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Illustration by Xinyu Li

The COVID-19 pandemic has brought losses to patients, families and healthcare professionals. A Singapore scoping review identified the different types of losses leading to grief—the death of family members, patients and colleagues, as well as the loss of usual routines, lifestyles and physical health. The grief experienced was multidimensional, affecting the emotional, physical, social and existential realms. Anger, guilt and fear resulted from unsatisfactory farewells, issues with funerals, social isolation, financial strain and stigmatisation.

Loss and grief identification and management are critical. Innovative strategies for management encompass communication, finance, counselling, education and spiritual care.

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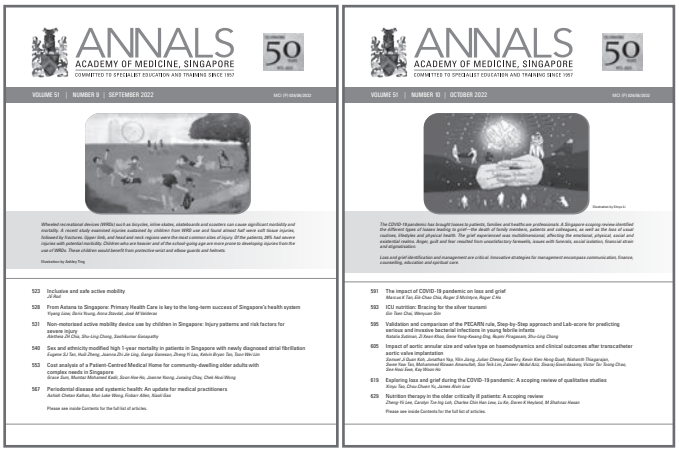

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EDITORIAL

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The impact of COVID-19 pandemic on loss and grief

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As of 17 October 2022, the COVID-19 pandemic has claimed more than 6.5 million lives globally, with 1,639 deaths reported in Singapore.[1] With numerous countries imposing measures such as lockdowns and social distancing measures that isolate individuals, there has been a steady increase in a variety of mental disorders like anxiety, depression and stress disorders.[2] This is worsened by uncertainty surrounding the COVID-19 pandemic, resulting in instability and anxiety in many aspects of life such as finances and relationships.[3,4] Grief experienced by the family from the death of a loved one has been further exacerbated during the pandemic. Proper farewells, consisting of funerals with burial or cremation procedures in accordance with traditions and cultural practices, have been hindered by the restrictions imposed by the respective governments.[5] In Singapore, Hindus had to alter their practices as those infected with COVID-19 could not be brought back to their home to comply with their religion. With the inability to carry out these rituals properly, it hampers their grief process, preventing the families from conducting proper farewell rituals for their loved ones.[6]

The process of grief in the COVID-19 era has been complicated by the voluntary or involuntary isolation from others in fear of the virus. Many were unable to attend the wakes in view of the restrictions in attendance and rituals during such processions. Many felt guilty due to the inability to bid their loved ones a proper farewell in person, leading to ruminations and excessive thoughts for the dead, thereby complicating the grieving process.[7] Such a lengthened process can lead to prolonged grief disorder (PGD) associated with intense yearning and longing for the loved one, which impacts their daily living.[8] This is seen in a cross-sectional study conducted in China where the prevalence of PGD was close to 40% due to the COVID-19 pandemic.[9] Thus, PGD is an important disorder to be identified early, with its associations with increased suicidal ideation and reductions in quality of life.[10]

While the loss of a loved one is a primary reason for grief during the pandemic, patients who survived the COVID-19 infection also experience grief. A loss of physical and mental well-being has been reported in patients after infection as they experience fatigue and psychiatric disorders such as anxiety, depression and sleep disturbances.[11,12] Many have a difficult recovery back to their usual baseline; additionally, some experienced a sense of isolation when hospitalised, feeling that they had been abandoned by their relatives.[12]

In this issue of the *Annals*, Tao et al.[13] published a scoping review on loss and grief in various groups such as patients, families and healthcare professionals during the COVID-19 pandemic. It described the grief experienced during the pandemic to be multidimensional, affecting the mental, social, physical and existential realms. The reasons identified leading to loss and grief during the pandemic included unsatisfactory farewells and issues with funeral arrangements as a result of pandemic restrictions, social isolation, financial strain and stigmatisation.

Tao et al. proposed a multidisciplinary approach to tackling the domains of communications, finance, counselling, education and spiritual care identified in the review. They suggested that these domains identified could be further categorised into 3 main themes: communication, reassurance, and preparedness to be applied in the Singapore context.

Firstly, high-quality communication and transparency between all parties, including the patient, should take place. Information that is understandable should be passed between the involved parties. Secondly, reassurance is essential in calming fears and anxiety among the groups. Finally, preparedness is imperative in allowing one to come to terms with loss and grief, and prevent the development of prolonged grief. Tao et al. also emphasised that current guidelines and management of grief during the pandemic have been lacklustre, and modifications of such guidelines should be done to

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better identify and manage grief during the present and future pandemics.

With mental health issues such as grief and loss being increasingly prevalent during the COVID-19 pandemic, more effort has to be invested to better manage these issues. Further research is needed to determine if the proposed strategies can be effectively translated into practice.

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EDITORIAL

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ICU nutrition: Bracing for the silver tsunami

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The global population's life expectancy is growing with a steady increase in the proportion of older patients admitted to the intensive care unit (ICU).[1] Up to 13% of the ICU patients are above the age of 80.[2] Older critically ill patients have lower physiological reserves of the various organ systems, as well as impaired immunity.[3] This presents unique challenges in managing these patients as they are more susceptible to critical illness, with a higher risk of poor outcomes. Malnutrition, which affects 12–45% of hospitalised older patients, is one of the risk factors that contribute to higher mortality.[4] It can lead to frailty, defined as an individual's innate vulnerability that makes overcoming and recovering from acute stress more difficult.[5] Frail patients were present in 43.1% of one multicentre European ICU cohort of 5,021 patients with a median age of 84 years, and being frail was an independent predictor of 30-day ICU mortality (hazard ratio 1.54, 95% confidence interval 1.38–1.73) compared with non-frail patients.[6] Malnutrition also contributes to sarcopenia, which is a progressive loss of skeletal muscle mass, strength and power.[5] The presence of sarcopenia, when paired with the rapid loss of skeletal muscle experienced by older ICU patients as a result of immobility, dysregulated host immunity, and systemic inflammation, frequently results in the development of ICU-acquired weakness and protracted weaning from the ICU and mechanical ventilation.[3]

Given the differences in physiology and clinical characteristics of older patients, it may be difficult to extrapolate adult ICU nutrition guidelines to this group of patients. Hence, it is timely that in this issue of the *Annals*, Lee et al. performed a scoping review to examine the extent of the research publications related to the nutrition therapy of older critically ill patients, summarised the key research findings, and identified research gaps in this area.[7] The authors identified 6 areas of interest: nutrition screening and assessments; muscle mass assessment; route or timing of nutrition therapy; determination of energy and protein requirements; energy and protein intake; and pharmaconutrition. One of the key findings was the paucity of large randomised control trials (RCTs) in elderly patients that could inform decision-making for the ICU team. Only 5 RCTs were identified from the 4,689 references retrieved using the described search strategy. The authors found that the subjective global assessment and the modified nutrition risk in critically ill (mNUTRIC) can be considered to assess malnutrition risk in older critically ill patients. Other nutrition assessment tools were either not validated among critically ill patients (e.g. Nutrition Risk Screening 2002), or in the case of controlling nutritional status index (CONUT), prognostic nutritional index (PNI), geriatric nutritional risk index (GNRI), and Onodera's prognostic nutritional index (OPNI), contain components (such as serum albumin and lymphocytes) that may be confounded by the inflammatory stress response in the ICU. Direct measurements of the muscle mass using imaging may seem intuitive since skeletal muscles reflect the patients' nutritional status; however, it is uncertain if the clinical and functional outcomes may be altered by a nutrition intervention individualised based on muscularity status. In addition, due to limited evidence, the authors conclude that recommendations regarding the route and timing of nutrition therapy in older critically ill patients should be no different from those of general critically ill patients. The use of indirect calorimetry or age- and population-specific predictive equations may be considered for determining the energy and protein requirements of older ICU patients. These older patients may need higher protein than younger ones in order to achieve nitrogen balance, but may be at higher risk of azotaemia. Finally, the authors did not find any change in clinical outcomes associated with the use of glutamine and fish oil in older ICU patients.

Credit must be given to Lee et al. for systematically searching the literature and reporting the results using a scoping review strategy, something that has not been done to date. The search was exhaustive, transparent, and the results were presented according to the various themes in a structured manner while following the PRISMA extension for scoping review checklist.[8] It

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is worth mentioning some of the important differences between a scoping review and a systematic review. Systematic reviews adhere to structured and pre-defined processes that require stringent methodologies to produce reliable and meaningful results. They are widely used to inform the establishment of clinical practice guidelines.[9] In contrast, scoping reviews are broad and exploratory in nature. They evaluate the extent of the available evidence, identify knowledge gaps, clarify ideas and concepts, investigate research conduct, and may serve as a platform for identifying specific questions for future systematic reviews.[9] Notably, scoping reviews typically do not address methodological limitations or the risk of bias in the available evidence, resulting in limited implications of the results for clinical practice.[9]

This review is not without limitations. Due to the wide range of topics related to ICU nutrition, it was impossible to have a complete review of all aspects of ICU nutrition in a single publication. There are other topics that may be of interest to the ICU healthcare providers, such as the risk of refeeding syndrome and the utility of thiamine in these patients, fluid and electrolyte therapy, glycaemic control, monitoring of feeding tolerance, and specific interventions that may address sarcopenia. There is also a significant bias in the post hoc analysis when the authors realised there were limited ICU studies that recruited older patients, and decided to report studies with subgroup analyses of older versus younger patients in "those that were known to the authors" on top of those eligible studies. Furthermore, it is debatable if merely being older is a granular enough phenotype to guide personalised nutrition in critically ill patients. Given the significant heterogeneity among older patients,[10] perhaps the use of novel biomarkers, such as gut microbiome diversity, proteomic and metabolomic assays, will allow us to be more precise in the delivery of ICU nutrition in the future.[11]

Despite these limitations, Lee et al. have mapped the available evidence on nutrition therapy in older ICU patients. Hopefully, this will spur future research studies and guidelines to help personalise nutrition in this particularly vulnerable group of critically ill patients.

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ORIGINAL ARTICLE

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Validation and comparison of the PECARN rule, Step-by-Step approach and Lab-score for predicting serious and invasive bacterial infections in young febrile infants

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ABSTRACT

Introduction: Differentiating infants with serious bacterial infections (SBIs) or invasive bacterial infections (IBIs) from those without remains a challenge. We sought to compare the diagnostic performances of single biomarkers (absolute neutrophil count [ANC], C-reactive protein [CRP] and procalcitonin [PCT]) and 4 diagnostic approaches comprising Lab-score, Step-by-Step approach (original and modified) and Pediatric Emergency Care Applied Research Network (PECARN) rule.

Method: This is a prospective cohort study involving infants 0–90 days of age who presented to an emergency department from July 2020 to August 2021. SBIs were defined as bacterial meningitis, bacteraemia and/or urinary tract infections. IBIs were defined as bacteraemia and/or bacterial meningitis. We evaluated the performances of Lab-score, Step-by-Step (original and modified) and PECARN rule in predicting SBIs and IBIs.

Results: We analysed a total of 258 infants, among whom 86 (33.3%) had SBIs and 9 (3.5%) had IBIs. In predicting SBIs, ANC ≥4.09 had the highest sensitivity and negative predictive value (NPV), while PCT ≥1.7 had the highest specificity and positive predictive value (PPV). CRP ≥20 achieved the highest area under receiver operating characteristic curve (AUC) of 0.741 (95% confidence interval [CI] 0.672–0.810). The Step-by-Step (original) approach had the highest sensitivity (97.7%). Lab-score had the highest AUC of 0.695 (95% CI 0.621–0.768), compared to PECARN rule at 0.625 (95% CI 0.556–0.694) and Step-by-Step (original) at 0.573 (95% CI 0.502–0.644). In predicting IBIs, PCT ≥1.7 had the highest sensitivity, specificity, PPV and NPV. The Step-by-Step (original and modified) approach had the highest sensitivity of 100%. Lab-score had the highest AUC of 0.854 (95% CI 0.731–0.977) compared to PECARN rule at 0.589 (95% CI 0.420–0.758) and Step-by-Step at 0.562 (95% CI 0.392–0.732).

Conclusion: CRP strongly predicted SBIs, and PCT strongly predicted IBI. The Step-by-Step approach had the highest sensitivity and NPV, while Lab-score had the highest specificity and AUC in predicting SBIs and IBIs.

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Keywords: Biomarkers, diagnostic approaches, febrile infants, Lab-score, PECARN rule, Step-by-Step approach

INTRODUCTION

The diagnostic approach and management of febrile infants <90 days of age remain a challenge, given that the majority of these infants have no localising signs and symptoms, and may appear clinically well at presentation.[1] In addition, the majority of these infants have benign viral illnesses, for which hospitalisation and antibiotics may not be warranted. Identifying infants with serious bacterial infections (SBIs) or invasive bacterial infections (IBIs) based on clinical assessment alone may lead to delayed or missed diagnosis.[2]

Previous diagnostic approaches include the Rochester criteria, which take into account clinical findings, white blood cell (WBC) and urinalysis,[3] as well as the

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CLINICAL IMPACT

What is New

- This study compared the discriminative ability of single biomarkers (absolute neutrophil count, C-reactive protein and procalcitonin) and predictive tools comprising Lab-score, Step-by-Step approach (original and modified) and Pediatric Emergency Care Applied Research Network (PECARN) rule in differentiating infants with serious bacterial infections (SBIs) and invasive bacterial infections.
- Step-by-Step (original) approach had the highest sensitivity and negative predictive value, resulting in the fewest missed cases of SBIs.

Clinical Implications

- Future research should study the application of a modified Step-by-Step algorithm as a safe tool for use in Singapore.

Philadelphia criteria, which incorporate clinical criteria, WBC, urinalysis, chest X-ray and lumbar puncture for cerebrospinal fluid (CSF) analysis.[3,4] A retrospective cohort study on infants in Singapore showed that the Rochester criteria performed with a sensitivity of 96% but had a low specificity of 15.7%, and classified up to 88% of febrile infants as high risk.[5] Newer diagnostic algorithms and clinical prediction rules have since been developed to incorporate newer biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT).[6] These include Lab-score,[7] Step-by-Step approach[8] and Pediatric Emergency Care Applied Research Network (PECARN) rule,[9] which have proven to be more accurate in predicting SBIs and IBIs than single biomarkers.

The first of these prediction models, Lab-score, was developed and validated in 2008 to identify febrile infants at risk of SBIs. Lab-score is based on 3 predictive variables, which have been independently associated with SBIs, namely CRP, PCT and urinary dipstick results.[10] The Step-by-Step approach was subsequently developed as an algorithm that sequentially evaluates infants' general appearance, age, urinalysis, and markers—including absolute neutrophil count (ANC), CRP and PCT—in predicting IBIs.[11] Kuppermann et al. developed and internally validated a promising prediction tool, the PECARN rule, which takes into consideration urinalysis, ANC and PCT, to aid the identification of SBIs among febrile infants.[9]

However, the diagnostic performances of these prediction rules in identifying SBIs and IBIs in our population remain unknown. Therefore, we seek to evaluate and compare the diagnostic performances of single biomarkers, Lab-score, Step-by-Step approach and PECARN rule in predicting SBIs and IBIs in febrile infants.

METHOD

Study design

This prospective observational study was conducted between July 2020 and August 2021 at KK Women's and Children's Hospital in Singapore, a tertiary paediatric hospital where the pediatric emergency department (ED) is visited by approximately 150,000 children aged 0–17 years annually.

Patient population

In our institution, all febrile infants aged 0–90 days are admitted for investigations and further inpatient management. Patients were recruited based on the following inclusion criteria: 0–90 days of age (actual age), and fever, defined as axillary or rectal temperature of at least 38°C either in the ED or prior healthcare settings within the preceding 24 hours. We excluded the following patients: pre-term infants aged <35 weeks; those with significant neonatal complications requiring prolonged perinatal hospitalisation of >7 days; those receiving prior intravenous antibiotics within 48 hours of presentation; and those with underlying genetic, chromosomal, immunological and haematological diseases. We excluded these infants because they innately formed a higher-risk population that would receive closer attention. We also excluded those with incomplete medical records or biochemistry results that would preclude the validation of the prediction rules.

Clinical and biochemical evaluation

Demographic data, clinical history and physical examination findings were recorded for all enrolled patients. We defined infants who were not well appearing as those with ≥1 abnormal component of the paediatric assessment triangle (appearance, work of breathing and circulation to the skin). In our institution, while haemodynamically unstable febrile infants are resuscitated in the ED, stable febrile infants receive their investigations after admission to the hospital. A comprehensive workup including blood, urine and cerebrospinal fluid (CSF) cultures is performed for all neonates 0–28 days old. Among infants 29–90 days old, the extent of investigations is decided at the discretion

of the treating physicians based on clinical assessment. Infants who are subsequently afebrile in the wards and examine well may not undergo all investigations. Therefore, we excluded those without the relevant blood test results since we could not analyse them. Blood samples were taken for WBC, CRP and PCT, and urine specimens were collected for urinalysis. A positive urinalysis was defined as positive for leucocyte esterase, nitrite or pyuria at >5 WBCs.

Classification, definitions and outcome measures

The definitions used to classify patients in the SBI group were: (1) bacterial meningitis, defined as growth of a single bacterial pathogen in the CSF (with culture-proven diagnosis for both bacteraemia and urinary tract infections [UTIs]); (2) bacteraemia, defined as growth of a single bacterial pathogen in blood (excluding growth of bacteria considered a priori as contaminants, e.g. coagulase-negative *Staphylococcus*); and/or (3) UTIs.[9] UTIs were defined by growth of single urine pathogen with at least 50,000 colony forming units (CFU)/mL from catheterised urine specimen; or 10,000–50,000CFU/mL from a catheterised specimen with positive urinalysis (positive for leucocyte esterase, nitrite or pyuria at >5 WBCs; or at least 100,000CFU/mL from urine collected via voided specimens).[9] All other patients were classified into the non-SBI group. IBI was defined by bacteraemia and/or bacterial meningitis.

Clinical prediction tools

Determination of Lab-score was based on the original study (Fig. 1A). Briefly, 1 point was attributed to positive urine dipstick; 2 points for PCT ≥0.5ng/mL or CRP ≥40mg/L; and 4 points to procalcitonin ≥2ng/mL or CRP ≥100mg/L. Lab-score ≥3 was deemed high risk. Step-by-Step approach was applied according to the original study (Fig. 1B). Additionally, in our institution, the Step-by-Step approach was modified from the original algorithm (Fig. 1C), and this modified approach is also applied in our study. Based on PECARN rule, febrile infants were classified as low-risk following negative urinalysis, ANC <4,090/mm^3 and PCT <1.7ng/mL (Fig. 1D). We note that the Step-by-Step approach was originally formulated to predict IBIs. However, we chose to study its validity for both SBIs and IBIs in order to conduct a comprehensive investigation on the performance of Step-by-Step, Lab-score and PECARN rule. Since the validation of Lab-score and its publication, multiple studies have evaluated the cutoffs at which each biomarker show the best discriminative ability.[11-15] We chose to follow the established thresholds in Step-by-Step and PECARN rule of CRP >20mg/L and PCT >0.5ng/mL and 1.ng/mL as cutoffs as these are more recently developed than Lab-score.

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 22 (IBM Corp, Armonk, US). Normally distributed continuous variables were expressed as mean ± standard deviation. Non-normally distributed data were expressed as median and interquartile range (IQR). Comparisons between groups were performed using 2-sample t-tests for normally distributed data and Mann-Whitney U tests for non-normal data. Categorical variables were expressed as percentages and were compared using Fisher's Exact tests. We presented the univariate and multivariable regression for clinical and biochemical predictors of SBIs and IBIs. In the multivariable regression, we included covariates based on clinical rationale and statistical significance. In the multivariable regression, biomarkers were treated as continuous variables.

Diagnostic performance measures including area under the receiver operating characteristic curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR) and negative LR were calculated. Point estimates for AUC analyses were presented with a 95% confidence interval (CI). For analysis on diagnostic performance, all biomarkers were categorised using cutoffs derived from the literature (see section on Clinical prediction tools). Statistical significance was defined as P value <0.05.

The study protocol was approved by the ethics review committee of KK Women's and Children's Hospital (IRB: 2017/2680).

