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There is paucity of data on the occurrence of cardiovascular events (CVEs) in critically ill patients with sepsis. A recent Singapore study aimed to describe the incidence, risk factors and impact on mortality of CVEs in these patients. It found that patients with sepsis had significantly more CVEs compared to those without, resulting in longer ICU and hospital stay. Factors associated with an increased risk of CVEs included age, ethnicity and comorbidity of ischaemic heart disease.

Awareness of the association between sepsis and CVEs allows earlier recognition of CVEs and initiation of therapies to improve the outcomes of patients.

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Gastroesophageal reflux disease in Asian infants: Similar condition, different perceptions

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Gastroesophageal reflux disease (GERD), a common problem in infancy, may lead to troublesome symptoms or complications such as oesophagitis or oesophageal stricturing in a small minority of infants.¹ In the majority of cases, however, frequent regurgitations, the commonest symptoms of GERD, resolves with age spontaneously without any medical intervention.^{2,3} Only a small proportion requires dietary modification or pharmacology therapy.³

In this issue of the *Annals*, McLoughlin et al. published a prospective study evaluating the prevalence and natural history of GERD in Singapore infants using the revised Infant Gastroesophageal Reflux Questionnaire (I-GERQ-R).⁴ The authors found that the peak prevalence of infant GERD was 26.5% at 6 weeks, decreasing to 7.7% at 3 months and 1.1% at 1 year. While the findings on the natural evolution of GERD in Singapore infants is similar to other prospective cohort studies,^{2,3} the survey on the parental perception in the study is novel and raised interesting observations.⁴

Unlike most observational studies on the natural history of GERD from the clinician's perspective, McLoughlin et al. also explored the perception and lifestyle modifications by parents of infants with symptoms of GERD in the predominantly Chinese community in Singapore. The majority of parents of infants with or without the diagnosis of GERD thought that symptoms of excessive crying and regurgitation could be attributed to "too much 'wind' in the child's stomach" or an "immature digestive system". Some mothers resorted to dietary modifications including elimination of spicy foods, or "cold food or drinks".

The authors acknowledged the influence of Asian culture and traditional beliefs on the perception of "wind". The concept of "wind" had been reviewed previously but a scientifically sound way of measurement has yet to be established.⁵ On the other hand, attempts have also been made to map and diagnose "heatiness" scientifically. "Heatiness" is another important traditional Chinese medicine concept, characterised as "redness, swelling, fever and pain", and is traditionally diagnosed by Chinese traditional medicine practitioners subjectively.⁶

"Bloating", "wind", "gas in stomach" are terms commonly used in education websites for parents in Western literature to describe discomfort or colic in babies.⁷ Air swallowing is a physiological phenomenon believed to be involuntary in infants during feeding. Evidence supporting air swallowing leading to excessive stomach distension and GERD in infants is lacking. Recently, however, oesophageal air swallowing temporarily associated with GERD-like symptoms (coughing and back arching associated with air swallowing) were demonstrated via multichannel intraluminal impedance in a study in 2 infants with symptoms suggestive of GERD.8 These GERD-like symptoms were not associated with acidic reflux at the lower oesophagus, and the reflux index were 1.4% and 5.9%, respectively.⁸ Although the sample size is very small, this novel finding may be used as an example of how modern "Western" medicine can help complement traditional belief of "wind" in counselling parents of infants with GERD, who have the perception of "wind" as reported by McLoughlin et al.

McLoughlin et al. also found that all infants with GERD in their study were positioned at 30-45° by their parents during and after feed. Loots et al. performed a small, randomised trial to compare the effect of left lateral position and head elevation to 20° with or without gastric acid suppression for 14 days in infants with symptoms of reflux. The authors found that left lateral positioning was more effective compared to head elevation in reducing gastroesophageal reflux (GER) episodes as well as vomiting, but not other symptoms of reflux.9 Thus, although head elevation after feeding has been a common advice given to parents to reduce GER, it may not be an effective measure to reduce symptoms of GERD. However, no position other than supine position is recommended for infants with GERD after feeding, especially when they are sleeping because of the risk of sudden infant death syndrome.¹

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McLoughlin et al. did not report whether the parents in their cohort of infants resorted to burping their infants to reduce regurgitation. Burping infants after feeding has been given as an advice to parents regularly.¹⁰ Parents are told to hold the baby upright and gently pat at the back until "wind" is released. This is thought to reduce the frequency of regurgitation. However, a small randomised, non-blinded, controlled trial from India involving 71 healthy babies reported a statistically higher incidence of regurgitation in the "burping" group as compared to control (8.1 versus 3.7 episodes/infant/week) with a difference of 4.36 episodes/infant/week (95% confidence interval 4.04–4.69).¹⁰ Thus some traditional remedies practised by parents may not be effective.

Besides confirming the self-limiting nature and natural history of infant GERD, the study by McLoughlin et al. also adds to our knowledge on the parental perception and lifestyle modification in this common childhood condition. It reinforces the fact that parental perception of GERD is strongly influenced by traditional cultural beliefs. By incorporating the recent finding of oesophageal air swallowing by Western medicine into the concept of "wind" as a cause of GERD, parental satisfaction is improved, indirectly gaining trust of the patients.¹¹ Burping of infants after feeding, while in itself is probably harmless, has not been shown to be effective in reducing the frequency of regurgitation. Thus, a neutral attitude to burping can be adopted. On the other hand, positioning the head of the infant in 30-45° after feeding should probably be discouraged, especially if the infant is sleeping after feeding.

The main limitation of the study by McLoughlin et al. was a lack of pH impedance study and the subjective nature of I-GERQ-R questionnaire. Future studies should consider using pH impedance as an objective measure to ascertain the effectiveness of positioning the head at 30–45° during and after feed in infants with symptoms of GERD. No study has researched the efficacy of this measure before. In conclusion, the work of McLoughlin et al. adds new insight into our knowledge on the parental perception of GERD and how parents cope with this common infant condition. It highlights that perception by clinicians and parents can differ in a clinical condition.

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Sepsis and cardiovascular events: The story so far

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Sepsis is a state of life-threatening organ dysfunction that results from a dysregulated host immune response to infection.¹ Sepsis is a common condition that leads to admission to the intensive care unit (ICU). Although advances have been made in the management of sepsis, mortality from sepsis remains high.² Among patients diagnosed with sepsis each year, up to 1 in 3 will succumb to the disease.²

Cardiac dysfunction is a well-recognised complication of sepsis and sepsis-related cardiomyopathy.³ However, in recent years, cardiovascular events (CVEs) such as myocardial infarction, acute coronary syndrome, congestive cardiac failure, cerebrovascular accident and cardiovascular-related deaths are becoming increasingly recognised as complications of sepsis. Although CVEs are a recognised complication of sepsis, most studies do not report risk factors associated with CVEs, posing a challenge to identify individuals at risk of developing sepsisrelated CVEs.⁴⁻⁷ Thus, it is a challenging task to identify patients with sepsis who are at risk of developing CVEs.

In this issue of the Annals, Ho et al. had conducted a study to examine the incidence of CVEs in a medical ICU.8 The authors should be commended for this research as they examined several parameters in the search for risk factors related to CVEs. Although studies have been performed on CVEs in sepsis, these mostly compared incidence between patients with and without sepsis.⁴⁻⁷ This is evident in studies conducted by Ou, Angriman, Yende and Jafarzadeh,⁴⁻⁷ where the incidence of CVEs in patients with sepsis was compared with a matched non-sepsis population. These findings showed that the incidence of CVEs is higher in patients with sepsis when compared with a matched non-sepsis population. A few studies reported risk factors associated with CVEs. Wu et al. not only reported risk factors associated with CVEs in sepsis but also mortality.9 His team showed that patients with sepsis who developed CVEs had a 2-fold mortality at 180 days and 365 days after the onset of CVEs.

In their work, Ho et al. performed a single-centre study looking at factors that may be associated with CVEs in sepsis.⁸ This was done retrospectively by

collecting data from the electronic medical record system of patients admitted to a medical ICU of a tertiary university-affiliated hospital from July 2015 to October 2016. A detailed data collection was performed, which included patients' baseline demographics, medical history, comorbidities and hospital admission details, such as length of hospital and ICU stay, presence or absence of sepsis, laboratory results and treatment details. Patients' disease severity was assessed with Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the Sequential Organ Failure Assessment (SOFA) score. Such details were not reported in earlier studies. From analysis of the data, Ho et al. found that 3 independent parameters were associated with an increased incidence of CVEs. These parameters were older patients, those with preexisting ischaemic heart disease, and patients of certain ethnicities, particularly Malay and Indian. Age has been reported to affect the incidence of CVEs in 2 earlier studies. While Wu et al.9 reported a similar finding of CVEs being higher in older patients, Angriman's study reported that CVEs were more common in those below 40 years of age.⁵ Wu also found that CVEs were associated with pre-existing neurological disorder, which was not reported by Ho et al. The latter further noted factors associated with a lower risk of developing CVEs. These were a body mass index (BMI) lower than 18.5 and the presence of chronic lung disease. The association between chronic lung disease and a lower incidence of CVEs is interesting. Existing evidence shows that cardiovascular complications are well established in chronic obstructive pulmonary disease (COPD).¹⁰ However, in this study, chronic lung disease was taken as a collective rather than individual diseases like asthma, COPD, bronchiectasis, etc. Ho et al. also showed that patients with sepsis who develop CVEs had longer hospital and ICU length of stay. The occurrence of CVEs in sepsis however did not affect the in-hospital mortality.

All studies performed thus far have been retrospective, with differences in the conclusions due to the various methods and analyses of the data collected. Comparing

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the differences in these studies will provide a better understanding of the differing conclusions.

Firstly, the source of data collection varies between the different studies. Studies by Ou,⁴ Yende⁶ and Wu⁹ relied on information from insurance databases, while Angriman⁵ and Jafarzadeh⁷ used population-based databases. The authors were able to collect data on thousands of patients who had sepsis, CVEs, prior medical conditions, length of stay and mortality. On the other hand, Ho et al. collected data from ICU inpatient electronic records. In total, 879 patients were recruited, of whom 682 had a diagnosis of sepsis. Despite the small sample size compared with earlier studies, more information was actually gathered from the electronic medical records, including laboratory results, clinical parameters and patients' clinical progress. Such data are not available from insurance and population-based databases, thus electronic medical records are more reflective of the "real world".

Secondly, these studies have different end points. Ou, Angriman, Yende and Jafarzadeh compared the incidence of CVEs between patients with and without sepsis. In contrast, Wu and Ho et al. compared outcomes between presence and absence of CVEs in patients diagnosed with sepsis. Unlike the studies mentioned earlier, studies by Wu and Ho et al. do not have a matched group of patients without sepsis, but instead focused only on patients who were diagnosed with sepsis.

Finally, mortality was reported differently in the various studies. Yende and Ou included mortality in patients with all cause of sepsis, and not exclusive to those who developed CVEs. Wu reported that patients with sepsis who developed CVEs had a higher mortality compared to those without CVEs. On the other hand, Ho et al. found no difference in mortality when these 2 groups of patients were compared. However, it is important to note that Wu reported mortality at 180 and 365 days, while Ho et al. only looked at inpatients requiring admission to a medical ICU but Wu did not mention ICU admission in his study.

As of now, current evidence suggests that CVEs are more common in patients with sepsis and possibly more likely to affect older patients. CVEs may be associated with higher mortality risk beyond 1 year of diagnosis. However, these observations are inconclusive and need more supportive evidence due to inconsistencies in conducting the studies.

The work by Ho et al. can serve as a "real-world" pilot study for CVEs in sepsis. Hopefully, more clinical studies will be conducted, ideally prospective multicentre trials. Such studies will lead to a better understanding of the condition and help identify patients with sepsis who are at risk, for better management of CVEs. This will be a useful addition to existing management bundles that are currently utilised in the management of sepsis.¹¹

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Prevalence, risk factors and parental perceptions of gastroesophageal reflux disease in Asian infants in Singapore

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ABSTRACT

Introduction: Infant gastroesophageal reflux disease (GERD) is a significant cause of concern to parents. This study seeks to describe GERD prevalence in infants, evaluate possible risk factors and assess common beliefs influencing management of GERD among Asian parents.

Methods: Mother-infant dyads in the Singapore PREconception Study of long-Term maternal and child Outcomes (S-PRESTO) cohort were prospectively followed from preconception to 12 months post-delivery. GERD diagnosis was ascertained through the revised Infant Gastroesophageal Reflux Questionnaire (I-GERQ-R) administered at 4 time points during infancy. Data on parental perceptions and lifestyle modifications were also collected.

Results: The prevalence of infant GERD peaked at 26.5% at age 6 weeks, decreasing to 1.1% by 12 months. Infants exclusively breastfed at 3 weeks of life had reduced odds of GERD by 1 year (adjusted odds ratio 0.43, 95% confidence interval 0.19–0.97, P=0.04). Elimination of "cold or heaty food" and "gas producing" vegetables, massaging the infant's abdomen and application of medicated oil to the infant's abdomen were quoted as major lifestyle modifications in response to GERD symptoms.

Conclusion: Prevalence of GERD in infants is highest in the first 3 months of life, and the majority outgrow it by 1 year of age. Infants exclusively breastfed at 3 weeks had reduced odds of GERD. Cultural-based changes such as elimination of "heaty or cold" food influence parental perceptions in GERD, which are unique to the Asian population. Understanding the cultural basis for parental perceptions and health-seeking behaviours is crucial in tailoring patient education appropriately for optimal management of infant GERD.

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CLINICAL IMPACT

What is New

• The highest prevalence of gastroesophageal reflux disease (GERD) among Asian infants was observed at 6 weeks.

• Children who were exclusively breastfed at 3 weeks had lower risk of GERD.

• Asian mothers appear to adopt cultural-based modifications in relieving infants of their GERD symptoms.

Clinical Implications

• This study highlights the need and importance of understanding the cultural basis of parental perceptions and health-seeking behaviours.

• Findings from this study can help health practitioners develop better therapeutic approaches and to provide culturally aligned education to support mothers of infants with GERD.

INTRODUCTION

Functional gastrointestinal (GI) disorders, such as colic, gastroesophageal reflux (GER) and constipation, are common in infants under 1 year. They are a frequent cause of concern for parents and result in a significant healthcare burden^{1,2} due to their negative impact on feeding behaviours, caregivers' mental wellbeing and quality of life for the whole family. Cultural factors may also influence parent-child interactions in response to GER symptoms, particularly lifestyle changes and infant feeding practices.

Current knowledge on the prevalence, natural history and factors contributing to infant GI disorders is limited. No studies have reported the prevalence of gastroesophageal reflux disease (GERD) in infants below 12 months, but some have reported the prevalence of infant regurgitation based on the ROME criteria for paediatric GI disorders.^{3,4} This study therefore aimed to describe the prevalence and natural history of GERD in infants during the first year of life in an Asian preconception cohort. We also evaluated possible risk factors for infant GERD and assessed common Asian parental beliefs, together with their influence on lifestyle modifications in response to GERD symptoms in these infants.

METHODS

Study design and participants

The Singapore PREconception Study of long-Term maternal and child Outcomes (S-PRESTO) study was designed to assess the impact of nutrition, lifestyle, mental health and other environmental factors during the preconception, antenatal and postnatal periods on mother-offspring health outcomes. The S-PRESTO study design and participants have been previously described.⁵⁻⁸ In brief, the study recruited 1,032 women aged 18-45 years of Chinese, Malay and Indian ethnicity (or a combination of these) without significant health conditions and who were planning to conceive. The 373 babies born were evaluated prospectively at multiple time points with ongoing follow-ups from birth. S-PRESTO was granted ethical approval by the SingHealth Centralised Institutional Review Board (Reference 2014/692/D) and written informed consent was obtained from all women at recruitment.

Maternal and infant characteristics

Maternal characteristics including socio-demographic factors, lifestyle habits, anthropometric measurements and clinical data were collected at multiple time points during the preconception and antenatal periods. Infant data, such as mode of delivery, birthweight and sex, were collected at birth, while other clinical data were recorded prospectively at multiple time points from birth. Mothers were also asked about their infant feeding practices at each postnatal visit starting at 3 weeks (see Appendix in the online Supplementary Materials).

Infant GERD symptoms and parental beliefs

Mothers were asked about their child's health status during the standard study follow-up periods at 6 weeks, 3, 6 and 12 months post-delivery using intervieweradministered questionnaires. These included questions from the revised Infant Gastroesophageal Reflux Questionnaire (I-GERQ-R)-a reliable and valid measure of infant GERD—with higher scores indicating greater symptom burden.9,10 An I-GERO-R score of ≥16 is diagnostic of GERD. The I-GERQ-R questionnaire was derived from the I-GERQ, which was validated for GERD diagnosis in infants aged 1-14 months. Additional information ascertained through the questionnaire included parental beliefs about their infant's troublesome GI symptoms, and potential factors believed to have caused the GI symptoms (online Supplementary Materials).

Statistical analysis

All data collected were analysed on STATA I/C version 16.0 (StataCorp LLC, College Station, Texas, US) and RStudio software version 1.3.1056 (RStudio, Boston, US), an integrated development environment for R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Chi-square and Fisher's Exact tests were used to analyse differences between infants with and without GERD. Risk factors for GERD were analysed using univariate logistic regression with a categorical outcome of having GERD in the first year of life. Multivariate logistic regression was used to create a model of risk factors that may influence the development of GERD. Results with *P* values ≤ 0.05 were considered significant.

RESULTS

Characteristics of participants

A total of 1,054 women attended the recruitment visit, with 1,032 enrolled in the study.⁸ Of these 1,032 participants, 475 became pregnant and 373 gave birth to liveborn singleton infants. Supplementary Fig. S1 shows the number of participants involved at various time points throughout the study. In all, 347 mothers completed the I-GERQ-R questionnaire or questions regarding their beliefs about GI symptoms at one or more time points and were included in this analysis. The demographic factors of participants are presented in Supplementary Table S1. The median age of mothers at recruitment was 30 years (range 20-40 years). The ethnic breakdowns were Chinese (76.1%), Malay (13.8%), Indian (5.8%) and mixed ethnicity (4.3%), similar to Singapore's general population. The majority of mothers had completed tertiary education (72.6%)and had never smoked (91.6%). All infants were healthy and free of major comorbidities.

Prevalence of infant GERD

The highest prevalence of GERD in infants was 26.5% (67/253) at age 6 weeks. This decreased to 7.7% (21/274) at 3 months, 2.6% (8/302) at 6 months and eventually 1.1% (3/273) at 12 months. The mean I-GERQ-R scores decreased with age alongside the decline in prevalence of GERD across time points (Fig. 1).

Infants with GERD were more likely to cry 3 or more hours a day than those without GERD (23/99 [23.2%] versus 22/1003 [2.2%]; P<0.01). Infants with GERD were likely to cry at a particular time of day than those without GERD; this was most often in the evening (32.8%) or night (41.4%), but the difference in evening/ night versus morning/afternoon crying was not significant. Fig. 1. Distribution of I-GERQ-R scores across 4 time points. The mean GERD scores decreased with age up to 12 months. The dotted line shows the cut-off of 16, indicating that the prevalence of GERD according to the I-GERQ-R definition also decreased with age. *P* values were calculated from comparison of means to the mean GERD score at week 6.

I-GERQ-R: revised Infant Gastroesophageal Reflux Questionnaire $^{\rm a}$ indicates $P{<}0.001$

Natural history of GERD

The natural history of GERD was analysed in a subset of 162 participants who had complete data at all 4 time points (Fig. 2). Seven of those with GERD at 6 weeks continued to have GERD at 3 months and only 1 infant with GERD at 3 months continued to have it at 6 months. One infant who had GERD at 6 weeks had no reported symptoms at months 3 and 6, but GERD symptoms were once again reported at 12 months. All other infants outgrew GERD by 12 months.





Figure shows the longitudinal follow-up of infants diagnosed with GERD in the first year of life, in infants with complete data at all 4 time points (n=162). Vertical arrows indicate new cases while horizontal arrows indicate ongoing cases.

Risk factors for GERD

There were significant differences in GERD prevalence by ethnicity, whereby 48.7% (74/152) of infants born to Chinese mothers reported symptoms of GERD in the first year of life, compared to a significantly smaller 25.0% (11/44, *P*<0.01) of those born to mothers of other



ethnicities. Compared to Chinese infants, Malay infants had lower odds of GERD (Table 1).

Infants who were exclusively breastfed at 3 weeks of life had reduced odds of GERD in first year of life, but this did not differ between various modes of breast milk feeding (expressed breast milk feeding versus a combination of being fed at the breast and being fed expressed breast milk) (Table 1). While a higher number of formula feeds per day at 3 weeks of life was associated with increased odds of GERD during infancy in univariate analyses (Supplementary Table S2), this was no longer apparent after adjusting for confounders (Supplementary Table S3). No other risk factors were associated with GERD in any of the adjusted models.

We also observed an association between GERD and frequency of feed refusal when hungry. Increasing frequency of feed refusal was associated with higher total I-GERQ-R scores at each time point (Table 2). When pooling all time points, 26% of infants who never/ rarely refused feeds during the first year of life had GERD, while 72.1% of those who has ever (sometimes/ often/always) refused feeds also had GERD. These findings were similar across ethnic groups, with similar proportions of infants who had frequent feed refusals during infancy fulfilling GERD diagnosis in both the Chinese (37/48, 77.1%) and Malay (4/6, 66.7%) ethnic groups.

