In the clustered columns are the absolute number of cases associated with each intervention. For myResponder, data were only available starting from January 2016.
OHCA: out-of-hospital cardiac arrest; DA-CPR: dispatcher-assisted CPR; myR: myResponder mobile application

in level and a slight reduction in rate of increase was observed with myResponder implementation.

Several studies from other countries have shown that the implementation of community-level interventions were associated with improved bystander CPR rates, although the interventions evaluated in each of these studies differed.[5,19,20] Other studies have evaluated the individual effect of DA-CPR and mobile phone dispatch services on B-CPR rates; the positive association between DA-CPR and B-CPR rates is well-studied,[21-23] while a randomised controlled trial in Stockholm showed that a mobile app similar to myResponder was significantly associated with increased rates of B-CPR.[24]

Our unpublished descriptive analyses revealed that a combination of factors—including a plateauing trend in DA-CPR; potential implementation lag time and lack of optimisation of myResponder that resulted in lower-than-expected activation rates; and a substantial overlap in cases with both DA-CPR and myResponder—may explain the plateauing trend in B-CPR rates and why the implementation of myResponder was not associated with any increased odds of B-CPR.

Meanwhile, other studies have reported variable survival outcomes after the implementation DA-CPR,[25] with a systematic review reporting limited evidence in improvement of survival associated with this intervention.[26] For example, higher survival rates were reported in King County (OR1.45, 95% CI 1.21–1.73)[22] and Arizona (OR 1.5, 95% CI 1.1–2.1) in the US,[25] while a reduction was seen in a study in Ottawa in Canada (4.8% in control period to 3.0% after intervention).[23] On the other hand, a text message alert system to activate trained volunteer to OHCA cases in the Netherlands was associated with increased survival-to-hospital discharge (OR 2.82, 95% CI 1.52–5.24).[27]

Several reasons may explain why we did not observe statistical significance for survival with both interventions. Firstly, the presence of B-CPR alone may not translate to improved survival if high-quality CPR is not administered. Both DA-CPR and myResponder do not track the quality of B-CPR done on patients, nor do they require laypersons to have valid certifications in CPR training before they are instructed to do DA-CPR or are dispatched to an OHCA scene as a myResponder volunteer. It is likely that patients had received B-CPR of variable quality with our interventions. For myResponder, it is conceivable that in some cases, volunteers were unable to arrive substantially early enough to improve the patient's chance of survival.

Table 2. Adjusted odds ratio comparing B-CPR, survival-to-hospital discharge, and Utstein survival

	B-CPR[a]		Survival to hospital discharge[b]		Utstein survival[c]	
	Adjusted OR (95% CI)	***P* value**	**Adjusted OR (95% CI)**	***P* value**	**Adjusted OR (95% CI)**	***P* value**
Period I (10 Apr–12 Jun)						
1st month of period (10 Apr)	1.00		1.00		1.00	
Trend change	1.00 (0.98–1.02)	0.86	1.03 (0.98–1.08)	0.21	1.14 (0.99–1.35)	0.09
Period II (12 Jul–15 Mar)						
Period I (10 Apr– 12 Jun)	1.00		1.00		1.00	
Level change	2.26 (1.79–2.88)	<0.001[d]	0.85 (0.46–1.62)	0.61	1.03 (0.30–4.33)	0.96
Trend change	1.03 (1.01–1.04)	0.006[d]	0.98 (0.93–1.03)	0.47	0.87 (0.74–1.01)	0.08
Period III (15 Apr–17 Dec)						
Period I to II (10 Apr– 15 Mar)	1.00		1.00		1.00	
Level change	0.95 (0.82–1.11)	0.52	1.21 (0.82–1.80)	0.34	1.76 (0.85–3.76)	0.13
Trend change	0.99 (0.98–1.00)	0.04[d]	0.99 (0.97–1.01)	0.30	1.00 (0.96–1.04)	0.94
Other Predictors						
Sex	-	-	0.98 (0.78–1.24)	0.89	-	-
Age	-	-	1.69 (1.38–2.08)	<0.00 [d]	1.66 (1.16–2.39)	0.006[d]
Location	1.79 (1.64–1.02)	<0.001[d]	2.09 (1.72–2.54)	<0.001[d]	2.17 (1.51–3.11)	<0.001[d]
Witnessed	1.26 (1.17–1.02)	<0.001[d]	2.03 (1.62–2.57)	<0.001[d]	-	-
Rhythm	-	-	8.74 (7.03–10.92)	<0.001[d]	-	-
Response time interval	-	-	1.49 (1.24–1.79)	<0.001[d]	1.32 (0.93–1.87)	0.11
Aetiology	-	-	0.64 (0.51–0.82)	<0.001[d]	2.05 (1.45–2.90)	<0.001[d]

[a]Adjusted for location and witness status. Sex, age and aetiology were excluded from the multivariable logistic regression.
[b]Adjusted for sex, age, location, witness status, rhythm, response time interval and aetiology.
[c]Adjusted for age, location, response time interval and aetiology. Sex was excluded from the multivariable logistic regression.
[d]*P* value<0.05.

Furthermore, only early CPR was assessed in this study; the effects of other links in the chain of survival such as public AED utilisation rates (rapid defibrillation), management by the EMS (basic and advanced EMS), and management at the emergency department and hospital (advanced life support and post-cardiac arrest care) were not evaluated.

Limitations and future research

As an observational study, we are unable to establish the causative relationship between our interventions and the increase in B-CPR rates over time. The Save-A-Life (SAL) initiative, an intervention piloted shortly after myResponder in July 2015,[28] was not explicitly accounted for in our segmented regression analysis. This intervention involved free, standardised CPR and AED training to members of the public, as well as installation of publicly accessible AEDs at the ground floor of government housing estates. Also, the Dispatcher-Assisted first REsponder (DARE) programme in Singapore was introduced in April 2014 as a simplified CPR/AED course for members of public to gain skills and confidence in performing compression-only CPR and using the AED under the instructions of a dispatcher. Both interventions were not identified as separate segments in our analysis as public education on CPR/AED, in different formats, has been ongoing throughout the observation period. Hence, the impact of public education as a whole could likely have contributed to the increasing B-CPR trend, although we are unable to quantify this due the limitation of our study's methodology. Nonetheless, we note that there was no

clear change in level or gradient at the time of implementation of both SAL and DARE on visual inspection of the month-on-month trendline for B-CPR rates. We were also unable to evaluate our interventions' impact on the long-term quality of life and functional outcome of the OHCA patients, due to missing data at the point of writing.

Records of time of arrival of myResponder bystanders were available but could be inaccurate as it requires the responder to indicate their own arrival, which they may not have done while being engaged at the scene. For B-CPR related to myResponder, additional in-app functions, such as geo-fencing, may help to better track responders' timeliness.

Future studies could be carried out to address some of the trends observed in this paper. To assess the plateauing B-CPR trend, a focused analysis on cases with no B-CPR can be conducted to examine the common factors that might explain the absence of B-CPR in these cases and to understand why our interventions had limited impact on these cases. We may also perform analyses to evaluate how myResponder can be further optimised to improve both B-CPR rates and survival. The possibility of myResponder augmenting B-CPR in nursing homes could be studied; a recent study suggests that a proportion of nursing home residents may have received inadequate resuscitation despite trained NH staff.[29] In addition, audiovisual CPR feedback appears to improve the quality of CPR during training[30] and the incorporation of a similar feedback function into myResponder could be considered. Lastly, as prehospital defibrillation significantly reduces mortality,[31] we can also explore how myResponder may be optimised to enable community responders to retrieve nearby AEDs more efficiently. Findings from these additional studies may help us to fine-tune these ongoing interventions to improve B-CPR rates and survival outcomes.

CONCLUSION

B-CPR rates in Singapore have shown an increasing trend alongside the implementation of community-level interventions such as DA-CPR and myResponder. The implementation of DA-CPR was associated with improved odds of receiving B-CPR over time while the impact of myResponder was less clear. A focus on high-quality CPR by laypersons and retrieval of AED via myResponder are potential future strategies to improve survival outcomes. Future studies are needed to better understand the plateauing B-CPR trend and to identify ways to optimise survival.

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ORIGINAL ARTICLE

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Behavioural changes during the COVID-19 pandemic: Results of a nationwide survey in Singapore

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ABSTRACT

Introduction: As part of infection control measures for COVID-19, individuals have been encouraged to adopt both preventive (such as handwashing) and avoidant behavioural changes (e.g. avoiding crowds). In this study, we examined whether demographics predicted the likelihood that a person would adopt these behaviours in Singapore.

Methods: A total of 1,145 participants responded to an online survey conducted between 7 March and 21 April 2020. We collected demographic information and asked participants to report which of 17 behaviour changes they had undertaken because of the COVID-19 outbreak. Regression analyses were performed to predict the number of behavioural changes (preventive, avoidant, and total) as a function of demographics. Finally, we sought to identify predictors of persons who declared that they had not undertaken any of these measures following the outbreak.

Results: Most participants (97%) reported at least one behavioural change on account of the pandemic, with changes increasing with the number of local COVID-19 cases ($P<0.001$). Additionally, women and those who were younger adopted more preventive behaviours (gender: $P<0.001$; age: $P=0.001$). Women were more likely to increase handwashing frequency, and younger individuals were more likely to wear face masks prior to legislation. Finally, women and those who were married adopted more avoidant behaviours (gender: $P<0.001$; marital status: $P<0.001$), with both groups avoiding crowded areas and staying home more than usual. Women also voluntarily reduced physical contact, whereas those who were married preferentially chose outdoor venues and relied on online shopping.

Conclusion: Our characterisation of behavioural changes provides a baseline for public health advisories. Moving forward, health authorities can focus their efforts on encouraging segments of the population who do not readily adopt infection control measures against COVID-19.

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Keywords: Behaviour, COVID-19, epidemic, infectious diseases, public health

INTRODUCTION

In response to the global outbreak of coronavirus disease 2019 (COVID-19), Singapore undertook a multipronged approach to contain the pandemic. Of note, when community transmission began early in the outbreak, the government started emphasising the role that individuals had to play by adopting health-preventive behaviours.[1,2]

In an infectious disease outbreak such as the COVID-19 pandemic, individual-level health-protective behaviours can be classified into preventive behaviours—measures that can prevent transmission (e.g. hand-washing and wearing a mask), and avoidant behaviours—measures that decrease contact with other individuals (e.g. avoiding crowded areas).[3] As COVID-19 is believed to be transmitted primarily through contact or droplet transmission, these measures can be effective in reducing the spread of the virus, particularly when pharmacological interventions are limited.[4,5]

For risk communication, it is useful to understand what characteristics predict whether an individual adopts health-protective behaviours. This allows public health messaging to be targeted, improving compliance in groups that may not do so as readily. For example, in the previous outbreak of severe acute respiratory syndrome (SARS), preventive and avoidant behaviours were more likely to be adopted by: women, older individuals,

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CLINICAL IMPACT

What is New

- In the early stage of the pandemic, most participants voluntarily adopted health-protective behaviours.
- Women and those who were married adopted the most number of behavioural changes.
- Preventive behaviours were more likely to be adopted than avoidant behaviours.

Clinical Implications

- Public health messages can be customised based on demographics (e.g. gender, marital status).
- Stronger measures (e.g. legislation) may need to be explored to increase avoidant behaviours.

and those with higher education levels.[3] In the current COVID-19 outbreak, health-protective behaviours have been observed among individuals who perceive a higher risk of infection, higher disease severity, or who are afraid of getting infected.[6–8] However, demographic predictors have differed between populations studied: while age and gender were linked to behavioural changes in South Korea, these associations were not found in the UK.[7,8] Furthermore, no demographic predictors were identified in a study in the US, while gender—but not age—predicted behavioural changes in a cross-country survey.[9,10] This heterogeneity suggests that the uptake of health-protective behaviours may be context-specific during the COVID-19 pandemic, owing perhaps to heterogeneity in the risks of infection or severe illness between countries.

To address the context-specificity of previous findings, we conducted a large-scale survey to examine how demographics predict the uptake of health-protective behaviours in Singapore. Our study was conducted from March to April 2020, a period when the country saw a rapid increase in COVID-19 cases (from 138 cases at the start of the study, to 9,125 cases at the end of the survey period).

METHODS

Study design and population

From 7 March to 21 April 2020, 1,145 participants responded to an online survey on COVID-19.[13] As the inclusion criteria, participants were aged ≥21 years old, and had lived in Singapore for ≥2 years. Given public health concerns, participants were recruited online via advertisements placed in community chat groups (e.g. Facebook and WhatsApp groups for residential estates, universities, or interest groups) or via paid Facebook advertisements targeting Singapore-based users. The study was approved by the Yale-NUS College Ethics Review Committee, and participants gave written consent in accordance with the Declaration of Helsinki. The questions reported in this study were part of a larger 20-minute survey exploring: behavioural and psychological responses to COVID-19; sources from which participants received COVID-19 news; and psychological well-being (https://osf.io/pv3bj).[11]

Predictor variables

As predictors, participants reported the following demographic details: gender, ethnicity, religion, country of birth, marital status, education, house type and household size. As behavioural changes may be influenced by the local COVID-19 situation, we also recorded the total number of local cases reported to date, and whether the country was locked down (referred to as "circuit breaker" in Singapore) when the survey was done.

Outcome variables

As the key outcome variables, participants indicated which of 17 health-protective behaviours they had voluntarily undertaken because of the pandemic (by indicating "yes" or "no" for each behaviour). Based on prior research,[3] we investigated 3 preventive behaviours, asking participants whether they had: (1) washed their hands more frequently, (2) used hand sanitisers and/or (3) wore a mask in public (prior to legislation). Additionally, we investigated 14 possible avoidant behaviours, whether participants had: (1) avoided crowded areas, (2) reduced physical contact (e.g. avoided shaking hands), (3) stayed home more than usual, (4) distanced from people with flu symptoms, (5) voluntarily changed their travel plans, (6) missed or postponed social events, (7) avoided visiting hospitals and/or healthcare settings, (8) chose outdoor over indoor venues, (9) distanced from people with recent travel to outbreak countries, (10) distanced from people with possible contact with COVID-19 cases, (11) avoided places where COVID-19 cases were reported, (12) stored up more household and/or food supplies than usual, (13) relied more on online shopping (prior to shop closures), and/or (14) avoided public transport. Across the 17 items, we assigned a score of "1" for "yes" responses, and these were summed to create three scores: the total number of behavioural changes adopted (out of 17), the total number of preventive behaviours adopted (subscale score out

of 3), and the total number of avoidant behaviours adopted (subscale score out of 14).

Finally, we included as a separate item the following statement: "I did not take any additional measures" (yes/no response). This question allowed us to identify participants who had not made any behavioural changes as a function of COVID-19: a group that may be of higher risk for transmission.

Statistical analyses

To describe participants' demographic characteristics, survey responses were summarised with counts and medians. As the primary analysis, we then ran a linear regression model with the total number of behavioural changes as the outcome measure, and participant demographics as predictors (age, gender, ethnicity, religion, country of birth, marital status, education, house type, household size, the total number of local cases reported to date, and whether the country was locked down at the time of survey completion) (Model 1). Given that prior research distinguished preventive and avoidant behaviours,[3,12] we repeated the linear regression model with the total number of preventive behaviours (Model 2), and the total number of avoidant behaviours as outcomes (Model 3). Finally, using the same demographic predictors, we ran a logistic regression model to identify individuals who had made no behavioural changes (Model 4).

For linearity, the number of local COVID-19 cases was log-transformed prior to regression analyses. For each regression model, the type 1 family-wise error rate was controlled at 0.05 through Bonferroni correction (Bonferroni-adjusted alpha level of 0.05 / 23 predictors = 0.002). All statistical analyses were conducted using R version 4.0 and STATA version 12.0 (StataCorp LLC, College Station, US).

RESULTS

Response rate

Of 1,390 individuals who clicked the survey link, 1,145 (82.4%) provided informed consent and participated in the survey. A further 192 (16.77%) participants were excluded from statistical analyses as they did not complete the primary outcome measures (on behavioural changes).

As shown in Table 1, the final sample of 953 participants was comparable to the resident Singapore population in: the proportion of Singapore citizens, marital status, and household size (≤10% difference). However, the pool of respondents had a greater representation of women (65.1% versus 51.1%), university graduates (72.7% vs 32.4%), persons of no religion (28.0% vs 18.5%) or of Christian belief (36.2% vs 18.8%). Conversely, there was a reduced representation of participants who lived in 1–3-room public housing flats (6.7% vs 23.7%). Survey respondents were also more likely to be of Chinese ethnicity than persons in the general population (87.0% vs 74.3%).

Overview of COVID-19 behaviour changes

On the whole, participants adopted a median of 8 (interquartile range [IQR] 5–11) behavioural changes owing to the COVID-19 pandemic. This corresponded to a median of 2 (IQR 2–3) preventive measures, and 6 (IQR 3–8) avoidant measures.

When we accounted for the number of possible changes within each category (dividing the scores by 3 and 14, respectively), we found that participants were more likely to adopt preventive than avoidant measures (paired t-test of averaged preventive vs avoidant scores: $t(952)=30.3$, $P<0.001$). Only 29 participants (3.04%) reported that they had not changed their behaviours at all.

Predicting behavioural change: regression models

In our first regression model, we sought to predict the total number of behavioural changes based on participant demographics (Table 2). We first observed that behavioural changes tracked the local COVID-19 situation: namely, as the number of local cases increased, individuals adapted their behaviours in response ($b=3.03$, $t(913)=3.96$, $P<0.001$). Having controlled for local transmission, gender emerged as a significant predictor, with women adopting an average of 0.14 more changes than men ($t(913)=-4.49$, $P<0.001$). Being married was also associated with a higher number of health-protective behaviours than being single ($b=1.09$, $t(913)=3.52$, $P<0.001$).

In our second and third models, we examined whether demographic predictors differed for preventive vs avoidant behaviours. In terms of demographics, while the adoption of preventive behaviours was predicted by gender ($b=-0.241$, $t(913)=-4.33$, $P<0.001$) and age ($b=-0.008$, $t(913)=-3.11$, $P=0.001$), the adoption of avoidant behaviours was predicted by gender ($b=-0.902$, $t(913)=-3.90$, $P<0.001$) and marital status (being married vs being single; $b=0.973$, $t(913)=3.45$, $P<0.001$).

Finally, in our fourth model, we found that no demographic predictor significantly identified the small

Table 1. Baseline demographics of participants

Characteristic	n	(%)
Age group (Mean=39.5, SD=12.6)		
Gender		
Female	620	(65.1)
Male	333	(34.9)
Did not answer	0	
Ethnicity		
Chinese	829	(87.0)
Indian	46	(4.8)
Malay	25	(2.6)
Filipino	15	(1.5)
Caucasian	13	(1.3)
Others	1	(0.1)
Did not answer	24	(2.5)
Religion		
Christianity (Protestant)	345	(36.2)
No religion	267	(28.0)
Buddhism	138	(14.5)
Roman Catholicism	98	(10.2)
Taoism/ Chinese traditional beliefs	38	(4.0)
Islam	33	(3.4)
Hinduism	27	(2.8)
Others	6	(0.6)
Did not answer	1	(0.1)
Marital status		
Married	534	(56.0)
Single	391	(41.0)
Widowed/ separated/ divorced	27	(2.8)
Did not answer	1	(0.1)
Education level		
1: Primary school	3	(0.3)
2: Secondary school	44	(4.6)
3: Junior college	82	(8.6)
4: Vocational training	14	(1.4)
5: Polytechnic/ diploma	114	(11.9)
6: University (undergraduate)	486	(51.0)
7: University (postgraduate)	207	(21.7)
Did not answer	3	(0.3)

Table 1. Baseline demographics of participants (Cont'd)

Characteristic	n	(%)
House type		
1: HDB flat: 1–2 rooms	8	(0.8)
2: HDB flat: 3 rooms	64	(6.7)
3: HDB flat: 4 rooms	233	(24.4)
4: HDB flat: 5 rooms or executive flats	265	(27.8)
5: Condominium or private apartments	260	(27.2)
6: Landed property	111	(11.6)
Did not answer	12	(1.2)
Household size		
1	44	(4.6)
2	124	(13.0)
3	210	(22.0)
4	292	(30.6)
5+	282	(29.5)
Did not answer	1	(0.1)
Country of birth		
Singapore	757	(79.4)
Others	196	(20.5)

proportion of individuals who had not undertaken any measures on account of COVID-19 (all $P>$ Bonferroni-adjusted alpha of 0.002).

Follow-up exploratory analyses

Examining whether behavioural changes tracked subjective responses to the COVID-19 situation

To understand the regression models, we conducted exploratory analyses on variables that had emerged as significant predictors. As behavioural changes tracked the number of COVID-19 cases, we examined whether this pattern of results arose from fear of the situation.[11] We found that participants' fear increased with the number of local cases (Spearman's rho = 0.18, $P<0.001$), and that all 3 metrics of behavioural changes increased with fear levels (Spearman's rho for total: 0.36, $P<0.001$; preventive: 0.23, $P<0.001$; avoidant: 0.35, $P<0.001$).

Understanding which behavioural changes differed as a function of gender, marital status and age

We further conducted follow-up chi-square analyses on the three demographic variables that had emerged as significant predictors in the regression models.

Table 2. Predicting behavioural changes during the COVID-19 outbreak

	Outcome[a]			
	(1) Total number of behaviours	**(2) Preventive behaviours**	**(3) Avoidant behaviours**	**(4) No behaviour changes adopted**
Age	-0.002 (0.011)	-0.008 (0.002)[b]	0.005 (0.010)	0.041 (0.018)
Gender (base = female)				
Male	-1.14 (0.254)[b]	-0.241 (0.055)[b]	-0.902 (0.231)[b]	0.757 (0.411)
Ethnicity (base = Chinese)				
Indian	-1.20 (1.39)	-0.743 (0.304)	-0.463 (1.26)	-31.4 (268)
Malay	-1.01 (0.949)	-0.397 (0.208)	-0.620 (0.863)	-13.4 (172)
Filipino	1.04 (1.10)	0.430 (0.242)	0.617 (1.00)	-29.4 (327)
Caucasian	-0.004 (1.05)	-0.318 (0.796)	0.313 (0.962)	-15.6 (292)
Others	1.42 (3.63)	-2.21 (0.085)	3.64 (3.30)	-14.6 (1080)
Religion (base = no religion)				
Christianity (Protestant)	0.795 (0.390)	0.172 (0.085)	0.623 (0.354)	-0.542 (0.518)
Buddhism	0.291 (0.632)	0.037 (0.138)	0.254 (0.574)	-1.20 (0.816)
Roman Catholicism	0.800 (1.34)	0.360 (0.294)	0.440 (1.21)	-13.7 (1.10)
Taoism/ Chinese traditional beliefs	1.63 (1.18)	-0.034 (0.259)	1.32 (1.07)	-0.555 (1.10)
Islam	0.647 (0.463)	-0.034 (0.101)	0.681 (0.421)	15.5 (172)
Hinduism	0.209 (0.310)	-0.014 (0.400)	0.223 (0.282)	31.3 (268)
Others	-4.07 (1.82)	-0.629 (0.400)	-3.44 (1.65)	2.08 (1.26)
Marital status (base = single)				
Married	1.09 (0.309)[b]	0.117 (0.067)	0.973 (0.281)[b]	-0.739 (0.552)
Widowed/ separated/ divorced	-0.495 (0.433)	0.009 (0.094)	-0.504 (0.393)	-0.750 (0.850)
Education level	0.003 (0.093)	-0.005 (0.020)	0.009 (0.084)	-0.342 (0.126)
House type	0.141 (0.113)	0.014 (0.024)	0.126 (0.102)	-0.064 (0.185)
Household size	-0.013 (0.114)	0.047 (0.025)	-0.060 (0.103)	0.124 (0.208)
Country of birth (base =Singapore)				
Other	-0.730 (0.338)	-0.152 (0.074)	-0.578 (0.307)	-0.169 (0.589)
Lockdown (base = no)				
Lockdown	-1.76 (0.017)	-0.621 (0.161)[b]	-1.138 (0.670)	-0.043 (1.21)
Number of local COVID-19 cases (log transformed)	3.03 (0.612)[b]	0.531 (0.134)[b]	2.50 (0.556)[b]	-0.151 (0.986)
R^2	0.123	0.091	0.124	0.144

[a] Data reported as beta estimates (standard error)
[b] Indicates significance at $P<0.002$ (following Bonferroni corrections)

Gender. As shown in Fig. 1, women were more likely than men to: (1) wash their hands more frequently ($\chi^2(1, N=953) = 22.17$, $P<0.001$); (2) avoid crowded areas, ($\chi^2(1, N=953) = 11.83$, $P=0.001$); (3) reduce physical contact ($\chi^2(1, N=953) = 9.28$, $P=0.002$); and (4) stay home more than usual ($\chi^2(1, N=953) = 9.79$, $P=0.002$).

Marital status. As shown in Fig. 2, marital status was significantly associated with: avoiding crowded areas ($\chi^2(2, N=952) = 26.29$, $P<0.001$); (2) staying home more than usual ($\chi^2(2, N=952) = 28.09$, $P<0.001$); (3) choosing outdoor over indoor areas ($\chi^2(2, N=952) = 33.04$, $P<0.001$); and (4) relying more on online shopping ($\chi^2(2, N=952) = 26.37$, $P<0.001$). In each case, single participants were least likely to adopt these behaviours than those who were not single (married, widowed, separated or divorced).

Age. Finally, wearing a mask in public differed between age groups ($\chi^2(4, N = 953) = 33.32$, $P<0.001$), with participants aged 21–30 most likely to adopt this behaviour (Fig. 3).

DISCUSSION

In this study, we documented for the first time how residents in Singapore had adapted their behaviours to minimise COVID-19 transmission. Focusing on the first phase of the pandemic, we found that the large majority of participants (97%) had undertaken at least one infection control measure, with participants reporting an average of 8 lifestyle changes owing to the pandemic.