RESULTS

Patient population and demographics

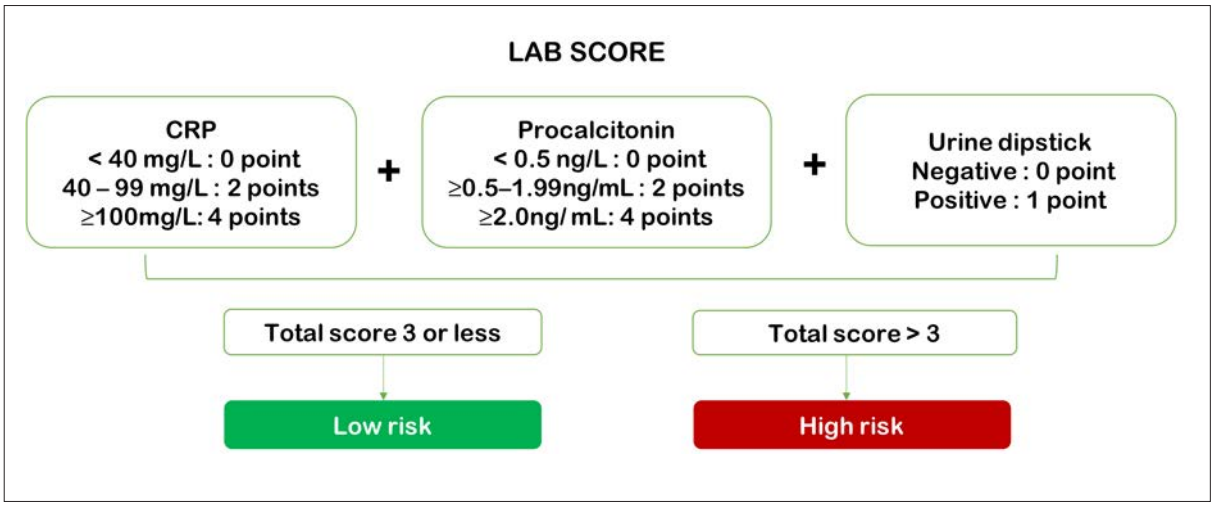
Among 468 febrile infants, we analysed 258 infants who met the inclusion criteria (Fig. 2). The overall median age was 47 days (IQR 14–64 days) and 100 patients (38.8%) were neonates. The median temperature at triage was 38.7°C (IQR 38.2–39.0°C). Sixty-one patients (29.3%) were born to mothers with group B *Streptococcus*. Eighty-six patients (33.3%) had SBIs and nine patients (3.5%) had IBIs. Table 1 shows the demographic and clinical characteristics of the study population in SBI, non-SBI, IBI and non-IBI groups.

Clinical characteristics and causative organisms

Among the 258 analysed infants, 77 (29.8%) had UTIs, 3 (1.2%) had bacteraemia and 1 (0.4%) had bacterial

Fig. 1. Risk stratification of febrile infants according to (A) Lab-score, (B) Step-by-Step (original) approach, (C) Step-by-Step (modified) approach, and (D) Pediatric Emergency Care Applied Research Network (PECARN) rule.

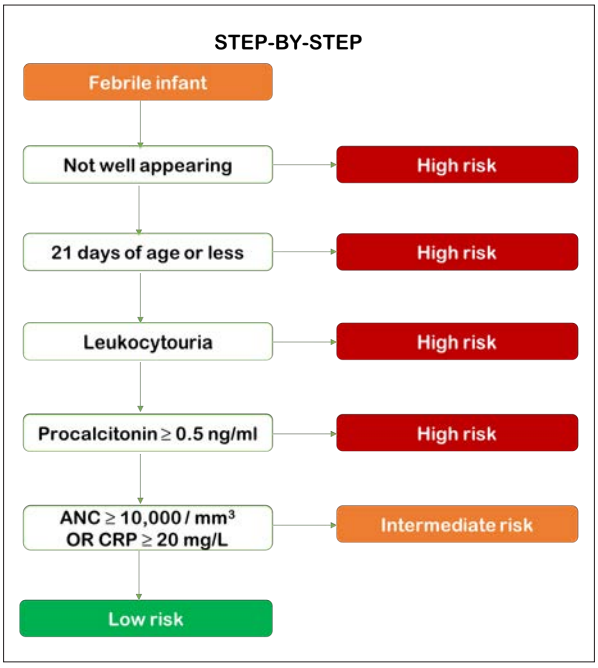
(A)



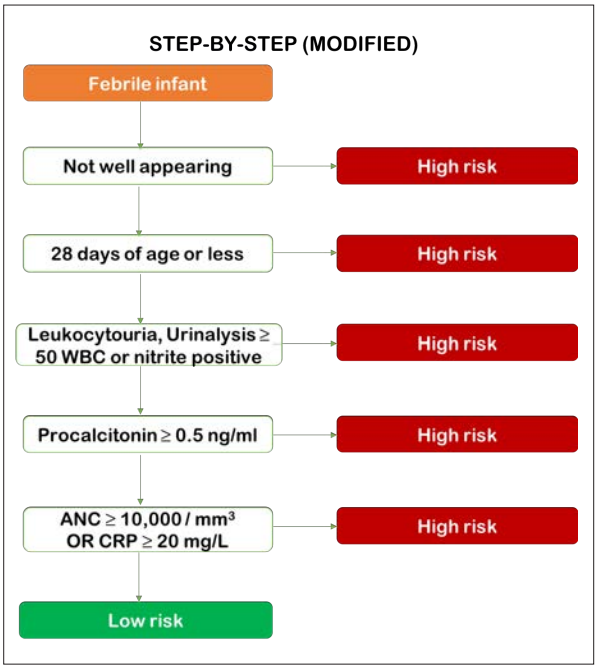
CRP: C-reactive protein

Adapted from Galetto-Lacour A, Zamora SA, Andreola B, et al. Validation of a laboratory risk index score for the identification of severe bacterial infection in children with fever without source. Arch Dis Child 2010;95:968-73.

(B)



(C)

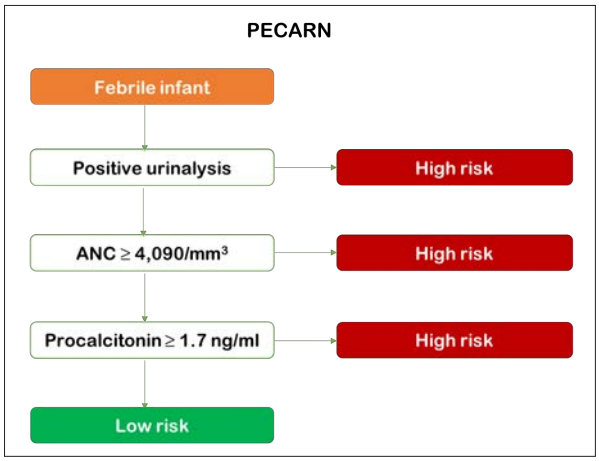


ANC: absolute neutrophil count; CRP: C-reactive protein; WBC: white blood cell

Adapted from Gomez B, Mintegi S, Bressan S, et al. Validation of the "Step-by-Step" approach in the management of young febrile infants. Pediatrics 2016;138:e20154381.

meningitis. In addition, 4 (1.6%) had concomitant UTI with bacteraemia and 1 (0.4%) had meningitis with bacteraemia (Table 2). The CSF of the child with meningitis grew group B *Streptococcus*. The CSF of the child with both bacteraemia and meningitis also grew group B *Streptococcus*. *Escherichia coli* was the most common pathogen causing both bacteraemia (2, 28.6%) and UTI (53, 65.4%).

(D)



ANC: absolute neutrophil count; PECARN: Pediatric Emergency Care Applied Research Network

Adapted from Kuppermann N, Dayan PS, Levine DA, et al. A Clinical Prediction Rule to Identify Febrile Infants 60 Days and Younger at Low Risk for Serious Bacterial Infections. JAMA Pediatr 2019;173:342-51.

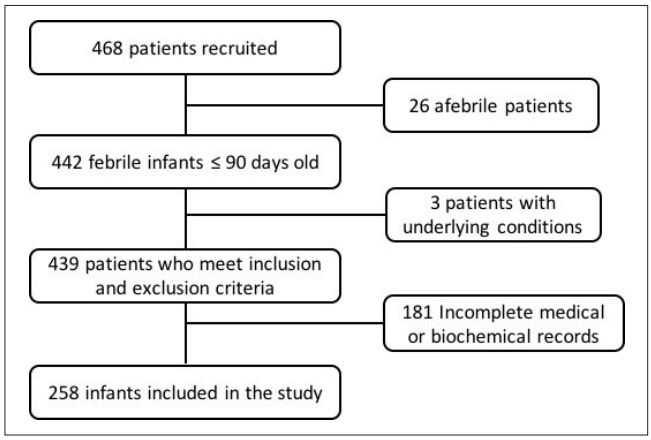


Fig. 2. Patient flow diagram.

Univariate and multivariate analyses for predictors of SBIs and IBIs

Median values for WBC, ANC, CRP and PCT were significantly higher in infants with SBI versus without SBI: WBC (15.8 vs 12.6, P<0.001), ANC (8.14 vs 5.38, P<0.001), CRP (37.4 vs 11.1, P<0.001), and PCT (0.46 vs 0.23; P<0.001). Only PCT was significantly higher in infants with IBI vs without IBI (9.27 vs 0.27, P<0.001) (Table 1).

In the univariate analysis, age, sex, temperature, positive urinalysis, WBC, ANC and CRP were significantly associated with SBIs (online Supplementary Materials, Supplementary Table S1). In the multivariable analysis, only temperature at triage and positive urinalysis were significantly associated with SBIs (online Supplementary Table S1). Male sex, temperature at triage, duration of fever, ANC, CRP and PCT were significantly associated with IBIs (online Supplementary Table S2). Only WBC and ANC were significantly associated with IBIs in the multivariate analysis (online Supplementary Table S2).

Diagnostic performance of single biomarkers, PECARN rule, Step-by-Step approach and Lab-score in predicting SBIs

We compared the diagnostic performances of single biomarkers ANC, CRP and PCT with cutoff levels at recommended thresholds as well as the 4 approaches. Notably, among the 3 single biomarkers, ANC ≥4,090/mm^3 had the highest sensitivity (80.2%) and NPV (80.2%) in predicting SBIs. PCT ≥1.7ng/mL had the highest specificity (95.9%) and PPV (77.4%) in predicting SBIs (Table 3). Among the 4 diagnostic approaches, the Step-by-Step (original) approach had the highest sensitivity in predicting SBIs (97.7%), which is notably higher than the sensitivity achieved with single biomarkers (Table 3). The Step-by-Step (original) approach had the highest NPV of 93.5% compared to PECARN rule and Lab-score (NPV of 86.3% and 77.6%, respectively).

CRP ≥20mg/L achieved the highest AUC of 0.741 (95% CI 0.672–0.810), higher than the AUCs achieved by the 4 approaches. Among the 4 approaches, Lab-score was found to have the highest AUC of 0.695 (95% CI 0.621–0.768), compared to PECARN rule with AUC of 0.625 (95% CI 0.556–0.694) and Step-by-Step with AUC of 0.573 (95% CI 0.502–0.644).

Diagnostic performance of single biomarkers, PECARN rule, Step-by-Step approach and Lab-score in predicting IBIs

In predicting IBIs, PCT ≥1.7ng/mL had the highest sensitivity, specificity, PPV and NPV among the single biomarkers. Additionally, it also achieved the highest AUC of 0.898 (95% CI 0.778–1.00), higher than those achieved by the 4 approaches (Table 4). Among the 4 approaches, Step-by-Step approach (both original and modified) had the highest sensitivity for predicting IBIs (sensitivity of 100%) whereas the PECARN rule and Lab-score both achieved a sensitivity of 88.9% (Table 4). Step-by-Step approach also had the highest NPV of 100% compared to the PECARN rule and Lab-score (Table 4). Lab-score had the highest specificity of 81.9%, compared to PECARN rule and Step-by-Step (original) approach (28.9% and 12.4%) (Table 4). Among the 4 approaches, the Lab-score had the highest AUC of 0.854 (95% CI 0.731–0.977) compared to PECARN rule with AUC of 0.589 (95% CI 0.420–0.758) and Step-by-Step (original) with AUC of 0.562 (95% CI 0.392–0.732).

Table 1. Patient characteristics and univariable analysis

Characteristics	Overall (n=258)	SBI (n=86)	Non-SBI (n=172)	*P* value	IBI (n=9)	Non-IBI (n=249)	*P* value
Age (median, IQR), days	47 (14–64)	55 (28–69)	36 (11–62)	**0.005**	31 (26–45)	51 (14–65)	0.590
Age at presentation, no. (%)				**0.041**			0.432
0–28 days	100 (38.8)	24 (9.3)	76 (29.5)		4 (1.6)	96 (37.2)	
29–60 days	81 (31.4)	32 (12.4)	49 (19.0)		4 (1.6)	77 (29.8)	
61–90 days	77 (29.8)	30 (11.6)	47 (18.2)		1 (0.4)	76 (30.5)	
Sex, no. (%)				**0.002**			0.582
Male	149 (57.8)	61 (23.6)	88 (34.1)		6 (2.3)	143 (55.4)	
Female	109 (42.2)	25 (9.7)	84 (32.6)		3 (1.2)	106 (41.1)	
Prematurity, no. (%)				**0.044**			0.482
No	245 (95.0)	85 (32.9)	160 (62.0)		9 (3.5)	236 (91.5)	
Yes	13 (5.0)	1 (0.4)	12 (4.7)		0	13 (5.0)	
Maternal GBS, no. (%)				0.622			0.190
No	147 (70.7)	51 (24.5)	96 (46.2)		4 (1.9)	143 (68.8)	
Yes	61 (29.3)	19 (9.1)	42 (20.2)		4 (1.9)	57 (27.4)	
Comorbidities, no. (%)				0.210			0.500
No	246 (95.3)	80 (31.0)	166 (64.3)		9 (3.5)	237 (91.9)	
Yes	12 (4.7)	6 (2.3)	6 (2.3)		0	12 (4.7)	
Well appearing, no. (%)							
No	17 (6.6)	6 (5.7)	11 (11.3)	0.859	2 (3.3)	15 (16.4)	0.543
Yes	241 (93.4)	80 (80.3)	161 (160.7)		7 (8.4)	234 (232.6)	
Temperature at triage, median (IQR), °C	38.7 (38.2–39)	38.9 (38.4–39.3)	38.5 (38.1–38.7)	**<0.001**	39.2 (38.7–38.9)	38.7 (38.2–39)	**0.002**
Duration of fever, mean (IQR), days	1 (0–4)	1 (0–4)	1 (1–2)	**0.034**	1 (1–4)	1 (0–3)	**0.024**
Positive urinalysis, no. (%)				**<0.001**			0.119
No	176 (68.2)	27 (10.5)	149 (57.8)		4 (1.6)	172 (66.7)	
Yes	82 (31.8)	59 (22.9)	23 (8.9)		5 (1.9)	77 (29.8)	
White blood cell count, median (IQR), $\times 10^9$/L	14.3 (3–31)	15.8 (3–31)	12.6 (4–30)	**<0.001**	11.7 (3–28)	14.3 (4–31)	0.796
Absolute neutrophil count, median (IQR), mg/L	6.8 (1–20)	8.14 (1–20)	5.38 (2–17)	**<0.001**	7.88 (1–20)	13.5 (2–20)	0.241
C-reactive protein, median (IQR), mg/L	21.1 (1–245)	37.4 (2–245)	11.1 (1–178)	**<0.001**	59.9 (3–194)	20.2 (1–245)	0.069
Procalcitonin, median (IQR), ng/mL	0.29 (0–121)	0.46 (0–86)	0.23 (0–121)	**<0.001**	9.27 (0–82)	0.27 (0–121)	**<0.001**

GBS: group B *Streptococcus;* IBI: invasive bacterial infection; IQR: interquartile range; SBI: serious bacterial infection

Table 2. Bacterial infections by age groups

Bacterial infections, no. (%)	Overall (n=258)	0–28 days (n=100)	29–60 days (n= 81)	61–90 days (n=77)
UTI	77 (29.8)	20 (20.0)	28 (34.6)	29 (11.2)
Bacteraemia	3 (1.2)	1 (1.0)	1 (1.2)	1 (0.4)
Bacterial meningitis	1 (0.4)	0	1 (1.2)	0
Bacteraemia and UTI	4 (1.6)	3 (3.0)	1 (1.2)	0
Bacteraemia and meningitis	1 (0.4)	0	1 (1.2)	0

UTI: urinary tract infection

Table 3. Diagnostic performance of single biomarkers, Pediatric Emergency Care Applied Research Network (PECARN) rule, Step-by-Step (original) approach, Step-by-Step (modified) approach and Lab-score for predicting serious bacterial infections

	Sensitivity	NPV	Specificity	PPV	Positive LR	Negative LR	AUC (CI)	*P* value
Step-by-Step (original)	97.7%	93.5%	16.9%	37.0%	1.18	0.136	0.573 (0.502–0.644)	0.057
Step-by-Step (modified)	91.9%	90.4%	38.4%	42.7%	1.49	0.211	0.651 (0.584–0.718)	<0.001
PECARN rule	88.4%	86.3%	36.6%	41.1%	1.39	0.317	0.625 (0.556–0.694)	0.001
ANC ≥4.09	80.2%	80.2%	40.1%	40.1%	1.34	0.49	0.602 (0.531–0.673)	0.008
CRP ≥20	61.6%	81.9%	86.6%	69.7%	4.61	0.44	0.741 (0.672–0.810)	<0.001
Lab-score	46.5%	77.6%	92.4%	75.5%	6.12	0.579	0.695 (0.621–0.768)	<0.001
PCT ≥0.5	41.9%	74.5%	84.9%	58.1%	2.77	0.68	0.634 (0.559–0.709)	<0.001
ANC ≥10	27.9%	72.0%	92.4%	64.9%	3.69	0.78	0.602 (0.525–0.678)	0.008
PCT ≥1.7	27.9%	72.7%	95.9%	77.4%	6.86	0.75	0.619 (0.542–0.696)	0.002

ANC: absolute neutrophil count; AUC: area under receiver operating characteristic curve; CI: confidence interval; CRP: C-reactive protein; LR: likelihood ratio; NPV: negative predictive value; PCT: procalcitonin; PPV: positive predictive value

DISCUSSION

In this prospective study, we compared the diagnostic performances of single biomarkers ANC, CRP and PCT, as well as 4 approaches—PECARN rule, Step-by-Step approach (original and modified) and Lab-score—in identifying febrile infants at risk of SBIs and IBIs. Overall, there were 86 patients (33.3%) who had SBI and 9 patients (3.5%) who had IBI. In predicting for SBI, WBC, ANC and CRP were shown to be good discriminators, with CRP ≥20mg/L achieving the highest AUC of 0.741. In predicting IBIs, PCT was shown to be a good discriminator, with PCT ≥1.7ng/mL achieving the highest AUC of 0.898. For SBI, the Step-by-Step approach (original) had the highest sensitivity and NPV, while Lab-score reported the highest specificity, PPV and AUC. For IBIs, the Step-by-Step (original) approach had the highest sensitivity and NPV, whereas the Lab-score reported the highest specificity, PPV and AUC.

Notably, the SBI rate in this study was higher compared with those reported in other centres.[10,16,17] In Singapore, KKH is one of 2 tertiary centres that receive referrals from primary care, which may account for the higher rates of disease, since otherwise well infants may be managed at the primary care level. UTIs account for the majority of the SBIs in this study, with *Escherichia coli* and *Klebsiella spp.* being the most common organisms, accounting for respectively 54 (66.7%) and 14 (17.3%) of UTI cases. The rates of UTI remain high across all age groups, including older infants 29–60 days (Table 2), emphasising the need to evaluate for UTI among older infants. *E. coli* also accounted for the majority of the cases with bacteraemia. This is consistent with previously reported studies.[10,18,19]

We found that CRP and PCT as single biomarkers were strong predictors of SBIs and IBIs. In line with the findings of previous studies,[6,20,21] CRP ≥20mg/L performed best in predicting SBIs with an AUC of 0.741.