Parental perceptions: Causes of infant's GI symptoms

Symptom-weighted ranking identified excessive crying and regurgitation as the most important symptoms affecting infants with GERD-31.8% (27/85) and 32.9% (28/85) during the first year, respectively. Other symptoms including "gassiness" or "bloatedness", not eating enough and "wind" in the baby's stomach were also quoted as causes for concern.

Table 1. Multivariate logistic regression model for the association of ethnicity and infant feeding habits at 3 weeks of life with gastroesophageal reflux disease in the first year of life^{a,b}

Model 1 (n=127)	aOR (95% CI)	P value
Ethnicity		
Chinese	1.00	-
Malay	0.14 (0.03–0.63)	0.01
Indian	0.19 (0.02–2.03)	0.17
Mixed ethnicity	0.2 (0.04–1.09)	0.06
Expressed BM (frequency) at week 3	0.96 (0.85-1.09)	0.51
Exclusive breastfeeding at week 3	0.44 (0.19–0.98)	0.05
Breast milk (direct + expressed) at week 3	1.12 (0.47–2.66)	0.80
Model 2 (n=127)		
Ethnicity		
Chinese	1.00	-
Malay	0.14 (0.03–0.63)	0.01
Indian	0.19 (0.02–2.05)	0.17
Mixed ethnicity	0.20 (0.04–1.11)	0.07
Expressed BM (frequency) at week 3	0.96 (0.84–1.00)	0.57
Exclusive breastfeeding at week 3	0.43 (0.19–0.97)	0.04
Expressed BM at week 3	0.98 (0.29–3.31)	0.98

aOR: adjusted odds ratio; BM: breast milk

^a All models adjusted for household income, maternal highest education level, multiparity, birthweight and gestational age.

^b For each type of feeding, parents were asked to indicate the frequency of feed. Exclusive breastfeeding was defined as an affirmative response to the question, "Is your baby still breastfeeding?" AND an indicated frequency of direct breastfeeding, expressed breast milk or donor breast milk of >0 time per day AND frequency of formula use, cow's milk, other milk and solid intake indicated as 0 time per day. Information on the mode of breast milk feeding such as fed at the breast (direct), fed expressed breast milk (EBM), or a combination of being fed at the breast and being fed EBM, was also collected among infants who were breastfed at each time point.

Figures in bold are significant

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Table 2. Association between frequency of feed refusal and gastroesophageal reflux disease (GERD) status at each time point

Frequency of feed refusal when hungry	No GERD no. (%)	GERD no. (%)	RR (95% CI) ^a	Mean GERD score (SD)	P value ^b
Week 6					
Never/rarely	180 (77.3)	53 (22.8)	1.0	11.76 (4.84)	
Sometimes/often/always	6 (30.0)	14 (70.0)	5.04 (2.81-7.26)	16.80 (4.95)	<0.001
Month 3					
Never/rarely	235 (95.9)	10 (4.1)	1.0	6.96 (3.98)	
Sometimes/often/always	18 (62.1)	11 (37.9)	7.45 (5.89–9.02)	14.41 (4.71)	<0.001
Month 6					
Never/rarely	267 (99.6)	1 (0.4)	1.0	4.37 (3.19)	
Sometimes/often/always	27 (79.4)	7 (20.6)	7.51 (6.31–8.71)	11.89 (4.43)	<0.001
Month 12					
Never/rarely	257 (100)	0	1.0	2.77 (2.53)	
Sometimes/often/always	13 (81.3)	3 (18.8)	6.11 (4.72–7.5)	8.88 (5.15)	<0.001

95% CI: 95% confidence interval; GERD: gastroesophageal reflux disease; RR: risk ratio; SD: standard deviation

^a Linear regression analysis carried out with GERD score as a continuous variable

^b *P* value obtained for both chi-square/Fisher's Exact test and linear regression were identical

A similar proportion of mothers of infants with (78.9%) and without GERD (73.0%) thought that too much wind in their child's stomach caused excessive crying (Fig. 3A). Likewise, 47.4% of parents of infants with GERD and 29.7% of parents of infants without GERD attributed this symptom to an "immaturity of child's GI system". There were no statistically significant differences in parental perceptions of symptom causality between infants with and without GERD.

A significantly larger percentage of parents of infants with GERD believed that their child's regurgitation was caused by "too much wind" (86.7%) (P<0.01) compared to parents of infants without GERD (34.3%) (Fig. 3B). Additionally, 47.6% of parents of infants with GERD and 45.7% of parents of infants without GERD attributed this symptom to an "immature GI system". Some parents also indicated other factors such as weaning to solids, excessive food consumption, or insufficient intake of fluids as potential causes.

Parental perceptions: Lifestyle interventions

At 6 weeks, 3 months and 6 months, all parents of infants with GERD had made at least one lifestyle change due to their child's excessive crying or regurgitation. The most common intervention implemented for excessive crying was repositioning the infant at an incline, followed by maternal dietary modifications (Fig. 4A). The dietary modifications commonly included elimination of spicy foods (26.3%), dairy (21.1%) and cold food or drinks (21.1%). Some mothers began taking supplements (10.5%), added probiotics (5.3%) or more vegetables (5.3%) to their diet. For parents of GERD infants, 36.8% reduced the volume of their child's feeds, compared to 18.8% of parents of non-GERD infants (P=0.08).

For infants with regurgitation as the primary troublesome GI symptom, all those with GERD were positioned at 30–45° incline during and after feeding, compared to 84.4% of infants without GERD (Fig. 4B). Feed volume reduction and maternal dietary modifications were the next most common interventions. Twenty percent of these mothers stopped consuming spicy food, and 13.3% cut down on dairy and citrus fruits.

Healthcare-seeking behaviours

Parents were most likely to consult a healthcare professional for their infants' GI symptoms in the earlier months of life: 19.2% of parents sought help at 6 weeks and again at 3 months, but only 6.7% did so at 6 months and 5.3% at 12 months. Parents of infants suffering from regurgitation (48.1%, 45.5%, 20.0% and 16.7% at 6 weeks, 3, 6 and 12 months, respectively) or who cried excessively (40.6%, 48.1%, 10% and 12.5% at 6 weeks, 3, 6 and 12 months, respectively) were consistently more likely to seek help than those suffering from other symptoms.



Fig. 3. Parental perceptions regarding the causes of their infant's troublesome gastrointestinal (GI) symptoms.

Common causes reported by mothers when their infant's GI symptoms were due to (A) excessive crying and (B) regurgitation. Other perceived causes included food allergies, being too "heaty" or too "cold", overfeeding and insufficient fluid consumption. GERD: gastroesophageal reflux disease; GI: gastrointestinal



Fig. 4. Lifestyle interventions practised by parents of infants suffering from gastrointestinal (GI) symptoms.

Common lifestyle modifications made by parents where causes of infant's GI symptoms were due to (A) excessive crying and (B) regurgitation. The most common lifestyle change made was a change in the positioning of during and after feeding.

GERD: gastroesophageal reflux disease; GI: gastrointestinal

Fifteen mothers indicated that their baby had turned blue or purple and/or had stopped breathing while awake, or struggled to breathe, due to GERD at any time during the first year of life. Only 7 indicated that they sought medical attention for their child's feeding issues; however, it is unclear whether it was done for this particular indication.

Parents with higher household income were significantly less likely to seek advice at any time in the first year than those with a lower household income (odds ratio 0.78, 95% confidence interval [CI] 0.66–0.93). Maternal education level, multiparity and ethnicity were not associated with healthcare-seeking behaviour.

DISCUSSION

This study provides data on the epidemiology, risk factors, longitudinal course and social impact of GERD in an Asian paediatric population. There is currently a paucity of data on GERD prevalence in Asian infants and much of the published literature is based on adults or children in Western populations. Of the studies in Asian populations, the majority used surrogate indicators of GERD such as individual symptoms of regurgitation/ reflux as outcome measures. This study utilised a robust, validated,^{9,10} questionnaire-based tool, the I-GERQ-R, to evaluate not only the prevalence but also the natural history of GERD longitudinally across the first 12 months of life in Asian infants. We also identified common Asian parental perceptions of GERD symptoms, causality and behavioural modifications triggered by the infants' GI symptoms, as well as characterised family profiles that might explain healthseeking behaviours.

It is important to distinguish GERD from GER, which is a normal physiological process even in healthy infants in the first few months of life.¹¹ Immaturity of the oesophagogastric junction allows gastric contents to move back up into the oesophagus but does not cause vomiting.¹² Infant GERD is characterised by reflux (due to transient lower oesophageal sphincter relaxation) in association with other symptoms and/or complications such as irritability, refusal to feed, failure to thrive and arching of the back,^{11,13} as well as chronic cough, choking, wheezing and apnoea. In this study, the I-GERQ-R tool enabled us to distinguish GERD from GER, which other studies utilising single symptoms such as regurgitation were not able to.

The highest prevalence of GERD in our population was at age 6 weeks. The prevalence decreased rapidly with age and almost all infants outgrew GERD by 1 year. As most other studies did not use validated tools for GERD diagnosis, direct comparisons of prevalence across different populations are not possible. The prevalence of GERD was recently estimated at 26.9% (95% CI 20.1–33.7) in a meta-analysis of 4 studies comprising infants from birth to 3 years.¹⁴ Other studies that reported regurgitation as the primary surrogate symptom for GERD estimated prevalence of 20–50%.^{14,15}

A major difference in infant GERD between different ethnic groups is the variation in the age at peak prevalence. GERD prevalence peaked at 4 months in Western populations.¹⁶ However, research on Japanese and Indonesian infants showed that peak prevalence of GER was at 1 month of age and prevalence consistently decreased with age until 12 months.¹⁷ Similarly, Thai infants regurgitated most during the first 2 months.¹⁸ Our data showed that the peak prevalence of infant GERD was at 6 weeks, which is consistent with other Asian populations.

Exclusively breastfed infants in this cohort had a reduced odds of GERD, but the mode of breast milk feeding did not appear to impact GERD risk. Some studies have, however, reported a protective effect of feeding at the breast against reflux.¹⁹⁻²² In a prospective study in the US, any combination of formula feeding (bottled breast milk + formula feeding, formula feeding alone, or mixed breast milk + formula feeding) were found to be risk factors for reflux compared to feeding at the breast.²¹ Turkish infants with regurgitation were also less likely to have been breastfed¹⁹ while formulafed Indonesian infants had an increased frequency of regurgitation and vomiting compared to those who were exclusively breastfed.²⁰ Formula feeds also differ from breast milk in milk content and hence digestibility, and are also associated with increased risks of bacterial contamination, all of which can increase the risk of reflux symptoms.²³ Additionally, infants exclusively breastfed may be able to self-regulate milk intake compared to formula-fed infants. Infant cues of satiety may be ignored or missed during bottle feeding, potentially resulting in overfeeding or larger volume of milk than is needed, leading to reflux.²⁴

We found that infants with a positive response to the feed refusal question were more likely to fulfil GERD criteria. This implies that feed refusal may be a distinguishing feature that clinicians could use in screening for GERD compared to more subjective symptoms such as excessive crying, where the full I-GERQ-R questionnaire cannot be feasibly performed. Additionally, as there is currently little evidence to suggest genetic differences in basic pathophysiological mechanisms of GERD, we postulate that environmental, cultural or dietary factors play a role in symptom recognition/reporting by parents. This is suggested by the higher prevalence of GERD in Asians in the US compared to Asians living in East Asia.25 Larger studies are needed to elucidate if there are indeed genetic factors linked to GERD pathophysiology.

Infant feeding practices in Singapore are influenced by tradition and social conditioning, and caregivers tend to seek advice from friends and family more often than from health professionals.²⁶ Maternal dietary modifications were common, and included the elimination of spicy foods, "cold" foods and drinks and "gas-producing" vegetables. Other changes made included massaging and applying of medicated oil to the infant's abdomen, actions thought to relieve gastrointestinal discomfort. The concept of "cold" or "heaty" foods, "wind", and "gasproducing" vegetables are common in complementary and alternative medicine practices such as traditional Chinese medicine, whereby a delicate balance of the yin and yang energies is essential for good health.²⁷ An imbalance in the yin-yang energy brought about by the consumption of associated foods, therefore, is thought to result in disease manifestations such as the GI symptoms reported here. Furthermore, maternal nutrition during lactation has been known to influence infant health, thus it is plausible that maternal diet and nutrition can also influence the quality of breast milk and therefore the symptoms of GERD in infants. However, further research in this field is required. While our findings are not surprising given that complementary and alternative medicine is a salient part of Asian culture, the study highlights the uniqueness and importance of understanding the cultural basis for parental perceptions, implementation of common non-pharmacological remedies, and health-seeking behaviours for infant GERD in other parts of the world.

There were several limitations in our study. The mothers in the S-PRESTO cohort were not fully representative of the general Singapore population72.6% completed a university education compared to 51% of general Singapore population in the same age category (females aged 25 to 39 years in 2014).²⁸ Although a majority of the respondents were mothers, data on whether respondents were the primary caregivers and time spent with infants in the first year of life were not collected and this may undermine the reporting of symptoms related to the child's feeding and GERD. Objective measures of GERD such as pH impedance studies were not performed due to their invasive nature. Self-reported symptoms may also misclassify disease outcomes. The I-GERQ-R questionnaire has also not been formally validated in a Singaporean/Asian population although it has been used extensively in other populations. However, as English is the primary language in Singapore and the majority of parents in this study were familiar with the terminology used in the I-GERQ-R, this would not likely impact the validity and applicability of the results.

CONCLUSION

The information on caregivers' perceptions and behaviours in response to their infants' GI symptoms can aid healthcare practitioners to develop better therapeutic approaches and provide culturally aligned education for parents and caregivers.²⁵ More can also be done by healthcare providers and society to support mothers who desire to continue breastfeeding for its numerous advantages, besides the reduction of distressing GERD symptoms. This approach may in turn improve maternal mental health and infant outcomes. Additionally, the use of the I-GERQ-R questionnaire, which has been validated for diagnosis of GERD,^{9,10} minimises the need to conduct invasive testing for GERD diagnosis. Further well-designed and sufficiently powered studies in paediatric GERD are needed to aid the development of clinical management and infant feeding guidelines specific to the unique cultural background of each population.

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Conflict of interest

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Sepsis, cardiovascular events and short-term mortality risk in critically ill patients

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ABSTRACT

Introduction: There is paucity of data on the occurrence of cardiovascular events (CVEs) in critically ill patients with sepsis. We aimed to describe the incidence, risk factors and impact on mortality of CVEs in these patients.

Methods: This was a retrospective cohort study of critically ill patients admitted to the medical intensive care unit (ICU) between July 2015 and October 2016. The primary outcome was intra-hospital CVEs, while the secondary outcomes were in-hospital mortality, ICU and hospital length of stay.

Results: Patients with sepsis (n=662) had significantly more CVEs compared to those without (52.9% versus 23.0%, P<0.001). Among sepsis patients, 350 (52.9%) had 1 or more CVEs: 59 (8.9%) acute coronary syndrome; 198 (29.9%) type 2 myocardial infarction; 124 (18.7%) incident atrial fibrillation; 76 (11.5%) new or worsening heart failure; 32 (4.8%) cerebrovascular accident; and 33 (5.0%) cardiovascular death. Factors associated with an increased risk of CVEs (adjusted relative risk [95% confidence interval]) included age (1.013 [1.007–1.019]); ethnicity—Malay (1.214 [1.005–1.465]) and Indian (1.240 [1.030–1.494]) when compared to Chinese; and comorbidity of ischaemic heart disease (1.317 [1.137–1.527]). There were 278 patients (79.4%) who developed CVEs within the first week of hospitalisation. Sepsis patients with CVEs had a longer median (interquartile range [IQR]) length of stay in the ICU (6 [3–12] vs 4 [2–9] days, P<0.001), and hospital (21 [10–42] vs 15 [7–30] days, P<0.001) compared to sepsis patients without CVEs. There was no difference in in-hospital mortality between the 2 groups (46.9% vs 45.8%, P=0.792).

Conclusion: CVEs complicate half of the critically ill patients with sepsis, with 79.4% of patients developing CVEs within the first week of hospitalisation, resulting in longer ICU and hospital length of stay.

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Keywords: Atrial fibrillation, cardiac failure, cerebrovascular accident, ICU, myocardial infarction, sepsis

INTRODUCTION

Sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host immune response to infection".¹ It is one of the most common conditions afflicting intensive care unit (ICU) patients, causing a high mortality rate. An estimated 48.9 million incident cases of sepsis and 11 million sepsis-related deaths were reported worldwide in 2017, accounting for almost 20% of all global deaths.² In addition to the high mortality risk, sepsis patients were found to have higher cardiovascular complications such as myocardial infarction (MI),³⁻⁵ heart failure,^{3,6,7} new onset atrial fibrillation (AF) and

stroke.^{5,8} Systemic inflammation and cytokine storm during sepsis is thought to trigger endothelial dysfunction, procoagulant response, atheroma instability, and myocardial dysfunction that contributes to cardiovascular complications.^{3,9}

The current literature focuses predominantly on hospitalised patients with community acquired pneumonia (CAP), which showed increased short-term cardiovascular risks with associated increased in-hospital and 30-day mortality.⁹⁻¹² However, the effect of sepsis as a whole on various cardiovascular complications has been less studied, with a paucity of data among ICU patients. Given

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CLINICAL IMPACT

What is New

• This is the first study in Singapore to the best of our knowledge to characterise the incidence of cardiovascular events (CVEs) among critically ill patients with sepsis, its risk factors and impact on mortality.

• CVEs complicate half of the critically ill patients with sepsis, with 79.4% of patients developing CVEs within the first week of hospitalisation, resulting in longer ICU and hospital length of stay.

Clinical Implications

• Awareness of the association between sepsis and CVEs presents a potential opportunity for earlier recognition of CVEs and initiation of appropriate therapies to improve the outcomes of patients.

the underlying pathophysiology of sepsis, we hypothesise that the increased cardiovascular risks should not be limited to pneumonia, and can be seen in other infections.

We aim to describe the occurrence of intra-hospital cardiovascular events (CVEs) among critically ill patients with sepsis, the risk factors for CVEs, and the association of CVEs with in-hospital mortality in these patients.

METHODS

Study design and patient population

This was a retrospective cohort study of all patients admitted to the medical ICU of Tan Tock Seng Hospital, a university-affiliated tertiary hospital between July 2015 and October 2016. Patients with missing demographic information were excluded from the study. Ethics approval was obtained from the Domain Specific Institution Review Board, with a waiver of informed consent (DSRB reference number 2019/01028).

Definitions

Sepsis was defined based on The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), where a life-threatening organ dysfunction (represented by an increase in Sequential Organ Failure Assessment [SOFA] score ≥ 2) occurs in the presence of confirmed or suspected infection.¹ For patients who had more than 1 ICU admission during the study period, we recorded data from the first sepsis episode.

The primary outcome was intra-hospital CVEs, defined as any of the following: (1) acute coronary syndrome; (2) type 2 MI; (3) incident AF; (4) new or worsening heart failure; (5) cerebrovascular accident (CVA); and (6) cardiovascular deaths.

MI was diagnosed in accordance to the Fourth Universal Definition of MI.¹³ Acute coronary syndrome referred to type 1 MI, and included ST elevation MI (STEMI) and non-ST elevation MI (NSTEMI) where there was rise and/or fall of cardiac troponin with at least 1 value above the 99th percentile, and at least 1 of the following: (1) symptoms of acute myocardial ischaemia; (2) new ischaemic electrocardiogram (ECG) changes; (3) development of pathological Q waves; (4) imaging evidence of new loss of viable myocardium; or (5) identification of a coronary thrombus by angiography or autopsy. Type 2 MI was diagnosed using similar criteria as above, except for (5), and occurred in the setting of myocardial oxygen supply and demand imbalance. Incident AF was diagnosed based on a newly recognised episode of AF in the ECG of patients who had no prior history of AF. New-onset or worsening heart failure was defined using the Framingham Criteria for congestive heart failure of at least 2 major criteria, or 1 major plus 2 minor criteria.¹⁴ CVA was determined based on clinical signs and brain imaging. Cardiovascular death was defined as fatal MI, fatal stroke, or death due to cardiogenic shock in patients with congestive heart failure. Secondary outcomes were ICU and in-hospital mortality, and ICU and hospital length of stay.

Data collection

The following data were collected from the electronic medical record system: age, sex, ethnicity, smoking status, body mass index (BMI), comorbidities, baseline medications, premorbid functional status, Acute Physiology and Chronic Health Evaluation II (APACHE II) and SOFA scores on day 1 of ICU admission, presence of sepsis and CVEs, laboratory results, ICU treatment details, ICU and hospital length of stay, and ICU and hospital mortality.

Statistical analysis

Continuous variables were reported as mean and standard deviation (SD), or median and interquartile range (IQR) where distributions were skewed. For categorical variables, frequencies and percentages were reported. The differences between the 2 groups of patients with CVEs and without CVEs were assessed with Student's t-test or Mann-Whitney U test for continuous variables, and Pearson's chi-square test or Fisher's Exact test for categorical variables. Multivariable modified Poisson regression was used to identify factors associated with intra-hospital CVEs and in-hospital mortality, and results were presented as relative risk (RR) with a 95% confidence interval (CI). This approach was chosen

since odds ratio estimated using logistic regression may significantly overestimate RR when the outcome is common.¹⁵ Variables with non-missing values and having a significant univariate test result were considered as candidates in the multivariable analysis. Correlations of the estimated coefficients for these candidate variables were examined to assess for possible multicollinearity. Clinical expert knowledge was also used to guide variables selection in the final model to account for clinically important predictors as well as potential confounding factors. All statistical tests were two-sided, and P<0.05 was considered statistically significant. Analyses were performed using Stata version 14.0 (StataCorp, College Station, US).