In terms of demographic predictors, health-preventive measures were most likely to be adopted by women

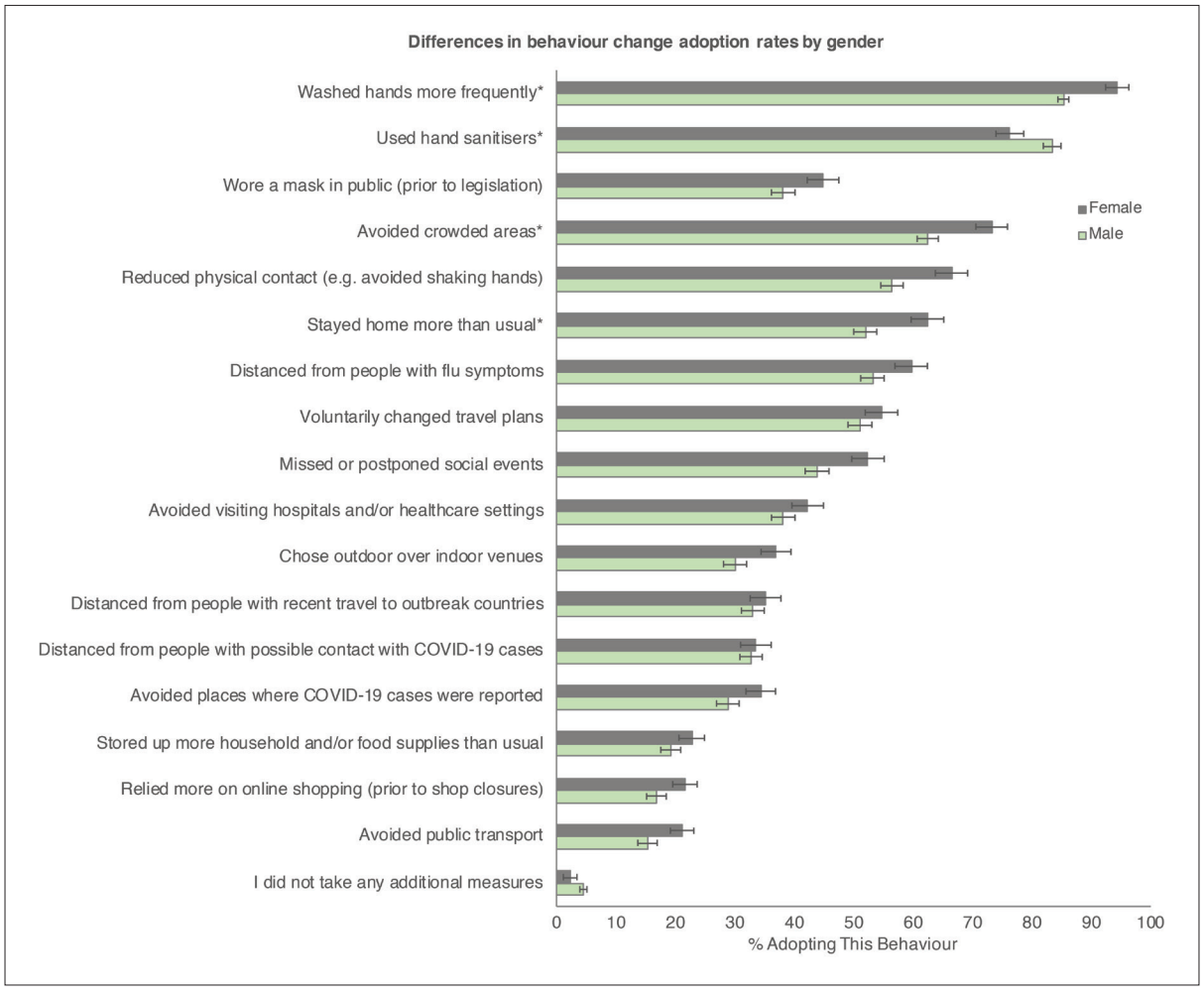

Fig. 1. Uptake of COVID-19 infection control measures as a function of gender. Asterisks indicate significance at $P<0.002$ (following Bonferroni corrections), and horizontal lines represent the 95% confidence intervals.

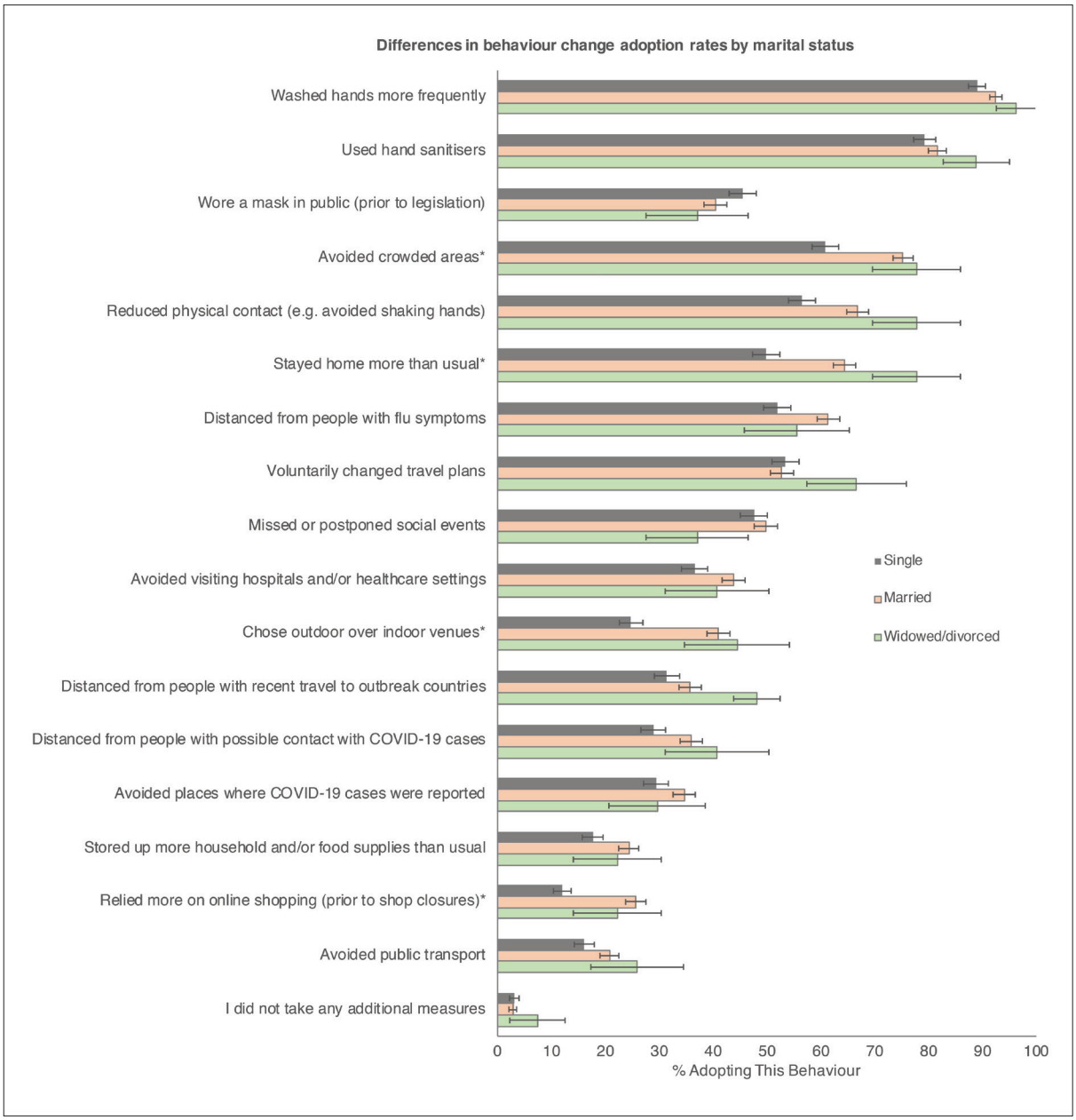

Fig. 2. Uptake of COVID-19 infection control measures as a function of marital status. Asterisks indicate significance at $P<0.002$ (following Bonferroni corrections), and horizontal lines represent the 95% confidence intervals.

and those who were married. When we distinguished between preventive (e.g. hand washing) and avoidant (e.g. avoiding crowded areas) behaviours, age emerged as an additional predictor for avoidant behaviours, with youths most likely to adopt mask-wearing.

Collectively, our results on gender and marital status replicate findings from previous infectious disease outbreaks[3,13] and the current COVID-19 pandemic (based on both an international and a South Korean sample[7,9]). These findings echo a broader pattern of risk that has emerged in epidemiological research, whereby being women and being married has been linked to the reduced risk of disease and of all-cause mortality.[14] Adding to this body of research, our findings highlight how being willing to adopt health-promoting behaviours during a pandemic may contribute to the resilience of these demographic groups.

Departing from prior research and popular belief, however, we found that age was inversely related to the take-up of preventive behaviours. In particular,

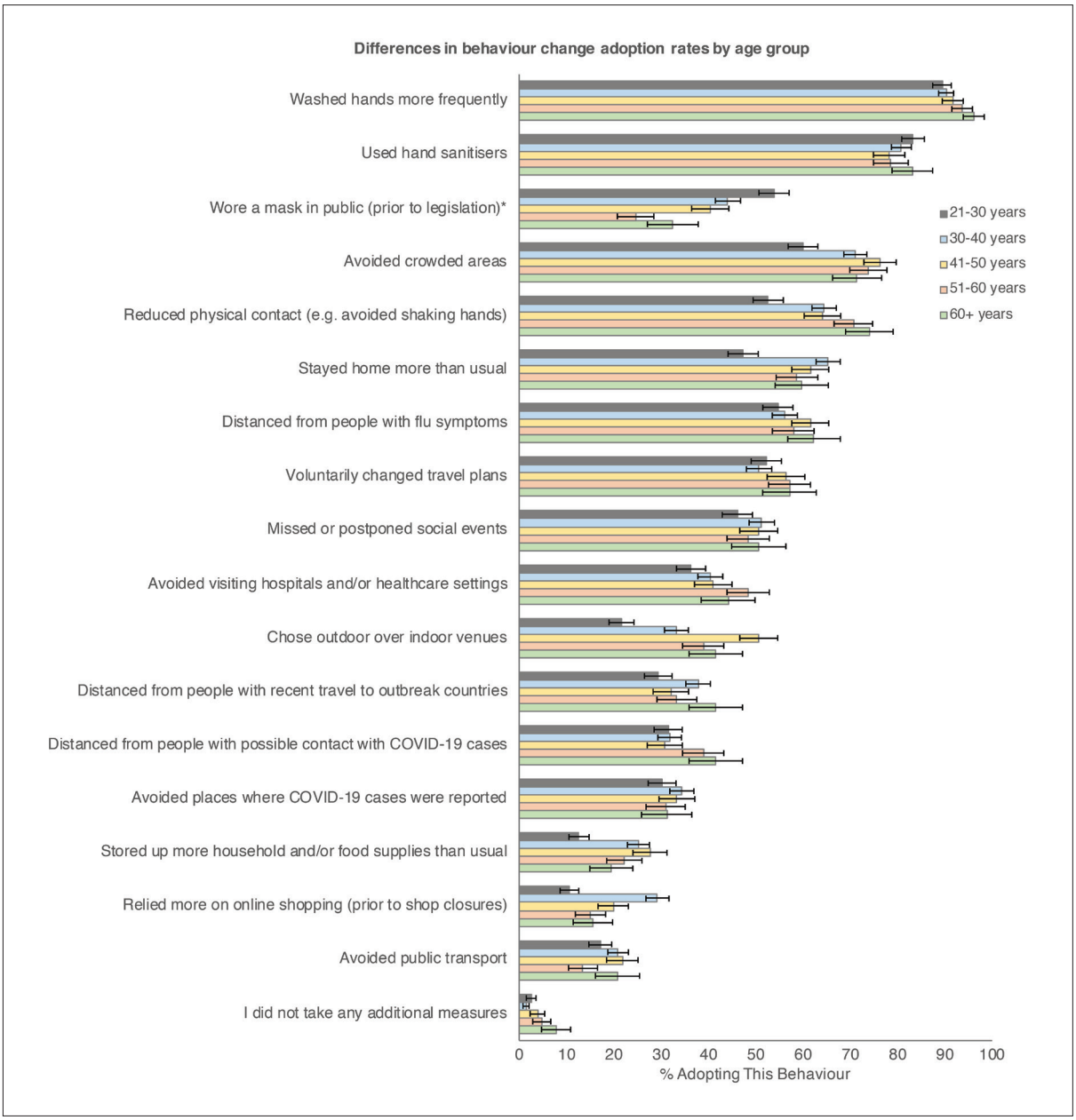

Fig. 3. Uptake of COVID-19 infection control measures as a function of age group. Asterisks indicate significance at $P<0.002$ (following Bonferroni corrections), and horizontal lines represent the 95% confidence intervals.

younger adults in our survey were more likely to wear masks than older adults, even before legislation stipulating that masks had to be worn in public. This finding is remarkable for several reasons. First, during SARS, older adults had been more likely to perform a range of preventive behaviours including mask-wearing, handwashing, respiratory hygiene, the using of utensils, and washing after touching contaminated surfaces.[3] Second, during the current outbreak, several high-profile events (e.g. coronavirus parties hosted by students) have resulted in the belief that youths are least likely to care about the outbreak, and thereby most likely to ignore infection control measures. Indeed, the Director-General of the World Health Organization released a statement telling youths that they were "not invincible", that "the virus could put (them) in hospital for weeks, or even kill (them)".[15-17].

Rather than finding that young persons take on risky behaviours, however, we observed that this demographic group was most associated with mask-

wearing. While this finding is counter-intuitive, it is in line with recent Hong Kong research whereby elderly participants—rather than the young—were least likely to worry about getting infected, and thus least likely to adopt protective behaviours.[18] Additionally, young persons' ready adoption of mask-wearing may reflect a general willingness to embrace change and innovation, since mask-wearing had not previously been a norm in Singapore (as it had in countries like Japan[19]).

Beyond demographic predictors, we found that behavioural changes tracked the severity of the COVID-19 situation. Namely, participants adapted more aspects of their daily lives when the number of local COVID-19 cases increased, or as they grew more fearful of the situation. Correspondingly, healthy levels of COVID-19 fears may be necessary to support public health efforts. At the same time, other studies have linked the uptake of health-protective behaviours (e.g. hand-washing) to better mental health during the pandemic.[20] In other words, it appears that while some fear is needed to encourage lifestyle modifications, the individual who proactively makes these modifications is more resilient to depression, anxiety and stress.[20]

Policy implications

Moving forward, our findings may contribute to the public health strategy in several ways. First, throughout the pandemic, government agencies have repeatedly noted how individuals have ignored official advisories. This phenomenon has been so widespread that the individuals have been nicknamed "covidiots" in the popular press—a portmanteau of coronavirus and idiot. Beyond naming and shaming, however, our research highlights characteristics that may predict non-compliance. This, in turn, will allow risk communication to be targeted: both in the current pandemic (for voluntary behavioural changes), and in the early phases of future pandemics (before measures such as mask-wearing are made mandatory).

On the other hand, our findings also highlight which demographic groups may be most likely to respond when governments launch new infection control measures (for example, SafeEntry or the TraceTogether application for contact tracing). Extrapolating from our research, these initiatives—if perceived to be health-protective—may be adopted first by women and those who are married. Correspondingly, the two demographic groups may be ideal for pilot trials or as advocates for the behaviours.

Finally, it is notable that across demographic groups, voluntary avoidant behaviours were less likely to be adopted than voluntary preventive behaviours. This could suggest the need for stronger measures (e.g. legislation) when public health agencies seek to increase avoidant behaviours to minimise activities deemed high-risk for COVID-19 transmission.

Limitations

In making these recommendations, we note that our study has several limitations. First, we relied on participants' self-reports, which may be vulnerable to memory or social desirability biases. Future research will thus need to explore whether our findings translate to actual behavioural changes during the pandemic, and to examine whether the frequency of behaviours (and not merely the uptake of behaviours) differs across demographic groups. Second, although our survey methodology captured behavioural changes at one particular time-point during the early phase of the pandemic, the recommendation of infection control measures is a moving target. In the case of mask-wearing, for example, official advisories changed from masks not being needed, to being encouraged, to finally being mandated (as of 14 April 2020). Correspondingly, further research is needed to examine whether our findings continue to hold even as official advisories change and more measures (e.g. safe distancing, contact tracing applications) are implemented.[22] Third, we note that despite having a large sample size and a wide range of participant backgrounds, our final study sample was not representative of the national population. This may limit the generalisability of our results, and future research will need to examine whether our conclusions apply to under-sampled groups (e.g. those living in 1–3 room HDB flats).

CONCLUSION

We conducted the first Singapore-based study of behavioural changes during the COVID-19 pandemic. Although the scale of this crisis has been unprecedented and many uncertainties remain, many of our findings reinforce long-standing patterns of how demographic characteristics can predispose an individual to disease. In this case, the uptake of various preventive and avoidance measures can minimise COVID-19 infection. Moving forward, our findings provide a template by which official messaging can be tailored for health promotion.

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ORIGINAL ARTICLE

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Vulnerability to rumours during the COVID-19 pandemic in Singapore

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ABSTRACT

Introduction: Amid the COVID-19 pandemic, many rumours have emerged. Given prior research linking rumour exposure to mental well-being, we conducted a nationwide survey to document the base rate of rumour exposure and factors associated with rumour vulnerability.

Methods: Between March and July 2020, 1,237 participants were surveyed on 5 widely disseminated COVID-19 rumours (drinking water frequently could be preventive, eating garlic could be preventive, the outbreak arose because of bat soup consumption, the virus was created in an American lab, and the virus was created in a Chinese lab). For each rumour, participants reported whether they had heard, shared or believed each rumour.

Results: Although most participants had been exposed to COVID-19 rumours, few shared or believed these. Sharing behaviours sometimes occurred in the absence of belief; however, education emerged as a protective factor for both sharing and belief.

Conclusion: Our results suggest that campaigns targeting skills associated with higher education (e.g. epistemology) may prove more effective than counter-rumour messages.

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Keywords: Fake news, infectious diseases, infodemic, misinformation, public health, social media

INTRODUCTION

The global outbreak of coronavirus disease 2019 (COVID-19) has come with increased psychological burden. In several meta-analyses, depression and anxiety symptoms have been found to be elevated among healthcare workers and the general population.[1-3] Others have reported a higher incidence of stress-related symptoms or post-traumatic stress disorder.[4,5] These findings highlight the urgent need to understand factors predicting anxiety and mood outcomes, allowing vulnerable individuals to be identified and interventions to be developed.

In terms of predictors, exposure to COVID-19 rumours has emerged as a risk factor for poor mental health.[6-9] This negative mental health impact has occurred against the backdrop of an "infodemic"—a surge of COVID-19 misinformation created and shared primarily via social media.[10] In particular, the fast-changing nature of the pandemic means that accurate information has not always been accessible, resulting in many uncertainties.[11,12] This has given rise to a large number of rumours.[13,14]

To date, several publications have used publicly available data to analyse and document the spread of rumours. For example, during the early stage of the pandemic (December 2019 to April 2020), search engine keywords reflected popular myths,[15,16] with a large number of searches pertaining to alternative medicines that had been speculated to prevent COVID-19 (e.g. garlic, Chinese medicinal herbs or the malaria medication chloroquine).[12] On social media platform Twitter, conspiratorial theories were posted regarding disease origins, suggesting for example that the virus had been developed as a bioweapon or had resulted from the introduction of 5G mobile networks.[17,18]

In turn, the spread of COVID-19 rumours has led to deleterious consequences. In Iran for example, a myth that alcohol consumption could prevent or treat COVID-19 resulted in over 700 deaths related to methanol poisoning, with deaths from methanol

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CLINICAL IMPACT

What is New

- Most participants had been exposed to rumours, and confessed to sharing them even when they do not believe this information.
- Participants with higher education levels receive more rumours, but were less likely to believe or share them.

Clinical Implications

- The spread of health misinformation can undermine public health campaigns.
- As rumours are shared even when individuals do not believe them, providing fact-checking information may not be enough to stem the spread of rumours.
- Strategies to target education or individual vulnerabilities may be more effective.

poisoning exceeding those attributed to COVID-19 in some provinces.[19] Returning to mental health outcomes, the extent to which an individual has been exposed to, has shared, or believed in COVID-19 rumours has also been found to predict anxiety symptoms.[7]

While demographic predictors of pandemic-related mental health are difficult to address (e.g. age, gender, pre-existing medical conditions),[5] a person's exposure to rumours may constitute a modifiable risk factor.[20-22] Correspondingly, efforts to develop interventions would benefit from an understanding of rumour vulnerability: the base rates by which individuals are exposed to, believe in, or share rumours; and factors predicting these rumour-related experiences.[23]

At present, little is known about individual vulnerability to COVID-19 rumours. While a handful of studies have surveyed individuals on their social media usage and enquired about rumour dissemination via these platforms,[24] we are not aware of any study that has identified persons most likely to encounter, believe in, or to share COVID-19 rumours. To address this gap in the literature, we thus conducted a nationwide survey examining rumour vulnerability during the COVID-19 pandemic.

METHODS

Study design and population

Our study was conducted from 7 March to 27 July 2020 in Singapore, which had a high number of COVID-19 cases in the early stage of the pandemic. During this time, we recruited 1,237 participants who met the following eligibility criteria: aged ≥21 years old, and had lived in Singapore for ≥2 years. All participants were recruited via social media advertisements within community groups (e.g. groups for residential estates, universities and workplaces), or through paid Facebook advertisements targeting Singapore-based users.

Upon study enrolment, participants provided informed consent and completed a 20-minute online survey via Qualtrics. As part of a larger study, participants reported their: demographics, responses to the pandemic, sources of COVID-19 news, and (as we report in this paper) familiarity with rumours.[7,25,26] The study protocol was approved by the Yale-NUS College Ethics Review Committee (Ethics Approval Number: 2020-CERC-001) and was pre-registered on ClinicalTrials.gov (NCT04305574).

Outcome variables

As the primary outcome variables, we assessed participants' familiarity with 5 rumours that had been widely spread during the COVID-19 pandemic: (1) drinking water frequently will help prevent infection (COVID-19 prevention); (2) eating garlic can help prevent infection (COVID-19 prevention); (3) the outbreak arose from people eating bat soup (COVID-19 origins); (4) the virus was created in a US lab to affect China's economy (COVID-19 origins); and (5) the virus was created in a Chinese lab as a bioweapon (COVID-19 origins). These rumours were presented in the survey as claims, rather than rumours to avoid influencing participants' response. Rumours were selected for their widespread distribution both internationally and within the local context.

For each rumour, participants indicated whether they: (1) had heard the claim before (yes/no); (2) thought the claim was true (yes/no); or (3) had shared the claim on social media such as Facebook and WhatsApp (yes/no). We assigned a score of 1 for "yes" responses, and summed across the rumours to create 3 scores: the total number of claims heard, the total number of claims believed, and the total number of claims shared. Finally, participants also indicated which of 13 possible sources they had encountered the rumours (e.g. Facebook, WhatsApp, online forums, television, etc.).

Predictor variables

As predictor variables, participants reported the following demographic details: age, gender, ethnicity, religion, country of birth, marital status, education, house type (a proxy of socio-economic status), and household size.

Using the survey timestamp, we also recorded two situation-related variables: the total number of local cases reported to date, and whether the country had been in a lockdown when participants completed the survey.

Statistical analysis

Using counts (%), we first summarised the baseline rates of rumour familiarity and rumour sources. As further exploratory analyses, we conducted Fisher's exact test to explore the relationship between believing and sharing each rumour.

We then ran linear regression models to predict the following outcome measures: the total number of claims heard (Model 1), the total number of claims shared (Model 2), and the total number of claims believed (Model 3). Each model involved the full set of predictor variables described before, with the number of COVID-19 cases log-transformed for linearity.

For each model, we applied Bonferroni correction to control the type 1 family-wise error rate at 0.05 (Bonferroni-adjusted alpha level of 0.05/22 predictors = 0.002). All statistical analyses were conducted using R version 4.0.

RESULTS

Response rate

Out of 1,751 individuals who accessed the survey link, 1,446 (82.6%) provided informed consent and participated in the survey. However, 209 (14.5%) participants did not complete the primary outcome measures (on COVID-19 rumours) and were excluded from statistical analyses.

The final sample of 1,237 participants is comparable to the resident population with regards to: the proportion of participants born in Singapore, ethnicity, household size and age (≤10% difference) However, our sample had more participants who were female (63.9% versus 51.1%), single (41.9% vs 18.8%), and university graduates (70.7% vs 32.4%); and fewer participants who lived in 1–3-room public housing flats (8.2% vs 23.7%) or who had Buddhist beliefs (14.6% vs 33.2%) (Table 1).

Base rates of familiarity with COVID-19 rumours

Out of 5 widely disseminated rumours, the average participant had heard of 3.34 (SD=1.33) rumours. The most commonly heard rumour, reported by 8 in 10 participants (84.6%), was that the outbreak had arisen from individuals eating bat soup. Despite high exposure to COVID-19 rumours, however, participants only believed an average of 0.27 claims (SD=0.59) and shared 0.18 (SD=0.63). The most commonly believed rumour was that drinking water could prevent infection (11.4%), whereas the most commonly shared rumour was that the disease had arisen from bat soup consumption (7.1%) (Fig. 1).

In other words, most participants who had heard each of the 5 rumours neither believed nor shared the claims. Using Fisher's exact test, we conducted exploratory analyses to examine how belief and sharing behaviours were related. First, for the claim about the US manufacturing the coronavirus to affect China's economy, none who shared this rumour believed that it was true (*P* value of 1 for Fisher's exact test). In the case of the other 4 rumours, however, there was a significant association between belief and sharing ($P<0.001$ for the rumours on drinking water and bat soup; $P=0.001$ for the rumour on garlic; and $P=0.02$ for the rumour on China creating the virus). Nonetheless, even with these 4 rumours, not all who propagated the rumours believed that they were true (Fig. 2).

Finally, Fig. 3 depicts how participants had encountered COVID-19 rumours. As has been previously reported,[27,28] social media platforms emerged as the leading sources, with 1 in 2 individuals reporting exposure through Facebook (55.5%) or WhatsApp (53.6%).

Predicting rumour hearing, sharing and believing

Model 1 examined if any demographic or situational factors predicted the number of rumours heard. As shown in Table 2, participants reported hearing more rumours when confirmed local cases were few (early in the pandemic) (beta *[b]* = -0.621, $t(1190) = -3.588$, $P<0.001$) or as lockdown restrictions were lifted ($b = 1.129$, $t(1190) = 4.289$, $P<0.001$). Additionally, there was a trend for education to predict rumour exposure, with those with higher education hearing more rumours ($b = 0.077$, $t(1190) = 2.625$, $P=0.009$). However, this association was not observed with Bonferroni correction.

In Models 2 and 3, the same set of predictors were used to predict the number of rumours shared and believed, respectively. For both these models, those who were more educated shared or believed fewer rumours (Model 2: $b = -0.046$, $t(1190) = -3.289$, $P=0.001$; Model 3: $b = -0.046$, $t(1190) = -3.488$, $P=0.001$).