Table 4. Diagnostic performance of the single biomarkers, Pediatric Emergency Care Applied Research Network (PECARN), Step-by-Step (original) approach, Step-by-Step (modified) approach and Lab-score for predicting invasive bacterial infections

	Sensitivity	NPV	Specificity	PPV	Positive LR	Negative LR	AUC (CI) *P* value
Step-by-Step (original)	100%	100%	12.4%	4.0%	1.14	0	0.562 (0.392–0.732) 0.526
Step-by-Step (modified)	100%	100%	29.3%	4.9%	1.41	0	0.647 (0.507–0.787) 0.135
PECARN rule	88.9%	98.6%	28.9%	4.3%	1.25	0.384	0.589 (0.420–0.758) 0.364
Lab-score	88.9%	99.5%	81.9%	15.1%	4.91	0.136	0.854 (0.731–0.977) <0.001
PCT ≥0.5	88.9%	99.5%	78.3%	12.9%	4.10	0.14	0.836 (0.712–0.960) 0.001
PCT ≥1.7	88.9%	99.6%	90.8%	25.8%	9.62	0.12	0.898 (0.778–1.00) <0.001
ANC ≥4.09	66.7%	96.5%	33.3%	3.5%	1.00	1.00	0.500 (0.308–0.692) 0.098
ANC ≥10	44.4%	97.7%	86.8%	10.8%	3.35	0.64	0.656 (0.450–0.862) 0.105
CRP ≥20	66.7%	98.4%	71.9%	7.89%	2.37	0.46	0.693 (0.511–0.874) 0.049

ANC: absolute neutrophil count; AUC: area under receiver operating characteristic curve; CI: confidence interval; CRP: C-reactive protein; LR: likelihood ratio; NPV: negative predictive value; PCT: procalcitonin; PPV: positive predictive value

CRP is a commonly available biomarker, but peaks later in the course of illness, typically 4–6 hours. In contrast, PCT levels rise quickly in response to bacterial infections, typically within 2–4 hours, but may take up to 6–12 hours to peak.[22] CRP performed better than PCT in predicting for SBIs in our population. We postulate that this could be because the majority of these infants receive their workup after hospitalisation rather than on presentation to the ED, therefore providing an adequate window for CRP to rise.

In predicting IBIs, PCT of >1.7 had the highest AUC of 0.898, compared to a PCT of >0.5ng/mL with an AUC of 0.836. The diagnostic values of PCT in this study correspond to those previously reported,[6,16,23,24] with most studies utilising the same thresholds. Indeed, systematic reviews and recent studies have concluded that PCT was superior to CRP in identifying IBIs.[25,26] However, the PCT cutoff values have been debated and vary from 0.12 to 1.0ng/mL, as different studies tried to differentiate invasive and non-invasive bacterial infections. We found that a PCT cutoff of 1.7ng/mL yielded similar sensitivity and NPV to a cutoff of 0.5ng/mL, and performed with much higher specificity (90.8% compared to 78.3%, respectively).

The PECARN rule in the original study by Kuppermann et al. reported a sensitivity of 97.7%, specificity of 60.0% and NPV of 99.6% in identifying infants who are at risk of SBIs.[9] In comparison, its validation in our cohort showed a lower sensitivity of 88.4%, specificity of 36.6% and NPV of 86.3% in predicting SBIs. The decrease in performance could be attributed to differences in patient populations and delivery of health services. Singapore is geographically a small nation and young infants with fever tend to arrive very early in the course of illness. Our population consisted of 23 infants in whom urinalysis was negative but urine cultures were positive for urinary tract infections. These accounted for a number of false negatives when the above algorithm was applied.

Unlike in the original derivation and validation study, Lab-score showed much lower sensitivities for predicting SBIs and IBIs in our cohort (46.5% and 88.9%, respectively), compared to 94% in the original study. Lab-score, which takes into account urinalysis, also resulted in missed cases in our population whereby urinalysis was normal but urine cultures turned positive. Although the sensitivity was low, specificity for Lab-score was high at 92.4% and 81.9% for SBIs and IBIs,

respectively. This resulted in the AUCs for Lab-score being higher in predicting SBIs and IBIs, when compared to the other approaches.

Due to the gravity of missed diagnoses in this vulnerable population, frontline physicians should choose a diagnostic approach with high sensitivity and NPV. The original Step-by-Step algorithm by Gomez et al. demonstrated a sensitivity of 92% and NPV of 99.3% for IBIs in febrile infants.[11] Our study showed a similarly high sensitivity and NPV in predicting SBIs (97.7% and 93.5%, respectively) and IBIs (100% and 100%, respectively). Notably, of all the approaches, the Step-by-Step (original) approach showed the highest sensitivity and NPV in predicting both SBIs and IBIs. However, due to low specificity, the overall AUC was not optimal (AUC of 0.573 for SBIs and 0.562 for IBIs). The team is working to refine the algorithm by recruiting a larger study population to drive locally derived thresholds rather than depend on the existing published thresholds.

Going forward, we are implementing a modified Step-by-Step algorithm to examine outcomes and missed cases, towards validating it as a safe tool for use in Singapore. Further studies should include that of non-invasive biomarkers such as heart rate variability[27] that may add to the emergency physician's armamentarium in deciding which febrile infant should receive priority in early investigations and broad-spectrum antibiotics.

Limitations

We recognise that our study has limitations. At the time of this study, PCT was not routinely assessed for all febrile young infants, resulting in the need to exclude some patients who did not have complete biochemical information. Some cases of bacterial meningitis might have been missed in our cohort because we only included culture-positive bacterial meningitis. However, we believe the number is small and it would not affect our final results. In addition, study investigators who were assessing outcomes were not blinded to the investigation results, which could have resulted in bias. However, we set out clear criteria for SBIs' and IBIs' limited subjectivity in outcome assessment. In the analysis, we recognise that performing a multivariable regression with the biomarkers may have suffered from collinearity, resulting in some biomarkers being rendered not significant at the final multivariable analysis. Finally, this is a single-centre study with limited generalisability due to differences in patient populations and physician practices.

CONCLUSION

In our population, Step-by-Step (original) approach had the highest sensitivity and NPV, while Lab-score has the highest specificity and AUC in predicting both SBIs and IBIs. CRP as a single biomarker was a strong predictor of SBIs, while PCT as a single biomarker was a strong predictor of IBIs.

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ORIGINAL ARTICLE

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Impact of aortic annular size and valve type on haemodynamics and clinical outcomes after transcatheter aortic valve implantation

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ABSTRACT

Introduction: Data on patients with small aortic annuli (SAA) undergoing transcatheter aortic valve implantation (TAVI) are limited. We aim to describe the impact of aortic annular size, particularly SAA and TAVI valve type on valve haemodynamics, durability and clinical outcomes.

Method: All patients in National Heart Centre Singapore who underwent transfemoral TAVI for severe symptomatic native aortic stenosis from July 2012 to December 2019 were included. Outcome measures include valve haemodynamics, prosthesis-patient mismatch (PPM), structural valve degeneration (SVD) and mortality.

Results: A total of 244 patients were included. The mean Society of Thoracic Surgeons score was 6.22±6.08, with 52.5% patients with small aortic annulus (<23mm), 33.2% patients with medium aortic annulus (23–26mm) and 14.3% patients with large aortic annulus (>26mm). There were more patients with self-expanding valve (SEV) (65.2%) versus balloon-expandable valve (BEV) (34.8%). There were no significant differences in indexed aortic valve area (iAVA), mean pressure gradient (MPG), PPM, SVD or mortality across all aortic annular sizes. However, specific to the SAA group, patients with SEV had larger iAVA (SEV 1.19±0.35cm^2/m^2 vs BEV 0.88±0.15cm^2/m^2, P<0.01) and lower MPG (SEV 9.25±4.88 mmHg vs BEV 14.17±4.75 mmHg, P<0.01) at 1 year, without differences in PPM or mortality. Aortic annular size, TAVI valve type and PPM did not predict overall mortality up to 7 years. There was no significant difference in SVD between aortic annular sizes up to 5 years.

Conclusion: Valve haemodynamics and durability were similar across the different aortic annular sizes. In the SAA group, SEV had better haemodynamics than BEV at 1 year, but no differences in PPM or mortality. There were no significant differences in mortality between aortic annular sizes, TAVI valve types or PPM.

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INTRODUCTION

The management of severe aortic stenosis (AS) in patients with small aortic annulus (SAA) represents a therapeutic challenge due to the increased mortality and major adverse cardiac events (MACE) seen in this group of patients even after surgical aortic valve replacement (SAVR).[1,2]

In recent times, the role of transcatheter aortic valve implantation (TAVI) has expanded significantly to include even those with low surgical risk.[3] With the increased life expectancy in this low-risk group, it has become imperative to understand the impact of aortic annular size and TAVI valve type on prosthesis-patient mismatch (PPM), structural valve degeneration (SVD) and other clinical outcomes. While the negative impact of PPM has been well elucidated in SAVR, the data within TAVI cohorts have been controversial.[4-6] Several studies have evaluated the medium-to-long-term valve durability of TAVI,[7-11] but there is limited data on patients with SAA especially in Western cohorts where

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CLINICAL IMPACT

What is New

- To the best of our knowledge, this is the first study in Southeast Asia evaluating the impact of aortic valve annular size, with a focus on small aortic annulus (SAA), for patients with aortic stenosis undergoing transcathether aortic valve implantation (TAVI).

Clinical Implications

- There were no significant differences in mortality between aortic annular sizes, TAVI valve types or prosthesis-patient mismatch (PPM) at 1 year.
- In the SAA group, while self-expanding valves may be considered given better haemodynamics and lower PPM than balloon expandable valves at 1 year, there was no significant differences in mortality.

patients with larger annular areas predominate; this information gap would be particularly useful in an Asian population, where a significant proportion have SAA.

This study aims to describe the impact of aortic annular sizing and TAVI valve type on valve haemodynamics and durability, as well as clinical outcomes in patients undergoing TAVI, with a particular focus on patients with SAA.

METHOD

All consecutive patients with severe symptomatic AS treated with TAVI at National Heart Centre Singapore from July 2012 to December 2019 were prospectively recruited into the registry (Centralised Institutional Review Board Reference 2014/2165). Details of the registry have been previously published.[12,13] In summary, a heart team was involved in the selection of patients, type of transcatheter aortic valve used, and approach. Registry participation did not impact clinical management. Written informed consent was obtained from all patients and ethical approval for the study was procured from the institutional review board. The TAVI procedure was carried out as per previously published standard protocols.[14,15] All patients underwent echocardiographic evaluation at baseline prior to intervention, before discharge, at 3 months follow-up and yearly thereafter.

All patients who had transfemoral TAVI performed for severe native aortic valve stenosis, and those with a computed tomography (CT) performed for valve sizing were included. Patients with severe aortic regurgitation, non-transfemoral TAVI, valve-in-valve TAVI, and use of other modalities for valve sizing (e.g. transoesophageal echocardiogram) were excluded.

All patients underwent pre-operative evaluation of the aortic valve and aortic root, as well as the aorto-ilio-femoral vasculature anatomy, with either a 64-detector or 320-detector row CT scanner (Canon Medical Systems Corp, Otawara, Japan). Acquisition protocols of multidetector computed tomography (MDCT) data were acquired as per recommended.[16-18] In brief, contrast-enhanced ECG-gated acquisition of the aortic root was performed after the injection of iodinated contrast, with the region of interest placed in the ascending aorta and axial slice of <1mm. All the MDCT data sets were recorded and stored for post-processing using 3mensio (3mensio Medical Imaging BV, Bilthoven, The Netherlands).[19] From the 3 multiplanar reformation planes and the 3-dimensional reconstruction, automatic segmentation of the aortic root and a centre line crossing the aortic lumen is provided. After validation of the lowest insertion points of all the aortic cusp and the perpendicular plane, the maximum, minimum and mean diameters, area and perimeter of the aortic valve annulus are measured using the systolic images, at 30–40% of the RR interval of the contrast-enhanced MDCT scans, for sizing of the device. This is based on either the annular area (for balloon-expandable valve [BEV]) or the perimeter (for self-expanding valve [SEV]) of the annular dimension. In addition, the coronary heights and the respective sinus of Valsalva, sinotubular junction and ascending aorta dimensions were obtained, as recommended.[16-18] Patients were stratified based on the aortic annular diameter derived on MDCT, either by area-derived (for BEVs) or perimeter-derived (for SEVs) method, with small annulus defined as <23mm, medium as 23–26mm, and large as ≥26mm, respectively.

Patients included in the registry were followed up based on a fixed schedule, with all patients completing in-hospital follow-ups, although not all patients completed 1-year follow-up. Outcome measures were based on Valve Academic Research Consortium 3-defined endpoints.[20] The primary outcome of this study was 1-year all-cause mortality. Secondary outcomes included in-hospital mortality, post-procedure complications, PPM and SVD. PPM was defined as an indexed aortic valve area (iAVA) of <0.85cm^2/m^2 based on the post-TAVI echocardiogram performed prior to the patient discharged on index admission for TAVI, with those between 0.65 and 0.85cm^2/m^2 classified as moderate, and <0.65cm^2/m^2 classified as severe. SVD

was defined by changes in mean pressure gradient (MPG) and aortic valve area (AVA) and/or new occurrence of aortic regurgitation (AR) compared with serial echocardiographic assessments performed post-procedure. Moderate SVD was defined as an increase in MPG≥10mmHg resulting in the mean gradient ≥20mmHg with a concomitant decrease in AVA ≥0.3cm^2 or ≥25%, and/or a new occurrence or increase of ≥1 grade of intraprosthetic AR resulting in ≥moderate AR. Severe SVD was defined as an increase in MPG≥20mmHg resulting in mean gradient ≥30mmHg with concomitant decrease in AVA≥0.6cm^2, and/or new occurrence, or increase of ≥2 grades of intraprosthetic AR, resulting in severe AR.

Continuous variables were expressed as mean±standard deviation (SD) and categorical data was expressed as proportions and percentages. Echocardiographic outcomes were limited in some patients and the percentages calculated for echocardiographic outcomes were based on the denominator of those with such parameters measured. Comparison between continuous data was performed using the independent t-test or one-way analysis of variance, while categorical data were compared using chi-square test or Fisher's exact test. Short-term outcomes between the different aortic annular sizes were compared using logistic regression, and longer-term outcomes were compared using cox regression with the corresponding hazard ratios (HRs) and 95% confidence intervals calculated. Subgroup analyses based on TAVI valve type and PPM were also performed. Univariate analysis was performed for clinically significant variables with P<0.10, and multivariate analyses was subsequently done to adjust for confounders. Statistical analyses were conducted using Stata version 16 (StataCorp, College Station, Texas).

RESULTS

A total of 244 patients with mean Society of Thoracic Surgeons (STS) score of 6.22±6.08 were included. The mean duration of follow-up was 1,147±798 days.

The majority of patients had a SAA, with 128 (52.5%) small (<23mm), 81 (33.2%) medium (23–26mm) and 35 (14.3%) large (≥26mm). There were more patients with SEV (65.2%) versus BEV (34.8%). Compared with other groups, patients with SAA weighed less (small 58.82±12.15kg vs medium 62.83±14.13kg vs large 64.73±12.45kg, P<0.001), were shorter (small 154.02±8.24cm vs medium 159.77±8.39cm vs large165.26±8.66cm, P<0.001), had lower body surface area (BSA) (small 1.55±0.18m^2 vs medium 1.66±0.2m^2 vs large 1.71±0.19m^2, P<0.001) and were predominantly female (small 64.84% vs medium 37.16% vs large 14.39%, P<0.001). There was also a lower proportion of patients with bicuspid valves (small 5.08% vs medium 18.75% vs large 29.41%, P<0.001). Mean left ventricular ejection fraction was higher for patients with SAA (small 57.16±11.24 % vs medium 49.80±14.49 % vs large 48.31±17.26%, P<0.001), as seen in Table 1.

The CT parameters for the different aortic valve annuli are also reflected in Table 1. Of note, aortic calcium score was significantly lower for patients with smaller aortic valve annulus (small 2,179.78±1,281.58 vs medium 27,86.05±22,076.32 vs large 3,221.67±1,740.49, P<0.007). There was, however, no significant difference for the presence of porcelain aorta.

In terms of pertinent periprocedural complications, there was no significant difference with regards to permanent pacemaker implantation (small 8.59% vs medium 7.41% vs large 8.57%, P>0.05) across the 3 groups.

Comparing haemodynamic outcomes, there was no significant difference in terms of PPM across different aortic annular sizes. While patients with SAA have a smaller AVA post-procedure (small 1.66±0.43cm^2 vs medium 1.75±0.45cm^2 vs large 1.93±0.52cm^2, P=0.0016) after correcting for BSA, iAVA did not show any significant difference (small 1.08±0.29 vs medium 1.09±0.32 vs large 1.12±0.25, P=0.821). This is also corroborated by no significant differences for MPG between the different aortic annuli. At 1 year, however, there were significantly more patients with larger annulus with at least moderate paravalvular AR (small 10% vs medium 15.38% vs large 33.33%, small vs medium P=0.358, small vs large P=0.036).

In terms of mortality, there were no significant differences with regards to in-hospital or 1-year mortality (Table 2), or throughout the entire follow-up period as demonstrated in the Kaplan-Meier survival curve (Fig. 1) (P>0.05).

From a valve durability standpoint, there were no patients who developed severe SVD up to 5 years of follow-up. Comparing the 3 groups, there was no significant difference in terms of SVD (Table 3). There were also no marked changes in AVA and MPG up to 5 years (Fig. 2).

Among those with SAA, patients who underwent SEV had a larger AVA (SEV 1.76±0.49cm^2 vs BEV 1.39±0.25cm^2, P=0.001), larger iAVA (SEV 1.19±0.35cm^2/m^2 vs BEV 0.88±0.15cm^2/m^2, P<0.001) and lower MPG (SEV 9.25±4.88mmHg vs BEV 14.17±4.75mmHg, P<0.001), at 1 year as illustrated in Fig. 3. However, there was no significant difference in

Table 1. Baseline and procedural characteristics of patients stratified by aortic annular size

Aortic annular size	Overall	<23mm	23–26mm	≥26mm	
	n=244	n=128	n=81	n=35	*P* value
Baseline characteristics					
Age, mean±SD, years	77.56±8.80	78.82±7.04	76.51±10.08	75.37±10.75	0.050
Male, no. (%)	134 (54.92)	45 (35.16)	59 (72.84)	30 (85.71)	<0.001
Body mass index, kg/cm^2	24.18±4.90	23.99±4.83	24.71±5.21	23.60±4.40	0.445
Weight, mean±SD, kg	59.95±13.26	56.82±12.15	62.83±14.13	64.73±12.45	<0.001
Height, mean±SD, cm	157.52±9.26	154.02±8.24	159.77±8.39	165.26±8.66	<0.001
Body surface area, mean±SD, m^2	1.61±0.20	1.55±0.18	1.66±0.20	1.71±0.19	<0.001
Smoker, no. (%)	38 (15.57)	14 (10.94)	17 (20.99)	7 (20.00)	0.110
Diabetes mellitus, no. (%)	92 (37.70)	45 (35.16)	32 (39.51)	15 (42.86)	0.650
Hypertension, no. (%)	203 (83.20)	111 (86.72)	64 (79.01)	28 (80.00)	0.300
Dyslipidaemia, no. (%)	179 (73.36)	96 (75.00)	62 (76.54)	21 (60.00)	0.150
Cerebrovascular disease, no. (%)	34 (13.93)	24 (18.75)	6 (7.41)	4 (11.43)	0.063
Chronic liver disease, no. (%)	14 (5.74)	8 (6.25)	3 (3.70)	3 (8.57)	0.548
Peripheral vascular disease, no. (%)	20 (8.23)	12 (9.45)	5 (6.17)	3 (8.57)	0.702
Obstructive lung disease, no. (%)	27 (11.07)	15 (11.72)	8 (9.88)	4 (11.43)	0.916
Coronary artery disease, no. (%)	174 (71.31)	93 (72.66)	59 (72.84)	22 (62.86)	0.490
Previous percutaneous coronary intervention, no. (%)	113 (46.31)	65 (50.78)	38 (46.91)	10 (28.57)	0.065
Previous coronary artery bypass graft, no. (%)	37 (15.23)	15 (11.81)	15 (18.52)	7 (20.00)	0.294
Atrial fibrillation, no. (%)	47 (19.26)	24 (18.75)	15 (18.52)	8 (22.86)	0.843
Estimated glomerular filtration rate, mean±SD	47.63±26.70	49.69±26.30	42.93±25.81	51.04±29.45	0.151
NYHA class III–IV, no. (%)	99 (40.57)	47 (36.72)	40 (49.38)	12 (34.29)	0.137
STS score	6.22±6.08	5.96±4.35	6.16±4.90	7.33±11.63	0.493
EuroScore II	5.57±6.94	5.09±5.35	5.75±6.55	6.97±11.69	0.369
Computed tomography measurements					
Aortic calcium score, mean±SD	2542.87±1698.76	2179.78±1281.59	2786.05±2076.32	3221.67±1740.49	0.007
Maximum diameter, mean±SD, mm	25.58±2.80	23.58±1.47	26.77±1.54	30.12±1.62	<0.001
Minimum diameter, mean±SD, mm	20.52±2.23	19.07±1.31	21.41±1.55	23.76±1.69	<0.001
Mean diameter, mean±SD, mm	23.03±2.31	21.29±1.18	24.08±0.89	26.94±1.13	<0.001
Area, mean±SD, mm^2	411.31±86.80	347.60±46.23	447.64±30.92	560.25±48.52	<0.001
Perimeter, mean±SD, mm	72.78±8.47	67.45±3.64	75.66±8.11	85.62±3.54	<0.001
Sinus of Valsalva average, mean±SD, mm	30.29±3.58	28.33±2.88	31.32±2.42	35.09±2.43	<0.001
Sintotublar junction, mean±SD, mm	26.04±3.52	24.50±3.10	26.93±2.78	29.57±3.28	<0.001
Sintotublar junction height, mean±SD, mm	19.69±2.76	18.40±2.04	20.41±2.36	22.74±3.00	<0.001
Ascending aorta diameter, mean±SD, mm	32.74±4.75	31.70±4.28	33.37±4.15	35.05±6.46	<0.001
Left main height, mean±SD, mm	13.83±7.70	13.21±10.24	14.04±2.97	15.63±2.74	0.249