RESULTS

There were 892 patients admitted to the ICU between July 2015 and October 2016. Due to incomplete demographic information, 13 patients were excluded from our study. There were 662 patients (75.3%) with sepsis and 217 (24.7%) without sepsis (Fig. 1). Patients with sepsis had significantly more CVEs compared to those without sepsis (52.9% versus 23.0%, P<0.001). Specifically, there were more acute coronary syndrome, type 2 MI, AF and heart failure in the sepsis group (Table 1).

Primary outcome: Sepsis and intra-hospital CVEs

Among the sepsis patients, 350 (52.9%) had 1 or more CVEs: 59 (8.9%) acute coronary syndrome; 198 (29.9%) type 2 MI; 124 (18.7%) incident AF; 76 (11.5%) new or worsening heart failure; 32 (4.8%) CVA; and 33 (5.0%) cardiovascular death (Table 1).

Baseline demographics, laboratory investigations and ICU treatment details for sepsis patients with and without CVEs are summarised in Table 2. Patients who had CVEs were older, had more comorbidities, were of greater disease severity (higher APACHE II and SOFA scores), had higher procalcitonin levels, and required more organ support modalities such as vasopressors, renal replacement therapy, packed cell transfusion and cardioversion. There was no difference in the source of infection except for ventilator-associated pneumonia, where there was a higher number of patients with CVEs (P=0.016).

In the multivariate analysis, 3 factors were independently associated with an increased risk of CVEs (adjusted RR [95% CI]): (1) age (1.013 [1.007–1.019]); (2) ethnicity—Malay (1.214 [1.005–1.465]) and Indian (1.240 [1.030–1.494]) when compared to Chinese ethnicity; and (3) comorbidity of ischaemic heart disease (1.317 [1.137–1.527]). Conversely, the occurrence of CVEs was lower (0.688 [0.529–0.895]) in patients who were underweight (BMI<18.5kg/m²) when compared to normal BMI (18.5–22.9kg/m²) and when patients had a comorbidity of chronic lung disease (0.733 [0.598–0.899]) (Table 3).

Secondary outcomes

The majority of patients (79.4%) developed CVEs early within the first week of hospital admission (Supplementary Fig. S1 in the online version of this article). Compared to sepsis patients without CVEs, sepsis patients with CVEs had a longer ICU length of stay (median [IQR] of 6 [3–12] vs 4 [2–9] days, P<0.001)



Fig. 1. Flowchart of clinical outcomes of patients admitted to intensive care unit. CVE: cardiovascular event; ICU: intensive care unit.

Table 1. Types of cardiovascular event

Cardiovascular event	All ICU patients No. (%) N=879	Sepsis No. (%) n=662	Without sepsis No. (%) n=217	P value
Acute coronary syndrome	65 (7.4)	59 (8.9)	6 (2.7)	0.003
Type 2 myocardial infarction	213 (24.2)	198 (29.9)	15 (6.9)	<0.001
Atrial fibrillation	144 (16.4)	124 (18.7)	20 (9.2)	0.001
Heart failure	81 (9.2)	76 (11.5)	5 (2.3)	<0.001
Cerebrovascular accident	39 (4.4)	32 (4.8)	7 (3.2)	0.318
Cardiovascular death	42 (4.8)	33 (5.0)	9 (4.2)	0.616
Any CVE	400 (45.5)	350 (52.9)	50 (23.0)	<0.001
Only 1 CVE	254 (28.9)	215 (32.5)	39 (18.0)	<0.001
2 or more CVEs	146 (16.6)	135 (20.4)	11 (5.1)	
No CVE	479 (54.5)	312 (47.1)	167 (77.0)	

CVE: cardiovascular event; ICU: intensive care unit

Table 2. Characteristics of patients with sepsis, with or without cardiovascular events

	All patients with sepsis n=662	Patients with sepsis and CVE n=350	Patients with sepsis and no CVE n=312	P value
Age, median (IQR), years	70 (60–78)	72 (62–79)	68 (56–77)	<0.001
Male, no. (%)	422 (63.7)	219 (62.6)	203 (65.1)	0.505
Ethnicity, no. (%)				0.063
Chinese	462 (69.8)	232 (66.3)	230 (73.7)	
Malay	92 (13.9)	56 (16.0)	36 (11.5)	
Indian	75 (11.3)	47 (13.4)	28 (9.0)	
Others	33 (5.0)	15 (4.3)	18 (5.8)	
Smoking status, no. (%), n=444				0.482
Smoker	126 (28.4)	66 (27.6)	60 (29.3)	
Ex-smoker	110 (24.8)	55 (23.0)	55 (26.8)	
Non-smoker	208 (46.8)	118 (49.4)	90 (43.9)	
Comorbidities, no. (%)				
Diabetes mellitus	303 (45.8)	185 (52.9)	118 (37.8)	<0.001
Hypertension	436 (65.9)	247 (70.6)	189 (60.6)	0.007
Hyperlipidaemia	338 (51.1)	205 (58.6)	133 (42.6)	<0.001
Ischaemic heart disease	163 (24.6)	114 (32.6)	49 (15.7)	<0.001
Heart failure	64 (9.7)	41 (11.7)	23 (7.4)	0.059
Atrial fibrillation	65 (9.8)	31 (8.9)	34 (10.9)	0.379
Other arrhythmias	11 (1.7)	7 (2.0)	4 (1.3)	0.553
Valvular heart disease	16 (2.4)	10 (2.9)	6 (1.9)	0.435
Cerebrovascular accident	98 (14.8)	56 (16.0)	42 (13.5)	0.359

Table 2. Characteristics of patients with sepsis, with or without cardiovascular events (Cont'd)

	All patients with sepsis n=662	Patients with sepsis and CVE n=350	Patients with sepsis and no CVE n=312	P value
Peripheral vascular disease	55 (8.3)	38 (10.9)	17 (5.5)	0.012
Chronic lung disease	137 (20.7)	60 (17.1)	77 (24.7)	0.017
Chronic kidney disease	133 (20.1)	83 (23.7)	50 (16.0)	0.014
Chronic liver disease	50 (7.6)	20 (5.7)	30 (9.6)	0.058
Cancer	83 (12.5)	38 (10.9)	45 (14.4)	0.167
Dementia	24 (3.6)	16 (4.6)	8 (2.6)	0.168
Charlson Comorbidity Index, median (IQR)	2 (1-4)	2 (1-4)	2 (1-4)	0.030
BMI, no. (%)				0.008
Underweight (<18.5kg/m ²)	94 (14.2)	35 (10.0)	59 (18.9)	
Normal (18.5–22.9kg/m ²)	305 (46.1)	174 (49.7)	131 (42.0)	
Overweight (23.0–27.4kg/m ²)	159 (24.0)	83 (23.7)	76 (24.4)	
Obese (≥ 27.5 kg/m ²)	104 (15.7)	58 (16.6)	46 (14.7)	
Premorbid ADL, no. (%), n=661				0.037
Independent	566 (85.6)	305 (87.1)	261 (83.9)	
Assisted	83 (12.6)	43 (12.3)	40 (12.9)	
Dependent	12 (1.8)	2 (0.6)	10 (3.2)	
Premorbid ambulatory status, no. (%), n=661				0.036
Independent	471 (71.3)	244 (69.6)	227 (73.0)	
Using walking aid/assisted	144 (21.8)	84 (24.0)	60 (19.3)	
Chairbound	37 (5.6)	21 (6.0)	16 (5.1)	
Bedbound	9 (1.4)	1 (0.3)	8 (2.6)	
APACHE II score, mean (SD)	29.4 (7.2)	30.2 (6.8)	28.5 (7.5)	0.003
SOFA score, mean (SD)	8.3 (3.6)	8.6 (3.5)	7.9 (3.6)	0.028
Laboratory investigation at point of ICU admission				
WBC >12x10 ⁹ /L or <4 x10 ⁹ /L, no. (%)	435 (65.7)	231 (66.0)	204 (65.4)	0.868
Thrombocytopenia (platelets <150 x10 ⁹ /L), no. (%)	157 (23.7)	80 (22.9)	77 (24.7)	0.582
Anaemia Hb <8g/dL, no. (%)	59 (8.9)	37 (10.6)	22 (7.1)	0.113
CRP (mg/L), median (IQR), n=637	102.7 (34.8–204.4)	101.4 (32.7–213.6)	103.2 (38.4–192.5)	0.856
CRP categorical, no. (%)				0.829
CRP <10mg/L	59 (9.3)	34 (9.9)	25 (8.5)	
CRP 10–100mg/L	254 (39.9)	136 (39.7)	118 (40.1)	
CRP>100mg/L	324 (50.9)	173 (50.4)	151 (51.4)	
Procalcitonin (ng/mL), median (IQR), n=642	2.6 (0.5–14.0)	3.8 (0.7–19.2)	1.5 (0.4–10.6)	<0.001
Procalcitonin \geq 0.5ng/mL, no. (%), n=642	483 (75.2)	275 (79.9)	208 (69.8)	0.003
Lactate (mmol/L), median (IQR), n=506	2.6 (1.5–5.3)	2.7 (1.6–5.5)	2.4 (1.4–4.9)	0.100
Lactate ≥2mmol/L, no. (%), n=506	310 (61.3)	181 (63.7)	129 (58.1)	0.197

Table 2. Characteristics of patients with sepsis, with or without cardiovascular events (Cont'd)

	All patients with sepsis n=662	Patients with sepsis and CVE n=350	Patients with sepsis and no CVE n=312	P value
Trop I (ng/mL), median (IQR), n=589	0.6 (0.2–2.6)	2.1 (0.6–5.5)	0.2 (0.1–0.5)	<0.001
BNP (pg/mL), median (IQR), n=312	761 (270–1896)	1206 (561–2683)	351 (168–900)	<0.001
Creatinine (µmol/L), median (IQR)	156 (94–308)	176 (106–359)	133 (84–262)	<0.001
Baseline medications, no. (%)				
Anti-platelet	218 (32.9)	147 (42.0)	71 (22.8)	<0.001
Anti-coagulation	30 (4.5)	13 (3.7)	17 (5.5)	0.284
Beta blocker	227 (34.3)	148 (42.3)	79 (25.3)	<0.001
Diuretic	142 (21.5)	88 (25.1)	54 (17.3)	0.014
Statin	330 (49.9)	197 (56.3)	133 (42.6)	<0.001
ACEi/ARB	224 (33.8)	136 (38.9)	88 (28.2)	<0.001
Anti-arrhythmic	21 (3.2)	12 (3.4)	9 (2.9)	0.690
Source of infection, no. (%)				
Community-acquired pneumonia	381 (57.6)	202 (57.7)	179 (57.4)	0.929
Hospital-acquired pneumonia	140 (21.2)	73 (20.9)	67 (21.5)	0.846
Ventilator-associated pneumonia	64 (9.7)	43 (12.3)	21 (6.7)	0.016
Urinary tract infection	50 (7.6)	31 (8.9)	19 (6.1)	0.179
Catheter-associated urinary tract infection	24 (3.6)	14 (4.0)	10 (3.2)	0.585
Intra-abdominal infection	74 (11.2)	34 (9.7)	40 (12.8)	0.205
Skin and soft tissue infection	18 (2.7)	11 (3.1)	7 (2.2)	0.478
Bone and joint infection	5 (0.8)	5 (1.4)	0	0.064
Infective endocarditis	3 (0.5)	3 (0.9)	0	0.251
Primary bacteraemia	4 (0.6)	1 (0.3)	3 (1.0)	0.348
Central nervous system infection	8 (1.2)	3 (0.9)	5 (1.6)	0.485
Line infection	36 (5.4)	21 (6.0)	15 (4.8)	0.499
Others	21 (3.2)	10 (2.9)	11 (3.5)	0.624
ICU treatment, no. (%)				
Ventilatory support				0.171
Mechanical ventilation (with/without NIV)	621 (93.8)	334 (95.4)	287 (92.0)	
NIV only	11 (1.7)	5 (1.4)	6 (1.9)	
No ventilatory support	30 (4.5)	11 (3.1)	19 (6.1)	
Vasopressor/Inotropic support	478 (72.2)	272 (77.7)	206 (66.0)	0.001
Renal replacement therapy	185 (28.0)	124 (35.4)	61 (19.6)	<0.001
Packed cell transfusion	231 (34.9)	142 (40.6)	89 (28.5)	0.001
Cardioversion	38 (5.7)	26 (7.4)	12 (3.9)	0.048

ACEi: angiotensin-converting enzyme inhibitor; ADL: activities of daily living; APACHE II: Acute Physiology and Chronic Health Evaluation II; ARB: angiotensin receptor blocker; BMI: body mass index; BNP: brain natriuretic peptide; CRP: C-reactive protein; CVE: cardiovascular event; Hb: haemoglobin; ICU: intensive care unit; IQR: interquartile range; NIV: non-invasive ventilation; SD: standard deviation; SOFA: Sequential Organ Failure Assessment; Trop I: troponin I; WBC: white blood cell

	Univariate regression		Multivariable regression (final model) ^a			
	RR	95% CI	P value	Adjusted RR	95% CI	P value
Age	1.012	1.007-1.018	< 0.001	1.013	1.007-1.019	<0.001
Ethnicity						
Chinese	Reference					
Malay	1.212	1.005-1.462	0.044	1.214	1.005-1.465	0.044
Indian	1.248	1.025-1.520	0.028	1.240	1.030-1.494	0.023
Others	0.905	0.616-1.330	0.612	1.029	0.692-1.531	0.886
Body mass index						
Normal (18.5-22.9kg/m ²)	Reference					
Underweight (<18.5kg/m ²)	0.653	0.493-0.864	0.003	0.688	0.529-0.895	0.005
Overweight (23.0–27.4kg/m ²)	0.915	0.766-1.093	0.328	0.867	0.729-1.031	0.106
Obese (≥27.5kg/m ²)	0.978	0.803-1.191	0.821	0.960	0.785-1.174	0.690
Charlson Comorbidity Index	1.035	1.004-1.068	0.027	-	-	-
Diabetes mellitus	1.328	1.150-1.534	< 0.001	1.155	0.988-1.352	0.071
Hypertension	1.243	1.054-1.465	0.010	0.900	0.746-1.087	0.274
Hyperlipidaemia	1.355	1.168-1.572	< 0.001	1.104	0.929-1.312	0.259
Ischaemic heart disease	1.479	1.290-1.696	< 0.001	1.317	1.137-1.527	<0.001
Heart failure	1.240	1.016-1.513	0.035	-	-	-
Peripheral vascular disease	1.344	1.108-1.630	0.003	-	-	-
Chronic lung disease	0.793	0.646-0.973	0.026	0.733	0.598-0.899	0.003
Chronic kidney disease	1.236	1.057-1.446	0.008	-	-	-

Table 3. Factors associated with cardiovascular events among sepsis patients: univariate and multivariable analysis

CI: confidence interval; RR: relative risk

a Further adjusted for sex

and hospital length of stay (median [IQR] 21 [10–42] vs 15 [7–30] days, P<0.001). There was no difference in ICU mortality (32.6% vs 34.6%, P=0.578) and inhospital mortality (46.4% vs 46.9%, P=0.792) between the 2 groups (Table 4).

Clinical characteristics of sepsis patients according to in-hospital mortality are represented in Supplementary Table S1. There was no difference in CVE occurrence among patients who died and those who survived (53.4% vs 52.4%, P=0.792). Multivariate analysis showed that age, pre-existing AF, thrombocytopenia (platelets <150x10⁹/L), hospital-acquired pneumonia, intraabdominal infection, and need for mechanical ventilation, vasopressor/inotropic support, cardioversion or renal replacement therapy were independently associated with a higher in-hospital mortality, whereas baseline use of statins was associated with a lower in-hospital mortality (Table 5). In terms of microbiological results, the majority were found to be culture negative (42.7%), followed by gramnegative bacteria (37.3%) and gram-positive bacteria (16.6%) (Supplementary Table S2).

DISCUSSION

In our study, we found a high burden of CVEs among critically ill patients with sepsis, more than 2-fold that of non-sepsis patients. The occurrence of CVEs significantly affects the patients' clinical course, with longer ICU and hospital length of stay, although there was no difference in in-hospital mortality. Importantly, CVEs were also common when the source of infection was not pneumonia. Many prior studies were focused on patients with CAP, reporting an increased risk of CVEs and short-term mortality. The incidence of CVEs ranged from 12–32%, and in-hospital mortality ranged from 21–43%.^{9-12,16-18} Variability in the reported numbers was

Table 4. Secondary outcomes

	All patients with sepsis n=662	Patients with sepsis and CVE n=350	Patients with sepsis and no CVE n=312	P value
ICU length of stay, median (IQR), days	5 (2–10)	6 (3–12)	4 (2–9)	<0.001
Hospital length of stay, median (IQR), days	18 (8–37)	21 (10-42)	15 (7–30)	<0.001
ICU mortality, no. (%)	222 (33.5)	114 (32.6)	108 (34.6)	0.578
In-hospital mortality, no. (%)	307 (46.4)	164 (46.9)	143 (45.8)	0.792

CVE: cardiovascular event; ICU: intensive care unit; IQR: interquartile range

Table 5. Factors associated with in-hospital mortality among sepsis patients: univariate and multivariable regression

	Univariate regression			Multivariable regression (final model) ^a			
	RR	95% CI	P value	Adjusted RR	95% CI	P value	
Age	1.016	1.010-1.023	< 0.001	1.013	1.007-1.020	<0.001	
Pre-existing atrial fibrillation	1.337	1.075-1.662	0.009	1.268	1.021-1.575	0.031	
Chronic lung disease	0.728	0.572-0.926	0.010	-	-	-	
APACHE II score	1.053	1.041-1.064	< 0.001	-	-	-	
SOFA score	1.110	1.088-1.133	< 0.001	-	-	-	
Ventilatory support							
No ventilatory support	Reference						
Mechanical ventilation (with/without NIV)	2.899	1.296-6.482	0.010	2.906	1.354-6.238	0.006	
NIV only	1.091	0.246-4.832	0.909	3.195	0.851-11.990	0.085	
Vasopressor/inotropic support	3.554	2.539-4.976	< 0.001	2.891	2.039-4.100	<0.001	
Packed cell transfusion	1.264	1.074-1.488	0.005	-	-	-	
Cardioversion	1.648	1.337-2.032	< 0.001	1.409	1.119-1.775	0.004	
Renal replacement therapy	1.340	1.138-1.579	< 0.001	1.212	1.035-1.418	0.017	
Thrombocytopenia (platelets <150 x10 ⁹ /L)	1.672	1.434-1.949	< 0.001	1.317	1.140-1.522	<0.001	
Anaemia (Hb <8g/dL)	1.315	1.046-1.654	0.019	-	-	-	
Baseline medication: use of statins	0.843	0.715-0.995	0.043	0.825	0.705-0.966	0.017	
Community-acquired pneumonia	0.714	0.607–0.840	< 0.001	-	-	-	
Hospital-acquired pneumonia	1.428	1.209-1.686	< 0.001	1.311	1.034-1.662	0.025	
Intra-abdominal infection	1.400	1.147-1.710	0.001	1.408	1.116-1.775	0.004	

APACHE II: Acute Physiology and Chronic Health Evaluation II; CI: confidence interval; Hb: haemoglobin; NIV: non-invasive ventilation; RR: relative risk; SOFA: Sequential Organ Failure Assessment

^a Further adjusted by sex and ethnicity. APACHE II and SOFA scores were not included as candidates in the multivariable analysis as they were correlated with other independent variables considered in the model

likely due to the heterogeneous population and study design, and the use of diverse methodologies to ascertain exposure (CAP) and outcome (CVE). For example, most studies investigated hospitalised patients, some studies were done in the outpatient setting, but very few looked at ICU population; some studies included only pneumococcal pneumonia; some studies defined MI as the only outcome while others included arrhythmia, heart failure and CVA.^{9-12,16-18}

Given the likely mechanism at play during systemic response to infection,^{9,10,16} we believed that development of various CVEs is inter-related and hence considered a

more integrative approach by evaluating cardiac complications as a combined clinical outcome rather than separate entities. We investigated the settings of sepsis as a whole and among ICU patients where there is paucity of data. These characteristics distinguished our analysis from previous publications.