DISCUSSION

During times of crisis, rumours have the potential to transmit misinformation and induce anxiety.[29,30] Against the backdrop of the COVID-19 pandemic, we thus documented how individuals in the community

Table 1. Baseline demographics of participants

Characteristic	n	(%)
Age (Mean=39.3, SD=12.7)		
Gender		
Female	791	(63.9)
Male	445	(36.0)
Did not answer	1	(0.1)
Ethnicity		
Chinese	1047	(84.6)
Indian	55	(4.4)
Malay	71	(5.7)
Others	63	(5.1)
Did not answer	1	(0.1)
Religion		
Buddhism	181	(14.6)
Taoism/ Chinese traditional beliefs	51	(4.1)
Islam	71	(5.7)
Hinduism	41	(3.3)
Roman Catholicism	125	(10.1)
Christianity (Protestant)	405	(32.7)
No religion	331	(26.7)
Others	30	(2.4)
Did not answer	2	(0.2)
Married status		
Single	518	(41.9)
Married	667	(53.9)
Widowed/ separated/ divorced	47	(3.8)
Did not answer	5	(0.4)
Educational level		
Primary school	4	(0.3)
Secondary school	65	(5.3)
Junior college	91	(7.4)
Vocational training	22	(1.8)
Polytechnic/ diploma	154	(12.4)
University (undergraduate)	623	(50.3)
University (postgraduate)	252	(20.4)
Did not answer	26	(2.1)

Table 1. Baseline demographics of participants (Cont'd)

Characteristic	n	(%)
House type		
HDB flat: 1–2 rooms	12	(1.0)
HDB flat: 3 rooms	89	(7.2)
HDB flat: 4 rooms	305	(24.6)
HDB flat: 5 rooms or executive flats	358	(28.9)
Condominium or private apartments	321	(25.9)
Landed property	131	(10.6)
Did not answer	21	(1.7)
Household size		
1	55	(4.4)
2	178	(14.4)
3	279	(22.6)
4	359	(29.0)
5+	364	(29.4)
Did not answer	2	(0.2)
Country of birth		
Singapore	1004	(81.1)
Others	232	(18.8)
Did not answer	1	(0.1)

were vulnerable to receive, believe in, or share specific COVID-19 rumours.

First, we observed that rumour exposure was endemic. Nearly all participants had heard at least one rumour and were familiar with an average of 3 out of 5 popular claims assessed. Additionally, most rumour transmission occurred via social media channels (e.g. Facebook and WhatsApp), as others have noted.[31,32]

Extending previous research, we further described how the base rate of believing or sharing rumours was far lower than the rate of exposure (with an average of <1 rumour believed or shared). Notably, belief and sharing behaviours did not always co-occur. In the extreme case of one rumour in particular (that the COVID-19 crisis had been manufactured by the US), not a single participant who reported forwarding the rumour actually believed in it. Although belief and sharing were linked for the other rumours we assessed, there continued to be individuals who shared rumours without believing their veracity.

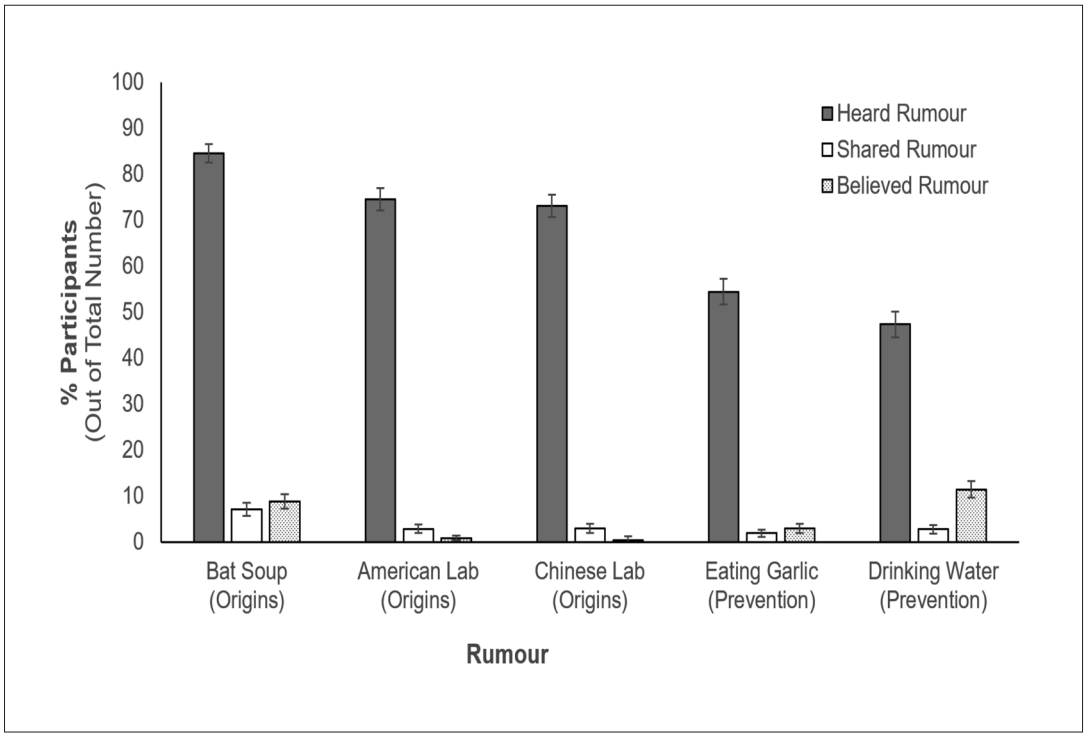

Fig. 1. Proportion of participants hearing, sharing and believing each COVID-19 rumour (that the virus originated from the consumption of bat soup, from an American lab, or from a Chinese lab; or that the virus can be cured by eating garlic or drinking water). Vertical lines represent the 95% confidence interval.

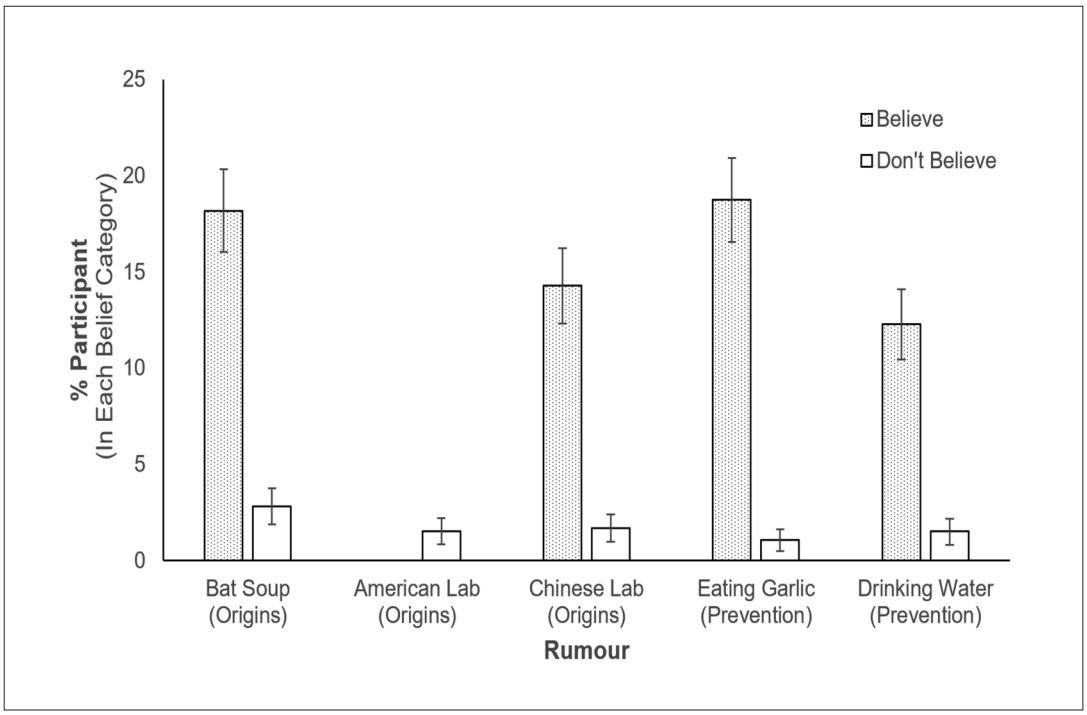

Fig. 2. For each rumour, the vertical bar depicts the number of participants who shared each rumour, represented as a percentage of participants who believed or disbelieved each rumour. Vertical lines represent the 95% confidence interval.

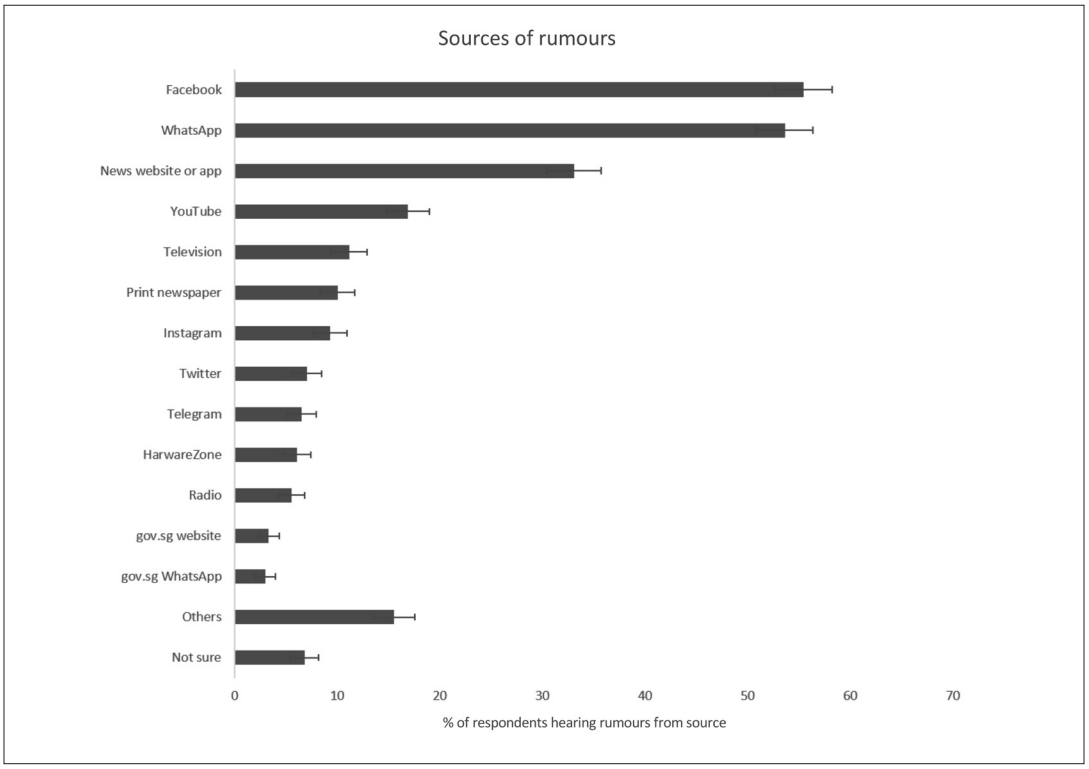

Fig. 3. Sources of where participants heard COVID-19 rumours. Horizontal lines represent 95% confidence interval.

Our finding that COVID-19 rumours were disseminated even when disbelieved highlights the sheer difficulty of managing the so-called "infodemic". Although similar findings had been reported outside the COVID-19 context,[33] the World Health Organization and individual governments continue to issue fact-checking statements as the prevailing strategy to debunk rumours.[34,35] Our results bring to question the utility of such statements, since individuals continue to share claims despite perceiving them to be untrue.

Based on our findings, an alternative strategy might be to target individual vulnerabilities instead of rumour content. This draws on previous findings suggesting that COVID-19 information-seeking differs across demographic groups.[36,37] In our context, given that rumour exposure changed with pandemic severity (e.g. the number of cases) and most individuals had encountered COVID-19 rumours, the ensuing question is why only certain individuals fell prey to such rumours. Here, we found that educational level was a consistent predictor of vulnerability: although higher education predicted that an individual would hear more rumours, higher education was nonetheless protective, associated with fewer rumours shared or believed. Consequently, it may be advantageous to increase public awareness of knowledge and skillsets associated with higher education, such as epistemology or scientific thinking.[33,38] We note, however, that the correlational nature of our dataset precludes causal inferences, and further research will be needed to examine the efficacy of such strategies in curbing pandemic-related rumours.

Limitations

In describing these findings, we highlight several limitations of our research methods. First, we relied on participants' self-reports regarding rumour exposure and behaviours. Although this strategy provided individual-level information (such as beliefs and demographics) not available in studies of actual rumour posts (e.g. when Twitter posts are mined), the survey method is vulnerable to recollection and reporting biases. Moving forward, future studies may opt to integrate digital documentation of rumour posts alongside self-reported measures.

As a second limitation, we only sampled rumours that were not time-sensitive. Given the limitations of the survey methodology, we could not track rumours that arose from fast-changing events on the ground (e.g. rumours about the first COVID-19-related death in Singapore, rumours about the availability of face masks). It thus remains to be seen whether our findings can be generalised to these forms of rumours.

Table 2. Predicting the number of rumours, heard, shared and believed during the COVID-19 outbreak

	Outcome Measure[a]					
	Model 1: Number of rumours heard		Model 2: Number of rumours shared		Model 3: Number of rumours believed	
Age	0.003	(0.004)	0.005	(0.002)	0.002	(0.002)
Gender (base = Female)						
Male	-0.084	(0.080)	-0.025	(0.038)	0.017	(0.036)
Ethnicity (base = Chinese)						
Indian	-0.456	(0.353)	-0.060	(0.169)	0.152	(0.159)
Malay	-0.537	(0.279)	0.349	(0.133)	0.184	(0.125)
Others	-0.234	(0.206)	0.022	(0.098)	-0.059	(0.092)
Religion (base = No religion)						
Christianity (Protestant)	0.093	(0.101)	-0.018	(0.048)	0.012	(0.045)
Buddhism	0.159	(0.125)	0.115	(0.060)	-0.025	(0.056)
Roman Catholicism	0.115	(0.144)	0.036	(0.069)	0.135	(0.065)
Taoism/ Chinese traditional beliefs	0.171	(0.207)	0.018	(0.099)	0.078	(0.093)
Islam	0.330	(0.325)	0.006	(0.155)	-0.104	(0.146)
Hinduism	0.215	(0.351)	-0.259	(0.167)	0.122	(0.157)
Others	0.560	(0.281)	0.047	(0.134)	0.072	(0.126)
Marital status (base = Single)						
Married	-0.041	(0.093)	-0.021	(0.045)	-0.036	(0.042)
Widowed/ separated/ divorced	0.002	(0.217)	0.037	(0.104)	-0.170	(0.098)
Education level	0.077	(0.029)	-0.046	(0.014)[b]	-0.046	(0.013)[b]
House type	0.092	(0.036)	-0.030	(0.017)	-0.042	(0.016)
Household size	-0.018	(0.036)	0.011	(0.017)	0.013	(0.016)
Country of birth (base = Singapore)						
Others	0.271	(0.108)	0.071	(0.051)	0.072	(0.048)
Lockdown (base = Lockdown period)						
Before lockdown	-0.437	(0.206)	-0.017	(0.098)	0.075	(0.092)
After lockdown	1.129	(0.263)[b]	0.011	(0.126)	-0.151	(0.118)
Number of local COVID-19 cases (log transformed)	-0.621	(0.173)[b]	-0.052	(0.083)	0.079	(0.078)
R^2	0.474		0.435		0.388	

[a] Data reported as beta estimates (standard error)
[b] Indicates significance at $P<0.002$ (following Bonferroni corrections)

Strengths

These study limitations need to be viewed alongside the putative strengths of our research methodology. To the best of our knowledge, our study represents the first attempt to identify individual vulnerabilities in the spread of COVID-19 rumours. The research involved a large sample size (1,237 participants), captured pandemic-related dynamics over a long duration (5 months), and examined specific rumours that had been widely disseminated.

CONCLUSION

In conclusion, our study revealed that educational level was a protective factor amid an onslaught of COVID-19 rumours. At a time when information regulation is crucial to resilience and well-being,[20,39] our findings provide a basis to manage the spread of rumours. In other words, it is not apparent that veracity makes a rumour likely to be shared. Instead, COVID-19 rumours are shared even when disbelieved, but may be stemmed through higher education.

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REVIEW ARTICLE

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Endovenous cyanoacrylate ablation for chronic venous insufficiency and varicose veins among Asians

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ABSTRACT

Introduction: Endovenous cyanoacrylate glue (CAG) ablation for the treatment of chronic venous insufficiency (CVI) and varicose veins has shown non-inferior outcomes with an excellent safety profile, high patient satisfaction rate, and excellent efficacy when compared to the gold standard of endothermal ablation. A review of the current literature for CAG use in CVI showed that most studies and longer-term data are from Caucasian-based populations, which are subject to different anatomical venous variations and socio-economical contexts. This review aimed to gather the current evidence for CAG use in Asian CVI patients.

Methods: Asian studies for the use of CAG in CVI were included in this review. Successful ablation rates, quality of life improvement and novel complications such as glue hypersensitivity reactions are described, along with anatomical descriptions of superficial venous anatomy in study patients. Use of CAG in Singapore and Asia was addressed.

Results: CAG has been gaining traction as an option for CVI treatment in Asians. In Singapore, it has been adopted with comparable low complication rates and significant improvement of quality of life after treatment. As we increase our understanding of the variations in venous anatomy in the Asian population, new techniques such as retrograde deployment of the device and use of CAG ablation for venous leg ulcers have been developed.

Conclusion: Further robust evidence in terms of large randomised control trials along with cost-effectiveness studies are needed to determine the true value of CAG ablation in the Asian setting.

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Keywords: Asian, chronic venous insufficiency, cyanoacrylate glue, endovenous, varicose veins

MINIMALLY INVASIVE ENDOVENOUS TECHNIQUES

In the past 2 decades, the management of chronic venous insufficiency (CVI) has been revolutionised by the introduction of minimally invasive endovenous techniques, which have replaced open surgical high tie and stripping as the treatment of choice. CVI is common in the Western population and is reported to affect 164 in 1,000 individuals.[1] The prevalence of CVI in the Asian population is reportedly lower than that in the non-Hispanic white population,[2] but is expected to rise because of ageing and an increasing incidence of obesity.[3] Some studies have shown that the Asian venous patient tends to present at a younger age with less severe symptoms, but these data may not be representative of the diverse Asian population.[4,5]

The guidelines of the Society for Vascular Surgery[6] and the National Institute of Clinical Excellence (NICE)[7] currently recommend the use of endothermal ablation techniques, specifically radiofrequency ablation (RFA)

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CLINICAL IMPACT

What is New

- Endovenous cyanoacrylate glue (CAG) ablation for chronic venous insufficiency and varicose veins has shown excellent safety profile, high patient satisfaction rate and excellent efficacy in the short term in Asian patients.
- New techniques for performing CAG ablation have been developed to adapt to variations in venous anatomy in Asian patients.

Clinical Implications

- CAG use is increasing in the Asian population, and has the potential to treat a wider group of chronic venous insufficiency patients, including those with venous leg ulcers.

and endovenous laser ablation (EVLA), as first-line treatment for truncal reflux, followed by ultrasound-guided foam sclerotherapy if RFA and EVLA are unavailable. The thermal energy used in RFA and EVLA to ablate the truncal vein can result, albeit rarely, in pain, skin burns, skin pigmentation, nerve damage, endothermal heat-induced thrombosis and arteriovenous fistula formation.[8,9] Furthermore, due to the use of thermal energy, it is necessary to infiltrate the area around the whole length of the target truncal vein with tumescent anaesthesia through multiple injections, to minimise complications such as nerve injury and heat-related damage to surrounding structures (that act as a heat sink) and make the procedure more bearable for the patients, especially if performed under local anaesthesia. This in turn is also a source of intraprocedural and post-operative discomfort for patients and is known to cause ecchymosis and haematomas to some degree in more than 50% of treated patients.[8]

NON-THERMAL, NON-TUMESCENT ABLATION TECHNIQUES

Recently, non-thermal, non-tumescent ablation techniques (NTNTs) have been introduced to obviate the need for tumescence and the complications of thermal ablation. These NTNTs include mechanochemical ablation (MOCA) using the ClariVein device[10] or sealing of veins by coaptation using cyanoacrylate glue (CAG). NICE has come up with guidelines for both MOCA and CAG, highlighting both their safety profile and efficacy, while minimising perivenous tissue damage or pain.[11,12] However, long-term data of both MOCA and CAG are not yet available, and thus they are not offered as the first line of treatment for CVI in the NICE guidelines algorithm. These NTNTs have led to a reduction in patient discomfort, haematoma formation and risks of nerve injury when compared with traditional thermal-based procedures, improving the patient's periprocedural experience further.

The current available evidence demonstrates high anatomical success rates for MOCA and CAG, with significant improvement in symptoms as demonstrated by improvement in quality of life as evidenced by the Venous Clinical Severity Score and Aberdeen Varicose Vein Questionnaire scores post-treatment.[13] A recent network meta-analysis looking at 20 randomised controlled trials from 1996 to 2018 comparing different treatment options for saphenous reflux, including both MOCA and CAG, suggested that CAG had the highest probability of being ranked first in terms of anatomical success. CAG was also the most likely to reduce post-operative pain score from baseline, while having the lowest occurrence of adverse events.[14]

Cyanoacrylate glue ablation

The main chemical compound of CAG is N-butyl cyanoacrylate, which polymerises rapidly in the presence of ionic substances such as blood and tissue fluids. This polymerised form has excellent tensile strength and is the primary component of medical glues. Almeida et al. was the first group to study endovenous injections of CAG and demonstrated it to be safe and reliable for the treatment of CVI in human patients.[15]

There are 3 CAG delivery devices commercially available, designed specifically to treat superficial vein incompetence: VenaSeal, VariClose and VenaBlock systems. All 3 follow the same basic principles: N-butyl cyanoacrylate rapidly solidifies and creates an inflammatory reaction within the vein walls, and additional external compression over the vein opposes the endothelium together. The major difference between these devices is the viscosity and the polymerisation time of the glue, which affects the procedure, technique, duration and complication rates.

VenaSeal closure system (Medtronic, Dublin, Ireland) is the most studied CAG device for incompetent great saphenous vein (GSV) and small saphenous vein (SSV) ablation. It uses a rapidly polymerising, high-viscosity CAG to prevent potential embolisation into the deep venous system.[16] Only 1 randomised controlled trial

has been performed to date. The VenaSeal Sapheon Closure System Pivotal Study (VeClose), a multicentre prospective randomised controlled trial conducted in the US, evaluated VenaSeal versus RFA outcomes of 222 patients (108 received VenaSeal and 114 received RFA) over 3 years.[17] The study found that VenaSeal was non-inferior to RFA in terms of treatment of incompetent GSV. These results were further validated by a multicentre prospective European trial.[18]

VariClose vein sealing system (Biolas Inc, Ankara, Turkey) is a newer device and is also utilised for both incompetent GSV and SSV ablation. It uses CAG with modifications to the chemical structure of N-butyl cyanoacrylate, resulting in lower viscosity and a faster polymerisation time compared with VenaSeal glue. There are no randomised controlled trials in the literature comparing VariClose to other techniques, but a systematic review of 1,000 limbs with VariClose suggests good efficacy with a 30-month occlusion rate of 94.1% and a high safety profile.[19]

VenaBlock system (Invamed, Ankara, Turkey) is the latest addition to the CAG armamentarium. It consists of a proprietary formula of N-butyl cyanoacrylate with dimethyl sulfoxide, which shortens the time for the initial polymerisation reaction to a mere 5 seconds. This dispensing system also has a guiding light at the tip of the catheter to visually guide the operator on the exact location requiring compression to ensure proper apposition within the fast polymerisation time. Two studies have been published in 2 independent patient populations in Turkey (total 1,111 patients), with promising reports of 12-month occlusion rates of 99.4% and reported rates of phlebitis in less than 2% of the population.[20,21]

A review of the published literature revealed that the majority of device-related venous outcome data were from Caucasian-based cohorts, which may not extrapolate to other racial cohorts with variations in venous anatomy. This article evaluates the utility of CAG in Asian patients with CVI and varicose veins, and reviews the available literature.

Anatomical variation in Asian populations

An understanding of venous anatomical patterns and its variation in the Singapore population, in contrast to other populations, will help care providers determine if studies performed in other populations are applicable to its own patients.

Previous venous studies on the Asian sub-population from Western countries[22,23] and small cohort reports from Thailand[24] suggest that the characteristics of CVI in Asian patients differ from those found in Caucasian populations. Recently, Lee et al. studied the CVI population in Singapore and the US and found that Asians tend to have smaller truncal saphenous vein diameters and longer segments of reflux as compared with their Caucasian counterparts, and CVI tend to present at later stages in contrast to previous data on the Asian population.[25] Interestingly, Asians were noted to have more advanced venous disease at presentation despite having veins of smaller diameters. This finding is in concordance with a study by Gibson et al. who demonstrated that GSV diameter is a poor surrogate marker for assessing the effect of varicose veins on a patient's quality of life.[26]

Anatomical difference also has its implications on the management of patients with CVI. Based on the Caucasian literature, CAG is indicated for patients with GSV diameters >5mm. However, applying these guidelines to an Asian population whose median GSV diameters were 2.9mm compared with 5.7mm in the Caucasian population[25] would lead to a severe undertreatment of Asian patients with CVI. Given the smaller diameter of their veins, it is likely that smaller aliquots of CAG are required to seal the vein than what is quoted in protocols and instructions for use designed for Caucasians.

Another significant finding by Lee et al. was that Asians had significantly longer lengths of venous reflux with a higher percentage of patients with reflux down to the ankle. This finding makes NTNTs even more suitable than thermal endovenous ablation for treatment of disease below the knee, with a significantly lower risk of saphenous nerve injury and skin damage.

The GSV exits the fascial envelope early in a larger proportion of Asians than in the Caucasian population,[25] which invariably means that the Asian population has veins that lie more superficially and closer to the skin surface (termed N3 veins). This is in tandem with the lower body mass index noted in Asian populations than in Caucasian populations.[27] This variation may result in a higher percentage of patients with thermal skin injury when using thermal endovascular ablation techniques such as RFA. Epifascial veins are also often tortuous and technically challenging to navigate endovenously and may lend themselves better to occlusion using CAG than thermal techniques.[28]

Asian experience with CAG

The first published VenaSeal outcome data from Asia were from Hong Kong in 2017, and focused on patients with bilateral varicose veins (predominantly

C2 and C3 disease) because of cost concerns.[29] Since then, other Asian countries, such as South Korea and Singapore, have also published their own experiences regarding VenaSeal use in their population. VenaSeal is the most commonly used and widely studied form of CAG in Asia. Two other CAG devices from Turkey (VariClose and VenaBlock) have recently entered the Singapore market. They have only been available at the institution of our last author (TYT), and local data on these systems have yet to be published. However, the experience has been satisfactory to date with fast procedural times and glue polymerisation rate.