Table 1. Baseline and procedural characteristics of patients stratified by aortic annular size (Cont'd)

Aortic annular size	Overall	<23mm	23–26mm	≥26mm	
	n=244	n=128	n=81	n=35	*P* value
Right coronary height, mean±SD, mm	16.39±2.53	15.26±2.17	17.03±2.04	19.03±2.31	<0.001
Porcelain aorta, no. (%)	36 (14.81)	18 (14.17)	16 (19.75)	2 (5.71)	0.142
Baseline echocardiographic parameters					
AvMPG, mean±SD, mmHg	48.31±16.30	47.64±16.14	49.71±17.32	47.52±14.58	0.648
AVA, mean±SD, cm^2	0.72±0.21	0.70±0.21	0.72±0.18	0.78±0.24	0.102
iAVA, mean±SD, cm^2/m^2	0.45±0.13	0.45±0.14	0.43±0.11	0.47±0.14	0.367
LVEF, mean±SD, %	53.43±13.87	57.16±11.24	49.80±14.49	48.31±17.26	<0.001
Aortic valve type					<0.001
Bicuspid, no. (%)	31 (13.36)	6 (5.08)	15 (18.75)	10 (29.41)	
Tricuspid, no. (%)	201 (86.64)	112 (94.92)	65 (81.25)	24 (70.59)	
Pre-procedure AR (≥moderate), no. (%)	73 (30.67)	42 (33.60)	22 (27.85)	9 (26.47)	0.582
Procedural details					
Contrast volume, mean±SD, mL	141.98±66.54	139.17±71.47	138.05±56.79	160.26±67.35	0.220
Procedural time, mean±SD, minutes	113.15±57.23	116.16±59.28	111.14±59.38	105.92±43.13	0.701
Valve type					0.017
BEV, no. (%)	81 (34.76)	33 (26.83)	31 (40.79)	17 (50.00)	
SEV, no. (%)	152 (65.24)	90 (73.17)	45 (59.21)	17 (50.00)	

AR: aortic regurgitation; AvMPG: aortic valve mean pressure gradient; AVA: aortic valve area; BEV: balloon-expandable valve; iAVA: indexed aortic valve area; LVEF: left ventricle ejection fraction; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons; SD: standard deviation; SEV: self-expanding valve

terms of PPM. There were also no significant differences with regard to the presence of AR or pacemaker implantation. Both inpatient and 1-year mortality was not significantly different between the groups (P>0.05) (Table 4).

Among patients with large aortic annuli, while there was a significant difference in iAVA during the index hospitalisation in those who underwent SEV compared to BEV (1.22±0.24 vs 1.02±0.24, P=0.042), there were no differences in aortic valve MPG. In addition, these differences were not seen at 1-year follow-up.

As seen in Table 5, for both medium and large aortic annuli, there were no significant differences in inpatient or 1-year mortality (P>0.05). Additionally, regardless of annular size, having at least moderate PPM did not have any significant differences in inpatient and 1-year clinical outcomes (P>0.05).

In the overall cohort, multivariate analyses (Table 6) demonstrated that aortic annular size (reference group small, medium HR 1.03, 95% confidence interval [CI] 0.54–1.98, P=0.929, large HR 1.85, 95% CI 0.83–4.09, P=0.133), TAVI valve type (reference group BEV, SEV HR 1.45, 95% CI 0.78–2.68, P=0.240) and moderate to severe PPM (HR 1.72, 95% CI 0.86–3.44, P=0.113) were not significant predictors of mortality. Independent predictors of mortality include obstructive lung disease (HR 2.21, 95% CI 1.05–4.64, P=0.036) and a lower estimated glomerular filtration rate (eGFR) (HR 1.02 95% CI 1.01–1.03, P=0.001).

DISCUSSION

In this study, we evaluated the impact of aortic annular sizing and TAVI valve type on valve haemodynamics and durability, as well as clinical outcomes in patients undergoing TAVI. In particular, there were substantial data on patients with SAA. We observed several significant findings: (1) annular size had no impact on valve haemodynamics, PPM or mortality; (2) in patients with small annular size, SEV had better valve haemodynamics than BEV but no differences in mortality; (3) moderate or severe PPM did not impact

Table 2. Inpatient and 1-year outcomes stratified by aortic annular size

	Overall	<23mm	23–26mm	≥26mm	*P* value (overall)	
	n=244	n=128	n=81	n=35	<23 vs 23–26	<23 vs ≥26
Inpatient outcomes						
AVA, mean±SD, cm^2	1.73±0.46	1.66±0.43	1.75±0.45	1.93±0.52	0.016	
iAVA, mean±SD, cm^2/m^2	1.09±0.30	1.08±0.29	1.09±0.32	1.12±0.25	0.821	
AvMPG, mean±SD, mmHg	10.63±4.85	10.37±5.02	11.27±5.02	10.03±3.62	0.331	
≥Moderate AR, no. (%)	28 (11.91)	16 (13.22)	7 (8.75)	5 (14.71)	0.333	0.823
≥Moderate PPM, no. (%)	43 (21.18)	24 (22.86)	15 (21.74)	4 (13.79)	0.863	0.293
Moderate PPM, no. (%)	30 (14.78)	18 (17.14)	9 (13.04)	3 (10.34)	0.466	0.378
Severe PPM, no. (%)	13 (6.40)	6 (5.71)	6 (8.70)	1 (3.45)	0.451	0.631
Cardiovascular death, no. (%)	4 (1.64)	2 (1.56)	1 (1.23)	1 (2.86)	0.846	0.619
MACE, no. (%)	16 (6.64)	7 (5.56)	6 (7.41)	3 (8.82)	0.593	0.489
Death, no. (%)	7 (2.87)	5 (3.91)	1 (1.23)	1 (2.86)	0.286	0.771
Myocardial infarction, no. (%)	3 (1.24)	1 (0.79)	1 (1.23)	1 (2.94)	0.754	0.351
Stroke, no. (%)	7 (2.87)	2 (1.56)	4 (4.94)	1 (2.86)	0.177	0.619
Major bleeding, no. (%)	1 (0.41)	1 (0.79)	0	0	-	-
New pacemaker implantation, no. (%)	20 (8.20)	11 (8.59)	6 (7.41)	3 (8.57)	0.76	1.00
1-year outcomes						
AVA, mean±SD, cm^2	1.70±0.42	1.64±0.45	1.73±0.38	1.94±0.31	0.043	
iAVA, mean±SD, cm^2/m^2	1.08±0.31	1.08±0.33	1.05±0.28	1.18±0.25	0.416	
AvMPG, mean±SD, mmHg	11.22±5.19	11.05±5.53	11.74±4.90	10.15±4.18	0.566	
≥Moderate AR, no. (%)	20 (13.89)	8 (10.00)	8 (15.38)	4 (33.33)	0.358	0.036
Death, no. (%)	19 (8.88)	8 (7.14)	6 (8.33)	5 (16.67)	0.779	0.119
Cardiovascular death, no. (%)	10 (4.67)	4 (3.57)	3 (4.17)	3 (10.00)	0.840	0.158

AR: aortic regurgitation; AvMPG: aortic valve mean pressure gradient; AVA: aortic valve area; iAVA: indexed aortic valve area; MACE: major adverse cardiac events comprising death, myocardial infarction and stroke; PPM: prosthesis-patient mismatch; SD: standard deviation

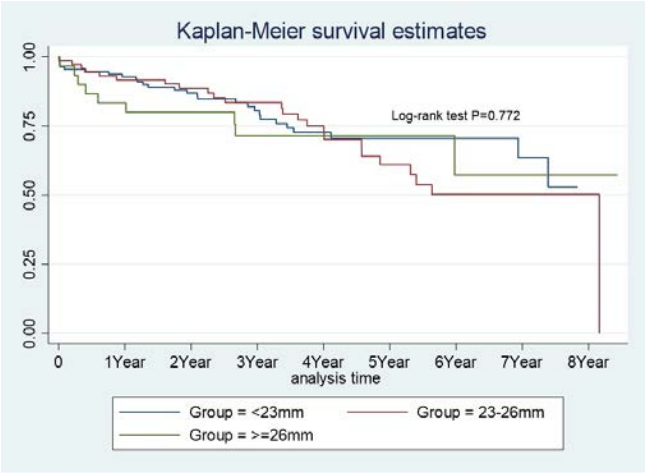

Fig. 1. Kaplan-Meier survival curve based on aortic annular size.

Fig. 2. Comparison of aortic valve area and mean pressure gradient over time based on aortic annular size.
AvMPG: aortic valve mean pressure gradient; AVA: aortic valve area

Table 3. Comparison of structural valve degeneration over time based on aortic annular size

	Overall		<23mm		23–26mm		≥26mm		*P* value
	n=244		n=128		n=81		n=35		
Moderate SVD	**n/total**	**%**	**n/total**	**%**	**n/total**	**%**	**n/total**	**%**	
1 year	13/122	10.66	6/65	9.23	6/46	13.04	1/11	9.09	0.802
2 year	10/105	9.52	3/56	5.36	6/38	15.79	1/11	9.09	0.239
3 year	8/75	10.67	3/36	8.33	4/30	13.33	1/9	11.11	0.806
4 year	5/57	8.77	3/26	11.54	2/25	8.00	0/6	0	0.656
5 year	3/34	8.82	1/14	7.14	2/17	11.76	0/3	0	0.770

SVD: structural valve degeneration

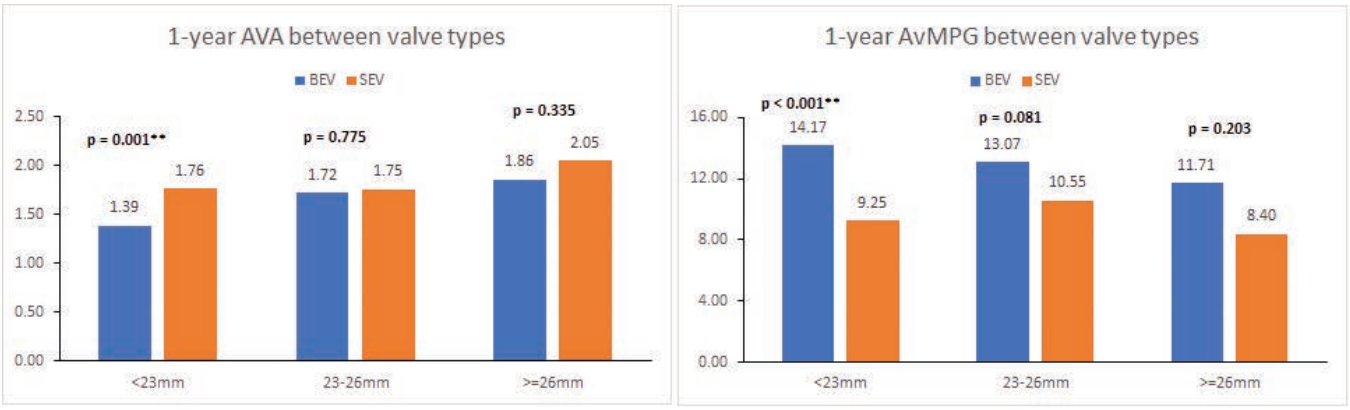

Fig. 3. Comparison of aortic valve area and mean pressure gradient over time based on aortic annular size and stratified by TAVI valve type.
AvMPG: aortic valve mean pressure gradient; AVA: aortic valve area; BEV: balloon-expandable valve; SEV: self-expanding valve

on mortality, at least at 1 year; and (4) annular size did not impact on longer-term SVD.

In terms of anatomic features, aortic annular size appears to be one of the most relevant factors that could theoretically play a major role in influencing valve haemodynamic performance and clinical outcomes.[21-23] In our cohort, however, we found that this theoretical risk with the SAA group was not apparent; the SAA group had similar valve haemodynamics, especially after correcting for BSA, and clinical outcomes as the other groups. These findings are corroborated by other similar studies, especially in other Asian populations where there are significant groups of patients with SAA.[22,24,25] Additionally, the SAA group in our cohort also had lower rates of paravalvular regurgitation post-intervention when compared to patients with larger aortic annulus. This is consistent with other studies with the postulation that the presence of an SAA minimises prosthesis-annulus incongruity, and allows for better apposition of the prosthesis to the native valve.[26] This might be clinically relevant in the long term as AR is known to be a determining factor of long-term mortality after TAVI.[27,28] On balance, longer observation and larger patient numbers may be required to validate a potential impact on long-term survival.

Studies have shown that SEV have better valve haemodynamics and lower PPM rates than BEV.[29,30] Anatomically, the result of better haemodynamics may be driven by the supra-annular location in SEV compared with intra-annular location in BEV.[21] These findings were also seen in our study but primarily in the SAA group. Importantly, there was no impact on mortality at 1 year regardless of valve type.

In terms of PPM, subgroup analyses of our cohort showed that moderate or severe PPM had no significant impact on mortality, at least at 1 year. The presence of severe PPM had been associated with negative outcomes, especially for patients post-SAVR.[31] However, the impact of PPM appears mixed for patients post-TAVI, with some reporting an increased risk of mortality,[4] while more recent studies showing no difference in clinical outcomes.[5,6,32] The theoretical negative impact of PPM can be explained by poorer haemodynamics resulting in a delay of regression of post-operative left ventricular hypertrophy, which may result in increased morbidity (through limitations in

Table 4. Inpatient and 1-year outcomes stratified by TAVI valve type for small, medium and large aortic annular size

	BEV	SEV	*P* value
Small	**n=33**	**n=90**	
Inpatient outcomes			
AVA, mean±SD, cm^2	1.55±0.41	1.72±0.43	0.076
iAVA, mean±SD, cm^2/m^2	0.97±0.27	1.15±0.28	0.006
AvMPG, mean±SD, mmHg	±4.72	9.25±4.52	0.004
≥Moderate AR, no. (%)	2 (6.45)	13 (15.29)	0.348
≥Moderate PPM, no. (%)	8 (29.63)	12 (16.22)	0.162
Moderate PPM, no. (%)	5 (18.52)	10 (13.51)	0.538
Severe PPM, no. (%)	3 (11.11)	2 (2.70)	0.117
Cardiovascular death, no. (%)	0	2 (2.22)	1.000
MACE, no. (%)	3 (9.09)	4 (4.55)	0.389
Death, no. (%)	3 (9.09)	2 (2.22)	0.119
Myocardial infarction, no. (%)	0	1 (1.14)	1.000
Stroke, no. (%)	0	2 (2.22)	1.000
Major bleeding, no. (%)	1 (3.03)	0	0.273
New pacemaker implantation, no. (%)	2 (6.06)	6 (6.67)	1.000
1-year outcomes			
AVA, mean±SD, cm^2	1.39±0.25	1.76±0.49	0.001
iAVA, mean±SD, cm^2/m^2	0.88±0.15	1.19±0.35	<0.001
AvMPG, mean±SD, mmHg	14.17±4.75	9.25±4.88	<0.001
≥Moderate AR, no. (%)	2 (8.70)	5 (9.62)	1.000
Death, no. (%)	3 (9.68)	5 (6.58)	0.688
Cardiovascular death, no. (%)	0	4 (5.26)	0.321
Medium	**n=31**	**n=45**	
Inpatient outcomes			
AVA, mean±SD, cm^2	1.78±0.36	1.79±0.48	0.920
iAVA, mean±SD, cm^2/m^2	1.09±0.27	1.12±0.34	0.703
AvMPG, mean±SD, mmHg	11.07±4.21	11.27±5.61	0.868
≥Moderate AR, no. (%)	1 (3.23)	6 (13.64)	0.228
≥Moderate PPM, no. (%)	5 (19.23)	7 (18.42)	1.000
Moderate PPM, no. (%)	3 (11.54)	5 (13.16)	1.000
Severe PPM, no. (%)	2 (7.69)	2 (5.26)	1.000
Cardiovascular death, no. (%)	0	1 (2.22)	1.000
MACE, no. (%)	2 (6.45)	4 (8.89)	1.000
Death, no. (%)	0	1 (2.22)	1.000
Myocardial infarction, no. (%)	1 (3.23)	0	0.408
Stroke, no. (%)	1 (3.23)	3 (6.67)	0.641

Table 4. Inpatient and 1-year outcomes stratified by TAVI valve type for small, medium and large aortic annular size (Cont'd)

	BEV	SEV	*P* value
Major bleeding, no. (%)	0	0	-
New pacemaker implantation, no. (%)	1 (3.23)	4 (8.89)	0.643
1-year outcomes			
AVA, mean±SD, cm^2	1.72±0.39	1.75±0.39	0.775
iAVA, mean±SD, cm^2/m^2	1.04±0.30	1.07±0.28	0.680
AvMPG, mean±SD, mmHg	13.07±5.58	10.55±4.19	0.081
≥Moderate AR, no. (%)	2 (10.53)	5 (17.24)	0.687
Death within 1 year, no. (%)	0	5 (11.63)	0.151
Cardiovascular death within 1 year, no. (%)	0	3 (6.98)	0.548
Large	**n=17**	**n=17**	
Inpatient outcomes			
AVA, mean±SD, cm^2	1.77±0.44	2.09±0.57	0.109
iAVA, mean±SD, cm^2/m^2	1.02±0.24	1.22±0.24	0.042
AvMPG, mean±SD, mmHg	10.71±3.33	9.67±3.75	0.416
≥Moderate AR, no. (%)	2 (11.76)	3 (18.75)	0.656
≥Moderate PPM, no. (%)	2 (15.38)	2 (13.33)	1.000
Moderate PPM, no. (%)	1 (7.69)	2 (13.33)	1.000
Severe PPM, no. (%)	1 (7.69)	0	0.464
Cardiovascular death, no. (%)	1 (5.88)	0	1.000
MACE, no. (%)	2 (11.76)	1 (6.25)	1.000
Death, no. (%)	1 (5.88)	0	1.000
Myocardial infarction, no. (%)	1 (5.88)	0	1.000
Stroke, no. (%)	0	1 (5.88)	1.000
Major bleeding, no. (%)	0	0	-
New pacemaker implantation, no. (%)	1 (5.88)	2 (11.76)	1.000
1-year outcomes			
AVA, mean±SD, cm^2	1.86±0.30	2.05±0.37	0.335
iAVA, mean±SD, cm^2/m^2	1.13±0.28	1.25±0.23	0.435
AvMPG, mean±SD, mmHg	11.71±3.64	8.40±4.83	0.203
≥Moderate AR, no. (%)	2 (28.57)	2 (50.00)	0.576
Death within 1 year, no. (%)	2 (13.33)	3 (21.43)	0.651
Cardiovascular death within 1 year, no. (%)	1 (6.67)	2 (14.29)	0.598
Overall	**n=81**	**n=152**	
Inpatient outcomes			
AVA, mean±SD, cm^2	1.69±0.41	1.79±0.47	0.144
iAVA, mean±SD, cm^2/m^2	1.03±0.27	1.15±0.30	0.007
AvMPG, mean±SD, mmHg	11.40±4.24	9.92±4.87	0.024

Table 4. Inpatient and 1-year outcomes stratified by TAVI valve type for small, medium and large aortic annular size (Cont'd)

	BEV	SEV	*P* value
≥Moderate AR, no. (%)	5 (6.33)	22 (15.17)	0.052
≥Moderate PPM, no. (%)	15 (22.73)	21 (16.54)	0.295
Moderate PPM, no. (%)	9 (13.64)	17 (13.39)	0.961
Severe PPM, no. (%)	6 (9.09)	4 (3.15)	0.094
Cardiovascular death, no. (%)	1 (1.23)	3 (1.97)	1.000
MACE, no. (%)	7 (8.64)	9 (6.04)	0.459
Death, no. (%)	4 (4.94)	3 (1.97)	0.241
Myocardial infarction, no. (%)	2 (2.47)	1 (0.67)	0.251
Stroke, no. (%)	1 (1.23)	6 (3.95)	0.426
Major bleeding, no. (%)	1 (1.25)	0	0.348
New pacemaker implantation, no. (%)	4 (4.94)	12 (7.89)	0.587
1-year outcomes			
AVA, mean±SD, cm^2	1.59±0.37	1.78±0.45	0.014
iAVA, mean±SD, cm^2/m^2	0.98±0.25	1.15±0.32	0.002
AvMPG, mean±SD, mmHg	13.39±4.94	9.63±4.65	<0.001
≥Moderate AR, no. (%)	6 (12.24)	12 (13.95)	0.779
Death within 1 year, no. (%)	5 (7.14)	13 (9.77)	0.531
Cardiovascular death within 1 year, no. (%)	1 (1.43)	9 (6.77)	0.169