The majority of CVEs occurred early during hospitalisation. This temporal pattern of cardiovascular risk being the highest immediately after the onset of respiratory infection was observed previously.^{10,19} In terms of the types of CVEs, we found that type 2 MI was the most common, followed by AF and heart failure. There were 20.4% of sepsis patients who had 2 or more types of CVEs, in keeping with the published literature on CAP where 20-40% of patients developed 2 or more cardiac complications.^{10,16} Our study specifically characterised acute coronary syndrome (or type 1 MI) and type 2 MI separately. Type 2 MI is common as sepsis increases tissue metabolic needs. At the same time, the tachycardia response in sepsis shortens diastolic filling time and compromises coronary perfusion. This is exacerbated further in patients with pre-existing coronary stenosis from chronic atherosclerotic plaques.^{16,19}

Several other mechanisms have been proposed to explain the pathogenesis of CVEs in sepsis (Supplementary Fig. S2).^{3,9,11,16,19-21} Sepsis triggers systemic inflammation and cytokine release, which causes micro- and macrocirculatory changes, as well as direct effects on cardiomyocytes. In the micro-circulation, there are endothelial dysfunction, glycocalyx damage, platelet activation and prothrombotic state-which increase the risk of atheroma instability and plaque rupture.^{16,20} When this occurs in the coronary circulation, it causes MI, while in the cerebral circulation it results in CVA. There are also changes in vascular tone with systemic vasodilatation and increase in capillary permeability, leading to septic shock and tissue hypoperfusion.9,16 Additionally, sepsis can cause myocardial dysfunction with reduction in stroke volume, further complicating shock.²¹ Cardiac arrhythmias, especially AF, can also worsen demand ischaemia, precipitate heart failure and contribute to cardioembolic stroke.8 Other factors that have been implicated in the development of CVEs include excessive neurohormonal activation; direct cytotoxic effect of microorganism; and modulating effect of treatments (e.g. water and sodium balance, and arrhythmogenic potential of certain medications).^{3,9,11,16,19-21}

In terms of factors associated with CVEs, increasing age, Malay and Indian ethnicities (as compared to Chinese) and comorbidity of ischaemic heart disease significantly increased the risk of a CVE occurrence. This is in concordance with multiple studies on CAP,

which described older age and pre-existing cardiovascular disease as major risk factors for cardiac events. Other risk factors included nursing home residence, chronic kidney disease and greater severity of pneumonia.9-12,17 Interestingly, our study found a lower risk of CVEs in patients with chronic lung disease. This is in contrast to a prior publication that reported chronic obstructive pulmonary disease (COPD) as an independent predictor for CVEs.²² In fact, the association between COPD and cardiovascular disease has been well established.²³ We postulate that the discordance seen was because our patients with underlying lung conditions included not only COPD, but asthma, bronchiectasis and other chronic lung diseases, who had chronic symptoms requiring long-term oxygen therapy or had chronic hypercapnia. These patients can rapidly decompensate and develop respiratory failure during an infective exacerbation, but with the appropriate treatment their conditions improved and did not spiral into septic shock and multiorgan failure. This was evidenced by a lower disease severity score and less requirements for organ support in this subgroup. Another possibility was the exclusion of patients with advanced, end-stage lung conditions deemed too sick to benefit from ICU admission, who instead had early endof-life discussion and management in the general ward.

The current study has important clinical implications. Firstly, it creates awareness of the high burden of CVEs among critically ill patients with sepsis, and its ramification on healthcare utilisation. Secondly, it emphasises timely recognition of CVEs, especially during an early phase of infection. A thorough investigation for the presence of CVEs should be included in the initial assessment of all sepsis patients admitted to ICU. Thirdly, it suggests that clinicians actively evaluate each patient for risk factors of CVEs. High-risk patients may benefit from closer monitoring and potentially preventive strategies. Those already on cardioprotective drugs should continue receiving them if no contraindications were present. Interestingly, in our patient cohort, we found that baseline use of statins was associated with decreased in-hospital mortality, but not CVEs, after adjusting for other potential confounders. We postulate that the baseline use of statins is a marker of pre-existing cardiovascular disease, which in itself is a major risk factor for CVEs. The protective effect of statins is likely attributed to their anti-inflammatory properties (which modulate the systemic inflammatory response in sepsis),²⁴ rather than their cardioprotective effects. Multiple observational studies have demonstrated that prior treatment with statins, antiplatelets and angiotensin-converting enzyme inhibitors were associated with reduced rates of severe sepsis and lower mortality in pneumonia.²⁴⁻²⁹ However, these findings were not replicated in randomised controlled trials, which were mostly single-centre, with small sample sizes.³⁰ A recent large randomised, doubleblind, placebo-controlled trial, involving over 16,000 patients, did not show the benefit of aspirin as a primary preventive strategy for sepsis.³¹ Further research is needed to inform interventions for preventing the development and progression of CVEs in high-risk patients with sepsis.

The strength of the current study is a real-world examination of the occurrence of multiple pre-defined CVEs in a fairly large sample size with no patient lost to follow-up. Nevertheless, our study had several limitations. It was a single-centre, retrospective study and may not be generalisable. Our patient cohort had a high prevalence of sepsis, which may be attributed to the liberal classification of sepsis used in the study. Patients with pre-existing poor organ function can easily decompensate in the presence of infection and fulfil the SOFA criteria and be classified as having sepsis. A common example was pneumonia and fluid overload, against the background of poor kidney and/or heart function. As they can be difficult to distinguish clinically and radiologically, there would be a tendency for ICU physicians to treat both conditions simultaneously, which may contribute to an overclassification of sepsis. We acknowledge that this is a reflection of real-life ICU patients who are inherently heterogeneous with multiple complex medical issues. However, despite this liberal classification, patients with sepsis demonstrated significantly higher inflammatory markers compared to those without sepsis.

CONCLUSION

CVEs complicate half of the critically ill patients with sepsis, with 79.4% of patients developing CVEs within the first week of hospitalisation, resulting in longer ICU and hospital length of stay. The number of critically ill patients is expected to rise with an ageing population and cause a further strain on healthcare resources. Awareness of the association between sepsis and CVEs presents a potential opportunity for earlier recognition of CVEs. Future research is needed to develop preventive strategies and effective therapeutics to improve the outcomes of these patients.

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Prevalence and correlates of psychological distress and coronavirus anxiety among hospital essential services workers in Singapore

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ABSTRACT

Introduction: The COVID-19 pandemic has affected almost all populations, with frontline workers experiencing a higher risk of mental health effects compared to other groups. Although there are several research studies focusing on the mental health effects of the pandemic on healthcare workers, there is little research about its impact on workers in outsourced hospital essential services. This study aims to examine the prevalence and correlates of psychological distress and coronavirus anxiety among staff working in 3 outsourced hospital essential services.

Methods: A cross-sectional study was conducted among outsourced hospital essential services workers in a tertiary hospital. Data on demographics, medical history, lifestyle factors, psychosocial factors and mental well-being were collected using self-administered questionnaires. Robust logistic regression was used to determine risk factors associated with psychological distress and dysfunctional anxiety related to COVID-19.

Results: A total of 246 hospital essential services workers participated in the study. The prevalence of psychological distress was 24.7%, and dysfunctional anxiety related to COVID-19 was 13.4%. Social support and workplace support were found to be independently associated with a lower risk of psychological distress, and social connectivity was associated with a lower risk of dysfunctional anxiety related to COVID-19.

Conclusion: These findings highlight the crucial roles of communities and workplaces in combating the mental health consequences of the pandemic. Public health programmes that aim to tackle the emerging mental health crisis in hospital essential services workers should incorporate strategies to address psychosocial factors, in addition to traditional self-care approaches.

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Keywords: Coronavirus anxiety, COVID-19, essential services workers, mental health, psychological distress, Singapore

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) has affected almost all geographies in the world since 2020. Many countries have imposed strict isolation measures to contain the spread of this disease. While the majority of the population has been working from home, essential workers continue manning the frontlines, facing risks such as infection and fatigue. Such work conferred a higher chance of mental stress than the rest of the population, leading to the increased likelihood of psychological distress among essential workers. In a recent systematic review,¹ stress, insomnia, depression and anxiety symptoms were increased among essential workers during the COVID-19 pandemic. In a study conducted in a tertiary hospital in Singapore, the prevalence of anxiety among non-medical healthcare workers was found to be higher than medical healthcare workers.² In spite of non-medical healthcare workers having a higher risk of poor mental health, little research has been done among this population, especially among workers in outsourced essential services sectors such as housekeeping, porter and maintenance services. These workers are subjected to employment and training policies different from those who are directly employed

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CLINICAL IMPACT

What is New

• To the best of our knowledge, this is one of the first few studies to investigate the mental well-being of hospital essential services workers (housekeepers, porters and maintenance staff) during the COVID-19 pandemic in Singapore.

Clinical Implications

• The findings of this study suggest that intervention strategies to improve the mental well-being of essential services workers should address psychosocial factors (social support, workplace support and social connectivity), in addition to traditional protective factors (exercise, sleep and diet).

by hospitals. In Singapore public hospitals, workers in these sectors are mostly migrant or older workers who are more vulnerable to the physical and mental health impact of COVID-19. Migrant workers are more prone to psychological stress due to lower socio-economic status, language barriers and cultural differences.³ In addition, migrant workers of Singapore who reside in purpose-built dormitories were not allowed to be in the community due to the movement restriction order imposed on them since April 2020. This restriction was only eased recently in 2022. Hence, these workers were more susceptible to the impact of COVID-19 pandemic due to prolonged confinement to their dormitories compared to the general Singapore population who were not imposed such strict level of restriction. Frontline older workers have a higher risk of anxiety and stress as they have increased risk of vulnerability to severe COVID-19 symptoms should they become infected. Hence, it is pertinent to assess the mental well-being of this understudied population during the pandemic. In this study, we examine the prevalence and risk factors of these essential workers' mental well-being, to help in effective public health intervention strategies.

METHODS

Study design and study population

This cross-sectional study was conducted among workers in 3 outsourced hospital essential services housekeeping, porter, and maintenance services—in a tertiary hospital from 15 September to 30 October 2020. A total of 246 essential services workers participated in the study and the overall response rate was 42.4% (30.3% for housekeeping service, 34.4% for maintenance service and 72.3% for porter service).

Survey instrument and data collection

Data were collected using self-administered questionnaires with the option of completing it online or on paper version. The questionnaire was available in 7 languages: English, Chinese, Malay, Hindi, Tamil, Bengali and Burmese. Participants could select the languages of questionnaires according to their personal preferences.

Mental well-being was assessed by the Kessler-6 Distress Scale (K-6) and Coronavirus Anxiety Scale (CAS). The K-6 was developed to detect general psychological distress, and has demonstrated good reliability and validity.⁴ There are 5 response options for each question, ranging from "none of the time" to "all of the time" and a score of 0 to 4 was assigned to each response, respectively. A total score was calculated by summing up the responses to each question. Psychological distress was defined as K-6 score of ≥ 5 .⁴

The CAS is a brief mental health screener developed to identify probable cases of dysfunctional anxiety associated with the COVID-19 crisis. It has been validated for use in clinical research and practice.⁵ There are 5 items asking participants how often they experienced the listed symptoms with the 5 response options ranging from "none of the time" to "nearly every day over the last 2 weeks". Responses for 5 questions were summed up to obtain the total score. A score of >9 was considered high anxiety.

Proximity to COVID-19 was assessed by the question "Have you experienced the following?" with "yes" and "no" options for 10 items. We categorised the proximity into 3 levels: Level 0 was no proximity; Level 1 was having friends, co-workers, co-habitants and family members being diagnosed with COVID-19 infection; and Level 2 was having been assigned to work in COVID-19 isolation facilities/wards or having been in any contact or close proximity with COVID-19 patients, having been quarantined or hospitalised, or being suspected or diagnosed of having COVID-19 infection.

We also measured psychosocial factors-perceived social support, workplace support, resilience, and social connectivity. Psychosocial factors are characteristics or facets that influence an individual psychologically and/or socially.⁶

Perceived social support was measured by the Multidimensional Scale of Perceived Social Support (MSPSS)⁷ and resilience was measured by the Brief Resilience Scale (BRS).⁸

Workplace support was assessed by asking the participants to rate the support they received from their peers/supervisors/employers and the logistical support they received from their organisation, with scores ranging from 0 to 9.

Social connectivity (talking to families or friends in person/online/on the phone), lifestyle factors (sufficient sleep, nutritious diet, exercise, smoking and alcohol intake), and spiritual activities (praying) were assessed by asking participants how often they did these activities in the past week, with 5 options ranging from "none of the time" to "all of the time" and scores assigned from 1 to 5, respectively. For smoking and alcohol intake, the responses were coded reversely. The lifestyle index was calculated by combing the scores from the 5 items, and a higher score indicated a healthier lifestyle. Monthly income comprised basic salary and overtime pay. In 2020, the median household income in Singapore was SGD9,189, median gross monthly income from work was SGD4,534 and the 20th percentile of gross monthly income was SGD2,300.9 Workers earning less than SGD1,400 per month are considered lower-wage workers.¹⁰ Perceived health status was assessed by asking participants to rate their health as poor, fair, good, very good or excellent.

Ethics approval was obtained from the SingHealth institutional review board (CIRB Ref: 2020/2757). Informed consent was obtained from each participant before the study was conducted.

Statistical analysis

In Table 1, means and standard deviations were presented for normally distributed variables, while medians and interquartile ranges were presented for skewed variables. Robust logistic regression was used to assess the association between risk factors and psychological distress/coronavirus anxiety. For multivariable analysis, we developed two-stage regression models. The first model included socio-demographic and lifestyle factors and the second model included the variables in model 1 plus psychosocial factors (social connectivity, social support, workplace support, and resilience) that were significant in the univariate analysis. There was no significant difference between participants using the online versus paper versions, thus we combined them for the analysis. All statistical tests were two-sided with a level of significance defined as a P value <0.05. All statistical analyses were performed using Stata 15 for Windows (Stata Corp, College Station, US).

RESULTS

Characteristics of the study population

A total of 246 outsourced essential services workers participated in this study. The majority of the participants were housekeeping staff (44.3%), with a total monthly income of <SGD1,400 (58.5%). The average age of study participants was 45.2 years. There was an approximately equal proportion of locals (Singapore citizens and permanent residents) (48.0 %) vs non-locals (50.8%), and males (52.4%) vs females (47.6%). Only 24.4% had Level 2 proximity to the COVID-19 infection. Most participants (92.3%) indicated that their health was good to excellent (Table 1).

Factors associated with psychological distress

The prevalence of psychological distress (K-6 score \geq 5) among this study population was 24.7%. Factors associated with a higher risk of psychological distress included higher proximity to COVID-19, younger age, being from a minority ethnic group, being single, having higher income, and completing the questionnaire in English. Factors associated with a lower risk of psychological distress included having a healthy lifestyle, higher resilience, and higher social and workplace support (Table 2 Univariate). Spearman correlation of the individual component of lifestyle index showed that sufficient sleep, eating nutritiously, and exercise were negatively correlated with psychological distress. No significant correlation was detected for smoking and alcohol intake (data not shown).

A healthy lifestyle was associated with a lower risk of psychological distress (odds ratio [OR] 0.75, 95% confidence interval [CI] 0.60–0.94) even after adjusting for proximity to COVID-19, age, ethnicity, marital status, health status and language. Language was also still significantly associated with psychological distress (OR 0.15, 95% CI 0.03–0.74) (Model 1, Table 2).

After including all significant factors in the univariate model, social support (OR 0.95, CI 0.91–0.99) and workplace support (OR 0.90, CI:0.82–0.99) emerged as independent factors associated with a lower risk of psychological distress (Model 2, Table 2).

Factors associated with the coronavirus anxiety

The prevalence of CAS was 13.4% among our study population. There was a higher prevalence of anxiety among participants with higher proximity to COVID-19, younger age, minority ethnic groups, non-locals, living in dormitories or private housing, and lower prevalence among participants with a healthy lifestyle, higher workplace support, and higher social connectivity

Characteristics	N=246
Age, (mean±SD), years	45.2±15.6
Sex, no. (%)	
Male	129 (52.4)
Female	117 (47.6)
Missing	0 (0)
Ethnicity, no. (%)	
Chinese	74 (30.3)
Malay	61 (25.0)
Indian	68 (27.6)
Others ^a	41 (16.7)
Missing	2 (0.8)
Marital status, no. (%)	
Never married	80 (32.5)
Currently married	140 (56.9)
Separated but not divorced/divorced/widowed	25 (10.2)
Missing	1 (0.4)
Resident status, no. (%)	
Locals ^b	118 (45.0)
Non-locals	125 (50.8)
Missing	3 (1.2)
Job category, no. (%)	
Housekeeping	109 (44.3)
Maintenance	31 (12.6)
Porter	94 (38.2)
Others ^c	11 (4.5)
Missing	1 (0.4)
Monthly income, no. (%)	
≤SGD1,400	144 (58.5)
SGD1,401–2,300	32 (13.0)
>SGD2,300	57 (23.2)
Missing	13 (5.3)
Year of experiences in current position (median, IQR)	2 (1.5)
Language, no. (%)	
English	144 (58.5)
Other languages	102 (41.5)
Missing	0 (0)
Have religion, no. (%)	202 (83.1)

Table 1. Characteristics of the study population

Table 1. Characteristics of the study population (Cont'd)

Characteristics	N=246
Accommodation now, no. (%)	
Dormitory	11 (4.5)
Public housing	133 (54.1)
Private housing	59 (24.0)
Hotel	12 (4.9)
Missing	31 (12.6)
Perceived health status, no. (%)	
Poor/Fair	18 (7.3)
Good/very good/excellent	227 (92.3)
Missing	1 (0.4)
Have chronic disease, no. (%)	36 (14.7)
Proximity to the COVID-19 infection, no. (%)	
Level 0	166 (67.5)
Level 1	14 (5.7)
Level 2	60 (24.4)
Missing	6 (2.4)

IQR: interquartile range; SD: standard deviation

^a Bengali, Myanmar, Vietnamese, others

^b Singapore citizens and permanent residents

^cExecutives, supervisors

(Table 3 univariate data). Spearman correlation of the individual component of lifestyle index showed that sufficient sleep and eating nutritiously were negatively correlated with CAS. No significant correlation was detected for exercise, smoking and alcohol intake (data not shown).

The association between lifestyle index and CAS was not significant after adjusting for socio-demographic factors, although the odds ratio did not change much (OR 0.88, 95% CI 0.74–1.04) (Model 1, Table 3).

Social connectivity was significantly associated with CAS even after adjusting for social demographic, lifestyle factors and workplace support (OR 0.39, 95% CI 0.19–0.77) (Model 2, Table 3).

DISCUSSION

In this study, we found that higher social support and workplace support were associated with a lower risk of psychological distress, while higher social connectivity was associated with a lower level of coronavirus anxiety.

The prevalence of psychological distress and coronavirus anxiety in this study population was lower than that of healthcare trainees in China and nurses in the Philippines.^{11,12} The prevalence of psychological

	Univariate			Multiva	riate (Mod	el 1)	Multiva	riate (Mo	odel 2)
Factors	Odds ratio	95%	6 CI	Odds ratio	95%	6 CI	Odds ratio	95	% CI
Proximity to the COVID-19 infection									
Level 0	Reference			Reference			Referen	ce	
Level 1	3.95*	1.23	12.69	2.18	0.39	12.10	3.62	0.32	40.78
Level 2	3.02**	1.52	6.01	1.85	0.47	7.32	1.80	0.43	7.59
Age	0.96***	0.94	0.98	0.96	0.90	1.01	0.97	0.91	1.03
Ethnicity									
Chinese	Reference			Reference			Referen	ce	
Malay	1.90	0.78	4.64	2.02	0.42	9.74	3.21	0.57	18.03
Indian	1.43	0.57	3.59	0.28	0.06	1.28	0.60	0.09	3.90
Others ^a	5.70***	2.20	14.78	1.18	0.24	5.85	1.39	0.22	8.88
Marital status									
Never married	Reference			Reference			Referen	ce	
Currently married	0.27***	0.14	0.53	0.53	0.14	1.91	0.47	0.10	2.13
Separated/Divorced/Widowed	0.30*	0.09	0.97	2.16	0.22	21.30	6.70	0.32	139.46
Monthly income									
≤SGD1,400	Reference			Reference			Referen	ce	
SGD1,401–2,300	2.06	0.83	5.12	1.71	0.30	9.82	3.41	0.64	18.13
>SGD2,300	3.26**	1.59	6.71	0.86	0.18	3.97	1.57	0.32	7.76
Language									
English	Reference			Reference			Referen	ce	
Other languages	0.18***	0.08	0.40	0.15*	0.03	0.74	0.12	0.01	1.01
Perceived health status									
Fair–poor	Reference			Reference			Referen	ce	
Good-excellent	0.39	0.14	1.10	0.19	0.02	1.61	0.61	0.04	10.13
Lifestyle index	0.76***	0.66	0.87	0.75*	0.60	0.94	0.84	0.65	1.09
Social connectivity	0.73	0.53	1.02				0.81	0.41	1.58
Resilience	0.82**	0.72	0.94				0.91	0.78	1.06
Social support	0.98*	0.96	1.00				0.95*	0.91	0.99
Workplace support	0.95**	0.91	0.98				0.90*	0.82	0.99

Table 2. Factors associated with psychological distress

CI: confidence interval

^a Bengali, Myanmar, Vietnamese, others

* *P* value <0.05, ** *P* value <0.01, *** *P* value <0.001

Values in bold are significant

distress was 30.9% of moderate to severe distress (K6 score \geq 5) among healthcare trainees in China,¹² and the prevalence of coronavirus anxiety among Filipino nurses was 37.8%.¹¹ The lower prevalence in our study population may be due to the timing of the study, which was conducted at a time when daily cases

were declining. In longitudinal studies conducted in China and the US, the prevalence of poor mental health was decreased in the follow-up studies.^{13,14} It is also important to highlight that half of our study population were migrants, who tend to have a high level of resilience.¹⁵ Although we did not find significant

Table 3. Factors associated with coronavirus anxiety									
	n	Inivariate		Multiva	riate (Model 1)		Multiva	riate (Model 3	(1)
Factors	Odds ratio	95%	CI	Odds ratio	95%	CI	Odds ratio	95%	10
Proximity to the COVID-19 infection									
Level 0	Reference			Reference			Referenc	e	
Level 1	2.03	0.40	10.32	1.03	0.05	20.54	0.81	0.02	30.01
Level 2	2.67	1.16	6.18	1.45	0.40	5.24	1.63	0.42	6.36
Age	*96.0	0.93	66.0	0.97	0.92	1.03	0.97	0.91	1.05
Ethnicity									
Chinese	Reference			Reference			Referenc	е	
Malay	0.69	0.21	2.23	0.97	0.14	6.68	1.01	0.13	7.81
Indian	0.81	0.26	2.49	0.41	0.09	1.76	0.55	0.12	2.54
Others ^a	2.97*	1.04	8.46	1.26	0.22	7.20	1.77	0.23	13.54
Resident status									
Locals ^b	Reference			Reference			Referenc	e	
Non-locals	3.74**	1.52	9.21	0.75	0.10	5.69	0.79	0.09	7.27
Accommodation now									
Dormitory	Reference			Reference			Referenc	e	
Public housing	0.20*	0.04	0.88	0.52	0.05	5.77	0.33	0.02	6.52
Private housing	0.76	0.17	3.33	1.03	0.16	6.75	1.05	0.12	9.15
Hotel	2.22	0.37	13.18	3.69	0.36	37.91	3.24	0.25	42.83
Lifestyle index	0.85*	0.74	0.97	0.88	0.74	1.04	1.11	0.86	1.44
Social connectivity	0.60**	0.43	0.84				0.39**	0.19	0.77
Workplace support	0.95*	0.91	66.0				0.97	06.0	1.05
C1: confidence interval ^a Bengali, Myanmar, Vietnamese, others ^b Singapore citizens and permanent residents [*] <i>P</i> value <0.05, *** <i>P</i> value <0.01 Values in bold are significant									

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association between resilience and psychological distress after adjusting for other psychosocial factors, it may be that our questionnaire was not able to fully capture all aspects of resilience, which is a multidimensional construct.¹⁶ Participants who used the English language version of the questionnaire were also found to be marginally associated with higher psychological distress than those who used other languages of the same questionnaire. This observation could be attributed to participants who chose the English language version of the questionnaire had better English language proficiency than others, and English language proficiency had been reported as a proxy for education level.^{17,18} Studies have reported that higher level of education is associated with a higher level of stress.^{19,20} Among our study participants, those who used the English language version of the questionnaire may be individuals who need to work in the middle layer between workers on the ground and upper level of management, or may have to bear higher responsibilities than those with lower level of English language proficiency. As such, participants with better English proficiency may experience more stress than others, especially during this pandemic when rapid changes in procedures and policies have to be communicated effectively to all stakeholders involved and implemented promptly.