CAG is indicated as treatment for patients with reflux of the saphenous trunks. In the initial reports from Western literature, the use of CAG was mostly limited to the treatment of GSV alone. However, its use was subsequently expanded to patients with reflux in the anterior accessory saphenous vein and SSV,[30] as well as incompetent perforators. These groups of patients have been included in the studies performed in the Asian population.[31,32]

In the Western literature, the 36-month occlusion rate of GSV has been quoted to be 92.9–94.7%.[18,33,34] No 36-month data have been published for the Asian population, but a pioneer study in Hong Kong by Chan et al. (55 patients, 108 GSVs) reported a 12-month GSV occlusion rate of only 75.7%.[35] A further analysis of the results showed that the low rates could be related to patient selection and the instructions for use technique used, proving that GSV diameters of >6.6mm were at a higher risk of proximal recanalisation on follow-up.[35] The closure rate of GSVs <6.6mm in diameter was 90% at 12 months post-operatively, but this value dropped to 58.6% for GSVs with diameters of >6.6mm.

A Singapore study leveraged on this knowledge and described a double-dosing technique[36] to improve truncal vein sealing rates. The investigators advocated delivering a double dose of 0.2mL instead of the usual 0.1mL at the saphenofemoral junction after the initial pullback of the delivery catheter. Where the GSV was focally dilated (>6mm) and at the level where significant branches joined the truncal vein and where incompetent perforators were located, double dosing of CAG was performed, along with gentle external massage using the ultrasound probe to deliberately allow CAG dispersion into incompetent venous reservoirs to cause occlusion. Double-dosing was associated with a small risk of saphenofemoral junction occlusion as a result of the CAG creeping proximally into the saphenofemoral junction, but the patients were noted to be asymptomatic and were managed conservatively. A higher frequency of phlebitis was also noted in the double-dosing CAG group, which could possibly be attributed to the larger amount of CAG delivered focally. Subsequently, a study by the same investigators in 2019 (77 patients, 88 GSVs) reported a 12-month occlusion rate of 91.5%,[31] which is comparable to results in the Western literature. These results were reproduced in a South Korean population by Park et al. (33 patients, 47 GSVs), where there was an initial outcome of 100% occlusion rate at 3 months, using additional CAG doses for regions with larger diameters, communicating veins or perforating veins.[32] The migration of CAG proximally past the saphenofemoral junction into deep venous system runs the risk of developing deep vein thrombosis and pulmonary embolism. Conversely, if the CAG is deposited more distally than intended, treatment may be suboptimal with possibly increased risk of recurrence. Proximal CAG migration is subject to individual operator variability when the ultrasound compression is applied during the initial CAG deposition, and further studies have been carried out to investigate the factors that determine CAG migration at the saphenofemoral junction. Park and Kim initially reported an inverse relationship between GSV diameter and remnant stump,[37] but a multivariate analysis by Lee et al., which employed the double-dosing technique for larger GSV veins (diameter >6mm), subsequently showed that the maximum diameter of proximal GSV was predictive of shorter stump lengths post-procedure.[38] The discrepancy in results is attributed to differences in methodology, with the volume of CAG delivered being a confounding factor, and further multicentre studies with standardised methodologies are required to evaluate this.

Phlebitis and hypersensitivity reaction with CAG

While CAG is overall safe and effective with the lowest odds of adverse events compared to other superficial venous therapies for CVI (including RFA, foam sclerotherapy, EVLA and MOCA),[14] a hypersensitivity reaction to N-butyl cyanoacrylate is a risk that is unique to CAG treatment. This phenomenon has also been described as a "phlebitis-like abnormal reaction", characterised as a painless, itchy, erythematous cutaneous/dermal reaction distributed over the target vein where CAG is delivered into.[39] Studies suggest that the phenomenon is a histotoxic inflammatory reaction,[40] and more likely to be a foreign body or allergic reaction to CAG rather than venous phlebitis, which characteristically has the symptoms of pain, tenderness and swelling over the affected veins.

Histological findings of the explanted vein in patients with more severe hypersensitivity reaction revealed lymphocytic follicles and giant cells typifying a chronic foreign body reaction, similar to findings of a vein explanted in healthy asymptomatic volunteers 5 years after CAGimplantation in GSV.[41] Some authors have hypothesised that phlebitis-like abnormal reaction is likely due to a type IV hypersensitivity reaction, a delayed immune cell response mediated by T cells, noting that it occurred in both limbs of patients who have had undergone bilateral treatment, rather than being localised to a single limb.[42] There is notably a delay between treatment and symptoms which usually occur 1–2 weeks after allergen exposure, in keeping with the pathophysiology of type IV hypersensitivity reaction. The reaction is frequently self-limiting and usually resolves with a short course of oral non-steroidal anti-inflammatory agents and/or anti-histamines and/or steroids. More serious reactions have been reported, such as the development of multiple "painless large pustules" with surrounding erythema around the targeted veins post-treatment, with subsequent progression to the eruption of these pustules and extrusion of white CAG casts from each wound.[43] Extra precautions are taken to minimise the contact of CAG with dermis and subcutaneous tissue, in which the retained polymer can serve as a nidus for infection or localised foreign body reaction, potentially requiring excision. This phenomenon can manifest as puncture site infections, postulated to be due to secondary gluenextravasation during sheath removal, and are observed to happen more frequently in patients undergoing treatment with CAG compared with other endovascular forms of treatment.[44]

It is unclear what the true rate of hypersensitivity reaction is among the different populations. Earlier studies, such as VeClose and the European Sapheon Closure System Observational Prospective Study (eSCOPE), have lumped this phenomenon with all occurrences of post-treatment phlebitis with reported rates of 18.5%[33] and 11.4%,[18] respectively. A study by Gibson et al. performed in the US documented that 6% of their patients experienced hypersensitivity reaction, but did not find any differences in the frequency of the condition by race in their patient population. However, it is important to note that there were only 23 non-white patients out of a total of 286 patients in the cohort,[41] resulting in sampling bias. In contrast, Park reported a rate of 25.4% for 271 veins treated in a South Korean population,[32] while Tang et al. reported that it affected 18% of patients undergoing CAG treatment in a multicentre Asian study conducted in Singapore.[31] The increased rate of hypersensitivity reaction in the Asian population may be due to differences in genetics and environmental conditions.[45] Anatomically, suprafascial GSVs are more common in the Asian population than in the Western population, and have a significant correlation with higher hypersensitivity reaction rates as the suprafascial location is closer to the skin and hence may have more pronounced signs and symptoms. The study by Park et al. showed that hypersensitivity reaction occurrences were significantly higher in the GSV group than in the SSV group, and even more so in cases with a suprafascial GSV length of >10cm.[42]

Current studies advocate the exclusion of patients with CAG allergies when considering CAG ablation for CVI treatment, and prophylactic doses of oral non-steroidal anti-inflammatory agents or steroids may be useful for minimising the occurrence of hypersensitivity reaction events. The last author (TYT) has stopped offering CAG ablation to patients with multiple drug allergies as hypersensitivity reaction has been observed to be higher in these patients.[31] Another problem patients face following CAG ablation is the pulling of the fibrosed truncal vein under the skin when they bend and extend their knee. This problem is more pronounced when the GSV lies close to the surface of the skin, especially in the distal thigh and proximal calf area.[31] We advocate not treating these superficial axial veins with glue. Further studies are required to define patient or procedural risk factors for hypersensitivity reaction, for better patient selection and techniques to decrease the frequency.

Satisfaction rates in Asian CAG ablation patients

A review of the Venous Clinical Severity Score and Aberdeen Varicose Vein Questionnaire scores in Asian populations showed marked improvement post-procedure, consistent with the experience in Western populations (Table 1). The baseline Venous Clinical Severity Scores were higher in the Asian population, which translated to a greater improvement in the scores post-CAG treatment.

The pain scores on post-operative day 1 in the Asian population remained low at 3 or less on the Visual Analogue Scale, and these are comparative to those in the Western population. Patient satisfaction scores remained high across both populations, with 82.6% and 87.0% of patients in the VeClose study[30] and Singapore cohort[46] respectively, with the majority of patients stating that they would definitely choose CAG ablation again if given the choice.

Table 1. Venous Clinical Severity Score and Aberdeen Varicose Vein Questionnaire scores in Western and Asian populations

Author/Study	Mean VCSS score		Mean AVVQ score	
	Baseline	Follow-up (months post-operatively)	Baseline	Follow-up (months post-operatively)
VeClose study, USA[a]	5.5	<2.0 (12 months)	18.9	9 (12 months)
eSCOPE study, Europe[b]	4.3	1.1 (12 months)	16.4	6.7 (12 months)
Chan et al., Hong Kong[c]	6.9	1.7 (12 months)	23.7	4.1 (12 months)
Tang et al., Singapore[d]	6.6	3.5 (3 months)	17.1	4.8 (3 months)
Park, South Korea[e]	4.2	1.2 (1 month)	Not reported	Not reported

AVVQ: Aberdeen Varicose Vein Questionnaire; VCSS: Venous Clinical Severity Score

[a] Morrison N, Gibson K, McEnroe S, et al. Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). J Vasc Surg 2015;61:985-94.

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CAG use in Singapore

In Singapore, our main experience with CAG devices is with VenaSeal, which was first available in Singapore in January 2016. It has been approved by the Health Sciences Authority and is used by both the public and private healthcare sectors for CVI treatment. The other 2 CAG devices (VariClose and VenaBlock) have also been approved by the Health Sciences Authority and are generally cheaper than VenaSeal, but no published outcomes in Asia exist as yet. NTNTs are now offered frequently as the treatment of choice for patients with CVI in Singapore, gaining traction over more conventional therapies such as RFA and foam sclerotherapy. Many patients choose CAG for treatment of their CVI, as doing so would eliminate the need for wearing compression stockings post-procedure.[45] Conservative treatment with compression stockings is associated with low compliance rates,[47] and in countries with a perennial hot and humid climate such as Singapore, compliance may be even lower.

Many techniques have been pioneered to overcome the anatomical variations seen in the Singapore population. Epifascial veins found among the local population are often tortuous and of a small diameter, and a double puncture technique[48] has been employed to overcome this anatomical challenge. Retrograde puncture techniques[49] with CAG have also been described from the proximal calf or thigh region to ensure that the distal portions of the GSV or SSV are adequately sealed. All these adjunct techniques, in addition to the instructions for use from the manufacturers, have enhanced the use of CAGs for the Asian population. NTNTs have also allowed the treatment of both GSV and SSV simultaneously with little risk to the saphenous nerve and sural nerve, respectively. This is particularly useful in a population with a higher prevalence of concomitant GSV and SSV reflux (83.0% in the Singapore cohort versus 32.7% in the US cohort, $P<0.01$).[25] Post-procedurally, patients return to normal daily activities at a mean of 5 days (interquartile range 3–7 days), and to work after 10 days (interquartile range 7–14 days).[31]

The techniques and benefits of NTNTs have rendered CAG relevant to the treatment of CVI in patients with venous ulcers. A preliminary study in Singapore has shown that concomitant CAG therapy with regular 4-layer compression bandaging decreased the time required for venous leg ulcers to heal and resulted in increased patient satisfaction rate with a significant decrease in Venous Clinical Severity Score and pain scores.[50] Various puncture techniques were employed, including the double puncture technique (Fig. 1), retrograde puncture technique at the thigh (Fig. 2) and knee (Fig. 3), in addition to the conventional antegrade puncture technique at the ankle (Fig. 4). These techniques allowed the delivery of CAG directly to the vein below the ulcer to ensure obliteration of the underlying venous plexus, without the risks of skin burns or nerve injuries from endothermal ablation. The use of VenaSeal in Singapore may be precluded by its

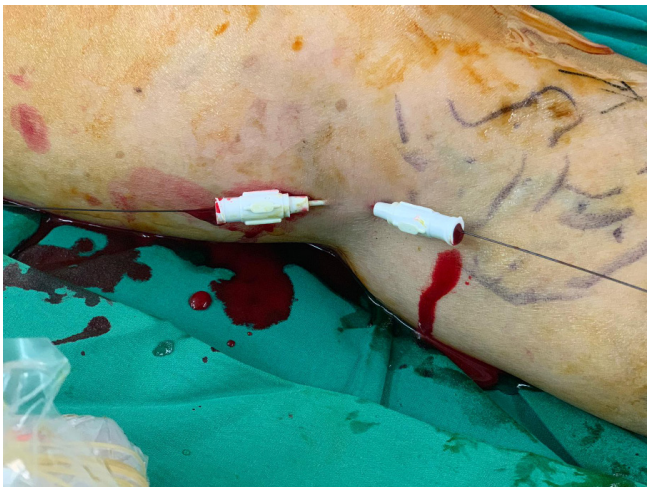

Fig. 1. Bidirectional puncture technique with 2 punctures at the knee in both antegrade and retrograde directions.

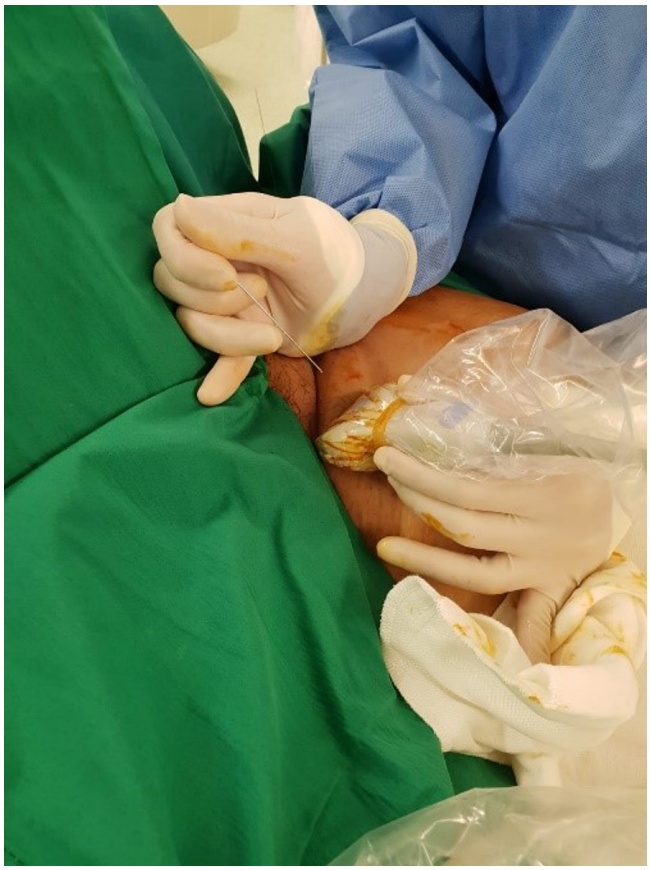

Fig. 2. Retrograde puncture technique with puncture site at the thigh, just below the saphenofemoral junction.

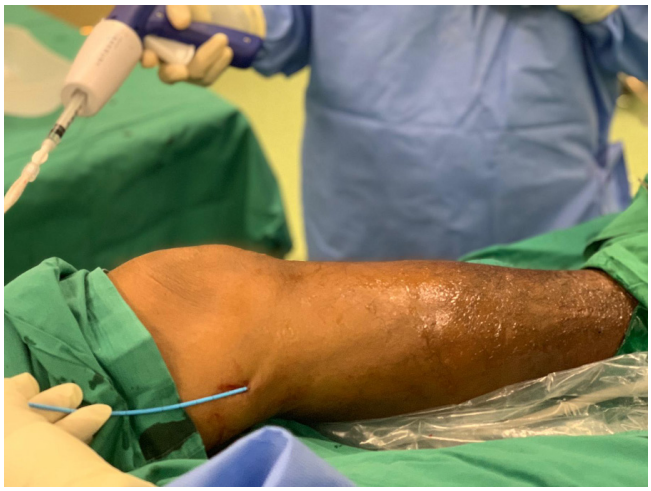

Fig. 3. Retrograde puncture technique with puncture site at the knee for reflux below the knee.

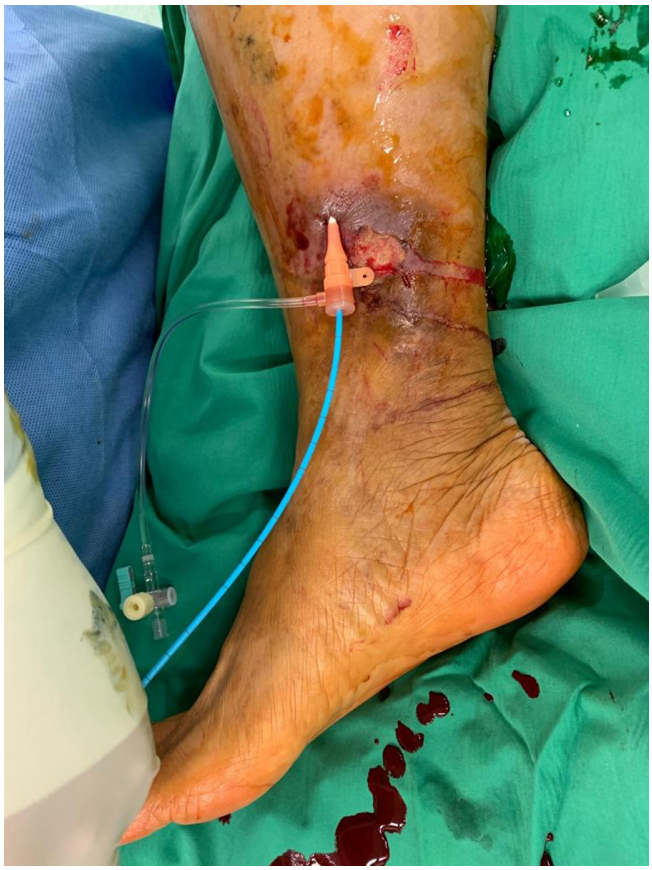

Fig. 4. Antegrade puncture technique with the puncture site at the ankle, next to the ulcer site.

higher cost. Additionally, the cost has to be borne in cash by patients unless it is covered by the patient's private insurance. Cost is a barrier for CAG use in patients, especially patients who require government healthcare subsidy.

CONCLUSION

CAG has been proven to be non-inferior to conventional methods for treating CVI, and is increasingly being used in both Western and Asian populations. As we increase our understanding of anatomical variations in

the Asian population, new techniques of CAG beyond the instructions for use have been developed to complement this knowledge. These techniques will increase the range of treatment options for patients with CVI, and provides a potential for CAG to treat a wider group of CVI patients, including those with venous leg ulcers. CAG treatment costs are high. Further robust evidence in terms of large randomised controlled trials along with cost-effectiveness studies is needed to determine the value of CAG in the Asian setting.

Disclosure

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COMMENTARY

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Optimum early orthopaedic surgery in COVID-19 patients

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Multiple guidelines have been established regarding the management of COVID-19 patients.[1,2] However, there remains a paucity regarding specific guidelines on the optimal timing for surgeries in COVID-19 patients requiring early orthopaedic surgery. This paper aims to provide evidence-based recommendations regarding the timing to proceed with early orthopaedic surgeries in COVID-19 patients.

Haemodynamically unstable patients. In an unwell patient, the clinical urgency of the operation should be weighed against the overall health of the patient. A balance needs to be maintained between the benefits of early surgery and the possibility of worsening the patient's respiratory function from anaesthetic and surgical stresses. This is especially so as COVID-19 is a respiratory condition that can cause multi-organ dysfunction in symptomatic patients, significantly increasing the risk of the surgeries. Symptomatic patients under treatment for COVID-19 may also be on medications such as high-dose steroids and anticoagulants, which can significantly increase the risk of surgeries, necessitating the need to balance between the benefits of early surgery and the overall health of the patient. Haemodynamically unstable patients should undergo immediate surgery as soon as possible if the surgery may improve their condition, for example in unstable pelvic fractures, exsanguinating injuries, compartment syndrome or necrotising fasciitis. Other non-emergent surgeries should be postponed until the patient is stabilised.

Open fractures. The British Orthopaedic Association, British Association of Plastic Reconstructive and Aesthetic Surgeons, American College of Surgeons and Orthopaedic Trauma Association have released guidelines for open fracture management.[3,4] Immediate surgical exploration for open fractures are recommended in the presence of gross contamination, compartment syndrome, vascular compromise and in a multiply injured patient, with full personal protective equipment (PPE) as soon as possible.[3] In the absence of the above, initial debridement can be safely performed within 24 to 48 hours without adverse effects, once the patient's COVID-19 status is confirmed.[3,4]

Whenever possible, skin defects overlying open fractures should be closed during the initial debridement and internal fixation can be performed.[3,4] If required, subsequent soft tissue reconstruction is recommended to be performed on day 7 before vessels become friable and fibrosed, with definitive internal fixation in the same setting.[3,4] This is to maximise the duration for the treatment of COVID-19 while mitigating the risks of further delay.

Without soft tissue reconstruction, consideration should be given to definitive management of the fractures with external fixators. This is to decrease the risk of respiratory failure in COVID-19 patients during anaesthesia and intramedullary nailing of diaphyseal fractures, protect healthcare workers and conserve resources. Should subsequent skeletal stabilisation be required without soft tissue reconstruction, the surgery is recommended to be performed on day 14 to maximise the duration for the treatment of COVID-19 while mitigating the risks of further delay.[3]

Closed fractures and dislocations of extremities. Immediate surgical intervention with full PPE is recommended for closed fractures and dislocations with compartment syndrome or vascular compromise. This is to prevent irreversible muscle damage, with subsequent revascularisation possibly causing systematic complications including myoglobinuria, renal failure and death. The other indication for immediate intervention is that of a multiply injured patient who require other immediate surgery. However, this should be decided according to the surgical duration and the possibility of performing it after confirming or treating the COVID-19.[5]

Urgent surgeries are indicated for irreducible large joint dislocations. These include shoulder, elbow, hip, knee, ankle and subtalar dislocations.[5-10] Whenever possible, joint dislocations should be reduced as soon as possible at bedside with full PPE. Failure of closed

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reduction then necessitates closed reduction under general anaesthesia or open reduction with full PPE. This is to avoid traction or compressive injuries to neurovascular structures.[5-10]

Early surgeries for closed fractures and dislocations are warranted in 6 scenarios. (1) Posterior sternoclavicular joint dislocations are recommended to be reduced within 48 to 72 hours as risk of failure of closed reduction increases beyond.[11] (2) Floating elbows and knees are recommended to undergo early fixation to improve functional outcomes.[12,13] (3) Closed fractures or dislocations with suspected nerve lacerations are recommended to have exploration and nerve repair early as Wallerian degeneration occurs within 24 to 48 hours.[14] (4) Hip fractures are recommended to undergo surgery within 48 hours with a significant decrease in fatality and risk of pressure sores.[15] (5) Though controversial, if fixation is decided for proximal humerus fractures, early fixation can be performed as studies report a decreased rate of avascular necrosis when performed within 48 hours.[16] Recent meta-analyses, however, identified that the timing of surgery has no bearing on the risks of avascular necrosis for young neck of femur fractures and talar neck fractures. Therefore, decision to proceed with early surgery is dependent on the consultant's practice.[17,18] (6) Closed fractures and dislocations with skin tenting and impending conversion to open fractures are warranted early surgery as per open fractures.

Other closed fractures and dislocations are recommended to have their surgeries on day 14 if decision is made for surgical fixation. This is to maximise the duration for the treatment of COVID-19 while mitigating the risks of further delay. An exception is for acromioclavicular joint dislocations, where surgeries can be performed on day 21 and still be associated with good functional outcomes and reduction.[19] Anterior sternoclavicular joint dislocations can also be left unreduced should closed reduction fails.[5]

Septic arthritis and periprosthetic joint infections. British Orthopaedic Association, British Society for Rheumatology, British Health Professionals in Rheumatology, Royal College of General Practitioners and British Society for Antimicrobial Chemotherapy published guidelines for septic arthritis.[20] They recommended early removal of intra-articular pus followed by antibiotics.[20] Options include repeated needle aspiration to dryness or surgical drainage done arthroscopically or open, with limited evidence to suggest one over another.[20] In the setting of COVID-19 patients, bedside aspiration is therefore recommended as soon as possible with full PPE, and early surgical drainage could be performed after confirming the COVID-19 status if surgical drainage is the institution's practice.

The International Consensus on Orthopaedic Infections published guideline for periprosthetic joint infections.[21] They recommended for surgery to be performed urgently once the patient is optimised, but not as an emergency.[21] The exact cut-off time for surgery to be performed has not been established, but a shorter duration of symptoms is significantly correlated with higher success rates of surgery. Therefore surgery should be performed once the COVID-19 status of the patient is confirmed.[21]

Infected wounds or abscesses. Superficial infection can be managed with trial of medical therapy with close observation for progression to deep tissue infection. Deep tissue infections are, however, recommended early surgery to minimise the risk of ascending infection and compartment syndrome once the COVID-19 status of the patient is confirmed. These interventions may be required urgently in the presence of systemic toxicity.

Lacerations or deep abrasions. Newer studies and guidelines have demonstrated no relationship between the timing of surgery and infection risk up until 19 hours after injury.[22] Wounds that require surgery should therefore be operated after confirming the COVID-19 status of the patients.

Tendon ruptures or muscle tears. The effect of the timing of tendon repair or muscle tears remain controversial.[23] Two studies showed no difference in outcomes even if the surgery is delayed for 3 weeks, while the last study demonstrated a decrease in final active range of motion of 0.3 degree with each day of delay for flexor tendon repair.[23] Accordingly, closed tendon ruptures or muscle tears should be operated after confirming the COVID-19 status, with the exact timing dependent on the consultant's practice. Patients with a wound overlying the tendon rupture or muscle tear should have early surgery as per the recommendations for lacerations and deep abrasions.

Locked joints. Locked joints are advised to have early surgeries to minimise stiffness and limited range of motion. However, there is limited evidence regarding the exact timing for these surgeries. The surgeries should be done after confirming the COVID-19 status, though the exact timing can be decided by the consultant in view of the controversial evidence.

Spinal trauma, cord compression or cauda equina. There is agreement that incomplete spinal cord injury may result in better neurological outcomes following early surgery, ideally within 6 hours.[24] Patients with incomplete spinal cord injury or cauda equina should therefore have their surgery performed immediately with

full PPE, or after confirmation of the COVID-19 status of the patient if possible within 6 hours.

In complete neurological deficit, however, some studies show no neurological improvement after early surgery, though surgery within 72 hours had lower risk of complications and length of stay.[25] Therefore, patients with complete neurological deficit or no neurological deficits can have their surgery after confirming the COVID-19 status, with close neurological monitoring to ascertain if there is worsening neurology.

Patients with central cord syndrome, without any fractures or dislocations rendering the cervical spine unstable, generally have better prognosis.[26] In the absence of evolving neurological deficits, they can have surgery after confirming the COVID-19 status as deemed appropriate by the consultant.