AR: aortic regurgitation; AvMPG: aortic valve mean pressure gradient; AVA: aortic valve area; BEV: balloon-expandable valve; MACE: major adverse cardiac events comprising death, myocardial infarction and stroke; PPM: prosthesis-patient mismatch; SEV: self-expanding valve; TAVI: transcatheter aortic valve implantation

Table 5. Inpatient and 1-year outcomes stratified by presence of PPM for small, medium and large aortic annular size

	Without PPM	≥Moderate PPM	*P* value
Small	**n=81**	**n=24**	
Inpatient outcomes			
AVA, mean±SD, cm^2	1.82±0.34	1.13	<0.001
iAVA, mean±SD, cm^2/m^2	1.20±0.22	0.69	<0.001
AvMPG, mean±SD, mmHg	8.98±3.68	14.86	<0.001
≥Moderate AR, no. (%)	10 (12.35)	3 (12.50)	1.000
Cardiovascular death, no. (%)	0	1 (4.17)	0.229
MACE, no. (%)	1 (1.25)	2 (8.70)	0.124
Death, no. (%)	0	2 (8.33)	0.051
Myocardial infarction, no. (%)	0	1 (4.35)	0.223
Stroke, no. (%)	1 (1.23)	0	1.000
Major bleeding, no. (%)	0	0	-
New pacemaker implantation, no. (%)	6 (7.41)	4 (16.67)	0.231
1-year outcomes			

Table 5. Inpatient and 1-year outcomes stratified by presence of PPM for small, medium and large aortic annular size (Cont'd)

	Without PPM	≥Moderate PPM	*P* value
AVA, mean±SD, cm^2	1.65±0.47	1.48±0.29	0.184
iAVA, mean±SD, cm^2/m^2	1.10±0.34	0.96±0.21	0.122
AvMPG, mean±SD, mmHg	10.74±5.82	13.44±4.69	0.095
≥Moderate AR, no. (%)	4 (7.69)	2 (12.50)	0.620
Death, no. (%)	2 (2.94)	3 (13.64)	0.092
Cardiovascular death, no. (%)	1 (1.47)	2 (9.09)	0.147
Medium	**n=54**	**n=15**	
Inpatient outcomes			
AVA, mean±SD, cm^2	1.90±0.37	1.22±0.23	<0.001
iAVA, mean±SD, cm^2/m^2	1.19±0.27	0.71±0.11	<0.001
AvMPG, mean±SD, mmHg	9.65±4.12	16.20±5.13	<0.001
≥Moderate AR, no. (%)	6 (11.11)	0	0.327
Cardiovascular death, no. (%)	0	0	-
MACE, no. (%)	2 (3.70)	1 (6.67)	0.527
Death, no. (%)	0	0	-
Myocardial infarction, no. (%)	1 (1.85)	0	1.000
Stroke, no. (%)	1 (1.85)	1 (6.67)	0.390
Major bleeding, no. (%)	0	0	-
New pacemaker implantation, no. (%)	4 (7.41)	2 (13.33)	0.604
1-year outcomes			
AVA, mean±SD, cm^2	1.78±0.37	1.55±0.36	0.075
iAVA, mean±SD, cm^2/m^2	1.10±0.28	0.92±0.21	0.057
AvMPG, mean±SD, mmHg	10.39±3.85	15.50±5.64	0.001
≥Moderate AR , no. (%)	7 (20.00)	0	0.171
Death within 1 year, no. (%)	4 (8.33)	1 (7.69)	1.000
Cardiovascular death within 1 year, no. (%)	2 (4.17)	0	1.000
Large	**n=25**	**n=4**	
Inpatient outcomes			
AVA, mean±SD, cm^2	2.02±0.50	1.30±0.12	0.009
iAVA, mean±SD, cm^2/m^2	1.18±0.21	0.73±0.10	<0.001
AvMPG, mean±SD, mmHg	9.84±3.58	12.00±3.56	0.274
≥Moderate AR, no. (%)	5 (20.00)	0	1.000
Cardiovascular death, no. (%)	1 (4.00)	0	1.000
MACE, no. (%)	3 (12.50)	0	1.000
Death, no. (%)	1 (4.00)	0	1.000
Myocardial infarction, no. (%)	1 (4.17)	0	1.000
Stroke, no. (%)	1 (4.00)	0	1.000

Table 5. Inpatient and 1-year outcomes stratified by presence of PPM for small, medium and large aortic annular size (Cont'd)

	Without PPM	≥Moderate PPM	*P* value
Major bleeding, no. (%)	0	0	-
New pacemaker implantation, no. (%)	3 (12.00)	0	1.000
1-year outcomes			
AVA, mean±SD, cm^2	1.93±0.29	2.13±0.47	0.432
iAVA, mean±SD, cm^2/m^2	1.17±0.24	1.23±0.27	0.755
AvMPG, mean±SD, mmHg	10.67±3.94	5.50±2.12	0.114
≥Moderate AR, no. (%)	4 (44.44)	0	1.000
Death within 1 year, no. (%)	5 (23.81)	0	0.549
Cardiovascular death within 1 year, no. (%)	3 (14.29)	0	1.000
Overall	**n=160**	**n=43**	
Inpatient outcomes			
AVA, mean±SD, cm^2	1.88±0.38	1.18±0.23	<0.001
iAVA, mean±SD, cm^2/m^2	1.19±0.24	0.70±0.12	<0.001
AvMPG, mean±SD, mmHg	9.34±3.82	15.07±6.18	<0.001
≥Moderate AR, no. (%)	21 (13.13)	3 (6.98)	0.424
Cardiovascular death, no. (%)	1 (0.63)	1 (2.33)	0.316
MACE, no. (%)	6 (3.80)	3 (7.14)	0.400
Death, no. (%)	1 (0.63)	2 (4.65)	0.114
Myocardial infarction, no. (%)	2 (1.27)	1 (2.38)	0.509
Stroke, no. (%)	3 (1.88)	1 (2.33)	1.000
Major bleeding, no. (%)	0	0	-
New pacemaker implantation, no. (%)	13 (8.13)	6 (13.95)	0.244
1-year outcomes			
AVA, mean±SD, cm^2	1.72±0.43	1.55±0.36	0.050
iAVA, mean±SD, cm^2/m^2	1.11±0.31	0.96±0.22	0.020
AvMPG, mean±SD, mmHg	10.61±4.99	13.67±5.43	0.005
≥Moderate AR, no. (%)	15 (15.46)	2 (7.14)	0.357
Death within 1 year, no. (%)	11 (8.03)	4 (10.26)	0.745
Cardiovascular death within 1 year, no. (%)	6 (4.38)	2 (5.13)	1.000

AR: aortic regurgitation, AvMPG: aortic valve mean pressure gradient, AVA: aortic valve area, MACE: major adverse cardiac events comprising death, myocardial infarction and stroke, PPM: prosthesis-patient mismatch, SEV: self-expanding valve

physical activity) and mortality in the long run. With improvements and advances in the bioprosthetic valve hemodynamic performance in the past decades, the negative effects of PPM may be attenuated.[32] Our study adds to the growing evidence that PPM may not necessarily be related to increased mortality at least at 1 year, although this warrants longer follow-up to evaluate its effects on medium-to-long-term mortality.

In terms of valve durability, our study showed that annular size did not have an impact on SVD. While the medium-to-long-term valve durability of TAVI has been evaluated.[7-11] these have been mainly in Western cohorts of patients with predominantly larger annular areas. In summary, these studies have shown that valve haemodynamics remained consistent for up to 7 years, with similar freedom from severe SVD for TAVI when

Table 6. Multivariate analysis for independent predictors of overall mortality

	Hazard ratio	95% Confidence interval	*P* value
Aortic annular size			
<23mm	(reference)	(reference)	(reference)
23–26mm	1.03	0.54–1.97	1.97)
≥26mm	1.84	0.83–4.07	0.133
Decreased eGFR	0.98	0.97–0.99	0.001
NYHA III/IV	1.35	0.75–2.45	0.317
Obstructive lung disease	2.21	1.05–4.64	0.036
Moderate or severe prosthesis patient mismatch	1.75	0.88–3.50	0.113
Valve type			
BEV	(reference)	(reference)	(reference)
SEV	1.45	0.78–2.68	0.240

BEV: balloon-expandable valve; eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association; SEV: self-expanding valve

compared to SAVR. Given that severe PPM and small prosthesis size have been postulated to be potential factors leading to accelerated bioprosthetic degeneration,[33] data from patients with SAA is valuable. This study adds further knowledge in this burgeoning field, demonstrating the stability of valve haemodynamics especially in the SAA cohort up to 5 years. We acknowledge that longer-term studies are warranted—especially among younger patients with smaller bioprostheses who are at risk of requiring future interventions through valve-in-valve TAVI or redoing SAVR in the longer term.

Intrinsic limitations in our non-randomised prospective observational single-centre study are the possibility of bias that may not be fully accounted for even with the adjustment of confounders. Furthermore, the smaller patient numbers may not have been enough to detect smaller differences. However, the data do provide valuable insights, especially in a cohort with a significant proportion of patients with SAA. Lastly, there were fewer patients with long-term follow-up data; such information may be needed, especially for studying the outcome of SVD and the impact of PPM. Nevertheless, interesting hypotheses have been raised, which will be the work for future research.

CONCLUSIONS

Valve haemodynamics and durability were similar across the different aortic annular sizes. In the SAA group, SEV had better haemodynamics than BEV at 1 year, but no differences in PPM or mortality. There were no significant differences in mortality between aortic annular sizes, TAVI valve types or PPM.

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REVIEW ARTICLE

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Exploring loss and grief during the COVID-19 pandemic: A scoping review of qualitative studies

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ABSTRACT

Introduction: The COVID-19 pandemic has brought about multiple losses to various groups, namely patients, families and healthcare professionals. Grief, which is the reaction to these losses, could cause strain on these individuals' physical and mental health if not identified and managed early. This scoping review analysed loss, grief and how they were managed among these groups during the pandemic.

Method: This scoping review utilised the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement extension for Scoping Reviews (PRISMA-ScR) and the Joanna Briggs Institute framework for scoping reviews. Only qualitative studies relating to loss and grief and their management were included. Of 166 studies screened, 69 were included in the study. Qualitative analysis and data coding of each record were conducted through qualitative data analysis software.

Results: Losses included the death of family members, patients, colleagues and others. They also included the loss of usual routines, lifestyles and physical health. The grief experienced was multidimensional, affecting mainly the emotional, physical, social and existential realms. Anger, guilt and fear resulted from unsatisfactory farewells, issues with funerals, social isolation, financial strain and stigmatisation. Management strategies could be categorised into 5 themes: communication, finance, counselling, education and spiritual care.

Conclusion: Loss and grief identification and management among patients, family members and healthcare professionals are critically important during this COVID-19 pandemic. Current operating guidelines have proven insufficient in managing loss and grief. Innovative strategies are essential to tackle the many dimensions of loss and grief. Nevertheless, further research is necessary to better understand the effectiveness of implemented policies.

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Keywords: Bereavement, death, mourning, outbreak, palliative care

INTRODUCTION

As of mid October 2022, the World Health Organization recorded that more than 620 million people worldwide have been infected by SARS-CoV-2, the virus causing COVID-19, while over 6.5 million have succumbed to the disease. Many have lost family members and friends as well as jobs and familiar lifestyles, increasing the prevalence of depression, anxiety and stress. Besides accentuating the pervasiveness of grief during the pandemic, such losses go beyond deaths of loved ones, and encompass many aspects of life.

Loss and grief are multidimensional in nature and should be seen as biopsychosocial constructs. Losses can be categorised into physical, psychological and social, following the model of George Engel.[1] The grieving process reflects a unique convergence of responses to loss, be it behavioural, emotional or spiritual. Although the pandemic safety measures were well-intentioned, they accentuated the losses by imposing disruptions to the grieving process. These caused significant deleterious effects on the mental and physical health of the suffering individuals. The aim of this paper is to look at loss, grief and the management of grief across 3 groups of individuals most affected by the pandemic, i.e. patients, loved ones of patients and healthcare workers.

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CLINICAL IMPACT

What is New

- This study explored the complex loss and grief that COVID-19 is causing, by underscoring the many challenges encountered in the pandemic.
- The scoping review described the approaches to care for the different groups of stakeholders affected by the pandemic.

Clinical Implications

- The findings can guide collaboration efforts among healthcare institutes and governments for multidisciplinary interventions to reduce the impact of loss and grief.
- The understanding also supports further research on COVID-19 loss and grief, given the pandemic's shift towards becoming endemic.

METHOD

This scoping review utilised the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement extension for Scoping Reviews (PRISMA-ScR) and the methods outlined in the Joanna Briggs Institute Evidence Synthesis Manual for scoping reviews: (1) identification of research question(s); (2) identification of relevant studies; (3) selection of studies; (4) data extraction and charting; (5) summarisation and reporting of results; and (6) consultation.

Identifying the review questions

The main research questions were as follows: What were the loss and grief experienced by individuals during the pandemic? What were the interventions to manage the loss and grief of these individuals?

Literature search strategy

To retrieve relevant literature, the following databases were hand-searched: MEDLINE (PubMed), Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsychInfo and Cochrane Library. This was filtered to only include qualitative studies. The retrieval period spanned from establishment of each database to 5 August 2021. Search terms engaged comprised "COVID-19" (MeSH terms), "2019 Novel Coronavirus Disease OR 2019 novel coronavirus infection OR 2019-nCoV Disease OR 2019-nCoV infection OR COVID-19 pandemic OR COVID-19 pandemics OR COVID-19 virus disease OR COVID-19 Virus infection OR COVID19 OR Coronavirus Disease 2019 OR Coronavirus Disease-19 OR SARS Coronavirus 2 infection OR SARS-CoV-2 infection", "Bereavement" (MeSH terms), "Grief" (MeSH terms), "bereave OR grief OR mourning OR loss", "qualitative research" (MeSH terms), and "qualitative study OR qualitative research".

Inclusion criteria

Inclusion criteria for the study were: (1) qualitative studies; (2) individuals with losses and grief during COVID-19; (3) loss and grief management; (4) qualitative findings on experiences of loss, grief and bereavement; and (5) studies reported in the English language.

Study selection and data extraction

The literature retrieval was conducted with reference to the aforementioned inclusion criteria. The full-text articles included on the basis of title and abstract were further reviewed in detail.

Data extracted in this study included types of loss and grief, as well as loss and grief management.

Quality assessment of included studies

For qualitative studies, the Critical Appraisal Skills Programme (CASP) Qualitative Checklist was used for quality appraisal. The tool evaluates studies in 10 domains: (1) clear statement of the aims of the research, (2) appropriate qualitative methodology, (3) appropriate research design for aims of the research, (4) appropriate recruitment strategy for aims of the research, (5) appropriate data collection method for research issue, (6) adequate consideration of the relationship between researcher and participants, (7) consideration of ethical issues, (8) sufficiency of data analysis, (9) clear statement of findings, and (10) value of research (online Supplementary Table S1).

Qualitative analysis

Thematic analysis was conducted on the qualitative data, following a general inductive approach. The included studies were imported into QDA Miner Lite software version 2.0.8 (Provalis Research, Montreal, Canada). Themes and subthemes regarding loss, grief and management were extracted to build a coding schedule.

RESULTS

Literature screening process and results

All searches were performed on 5 August 2021. A preliminary search yielded 166 relevant studies after the removal of duplicates and the final sample size was narrowed down to 69 (Fig. 1).

The sample size for each group of individuals varied from 1 to 20. The most frequently mentioned affected groups were patients (8 studies), family members (17 studies) and healthcare professionals (20 studies). Among these, Dhavale et al. covered both patients and family members.[2] Others included the general community, religious community, disadvantaged community, students, pregnant women, elderly, and lesbian, gay, bisexual, transgender and queer or questioning (LGBTQ) youths (Table 1). With the exception of 7 studies, the patient demographics of the remaining 62 studies were diverse (online Supplementary Table S1).

Table 1. Summary of included studies

Groups	Number of articles (%)
Patients	8 (11.6)
Family members	17 (24.6)
Healthcare professionals	20 (29.0)
General community	5 (7.3)
Religious community	2 (2.9)
Disadvantaged community	4 (5.8)
Students	5 (7.3)
Pregnant women	6 (8.7)
Elderly	2 (2.9)
LGBTQ youths	1 (1.5)
Total	69

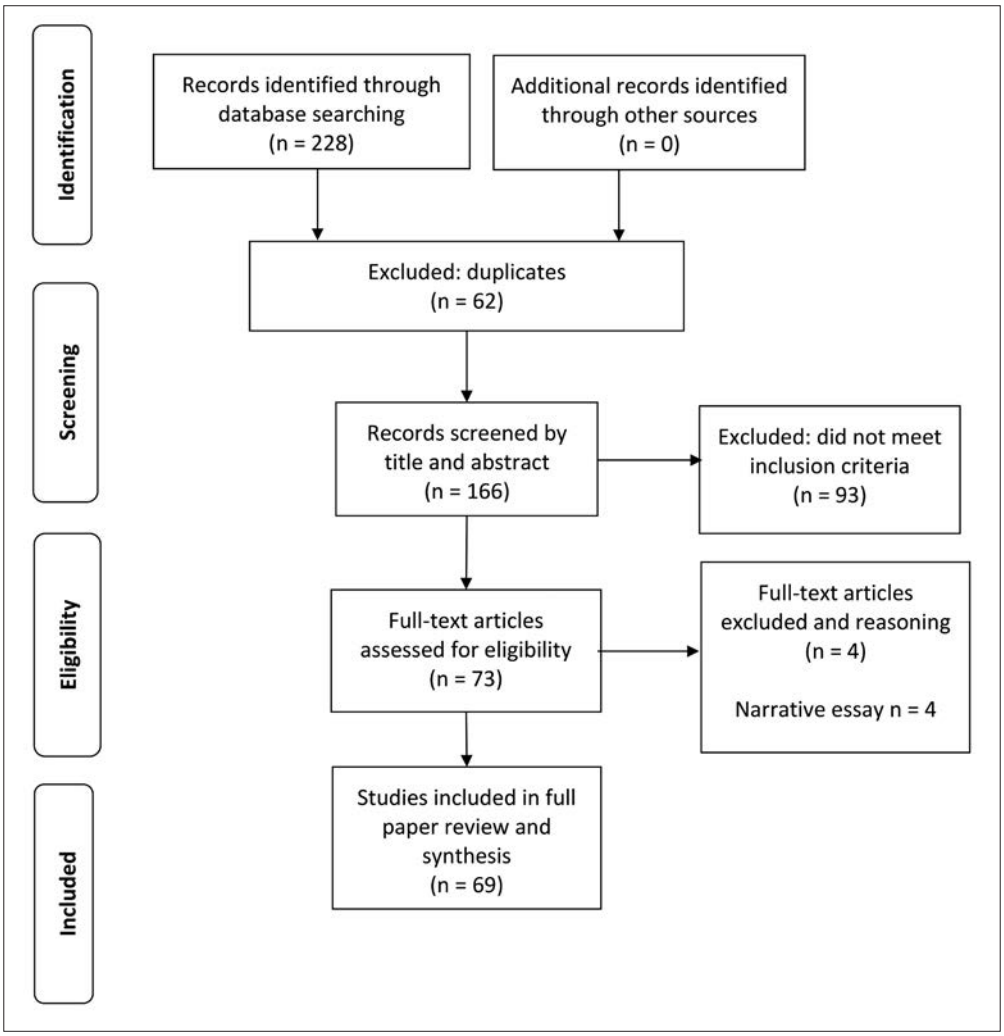

Fig. 1. The process of narrowing down the sample size of studies.