A healthy lifestyle (exercise, eating nutritiously and sufficient sleep) was also associated with lower psychological distress after adjusting for sociodemographic factors. The benefits of exercise, balanced nutrition, and good sleep for mental well-being have been well-established.²¹⁻²³ Studies conducted during the COVID-19 pandemic also consistently reported beneficial effects of exercise, diet and sleep on mental well-being.^{21,22} However, previous studies did not account for psychosocial factors such as social and workplace support and social connectivity. In this study, the association between lifestyle factors and psychological distress was no longer significant after adjusting for psychosocial factors. Social support and workplace support were associated with a lower risk of psychological distress and social connectivity was associated with a lower risk of anxiety, independent of socio-demographic and lifestyle factors. Our findings were consistent with the findings in other populations.^{11,24} In a study done in an acute hospital in Canada, low support from supervisors and colleagues was found to be associated with a higher risk of psychological distress.²⁴ In another study, personal resilience, social support, and organisational support were found to reduce anxiety.¹¹ Studies also showed that social connectivity independently predicted psychological distress, depression, and anxiety symptom severity.^{25,26}

The findings from these studies and our study highlighted the important role of social support and social connectivity in mental well-being. Perceived support and social connectivity were the most significant predictors, rather than traditional protective factors such as exercise, sleep and diet. This may be due to the unique nature of this pandemic, which required strict isolation measures to combat. Limited knowledge about this novel virus may also lead to elevated fear and uncertainty in the population. Moreover, the workforce was facing rapid changes in policy and procedures daily, causing enormous job stress. Social support attenuates fear and uncertainty, and reduces the effect of physiological and psychological threats.^{27,28} Thus, when faced with fear and uncertainties, there is more need for social support and social connectivity.^{29,30} In a randomised clinical trial, it was reported that 10-minute telephone calls delivered by a trained layperson reduced loneliness, anxiety and depression among adults during the COVID-19 pandemic.³¹ Social connectivity may also improve physical health. In an experimental study, it was found that social connectivity positively predicted a change in vagal tone.³² Hence, an intervention to improve social connectivity should be considered where social isolation is imposed to control the spread of infection. In Singapore, there are some programmes to improve social connectivity in a particular population and these programmes could be adopted for other vulnerable populations. When there was a lockdown in foreign workers dormitories in Singapore, free Wi-Fi services were provided to foreign workers allowing them to stay in touch with their families in overseas.³³ Similar service could be extended to low-income communities to stay connected with their loved ones during lockdown. Another programme is a befriending service provided by a social service agency for seniors who are at risk of social isolation.³⁴ Trained befrienders provide social and psycho-emotional support through weekly home visit to seniors. During pandemic, the agency utilises technology to keep engaging seniors through digital clinics. This service could also be offered to other populations socially disconnected due to social isolation measures during the pandemic, to reduce depression and anxiety.

Despite having high hopes of returning to normal life with the availability of vaccines, we may not be able to rule out the possibility of another lockdown in the near future, due to the occurrence of new virus variants. Even if we overcome this COVID-19 pandemic, infectious diseases experts warn that the current pandemic is unlikely to be the last. Thus, public health intervention strategies should integrate activities to improve the psychoneuroimmunity of the population. At the microlevel, healthy lifestyles and social connectivity should be encouraged and promoted. At the meso level, social support and workplace support should be increased among communities and workplaces. At the macro level, advocacy for guidelines and policies to effectively combat the emerging mental health crisis are pertinent. Employers play an important role in addressing these factors. Employers could support health promotion programmes at workplaces to encourage their employees to adopt and maintain healthy lifestyles, since those with higher organisational support tend to participate in health promotion programmes.³⁵ Workplace support should not only cover basic needs such as food on-site, groceries and childcare support; it should also create a culture that encourages open communication, and a safe and supportive working environment to improve mental well-being of employees.36,37

Our study has some limitations. As this is a cross-sectional study, we cannot establish a causal relationship. Our study only included outsourced hospital essential services workers in 3 sectors as there were operational challenges of recruiting other outsourced hospital workers in other departments (e.g. security, temperature screeners, etc.) for this study. The small sample size and low response rate may limit the generalisability of the results. Nevertheless, we managed to obtain a high response rate among porters (72.3%) and thus the findings in the group may be generalisable. In addition, we used a mixed mode of survey administration (online and paper version) that is found to produce more representative results as different modes appeal to different populations.³⁸ Moreover, this is one of the first few studies conducted among outsourced essential services workers. Our study included both local and foreign workers in Singapore, and we were able to assess comprehensive risk factors, allowing us to identify independent factors at the micro and meso levels.

CONCLUSION

Psychosocial factors should be included in public health strategies to improve the mental well-being of the vulnerable population of essential services workers. More research is needed to understand the impact of this pandemic on such workers.

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Consensus statement on Singapore integrated 24-hour activity guide for children and adolescents

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ABSTRACT

Introduction: Lifestyle activities, such as regular physical activity, are important for good metabolic health and the prevention of non-communicable diseases. Epidemiological studies highlight an increase in the proportion of overweight children in Singapore. A workgroup was formed to develop recommendations to encourage children and adolescents (aged 7–17 years) to adopt a holistic approach towards integrating beneficial activities within a daily 24-hour period for good metabolic and general health.

Methods: The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision framework was employed to formulate the public health question, assess the evidence and draw conclusions for the guide. The evidence for international 24-hour movement guidelines, and guidelines for physical activity, sedentary behaviour, and sleep and eating habits were reviewed. An update of the literature review from August 2018 to end of September 2020 was conducted through an electronic search of Medline and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases.

Results: Ten consensus statements were developed. The statements focused on the overall aim of achieving good metabolic health through integration of these activities and initiatives: light and moderate- to vigorous-intensity physical activity on a regular basis; muscle- and bone-strengthening activities; limiting sedentary behaviour; regular and adequate sleep; good eating habits and choosing nutritionally balanced foods and drinks; practise safety in exercise; and aiming to achieve more or all aforementioned recommendations for the best results.

Conclusion: This set of recommendations provides guidance to encourage Singapore children and adolescents to adopt health-beneficial activities within a 24-hour period.

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Keywords: Eating habits, metabolic health, physical activity, sedentary behaviour, sleep

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CLINICAL IMPACT

What is New

• This article reviews the relationship between lifestyle activities and health outcomes among children and adolescents in Singapore.

• Appropriate eating habits could optimise metabolic health and prevent the onset of non-communicable diseases.

Clinical Implications

• This article provides an updated review of evidence supporting the benefits of regular physical activity, low sedentary behaviour, adequate sleep and good eating habits for healthy children and adolescents in Singapore.

INTRODUCTION

The World Health Organization's Global action plan for the prevention and control of noncommunicable diseases 2013–2020 provided guiding principles for national efforts in controlling and reducing non-communicable diseases (NCDs).¹The major NCDs include cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes-they form a major public health challenge, and are a heavy burden on the health and social systems.² The metabolic risk factors for NCDs are hypertension, overweight or obesity, hyperglycaemia and hyperlipidaemia, and these risk factors are often manifestations of unhealthy but modifiable lifestyle behaviours that include physical inactivity and unhealthy diet.¹ Therefore, the prevention of these metabolic risk factors through community-based interventions to support behavioural changes have been highlighted as important and cost-effective strategies to reduce NCDs.3

Many national guidelines for promoting healthy lifestyle behaviours focus on specific behaviours such as physical activity⁴ or healthy eating habits.⁵ With increasing recognition of the detrimental health effects of sedentary behaviour, recommendations on sedentary behaviour have been included in some physical activity guidelines.^{6,7} However, there is emerging evidence that further points to strong relationships among these lifestyle behaviours and their health effects. Specifically, various combinations of physical activity, sedentary behaviour and/or sleep can achieve similar health benefits.^{8,9} This novel evidence-based approach of assimilating multiple lifestyle behaviours, framed within a 24-hour period into a singular guide, has provided a fresh and practical perspective on health promotion.^{10,11} To the best of our knowledge, this paper describes the first Singapore consensus statement on health promotion recommendations for children and adolescents using this integrated approach, and is the only integrated guide to date that includes eating habits.

Promoting healthy lifestyle behaviours

For children and adolescents, physical activity is encouraged for leisure (e.g. play, sports or planned exercise), as part of physical education, or for transportation (e.g. walking, running and cycling) in the context of home, school or community setting.¹² Children and adolescents should have access to safe and equitable opportunities to participate in varied physical activities that are enjoyable, as well as age- and ability-appropriate, either individually or in groups.¹³

Periods of sedentary behaviour and recreational screen time should be kept to a minimum.¹⁴ Management of these periods can be improved by setting boundaries (e.g. duration) or interrupted with regular breaks for physical activity.¹⁵ Establishing a consistent bedtime routine is important to help children and adolescents achieve regular and adequate sleep time.¹⁶ Adoption of healthy eating habits and choosing nutritious foods and drinks in appropriate portions will not only supply adequate energy for daily activities, but also support optimal growth and development.¹⁷

Studies on Singapore children and adolescents

Statistics from the Ministry of Education, Singapore revealed that the proportion of overweight children increased from 11% in 2013 to 13% in 2017.18 Research on children and adolescents in Singapore has shown that they could only meet up to 40% of the recommended level of physical activity, and more than 70% of adolescents exceeded >2 hours of electronic screen time daily.^{19,20} However, a study by Lye et al. involving 233 adolescents showed that none of the participants achieved the recommended 60 minutes of moderateto vigorous-intensity physical activity, and that they engaged in significantly more time in sedentary activity.²¹ Furthermore, screen time has increased due to the COVID-19 pandemic and introduction of home-based learning.²² A 2020 survey of 100 children aged 5–14 years also revealed that 32% did not participate in moderateintensity physical activity. In fact, on weekdays, 23% had prolonged sedentary behaviour of >10 hours/day, and 18% had insufficient sleep of <8 hours/day.²³ These developments have prompted healthcare professionals to provide guidance using an integrated approach for children and adolescents in Singapore towards better health.

Aim of consensus statement

Our objective is to provide guidance to encourage children and adolescents in Singapore to adopt a holistic approach towards integrating all types of activity within a daily 24-hour period. These activities (including light, moderate and vigorous physical activity, sedentary behaviour and sleep) are closely inter-related in terms of health benefits and time consumption. The inclusion of eating habits in our recommendations also completes our discussion towards an optimal metabolic cycle. It is equally vital to understand the importance of each type of activity and to organise these activities throughout a day and night schedule for the best health outcomes.

These recommendations to follow are for all healthy children and adolescents (aged 7–17 years)—irrespective of sex, cultural background or socio-economic status. Children and adolescents with special needs or medical conditions should consult a qualified medical professional for additional guidance.

METHODS

The consensus workgroup consisted of physicians (paediatricians, sports physicians and family physicians), allied health professionals (exercise physiologist and dietitian), academics and researchers from multiple institutions.

The workgroup assessed and included evidence reviews from both the Canadian 24-hour movement guidelines for children and youth, and the Australian 24-hour movement guidelines for children and young people, which were published in Medline, Embase, PsycInfo and SPORTDiscus from inception through to July 2018.^{8,24-27} An update of the literature review from August 2018 to end of September 2020 was conducted through an electronic search of Medline and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases, using the following keywords: "physical activity", "sedentary behaviour", "sleep", "eating habit", "paediatric", "child" and "adolescent". Only results in English language were considered. Studies identified included systematic reviews, randomised control trials and cohort studies. Health outcomes included cardiometabolic risk factors, physical fitness, bone health, adiposity, emotional or psychological well-being, behavioural or cognition development, quality of life, and safety or injury.

The workgroup used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) framework to evaluate the quality of the evidence and strength of recommendation, and to provide a structured and clear methodology for healthcare recommendations.^{28,29} The full EtD framework is available in the online supplementary material of this article. The online annexes include the presentation of all consensus statements, a practical reference for promotion of physical activity and a summary version of this activity guide. These recommendations are intended for healthcare professionals who provide holistic care for children and adolescents, including educating, encouraging and promoting beneficial activities for practice through to adulthood for a lifetime of good health.

Limitations

The workgroup utilised the online interactive EtD (iEtD) tool²⁹ for the EtD framework, and the information presented is limited by the online tool.

RESULTS

Consensus statements

1. For physical, mental and social health, children and adolescents should acquire a lifestyle that integrates regular physical activity, limited sedentary behaviour, adequate sleep, and good eating habits within each 24hour period.

Physical activity is essential for healthy growth and development in children and adolescents.24 Research shows that regular physical activity improves aerobic fitness, body composition, metabolic risks, musculoskeletal health, mental health and academic results in children and adolescents.^{6,24,30} Emergent evidence shows that prolonged sedentary behaviour, particularly unregulated and unrestrained screen time, is associated with a range of adverse health outcomes including obesity.^{31,32} Sleep duration and quality significantly impact child and adolescent health, as shorter sleep duration is associated with childhood obesity.^{26,33} Good eating habits, together with consumption of nutritious foods and drinks, balance the metabolic cycle by supplying energy for daily activities, growth and development.¹⁷ The challenge is to incorporate adequate physical activity, low sedentary behaviours, and adequate sleep duration for the best health outcomes in children and adolescents.³⁴

2. Accumulate at least an average of 60 minutes/day of moderate- to vigorous-intensity physical activity in a week, where more is better.

The premise of a healthy lifestyle includes regular physical activity participation. In children and adolescents, regular physical activity or physical sport participation is associated with lifelong health benefits.^{7,24,35,36} Activities of all types and performed across all intensity levels should be encouraged to promote habitual physical activity or active play, physical sports engagement, and development of health-related and skill-related fitness.^{7,35,37,38}

To achieve substantive health benefits, children and adolescents should aim to accumulate an average of \geq 60 minutes of physical activity (including active or outdoor play, games, sports, physical education, and planned exercise or transportation) per day in a week, and most of these activities should be of at least moderate intensity.^{6,7,24,36} For greater health gains, vigorous intensity activities should in incorporated where possible.^{6,7,24}

3. Engage in muscle- and bone-strengthening exercises at least 3 times a week. This could be part of the daily minimum accumulation of 60 minutes of moderate- to vigorous-intensity physical activity.

Muscle- and bone-strengthening exercises should be incorporated into a child's physical activity regime.^{6,7,36,39} These exercises range from weight-bearing activities, resistance exercise using body or light weights, or light-impact exercises such as skipping, hopping or jumping.^{39,40} The inclusion of these activities promotes strength gains, and development of strong joints and healthy bones, both of which are vital for optimal growth and development.^{39,41} Building an early foundation of good joint and bone health during childhood helps to prevent injuries, improve exercise performance, and prevent the development of bone-related health issues in the future.^{40,41}

4. Engage regularly in a variety of light physical activities throughout the day.

Light physical activities can range from static (e.g. standing) to dynamic (e.g. slow walking).⁴² Every choice counts, given that even light-intensity physical activity has health benefits; choosing the more active option, even if it is for light-intensity physical activity, is beneficial.⁴³ Some examples include standing and moving about rather than sitting down, taking a walk rather than driving, and taking the stairs instead of the lift or escalator. Children should be encouraged to participate in active play, especially outdoor play, rather than playing with screen devices.⁴⁴ Setting a target to achieve an accumulated 12,000 steps/day also helps children and adolescents meet the daily physical activity recommendation.^{37,38,45}

5. Limit recreational screen time as much as possible.

Recreational screen time activities include watching the television; using the computer, tablet or phone; and engaging in video games that are physically non-active or inactive in nature.^{46,47} Among all the sedentary activities, recreational screen time >2 hours daily is associated with the most adverse health outcomes in children and adolescents.^{32,47} The benefits of limiting this screenbased sedentary behaviour include reduced adiposity, improved motor and cognitive development, and better psychosocial health.^{32,48} Providers should address this behaviour by assessing the duration and use of recreational screen time, and suggesting parenting strategies to limit screen time as much as possible.^{32,46,48,49}

6. Build in regular breaks to move around during times of prolonged sitting or inactivity.

There are inevitable situations when children are required to remain seated for prolonged periods, such as during lessons in the classroom or a long-distance trip. Prolonged sedentary behaviour is damaging to health, but when this is unavoidable, include regular breaks to encourage frequent movement and physical activity. While this contributes to a child's overall physical activity levels,⁵⁰ it is also beneficial for their mental and social health.³⁰ These activity breaks also help children to better concentrate in school.⁵¹ A few minutes of "movement break" (i.e. intervals for movement and physical activity) for every 30–60 minutes of sedentary time, together with play during break times, should help limit the impact of prolonged physical inactivity.⁵²

7. Have regular sleep of at least 9 hours (for 7–13year-olds) and at least 8 hours (for 14–17-year-olds).

Sleep is a critical component of mental and physical health that is often sacrificed to make time for daytime activities. Achieving the number of recommended hours of sleep regularly is associated with better health outcomes in terms of attention, memory, learning, behaviour, emotional regulation, quality of life, and mental and physical health.⁵³ Insufficient sleep increases the risk of accidents and injuries, especially during physical activity, and in the long term, is associated with obesity, hypertension, diabetes and depression.⁵³⁻⁵⁵ Children (7–13 years) should regularly sleep 9–12 hours per 24 hours, and teenagers (14–17 years) 8–10 hours.^{53,56}

8. Take the necessary precautions before, during and after exercise and see a doctor if you feel unwell during the exercise.

The benefits of physical activity outweigh its risks. Safety is key in minimising injuries during physical activities or in organised sports. This will ensure the child's well-being and continued participation in exercise and sports in the long term.⁵⁷ Good practices

include the use of appropriate equipment and footwear, exercising in conditions that are free of hazards (such as broken equipment and uneven surfaces), and avoid exercising in extremely hot and humid conditions.⁵⁸ We encourage children to regularly perform warm-ups before exercise and cool-down stretching post activity,⁵⁸ hydrate adequately, and apply protection against the sun and insects before and during exercise.⁵⁹

For all participants in organised sports, it is important to understand and follow the rules of the specific sport, as well as having adequate practice of the skills needed for the relevant activities.⁵⁸ It is also beneficial to have the proper conditioning for fitness, strength and flexibility appropriate to the sports activities undertaken.^{58,60} Children should engage in a variety of activities throughout the year, and avoid specialising in a single sport at a young age.^{60,61}

If the child is unwell, he/she should avoid strenuous activities.⁵⁹ If the child experiences chest pain, breathlessness, palpitations or dizziness, he/she should stop the activity and seek medical attention if these symptoms are persistent.⁶² Children with pre-existing medical condition(s) should discuss with their doctors for the necessary precautions and/or restrictions before engaging in strenuous exercises.⁵⁹

9. Have regular meals consisting of nutritionally balanced foods and drinks to support daily activities, in order to optimise growth, maturation and development.

The social and ecological environment can strongly influence the dietary choices of the individual and their families.⁶³ Through parental modelling, a regular household eating routine provides opportunities for coordinated family meals and regulation of appetite, therefore affecting the overall diet quality of children and adolescents.^{63,64} Consuming a nutritious breakfast as part of a daily routine has also been associated with positive outcomes, including better diet quality and healthy body weight, and is strongly encouraged.⁶⁴

Part of achieving a healthy eating pattern requires a conscious selection of food and drinks in ageappropriate portions that support a child's activity levels and growth. Suitable portions can be planned using visual aids, such as My Healthy Plate, a visual guide designed by the Singapore Health Promotion Board. A variety of foods across and within all food groups are required to meet nutrient requirements.^{22,64} Nutritionally balanced foods and drinks include all vegetables, fruits, whole grains, lean meats and poultry, seafood, legumes, unsalted nuts, low-fat dairy products; foods free of saturated and trans fats; and foods prepared with limited solid fats (e.g. butter), sugars and refined starches.⁶⁵ Limiting consumption of added sugars; sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates; and sugar-sweetened beverages to not more than 10% of total energy intake can curb the risk of increased adiposity and being overweight in children, as well as the formation of dental caries.⁶⁶

10. Aim to achieve most or all recommendations on physical activity, sedentary behaviour, sleep and diet for the best results.