In the event of haemodynamic instability due to neurogenic shock, the optimal timing of surgery is as per recommended for other haemodynamically unwell patients.

Elective surgeries. Elective surgeries, except for oncological surgeries, should be postponed in the face of the pandemic. Oncological surgeries should be performed after confirmation of COVID-19 status, and if possible, after treatment of COVID-19. If any of the patients scheduled for other elective surgeries become a suspected or confirmed COVID-19 patient, the operation should be postponed until treatment is completed.

Evidence-based recommendations regarding the timing to proceed with early orthopaedic surgeries in COVID-19 patients are summarised in Table 1. These are made based on 3 main principles. Firstly, when faced with an unwell patient, saving lives takes precedence over saving limbs. Secondly, in a well patient, the clinical urgency of the operation should be weighed against the possibility of delaying the operation until the infectivity of the patient's COVID-19 is eliminated or lowered, or at least until the COVID-19 status of the patient is known. Lastly, elective surgeries, except for oncological surgeries, should be postponed during the pandemic.

Table 1. Summary of recommendations for the optimal timing for early orthopaedic surgeries in COVID-19 patients

Condition	Recommendation
Haemodynamically Unstable Patients	
Unstable pelvic fractures	Immediate surgery
Exsanguinating injuries	Immediate surgery
Compartment syndrome	Immediate surgery
Necrotising fasciitis	Immediate surgery
Other conditions	Postponed until the patient is stabilised
Open Fractures	
Gross contamination	Immediate surgery
Compartment syndrome	Immediate surgery
Vascular compromise	Immediate surgery
Initial debridement of open fractures without gross contamination, compartment syndrome or vascular compromise	Within 24 to 48 hours[a]
Subsequent soft tissue reconstruction with definitive skeletal stabilisation	7 days following injury[b]
Skeletal stabilisation without soft tissue reconstruction	14 days following injury if surgery is required[b]
Closed Fractures and Dislocations of Extremities	
Impending conversion to open fractures	As per open fracture recommendations above
Vascular compromise	Immediate surgery
Multiply injured patient who require other immediate surgery	Decided according to the surgical duration and the possibility of delaying surgery
Irreducible large joint dislocations	As soon as possible[a]

Table 1. Summary of recommendations for the optimal timing for early orthopaedic surgeries in COVID-19 patients (Cont'd)

Condition	Recommendation
Posterior sternoclavicular joint dislocations	Within 48 to 72 hours[a]
Floating elbows and knees	Within 24 to 48 hours[a]
Closed fractures with nerve lacerations	Within 24 to 48 hours[a]
Hip fractures	Within 48 hours[a]
Proximal humerus fixation	Within 48 hours[a]
Young neck of femur fractures	Dependent on consultant's decision[a b]
Talar neck fractures	Dependent on consultant's decision[a b]
Acromioclavicular joint dislocations	21 days following injury[b]
Anterior sternoclavicular joint dislocations	Leave unreduced should closed reduction fails
Other closed fractures and dislocations	14 days following injury[b]
Septic Arthritis and Periprosthetic Joint Infections	
Septic arthritis bedside aspiration	As soon as possible
Septic arthritis surgical drainage	After confirming COVID-19 status of patients
Periprosthetic joint infections	After confirming COVID-19 status of patients
Infected Wounds or Abscesses	
Superficial infections	Managed with trial of medical therapy
Deep tissue infections	After confirming COVID-19 status of patients
Lacerations or Deep Abrasions	
Lacerations or deep abrasions	After confirming COVID-19 status of patients
Tendon Ruptures or Muscle Tears	
Open tendon ruptures or muscle tears	As per lacerations or deep abrasions recommendations above
Closed tendon ruptures or muscle tears	After confirming COVID-19 status of patients, but exact timing dependent on consultant's decision
Locked Joints	
Locked joints	After confirming COVID-19 status of patients, but exact timing dependent on consultant's decision
Spinal Trauma, Cord Compression or Cauda Equina	
Incomplete spinal cord injury	Within 6 hours[a]
Complete spinal cord injury	Within 72 hours[a]
Spinal trauma with no neurological deficit	After confirming COVID-19 status of patients
Central cord syndrome without any fractures or dislocations	After confirming COVID-19 status of patients if deemed appropriate by the consultant
Neurogenic shock	As per haemodynamically unstable recommendations above
Elective Surgeries	
Oncological procedures	After confirming COVID-19 status of patients, and if possible, after treatment of COVID-19
Other elective surgeries	Postponed in the face of pandemic

[a] Confirmation of COVID-19 status should be obtained during the timeframe if possible
[b] Treatment should be started for COVID-19 positive patients during the timeframe if possible

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LETTER TO THE EDITOR

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Empagliflozin-induced severe osmotic nephrosis and acute renal injury in advanced chronic kidney disease

Dear Editor,

Diabetic kidney disease remains a significant disease burden globally and is associated with increased medical costs once chronic kidney disease (CKD) ensues.[1,2] Therefore, optimisation of CKD management through glycaemic control and albuminuria reduction are key strategies for retarding renal deterioration. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a new class of antidiabetic medications that has garnered vast interest since increasing evidence has highlighted—apart from their glycaemic lowering properties—notable cardio- and reno-protective effects.[1,2] However, concerns of increased acute kidney injury (AKI) have been raised and a few studies reported tubular injury and osmotic nephrosis with SGLT-2 use.[3,4] We present a case of biopsy-proven osmotic nephrosis and severe acute renal injury following an inadvertent overdose of empagliflozin in a patient with advanced CKD (defined as ≤30mL/min/1.73m^2 body surface area).

Case study. A 65-year-old Malay woman with advanced diabetic kidney disease presented to the emergency department in June 2020 with a 5-day history of vomiting, diarrhoea and lethargy. She had a history of type 2 diabetes, hypertension, and locally advanced endometrial cancer in remission. Her medications consist of an empagliflozin and metformin combination tablet (Jardiance Duo®), linagliptin, glipizide, indapamide and iron polymaltose, all of which she had been receiving from her primary care physician for at least 2 years. Her baseline creatinine was 160–180µmol/L and estimated glomerular rate (eGFR) was 27–32mL/min/1.73m^2. Two weeks before her admission she unintentionally doubled her dose of Jardiance Duo® and thus, took a total of 50mg of empagliflozin and 2g of metformin in a day. On admission, she had oliguric acute kidney injury (kidney disease: improving global outcomes [KDIGO] stage 3) with decompensated high anion gap metabolic acidosis, hyperlactataemia, hypoglycaemia, anaemia and concomitant leukocytosis with neutrophilia. She remained haemodynamically stable, afebrile and clinically euvolemic. Her physical examination was unremarkable. Her laboratory values revealed a serum creatinine of 948µmol/L, urea 34.5mmol/L, potassium 4mmol/L, bicarbonate 8mmol/L, venous pH 7.1, lactate 5.2mmol/L, white cell count 19x10^9/L, haemoglobin 9.2g/dL, and platelets 317 x 10^9/L. Her urinalysis showed active sediments with pyuria (314 white cells/high power field [HPF]) and haematuria (11 red cells/HPF), her urine culture yielded *Escherichia coli* (>100,000 colony-forming unit/mL), and her urine protein: creatinine ratio was 189mg/mmol. Her renal ultrasound was unremarkable apart from changes consistent with CKD and bilateral simple cysts, and her chest X-ray was clear. Secondary workup including serum protein electrophoresis, immunofixation, complement levels, anti-double-stranded DNA, anti-nuclear antibodies, anti-neutrophilic cytoplasmic antibodies, anti-glomerular basement membrane antibodies, hepatitis B, hepatitis C, and human immunodeficiency virus was negative. There was no evidence of haemolysis. Haemodialysis was initiated on admission. Concomitantly, an adequate trial of intravenous volume expansion was administered but this did not lead to significant improvement in kidney function and the patient remained oliguric. A kidney biopsy was subsequently performed which revealed acute tubular necrosis and diffuse osmotic nephrosis on a background of diabetic glomerulosclerosis with 25% tubulointerstitial fibrosis (Fig. 1). Immunofluorescence was negative and there were no electron-dense deposits. The cause of the patient's severe renal injury was multifactorial, owing to the haemodynamic effects of empagliflozin, and contributed by pre-renal AKI secondary to infective gastroenteritis. In the absence of clinical symptoms, or radiological and histological evidence of a urinary tract infection, the bacteriuria was unlikely a major contributory factor of AKI. Treatment was supportive with cessation of empagliflozin. She required 1 session of intermittent dialysis and was weaned off dialysis following renal recovery. Her creatinine improved to a new baseline of 296µmol/L 2 weeks later.

Discussion. Following current evidence-based medicine, the patient was started on empagliflozin for diabetic control, anti-proteinuric effects, and retardation of CKD progression. The proposed mechanism for reno-protection is centred around the reduction of intraglomerular pressure. SGLT-2 inhibitors induce glycosuria by inhibiting the reabsorption of glucose in the proximal tubule. This induces proximal tubule natriuresis that activates tubuloglomerular feedback, leading to afferent vasoconstriction.[5,6] This effect, together with increased tubular back pressure from increased fluid delivery to the distal tubule through osmotic effects

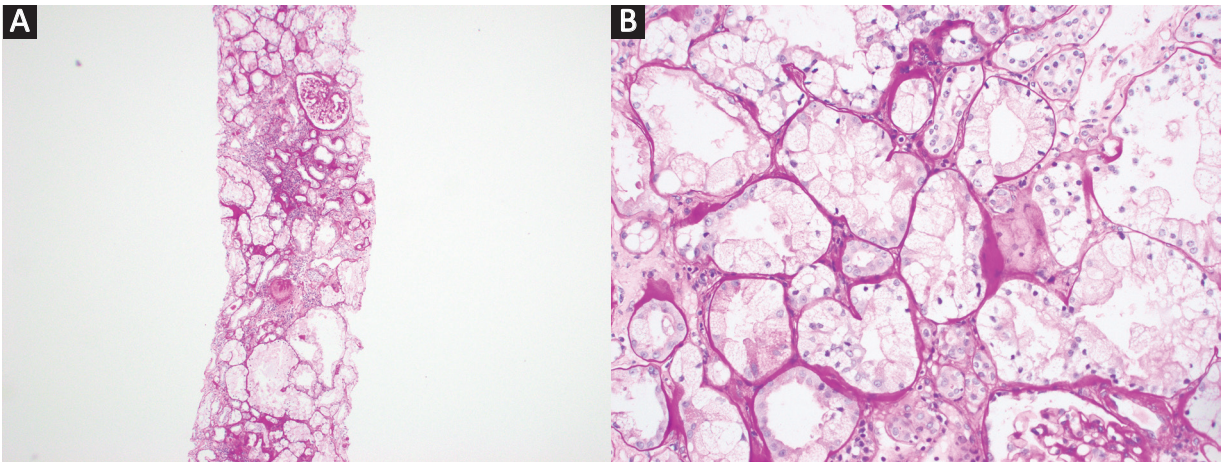

Fig. 1. Histological images, periodic acid-Schiff (PAS) stain. (A) Low power view, x2 magnification; renal cortical tissue with acute tubular injury featuring pale and swollen proximal tubules. (B) High power view, x20 magnification; proximal tubules with isometric fine vacuolisation of the cytoplasm (osmotic tubulopathy) and 25% tubulointerstitial fibrosis.

from non-reabsorbed glucose, consequently lowers intraglomerular pressure.[7] There is limited evidence on the renal sequelae following an overdose. Extrapolating from its vasoconstrictive effect on the afferent arteriole and its diuretic properties, it is not surprising that AKI ensues after an overdose. A case study reported AKI in a healthy patient following an overdose of ipragliflozin (1,500mg) and olmesartan (800mg), which resolved once blood ipraglifozin lowered to an acceptable level.[8] Osmotic nephrosis, the predominant lesion in our patient's histology report, was likely associated with empagliflozin use. This has also been reported with canagliflozin and dapagliflozin.[3] Osmotic nephrosis is associated with the use of hyperosmotic agents and can occur in severe hyperglycaemia, or in glycosuria induced by SGLT-2 inhibitors.[3] It occurs within a week of the inciting event and is acutely reversible on withdrawal of the causative agent. Correspondingly, our patient's kidney function recovered with cessation of SGLT-2 inhibitor use.

Presently, there is limited evidence on SGLT-2 use in patients with advanced CKD, with the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) study being the only published randomised controlled trial showing continued benefit in such patients.[9] Notably, earlier trials did not include patients with advanced CKD. SGLT-2 inhibitor use remains contraindicated at eGFR 30mL/min/1.73m^2 or less. The American Diabetes Association standard of care only endorses SGLT-2 inhibitor use for diabetic patients with eGFR ≥30mL/min/1.73m^2 and macroalbuminuria (>300 mg/g).[10] Further information regarding risk profiling is needed and may be revealed in the ongoing randomised controlled EMPA-KIDNEY trial, which will evaluate the renal and cardiovascular benefits of SGLT-2 in patients with eGFR as low as 20mL/min.

Our patient with advanced CKD developed severe acute renal injury following an overdose of empagliflozin. This is the first reported case of histologically proven osmotic nephrosis associated with empagliflozin. With current evidence showing overwhelming cardiovascular and renal benefits, notwithstanding glucose-lowering effects, SGLT-2 inhibitor use is progressively being incorporated into standard practice. Further studies are needed to delineate individual safety profiles, patient selection and optimal dosing recommendations for its continued use in advanced CKD patients.

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LETTER TO THE EDITOR

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Carbamazepine-induced toxic epidermal necrolysis in a patient despite testing negative for HLA B*15:02 allele

Dear Editor,

Carbamazepine (CBZ) has been used in Singapore since 1988[1] as an effective drug for the treatment of conditions such as epilepsy, neuropathy, neuralgia and psychiatric conditions. However, it is a high-risk drug for Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), particularly in Asians, and in 2004, a genetic marker human leukocyte antigen (HLA)-B*1502 in Han Chinese was identified.[2] In Singapore, these findings were validated and the carriage of HLA-B*1502 was associated with CBZ-induced SJS/TEN (odds ratio 181, $P<0.0001$).[3] This led to the recommendations for HLA-B*1502 genotyping prior to initiation of CBZ in new patients of Asian ancestry as standard of care, to reduce the risk of developing SJS/TEN.[3]

Through this implementation, there has been more than 1,000 tests performed annually, and the number of reported cases of SJS/TEN associated with CBZ has decreased sharply by >90% after policy implementation.[4]

We report a case of a patient who was given CBZ and developed TEN despite testing negative for the HLA B*15:02 allele. This case serves to remind clinicians that a negative test result for the HLA B*1502 allele—while making it less likely—does not preclude the possibility of SJS/TEN development in a patient prescribed with CBZ, and that early recognition of this syndrome is important given its significant morbidity and mortality.

A 27-year-old Chinese man with a history of autism spectrum disorder—previously prescribed with sodium valproate CR 750mg ON, fluoxetine 40mg OM, and risperidone 2mg BD, clonazepam 1mg TDS—presented with worsening aggression and violent behaviour. He was seen by his psychiatrist who then recommended CBZ for treatment of his aggressive behaviour. Prior to initiation of CBZ, he underwent a serum polymerase chain reaction test for HLA-B*15:02 allele and tested negative.

On the 11th day after starting CBZ, he developed a fever. His fever persisted for 3 days despite empirical treatment with antibiotics. Given mild derangements in his liver function tests, an infective aetiology was suspected and he underwent extensive investigations, including computed tomography scan of his brain, chest, abdomen and pelvis, and a transthoracic echocardiogram that did not reveal any sources of sepsis or occult infection. Viral hepatitis markers, atypical bacterial infections (e.g. *Mycoplasma spp.*) and autoimmune markers were also screened and showed no abnormalities. Four days after the onset of fever, he started developing erythematous macules on his trunk, upper thighs and arms. A dermatology consult was made and a diagnosis of TEN was considered. A skin biopsy was immediately performed. Several of his psychiatric medications, including CBZ, were stopped due to their possible implications as a culprit drug.

His skin biopsy was reported as vacuolar interface changes associated with numerous apoptotic bodies at the dermal-epidermal junction. At this point, his rash progressed rapidly with the formation of flaccid blisters and erosions, along with conjunctival and oral mucosal involvement. Nikolsky's sign was positive with body surface area (BSA) of 50%, and a diagnosis of TEN was made. His SCORe of Toxic Epidermal Necrolysis (SCORTEN) was 2 at the time of diagnosis, due to the presence of tachycardia, and the affected BSA being >10%. He was started on supportive treatment, and cyclosporine A was also initiated at a dose of 1mg/kg/day intravenously.

A detailed review of his exposure to new drugs in the recent 3 months prior to the onset of TEN was made, and a few potential culprits were identified, namely CBZ, zuclopenthixol, co-ping was performed again, which was negative. An extended HLA typing was also done and the results are in Table 1.

In the subsequent days, the patient remained persistently febrile and tachycardic, with progression of his involved BSA to 80–90% (Fig. 1). He was managed with meticulous supportive care with intravenous fluids, regular scheduled dressing changes using non-adherent dressings, and an ongoing infusion of cyclosporine 70mg once daily. He remained clinically stable although initial improvement in his cutaneous and mucosal involvement was marginal.

However, 6 days after he was transferred to the burns unit, he developed type 1 respiratory failure. He responded initially to doses of furosemide as treatment

Table 1. Results of extended HLA typing: none matched existing reports of alternative HLA alleles associated with higher risk of CBZ-induced TEN

HLA typing (using sequence-based typing)	Results
HLA A	A*02:07 A*11:01/295/303/324/328/353
HLA B	B*27:04/61/168/173 B*40:01/72/124/183/353/379/386/416/417/431/439/443
HLA C	C*04:01/29/30/33/114/172/275/277/320/375/380/391 C*12:02/41/72/132/146/228/261/285/304

CBZ: carbamazepine; HLA: human leukocyte antigen; TEN: toxic epidermal necrolysis

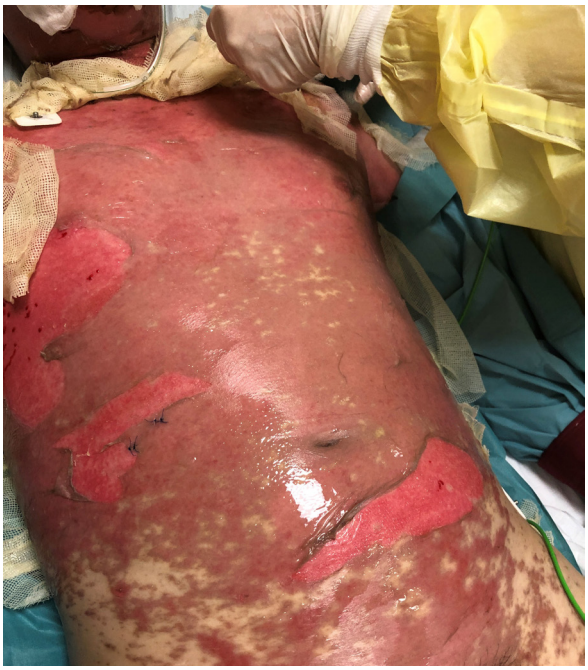

Fig. 1. Extensive denudation of the entire trunk and upper limbs, with some areas of flaccid blisters formation on the lower abdomen.

for fluid overload but rapidly deteriorated overnight and eventually died from cardiac arrest.

The majority of CBZ-induced SJS/TEN in Han Chinese and Southeast Asians are associated with HLA-B*1502. Initial studies on CBZ-induced SJS/TEN in Taiwan and Singapore reported that the negative predictive value of HLA-B*1502 was from 99.9–100%.[5] A subsequent study based on a larger population group in Taiwan demonstrated that while HLA-B*1502 was significantly associated with a higher risk of SJS/TEN—almost 100 times higher than for a non-carrier—the negative predictive value was lower at 92%.[6]

In light of these findings and our case report, there are a few practical implications for patients of Asian descent in Singapore. First, regardless of testing negative for HLA B*1502, patients who are to be initiated on CBZ should still be counselled on the low risk of developing SJS/TEN.

Second, it must also be recognised that HLA-B*1502 is only a genetic marker for SJS/TEN. It does not predict other severe adverse drug reactions such as drug reaction with eosinophilia and systemic symptoms,[6] which is also highly associated with CBZ and other anti-epileptics.[7] Therefore, it is essential that all patients newly initiated on CBZ are closely monitored and counselled to watch for reactions even if they are HLA-B*1502 negative.

In our patient, we sought to review further other HLA alleles that might have rendered him susceptible to developing CBZ-induced TEN. A review of literature has shown some associations with HLA-A*31:01, HLA B*15:11, HLA B*15:18, HLA-B*59:0.[8-10] We proceeded with an extended testing for HLA A, B and C alleles, but none corresponded to existing risk markers. As more of such HLA B-negative SJS/TEN cases are identified, genotyping should be performed to identify other potential risk markers, although its cost-effectiveness is debatable. Such markers, if present, might further refine future genetic screening tests in addition to tests for HLA-B*1502.

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A resuscitation course designed for a psychiatric hospital

Dear Editor,

It is challenging to maintain the resuscitation skills of doctors in a psychiatric hospital. Our study describes a resuscitation course designed specifically for the Institute of Mental Health (IMH) in Singapore to address competency gaps, which proved to be relevant and helpful to the trainees.

The IMH is the only tertiary psychiatric hospital in Singapore. It does not provide acute medical care. When a patient is in cardiac or respiratory arrest and code blue is activated, 2 on-call doctors and a designated nursing team respond and perform advanced cardiac life support (ACLS) before the arrival of the ambulance team and the subsequent transfer of the patient to a general hospital.

The on-call doctors are non-specialists rotated to different departments within IMH or other hospitals once every 6 months. They attend an ALCS course once every 2 years. Despite such training, it is a challenge to maintain their resuscitation skills because of the low volume of code blue situations in IMH.

The code blue committee oversees the training of IMH staff to manage code blue situations. The committee conducts code blue drills 6 times a month to expose IMH staff to simulated code blue situations and identify gaps in the management. The committee identified several competency gaps comprising poor airway management, lack of familiarity with the defibrillator used in IMH and an inability to lead resuscitation efforts.

In July 2015, the code blue committee developed a resuscitation course for the IMH setting to address the gaps in the doctors' competency. This compulsory 3-hour course is conducted 6 times per year outside official working hours to minimise disruption to the doctors' clinical work. It is compulsory for doctors who have to respond to code blue to attend this course once every 6 months.

During the course, the trainees are divided into groups of 4. Trainers are emergency physicians from various emergency departments in Singapore who will interact and rotate through several training stations with the trainees. A considerably small trainer to trainee ratio (1:4) aims to keep trainees engaged and training hours optimal. While resource-intensive, the course has been sustainable due to the goodwill of the senior management, nurses and emergency physicians.

The training stations include (1) watching a video demonstrating an ideal code blue response in IMH, (2) a hands-on session to learn airway management techniques including how to use Magill forceps to remove foreign body from the throat and the use of a laryngeal mask airway, (3) operation of the defibrillators used in IMH, (4) recognition and management of cardiac arrest rhythms, (5) familiarisation with the emergency drugs used in IMH, and (6) a code blue drill.

The video of an ideal code blue response was filmed in IMH to demonstrate the resuscitation process in the practicable setting. Thirty percent of code blue situations in IMH are related to choking especially for patients with intellectual disability who have the tendency to grab and swallow food quickly. Airway management is an important component in this course.

Familiarisation with equipment which are different from those used in general hospitals (defibrillator and emergency drug kit) are emphasised, including the burette (micro-drip) for slow infusion of medication as infusion pumps are only available in the isolation wards.

The code blue drill during the resuscitation course emphasises practical leadership skills through designated roles and instructions for each team member.

In 2017, a study on the effectiveness of the resuscitation course was done through quantitative and qualitative evaluation.

Quantitative data were collected with consent from 107 doctors via self-rated feedback forms before and after the course. Most trainees found the resuscitation course relevant in preparing them for code blue situations in IMH (Table 1).

For 72% of these doctors, their last medical rotation (emergency medicine, internal medicine or anaesthesia) was more than a year ago.

Most trainees found the resuscitation course relevant in preparing them for code blue situations in IMH, especially for certain components of the training—the video on the resuscitation process, demonstration of the use of AED/Defibrillator in IMH, showing contents of emergency drug kit and teaching how to lead a resuscitation team and give clear instructions. (Table 1)

Table 1. Feedback on whether various aspects of the resuscitation course were helpful to the trainees (N=107)

Resuscitation course in IMH more pertinent than the ACLS course outside IMH?	n	%
No	10	9.3
Yes	85	79.4
Missing data	12	11.2
Video on a resuscitation process shown during the course in IMH helpful?	n	%
No	6	5.6
Yes	97	90.7
Missing data	4	3.7
Use of the Nihon Kohden AED/defibrillator is demonstrated and the participants given the opportunity to operate the AED/defibrillator helpful?	n	%
No	1	0.9
Yes	103	96.3
Missing data	3	2.8
The content in the emergency kit shown and explained to the participants helpful?	n	%
No	0	0
Yes	104	97.2
Missing data	3	2.8
Did the instructors teach you how to lead and give clear instructions during resuscitation?	n	%
No	0	0
Yes	104	97.2
Missing data	3	2.8
Instructors providing the answers and explanation to the questions in Short Answer Questions helpful?	n	%
No	0	0
Yes	104	97.2
Missing data	3	2.8
Training adequate for you to manage code blue in IMH?	n	%
No	4	3.7
Yes	100	93.5
Missing data	3	2.8

ACLS: advanced cardiac life support; AED: automated external defibrillator; IMH: Institute of Mental Health, Singapore

Qualitative data were collected by conducting semi-structured interviews with 15 doctors, 3 months after the training. Two main themes emerged from the data. Awareness and relevance of the course and the challenges of responding to code blue in a psychiatric hospital. Participants highlighted the relevance of the course as a refresher given that code blue situations are rare. Hands-on and scenario-based training by knowledgeable and experienced trainers using defibrillators specific to those used in IMH, drills and emphasis on managing common incidences of choking at the institution are aspects that participants found useful, in addition to ACLS knowledge and algorithms.

The study has some limitations and points of novelty. The performance of the trainees in a code blue situation was not monitored after the course. The feedback forms were not based on a validated instrument, as the investigators were unable to find a validated instrument relevant to a psychiatric hospital.

Ready competence of doctors is critical in managing code blue situations. Resuscitation skills tend to decay significantly after 6 months, and retraining is required to maintain knowledge and skills.[1-6] This course is a localised approach to address competency gaps unique to IMH, which are not addressed in an ACLS course.