Data analysis

Patients

Eight (11.6%) of the included studies addressed loss and grief among the general patient population, highlighting patients' loss of physical health and the attendant emotional responses.[2-9] Initial symptoms such as fever, cough, anosmia and dysgeusia gave rise to anxiety and fear while social isolation resulted in boredom and loneliness.[2-9] Anxiety revolved around the family's well-being and the risk of transmitting the infection to them.[2,3] This was compounded by the inability to communicate with medical staff.[4,7,8] Communication barriers with the latter included language issues, use of medical jargon, lack of updates on the patient's health status and perceived inaccessibility of staff.[4,7,8] Inadequate communication translated to a sense of lack of autonomy in medical decision-making.[4,7] Patients felt that their opinions did not matter and were left out of the decision-making process.[4,7] There was an inequality in the balance of power between patients and staff, where patients face a loss of their "sense of self and autonomy".[4,7]

The unfamiliarity of the situation brought about by this viral pandemic sparked fear among patients. The changes in healthcare setting raised doubts on the outlook of public health.[2,6,7,9] Patients are uncertain about their quality of care in healthcare institutes.[2,6,8] This was exacerbated by misinformation disseminated through social media and other online platforms.[3]

Regulations barring visitors from healthcare facilities caused loneliness in patients due to physical separation from their families.[2-4,6-9] When prolonged, this isolation resulted in existential concerns.[3,4] Patients were afraid of losing their identity, being forgotten by society, and even not remembering their loved ones from cognitive loss.[4] Upon recovery, patients were worried about hospitalisation costs, their job status and the availability of follow-up care from severely stretched medical facilities.[2,3,6,9] The uncertainties surrounding their health and the risk of potential relapses caused patients to self-stigmatise and lose confidence in themselves.[3,9] This was aggravated in some places by the hospitals' inadequate protection of patient identities, resulting in patients being stigmatised and ostracised by society or "social death by the community".[3]

Family members

Seventeen studies (24.6%) looked at families who suffered the loss of an immediate family member to COVID-19.[2,10-25] The sense of loss and desolation was exacerbated by strict visiting restrictions that led, in turn, to reliance on medical staff for updates.[10,12,14,16,17,23] However, the perceived inadequacy of healthcare such as suboptimal medical intervention, absence of compassion and empathy, unanswered doubts, and contradicting accounts, contributed to the grief.[10,12,14,16,17,23] Residual feelings of guilt stemming from an unsatisfactory farewell as families were unable to physically accompany patients in their last moments, were also pervasive.[2,11,12,14-17,19,23,24] Families were also concerned about their own exposure to COVID-19 where logistical barriers to screening left them feeling abandoned by the healthcare system.[2,21,22]

The families' grief was accentuated during the immediate post-death and mourning period as a result of inconsistencies in the burial ceremonies, which caused anger at times.[13,15] They were either altered to "abnormal or unreligious burials" that lacked meaning, or worse, absent altogether.[11,14-16,19,21,22,24] Families thought these "incomplete ceremonies" were the product of "unjustified government policies" dehumanising their loved ones.[2,14,19,21] They were critical of the government for treating their loved ones as statistics in a system rather than as human beings.[14,21]

The loneliness of mourning in isolation, the desolation from multiple losses of family members dying in quick succession, and an inability to fully commit towards work and family, translated to a lack of closure.[13,15,16,19,20,22,24] The cancellation of social events, and difficulty in accessing formal counselling services denied people of outlets for their emotions, further prolonged this grieving process.[15,16,18,20] Beyond this, families were worried about their future.[11,13,24] In specific countries, government policies based on culture sparked instabilities within the family, especially when the deceased was the father of the household.[2,11,13,15,20,25] This was borne out by widows losing custody of the child and having to leave the household upon remarriage.[11] Financial burdens from unpaid medical bills and job losses from retrenchments aggravated existing difficulties in earning a livelihood and continuing the children's education.[2,11,13,15,20,25] Families of COVID-19 victims too were concerned about stigmatisation and feared that the community might be afraid to interact with them, causing social isolation.[11,15,24] Alternatively, these families might be labelled as pitiful or miserable, complicating the already limited social interactions available to them.[11,24]

Healthcare professionals

Twenty studies (29.0%) reported on healthcare professionals (HPs) who incurred a loss of routine, social connection and medical personal protective equipment (PPE).[26-45] Iheduru-Anderson[26] highlighted a shortage

of PPEs that had HPs feeling vulnerable due to the potential loss of physical health and grievance towards the "betrayal by employers".[26-29,31,35,40,45] They were angry at this perceived injustice and felt like the proverbial sacrificial lamb.[26,27,35] Paradoxically, donning PPE made them feel guilty of depriving others of protection.[26,27] Some other findings included the following: meetings with patients were limited or stopped altogether; there were no operating guidelines and healthcare facilities appeared to lack clear direction; information at workplaces was unreliable; and decision-making by departments was conflicting.[26-29,31,33,40,41,43,45] HPs were thus negatively impacted by these disruptions in normal work life. In addition, the loss of multiple patients simultaneously also left many feeling demoralised and inadequate.[26,27,35,40] Moral distress with ethical dilemmas was prevalent as autonomy and informed consent were forsaken to expedite decision-making processes.[26-28,41,43]

HPs found work physically and mentally draining as insufficient manpower gave rise to work overload, while off-days were replaced by stacked shifts.[26,27,34,36,37,43,45] Despite feeling exhausted, HPs felt the pressure to forego rest in order to adapt to the rapidly changing circumstances.[26,28,31,35,37] Repeated discussions about death with families and watching loved ones say goodbye to dying patients left many HPs overwhelmed, while some believed that hospital protocols were bereft of compassion and humanity.[26,27] HPs also feared contracting COVID-19 and transmitting the disease to their family.[26-28,31,32,34,38-40] In some countries, the unreliable screening process and slow results translated into HPs "social distancing" alone at home for longer periods.[35,39,43,45] This inadequate social contact wore down their mental well-being.[28,29,31,33,37,41,42] The fear of possibly losing their lives left HPs suffering from insomnia.[27,29,31,35,36,45] Stigmatisation by the general public further worsened the situation as some demonise HPs for spreading COVID-19.[26,28,29,36,40]

Others

Some studies described the experiences of specific groups such as the general community, elderly, disadvantaged, religious communities, students, LGBTQ youths and pregnant women. There were similarities with the above groups except for some unique observations.

General community

Several studies found the general community fearful and critical of government guidelines around social distancing and isolation.[46-50] Despite self-adherence to these guidelines, lack of adherence by others triggered a lack of trust in governmental enforcement efforts.[46]

Religious community

Religious communities reported divine struggles, losing faith in God due to their expectations not being met.[51,52] Some expressed doubts in the existence of God or forgot their connection with God entirely due to fear and anxiety towards the pandemic.[52]

Disadvantaged community

Disadvantaged communities highlighted fear due to the impracticality of social distancing and over-burdening of infrastructure.[53-56] The population size of such communities did not allow proper social isolation due to the limited size of their living quarters.[53,55,56] Stay-home orders also placed more burden on mobile toilets in these places, causing people to use nearby bushes as make-shift toilets without proper sanitation, thereby further lowering hygiene standards.[55]

Students

Students reflected concerns over ineffective learning environments due to a sudden transfer to virtual learning, where they were unable to retain information and connect with people.[57-61] Potential technological breakdowns led to time wastage waiting for system recovery, while being constantly online gave rise to worries about work-life balance.[58,60] The lack of physical teaching and supervision also led to the fear of their inability to complete course requirements.[58,60,61]

Pregnant mothers

Expectant mothers were fearful of catching COVID-19, especially near their delivery date, due to a lack of information about the birth and risk involved.[62-67] They also felt robbed of important life moments as they were unable to celebrate milestones, such as holding baby showers.[62,65]

Elderly

The elderly population indicated greater anxiety due to social isolation measures.[68,69] The perceived isolation and social disconnectedness predisposes them to anxiety disorders, especially in times of crisis.[68]

LGBTQ youths

LGBTQ youths, on the other hand, reported a loss of safe space.[70] They were anxious about staying home with unsupportive parents and lacking access to school support networks. These youths were also worried about judgemental parents overhearing their telephone conversations.

Interventions to manage loss and grief

Suggested interventions were multidisciplinary and multipronged. They involved multiple domains such as communication, finance, counselling, education, spiritual care and preparedness.

Communication

Communication should involve patients, family members and HPs. Daily updates should be provided to patients and families. The healthcare team must simplify their language, avoid medical jargon, and reassure patients and families that the former are receiving optimal care. Engaging patients and families in medical decision-making, and allowing them to express their concerns in an open, honest and respectful manner would relieve their worry. Although telecommunication technology could bolster family support and care, HPs should still check communication preferences and ensure digital literacy. They could be trained to communicate better with patients and families on end-of-life issues. Better communication between HPs could lead to teambuilding, companionship and better organisational rapport between supervisors and peers.

Finance

Financial aid was relevant for patients and families. Many have lost their jobs and sources of income due to the pandemic. Self-employed individuals closed down their businesses and lost all that they worked for. The down-turn in market, social distancing and lockdown measures led to a sharp decline in consumerism. Those in the food and beverage or aviation industry were especially affected, facing massive layoffs. When coupled with the medical bills that follow hospital admission due to the virus, financial burdens were at an all-time high. Government subsidies and grants would go far in resolving medical bills, living expenses and child education for these groups of individuals.

Counselling

Counselling was cardinal in "encouraging constructive processing of negative feelings".[7] The first step was for HPs to pay more attention to the mental status of patients and family members. Programmes and protocols needed to be developed to protect their psychological well-being. These could include counselling sessions for individuals to vent their feelings or concerns, regular follow-up phone-calls, or the provision of social support networks. Social media could garner community support for collective mourning, thus promoting emotional relief. For HPs, building resilience to counterbalance loss and trauma should be nurtured. Condolence or bereavement meetings to acknowledge patient death and debrief should be held regularly. Peer support and professional psychologists should be on standby as part of crisis intervention programmes. Policies protecting work-life balance and ensuring sufficiency of equipment should be established for HPs.

Education

Education was about providing timely and reliable information. This could present as pandemic awareness programmes and health promotion campaigns. Society should be encouraged to refrain from stigmatising and discriminating against patients, their families and HPs. Dissemination of accurate and up-to-date information about the disease helped to provide proper expectations of health outcomes and management. Patients could be taught self-help physiotherapy, or to incorporate technology such as virtual reality into their rehabilitation process. For HPs especially, healthcare facilities needed to provide clear guidelines and policies on palliative care to support the staff and reduce inconsistencies.

Spiritual care

Spiritual care went beyond rallying belief in a faith system and finding substance in a greater being. Governments could respect the preferences and religious identities of patients and their families without judgment. Funerals should be conducted in accordance with religious burial rites as far as possible, and in the company of family and friends. Otherwise, rituals were to be adjusted to balance patient and family needs while conforming to safety policies. To build on this, the government could provide education and referrals for families struggling with the logistics of special funeral arrangements. Objects with symbolic meaning could also be installed to remember victims.

DISCUSSION

The COVID-19 pandemic gave rise to an influx of articles that highlighted the loss and grief experienced by specific groups of individuals, while exploring pre-existing interventions and proposing new ones to tackle the issues at hand. Some of these articles approached the topic through thematic analysis as well. However, these existing studies were notably of narrower scope in terms of groups studied. Our analysis found that across all the literature reviewed, a few overarching themes regarding loss, grief and interventions could be identified and categorised: communication, finance, counselling, education and spiritual care. Our study also found that these 5 themes could be further harmonised into 3 approaches for application: communication, reassurance and preparedness.

Communication

In this study, we found that high-quality communication was paramount. This encompassed communication of understandable information addressing the availability of staff, medical care plan, inclusion of patients and families in care, and information dissemination to HPs. Inadequacies in communication induced emotional responses such as anxiety and frustration, which led to dissatisfaction and a lack of confidence among all stakeholders. These findings have implications for healthcare systems that wish to improve their care during the COVID-19 pandemic and beyond. Study findings emphasised the importance of effective strategies targeting the improvement in quantity and quality of communication. There should be regular training for HPs on elements of communications that patients and families favour for better rapport and satisfaction. These can come in the form of workshops, where HPs practise communication skills with simulated patients and are provided feedback at the end. Healthcare leaders could support everyone with clear instructions and regular updates. Daily updates on the latest protocols could be emailed to every HP, while scheduling briefings for everyone at the start of a new week or when there is launching of new protocols.

Despite the expansion of telecommunication, not everyone has the required equipment and digital literacy. Governments and healthcare institutes need to collaborate to overcome barriers to digital inclusion—social support, collaborative learning and provision of equipment. A multidisciplinary taskforce can be set up to assess each region's digital literacy, and free digital literacy workshops provided to those regions flagged out. In the setting of stretched social support manpower, creation of videography materials or brochures could also be a fall-back to educate patients and families on realistic expectations and resources for self-help. Current standard operating protocols could be updated to bolster efforts in orchestrating clear consistent messaging on the aforementioned levels. Collaborative efforts between the government and healthcare institutions are necessary to plan the processes of the new protocols. A separate committee of auditors could be established to ensure proper implementation that reaches all strata.

Reassurance

Our study highlighted the importance of reassurance in one's future. Worries about the impact of COVID-19 on lives were a recurrent theme in our findings. These were general concerns about physical health, financial difficulties, stigmatisation and more targeted concerns about the learning environment. COVID-19 aroused fear of the unknown and anxiety from unpredictable and uncontrollable situations, affecting the well-being of individuals due to their focus on negative emotions. For physical health, the authorities could streamline the screening process to resolve worries about exposure and relapses. Release of the definitive results of the screening could be prioritised, with the detailed medical report provided later. The government could establish financial benefit packages to support jobs and finances. The masses can be incentivised to patronise small businesses through the introduction of subsidies to ease living expenses, while helping to sustain the livelihood of small businesses as well. Data protection education to prevent leakage of personal data must be regularly held within institutes. Frequent campaigning through physical brochures or televised advertisements can promote awareness in limiting stigmatisation. As for students, the promotion of adaptability was vital to their engagement. Institutes need to reassure students of the continuity of their education with concrete schedules and timetables. Introduction to digital learning through crash courses and digital literacy assessments will lower students' dependency on physical delivery and heighten their confidence.

Preparedness

Lastly, our findings urged preparedness in both aspects of preventing loss and combating grief.

Preparedness applies to healthcare resources, protocols and government directives. Healthcare facilities needed to assign store managers to maintain an appropriate stockpile of equipment for emergencies. At the same time, regular business continuity planning is required to address foreseeable causes of equipment shortage.

Being ill-prepared predisposed individuals to complicated grief. Inability to adapt after loss delays the transition from acute to integrated grief, which can result in prolonged grief, as well as separation and traumatic distress (recurrent painful emotions and sense of disbelief). There should be training for HPs to identify distress and assist in the grieving process, with a support network of psychiatrists on standby. Some healthcare facilities do have welfare committees and counselling services readily available, but there is a lack of spiritual care protocols in place. Healthcare institutes could address this by setting up pastoral services to provide better engagement with religious groups. The pandemic makes it impractical to hold extended wakes or have large attendances but alternatives do exist. Relevant services could prepare alternatives such as virtual platforms instead of physical wakes, where the event is live-

streamed to overcome social distancing measures. No matter which option, uniform application of selected regulations across the nation is key. It is essential to craft relevant healthcare protocols and government directives for pandemics beforehand and ensure proper enforcement throughout. These should include the guarantee of reliable information, work-life balance, and burial processes. Clear and consistent instructions that integrate the perspectives of the masses inspires confidence and security. This ties back to the aspect of communication, where the necessity of these directives must be clearly explained to the masses, i.e. not to trivialise death, but to curb the spread of the pandemic and ensure everyone's safety.

Psychological interventions in the form of cognitive behavioural therapy (CBT) and mindfulness-based cognitive therapy (MBCT) can help to prepare individuals for acute grief. CBT can prevent poor coping behaviour such as avoidance and antagonistic confrontation, while challenging cognitive biases. Stress management is enhanced, improving psychological outcomes through inhibiting the prolongation of grief. MBCT utilises various mindfulness meditation practices to cultivate non-judgemental awareness. To cross physical boundaries, MBCT can be hosted on virtual platforms, which will prove beneficial to those in quarantine or in isolation facilities without access to mental health professionals. Virtual platforms are also an avenue for mutual peer support to cultivate resilience and foster companionship.

Strengths and limitations

To our knowledge, this review is the first in Singapore to synthesise evidence regarding broad principles of loss, grief and their management in the context of the COVID-19 pandemic. In addition, the quality of evidence of this study is high as evidenced by the CASP tool.

Nonetheless, this review was limited by the exclusion of non-English language reports that might be relevant, thus diminishing the scope of the study. In addition, the qualitative nature of the studies rendered the reported findings subjective, leaving grounds for dispute on the validity of our data. Furthermore, this review might not have achieved data saturation as not all plausible themes might have been captured. Given COVID-19's fast-changing development, this study only reflects a specific point in time of the pandemic. However, we believe our findings are still applicable to the general population as our sample size is relatively large for a qualitative evaluation (n=69). At the point of writing, the pandemic is still evolving rapidly, challenging healthcare systems and becoming endemic with the rollout of vaccination programmes in many countries. Many more people will be experiencing loss and grief in the near future. Studies must examine the experiences of these individuals during as well as after the pandemic is controlled. The effectiveness of the suggested system-level interventions should also be explored. Differences in cultural contexts will lead to significant variations in the implementation and effectiveness of system-level interventions. The specific intricacies could be further studied when more evidence citing cultural contexts is published. Further research can also be conducted for translating the suggested interventions proposed in this study to real clinical settings.

CONCLUSION

The COVID-19 crisis has caused many to suffer losses and experience grief. To maintain the biopsychosocial well-being of the people, governments and healthcare systems need to identify the demographics facing such conditions. The results of the present study show that patients, families and HPs are the main groups suffering from multifaceted losses and grief. Moreover, the impact of COVID-19 and current societal restrictions filled those afflicted with fear for their future, which further aggravated their emotional and psychological well-being.

In response, we propose collaborative efforts between the government, welfare organisations and healthcare systems to raise public awareness and establish guidelines to ensure the physical and psychological well-being of society. Healthcare officials and government policy-makers can use the findings of the present study to provide comprehensive and holistic support (physical and financial-social), and minimise psychological and spiritual distress to those suffering grief during this pandemic.

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REVIEW ARTICLE

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Nutrition therapy in the older critically ill patients: A scoping review

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ABSTRACT

Introduction: There is a lack of guidelines or formal systematic synthesis of evidence for nutrition therapy in older critically ill patients. This study is a scoping review to explore the state of evidence in this population.

Method: MEDLINE and Embase were searched from inception until 9 February 2022 for studies that enrolled critically ill patients aged ≥60 years and investigated any area of nutrition therapy. No language or study design restrictions were applied.

Results: Thirty-two studies (5 randomised controlled trials) with 6 topics were identified: (1) nutrition screening and assessments, (2) muscle mass assessment, (3) route or timing of nutrition therapy, (4) determination of energy and protein requirements, (5) energy and protein intake, and (6) pharmaconutrition. Topics (1), (3) and (6) had similar findings among general adult intensive care unit (ICU) patients. Skeletal muscle mass at ICU admission was significantly lower in older versus young patients. Among older ICU patients, low muscularity at ICU admission increased the risk of adverse outcomes. Predicted energy requirements using weight-based equations significantly deviated from indirect calorimetry measurements in older vs younger patients. Older ICU patients required higher protein intake (>1.5g/kg/day) than younger patients to achieve nitrogen balance. However, at similar protein intake, older patients had a higher risk of azotaemia.

Conclusion: Based on limited evidence, assessment of muscle mass, indirect calorimetry and careful monitoring of urea level may be important to guide nutrition therapy in older ICU patients. Other nutrition recommendations for general ICU patients may be used for older patients with sound clinical discretion.

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Keywords: Critical care nutrition, geriatric patients, intensive care medicine, older adults, scoping review

INTRODUCTION

The increasing levels of life expectancy and decreasing fertility are shifting the age structure of the world population towards older ages.[1] From year 2020 to 2050, population aged ≥65 years is expected to rise from 9.3% to 16%.[1] The number of older intensive care unit (ICU) patients are expected to rise correspondingly.

The growing number of older patients may warrant more specific nutrition recommendation. Ageing is associated with increased fat mass and decreased muscle mass.[2] These changes in body composition may have important implications to nutritional requirements and metabolism. However, to date, no guidelines for nutrition therapy specifically for older ICU patients exist. This might be due to the lack of systematic summary of critical care nutrition studies on older patients. Nevertheless, several narrative reviews are available to provide recommendations based on expert opinion.[3,4] Therefore, we aimed to systematically search the literature and explore the state of evidence of critical care nutrition in older ICU patients through a scoping review.

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CLINICAL IMPACT

What is New

- Results from this review suggest that the recommendations from the general adult critically ill population are also applicable to older patients, with some exceptions.

Clinical Implications

- Evaluation of nutrition risk and status should be done early upon intensive care unit admission to guide nutrition therapy.
- Objective assessment of muscle mass or muscularity status using imaging methods such as ultrasound may be considered to monitor the progress of nutrition therapy.
- Indirect calorimetry should be used to determine energy requirements if feasible.
- Older critically ill patients may require higher protein intake (~1.5kcal/kg/day) than younger patients, with careful monitoring of urea level to prevent azotaemia.