These recommendations on physical activity, sedentary and sleep behaviours are of comparable importance, and meeting more of these recommendations will correspondingly improve the health indicators for physical, mental and social health.^{9,67} Therefore, children and adolescents who can meet all recommendations (i.e. high moderate- to vigorous-intensity physical activity, low sedentary behaviour, adequate sleep, and age- and intensity-appropriate diet) are shown to have the best health outcomes.^{8,68,69}

Similar health outcomes can be achieved by meeting the same number of recommendations in various combinations.⁶⁷ This means that comparable health indicators can be achieved through high moderate- to vigorous-intensity physical activity and low sedentary behaviour; adequate sleep and low sedentary behaviour; or high moderate- to vigorous-intensity physical activity and adequate sleep.^{8,67,70} In conclusion, children and adolescents can start with any of these recommendations, with the eventual aim of meeting all recommendations for the best health outcomes.

About the workgroup

This document was developed by the Singapore Integrated 24-Hour Activity Guide for Children and Adolescents Study Workgroup, which comprised key members from the Singapore community, including members from the College of Paediatrics and Child Health of the Academy of Medicine, Singapore; Singapore Integrated Platform for Research in Advancing Metabolic Health Outcomes in Women and Children (IPRAMHO), led by KK Women's and Children's Hospital (KKH), in partnership with SingHealth Polyclinics (SHP) and the National Healthcare Group Polyclinics (NHGP), Perinatal Society of Singapore, and Exercise is Medicine Singapore. The initiative is supported by the research group of IPRAMHO, a National Medical Research Councilfunded joint collaborative pot centre grant of KKH, SHP and NHGP. This multidisciplinary group is initiated by Assoc Prof Ng Kee Chong and Prof Tan Kok Hian, and chaired by Dr Benny Loo Kai Guo.

Disclaimer

This guide endorsed by the College of Paediatrics and Child Health of the Academy of Medicine, Singapore, and supported by the Health Promotion Board, Singapore. Partners of the guide include Exercise is Medicine Singapore, Sports Medicine Association Singapore, Perinatal Society of Singapore, Singapore Paediatric Society, College of Family Physicians Singapore, and Singapore Medical Association. The guide acts as an educational aid and reference for healthcare professionals practising in Singapore. The guide does not define a standard of care, nor is it intended to dictate an exclusive course of management. It presents recognised clinical methods and techniques for consideration by practitioners for incorporation into their practice. It is acknowledged that management may vary and must always be responsive to the need of individual patients, resources, and limitations unique to the institution or type of practice.

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Online annexes

1. Consensus Statement on Singapore Integrated 24-Hour Activity Guide for Children and Adolescents: Consensus Statements

2. Practical Reference for Physical Activities for Children and Adolescents

3. Consensus Statement on Singapore Integrated 24-Hour Activity Guide for Children and Adolescents: Summary Guide

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The Lancet Commission on diagnostics: What it means for Singapore

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Effective healthcare systems depend on a functioning healthcare value chain-defined as a care cascade comprising screening, diagnosis, treatment and followup. The tremendous heterogeneity and global disparity regarding this healthcare value chain has been one of the fundamental problems with prioritised urgency since the United Nation's Millennium Development Goals were established in 2000 and subsequently revised as the Sustainable Development Goals (SDGs) in 2015.^{1,2} Over the past decade, global health initiatives have developed a disease-centric focus and targeted downstream areas within the care cascade. Numerous commission reports have improved our understanding of the challenges within communicable diseases, child mortality, maternal health and global surgical areas.^{3,4} The reports have garnered financial backing and support from non-profit organisations, risen among government priorities and translated into international healthcare collaborations with improved health outcomes.^{5,6} While this is commendable and encouraging, there is an increasing need to address problems occurring upstream of the healthcare value chain, namely, screening and diagnostics.

Achieving SDG targets and universal health is crucially dependent on strengthening upstream screening and diagnostic areas, primarily along 2 fronts—pathology and laboratory medicine (PALM) and diagnostic imaging (DI). They remain a formidable challenge. For example, a three-part series on PALM in low-income and middle-income countries (LMICs) has highlighted how this crucial area has been largely neglected and severely inadequate.⁷⁻⁹ Access to reliable and prompt PALM services is key for therapy. In a similar vein, a crucial recurrent theme underpinning commission reports, such as the global surgery and oncology commissions, is the limited availability of DI resources in LMICs. The limitation precludes accurate and timely diagnosis of disease conditions, thereby curtailing surgical and oncologic treatments.^{4,10} The three-part series on PALM concluded by offering a roadmap with tangible metrics and actionable solutions, and challenged the global health community for future concerted efforts to advance the diagnostics agenda.

The Lancet Commission on diagnostics (LCD) has recently published its landmark report on the state of global diagnostics (both PALM and DI).¹¹ Given the paucity of data on the availability of diagnostics within LMICs, the commission provides a comprehensive report on the subject and offers a tiered assessment of diagnostic disparity between primary care clinics and tertiary hospitals in LMICs. Diagnostic gaps, a crucial bottleneck in the care pathway in LMICs, were first identified. An estimated 47% of the global population has little to no access to proper diagnostics. The second objective of the report was to examine the complex barriers and factors that hindered the equitable advancement of PALM and DI services. Several factors were highlighted, which included workforce, infrastructure, financing, innovation and government policies. The third objective of the report was to justify the economic need for investing in diagnostics that would yield a net positive benefit-cost ratio in almost all scenarios. For example, a net yield return of USD179.19 can be achieved per USD1 invested in oncology imaging.¹⁰ Finally, the report puts forward a template of recommendations, targeted at both national and international levels, to coordinate and accelerate global efforts to improve equitable diagnostic access that has for far too long been largely left out of the global health conversation.

The COVID-19 pandemic has revealed, through the lens of diagnostics, 2 astonishing realities. One, in the face of intense health and economic pressures, the world was able to innovate, finance and manufacture highly accurate diagnostic tests and vaccines against COVID-19 in record time when it would have normally taken a

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decade.12 This highlights the global competency in mobilising international collaborative efforts to swiftly address a pandemic. The second reality, or the unintended consequence of the COVID-19 era response, was the stark differences among economies and demographics with regards to diagnostic access and provision of medical treatment.13 The LCD report was timely in revealing the disparity magnified by COVID-19 in diagnostic access among global economies. Many high-income countries (HICs) have existing medical infrastructure, commercial companies with vested financial interest, public health and political interest, robust manufacturing and efficient distribution systems. In many LMICs however, such resources and networks do not exist. As such, a further implication for many LMICs with disproportionately limited COVID-19 diagnostic access and vaccine availability compared to HICs, is that existing global efforts to improve diagnostic equitability will inevitably face significant setbacks.

The wide disparities in diagnostic access and health outcomes that are evident and magnified during the COVID-19 pandemic exist also within HICs. In recognising this issue and in anticipation of future disease outbreaks, Singapore's future transformative healthcare agenda should examine the critical role of diagnostics and include a focus on 3 crucial themes, based on takeaways from the LCD report.

Healthcare workforce expansion and upskilling for contemporary diagnostic skills. Shortages in the diagnostic workforce are contributed by an increased demand in technological capacity for advanced imaging, as well as a stagnating pool of trained radiologists and radiological technicians. Across HICs, the ratio of radiologists per 100,000 population ranges from 4.7 (UK) to nearly 12.0 (Sweden), with 8.7 reported for the US in 2014. A ratio of 8.0 per 100,000 population represents the bare minimum needed to meet the rise in imaging demand by 2022 in the UK.¹⁴ Singapore's ratio of radiologist per 100,000 population in 2014 was 5.2 (total 286 radiologists), which increased to 6.4 in 2017 (total 357 radiologists), and to 7.2 in 2020 (total 409 radiologists).¹⁵ The growth in radiological technicians over the same period was a ratio of 23.8 per 100,000 in 2014 (total 1,300 technicians) to 28.1 in 2017 (total 1,579 technicians), representing a 21% increase.¹⁶ While these growth rates are encouraging, continued efforts to ensure a steady pipeline of next-generation radiologists and radiological technicians will be important.

In the PALM arena, similar shortages are encountered for both pathologists and trained laboratory allied health professionals. Singapore's ratio of pathologist per

100,000 population in 2014 was 2.6 (total 146 pathologists), which increased to 3.1 in 2017 (total 176 pathologists) and has remained at 3.1 in 2020 (total 180 pathologists).¹⁷ For comparison, the ratio of pathologists for the US in 2017 was nearly 4.0 per 100,000.¹⁸ Even in the US, a first-world country, pathologists remain in strong demand.¹⁹ The relative lack of pathologists in Singapore has existed for decades, and while active attempts to train staff internally have partially stemmed the shortage, we remain in a state where pathologist vacancies await to be filled. Therefore, the status quo approaches to training and educating diagnostic specialists, technicians and pathologists are inadequate, and long-term national strategic plans to address this gap should be among the top focus areas for Singapore's future healthcare goals.

Governance and regulatory frameworks to support and oversee diagnostic quality and safety. While Singapore has established government authorities and professional bodies to evaluate the safety and efficacy of diagnostic medical devices, adaptation to the changing diagnostic landscape without being excessively restrictive is needed. Among the changes in public perception and clinical practice of diagnostics is the push for more upstream screening and preventive measures. There should be new regulatory policies and standards that expand the focus on quality, safety and cost containment, and to incorporate rigorous costeffectiveness analyses that take into account future health benefit and savings.

Furthermore, the pandemic era has accelerated the diagnostic frontier, particularly along the point-of-care (POC) testing front, with innovative self-administered testing. This has addressed previous traditional access barriers. As access to more innovative, decentralised diagnostics become more prevalent, evaluation of their quality, safety and reliability are of paramount importance in future. New channels are needed to streamline and fast-track innovative diagnostic kits, devices and methods for targeting unmet diagnostic needs and patients with barriers to healthcare access, without comprising accuracy and reliability.²⁰

Fostering development and appropriate use of technology to benefit everyone. The shift towards upstream diagnostics is in accordance with the "3 Beyonds" mandate of the Ministry of Health, Singapore: (1) beyond healthcare to health; (2) beyond hospital to community; and (3) beyond quality to value.²¹ A part of bringing patients more value and shifting towards a community-oriented mindset is to first identify those patients most "at risk" of health complications and those who face heightened barriers to diagnostic

access-one of the salient themes in the LCD report. Targeted timely upstream diagnostic access, accompanied by appropriate medical interventions for this patient group, has achieved both better clinical outcomes and economic savings. In Singapore, citizens from lower socio-economic backgrounds may face hurdles to diagnostic access, exhibit health-seeking reluctance and incur significant healthcare costs down the road.²² The future diagnostic agenda initiatives should not neglect this demographic, and should entail proactive education and provision of low-cost health screening of common diseases in a national effort. Similar to POC diagnostics, health technology advances in cutting-edge artificial intelligence and robotics have been exponential during the pandemic, prompted by the need for virtual teleconsultation, social distancing guidelines, workforce shortages and Smart Nation initiatives.²³ While innovation is key to drive diagnostic progress, it is important to consider a tiered network in which technologies are integrated within the existing healthcare infrastructure to maintain cost and ensure the appropriate prioritisation of diagnostic needs and resource allocation.²⁴

Singapore's healthcare has many challenges and its future diagnostic agenda should incorporate elements from the 3 themes outlined above-namely, healthcare workforce, government and regulatory frameworks, and fostering development and appropriate use of technology to benefit everyone. Beyond its own challenges, Singapore is a regional leader in healthcare and as such, there is a moral imperative to leverage its economics and healthcare expertise to collaborate with neighbouring countries to advance diagnostic access in a pursuit of equitable health for all. While the COVID-19 pandemic has exemplified the attainability of global cooperation with regards to streamlining diagnostic and therapeutic advances, it has also magnified the blatant disparities in diagnostic access between LMICs and certain demographic groups within HICs. Without timely intervention, the interdependent nature of both global economy and global health will likely result in further diagnostic disparities. With the LCD report, a framework to transform access to diagnostics has been laid, and a call for Singapore and countries in the region to act and lead for the future of diagnostics is clear.

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COVID-19 vaccination acceptance of healthcare workers in Singapore

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The Coronavirus disease 2019 (COVID-19) pandemic resulted in 511.0 million cases of confirmed SARS-CoV-2 infection and almost 6.2 million deaths globally as of end April 2022.¹ With the introduction of vaccines that are effective in reducing severe COVID-19 illnesses and deaths, Singapore had since pivoted from a COVID-19 elimination strategy to a COVID-19 resilient strategy, aiming to achieve near-normalcy while protecting lives and minimising the impact on the healthcare system and the economy.² An overall high vaccination rate was crucial in Singapore's 3-pronged strategy to Test, Trace and Vaccinate,^{3,4} so as to safely transition towards a COVID-19 vaccine-driven endemic state.

Singapore's national COVID-19 vaccination programme currently employs 2 mRNA vaccines— Pfizer-BioNTech/Comirnaty and Moderna COVID-19 vaccines—and 1 inactivated vaccine—Sinovac-CoronaVac—which are authorised for use under the nation's Pandemic Special Access Route.⁵ Vaccination rollout was implemented in phases, starting with healthcare and frontline workers who provide essential health services and face significant risk of being infected from their workplace exposure to at-risk patients. This was followed by the elderly and those with medical comorbidities, before extending to the rest of the population.⁶

Singapore's phased COVID-19 vaccination strategy, starting with healthcare workers, was rolled out from early January 2021. Singapore Health Services (SingHealth) is Singapore's largest public healthcare cluster, which comprises a network of acute hospitals, national specialty centres, community hospitals and polyclinics offering over 40 clinical specialties. A combined strength of 40,767 healthcare and administrative support staff, as well as service partners (in domains such as housekeeping, security and information technology) enabled the cluster to achieve an annual workload of more than 239,000 inpatient admissions, 285,000 inpatient and day surgeries, 412,000 emergency department attendances, 2.4 million specialist outpatient attendances and 1.5 million primary care attendances.⁷

COVID-19 vaccination with the Pfizer-BioNTech/ Comirnaty COVID-19 vaccine for SingHealth's staff population commenced on 8 January 2021. Over a 7-month period from January 2021 to July 2021, 38,244 (93.8%) of 40,767 staff and service partners were fully vaccinated with the 2-dose regime of the Pfizer-BioNTech/Comirnaty COVID-19 vaccine and 39,206 (96.2%) received at least 1 dose (Fig. 1). By November 2021, more than 99.5% of SingHealth's population are fully vaccinated.



Fig 1. Timeline of the Singapore Health Services COVID-19 vaccination programme.

The principles of the World Health Organization (WHO) Tailoring Immunization Programmes (TIP)⁸ have been instructive to achieve the high vaccination rate in SingHealth's healthcare workforce. The conventional approach to planning and implementation of a mass vaccination programme is one that is centred around logistics, cold chain and access optimisation. The TIP further draws from health behavioural change theories, emphasising social and behavioural insights behind vaccination acceptance and participation, and are

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essential to shape relevant interventions to achieve a high vaccination uptake.

Incorporating the principles of TIP in SingHealth's COVID-19 vaccination programme had helped planners understand the perspectives of staff and the factors affecting the decision to proceed with vaccination. Regular polling of all SingHealth staff was conducted across a 4-month period, and staff responses were collated anonymously (Table 1). The results provided a sensing of the ground sentiments across the 4 vocational groups in SingHealth, and over time, reflected positive shifts towards vaccination acceptance with maturation of the vaccination programme.

Qualitative interviews and surveys were also conducted to delve deeper into the factors associated with vaccine hesitancy. The COM-B model, arising from the WHO TIP, is a behavioural theory that identifies 3 key determinants: Capability (C), Opportunity (O) and Motivation (M), which influence the behaviour (B) of vaccine hesitancy.⁸ Table 2 shows a list of some of the commonly cited reasons for the vaccine hesitancy among SingHealth staff. Interventions and vaccination efforts were targeted at these 3 determinants to address gaps in the vaccination programme and improve the vaccination take-up rate.

First, capability refers to an individual's internal factors such as knowledge and awareness of the COVID-19 vaccines; the risks, benefits and contraindications of COVID-19 vaccines; and the individual's own fitness for vaccination. During the start of the SingHealth vaccination roll-out, 6 cluster-wide townhalls chaired by the group's senior management and medical specialists were organised to equip staff with the necessary knowledge of the relatively new COVID-19 vaccines. Two subsequent tranches of townhalls were organised to provide updated information regarding the relaxation of the vaccination guidelines and to address specific concerns relating to allergies, pregnancy and breastfeeding.

One of the biggest concerns were the emerging reports of severe allergic reactions and anaphylaxis to the COVID-19 vaccines and the medical eligibility for receiving the vaccine. An Expert Committee on Allergy involving allergists from across SingHealth was hence

Table 1.	COVID-19	vaccination	acceptance	e across 4	vocational	groups i	n SingHealth
						0	

		Dec 2020	Jan 2021	Feb 2021	Mar 2021
Medical staff	Yes	47.7%	55.2%	76.0%	83.2%
	No	12.8%	12.8%	10.3%	8.9%
	Undecided	39.5%	32.0%	13.7%	7.9%
	Total number	2782	2782	2769	2758
Nursing staff	Yes	39.9%	43.7%	65.4%	75.6%
	No	23.0%	23.3%	19.5%	16.5%
	Undecided	37.1%	33.0%	15.1%	7.9%
	Total number	11840	11840	11774	11703
Administrative and ancillary staff	Yes	39.3%	42.6%	63.0%	73.5%
	No	21.3%	21.5%	18.6%	15.6%
	Undecided	39.4%	35.9%	18.4%	10.9%
	Total number	11172	11172	11442	11345
Allied health professionals and research staff	Yes	37.4%	42.7%	64.9%	74.5%
	No	19.7%	20.0%	16.0%	12.7%
	Undecided	42.9%	37.1%	19.1%	12.8%
	Total number	6324	6324	6314	6343
All staff combined	Yes	42.8%	46.4%	66.3%	76.1%
	No	20.0%	20.8%	17.6%	14.5%
	Undecided	37.2%	32.8%	16.1%	9.4%
	Total number	32118	32118	32299	32149

Reasons for hesitancy in receiving Pfizer-BioNTech/Comirnaty COVID-19 vaccine
 Pre-existing medical conditions that may not be suitable for COVID-19 vaccination Currently undergoing family planning, pregnancy or breastfeeding, of which there are unknown risks to the pregnancy and the foetus
 Lack of real-world safety data and long-term effects of the vaccine Inadequate real-world data on the effectiveness of the Pfizer-BioNTech/Comirnaty COVID-19 vaccine
 Fears of side effects of the vaccine Concerns with the mRNA technology used to develop the Pfizer-BioNTech/Comirnaty COVID-19 vaccine

Table 2. Commonly cited reasons for vaccine hesitancy among SingHealth staff (December 2020–March 2021)

set up to harmonise the medical assessment protocols for suitability to receive the mRNA vaccine. SingHealth staff who had a history of allergies or allergic reaction to the first dose of the COVID-19 vaccines were seen either on the same day or given a fast-track appointment for clinical evaluation on the suitability to receive the vaccine.

Second, opportunity refers to external factors such as access, availability and convenience of COVID-19 vaccination-related services and information. Electronic direct mail, memos with bite-size information snippets and Frequently Asked Questions about the COVID-19 vaccines were regularly disseminated to SingHealth staff via emails and the Intranet as part of the communications strategy to educate with accurate and updated information relating to the COVID-19 vaccines. An "open door" policy was adopted within SingHealth with a dedicated COVID-19 vaccination email for staff to send in queries relating to COVID-19 vaccination, which would be answered in a timely manner. Staff could also get in touch directly with Infectious Diseases and Occupational Medicine specialists for informal consultations regarding their medical conditions and medical concerns. SingHealth also availed its Staff Clinics and polyclinics across the Cluster for walk-in medical consult service for staff who developed side effects from the COVID-19 vaccines. Based on SingHealth's vaccination adverse events reporting, the commonest side effects were dermatological, followed by respiratory and cardiovascular symptoms (Table 3). This is in contrast to the vaccinationrelated presentations in another healthcare institution in Singapore, where cardiovascular symptoms such as giddiness, palpitations and chest discomfort accounted for the majority of cases.⁹

To create an enabling environment for easy access and convenience to the vaccination services, dedicated vaccination centres were set up in almost all SingHealth institutions for staff to receive the COVID-19 vaccination at their workplaces without having to take time off to travel to a community vaccination centre. For example, the Singapore General Hospital had a daily capacity to vaccinate more than 600 staff to accelerate the staff vaccination uptake from the outset. A dedicated appointment booking system was developed with Integrated Health Information Systems for staff to book vaccination appointments at their preferred time slots via the SingHealth Intranet portal.