During the COVID-19 pandemic, movement across institutions by doctors in Singapore was restricted. This meant that the IMH resuscitation course could not be conducted in its usual format with the emergency physicians from various general hospitals as trainers. However, a small group of IMH doctors who regularly attended the IMH resuscitation course had gained confidence and experience to conduct training for most of the unique-to-IMH hands-on stations.

Institutions that have a low volume of code blue situations may consider sending their response team for the ACLS course to build initial basic life support skills, but augment this with a resuscitation course localised for their environment. During a pandemic where cross-institutional movement is restricted, this localised course can allow institutions to maintain the resuscitation skills of their response team within their premises.

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Impact of COVID-19 on mental health and occupational burnout in a surgical unit in Singapore

Dear Editor,

In this study, we assessed the impact of COVID-19 on the psychological well-being and burnout among staff who manage critically ill general surgery and trauma patients as part of the Acute Care Surgery (ACS) service at the Singapore General Hospital, Singapore. The ACS team may be exposed to COVID-19 during consultations, high-risk surgical procedures and endoscopy that may aerosolise the virus. Our assessment revealed a positive mindset among the respondents, and that protective factors are paramount to maintain positive well-being.

In response to the COVID-19 pandemic, the Singapore government escalated its Disease Outbreak Response System Condition level to Orange on 7 February 2020, triggering containment and mitigation strategies.[1] The psychological sequelae of the pandemic deserve attention.[2] Data from previous outbreaks show that healthcare workers have suffered from post-traumatic stress disorder, depression and substance abuse.[3] In Wuhan, the initial epicentre of COVID-19, healthcare workers faced enormous challenges such as increased risks of infection and transmission of the disease to patients and family, and working with inadequate supply of personal protective equipment (PPE).[4]

The rapid surge of cases in Singapore has increased the workload and pressure placed on our healthcare staff. Few studies have addressed these issues outside of China during the current pandemic.[5-7]

This study was approved by the Institutional Review Board. It was a single-centre, cross-sectional study conducted via an online questionnaire (Qualtrics, Provo, US), accessible on personal computers and mobile devices. Doctors at all levels of seniority in the ACS service were invited to participate 2 months after the first case of COVID-19 in Singapore (23 January 2020). The questionnaire aimed to collect the respondents' subjective assessments of fear, anxiety, depression and burnout during this period. All responses were anonymised and results were aggregated before analysis.

The questionnaire comprises 4 parts that collected (1) demographic data, (2) perceived health status, (3) perceived risk of COVID-19 exposure in relation to workplace safety and contact with patients suspected or confirmed with COVID-19, and (4) impact on surgical training and personal development. Consolidated data for (2), (3) and (4) in Fig. 1 present the respondents' self-assessment of their psychological well-being and syndromes of burnout that they have experienced.

The Maslach Burnout Inventory (MBI) is a well-validated psychological tool used in research on burnout in various occupations and workplaces.[8,9] The MBI-Human Services Survey for Medical Personnel (MBI-HSS (MP)) was designed and adapted to assess burnout in healthcare workers. It comprises 22 statements to assess 3 burnout syndrome domains: emotional exhaustion, de-personalisation and personal accomplishment.

Nine out of 22 items from the MBI-HSS (MP) were selected for this study based on relevance and relatability. Respondents indicated their level of agreement/disagreement with each statement via a 5-point Likert scale.

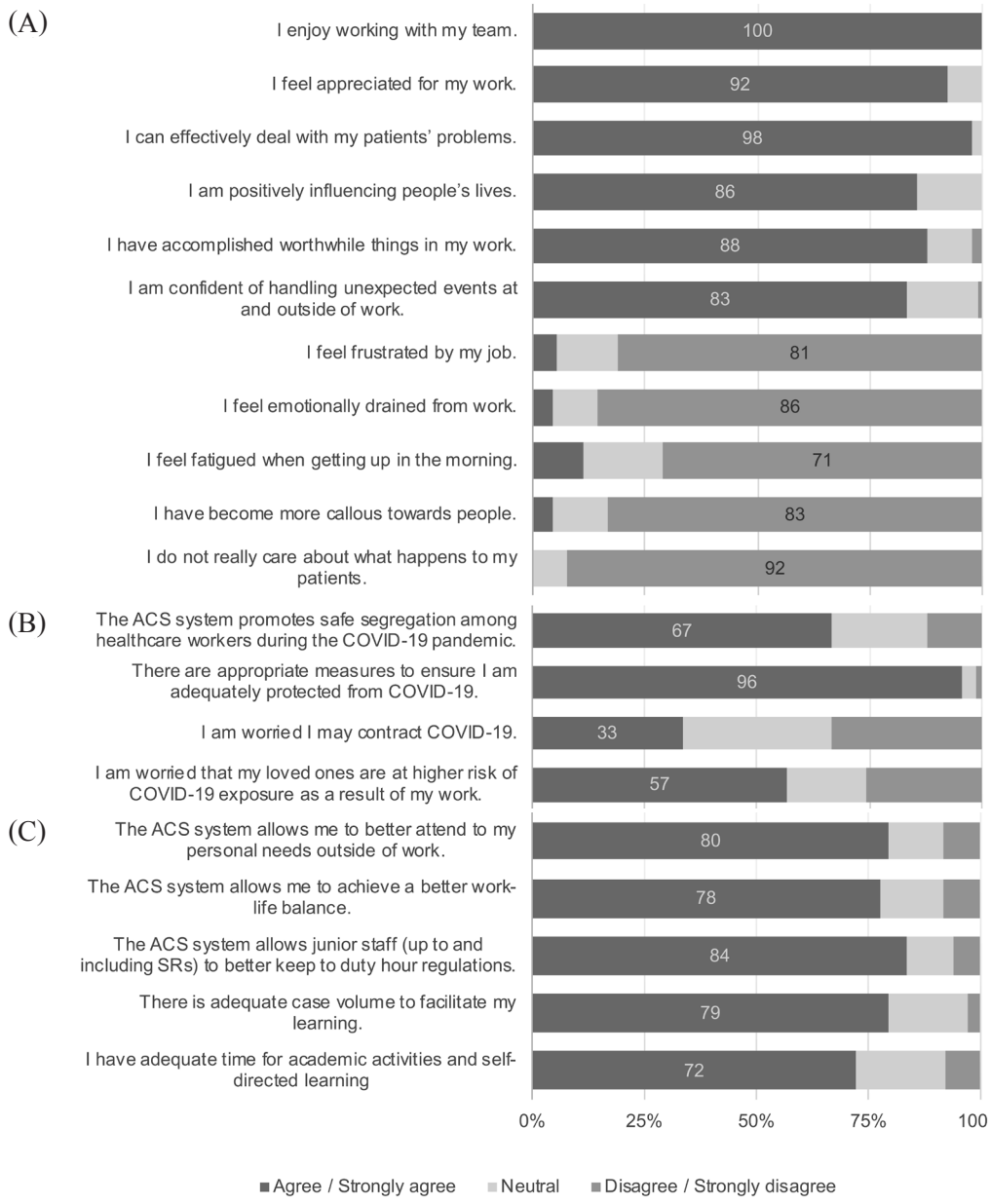
The data were tabulated using Qualtrics and further analysed using Microsoft Excel version 2013 (Microsoft Corp, Redmond, US). Responses for agree/strongly agree and disagree/strongly disagree were coalesced for ease of reporting.

The survey response rate was 98% (90/92 respondents) of doctors who worked in the ACS team from February to March 2020. The majority of the respondents (59%) were junior doctors comprising house officers, both medical officers and residents who were unmarried (71%) with no dependants living in the same household (63%).

Shown in Fig. 1, more than 80% of respondents agreed with the positive statements that reflect fulfillment and satisfaction at work. Notably, 100% of respondents enjoyed working within their teams, and 83% expressed confidence in handling unexpected events that may occur at and outside of work—in the context of the pandemic, significant events outside of work include being quarantined, having a loved one contract COVID-19, closure of important services and a nationwide lockdown.

Less than 12% of respondents agreed with the negative statements that assessed for energy depletion or exhaustion, increased mental distance from work or feelings of negativism, and reduced professional efficacy. No respondents expressed apathy towards the care of their patients.

Fig. 1. Response to statements pertaining to (A) psychological well-being and occupational burnout, (B) COVID-19 exposure and (C) impact on surgical training and personal development.



ACS: Acute Care Surgery; SRs: senior residents
Numbers indicate percentages.

One third (33%) of respondents were concerned that they may contract COVID-19 and 57% were concerned that their loved ones would be at higher risk of COVID-19 exposure as a result of their work.

However, the majority of respondents agreed that the ACS system promoted safe segregation among healthcare workers during the COVID-19 pandemic (67%) and there were appropriate measures to ensure they were adequately protected (96%). Having dependants living in the same household was associated with a higher concern for COVID-19 exposure compared to those with no dependants at home (70% vs 49%). Most respondents also agreed that the ACS system allowed junior staff to better keep to duty hour regulations (84%), better attend to personal needs outside of work (80%) and achieve better work-life balance (78%). Eighty-nine percent agreed that the number of calls they perform each month is manageable, 78% agreed

that they had at least 1 day free from all clinical responsibilities before their next call, and 67% agreed that they have never exceeded 30 hours of continuous on-site duty when they were on call despite increased workload and manpower demands during the COVID-19 pandemic. There were no significant differences between responses from junior and senior staff members.

The majority of respondents had adequate time for academic activities and self-learning (72%), and despite the postponement of elective non-cancer surgeries, 79% of respondents agreed that there remained adequate case volume for learning.

As the pandemic progresses, anxiety, depression and stress regarding workplace safety can intensify and lead to deteriorations in mental health given concerns of PPE shortages, loneliness and separation from loved ones.[5,10,11] Therefore, it was encouraging that 96% of respondents felt adequately protected from COVID-19. The ACS team was able to observe social distancing by limiting visits to the emergency department to review unstable patients, cancelling elective surgery and clinics, and designating wards for patients infected/suspected with COVID-19, together with ramped-up cleaning. Helplines for confidential mental health advice were made available. Support from the Singapore government ensured sustained supply of PPE, powered air-purifying and N95 respirators, masks, face-shields, hair nets and gloves. Thus, safety of the staff was not compromised. A recent meta-analysis supported our findings that reduced psychological morbidity for healthcare workers was associated with clear communication, access to PPE, adequate rest and availability of psychological support.[12] Other systemic measures include identification of groups that are at high risk of psychological distress, early psychological screening and prompt intervention using cognitive or mindfulness-based behavioural therapy.[13]

Although reassuring to see few respondents had expressed feelings of frustration, emotional drainage, callousness or fatigue from their work, long-term assessment is required to assess the strength of these findings, following reported prevalence of 50% burnout rate such as those in general surgery.[14]

The main strength of this study was the near complete response that bolstered its internal validity. However, as this is a single-centre study performed at a single time point with a small sample size, it may not be representative of other trauma and acute surgical units, and long-term studies are needed to ascertain if the positive findings persist with progression of the pandemic. Nonetheless, we have found that the following protective factors are paramount in maintaining positive well-being of our population—availability of PPE, appropriate hospital safeguards, team structure to limit exposure and cross-infection, safe working hours and efforts to provide reward for those at the frontline.

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Use of haemodialysis plastic cannula with ultrasound guidance in difficult arteriovenous access

Dear Editor,

The blind technique using metal needles has been the traditional method of cannulating arteriovenous (AV) accesses for haemodialysis. While most mature AV accesses can be cannulated with metal needles successfully, the incidence of miscannulation can be high in difficult accesses due to their location and depth, or in new accesses.[1] Cannulation-related complications were reported to be as high as 31% and may eventually lead to access failure.[2] Technical difficulty also increases following a miscannulation as infiltration and haematomas may increase the depth of the AV access.[3,4]

The use of metal dialysis needles for cannulation of AV accesses is the current standard of care in our institution, the Singapore General Hospital, Singapore. Plastic dialysis cannulae were recently introduced in the hospital to help improve cannulation of difficult dialysis accesses under ultrasound guidance. This quality audit aims to report the outcomes of ultrasound-guided cannulation of difficult AV accesses using plastic cannulae.

We performed a retrospective audit of patients referred to the Interventional Nephrology Service for ultrasound-guided cannulation of AV access between September 2017 and March 2019. Referred patients had either failed cannulation by dialysis nurses or were assessed to have a high chance of cannulation failure with the blind technique. This quality audit performed with de-identified data is exempt for review by the Institutional Review Board. Outcome measures were defined as the number of successful cannulations, number of passes needed, proportion of patients that successfully completed the prescribed length of haemodialysis, and blood flow achieved.

Twenty-eight ultrasound-guided plastic cannula placements were performed in 22 patients. The median age was 61.5 years (interquartile range [IQR] 53.8–74.5), 50% were women, and majority were of Chinese ethnicity (72.7%). Most accesses were AV fistulas (77.3%). The most common anatomical anastomosis was radiocephalic (50.0%). Seven accesses (31.8%) were new and had never been successfully used for dialysis. The median access flows of new and all accesses were 509mL/min (IQR 251–817) and 615mL/min (IQR 515–2200), respectively. Indications for ultrasound-guided cannulation included failed blind cannulation by dialysis nurses (48%), swollen access (41%) and new access for trial of cannulation (9%).

A total of 27 arterial and 28 venous site cannulations were recorded (Table 1). All cannulations were successful without immediate complications. Mean blood flow achieved was 214±24.4mL/min. One patient did not achieve the prescribed blood flow due to extreme negative pressures at the arterial needle.

Among the 22 patients, 11 (50%) required only 1 dialysis session with plastic cannula, with subsequent metal cannulation performed successfully by dialysis nurses. Three patients (13.6%) required a second dialysis session with plastic cannula. One patient (4.5%) underwent angioplasty after the first session with plastic cannula, and subsequent metal cannulation was successful. Six patients (27.3%) underwent 1–2 dialysis sessions using plastic cannulae, and subsequently transited to a tunnelled dialysis catheter as the AV accesses were poorly matured. One patient required multiple plastic cannulations over a 2-week period to allow resolution of the peri-fistula swelling.

Our audit shows that high cannulation success rates for difficult AV accesses can be achieved with ultrasound-guided cannulation using plastic cannulae. The metal and plastic cannula needles used by our institution are both 16-gauge needles, with V-shaped tips. However, the metal needle (SGD0.47/piece, approximately USD0.35) is 30mm in length while the plastic cannula (SGD3.00/piece, approx. USD2.23) is 38mm. Cannulation of the deeper AV access is therefore possible with the longer plastic cannula. Although longer metal needles are commercially available, leaving longer metal needles in situ for 4–5 hours may induce longer segments of endothelial injury from needle contact, and consequently neointimal hyperplasia and stenosis.[5,6] In comparison, plastic cannulae have the potential to negotiate tortuous AV accesses, reducing risks of infiltration and access intervention along the cannulation segment.[6]

Our results showed that the use of plastic cannulae prevented temporary dialysis catheter insertions in 16 out of 22 patients. This helped to minimise

Table 1. Immediate and dialysis outcomes of cannulation using plastic canula according to sites

Outcomes	Values, n (%)	
	Arterial site (n=27)	Venous site (n=28)
Successful cannulation	27 (100)	28 (100)
Complications during cannulation	Nil	Nil
Successful at first pass	25 (93)	25 (89)
Completed prescribed length of dialysis	27 (100)	28 (100)
Achieved blood flow prescribed	26 (96)	Not applicable

catheter-related risks of bloodstream infections, dysfunction, thrombosis and central vein stenosis,[7] hence avoiding additional procedural costs and prolonged hospitalisations. Ultrasound-guided plastic cannulation may therefore be a feasible bridging method to reduce emergency placement of dialysis catheters while awaiting resolution of AV access swelling, or definitive procedures such as angioplasty for salvage of non-maturing AV fistulas.[8]

Miscannulations of AV accesses can be distressing for both dialysis nurses and patients. Placement of plastic cannulae may increase the confidence and ease of subsequent metal cannulation by dialysis nurses, through the use of previous cannulation marks and tracks. This would be useful for patients who require early use of fistulas, or whose accesses are less prominent due to overlying subcutaneous tissue. Future training for dialysis nurses could include ultrasound-guided cannulation techniques and the use of plastic cannulae to help reduce miscannulations.

Despite the proven benefits of plastic cannulae over metal needles, its use is hampered by cost.[4,9] In our institution, the price difference of SGD2.50 (approx. USD1.86) per needle would result in increased annual cost of almost SGD800 (approx. USD594.50) per patient. Plastic cannulae are hence only used in patients who have failed, or are likely to fail metal needle cannulation. We had also routinely administered subcutaneous lignocaine prior to insertions of plastic cannulae, hence patients did not report increased pain compared to metal needle cannulations. There is also a theoretical risk of bloodstream infection from the cannulae, which may be associated with high mortality in dialysis patients.[10] However, no infections were observed, and the cannulae were removed immediately post-dialysis. No other issues, such as cannula dislodgement or increased bleeding after removal of the plastic cannula, were observed.

Due to the small population size, our observations may not be generalisable to other institutions. There was also no control group comparing insertion of conventional metal needles under ultrasound guidance. In addition, certain data such as access vintage, patency rates and depths of AV access were not available. These can be included in future studies looking at the utility of plastic cannulae. Ultrasound-guided cannulation with plastic cannulae can be safely performed in difficult AV accesses with high success rates, may reduce the use of dialysis catheters, and may be used as a bridging approach while awaiting definitive interventions.

This audit was presented in oral presentation form at the 4th meeting of the Asian-Pacific Society of Dialysis Access, 11–12 July 2019.

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Pulmonary endarterectomy and balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension: The Singapore experience

Dear Editor,

Chronic thromboembolic pulmonary hypertension (CTEPH) is a pulmonary hypertension caused by mechanical obstruction of the pulmonary arteries by organised thrombi and microvascular arteriopathy. It occurs as a complication of pulmonary embolism, and if left untreated, results in right heart failure and death.[1] The gold standard for treatment is pulmonary endarterectomy (PEA) which removes obstructive thromboemboli surgically. For inoperable cases, balloon pulmonary angioplasty (BPA) is an alternative that uses balloon dilatation to open up the arteries. Medical therapy is reserved for cases that are not suitable for PEA, BPA, or residual pulmonary hypertension occurring post-procedures.

We established the first CTEPH multidisciplinary team in Singapore and conducted a retrospective review of all consecutive patients who underwent PEA or BPA for CTEPH at our tertiary cardiac centre from June 2015 to January 2019. All patients were evaluated by the team after diagnosis.[2] Efficacy outcomes studied included change in New York Heart Association (NYHA) functional class and pulmonary haemodynamics. Safety outcomes included peri-procedural complications and mortality.

Clinical characteristics. There were 25 CTEPH cases, of which 16 underwent PEA and 11 underwent BPA (2 had residual pulmonary hypertension post-PEA). The median age was 55 years (interquartile range [IQR] 26–77), with the majority being women (68%) (Table 1). All patients underwent baseline cardiac catheterisation and 88% of them had invasive pulmonary angiography. Baseline mean pulmonary artery pressure (PAP) was 44.3mmHg (standard deviation [SD] 9.4) and pulmonary vascular resistance (PVR) was 9.3Wu

Table 1. Baseline clinical characteristics of study population

	Total N=25	PEA n=16	BPA n=11[a]
Age, mean (SD), years	55.7 (12.6)	54.8 (9.9)	57.0 (16.1)
Women, no. (%)	17 (68.0)	10 (62.5)	8 (72.7)
BMI (SD)	25.3 (3.8)	26.4 (2.9)	24.8 (5.2)
Blood group (Non-O), no. (%)	15 (60.0)	13 (81.3)	4 (36.4)
History of acute PE, no. (%)	20 (80.0)	12 (75.0)	10 (90.9)
History of DVT, no. (%)	10 (40.0)	8 (50.0)	3 (27.3)
History of IVC insertion, no. (%)	3 (12.0)	2 (12.5)	2 (18.2)
Comorbidities			
CAD/IHD, no. (%)	5 (20.0)	4 (25.0)	2 (18.2)
Hypertension, no. (%)	10 (40.0)	6 (37.5)	5 (45.5)
Dyslipidaemia, no. (%)	9 (36.0)	6 (37.5)	5 (45.5)
Diabetes mellitus, no. (%)	6 (24.0)	4 (25.0)	3 (27.3)
Thrombophilic disorder, no. (%) Protein C or protein S deficiency, no. (%) Antiphospholipid syndrome, no. (%)	5 (20.0) 2 (40.0) 3 (60.0)	4 (25.0) 1 (25.0) 3 (75.0)	1 (9.1) 1 (100.0)
Cancer, no. (%)	2 (8.0)	2 (12.5)	0 (0)
Smoking, no. (%)	6 (24.0)	6 (37.5)	1 (9.1)

BPA: balloon pulmonary angioplasty; CAD/IHD: coronary artery disease/ischaemic heart disease; DVT: deep vein thrombosis; IVC: inferior vena cava; PE: pulmonary embolisation; PEA: pulmonary endarterectomy; SD: standard deviation
[a] 2 patients who had prior PEA underwent BPA for residual disease

(SD 5.3). There were 3 patients who had coronary artery revascularisation.

The commonest presentations in patients were: breathlessness on exertion 15 (60%); fatigue 7 (28%); and peripheral oedema 2 (8%). Baseline NYHA classes were II or III, with a mean 6-minute walk distance (6MWD) of 396m (SD 156). Patients had a median of 105 days (IQR 29–180) of symptoms before presentation. Prior to intervention, 3 (12%) required home oxygen therapy; 14 (56%) were on pulmonary vasodilators; 19 (76%) on warfarin; 5 (20%) on direct oral anticoagulation; and 1 (4%) on low molecular weight heparin.

Pulmonary endarterectomy. A total of 16 PEAs were performed. Phase 1 of the programme (pre-proctorship) was from June 2015 to June 2016, during which 4 PEAs were performed with 2 (50%) in-hospital deaths. Phase 2 started after a Health Manpower Development Programme attachment to Papworth Hospital, UK in June 2016, where 10 proctored surgeries were performed. In Phase 3 (post-proctorship), 2 PEAs were done by local surgeons. No in-hospital mortality occurred among the 12 cases in phase 2 and 3. One patient required temporary veno-venous extracorporeal membrane oxygenation (ECMO) support for reperfusion lung injury. Seven cases of post-operative subdural haemorrhage were noted (1 required Burr hole drainage, while the rest were conservatively treated). In the surviving 14 patients, at 36 months post-PEA, there was a significant reduction in PVR from 11.6Wu (SD 5.2) to 4.2Wu (SD 3.7) (P=0.008). Mean PAP reduced from 48.6mmHg (SD 5.5) to 30.4mmHg (SD 16.4) (P<0.001), and N-terminal prohormone B-type natriuretic peptide from 1,441pg/mL (SD 1,847) to 201pg/mL (SD 153) (P=0.010). There was improvement in cardiac output from 3.1L/min (SD 1.1) to 4.2L/min (SD 0.4) (P=0.004), 6MWD from 357m (SD 104) to 417m (SD 87), and NYHA class to I and II (P=0.003).

At 3–6 months post-PEA, 11 (69%) patients were able to stop pulmonary vasodilators. Three (19%) had persistent pre-capillary pulmonary arterial hypertension. Two of them had residual disease deemed suitable for BPA (perfusion defects on dual-energy computed tomography pulmonary angiography corresponding to anatomical obstruction). The remaining patient was likely small vessel CTEPH and was treated with medication.

Balloon pulmonary angioplasty. A total of 49 BPA sessions were performed for 11 patients, averaging 4.5 sessions per patient, and 7 (SD 2) segments per session. Five patients (45.5%) completed BPA, 5 (45.5%) had ongoing sessions, while 1 (9%) declined further sessions. Three patients (27%) had BPA for persistent pulmonary hypertension after PEA. Technical (lesion) success rate, defined as lesion crossing and dilatation without flow-limiting major dissection, was over 90%. There were no major complications such as in-hospital death, stroke, and severe lung injury requiring mechanical ventilation or ECMO support. Guidewire-related perforation of segmental pulmonary arteries, manifesting as recurrent cough and haemoptysis, occurred in 4 sessions (8%). All were successfully managed with gel foam embolisation. In the 8 patients who had completed at least 3 sessions and at least 6 months of post-BPA follow-up, there were reduction of mean PAP from 40.9mmHg (SD 9.6) to 28.5mmHg (SD 7.7), and PVR from 6.5Wu (SD 1.5) to 3.8Wu (SD 1.7). There was modest improvement in cardiac output from 4.3L/min (SD 0.7) to 4.6L/min (SD 0.7), and NYHA functional class by at least 1 grade. Of the remaining 3 patients, 2 are still undergoing treatment and reporting symptomatic improvement; 1 had multiple respiratory comorbidities and residual pulmonary hypertension after previous PEA, and did not have symptomatic or haemodynamic improvement after 2 BPA sessions (Table 2).

Interventional options. To the best of our knowledge, this is the first multidisciplinary therapeutic management of CTEPH in Southeast Asia. The pros and cons of different imaging modalities and our institution's preference (i.e. dual-energy computed tomography pulmonary angiography) have been previously discussed.[3] Although our study number was small, we report satisfactory survival rates and functional outcomes.

PEA is a sophisticated surgery with a steep learning curve. It requires cardiopulmonary bypass and deep hypothermic circulatory arrest to enable a complete endarterectomy. The surgery involves dissection into subsegmental branches of pulmonary arteries, a technically demanding procedure that requires specialist training. Successful surgery also depends on specific intensive care peri- and post-operatively.[4] In-hospital mortality rates range from ≤3.5–7.4% or higher depending on centre experiences.[5] In our experience, with proctorship and greater team experience, PEA outcomes improved significantly. The unexpectedly high initial incidence of subdural haemorrhage prompted a modification of the protocol, to be less aggressive in achieving negative fluid balance and to initiate anticoagulation only after computed tomography of brain suggests no evidence of bleeding post-

Table 2. Pulmonary artery pressure, pulmonary vascular resistance and New York Heart Association classification of patients before and after balloon pulmonary angioplasty

Condition	Patient	Total number of procedures	Mean number of segments treated per procedure	Mean PAP, mmHg		PVR, Wu		NYHA class	
				Before	After	Before	After	Before	After
"De-novo" CTEPH Completed BPA	A	9	9.0	44	21	6.1	2.1	3	2
	B	6	8.5	46	33	5.3	2.1	3	2
	C	4	8.0	30	18	7.5	1.9	2	1
	D	4	7.8	40	27	9.7	2.1	2	2
"De-novo" CTEPH BPA ongoing	E	6	6.0	54	30	8.4	3.8	3	3
	F	6	6.0	42	30	4.4	5.6	2	2
	G	2	6.5	33	35	2.6	3.6	2	2
CTEPH post-PEA with residual PH Ongoing BPA/Declined further BPA after initial BPA	H	2	6.0	45	44	4.0	4.5	2	2
	I	3	6.0	49	43	8.0	6.5	2	1
	J[a]	1	5.0	19	22	2.7	2.7	2	2
Mixed aetiology CTEPH with CTD	K	4	5.0	30	25	5.4	3.5	2	2

BPA: balloon pulmonary angioplasty; CTD: connective tissue disease; CTEPH: chronic thromboembolic pulmonary hypertension; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PEA: pulmonary endarterectomy; PH: pulmonary hypertension; PVR: pulmonary vascular resistance

[a] PEA performed overseas, BPA done for residual disease and persistent symptoms

operatively. [6] This has been shown to better suit the Singapore population.