METHOD

This scoping review is conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) extension for scoping reviews checklist (online Supplementary Materials, Supplementary Appendix S1).[5]

We included original studies that enrolled critically ill patients aged ≥60 years, and investigated any area related to critical care nutrition. Conference abstracts and studies that did not enrol critically ill patients or investigate any nutrition-related topics were excluded. We searched MEDLINE and Embase from inception until 9 February 2022. The detailed search strategy is available in the online Supplementary Appendix S2. No language or study design restrictions were applied. The search was supplemented by screening the reference lists of published reviews.

We imported all references into Covidence (Veritas Health Innovation, Melbourne, Australia) to screen them and remove duplication. Two authors screened the titles and abstracts, and reviewed the full-text article of the potential studies to confirm their eligibility. Disagreements were resolved by consulting a third senior author.

Based on the authors' judgement, the included studies were grouped based on the topic investigated. The characteristics (e.g. first author name, year of publication, study design, sample size, mean/median age of patients) and main findings of the studies were summarised in separate tables for each topic identified in the included studies. Each co-author was assigned a topic to summarise, and accuracy of this was checked by the first author A generic table was provided to each co-author, which can be adapted to suit the summary work of each assigned topic. Critical appraisal of the included studies was not performed.

Post hoc, since there were limited ICU studies that specifically recruited older adults, we decided to include studies that enrolled adult patients but had subgroup analyses of older versus younger patients. However, such analyses were not apparent in the title or abstract, which reduced identifiability Hence, we only reported findings in the eligible studies and those that were known to the authors.

RESULTS

The databases identified 4,689 references, and 81 full-text articles were retrieved. About 1,148 citations were screened from previous review articles. Online Supplementary Appendix S3 shows the PRISMA flowchart and Appendix S4 lists the reason of exclusion of all retrieved studies that were excluded. We included 32 original studies, of which 5 were randomised controlled trials (RCTs). These studies were published from 1997 to 2021, with sample sizes ranging from 25–1,279. They were divided into 6 topics: nutrition screening and assessments (n=10), muscle mass assessment (n=5), route or timing of nutrition therapy (n=3, including 2 RCTs), determination of energy and protein requirements (n=6), energy and protein intake (n=4), and pharmaconutrition (n=4, including 3 RCTs).

Nutrition screening and assessments

Ten observational studies (5 prospective and 5 retrospective) were included, with sample sizes ranging from 87–1,250 (online Supplementary Materials, Supplementary Table S1).

Prevalence data

Studies that used validated nutrition assessment tools in critically ill patients[6] (i.e. Subjective Global Assessment [SGA][7,8] and Mini Nutrition Assessment [MNA])[8] showed that malnutrition prevalence in older patients ranged from 23.2–34.4%. Studies that used validated nutrition screening tools (i.e. MNA-short form [MNA-SF],8 Nutrition Risk Screening 2002 [NRS-2002],[8-10]

and Malnutrition Universal Screening Tool [MUST])[11] found that malnutrition-risk prevalence ranged from 25.8–71.2%. Other studies used nutrition screening tools that mainly relied on biochemical indices such as serum albumin (i.e. controlling nutritional status index [CONUT],[12] prognostic nutritional index [PNI],[12] geriatric nutritional risk index [GNRI],[10,11,14] and Onodera's prognostic nutritional index [OPNI]).[10] They reported 43.9–76.3% of older ICU patients had biochemical derangements. A study that used mid-arm circumference reported that 23.3% of older ICU patients had measurements below the 10th percentile of a population-specific database.[15] One study that used an ICU-specific nutrition score (modified nutrition risk in critically ill [mNUTRIC])[11] reported nutrition risk in 91.1% of the older ICU patients.

Prognostic data

Malnutrition assessed by the SGA, but not MNA, was associated with hospital mortality/needing hospice care and lower risk of being discharged home.[8] However, it was not associated with ICU and hospital length of stay (LOS).[8]

Malnutrition risk identified by NRS-2002 and MNA-SF was associated with a higher risk of hospital mortality/needing hospice care, but only NRS-2002 could prognose the risk of being discharged home.[8] Malnutrition risk identified by NRS-2002 was also associated with an increased risk of infection, complications, ICU mortality and longer ICU LOS.[9] Malnutrition risk defined by MUST was associated with higher mortality at 1-year post-discharge.[11]

Biochemical derangement measured by GNRI was associated with mortality (hospital or 30-day) and hospital LOS,[10,13,14] but not associated with ICU mortality and ICU LOS.[15] Similarly, biochemical derangements measured by CONUT and PNI were not associated with ICU mortality.[12]

Low mid-arm circumference was associated with a higher risk of 6-month mortality.[15] Older ICU patients with high mNUTRIC score had increased ICU, hospital or 30-day mortality, and ICU/ hospital length of stay.[10,16] However, patients with high mNUTRIC and achieved ≥80% prescribed calories and protein had lower ICU and/or hospital mortality.[16]

Muscle mass assessment

Five observational studies were included (2 prospective, 2 retrospective and 1 case-control study) with sample sizes ranging from 50–150 patients. All studies used imaging methods to assess muscle mass (online Supplementary Table S2).

Three studies assessed muscle mass using computed tomography (CT) scan and enrolled ICU patients aged ≥60[17,18] or ≥65.[19] Two studies measured skeletal muscle index[19] or skeletal muscle area (SMA)[17] at the third lumbar vertebral level (L3), and 1 study measured the dorsal muscle group area at the twelfth thoracic vertebral level.[18] The definitions for low muscularity (LM) used were from cancer patients,[20] ICU patients,[21] or derived internally.[18] The prevalence of LM was 71% in 1 study.[19] All studies found that muscularity status was associated with hospital mortality.[17-19] Furthermore, LM was associated with lower ventilation-free days and ICU-free days.[19]

Two studies enrolled adult ICU patients and demonstrated that older patients had significantly lower SMA at L3[22,23] and a higher prevalence of low muscularity,[22] compared to younger patients. Using ultrasound, 1 study found that mid-upper arm, forearm, abdomen and thighs muscularity was significantly lower in older than younger patients.[23] However, another study could not demonstrate a significant difference in quadriceps muscle layer thickness between older or younger ICU patients (1.2±0.5cm vs 1.4±0.7cm, respectively; P=0.57).[22]

Route or timing of nutrition therapy

Two RCTs and 1 retrospective observational study were included, with sample sizes ranging from 141–325 patients (online Supplementary Table S3). The first RCT investigated the effect of enteral nutrition (EN), parenteral nutrition (PN), and combined EN with supplemental PN.[24] Patients on PN had a higher rate of infectious and non-infectious complications than the other 2 groups. In contrast, mechanical ventilation (MV) duration, ICU and hospital LOS, and 20-day mortality were all significantly lower in the combined EN and supplemental PN groups compared to EN or PN group. The energy and protein received by each group was not reported.[24] The second RCT assigned patients to postpyloric vs gastric EN, and found that the incidences of ventilator-associated pneumonia, vomiting and abdominal distension were significantly lower in the postpyloric group. However, this was not translated into lower use of renal replacement therapy, shorter MV duration, ICU and hospital LOS, or a lower rate of ICU and hospital mortality.[25] Lastly, an observational study among older ICU patients with thermal injuries reported that early (<24h), compared with late (>24h) EN initiation was associated with a shorter ICU and hospital LOS, and a lower risk of sepsis, superficial skin infection, pneumonia and mortality.[26]

Determination of energy and protein requirements

Three prospective and 2 retrospective observational studies were included (online Supplementary Table S4), with sample sizes ranging from 25–103 patients. All studies included MV patients and found that predictive equations were not ideal in predicting resting energy expenditure (REE) measured by indirect calorimetry (IC) in older patients.[27-31]

Among 8 unique predictive equations with their variants, 1 study found that the Penn State (PSU) equation that included the Mifflin-St Jeor equation was the best equation for non-obese older (≥60 years) ICU patients.[28] Among obese older ICU patients, the PSU (modified) equation may be the best choice.[29] In another study comparing 6 predictive equations (without the PSU equation), the Harris-Benedict equation with a correction factor of 1.2 agreed most closely with IC measurements.[30]

In studies comparing older vs younger patients, measured resting metabolic rate (after controlling for basal metabolic rate)[32] or REE[31] was not different between groups. However, the absolute deviation (either over- or underestimation) of predicted (25 kcal*ideal body weight in kg) from measured REE was significantly higher in older vs younger patients (9.3±6.9 vs 6.3±6.6kcal/kg, respectively; $P<0.01$).[31] In critically ill trauma patients, the incidence of azotaemia (blood urea nitrogen >25mg/dL) was higher among older than younger patients with similar protein intake.[32]

Energy and protein intake

Four retrospective observational studies were included, with sample sizes of 55–1,279 (online Supplementary Table S5).

Three retrospective studies were conducted on critically ill trauma patients. The first study investigated a hypocaloric (21–25kcal/kg/day), high protein (≥2g/kg/day) regime for >10 days. No differences in nitrogen balance or clinical outcomes were found between older vs younger group.[33] Another study found that nitrogen balance can only be improved with a protein intake of >1.5g/kg/day in older patients, compared with >0.99g/kg/day in younger patients.[34] The third study showed that the calories received did not predict the time-to-discharge alive from the hospital for both older and younger groups.[35] Among MV COVID-19 patients, a retrospective analysis found no correlation between calories and protein intake with ICU LOS, hospital LOS, length of vasopressor use, and duration of MV in the older or the younger group.[36]

Pharmaconutrition

Four studies (3 RCTs and 1 non-randomised interventional trial) investigated the effect of pharmaconutrition (intravenous [IV] glutamine, EN glutamine or IV fish oils) in older ICU patients (online Supplementary Table S6).

Two RCTs from the same group of authors randomised patients into 3 groups (control vs IV glutamine vs IV glutamine + intramuscular recombinant human growth hormone)[37] and 2 groups (control vs IV glutamine).[38] IV glutamine was administered at 100mL/day for 2 weeks. Both studies found that IV glutamine reduced Acute Physiology and Chronic Health Evaluation II (APACHE II) and multiple organ dysfunction syndrome (MODS) scores at day 14, but this was not translated into improvements in MV duration, ICU LOS, or 28-day survival rate.[37,39]

One non-randomised trial compared standard EN vs IV fish oils at a dose of 0.2g lipid/kg body weight over 6 hours for 3 consecutive days. No differences were found between groups for ICU LOS, duration of MV and ICU mortality.[38]

The last study randomised patients into total parenteral nutrition (TPN) with gradual transition to full EN; EN + lower glutamine dose (0.3g/kg/day); and EN + higher glutamine dose (0.6g/kg/day). Compared to the TPN group, both glutamine groups had higher transferrin and prealbumin levels at day 7, and higher haemoglobin level at day 14. There was no difference in the incidence of diarrhoea and bloating between the groups at day 7 and 14. No clinical outcomes were reported.[40]

DISCUSSION

This scoping review found limited evidence for nutrition therapy in older critically ill patients. There were only 5 RCTs (sample size range: 90–147 patients) for 2 topics: route or timing of nutrition therapy and pharmaconutrition. In contrast, among general critically ill patients, up to December 2008, there were already 207 RCTs with 23,091 patients across 34 topics.[41] The results of each topic are discussed in the following sections.

Nutrition screening and assessments

Determination of malnutrition and its risk among ICU patients is important for prognostication and may be used to guide nutrition intervention. This is especially relevant for older patients as they may be at higher risk of malnutrition or already malnourished before ICU admission due to various physical or social factors.[42] Of the 2 nutrition assessment tools (SGA and MNA),

only SGA could prognose poorer clinical outcomes, and it is the most validated nutrition assessment tool in the general critically ill patients.[6] Of note, mid-arm circumference, a unidimensional assessment, may be inadequate to assess for malnutrition.

The American Society for Parenteral and Enteral Nutrition 2016 guidelines recommended using NRS-2002 and NUTRIC/mNUTRIC score to guide nutrition intervention.[43] Notably, only the NUTRIC/mNUTRIC was developed and validated among critically ill patients.[44,45] Hsu et al. reported that most older ICU patients had high mNUTRIC score (91.1%), and achieving ≥80% of prescribed calories and protein was associated with lower mortality.[16] However, the result of this observational study needs to be confirmed by high-quality RCTs.

Tools such as CONUT, GNRI, PNI and OPNI use biochemical markers like serum albumin and total lymphocytes to establish malnutrition risk. However, serum albumin and lymphocytes in an acute clinical setting reflect inflammatory status and disease severity rather than nutritional status.[46] These markers may have some prognostic value but using such tools may misguide treatment as they do not respond to nutritional interventions in an acute setting.[46]

Similar to general adult critically ill patients, current evidence suggests that mNUTRIC and SGA may be the best available tools to aid prognostication of clinical outcomes in older critically ill patients. High-quality RCTs are needed to determine whether these tools can identify patients who may benefit from higher nutrition delivery.

Muscle mass assessment

Skeletal muscle is the most abundant tissue and the main reservoir of amino acids for vital organs during the stressed state.[47,48] The direct measurements of muscle mass using imaging procedures such as CT and ultrasound at ICU admission may more precisely reflect patients' nutritional status.[49] Indeed, 3 studies consistently demonstrated higher hospital mortality in older critically ill patients with low muscularity at ICU admission.[17-19] Compared to younger patients, older patients tended to have lower skeletal muscle mass and higher prevalence of low muscularity at ICU admission.[22,23] For this reason, older ICU patients may experience greater nutrition-related complications than younger patients. Therefore, it may be crucial for older critically ill patients to receive early nutrition assessment and intervention. Further investigation is needed to determine whether a nutrition intervention that is tailored to age and/or muscularity status will result in improved clinical and functional outcomes.

Route or timing of nutrition therapy

First, it is well established that in haemodynamically stable patients with functional gastrointestinal tract, early rather than delayed EN is associated with significant clinical benefit.[50] Second, postpyloric EN is also known to reduce the risk of pneumonia and gastrointestinal complications without reducing the risk of mortality.[51] Regarding EN vs PN, infectious complications were found to be greater in the PN group if the calories received are higher than in the EN group.[52] However, the actual energy and protein received between groups were not reported.[24] The included study found significant clinical benefits of combining EN and PN;[24] however, this is not supported by a meta-analysis of RCTs in general ICU patients.[53] Overall, the evidence regarding the route and timing of nutrition therapy is limited but unlikely to be different from the findings of general critically ill patients.

Determination of energy and protein requirements

In general, REE should be measured using IC when available and feasible. In situations when IC measurements are not possible, PSU (Mifflin) or PSU (modified) may be used for non-obese and obese older critically ill patients, respectively. However, the PSU equations were developed >10 years ago and based on a Caucasian population.[28,29] It may be more appropriate to use a population-specific equation that is developed among critically ill patients, if available.[54,55] On the other hand, the benefits of using IC in older ICU patients remain unclear since none of the included studies investigated clinical outcomes. Recently, a systematic review and meta-analysis of RCTs demonstrated that IC-targeted energy delivery significantly reduced short-term mortality.[56]

Weight-based predictive equations were less accurate in older vs younger patients,[31] and older patients were also at higher risk of azotaemia than younger patients at similar protein intake.[32] Based on these limited evidence, the use of IC (if feasible) or age- and population-specific predictive equations, and careful monitoring of urea levels may be used to guide energy and protein prescription, respectively, in older ICU patients. Other protein monitoring strategies such as nitrogen balance, urea/creatinine ratio and monitoring of muscle mass trajectory may also be useful, though current evidence is lacking in this population.

Energy and protein intake

Older, compared to younger patients, required higher protein to achieve nitrogen balance (1.5 vs 0.99g/kg/day);[34] however, calories and protein intake were not associated with any clinical outcomes.[35,36] This is similar to 2 meta-analyses of RCTs in general ICU patients showing that higher calories and/or protein intake were not associated with any improvement in clinical outcomes.[57,58] Overall, the optimal energy and protein dose for older critically ill patients are yet to be determined. Physiologic data suggest that older patients require higher protein intake than younger patients;[34] however, caution needs to be exercised with higher protein as older patients are at a higher risk of azotaemia than younger patients at similar protein intake.[31]

Pharmaconutrition

The use of IV or EN glutamine and IV fish oils were not associated with clinical outcomes,[37-39] despite 2 studies showing improvement of APACHE II and MODS scores in the IV glutamine group.[37,39] Generally, the routine use of glutamine is not recommended except in burns and trauma ICU patients.[43,59] A recent meta-analysis of RCTs demonstrated that fish oils as part of PN formula or administered as a standalone medication was associated with improved clinical outcomes.[60] Further studies are needed to elucidate whether the treatment effect of pharmaconutrition is different in older vs younger patients.

Limitations

The low number and poor quality of evidence of the included studies for each topic preclude any reliable conclusion or clinical recommendations. These findings will hopefully encourage more high-quality original nutrition studies in this increasing population. The selection of studies with subgroup analysis of older vs younger patients that are known to the authors may have contributed to bias in the findings. However, we disclosed this in the methodology, and the similarity of our findings with published recommendations for general critically ill patients attest to a low risk of bias.[61] Future research may continue to build on our work by adding more studies that might have been missed by us into our tables.

This review did not identify studies on other aspects of critical care nutrition such as the use of micronutrients, monitoring of feeding tolerance, refeeding syndrome and glycaemic control; or the use of supplementation such as hydroxymethylbutyrate and leucine in older patients with sarcopaenia; or the effect of nutrition on functional outcomes. More studies are needed in these aspects.

CONCLUSION

The scarcity of data on nutrition therapy in older critically ill patients precludes any reliable clinical recommendations. Our review suggests that the recommendations from the general adult critically ill population are also applicable to older patients with the following exceptions. Evaluation of nutrition risk (mNUTRIC) and status (SGA) should be done early upon ICU admission to guide nutrition therapy, as older patients are at higher risk of having lower muscle mass compared to younger patients. Objective assessment of muscle mass or muscularity status using imaging methods such as ultrasound may be considered to guide and monitor the progress of nutrition therapy. IC or age- and population-specific predictive equations should be used to determine energy requirements. Older critically ill patients may require higher protein intake (~1.5kcal/kg/day) than younger patients with careful monitoring of urea level to prevent azotaemia.

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REVIEW ARTICLE

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Managing adult asthma during the COVID-19 pandemic: A 2022 review and current recommendations

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ABSTRACT

Introduction: This review aims to examine asthma management during the COVID-19 pandemic.

Method: Relevant recommendations and articles were identified by respiratory professional societies and PubMed search using the terms "asthma" and "COVID-19", and examined for relevance and inclusion in this study.

Results: Recommendations for the management of asthma have remained similar but are now supported by new evidence between the years 2020 and 2022. Patients with well-controlled, mild-to-moderate asthma are unlikely to be at increased risk of acquiring COVID-19 or having worse outcomes from COVID-19. All asthma patients should receive COVID-19 vaccination. Spirometry can be performed with the usual strict infection control procedures unless there is a suspicion of COVID-19. Mask-wearing and other health measures remain important for asthma patients.

Conclusion: While previous recommendations were largely based on expert opinion, the tremendous amount of literature published since the pandemic first emerged 2 years ago has helped guide respiratory professional bodies to update their recommendations. This study provides a timely review of the various recommendations and can be used to guide healthcare professionals in managing asthma patients, as the world prepares for a future with COVID-19 becoming endemic. The long-term consequences of COVID-19 infection in asthma patients and the ripple effects of COVID-19 remain uncertain and deserve ongoing study.

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Keywords: Asthma, coronavirus, COVID-19, SARS-CoV-2

INTRODUCTION

Asthma is the most prevalent chronic respiratory disease, estimated to affect more than 300 million people worldwide.[1] First recognised in December 2019, the coronavirus disease 2019 (COVID-19), which is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has evolved into an ongoing global pandemic.[2] In May 2020, a summary of recommendations for the management of asthma during the COVID-19 pandemic was drawn up by appraising and comparing recommendations from several professional bodies.[3] The article was born of an urgent need to provide preliminary guidance for healthcare professionals to manage their patients. Since then, there has been a torrent of studies and literature on asthma and COVID-19, with a plethora of new information from both qualitative and quantitative research, given the concerted global efforts to combat the pandemic. Periodic and timely review of the available evidence will assist healthcare professionals in providing the best possible care for asthma patients, as the world prepares for a likely future in which COVID-19 becomes endemic. In addition, it is important to recognise that the impact of the COVID-19 crisis is highly heterogeneous across the globe, which in turn affects the responses by individual countries and policymakers.[4]

This article aims to provide an update on recommendations for managing asthma in the Singapore context. Healthcare professionals should complement these recommendations with shared decision-making with individual patients.