Third, motivation refers to the confidence and trust in the COVID-19 vaccines. It was important to build trust in the COVID-19 vaccines before an opinion had been formed against it. SingHealth institutions' senior management and heads of departments served as role models who led by example by receiving the COVID-19 vaccinations first. Recognising that adverse events post-vaccination might lead to loss in confidence, these events were monitored via reaction monitoring reports by the SingHealth Duke-NUS Institute for Patient Safety & Quality, which also looks for trends in adverse reactions observed among staff. In addition, Neurology and Cardiology specialist panels were convened to review and adjudicate all suspected cases of postvaccination adverse events, so as to minimise speculation and incorrect attribution of the adverse events to the COVID-19 vaccines. There was also a strong emphasis on the social benefits of receiving the COVID-19 vaccines, in which social norms in favour of receiving the COVID-19 vaccination were publicised and made more salient on electronic direct mails and the SingHealth Intranet. Vaccinated staff received special identification stickers on their name tags to indicate their COVID-19 vaccination status and were no longer required to log their daily temperature on the staff surveillance system.

Over the 7-month period from January to July 2021, vaccination continued to remain voluntary with no additional workplace penalties or discrimination against non-vaccinated staff. Instead, a personalised approach was adopted in which vaccinated supervisors took on the role as advocates and engaged individual staff who might still be hesitant, to understand the potential concerns that could be addressed.

System/Symptoms	SingHealth staff number (%) N=1044	Lim et al. ⁹ National University Hospital staff number (%) N=196
Dermatological	585 (56.0) - Rash, itch, hives, mucosal swelling	46 (23.5) - Rash, itch
Respiratory	142 (13.6) - Throat discomfort, sensation of breathlessness, wheeze, cough	13 (6.6) - Throat discomfort: 9 (4.6) - Sensation of breathlessness: 4 (2.0)
Cardiovascular	97 (9.3) - Giddiness, palpitations, tachycardia, hypotension	93 (47.4) - Giddiness: 64 (32.7) - Palpitations/chest discomfort: 29 (14.8)
Neurological	71 (6.8) - Headache	30 (15.3) - Numbness over injection arm: 16 (8.2) - Headache: 11 (5.6) - Blurred vision: 3 (1.5)
Musculoskeletal	53 (5.1) - Myalgia, arthralgia	-
Gastrointestinal	44 (4.2) - Nausea/vomiting/diarrhoea/ abdominal pain	11 (5.6) - Nausea/vomiting/reflux
Anaphylaxis	10 (0.96)	-
Others	42 (4.0) - Lethargy/malaise: 41 (3.9) - Otalgia: 1 (0.1)	3 (1.5)

Table 3. Comparison of vaccination adverse events between 2 healthcare entities

⁹ Lim SM, Chan HC, Santosa A, et al. Safety and side effect profile of Pfizer-BioNTech COVID-19 vaccination among healthcare workers: A tertiary hospital experience in Singapore. Ann Acad Med Singap 2021;50:703-11.

There were 2 key takeaways from the SingHealth COVID-19 vaccination experience. First, it was important to recognise that the provision of knowledge and information does not necessarily translate to positive change in vaccination behaviour, especially in the current era of an overabundance of misinformation. Healthcare workers with a higher level of health literacy than the general population tended to trust information in line with what they already believed in. They would be more discerning and critical of new information presented, and additional efforts were required in ensuring a robust narrative detailing quality evidencebased research to address biases and concerns behind their vaccine hesitancy. Second, clear and transparent communication helped to build trust and credibility in the overall approach to the vaccination programme. This included the disclosure of any uncertainty or gaps in knowledge and data, potential limitations, and known risks of the COVID-19 vaccines, even if they may result in some degree of vaccine hesitancy. Such disclosure must be addressed upfront so as not to create a sense of uncertainty and delusion, which can manifest into distrust. Being transparent helped with building trust in the overall vaccination programme and increased the persuasive effect in the long term.

The SingHealth experience demonstrated how behavioural science can be applied in the planning and rollout of a COVID-19 vaccination programme. Vaccination behaviour continues to be a complex issue that must be addressed given the ever-changing COVID-19 pandemic and will be an integral component to help achieve high vaccination rates.

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BNT162B2 COVID-19 mRNA vaccination did not promote substantial anti-syncytin-1 antibody production nor mRNA transfer to breast milk in an exploratory pilot study

Dear Editor,

Vaccine hesitancy still threatens global efforts to end the COVID-19 pandemic caused by SARS-CoV-2 and its emerging variants. Social media-driven "conspiracy theories" cast doubts on vaccine safety for reproductive health,¹ including concerns that vaccine-induced SARS-CoV-2-neutralising antibodies (NAb) cross-react with human syncytin-1-a protein involved in gamete fertilisation and normal placental development²---resulting in infertility or pregnancy loss. Protein sequence similarities between syncytin-1 and SARS-CoV-2 spike protein S2 domain raise this possibility.³ Concerns over BNT162B2 mRNA persistence may prompt affected women to defer vaccination due to a perceived lack of reproductive toxicity or breastfeeding safety data, though COVID-19 vaccination is not contraindicated pre-conception, in pregnancy, or for breastfeeding.⁴ Given the enduring susceptibility of pregnant women to COVID-19 complications, and the risk when facing variants of higher transmission potential, such vaccine hesitancy is worrying.⁵

To address these issues, we performed an observational study of a convenience sample of female at-risk frontline workers receiving BNT162B2 to investigate post-vaccination presence of vaccine mRNA and antisyncytin-1 antibodies. We analysed 42 plasma and 30 breast milk samples from 15 consented female frontline staff at the National University Hospital, Singapore, collected before and after the first dose of BNT162B2, in this institutional review board-approved study (DSRB2012/00917). The participants included 5 breastfeeding mothers and 2 women inadvertently vaccinated in early pregnancy. The study was approved under National Healthcare Group Domain-Specific Review Board (Domain D) DSRB2012/00917 and the methods were conducted in accordance with the Declaration of Helsinki. All study participants provided written informed consent.

Plasma was collected at Day 0 (pre-vaccination), 1–4 days and 4–7 weeks. Breast milk samples were collected daily for the first week, the timing designed to capture the presence of mRNA in plasma and breast milk (degraded within days), and peak neutralising activity (about 3 weeks post-vaccination) to answer our research questions.⁶ Blood and breast milk-derived total RNA

was amplified by real-time reverse transcription polymerase chain reaction using TaqMan primers and probe amplifying an 87bp segment of the BNT162B2 mRNA spike-encoding region.⁷ Negative controls were water and pre-vaccination plasma RNA; positive controls were day 1 post-vaccination RNA. Illumina Nextera XT DNA Library Preparation Kit was used for library production and barcoding. Paired end-sequencing of 300bp read length was performed on the iSeq100 sequencer and sequenced reads were aligned to human references using HISAT2 with comparison to published Pfizer sequences.

Anti-syncytin-1 antibodies were determined using standard semi-quantitative ELISA methodology, incubating plasma in Maxisorp plates coated with 100ng of human syncytin-1 recombinant protein (MyBioSource). Negative control pre-vaccination plasma gave an optical density reading at absorbance wavelength 492nm (OD₄₉₂) of ~0.1. Positive controls comprised pre-vaccination plasma spiked 1:250 with rabbit anti-human syncytin-1 antibody (MyBioSource) following optimisation, as it produced consistent OD₄₉₂ of ~0.9. Briefly, all samples and controls were diluted 1:50 with dilution buffer (2% bovine serum albumin [BSA] in phosphate-buffered saline with Tween [PBST]), incubated at room temperature in prepared plates. Positive controls were incubated with goat antirabbit secondary antibody (1:1000 dilution) (Thermo Fisher Scientific Inc, Waltham, US), samples incubated with goat anti-rhesus secondary antibody (1:4000 dilution) (SouthernBiotech, Birmingham, US), colorimetric reactions generated with o-phenylenediamine dihydrochloride (Sigma) and OD_{492} analysed with background correction.

SARS-COV-2 NAb were detected using SARS-CoV-2 Surrogate Virus Neutralization Test Kits (GenScript Biotech Corp, Piscataway, US). Samples and controls were pre-incubated with horseradish peroxidase (HRP) Receptor Binding Domain (RBD), allowing binding of circulating NAb to HRP-RBD. The mixtures were added to capture plates (pre-coated with human angiotensin converting enzyme-2 protein), washed to remove circulating NAb HRP-RBD complexes, and colorimetric reactions to the remaining unbound HRP-RBD elicited and read at OD₄₅₀. Inhibition (inversely



Fig. 1. BNT162B2 mRNA detection, sequence alignment of plasma with vaccine RNA, neutralising activity and anti-syncytin-1 antibodies. (A) Amplification of BNT162B2 mRNA at Ct<30 was observed in all plasma samples between 1 and 4 days post-vaccination, but not in 4-week plasma (subjects 101 and 102), after a single dose. Negative control (pre-vaccination plasma) and water blanks did not amplify, demonstrating TaqMan primers/probe specificity. (B) Five breast milk samples collected on days 0–7 (lipid and supernatant factions analysed separately) did not amplify vaccine mRNA. (C) Spike protein-encoding region of the BNT162B2 mRNA amplified by whole transcriptome sequencing of extracted RNA; primers and probe sequences are listed. (D) Magnified sequence from 2500–3100bp showing almost perfect alignment between sample RNA, BNT162B2 and MT380725 (native SARS-CoV-2 spike protein) sequences. (E) All subjects were negative (<30% inhibition) for SARS-CoV-2 neutralising antibodies (NAb) on days 0–4 and strongly positive by 4–7 weeks (P<0.0005). (F) All samples showed low-level binding antibodies to human syncytin-1 antigen well below the positive limit (0.9 OD492). Small increases were observed at successive time points (P<0.05) but all levels remained below 0.9 OD492. (G) Weak correlation was observed between NAb and anti-syncytin-1 antibodies at all time points (Pearson correlation coefficients r<0.8, not significant). d: day; w: week

--- dashed line: mean; error bar: standard deviation

proportionate to anti-SARS-CoV-2 NAb titres) was calculated based on OD_{450} absorbance, and $\geq 30\%$ was interpreted as a positive result (manufacturer's instructions). Results are expressed as mean±SD and analysed by one-way analysis of variance using Tukey correction for multiple comparisons, and Pearson correlation coefficients (GraphPad Prism v9.2.0 for Windows, GraphPad Software Inc, San Diego, US).

Participants were of Malay, Indian and Chinese ethnicities, mean age 40.4±12.2 years, and had all received 2 doses of BNT162B2 according to the prescribed schedule, except the 2 pregnant subjects (101 and 102) who had each received a single dose. Plasma BNT162B2 mRNA was detected within 4 days of vaccination (n=13, Ct<30 in all samples, Fig. 1A), but none was observed in breast milk (n=30 samples, Fig. 1B). Early plasma samples were not obtained from the 2 pregnant participants at the time of vaccination as they were not yet recruited; subsequently their plasma samples did not amplify BNT162B2 mRNA at week 4 after a single vaccine dose. High-quality sequenced reads from whole transcriptome sequencing were assembled to obtain draft genomic scaffolds of 4196bp, comparable in size to BNT162B2 mRNA (Fig. 1C); we observed perfect alignment from 120-4077bp against the published sequence, and multiple sequence alignment to MT380725 (SARS-CoV-2 spike protein, GenBank) demonstrated agreement at the nucleotide level (Fig. 1D). We found weak inhibition <30% at day 0 (mean activity 6.95±6.45%) and day 1–4 $(14.68\pm4.73\%)$, and strongly positive inhibition 4–7 weeks post-vaccination (98.65±1.24%, Fig. 1E), including in the pregnant participants (>89.0%). At the same time points, anti-syncytin-1 binding activity increased from $OD_{492} 0.12\pm 0.03$ (day 0) to 0.34 ± 0.11 (day 1-4) and 0.28 ± 0.09 (4–7 weeks, both increases P<0.05). All values were below the assay's positive threshold and were interpreted as negative (Fig. 1F). Non-significant correlation was found between NAb and anti-syncytin-1 activity (Pearson's r 0.1–0.4, Fig. 1G).

Our finding, that vaccinated women with detectable mRNA and high NAb did not produce a corresponding positive anti-syncytin-1 response, is important because it suggests that cross-reactivity to trophoblast syncytin proteins is unlikely. This is corroborated by a recent study also demonstrating no cross-reactivity between anti-SARS-CoV-2 antibodies and syncytin-1 pre- and post-vaccination.⁸ We are unable to comment on the significance of the low-level increase in anti-syncytin-1 levels as clinical thresholds have not been established, but we interpret these as negative results based on the assay limits we established. We encourage a restrained

interpretation of our findings, as spontaneous miscarriage is the most common outcome reported after COVID-19 mRNA vaccination.⁹ Our pilot study adds a unique angle by demonstrating the absence of anti-syncytin-1 antibodies in parous and non-parous women who were vaccinated in early pregnancy, in the postnatal period and remote from childbirth. Our limited data also complements other breast milk safety studies,¹⁰ and supports recommendations to continue breastfeeding throughout vaccination. While our numbers are small, they support vaccination in this at-risk group, though longitudinal surveillance of a larger cohort of vaccinated women is desirable to parse long-term immunological impact of this mRNA vaccine.

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Transvaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) hysterectomy in Singapore

Dear Editor,

Hysterectomy is one of the most common gynaecological procedures, and various approaches are available such as abdominal, laparoscopic and vaginal.¹ Several studies demonstrated that vaginal hysterectomy is preferable to laparotomy for superior surgical safety, less postoperative pain, and shorter hospital stay.^{2,3} However, its use is limited by large uteruses or narrow vaginal access, hindering surgical access to the upper uterine pedicles. Hysterectomy by transvaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) is increasingly used as an innovative surgical technique in recent years. vNOTES uses the single-port approach via vaginal access to overcome the limitations of a narrow space and difficult access to uterine pedicles in vaginal hysterectomy.⁴⁻⁶ We introduced vNOTES in a tertiary centre in Singapore and aimed to discuss its technique and benefits.

Preoperative preparation. vNOTES was introduced in the Department of Obstetrics and Gynaecology, Singapore General Hospital, Singapore, in 2021. We reviewed the indication of the hysterectomy and preoperative imaging. Next, we performed an abdominal examination and a pelvic examination for non-virgo intacta patients. The patients were counselled about the vNOTES approach and consented to it. Exclusion criteria for vNOTES hysterectomy included those with dense pelvic adhesions, adnexal masses suspicious of malignancy or metastatic cancer that required debulking surgery. The surgery was done either by the senior gynaecological oncologist or trainees under his supervision.

Surgical procedure. Under general anaesthesia, the patient was placed in a lithotomy position, cleaned, draped and catheterised. Intravenous antibiotics prophylaxis was administrated preoperatively. First, the surgeon grasped the cervical lip with vulsellum forceps and made a circumferential incision on the cervix. Next, sharp dissection was used to perform an anterior colpotomy, followed by a posterior colpotomy to enter the peritoneal cavity. Bilateral uterosacral and cardinal ligaments were clamped, cut and ligated with braided absorbable sutures (VICRYL, Ethicon Inc, Somerville, US). The cervix was routinely stitched close with VICRYL. One end of an XXS Alexis retractor (Applied Medical Resources Corp, Rancho Santa Margarita, US)

was inserted into the Pouch of Douglas (Fig. 1A), while the other end was inserted into the vesicovaginal space. The cervix would be within the retractor. Next, the retractor was attached to a sterile size 71/2 left-hand glove, which served as the hand-made gloved port for single-port laparoscopy. Three 5mm ports and one 12mm plastic port were fitted into the thumb, little finger, middle finger and index finger sleeves, and secured with sutures to prevent air leak (Fig. 1B). Pneumoperitoneum was created in the abdomen with carbon dioxide. A 50mm 30-degree rigid laparoscope, conventional laparoscopic instruments and energy device (LigaSure, Valleylab, Tyco International Healthcare, Boulder, US) were used. LigaSure was employed for securing the uterine and upper pedicles. Ureters were visualised before ligating the infundibulopelvic ligaments. Specimens were retrieved vaginally. Once haemostasis was secured, the Alexis retractor was removed with the gloved port. The vault was closed with interrupted VICRYL.



Fig. 1. (A) Alexis retractor inserted into the peritoneal cavity via the posterior colpotomy. (B) Handmade gloved port. Size $7\frac{1}{2}$ left sterile glove is attached to the distal ring of Alexis retractor. Conventional rigid laparoscopic instruments are anchored to the gloves with an airtight seal.

Post-surgical care. The patients were allowed diet and received oral paracetamol or non-steroidal antiinflammatory drugs for analgesias. Opioids were given if the woman had drug allergies.

Technique. We used a homemade gloved port rather than ready-made single-port devices used in other studies. Hayashi et al.⁷ evaluated that hand-made glove-ports were cost-effective, efficacious and appropriate in single-port surgery, which is also applicable for vNOTES since the technique was similar.

Learning curve and operating times. Wang et al. stratified cases into the first 20 and sequential 13 cases⁸ and suggested that the learning curve for vNOTES was steep, but it significantly improved with surgical experience. They reported significantly shorter operation time, less estimated blood loss and shorter hospital stay in the sequential 13 cases. The senior gynaecologist leveraged his vast experience in performing vaginal hysterectomies, laparoscopic surgeries including single-port laparoscopy, robotic surgeries, and oncological surgeries, to introduce vNOTES as a novel technique. Initial operating times could be prolonged due to the learning curve of the primary surgeon and the trainees, or complexity of the cases.

Preliminary outcomes. From February to July 2021, 15 patients underwent vNOTES hysterectomy, with either bilateral salpingo-oophorectomies or salpingectomies. Indications for surgery were uterine fibroids, adenomyosis, ovarian cysts, endometrial hyperplasia and carcinoma. None of the patients needed conversion to conventional laparoscopy or laparotomy. The mean age was 54.7 years old (range 39–72), and the average body mass index was 27.4kg/m² (range 19–38). Two were virgo intacta, 3 patients were nulliparous, 9 patients had previous vaginal deliveries, and 1 had 3 previous caesarean sections with ligation. There were no complications as of follow-up until December 2021.

Modifications to the technique. A posterior colpotomy was done first for cases where anterior colpotomy was difficult to perform due to adhesions. An Alexis retractor was inserted into the Pouch of Douglas while the other end was positioned anterior to the uterovesical fold. Pneumoperitoneum was created, and dissection of the uterovesical fold was performed under laparoscopic guidance. The retractor would be repositioned when the bladder was separated from the uterus.

Women with previous abdominal surgeries. Three women with previous abdominal surgeries had omental or bowel adhesions to the anterior abdominal wall. We avoided performing adhesiolysis as the vNOTES approach allowed direct access to the vascular pedicles. Hence, vNOTES eliminated the risk of complications from adhesiolysis such as postoperative ileus, bleeding or bowel injuries. Additional benefits include enhanced recovery through early feeding, ambulation and eliminating port-related complications, such as bleeding, infection and port-site hernias.

Obese women. With vNOTES, obese patients required less acute Trendelenburg position than

conventional laparoscopy due to easier visualisation of the pelvic organs. This reduced the impact on ventilation of the patient, hence, reducing anaesthetic risks.

Vaginal hysterectomy is difficult to perform in patients who are virgo intacta, nulliparous, have bulky uteruses or uteruses without prolapse. Furthermore, performing oophorectomies in the same setting can be technically challenging if the ovaries are drawn up abdominally due to anatomy or adhesions from previous surgeries.

In conclusion, the introduction of vNOTES allowed surgeons to circumvent the limitations of vaginal, laparoscopic and abdominal hysterectomies. Therefore, gynaecologists should consider this approach due to its benefits.

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Optimum follow-up period of arthroscopic and mini-open rotator cuff repairs

Dear Editor,

Rotator cuff disorders are the most common cause of disability related to the shoulder,¹ and rotator cuff repairs—via mini-open or arthroscopic techniques—are considered in patients with refractory symptoms.² While there are multiple studies analysing short- and long-term follow-ups, there are no clear consensus regarding the minimum follow-up time, which ranges from an average of 2 years to close to 10 years.³⁻⁵ However, extended period of surveillance may lead to greater resource consumption, logistical considerations and increased clinical workload without significant clinical benefit. The aim of this study was thus to evaluate the optimal minimum follow-up period for patients who have undergone rotator cuff repairs.

The authors compared prospectively collected preoperative and 6, 12 and 24 months postoperative functional outcome scores on all patients who had either undergone a mini-open or arthroscopic isolated rotator cuff repair for partial and full thickness tears at our tertiary university hospital. These scores included the Constant Shoulder (CS) Score, American Shoulder and Elbow Surgeons (ASES) Score, 36-item Short Form Health Survey Physical Component Score (SF-36 PCS) and 36-item Short Form Health Survey Mental Component Score (SF-36 MCS). Exclusion criteria were patients with revision repairs, missing functional assessment at any follow-up point, concomitant glenohumeral arthritis, adhesive capsulitis, proximal humeral fractures, inflammatory arthritis or cervical radiculopathy. All patients underwent identical postoperative cuff repair protocols with the physiotherapist: active assisted exercises at 3 weeks post-surgery, active movement at 6 weeks and cuff-strengthening programme thereafter.

Complications were defined as any adverse event as a result of surgery and included infection, symptomatic re-tears, persistent (at least 6 months) secondary stiffness and pain post-surgery, and neurovascular injury.^{6,7}

Statistical analysis was performed using SPSS Statistics software version 23.0 (IBM Corp, Armonk, US). Paired t-test analysis was used to examine differences between the various timelines, and chi-square testing was used to analyse continuous variables. Mixed model analysis was used to compare subgroups. P<0.05 was considered to be significant. Appropriate ethical and Institutional Review Board clearance (National

Healthcare Group Institutional Review Board Approval Number: 2019/00178) was obtained before patient records were accessed.