BPA is reserved for CTEPH patients with technically inoperable disease or with unfavourable risk-to-benefit ratio for surgery.[2] It is not a first-line treatment because it does not physically remove the organised thrombi. Instead, it improves haemodynamics by compressing obstruction to the side of vessel walls with sequential balloon dilatation. As such, BPA is usually reserved for CTEPH involving smaller vessels. In appropriately selected cases and with experience, BPA has been shown to significantly improve patient symptoms, exercise tolerance and pulmonary haemodynamics, without major procedural complications.[7]

Regional experience. Due to the complexity of PEA, much effort and training is needed in Asia Pacific before it becomes widely adopted. In Japan, PEA was carried out in 73 patients in 2017 with a 30-day mortality of 4.1% and in-hospital mortality of 9.6%.[8] In China, Australia, South Korea, Taiwan and India, single-centre studies with smaller numbers have been reported from 1994–2010, with 30-day mortalities ranging from 0–12.19%.[9-13] For BPA, Japan first reported 308 CTEPH patients who underwent 1,408 BPA procedures between 2004 and 2013 at 7 institutions. The overall 3-year survival rate was 94.5%.[7] Several other Asian Pacific countries have also published single-centre experiences in small numbers (<50 total cases), with improvements in haemodynamics, symptoms and exercise capacity, as well as generally low rates of major complications and mortality.[14,15] The management of CTEPH patients requires a multidisciplinary team for consistent and beneficial outcomes. We have shown PEA and BPA to be safe and efficacious in suitable patients. With experience, BPA is poised to play a greater role in the management of CTEPH in the region.

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Percutaneous paravalvular leak repair for severe aortic regurgitation after transcatheter aortic valve implantation (TAVI)

Dear Editor,

Paravalvular leaks (PVLs) are not uncommon after surgical valve replacement. The need for re-operation for clinically significant leaks is between 1 and 3%.[1] Percutaneous PVL closure has become increasingly performed and is an alternative to surgery.[1] PVLs occur more frequently after transcatheter aortic valve implantation (TAVI), as the transcatheter heart valve (THV) is anchored by radial force alone.[2] The experience of percutaneous repair of significant paravalvular aortic regurgitation (AR) after TAVI is limited.[3-9] We report a case of heart failure due to severe PVL after TAVI that has been treated with percutaneous repair with a good 4-year clinical outcome.

A 72-year-old man presented with exertional dyspnoea (New York Heart Association [NYHA] Class III) over 6 months. Echocardiography demonstrated a severely impaired left ventricular ejection fraction (LVEF) of 30% and severe paravalvular AR around a bioprosthetic valve (Fig. 1A). Transoesophageal echocardiogram (TEE) confirmed severe paravalvular AR with a pressure half-time of 213ms, holodiastolic reversal in the descending thoracic aorta, and PVL jet occupying 35% of the prosthesis circumference. The PVL defect width was approximately 6mm.

The man underwent TAVI 4 years ago with a 31mm self-expanding CoreValve (Medtronic plc, Dublin, Ireland) bioprosthesis for severe aortic stenosis. LVEF was 25%. Pre-TAVI computerised tomography showed that the aortic annulus perimeter and diameter were 86.5mm and 27.5mm, respectively. The 31mm CoreValve was selected at that time as the largest balloon-expandable valve, the 26mm Sapien XT (Edwards Lifesciences Corp, Irvine, US) available in Singapore at that time, was too small. CoreValve position and expansion were satisfactory, but there was residual moderate paravalvular AR despite post-dilatation with a 25mm Z-Med balloon (BVM Medical Ltd, Hinckley, UK). Nevertheless, the man experienced symptomatic improvement (NYHA Class II) with increase in LVEF at 1 month to 45%. His other medical conditions included right lobectomy for lung carcinoma, chronic obstructive pulmonary disease, as well as coronary and iliac artery angioplasty and stenting.

Due to the high surgical risk, percutaneous PVL closure was performed. The procedure was performed under general anaesthesia and TEE guidance. Attempts to cross the paravalvular defect retrograde via right and left femoral artery using various catheters and wires were unsuccessful (Fig. 2A). Via the right radial artery,

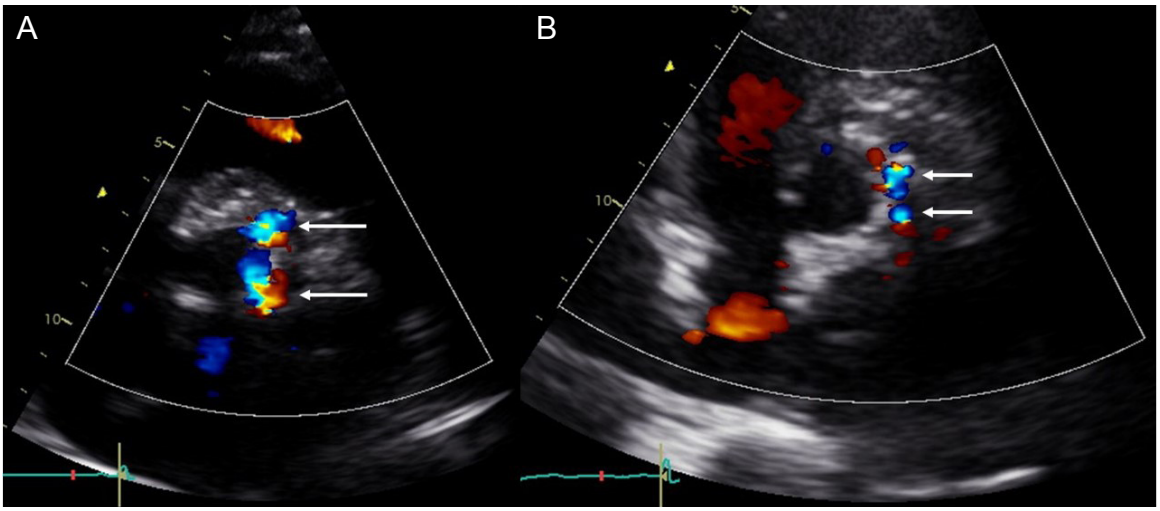

Fig. 1. (A) Echocardiographic image of the CoreValve THV in parasternal short axis view at baseline. The arrows denote 2 jets of PVLs along the THV circumference from 1 to 4 o'clock positions. (B) Echocardiographic image of the CoreValve THV in parasternal short axis view showing a reduction in PVL (arrows denote PVL from 2 to 3 o'clock positions) post-procedure.
PVL: paravalvular leak; THV: transcatheter heart valve

an angled hydrophilic guide wire and a 5-French sized multipurpose A1 catheter finally crossed the PVL into the left ventricular cavity (Fig. 2B). Both TEE and fluoroscopy confirmed that the wire and catheter were within the paravalvular defect. Attempts to exchange the 5-French guide catheter for a 6-French sized catheter over an extra-stiff wire were unsuccessful as the 6-French catheter was too large to cross the defect. Through a 5-French Judkins right 4 curve guide catheter, an 8mm Amplatzer Vascular Plug (AVP) 2 was advanced but extreme resistance was felt midway and the AVP2 could not be advanced further. The AVP2 was then removed and a smaller profile 8mm AVP4 was successfully deployed across the PVL (Fig. 2C). The diastolic pressure rose from 40mmHg at baseline to 50mmHg, and the left ventricular end diastolic pressure decreased from 23mmHg to 19mmHg. Echocardiography showed a reduction from severe to moderate paravalvular AR (Fig. 1B). We decided not to deploy a second plug to further reduce the AR due to the technical difficulties and risk of dislodging the first plug.

The patient was discharged the next day. He reported symptomatic improvement (NYHA class II), and echocardiography revealed that LVEF had returned to baseline (45%) at 3 months. He remained in Class NYHA II at 4 years after percutaneous PVL closure, without evidence of haemolysis. Echocardiography revealed unchanged LVEF (45%), moderate paravalvular AR (pressure half-time 465ms, PVL jet occupying 15% of the prosthesis circumference) and a mean aortic valve gradient of 8mmHg.

TAVI has become an established treatment for patients with severe aortic stenosis,[10] and clinical outcomes have improved with newer devices. Although PVLs after TAVI have become less frequent,[11,12] they still occur and may occasionally be clinically significant. It has been demonstrated that mild or greater PVL after TAVI can increase long-term mortality.[2] Successful percutaneous symptomatic PVL repair after TAVI has been shown to reduce hospitalisation related to heart failure and mortality as compared to conservative treatment.[4]

Most PVLs after TAVI remain stable or improve over time, though it may worsen in approximately 20% of patients.[2] PVLs occur due to an undersized THV relative to the aortic annulus, heavy calcification preventing sealing of the THV against the annulus, or a suboptimal THV implant position.[2] If the THV position was ideal, the simpler manoeuvre would be to perform a balloon post-dilatation to ensure full THV expansion and sealing. This was not performed in our patient at the second intervention as the THV appeared well expanded on fluoroscopy, and to avoid leaflet damage that may worsen the AR and reduce THV durability.

The success rate of percutaneous repair for symptomatic PVL after TAVI ranges from 60–89%. Complications, though infrequent, can include cardiac tamponade, stroke or THV dislodgement.[3-6] It is

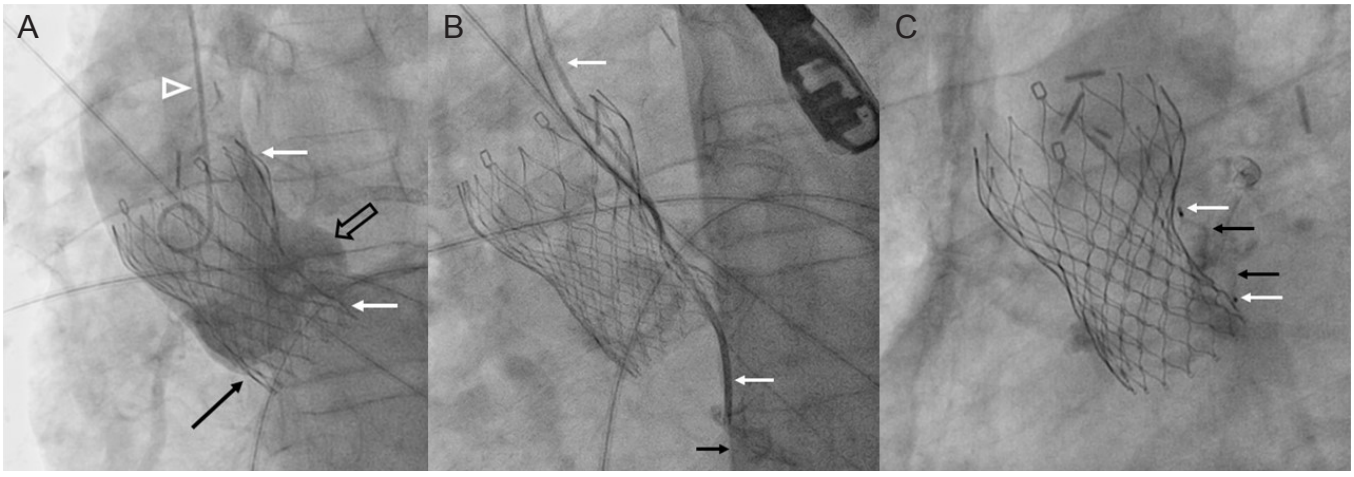

Fig. 2. (A) Fluoroscopic image of the CoreValve THV during an aortogram. White arrows denote the length of the CoreValve frame, black arrow denotes the plane of the native aortic annulus, black open arrow denotes the limited space in the sinus of Valsalva, and white arrowhead denotes the pigtail catheter. (B) Fluoroscopic image showing multipurpose catheter (white arrows) crossing the CoreValve frame and paravalvular defect. Contrast injection (black arrow) confirms that the catheter is in the left ventricle. (C) Fluoroscopic image showing the AVP2 plug deployed within the paravalvular defect (external to the CoreValve frame). The white arrows denote the radiopaque tips and black arrows denote the body of the plug.
AVP2: Amplatzer Vascular Plug 2; THV: transcatheter heart valve

technically challenging with a lower success rate as compared to PVL closure of surgical bioprostheses.[6] This is due to the retained native calcific aortic leaflets (compressed between the THV frame and aortic wall) and aortic annular calcium that is not removed (unlike surgical aortic valve replacement). The self-expanding THVs tall stent frame pose additional challenges and the supra-annular location of its leaflets limits the space for catheter manipulation. Procedural failures have been due to the inability to cross the defect with a wire or catheter.[3,4]

The devices used most frequently in PVL closure are the AVPs, which were developed for use in arterial and venous embolisation. The availability of the low profile AVP4 plug has increased procedural success as it can be delivered through small 4-French diagnostic catheters, which are more likely to cross irregularly shaped calcific defects.[7,9] This has led to procedural success in our case.

To the best of our knowledge, we report Asia's first percutaneous closure of severe PVL after TAVI with a 4-year outcome. It illustrates that sustained clinical benefit can be derived from partial reduction of paravalvular AR post-TAVI. Percutaneous repair for severe paravalvular AR after TAVI is feasible despite technical challenges. This resulted in symptomatic improvement and a good outcome in a high-risk patient.

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LETTER TO THE EDITOR

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Pilot study of single-session radiofrequency ablation of benign thyroid nodules in Singapore

Dear Editor,

Radiofrequency ablation (RFA) has been shown to be safe and efficacious in the treatment of benign thyroid nodules.[1] Ion agitation during RFA generates high temperatures between 60 and 100 degree Celsius to cause tissue damage and size reduction.[2]

We conducted a prospective pilot study of 10 patients who underwent thyroid RFA between September 2016 and December 2018. Inclusion criteria included benign thyroid nodules that cause symptoms such as neck pain, dysphagia, foreign body sensation and cosmetic issues; benign autonomously functioning thyroid nodules causing thyrotoxicosis; and nodules that were clearly visualised on ultrasound (US) imaging. Exclusion criteria included nodules of less than 60% solid component, nodules that were poorly visualised on US imaging, subjects younger than 21 years of age, presence of a pacemaker in subjects, underlying coagulopathy, poor skin condition, known thyroid carcinoma, and allergy to local anaesthetic.

All patients underwent 2 separate nodule sampling by US-guided fine needle aspiration cytology and/or core needle biopsy. Only nodules that were proven to be benign on 2 samples were ablated. Complications were documented with reference to the Common Terminology Criteria for Adverse Events V4.0. They included, but were not limited to, minor complications such as pain, bleeding, haematoma formation, and major complications such as skin burns, voice change and injury to surrounding neck structures.

Physical examination and US imaging were obtained at baseline, 2 weeks, 6 months and 12 months after a single RFA procedure. Nodule volume reduction, cosmetic and symptom scores were assessed. Nodule volume was calculated using the equation: $V=\pi abc/6$ (V=volume, a=maximum diameter, b and c=the other 2 perpendicular diameters). The size, shape, margin, proportion of solid/cystic components, echogenicity, calcification, internal vascularity, and extracapsular invasion of each nodule were recorded. Nodules with malignant US features were excluded. The cosmetic score: 1=no palpable mass, 2=palpable mass, 3=mass visible on swallowing, 4=readily detected cosmetic problem; and symptom score (visual analogue scale of 0–10) were obtained at every visit. Therapeutic success was defined as a volume reduction of >50% at 12 months, a benchmark used by other thyroid RFA studies.[3-5] Baseline laboratory tests, which included complete blood count, coagulation profile and thyroid function tests, were performed. Incidentally, all the treated nodules were cold nodules.

RFA procedures were conducted by interventional radiologists. The moving shot technique, proposed by Baek et al.,[4] was used. Grounding pads were applied to the patient's thigh. RFA was performed using the STARmed RF system (STARmed, Goyang, South Korea), which consists of a VIVA RF generator and electrode. The danger triangle, consisting of the recurrent laryngeal nerve and oesophagus, was avoided. After the procedure, a post-treatment US appearance of the thyroid nodule and complications were recorded. The patients were discharged after at least 1 hour of observation.

There were 8 female and 2 male patients. The mean age was 43 years (interquartile range [IQR] 36.3–50.5). All patients had benign histology (8 patients had nodular goitres and 2 had colloid nodules) (Table 1). Each patient underwent a single RFA session for a single thyroid nodule. The mean ablation time and power were 9.7 minutes (IQR 6.1–14.3) and 5.7kCal (IQR 3.4–8.1), respectively. Seven out of 10 patients met the criteria for therapeutic success (volume reduction of >50% at 12 months). The median pre-ablation nodule volume was 18.1mL (IQR 9.7–26.4) and the median nodule composition was 85% solid (IQR 67.5–92.5). Mean and median nodule volume reduction were 44.4% and 57.1% (IQR 7.4–67.4), respectively at 12 months. Two out of the 3 patients who did not achieve a volume reduction of >50% had a 3-point reduction in their cosmetic scores still. There was a median cosmetic score reduction of 3 points (IQR 2–3). Patients who were symptomatic pre-treatment had a median symptom score reduction of 1 point (IQR 1–4). All patients indicated that they would recommend the procedure to other patients.

All complications were minor. All patients complained of varying degrees of pain, but it did not warrant stoppage of the RFA procedures. Four patients had minor bleeding and/or haematoma formation that

Table 1. Pre- and post-ablation change in nodule volume, cosmetic and symptom scores

Patient	Age (years), sex, ethnicity	Histology	Solid component, %	Pre-ablation volume, mL	Volume at 6 months, mL	Volume at 12 months, mL	Reduction in volume at 12 months, %	Pre-ablation cosmetic score	Cosmetic score at 12 months	Reduction in cosmetic score	Pre-ablation symptom score	Symptom score at 12 months	Reduction in cosmetic score
1	41, Female, Filipino	Colloid nodule	70	7.7	1.9	0.4	94.8	3	1	2	7	1	6
2	47, Male, Chinese	Nodular goitre	90	21.1	10.1	20.6	2.4	4	1	3	5	1	4
3	52, Female, Chinese	Nodular goitre with cystic degeneration	60	24.6	18.9	11.7	52.4	4	1	3	0	0	0
4	39, Female, Chinese	Nodular goitre	70	31.8	10.2	7.7	75.7	4	1	3	3	2	1
5	50, Female, Chinese	Colloid nodule	90	7.7	3.0	2.9	62.3	3	1	2	1	0	1
6	28, Female, Chinese	Nodular goitre with cystic degeneration	100	10.4	11.4	13.6	-31.7	4	4	0	1	1	0
7	41. Female, Chinese	Nodular goitre with cystic degeneration	90	14.2	11.8	12.9	9.1	4	1	3	3	1	2
8	27, Female, Chinese	Nodular goitre	100	16.8	6.6	7.2	57.1	4	4	0	1	0	1
9	43, Female, Chinese	Nodular goitre	80	54.3	17.8	19.2	64.6	4	1	3	0	0	0
10	62, Male, Chinese	Nodular goitre with cystic degeneration	60	19.4	9.6	8.3	57.2	4	1	3	0	0	0
	All patients		Solid component median (IQR), %	Pre-ablation volume median (IQR), mL			Reduction in volume at 12 months mean (IQR), % median (IQR), %			Reduction in cosmetic score median (IQR)			Reduction in cosmetic score median (IQR)
			85 (67.5–92.5)	18.1 (9.7–26.4)			44.4 57.1 (7.4– 67.4)			3 (2–3)			1 (1–4)

IQR: interquartile range

resolved 2 weeks post-procedure. There was no major complication.

The results of our study were similar to a 2018 study by Hamidi et al.[3] that achieved a median volume reduction of 44.6% (IQR 42.1–59.3). This was most likely due to the similarities in nodule profiles (predominantly solid and large nodules) and that only a single ablation session was conducted in both studies. In contrast, other studies with single ablation attempts by Baek et al.[4] and Faggiano et al.[5] achieved higher mean volume reduction of 82.6% and 84.9%, respectively. We postulate that this may be related to their lower pre-ablation nodule volumes of 7.5mL (standard deviation [SD] 4.9) and 13.3mL (SD 1.8), respectively. Other studies that achieved a higher volume reduction had multiple ablation attempts.[6-8]

The limitations of our study are a small study number and the lack of long-term data. Further larger and longer-term studies are needed to evaluate the efficacy and safety of single-session RFA of benign thyroid nodules in the Singapore population. The result of this pilot study suggests that RFA of benign thyroid nodules is safe and efficacious for treating predominantly solid benign thyroid nodules in the Singapore population.

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Dynamic mitral regurgitation treated with MitraClip

Dear Editor,

The dynamic nature of mitral regurgitation (MR) has been well appreciated but clinically under-recognised. In addition, evidence on therapeutic options for dynamic MR has been lacking. We report the case of a 48-year-old woman who underwent coronary revascularisation and extra-corporeal membrane oxygenation (ECMO) support after post-operative cardiac collapse from left main (LM) coronary artery occlusion. However, she had difficulty coming off the ventilator due to recurrent pulmonary oedema from dynamic MR. She was treated with percutaneous mitral valve repair using the MitraClip system (Abbott Vascular, Santa Clara, US) and was successfully discharged.

The 48-year-old woman with right breast cancer was admitted for mastectomy and breast reconstruction. She had no past medical history. Post-operatively, she developed acute chest pain and hypotension. Electrocardiogram showed anterior ST-segment elevation, and the cardiac catheterisation laboratory was activated.

During the procedure, she had recurrent collapse from ventricular arrhythmias requiring cardiopulmonary resuscitation and repeated defibrillation. Intra-aortic balloon pump (IABP) was inserted and coronary angiography showed isolated LM coronary artery occlusion (Figs. 1A and 1B). After aspiration thrombectomy, a 3.5 x 18mm stent was implanted from LM into proximal left anterior descending (LAD) artery (Figs. 1C and 1D) establishing Thrombolysis in Myocardial Infarction (TIMI) 3 flow.

In view of haemodynamic and electrical instability, ECMO was implanted. Transthoracic echocardiogram (TTE) showed severely depressed left ventricular ejection fraction (LVEF) of 15–20% with trivial MR. She was transferred back to the intensive care unit (ICU) and her stay was complicated by acute kidney injury requiring renal replacement therapy, abdominal haematoma requiring surgical evacuation and pneumonia. Inotropes were weaned off gradually and the ECMO was successfully explanted on day 8 of myocardial infarction. In view of the prolonged stay and ventilation required, she underwent a tracheostomy. However, despite adequate ultrafiltration, she had recurrent acute pulmonary oedema and was unable to come off the ventilator. She developed hypotension again requiring inotropes to be reinstated. Repeat TTE showed an improved LVEF of 25–30% with moderate MR.

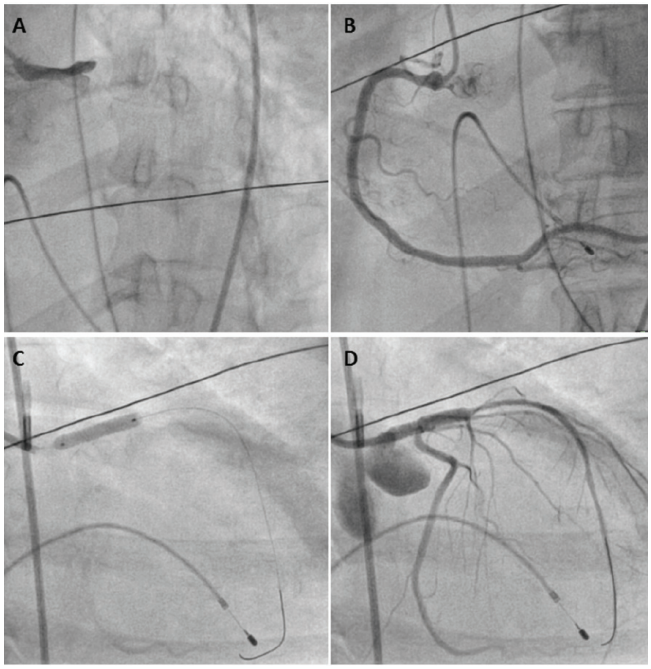

Fig 1. Fluoroscopic images showing (A) left main (LM) coronary artery occlusion with (B) normal right coronary artery. (C) 3.5 x 18mm stent implanted from LM into proximal left anterior descending (LAD) artery. (D) Final angiography showing patent LM, LAD and left circumflex arteries.

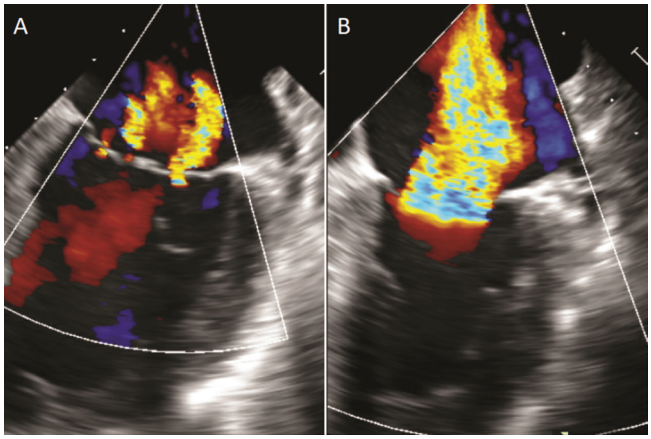

Fig. 2. Transesophageal echocardiogram images showing (A) moderate mitral regurgitation (MR) at systolic blood pressure (SBP) of 82mmHg, which worsened to (B) severe MR at SBP of 130mmHg.

Duplex of the renal arteries did not reveal any stenosis. Transesophageal echocardiogram (TEE) was done in the ICU to better evaluate the mitral valve. The MR aetiology was functional with normal mitral valve morphology but tenting of the leaflets and a dilated annulus of 3.5cm. At systolic blood pressure (SBP) of 82mmHg, there was moderate central MR and a pulmonary artery systolic pressure (PASP) of 47mmHg (Fig. 2A). However, the patient became agitated transiently and SBP went up to 130mmHg with increase in MR to severe and PASP to 79 mmHg (Fig. 2B). Repeat coronary angiography was done, which showed patent LM to LAD stent, and IABP was re-inserted.

A Heart Team discussion including critical care physicians proposed that the severe functional MR was causing recurrent pulmonary oedema and haemodynamic compromise. Her European System for Cardiac Operative Risk Evaluation (EUROSCORE) II and Society of Thoracic Surgeons (STS) scores were 42.5% and 50.0% respectively. She was deemed to be at high risk for open-heart surgery, and hence decision was made for percutaneous edge-to-edge repair of the mitral valve with the MitraClip system. MitraClip was performed with implantation of 2 clips. First clip was placed slightly medial in A2/P2 region with reduction of MR to 2+ (Figs. 3A and 3B). Second clip was placed just lateral to the first clip with reduction of MR to 1+ (Fig. 3C), systolic predominance on pulmonary venous flow (Fig. 3D) and a trans-mitral mean pressure gradient of 3mmHg at SBP 110mmHg. Following the procedure, her IABP was removed and she was successfully weaned off inotropes and ventilator. She was debilitated from the events, and stayed another 2 months in the hospital for rehabilitation. She made good progress with decannulation of the tracheostomy tube and achieved renal recovery without the need for long-term dialysis. She was discharged home and was able to walk with a walking frame.

MR severity at 1 year remained mild-to-moderate (Fig. 4). Unfortunately, she declined implantable cardioverter defibrillation implantation. She collapsed from ventricular tachycardia, which led to another long 4-month admission complicated by heart failure, sepsis from pneumonia and fungaemia, and prolonged intubation requiring another tracheostomy. Eventually, she and her family opted for a palliative route, and she died peacefully at home, one and a half years after MitraClip implantation.

Dynamic MR has been shown to be associated with poor outcomes and exercise capacity.[1-3] In diseased ventricles, the delicate balance of tethering and closing forces that is necessary for optimal mitral valve leaflet coaptation is often disrupted, resulting in MR. Both volume overload and increase in afterload, provoked either physiologically (exercise) or pharmacologically (vasopressors or fluid infusion), can result in further alterations in left ventricular geometry and hence, worsening of MR. This translates to a rapid rise in left atrial and pulmonary pressures, leading to the development of pulmonary oedema. However, it can be a challenge to recognise dynamic MR as the cause of symptoms and a high index of clinical suspicion is required. In our case, after excluding other causes of recurrent acute pulmonary oedema (i.e. ischaemia, renal artery stenosis), it was important to observe for dynamic change in MR severity in concordance with changes in blood pressure.

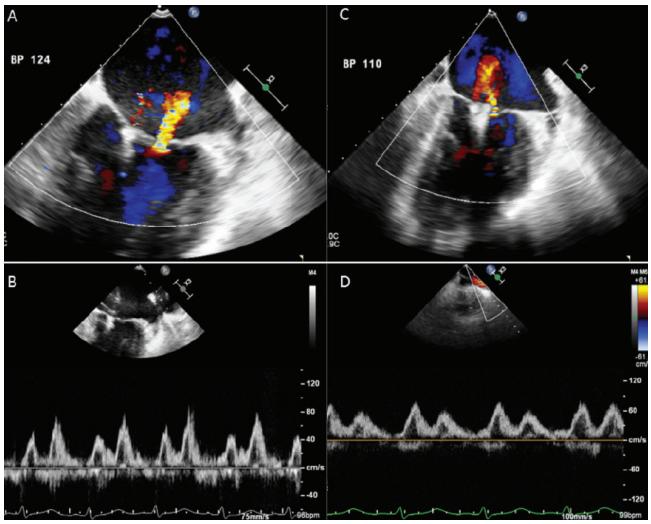

Fig. 3. Transesophageal echocardiogram images showing (A) first clip deployed slightly medial in A2/P2 region with residual lateral 2+ mitral regurgitation (MR) and (B) systolic blunting in pulmonary venous flow. (C) Second clip deployed just lateral to the first clip with reduction of MR to 1+ at systolic blood pressure 110mmHg and (D) systolic predominance in pulmonary venous flow.

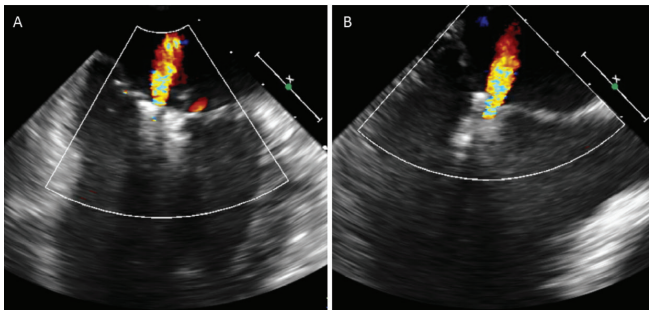

Fig. 4. Transesophageal echocardiogram images showing mild-to-moderate mitral regurgitation 1 year after MitraClip implantation in the (A) intercommissural and (B) left ventricular outflow tract views.

There is a lack of data on effective therapies for dynamic MR. Extrapolation from treatment options for secondary MR has been made based on their individual targets on geometric determinants for dynamic MR.[4] However, how each therapy, or a combination therapies directly impact symptoms and outcomes in this group of patients remains unclear. There are only a few reports of percutaneous repair with the MitraClip system for dynamic MR.[5,6] Our case demonstrated its successful use in a critically ill patient with recurrent acute pulmonary oedema from dynamic MR who was at prohibitive risk for surgery and its sustained impact at 1 year.

Lastly, after MitraClip leaflet grasping for dynamic secondary MR, it is important to drive the blood pressure up to assess the severity of residual MR. As often during MitraClip procedures, patients are anaesthetised and well diuresed, resulting in a degree of MR that is not reflective of the awake and ambulatory states. If necessary, clip adjustments or additional clips may be required to address the geometric alterations from the increase in afterload.

In the appropriate clinical context, dynamic MR is an important consideration in patients with recurrent acute pulmonary oedema. Our case demonstrated the successful use of percutaneous edge-to-edge repair of the mitral valve with the MitraClip system to effectively address symptomatic dynamic MR in a critically ill patient at prohibitive surgical risk.

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Seeing through the eyes of patients with age-related macular degeneration

Dear Editor,

Age-related macular degeneration (AMD) is a severe ocular disease characterised by progressive deterioration of the macula, the most sensitive central part of the retina.[1] It is the most common cause of irreversible vision loss among individuals aged ≥60 years in developed countries,[2] and accounts for about 6% of all causes of blindness worldwide.[3] A population-based cross-sectional study in Singapore revealed its age-standardised prevalence was 5.1% (95% confidence interval [CI] 4.6–5.5) for early AMD and 0.5% (95% CI 0.4–0.6) for late AMD.[4] Given Singapore's rapidly ageing population, the prevalence of AMD among its residents aged ≥40 years is projected to increase by 54% from 125,274 (95% CI 123,241–127,307) cases in 2015 to 193,435 (190,295–196,575) cases in 2040.[5]

Patients with AMD often have relative scotomas and metamorphopsia in their central visual field. The Amsler grid is an inexpensive and rapid test designed to specifically test visual field defects in the central 10 degrees.[6] Utilising a suprathreshold target to analyse the central vision, it is good for detecting metamorphopsia but is not sensitive for the detection of relative scotomas.[7] Attempts have been made to characterise the size, shape, slope and extent of scotomas using a 3-dimensional computer-automated threshold Amsler grid test, which may have the potential as a screening tool for the early diagnosis of AMD.[8]

The Snellen visual acuity chart is the most commonly used chart to evaluate vision in clinical practice. In the last few decades, the Early Treatment Diabetic Retinopathy Study chart has become the gold standard test to measure visual acuity and evaluate eyes with macular disease in clinical trials.[9] However, these tests are non-timed and thus may not simulate real-world situations such as driving, where there is a limited amount of time to recognise objects, read signs and make important vision-based decisions.[10] This is important for patients with AMD because they find difficulties with many vision tasks that are time-dependent such as reading, driving and recognising faces in fluid social situations.[11]

In an effort to realistically depict how AMD patients see themselves in the mirror, one of us (AH), a professional portrait artist, has painted 17 portraits of individuals suffering from varying severities of AMD as seen through the patients' own eyes (Fig. 1). The portraits were conceptualised by first obtaining detailed information from an AMD patient on the specific visual abnormalities he or she experienced, such as metamorphopsia and relative scotoma through a face-to-face interview. Based on this information, a photograph of the patient was manipulated to match the patient's perception of himself or herself in the mirror and a preliminary portrait of the patient was sketched. The portrait was then adjusted to reflect more accurately the patient's perception. Re-painting and verification by the patient were repeated several times before the portrait was finalised. Interestingly, we found that AMD patients who had their portraits painted rarely reported image distortion but more often reported scotoma(s).

Fig. 1. Two portraits depicting visual abnormalities due to age-related macular degeneration as seen by the patients themselves.

To showcase these portraits, we organised a unique public art exhibition in conjunction with the AMD Awareness Week campaign in Singapore in 2010.[12] The exhibition was very well-received and we believe such artworks are useful to raise public awareness of AMD and enable a more accurate perception and understanding of the visual problems experienced by AMD patients in their daily lives.[13-15]

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Maternal obesity and risk of adverse obstetric outcomes in Malaysia

Dear Editor,

Obesity during pregnancy is associated with increased risk of adverse health outcomes such as gestational diabetes mellitus (GDM), hypertension and pre-eclampsia.[1] Unlike the well-known association between maternal hyperglycaemia and pregnancy outcomes, the effect of obesity in pregnancy has drawn some controversial conclusions.[1] Data are even scarcer in Southeast Asia countries. In this research, we examined prospectively the effect of obesity in pregnancy and gestational weight gain (GWG) on pregnancy outcomes.

A prospective study was conducted from October 2017 to March 2019 in 5 maternal and child health centres in Kuching, Malaysia, and was approved by the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia. This study was also registered under the National Medical Research Register (NMRR ID: NMRR-16-2725-31652). All participants who fulfilled the study criteria were recruited after informed consent. This study received research grant from the Universiti Malaysia Sarawak Special Grant Scheme F05/SpGS/1548/2017.

All participants in their first trimester who were more than 18 years of age underwent a 75g oral glucose tolerance test (OGTT). Participants were excluded if their fasting plasma glucose was ≥7.0mmol/L and/or 2-hour plasma glucose was ≥11.1mmol/L (undiagnosed diabetes mellitus [DM]); or fasting plasma glucose was ≥5.1mmol/L and/or 2-hour plasma glucose was ≥8.5mmol/L (GDM). All other participants underwent second OGTT between 24 and 28 weeks of gestation and were excluded if they were diagnosed with GDM. We also excluded participants with underlying DM, genetic disorders affecting growth or congenital anomalies, multiple pregnancy, conception using artificial insemination, or human immunodeficiency virus/Hepatitis B/Hepatitis C infection.

We divided the participants into subject or control groups based on first trimester body mass index (BMI) as weight gain during first trimester of pregnancy is negligible.[2] The World Health Organization has recommended a BMI cut-off of 23kg/m^2 as overweight for Asians, and ≥25kg/m^2 as obese. Based on this, participants with a BMI of ≥23kg/m^2 were recruited as subjects (obese group) and those with a BMI of 18.5–23kg/m^2 were recruited as controls. Total GWG was calculated based on the difference between first and third trimester weight. As multiparity (≥2 live births) is associated with higher risk of pregnancy-induced hypertension (PIH), we categorised parity of the mothers as 0–1 live birth and ≥2 live births.

Demographic data were recorded. At first trimester, the participants' weight and height were recorded for calculation of BMI. At every trimester visit, the following were recorded: (1) blood pressure (BP) using sphygmomanometer after 15 minutes of rest, (2) mid-stream urine for presence of proteinuria, and (3) weight. The participants were followed up until the point of delivery. Occurrence of adverse pregnancy outcomes was documented.

The outcomes measured in this study included the occurrence of PIH, pre-eclampsia, gestational age at delivery, need of induction of labour (IOL) and primary caesarean section for delivery. PIH is defined as new-onset hypertension (>140/90mmHg) after 20 weeks gestation without significant proteinuria. Pre-eclampsia is defined as systolic BP>140mmHg, diastolic BP>90mmHg and proteinuria (>1+) on ≥2 occasions ≥6 hours apart after 20-week gestation. The need of IOL is the process of initiating labour using either pharmacological or non-pharmacological methods.

Statistical analysis was performed using SPSS version 19.0 (IBM Corp, Armonk, US). Univariate analyses were used to compare dichotomous outcomes, and Student's t-test was used to compare continuous outcomes. Multiple logistic regression models were used to evaluate outcomes, adjusting for maternal age, parity, smoking status and gestational age. Adjusted odds ratios and 95% confidence interval were calculated. A value of P<0.05 was considered significant.

A total of 123 obese mothers and 102 controls consented to the study. There was no significant difference in baseline demographic data (Table 1).

Obese mothers gained 6.5kg±4.0 throughout the pregnancy over 267.8 gestational days±11.0. Non-obese mothers gained 8.4kg±3.8 throughout the pregnancy over 268.7 gestational days ±7.3. There was no significant difference in gestational age between the groups (P=0.953).

The maternal outcomes are summarised in Table 2. Significantly more obese mothers developed PIH and underwent primary caesarean section compared to the control group. All subjects with PIH were given

Table 1. Baseline demographic data

	Obese (N=123)	Control (N=102)	*P* value
Age, mean (SD)	30.1 (5.0)	28.9 (4.9)	0.09
Education level, n (%)			0.71
No formal education	1 (0.81)	1 (0.98)	
Primary	5 (4.07)	5 (4.90)	
Secondary	73 (59.35)	67 (65.69)	
Tertiary	44 (35.77)	29 (28.43)	
Employment status, n (%)			0.42
Employed	66 (53.0)	61 (59.0)	
Unemployed	57 (47.0)	41 (41.0)	
Household income, median (IQR)	24,000 (30,000)	24,000 (21,900)	0.37
Smoking status, n (%)			1.0
Yes	1 (0.81)	1 (0.98)	
No	122 (99.2)	101 (99.0)	
Family history of type 2 diabetes, n (%)			0.12
Yes	27 (22.0)	14 (13.7)	
No	96 (78.1)	88 (86.3)	
Family history of hypertension, n (%)			0.07
Yes	52 (42.3)	31 (30.4)	
No	71 (57.7)	71(69.6)	
Family history of cardiovascular disease, n (%)			0.18
Yes	11 (8.9)	4 (3.9)	
No	112 (91.1)	98 (96.1)	
Body mass index, kg/m^2	29.0 (4.45)	20.4 (1.48)	<0.001
Parity, n (%)			0.106
0–1	71 (31.6)	66 (64.7)	
2–4	52 (23.1)	36 (35.3)	

IOL between 37 and 40 weeks gestation. In this study, primary caesarean section is defined as the first caesarean section performed on the mother to deliver the baby regardless of parity. Reasons for primary caesarean section are outlined in Table 3. There were 4 women (3.25%) from the obese group who developed pre-eclampsia and 5 required IOL; there were none from the control group for both outcomes, although the difference was not statistically significant. All 4 women with pre-eclampsia underwent caesarean section deliveries. The reasons for requiring IOL are premature rupture of membrane (n=1) and post-term pregnancy (n=4).

There was no significant association between total GWG with PIH (*P*=0.73), pre-eclampsia (*P*=0.80), need of IOL (*P*=0.14) and primary caesarean section (*P*=0.64 for obese group and *P*=0.61 for non-obese group). There was also no significant association between multiparity and PIH (*P*=0.105).

The results suggest that obese mothers have higher risk of adverse pregnancy outcomes compared to non-obese mothers regardless of parity and despite no excessive GWG. Our findings show that obese mothers are more likely to develop PIH, and require primary caesarean section, with acute fetal distress as the most common reason for the surgery. More obese mothers developed pre-eclampsia, and required IOL.

Obesity is one of the known risk factors leading to PIH and pre-eclampsia.[3,4] Women with PIH are at increased risk of developing pre-eclampsia, renal dysfunction and placenta abruption on top of adverse effects on the fetus.[5] A large Swedish study showed that the risk of pre-eclampsia rose with maternal weight from 2.8% in lean women to 10.2% in obese women.[6] Pre-eclampsia is one of the main causes of maternal and fetal morbidity and mortality in developing countries.[7] Despite novel therapies being developed for pre-eclampsia, the only cure is to deliver the baby, followed by expulsion of the placenta. However, the decision on the optimal timing and mode of delivery depends heavily on maternal and fetal risks in continuing the pregnancy, and neonatal risk in ending the pregnancy.[8]

Our study found a higher caesarean section rate among obese mothers compared to controls, of which the main cause was acute fetal distress, increasingly cited

Table 2. Univariate analysis on pregnancy outcomes between the groups

Pregnancy outcomes	Obese, n (%)	Control, n (%)	*P* value
Pregnancy-induced hypertension	8 (6.5%)	0 (0%)	0.009
Pre-eclampsia	4 (3.3%)	0 (0%)	0.128
Delivery via induction of labour	5 (4.1%)	0 (0%)	0.065
Delivery via primary caesarean section	26 (21.1%)	6 (5.9%)	0.001

Table 3. Reasons for primary caesarean section

Reasons	Obese, n (%)	Control, n (%)
Acute fetal distress	17 (13.8)	5 (4.9)
Failed induction of labour	3 (2.4)	0
Maternal heart disease	0	1 (1.0)
Pregnancy-induced hypertension	2 (1.6)	0
Pre-eclampsia	4 (3.3)	0
Total	**26 (21.1)**	**6 (5.9)**

as an indication for caesarean section in the last two decades. Many caesarean deliveries have retrospectively been found to be unnecessary, raising the question whether continuous cardiotocography interpretation could have limitations in predicting true adverse neonatal outcomes.[9,10] Previous studies demonstrated that increasing BMI is strongly associated with caesarean section rate. However, these studies could have been affected by several confounding variables, such as underlying GDM, DM and hypertension, which were excluded from our study.

Earlier studies identified GWG as an independent risk factor for adverse pregnancy outcomes in obese women and those with GDM.[11,12] However, in our study, although non-obese mothers had significantly higher GWG compared to the obese group, it did not affect the pregnancy outcome. This is likely because GWG in our subjects was within the recommended weight gain range, unlike in earlier data.

Our study suggests the need to prevent obesity in pregnancy, despite not having other cardiovascular risk factors or excessive GWG. Obesity in pregnancy should receive equal emphasis as other disorders in pregnancy such as DM and chronic hypertension. However, effective weight loss in pregnancy cannot be done safely without possible adverse effects on the growing fetus.[13] Hence, we encourage active intervention for weight loss to achieve a healthy BMI pre-conception. Public education and awareness via health promotion and campaigns are needed to recognise obesity in pregnancy as a risk for adverse obstetric outcomes.

Our study is limited by the lack of data on lifestyle and dietary pattern of the subjects, which could have affected GWG. Moreover, as this study was conducted in Sarawak, the findings may not be generalisable to the population of Malaysia at large.

Nevertheless, to the best of our knowledge, this is the first prospective study done in Malaysia that examined the association between obesity in pregnancy on adverse pregnancy outcomes. These findings also add to current available evidence on the importance of classifying obesity in pregnancy as high-risk pregnancy, which requires appropriate antenatal care to reduce adverse obstetric outcomes. Unlike previous studies that also included late-bookers, which may falsely raise the number of obese subjects, we included only women from the first trimester to better reflect their pre-pregnancy weight. We did not use maternal memory of pre-pregnancy weight to avoid inaccurate recall and bias. We used BMI to categorise our subjects as it is a better indicator of body composition instead of weight alone. Moreover, we excluded women who developed GDM in late pregnancy through a repeated OGTT.

In conclusion, obesity is an independent risk for adverse obstetric outcomes, especially PIH and in requiring primary caesarean section, even without excessive GWG. Further well-designed prospective studies examining this association are crucial.

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Verrucous nipples

A 29-year-old woman (gravida 3, parity 3) at 20 weeks of gestation presented with skin growth at bilateral nipples and areola for past 5 years. It was first noticed during her first pregnancy. The lesions were gradually increasing in size, otherwise asymptomatic. Previously, she had difficulty to breastfeed twins from her second pregnancy. She has no known medical illness. She denied personal and family history of atopy. Physical examination revealed verrucous hyperpigmented plaques on bilateral areola and nipples. No genital or mouth lesion was seen.

What is the most likely diagnosis?

A. Eczema of the nipple
B. Hyperkeratosis of nipple and areola
C Mammary Paget's disease.
D. Papillomatosis of the nipple
E. Viral warts

Diagnosis. Nipple eczema is a dermatitis involving the nipple and areola, and is characterised by oozing, crusting and scaling. Absence of personal and family history of atopy makes the diagnosis of eczema unlikely. Additionally, the lesion is relatively asymptomatic as pruritus is a key symptom in eczema.

Mammary Paget's disease is a rare cutaneous malignancy that is associated with breast carcinoma. It usually occurs in patients between the ages of 50 and 60 years. Mammary Paget's disease is characterised by chronic eczematous lesion where it may look erythematous, with scaling, swelling, ulcerating and oozing. The diagnosis is confirmed by skin biopsy.

Nipple papillomatosis is a benign growth of numerous papillomas from the lactiferous duct epithelium of the nipple. It is commonly diagnosed in women aged 35 to 55 years old. It is usually asymptomatic, though patients can experience mild tenderness from it. The diagnosis is confirmed by a skin biopsy.

Viral warts are caused by infection with human papillomavirus resulting in benign proliferations of the skin and mucosa. It commonly presents as hyperkeratotic and verrucous papules. Common affected sites are hands, feet, face and genitalia. Dermoscopy and skin biopsy can help to confirm the diagnosis.

This woman had secondary hyperkeratosis of the nipple and areola. It can occur in puberty and pregnant women. She started having the lesion during her first pregnancy. The histopathological findings confirmed the diagnosis (Figs. 2A to 2C). From the skin biopsy, epidermal acanthosis with thickened epithelium predominantly composed of basaloid cells was seen in the epidermis. There were interspersed horn cysts. The dermis showed minimal perivascular lymphoplasmacytic infiltrates, no atypia or evidence of malignancy.

Discussion. Hyperkeratosis of the nipple and areola is a rare condition with unclear pathogenesis. Despite its rarity, its classification has been revised twice. The latest classification suggested by Pérez-Izquierdo divides hyperkeratosis of the nipple and areola into 2 types: (1) the primary or idiopathic type that typically presents in adolescent females, and (2) the secondary type associated with another skin condition, which can be unilateral or bilateral depending on the underlying dermatoses.[1]

Unilateral secondary hyperkeratosis of the nipple and areola may occur in seborrhoeic keratosis, papillomatous melanocytic naevus, epidermal naevus, leiomyoma, acanthosis nigricans, nipple papillomatosis,

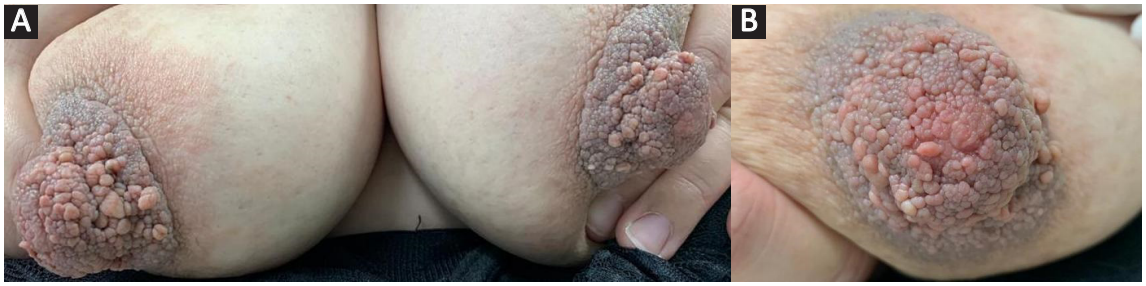

Fig. 1. (A and B): Verrucous hyperpigmented plaques on bilateral areolae and nipples.

Answer: B

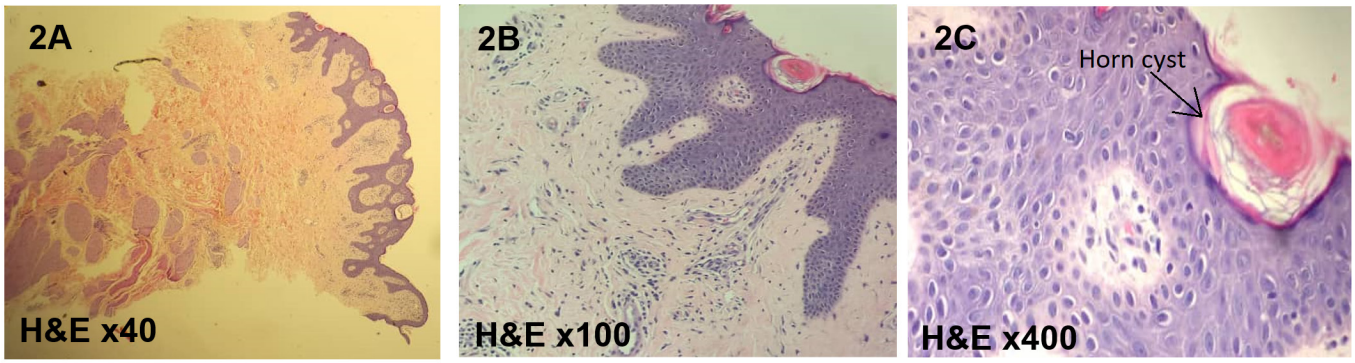

Fig. 2. (A): Thickened epithelium with acanthosis at low power magnification. (B) and (C): Epidermis has predominantly basaloid cells with horn cyst (see arrow) at higher power magnification.

jogger's or cyclist's nipple, mammary Paget's disease of the skin, and skin cancer. Bilateral secondary hyperkeratosis of the nipple and areola may occur with ichthyosis, atopic dermatitis, psoriasis, Darier disease and targeted cancer therapies such as vemurafenib. Breast lesions developed during pregnancy and in males receiving oestrogen therapy are also included as secondary hyperkeratosis of the nipple and areola.[2]

There is no definitive treatment for hyperkeratosis. Clinically proven topical therapeutic options include keratolytic (salicylic acid, 6%), emollients, corticosteroids, tretinoin, and calcipotriol. Interventional treatments such as shave excision, cryotherapy and carbon dioxide laser have also been reported as options.[3]

For the patient's third pregnancy, she considered breastfeeding by extraction of breastmilk (as she did for her second pregnancy). She was concerned about wound healing from surgical excision affecting the extraction of breast milk, and vice versa. Thus, she declined surgical treatment initially. However instead of breastfeeding, she started her child on formula milk after delivery. In the last follow-up, she expressed her readiness for surgical excision.

Conclusion. Hyperkeratosis of the nipple and areola is a rare and benign condition. It does not resolve without treatment and may recur after treatment. It is usually cosmetically unacceptable and may cause psychologic disturbances in affected persons. Functionally, it can interfere with breastfeeding.

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