A total of 183 patients underwent either arthroscopic or open rotator cuff repair at our institution in 2011–2017. After the application of exclusion criteria, 117 patients were analysed in this study. Among them, 59 patients (50.4%) had undergone an arthroscopic repair and 58 (49.6%) a mini-open repair. There were no conversions from arthroscopic to the open procedure. Of the 117 patients, 45 (38.5%) were female, 104 (88.9%) were non-smokers and 13 (11.1%) were smokers. There were no significant differences in the arthroscopic and mini-open cohorts.

The CS scores at preoperative, 6 months, 1 year and 2 years were 55.3, 69.0, 80.6 and 82.2, respectively. There were significant differences when comparing the preoperative CS score with each of the postoperative CS scores at 6 months, 1 year and 2 years (P<0.01). Similarly, there were significant differences when comparing the postoperative CS score at 6 months with the postoperative CS scores at 1 year and 2 years, respectively (P<0.01). However, there was no significant difference between 1 year and 2 years postoperative CS scores (P=0.37).

The ASES (total) scores at preoperative, 6 months, 1 year and 2 years were 67.4, 81.8, 89.9 and 89.4, respectively. There were significant differences when comparing the preoperative ASES (total) score with each of the postoperative ASES (total) scores at 6 months, 1 year and 2 years (P<0.01). Similarly, there were significant differences when comparing the postoperative ASES (total) score at 6 months with the postoperative ASES (total) scores at 1 year and 2 years, respectively (P<0.01). However, there was no significant difference between 1-year and 2-year follow-ups (P=0.75).

The SF-36 PCS scores at preoperative, 6-months, 1 year and 2 years were 41.8, 47.0, 49.6 and 51.0, respectively. There were significant differences when comparing the preoperative PCS score with each of the postoperative PCS scores at 6 months, 1 year and 2 years (P<0.01). Similarly, there were significant differences when comparing the postoperative PCS score at 6 months with the postoperative PCS scores at 1 year and 2 years, respectively (P<0.01). However, there was no significant difference between 1-year and 2-year follow-ups (P=0.06).

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	Time period	Mean (95% CI)	P value (versus preop)	<i>P</i> value (vs 6 months)	<i>P</i> value (vs 12 months)	Mean (95% CI)	<i>P</i> value (vs preop)	<i>P</i> value (vs 6 months)	<i>P</i> value (vs 12 months)
			Mini-open group				Arthrosco	pic group	
Constant	Preop	56.07 (5.15)	NA	·	ı	54.51 (4.78)	NA	,	
	6 months	67.64 (4.71)	<0.01	NA	ı	70.39 (4.00)	<0.01	NA	
	12 months	80.40 (3.77)	<0.01	<0.01	NA	80.75 (3.75)	<0.01	<0.01	NA
	24 months	82.31 (3.38)	0.01	<0.01	0.45	82 (3.50)	<0.01	<0.01	0.63
ASES Score (Function)	Preop	35.24 (3.26)	NA	ı	ı	35.12 (3.65)	NA	,	,
	6 months	47.70 (2.90)	<0.01	NA	ı	46.52 (2.54)	<0.01	NA	
	12 months	53.95 (2.47)	<0.01	<0.01	NA	53.24 (1.94)	<0.01	<0.01	NA
	24 months	55.52 (1.88)	<0.01	<0.01	0.14	54.63 (1.88)	<0.01	<0.01	0.62
ASES Score (Strength)	Preop	14.90 (0.75)	NA	,	ı	15 (0.77)	NA	,	
	6 months	17.10 (0.73)	<0.01	NA	Ţ	17.42 (0.71)	<0.01	NA	
	12 months	18.26 (0.52)	<0.01	0.01	NA	18.85 (0.57)	<0.01	<0.01	NA
	24 months	19.14 (0.45)	<0.01	<0.01	0.20	18.95 (0.54)	<0.01	<0.01	0.80
ASES Score (Total)	Preop	67.48 (3.82)	NA		ı	67.29 (4.57)	NA	,	
	6 months	80.02 (4.26)	<0.01	NA	ı	83.51 (3.22)	<0.01	NA	
	12 months	88.55 (3.59)	<0.01	<0.01	NA	91.29 (2.76)	<0.01	<0.01	NA
	24 months	89.12 (3.17)	<0.01	<0.01	0.81	89.75 (3.20)	<0.01	<0.01	0.47
SF-36 PCS	Preop	41.73 (1.70)	NA	ı	I	41.82 (1.51)	NA	,	
	6 months	46.42 (1.82)	<0.01	NA	ı	47.47 (1.67)	<0.01	NA	
	12 months	49.53 (1.62)	<0.01	0.01	NA	49.73 (1.73)	<0.01	0.06	NA
	24 months	50.76 (1.84)	<0.01	<0.01	0.32	51.15 (1.67)	<0.01	<0.01	0.24
SF-36 MCS	Preop	52.64 (2.42)	NA	·	ı	51.85 (2.52)	NA	,	
	6 months	57.19 (1.73)	<0.01	NA	ı	56.70 (2.22)	<0.01	NA	
	12 months	59.51 (1.58)	<0.01	0.05	NA	59.28 (1.47)	<0.01	0.05	NA
	24 months	59.92 (1.20)	<0.01	0.01	0.68	59.27 (1.69)	<0.01	0.07	0.99
ASES: American Shoulder an 36-item Short Form Health S	nd Elbow Surgec urvey Physical C	ons; CI: confidence inte Component Score	srval; NA: not applic	cable; preop: preop	erative; SF-36 MC	S: 36-item Short Form	Health Survey M	lental Component So	core; SF-36 PCS:

The SF-36 MCS scores at preoperative, 6-months, 1-year and 2 years were 52.3, 57.0, 59.4 and 59.6, respectively. Analysing the SF-36 MCS category also showed a similar trend across the follow-up scores, with statistically significant (P<0.01) improvements seen across all follow-up points except between those at 1-year and 2-year reviews (P=0.76).

A mixed model analysis between operation subtypes did not show any statistically significant variation in the functional outcome scores. Subgroup analysis showed that the results followed a similar pattern with no significant differences in functional scores between 1-year and 2-year follow-ups (Table 1). Additionally, comparisons of arthroscopic versus mini-open groups did not show any significant differences across all time periods.

In terms of complications at 6 months, 4 patients had secondary adhesive capsulitis. At 1 year postoperative, 2 more patients had secondary adhesive capsulitis, 1 patient had atraumatic, clinically symptomatic re-tears, and 2 patients had surgical site infection, of which 1 was a deep infection requiring a glenohumeral joint washout. At 2 years postoperative, 1 more patient had atraumatic, clinically symptomatic re-tears. There were no neurovascular complications at all time points. There was a significant reduction in complication found at 2 years compared to 1 year (P=0.01).

This study may suggest that the optimal length of follow-up post-cuff repair is 1 year, as it reached an equilibrium in all functional scores, and was significant in identifying the majority of complications.

The majority of the current literature similarly mirrors the results of our study where patients reach an equilibrium in terms of function and range of motion around the 1-year mark post-surgery.^{3,8} In terms of complications, the first 6 months post-surgery appears to be the most critical in re-tear rates.⁶ However, these studies were focused on radiological surveillance, and radiological evidence of re-tear may not result in any significant difference in clinical or functional outcomes.⁹

The identification of an optimal follow-up period is key as it has the potential benefits of economic savings from unnecessary, continued clinical follow-up and investigations. This is especially so when projected over an estimated life expectancy.¹⁰

This study is not without its limitations. Firstly, it did not analyse individual patient/surgical factors such as the size of tear or type of repair. Other limitations include its retrospective, non-randomised nature, as well as a lack of other outcomes such as the range of motion and radiological assessment.

In summary, this study suggests that a 1-year followup period is sufficient in evaluating postoperative recovery and complications following arthroscopic and mini-open rotator cuff repairs.

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## Psychosocial impact and treatment trends of hidradenitis suppurativa in Singapore

#### Dear Editor,

Hidradenitis suppurativa (HS) is a common disease with a prevalence of about 1%.¹ Patients commonly suffer from pain, disfigurement and psychosocial embarrassment, and have a worse quality of life compared to other dermatologic conditions.^{2,3} It is frequently misdiagnosed as other skin infections and delays in diagnosis are associated with more psychosocial impairment.⁴ We examined the prevalence of psychosocial morbidity in a Singaporean Chinese cohort of HS patients and determine if the degree of morbidity is related to any disease or patient factors.

Fifty-eight Singaporean Chinese were recruited as part of another study that examined genetic variations in HS.⁵ HS was diagnosed clinically by dermatologists and site of involvement (axillary, inguinal, perineal or perianal, and buttock) recorded. The severity of disease was staged using the Hurley system. Information such as age, race, sex, smoking, height, weight, and history of surgical intervention, acne vulgaris, hyperlipidaemia, hypertension, pilonidal cyst, polycystic ovarian syndrome, and family history of HS was collected. Patients were asked 4 questions about the degree of symptom burden, embarrassment, interference with work and school, and interference with daily activities. These questions were adapted from the Dermatology Life Quality Index (DLQI) and responses were recorded on an ordinal scale from 0 (not at all) to 3 (very much so) (Table 1).

"Symptom burden", "embarrassment", and "interference with daily activities" were dichotomized into "0 or 1" and "2 to 3" responses, while "interference with work and school" was dichotomized into "0" and "1 to 3" responses due to the data skew. Logistic regression analysis was performed with the above dichotomized responses as dependent variables and age, sex, smoking history, body mass index (BMI), axillary involvement, inguinal involvement, perineal or perianal involvement, buttock involvement, Hurley stage, history of surgical intervention, and family history of HS as independent variables. A two-sided *P* value of <0.05 was considered statistically significant. The study was approved by our institution's ethics review board and all subjects signed informed consent.

The mean age was  $31.1\pm10.7$  years. Of the 58 patients, 72.4% were male, 36.2% were smokers and 24.1% had a BMI  $\geq$ 30. Axillary, inguinal, perineal, and buttock regions were involved in 37.9%, 34.4%, 12.2% and 39.7% of patients, respectively; 55.2%, 27.8% and 17.2% had Hurley 1, 2 and 3 stage, respectively. In this study, 43.1% of patients had a history of surgical intervention, which ranged from incision and drainage of active lesions to wide excision. Forty-four (75.9%) patients had acne vulgaris, 2 had pilonidal cysts or abscesses, 1 had polycystic ovarian syndrome, 6 had hypertension and 11 had hyperlipidaemia. Ten patients had a family history of HS.

In the past 1 month, 86% of patients experienced symptoms, 78% of patients were embarrassed, 48% reported interference with work or school, and 78% reported interference with their daily activities (Table 1). Patients with a higher BMI (P=0.01), females (P=0.02), and those with a history of surgical intervention (P=0.02) reported worse symptoms.

Table 1. Questionnaire					
Dependent variable	Question	Number of responses, no. (%)			
		0 (not at all)	1 (a little bit)	2 (somewhat)	3 (very much so)
Degree of symptom burden	Over the past 1 month, how itchy, sore or painful has your condition been?	8 (14)	27 (47)	18 (31)	5 (8)
Degree of embarrassment	At present, how embarrassed are you by your condition?	13 (22)	19 (33)	23 (40)	3 (5)
Degree of interference with work and school	Over the last 1 month, how much has your condition prevented you from attending work or school?	30 (52)	20 (34)	7 (12)	1 (1)
Degree of interference with daily activities	Over the past 1 month, how much has your condition interfered with your daily activities? (e.g. shopping, gardening, going out with friends, housework, hobbies, etc.)	13 (22)	26 (45)	15 (31)	4 (2)

Pain, itch or soreness was common, and females, those with a higher BMI, and those with a history of surgical intervention were more symptomatic. The degree of symptoms was independent of the site of involvement in this study. Pain may be acute and inflammatory or chronic and neuropathic in nature.⁶ Patients may seek surgical treatments to relieve pain. Some surgical treatments, such as incision and drainage, may only temporarily relieve pain. Apart from diseasemodifying treatments, pain management in HS is crucial. Simple measures include good wound care and wearing loose clothing. Weight loss may reduce skin occlusion and friction. Commonly prescribed analgesics include paracetamol, non-steroidal anti-inflammatory drugs and opioids. When opioids are prescribed, short courses are recommended to reduce dependence.7 When pain develops a neuropathic quality, medications such as gabapentin, pregabalin and antidepressants may be considered. Occasionally, a referral for psychological therapy such as cognitive behavioural therapy may be warranted.8

Many patients are embarrassed to reveal their scars, by the malodour or by drainage causing staining of their clothes. This may lead to social withdrawal, poor interpersonal relationships, and increase risk of depression.⁹ Similar to pain, clinicians must be cognisant of this aspect of disease burden and spare some time to manage it sensitively.

There is a huge impact of HS on work, school and daily life. HS may cause impairments in function due to pain, fatigue, hospitalisation, poor interpersonal relationships, or psychiatric comorbidity. Furthermore, the mean age of 31 years of age is when people are most active economically, which can potentially lead to loss of income. In particular, those with a higher Hurley stage experienced greater interference in daily activities (P=0.04), and clinicians may consider using the Hurley stage to predict degree of socio-economic distress as a quick tool in a busy clinic.

The results of this study may not be generalisable to other ethnic groups as this was a Chinese population. The findings may not reflect the psychosocial burden faced by patients managed by other physicians. The Hurley system is unable to distinguish active disease from old burnt-out lesions, and it may underestimate the disease burden in patients suffering from active abscesses and inflammatory nodules. Although the questionnaire used in this study is not a validated quality-of-life assessment scale, it was adapted from the DLQI to allow patients to complete the questions more rapidly. Furthermore, it assesses a longer period of a month instead of a week, which may be more fitting for HS given the chronic nature of the disease.

HS is a chronic debilitating disease that results in significant psychosocial comorbidity. Patients who are female, have a higher BMI, have a history of surgical intervention, or have a higher Hurley stage are more likely to suffer a greater degree of psychosocial burden. Holistic management of HS should encompass early disease-modifying treatment and prompt management of chronic pain, psychological and socio-economic complications.

#### Disclosure

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#### IMAGES IN MEDICINE

### Nitrous oxide and cervical myelopathy

A 25-year-old woman presented with progressive paraesthesia and numbness, both of which started from the left hand. Her symptoms progressed to the fingertips of her right hand and bilateral soles over a few days. There was associated confusion and altered mental status on admission. There was no weakness of the face and limbs, visual impairment, speech difficulty, swallowing impairment, or urinary and bowel incontinence. She had no significant medical history, though it was revealed that she had been inhaling nitrous oxide  $(N_2O)$ from 3-4 canisters of whipped cream charger daily for 2 months. N₂O, commonly known as "laughing gas", is often is often used as a recreational inhalant. There was loss of proprioception and vibration senses over the bilateral thumbs and toes. Pain and temperature senses were intact. Deep tendon reflexes were normal and Babinski reflex was positive bilaterally. She had sensory ataxia and her gait was unsteady. Her clinical presentation pointed to a pathology at the posterior column of the spinal cord.

She had a borderline low vitamin B12 level of 131pmol/L (normal: 133–675pmol/L), with normal folate but elevated homocysteine of  $101\mu$ mol/L (normal: 5–15 $\mu$ mol/L). Her serum copper level was normal. Other test results including those for full blood count, thyroid panel, HbA1C, syphilis and human immunodeficiency virus antibodies, erythrocyte sedimentation rate, and systemic autoimmune screen were normal. Anti-aquaporin-4 antibody, anti-intrinsic factor and anti-parietal cell antibodies were negative. The nerve conduction study results were normal.

Magnetic resonance imaging (MRI) of the brain was normal. MRI of the cervical spine was performed (Fig. 1). Her lumbar puncture was normal. Cerebrospinal fluid (CSF) infection screen was negative. CSF oligoclonal bands were absent.

What is your diagnosis?

- A. Subacute combined degeneration (SCD) of the spinal cord
- B. Syringomyelia
- C. Multiple sclerosis (MS)
- D. Neuromyelitis optica (NMO)
- E. Spinal cord infarction (SCI)

Our patient presented with clinical features suggestive of a pathology at the posterior column of the cervical



Fig. 1. Magnetic resonance imaging (MRI) of the cervical spine. (A) Axial T2 sequence at C3 level. (B) Sagittal T2 sequence. Arrowheads indicate T2 hyperintensity over the cervical spinal cord. (C) Axial post-contrast T1 sequence at C3 level. (D) Sagittal post-contrast sequence. Arrows indicate no contrast enhancement at cervical spinal cord.

cord. Her MRI demonstrated long segment symmetrical T2 hyperintensity over both the posterior column at C2–C5 levels (Fig. 1B) and an inverted V sign (Fig. 1A), suggestive of vitamin B12 deficiency myelopathy. No contrast enhancement was seen on post-contrast T1 sequence (Figs. 1C and 1D). These findings are typical of SCD. Given the history of  $N_2O$  inhalation, with presence of low vitamin B12 level and high homocysteine level,  $N_2O$ -induced SCD should be the top differential diagnosis.¹

 $N_2O$ , is commonly is commonly used as an anaesthetic agent for dental and medical procedures. However, its misuse and complications have been increasing in recent years.² The Global Drug Survey 2021 reported  $N_2O$  to be the 14th most abused drug globally.³ In Singapore,  $N_2O$  is not banned, and is available in the open market. In the baking industry, "whippet" chargers are used in propelling whipped cream in cans, with each canister priced affordably. Common clinical features of  $N_2O$  abuse include myeloneuropathy, paraesthesia, gait ataxia, amnesia, confusion, and bowel/bladder and sexual dysfunction.⁴

 $N_2O$  interferes with methionine synthesis by inactivating methylcobalamin, resulting in vitamin B12 deficiency.

Vitamin B12 level can be normal, with functional deficiency¹ that can be diagnosed based on high methylmalonic acid and/or homocysteine level.² The abnormal methylation of myelin protein results in demyelination within central and peripheral nervous systems. Interestingly, N₂O-mediated inactivation of vitamin B12 is not commonly associated with haematological disorders such as anaemia. Additionally, the prognosis of N₂O-mediated SCD is also not related to presence of anaemia, low serum B12 level or MRI abnormalities.⁵

SCD commonly involves the dorsal column. On the MRI, the inverted V sign in axial T2 sequence is a characteristic feature of SCD.^{1,2} Most patients have MRI lesions extending over 3–6 spinal segments, most commonly involving the cervical spine.^{1,2} Cervical cord is extremely vulnerable to N₂O neurotoxicity due to the high density of myelinated fibre in the fasciculus gracilis. Cord enhancement is anticipated in inflammation and neoplasms, a feature which is not seen in SCD. The minimal contrast enhancement in SCD is likely due to breakdown of the blood-brain barrier caused by perivascular demyelination and inflammation.⁶

Typically, syringomyelia causes cape-like loss of pain and temperature sensation along the back and arms. Furthermore, motor deficits in the upper limbs are disproportionately greater than the lower limbs. In our patient, her pain and temperature senses were intact. She had no motor deficits and she presented with altered mental status and confusion, which are atypical of syringomyelia. Syringomyelia has MRI features such as the presence of a cyst in the spinal cord parenchyma.⁷ The presence of fluid flow voids or cysts, which reflects the pulsatile movements of syrinx fluid, can be seen in up to 40% of patients.⁸ Our patient's clinical and MRI findings were not consistent with that of syringomyelia.

To diagnose MS, clinical features and imaging findings that are consistent with lesions disseminated in space and time are required. MS was an important potential diagnosis to consider for our patient, but she did not have a history of recurrent episodes of neurological deficits and optic neuritis. Although MS has preferential involvement of the cervical cord and posterior column, it rarely exceeds 2 segments in length.⁹ This is different from our patient's MRI features, which showed long segment spinal cord involvement. Furthermore, the presence of oligoclonal bands in the cerebrospinal fluid (CSF), and/or an MRI of the brain demonstrating additional lesions at periventricular, juxtacortical/cortical and infratentorial are required for the diagnosis of MS. Our patient's brain MRI was normal and CSF oligoclonal bands was negative.

NMO usually presents with long segment, contrastenhanced spinal cord lesions on the MRI, especially for the active lesions.¹⁰ Other common clinical features include optic neuritis, narcolepsy, area postrema and brainstem syndromes. The presence of anti-aquaporin-4 antibody is sensitive and specific to NMO. Our patient had no other clinical and radiological features suggestive of NMO, and her anti-aquaporin-4 antibody was negative.

The diagnosis of SCI is unlikely as her symptom onset was subacute. SCI typically has an abrupt onset to nadir within 12 hours. Although SCI can present with longitudinally extensive lesion on the MRI, posterior column infarcts are rare, and usually occur in older age.¹¹ Our patient is young and has no significant cardiovascular risk factors.



Fig. 2. Magnetic resonance imaging of the (A) axial T2 sequence and (B) sagittal sequence at C3 level showing improvement of T2 hyperintensities (arrows).

The final diagnosis was subacute combined degeneration of the spine from  $N_2O$  misuse. After treatment with high-dose mecobalamin replacement, the patient's symptoms resolved with, improvement of MRI findings (Fig. 2).

To the best of our knowledge, this is the second reported case of  $N_2O$  misuse from "whippets" in Singapore.¹² Literature has mostly reported incidents of SCD in controlled, anaesthetic environments, while our case highlights the phenomenon of SCD caused by recreational abuse of  $N_2O$ .¹³ Given the under-regulated  $N_2O$  market and potentially detrimental complications following its misuse, it is therefore important for physicians to be educated about this phenomenon.

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