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CLINICAL IMPACT

What is New

- This review provides an update on the recommendations for the management of asthma during the COVID-19 pandemic in 2022.
- COVID-19 has not been shown to affect the safety and efficacy of current asthma therapies. Inhaled therapies and biologics should be continued.
- Patients with poorly controlled asthma are at risk of increased mortality from COVID-19.
- Holistic and optimal care to ensure good control of asthma during COVID-19 is pertinent.

Clinical Implications

- Healthcare professionals should continue to keep abreast of the COVID-19 situation and latest recommendations from asthma guidelines.
- Long-term consequences of COVID-19 infection in asthma patients and the ripple effects of COVID-19 remain uncertain and deserve ongoing study.

METHOD

COVID-19 guidance related to asthma published by various professional bodies was reviewed for updates by comparing with the versions accessed in May 2020. The guidance documents were, namely, the Global Initiative for Asthma (GINA) guidance about COVID-19 and asthma,[5] and GINA's 2021 update to its Global Strategy for Asthma and Prevention,[6] which included a section on advice on asthma management during the COVID-19 pandemic; the National Institute for Health and Care Excellence (NICE) COVID-19 rapid guideline for severe asthma;[7] the British Thoracic Society (BTS) Advice for Healthcare Professionals Treating People with Asthma (adults) in relation to COVID-19;[8] and the National Asthma Council Australia's section in the Australian Asthma Handbook on managing asthma during the COVID-19 pandemic.[9] To supplement the information from the professional bodies, a search of the PubMed database using the Medical Subject Headings (MeSH) for the terms "asthma" and "COVID-19" was conducted. All articles published between January 2019 and December 2021 were included, with no restrictions on article type. The articles were screened for relevance and new information and, where appropriate, were discussed in the current review.

In the process, we sought to answer a few key clinical questions. These included but were not limited to the following:

1. Does having asthma affect the risk of getting infected with SARS-CoV-2, or increase the risk of worse outcomes in infected patients?
2. Is the treatment of asthma affected by the COVID-19 pandemic?
3. Is the management of patients with severe asthma affected by the COVID-19 pandemic?
4. What should be considered in terms of when and how to offer lung function testing to patients?
5. Is there new evidence regarding the use of nebulisers during the COVID-19 pandemic, or should nebuliser use continue to be avoided?
6. What are the recommendations for vaccinating patients with asthma, allergy, or both, against COVID-19? What other vaccines are recommended for asthma patients?
7. What are the recommendations regarding mask-wearing and social distancing measures for asthma patients?
8. Is there a role for telemedicine in managing asthma patients during the COVID-19 pandemic?

RESULTS

In addition to the review of recommendations from GINA, NICE, BTS and National Asthma Council Australia, the PubMed search yielded a total of 455 results.

Asthma and risks of COVID-19

Clinical question: Does having asthma affect the risk of getting infected with SARS-CoV-2, or increase the risk of worse outcomes in infected patients?

Key messages:

1. Asthma has not been shown to be associated with an increased risk of acquiring COVID-19.
2. Asthma patients who acquire COVID-19 do not appear to be at increased risk of hospitalisation or worse outcomes.
3. Some subgroups of asthma patients may be at higher risk, such as those with non-allergic asthma, those who had recently needed oral corticosteroids (OCS), hospitalised patients with severe asthma, and older patients with comorbid cardiovascular risk factors.

Much evidence on the association between asthma and COVID-19 has been accumulated, and asthma has

thus far not been shown to be associated with an increased risk of acquiring COVID-19.[10] Data from a systematic review and meta-analysis of 150 studies worldwide similarly did not find clear evidence of increased risk of COVID-19 diagnosis in asthma patients.[11] Strengths of the review include the multiple meta-analyses performed to compare the various outcomes of interest, the large number of studies included in the analyses, the comparison of asthma prevalence in the studied populations against the known prevalence in the general populations of multiple geographical regions, as well as the use of multivariate analysis to account for confounding variables when investigating the association between asthma and COVID-19 mortality. There has also been no clear evidence of hospitalisation or worse outcomes due to COVID-19 in asthma patients.[12-15] In a systematic review and meta-analysis of 389 studies that included clinical trials, observational studies, retrospective studies, case series and conference abstracts, asthma was not found to be associated with an increased risk of hospitalisation, length of hospitalisation, ICU admission or death among patients with COVID-19.[16]

However, limited evidence suggests that some subgroups of asthma patients may be at higher risk. The World Health Organization (WHO) proposes that non-allergic asthma was associated with worse outcomes compared with allergic asthma.[10] This suggestion is based on a propensity score-matched nationwide cohort study performed in South Korea, which found that individuals with non-allergic asthma had a greater risk for severe outcomes of COVID-19 (adjusted odds ratio 4.09, 95% confidence interval [CI] 1.69–10.52) than those with allergic asthma (adjusted odds ratio 1.40, 95% CI 0.83–2.41).[17] GINA notes that the risk of COVID-19 death increased in people who had recently needed OCS for their asthma[18] and in hospitalised patients with severe asthma,[19] suggesting that poorly controlled asthma might result in an increased risk of COVID-19-related death. In addition, as with the general population, the risk of more severe outcomes may be increased in some subsets of asthma patients, for example, older patients with comorbid cardiovascular risk factors such as hypertension, dyslipidaemia and diabetes.[20]

The current evidence is nevertheless reassuring for patients with well-controlled asthma. It remains important to continue good asthma management with strategies to maintain good symptom control, reduce the risk of severe exacerbations and minimise the need for OCS use.

General management of stable asthma

Clinical question: Is the treatment of asthma affected by the COVID-19 pandemic?

Key messages:

1. Physicians should continue to manage asthma according to recommendations from current asthma guidelines, including those from Singapore guidance where applicable
2. All asthma patients should continue all of their prescribed medications, especially inhaled corticosteroids.
3. Where indicated, short courses of OCS should be given, such as for acute exacerbations of asthma.
4. Patients should be provided with updated written asthma action plans to help them manage any worsening asthma and to reduce the need to visit healthcare facilities.

Recommendations by the various professional bodies remain similar but are now supported by new evidence that has emerged.[6,8,9] Therefore, key recommendations in the previous review remain relevant.[3] Physicians should continue to manage asthma according to current asthma guidelines, including those from Singapore guidance where applicable, and continue to ensure optimal control of asthma. It is recommended that all asthma patients continue their prescribed medications, especially inhaled corticosteroids. An updated written asthma action plan should be provided for self-management of asthma, to reduce the need to visit healthcare facilities. When indicated for exacerbations, short courses of OCS should be given. Patients should also continue to follow other advice for the general public (e.g. observing good personal hygiene, avoiding crowded areas where possible, and wearing masks especially in crowded areas and when indoors).

Management of severe asthma

Clinical question: Is the management of patients with severe asthma affected by the COVID-19 pandemic?

Key messages:

1. Where appropriate, biologic therapies should be used in eligible severe asthma patients to reduce OCS exposure and complications arising from long-term use.
2. There is currently no evidence that biologic therapies for asthma suppress immunity.
3. At-home administration of biologics can be considered, particularly during periods when community transmission rates are high.

The previous recommendations for the management of asthma in the COVID-19 pandemic from the asthma management guidelines remain relevant.[3] As with all asthma patients, all treatments, including maintenance OCS, should be continued in those with severe asthma to reduce the risk of severe exacerbations. Where appropriate, biologic therapies should be used in severe asthma patients who qualify for such treatment, to reduce OCS exposure and complications arising from long-term use. To date, there is no evidence that asthma biologic therapies are associated with a higher risk of SARS-CoV-2 infection or more severe COVID-19.[8,21] As the risk of COVID-19 death may be increased in people who had recently needed OCS for their asthma[18] and in hospitalised patients with severe asthma,[19] patients with severe asthma should continue to receive all therapies according to current guideline recommendations in order to reduce the risk of COVID-19-related death.

To further reduce the risk of getting infected with SARS-CoV-2 in the course of travelling to and visiting healthcare facilities, at-home administration of biologics can be considered. The professional bodies currently do not mention this aspect of treatment. However, there is increasing evidence that at-home administration of asthma biologics, with the availability of newer self-injectable forms of the biologics, is as equally efficacious and safe as in-office administration, while increasing patient convenience.[22] This convenience has to be balanced against the benefits of in-office administration, such as the ability to monitor for safety concerns, confirm adherence, and allow patients to have their questions addressed, which may improve asthma care.[23] The place of administration ultimately needs to be individualised, but at-home administration could be a useful option, particularly during periods when community transmission rates are high.

Role of spirometry

Clinical question: What should be considered in terms of when and how to offer lung function testing to patients?

Key messages:

1. Lung function testing should not be curtailed indefinitely and should be resumed within the constraints of a COVID-19 endemic scenario.
2. Patients should be screened for infection prior to performing spirometry.
3. Protection of healthcare workers should be a priority. This includes implementing strict infection control procedures and, where possible, the use of equipment with extra safety features, such as the SpiroBooth.

GINA, the Australian guidelines and NICE previously recommended that lung function testing should be avoided, as spirometry can propagate viral particles and expose staff and patients to the risk of infection.[6,7,9] However, even with good history-taking and physical examination, spirometry remains an essential objective measure to establish the diagnosis of asthma.[6,24]

To date, there is no evidence that the SARS-CoV-2 virus can remain viable in the air, compared to other infectious diseases such as tuberculosis, measles and chickenpox.[25] However, given the inconclusive evidence on whether lung function tests carry a risk of virus transmission and considering that SARS-CoV-2 variants may have higher transmissibility, heightened safety precautions are still recommended.

The COVID-19 pandemic is likely to become endemic.[26] With this scenario in mind, non-COVID-19 medical care cannot be held back indefinitely.[27] In terms of lung function testing, it is important to reconsider how best to operate within the constraints of a COVID-19 endemic scenario.

Precautions should be undertaken to protect lung function staff and minimise cross-infection risk, given the ongoing need to perform testing.[28] Innovations such as the SpiroBooth, which is a self-contained, purpose-built booth to safely perform spirometry that features a high-efficiency particulate air filter and an automated ultraviolet disinfection system, have also emerged during the pandemic to maintain capacity and operational efficiency while ensuring patient and staff safety during lung function testing.[29] To test its effectiveness, the study attempted to replicate real-world conditions by using infectious airborne particulate matter for their validation process, confirming a 99.89% efficiency of the high-efficiency particulate air filter. However, considering its space requirements and cost of SGD20,000 (approximately USD15,000), it has been recommended that the SpiroBooth should be used only if there is a high volume of spirometry tests performed.[29]

In this regard, spirometry can be performed but patients should be screened for and deemed unlikely to have COVID-19 or any other acute respiratory infection.[6,9] The same strict infection control procedures previously recommended should be adhered to.[3] Hand hygiene should be performed before and after each test. Appropriate personal protective equipment, including gowns and gloves, N95 or P2 masks, and protective eyewear, should be used. A high-efficiency inline filter should be used. Spirometry should be performed in a designated area with minimal fixtures that should be regularly cleaned and disinfected, and with a minimum number of people present. Disinfection of all surfaces of

the spirometer and the surroundings in between patients should also be judiciously performed.[3] Spirometry should be deferred after COVID-19 infection as a precautionary measure until further supporting evidence is available, and a wait of 30 days has been recommended.[25]

Use of nebulisers

Clinical question: Is there new evidence regarding the use of nebulisers during the COVID-19 pandemic, or should nebuliser use continue to be avoided?

Key messages:

1. SARS-CoV-2 transmission through aerosolised respiratory droplets during nebuliser use cannot be ruled out but the evidence is uncertain.
2. Pressurised metered dose inhalers in combination with a spacer are at least as effective as a nebuliser for the delivery of respiratory medications and should be considered first.
3. If necessary, nebulisers may be used, but proper precautions should be taken to reduce the risk of viral transmission.

Nebuliser use was generally recommended against during the pandemic, in view of the risk of transmitting infection to other patients and healthcare workers.[3] However, there were discrepancies in recommendations from professional bodies. While GINA, the Australian guidelines, and the American College of Allergy, Asthma and Immunology adopted the stance, NICE and BTS advised that patients may continue to use their nebulisers, as they were of the view that the aerosol comes from the fluid in the nebuliser chamber and will not carry virus particles from the patient.[3]

To date, the potential risk of SARS-CoV-2 transmission through aerosolised respiratory droplets during nebuliser use cannot be ruled out, but the evidence is uncertain. The existing literature, limited to several small studies, was reviewed by Woods, who concluded that there was no conclusive evidence of such transmission.[30] In addition, historically, the risk of transmission of acute respiratory infections due to nebuliser use was not significant.[31] Studies specific to other coronaviruses also did not indicate an increased risk.[32]

Nevertheless, pressurised metered dose inhalers, in combination with a spacer, are at least as effective as a nebuliser for the delivery of respiratory medications in most cases, even during symptomatic exacerbations, and should remain as the first choice in most patients.[3]

The use of home nebulisation is regarded as safe for the patient using the nebuliser. To reduce the possible risk of infecting other people, patients should follow social distancing guidelines and undertake precautions such as increased cleaning and disinfection of nebulisers, ensuring proper distancing from others while using nebulisers, and using nebulisers only in properly ventilated areas.[32,33]

In the case of nebulisers being administered to patients by healthcare personnel, strict adherence to infection control measures such as the use of personal protective equipment is recommended.[33] It is also recommended to use negative pressure rooms, dispose or disinfect equipment after each use, and maintain an appropriate distance from the patient during nebulised treatment.[32,33]

COVID-19 vaccines and asthma

Clinical questions: What are the recommendations for vaccinating patients with asthma, allergy, or both, against COVID-19? What other vaccines are recommended for asthma patients?

Key messages:

1. All patients with asthma should get vaccinated against COVID-19 if eligible.
2. The usual precautions for vaccination of the general population apply to patients with asthma.
3. Severe asthma patients on biologic therapy can and should also be vaccinated against COVID-19, with a 1–7-day interval between the biologic and the vaccine.
4. Second-dose administration appears to be safe even in patients who report immediate and potential allergic reactions after the first dose of the Pfizer-BioNTech or Moderna vaccines.
5. Patients with asthma should continue to be encouraged to receive the influenza and pneumococcal vaccines.

The first vaccine to be listed for the WHO Emergency Use Listing was the Pfizer-BioNtech/Comirnaty vaccine, which was listed on 31 December 2020, and since then, several other vaccines have also gained Emergency Use Listing.[34]

Both the GINA[6] and the Australian guidelines[9] recommend that patients with asthma get vaccinated against COVID-19 if eligible, while BTS[35] even classifies severe asthma patients as clinically vulnerable patients who should be prioritised for vaccination. There is no evidence that having asthma, allergic rhinitis, or taking treatments for these conditions increases the risk of adverse reactions from current approved vaccines.[9,35] A study in severe asthma patients has shown that few patients reported side effects and that there was an absence of asthma exacerbations,

demonstrating that the SARS-CoV-2 vaccine is safe and well-tolerated in this population.[36]

The usual precautions apply to patients with asthma, as with the general population. The vaccines should be administered in a healthcare setting where patients can be actively monitored after administration, and any adverse reactions, including anaphylaxis, can be promptly treated.[6] The vaccines should not be administered to patients with a history of severe allergic reaction to the vaccines and their components.[6,9] Examples of the vaccine components include polyethylene glycol in the Pfizer-BioNtech/Comirnaty vaccine, and polysorbate 80 in the AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID-19 developed by the University of Oxford and AstraZeneca.[6,9]

Severe asthma patients on biologic therapy can and should also be vaccinated against COVID-19.[6,9,35] BTS advises a 7-day interval between the vaccine and asthma biologic, while GINA[6] and the Australian guidelines[9] state that simply not giving biologic therapy and a COVID-19 vaccine on the same day is acceptable. These recommendations are not based on any proven interactions but were made on the basis of allowing adverse effects of either the asthma biologic or COVID-19 vaccine to be more easily distinguished.[6,9,35] The 7-day interval may be reasonable, as most adverse events would have occurred in this period, at least for the mRNA vaccines. In a phase 3 clinical trial of the Moderna mRNA-1273 vaccine, injection-site events lasted a mean of 2.6 days and 3.2 days after the first and second doses, respectively, while systemic adverse events lasted a mean of 2.6 days and 3.1 days after the first and second doses, respectively.[37] Delayed injection-site reactions (those with onset on or after day 8) were rare, occurring in 244 participants (0.8%) after the first dose, and 68 participants (0.2%) after the second dose.[37] The reactions were also not severe, typically resolving over the following 4–5 days, and such reactions are not contraindications to subsequent vaccination.[37,38] In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial of the BNT162b2 (Pfizer-BioNTech) vaccine, similar results were observed, with most adverse events being transient reactogenicity events that resolved within a couple of days after onset.[39] While there were reports of lymphadenopathy, which can last for up to 10 days, the overall incidence was low, with 64 vaccine recipients (0.3%) and 6 placebo recipients (<0.1%) affected.[39]

Even in patients who reported immediate and potential allergic reactions after the first dose of the Pfizer-BioNTech or Moderna vaccines, second-dose administration appears to be safe.[40] In a multicentre, retrospective study conducted in the US, 159 patients tolerated the second dose despite having a first-dose reaction. This included 19 patients who had anaphylaxis following the first dose. While 32 (20%) of the patients reported immediate and potentially allergic symptoms from the second dose, these were mild, self-limiting, and/or could be treated adequately with antihistamines.[40]

For patients who already had COVID-19 and recovered, it is unclear if they would be protected from getting infected again, and such patients may therefore still benefit from vaccination. The Centers for Disease Control and Prevention (CDC)[41] and BTS[35] advise that patients who have recovered from COVID-19 still get vaccinated. BTS recommends that vaccination should be deferred until clinical recovery to around 4 weeks after onset of symptoms or 4 weeks from the first confirmed positive specimen in those who are asymptomatic, as clinical deterioration can occur up to 2 weeks after infection,[35] while the CDC recommends a 90-day interval for patients who were treated for COVID-19 with monoclonal antibodies or convalescent plasma.[41]

Vaccination against influenza and pneumococcal disease is still recommended for all patients[3] and patients with asthma should be reminded to receive such vaccines. By protecting patients against these respiratory diseases, their need for visits to healthcare facilities is reduced, thereby decreasing their risk of exposure to SARS-CoV-2. By reducing these respiratory infections, healthcare resources can also be conserved for managing the COVID-19 pandemic. In terms of separation between COVID-19 vaccination and other vaccinations, GINA recommends a 14-day interval between COVID-19 vaccination and influenza vaccination, while the Australian guidelines[9] and BTS[35] recommend a 7-day interval between inactivated influenza vaccines and a COVID-19 vaccine, with BTS advocating the same 7-day gap between giving a pneumococcal vaccine and a COVID-19 vaccine.[35] As with asthma biologic therapies, these recommendations were made out of an abundance of caution rather than due to any proven interactions. The Australian Technical Advisory Group on Immunisation accepts a shorter interval (i.e. less than 7 days, or even co-administration) in certain scenarios, such as when COVID-19 transmission rates are high, or when other vaccines are urgently indicated to prevent disease (e.g. when there is an influenza outbreak or a tetanus-prone wound). In addition, should there be logistical concerns due to scheduling issues, not having a 7-day interval is better than risking not administering the vaccine at all.[42]

Some unanswered questions remain regarding the adequacy of serological response to COVID-19 vaccination in asthma patients and, in particular, severe asthma patients on biologics or long-term OCS. As with the general population, the efficacy of existing vaccinations against emerging SARS-CoV-2 variants and the role of booster shots in patients with "inadequate" responses also remain unknown. These are critically important topics, and more evidence is needed to provide clinical guidance in the coming months.

Mask-wearing and social distancing measures

Clinical question: What are the recommendations regarding mask-wearing and social distancing measures for asthma patients?

Key messages:

1. Mask-wearing and social distancing measures may contribute to reductions in asthma exacerbations and influenza-related illness.
2. Wearing a face mask is unlikely to increase the risk of adverse effects for those with chronic respiratory disease.

Mask-wearing has become an important part of public health measures to help reduce the community spread of COVD-19, complementing other strategies such as physical/social distancing and hand hygiene. As vaccination rates increase, some countries have also relaxed their guidance regarding mask-wearing. However, health advice in different countries and regions has varied widely; even within the same region, the advice given may change rapidly or is frequently confusing, with differences in mask mandates, and levels and timelines of reopening.[43] For instance, the CDC recommendations on mask-wearing differ depending on the number of COVID-19 cases in the area, the setting and activity, and the individual's health status.[44]

Nevertheless, current evidence suggests that the benefits of mask-wearing outweigh the potential harms when COVID-19 is spreading in a population, with the main trade-off being personal freedom.[45] For the general public, mask-wearing is very safe. Common complaints may include skin problems (e.g. itch, rash, flare-ups of existing problems like acne or dermatitis) and headache, but can be easily improved with prevention measures, such as the use of moisturisers and ensuring that masks are well-fitting.[46]

With regards to patients with asthma, the professional bodies do not have specific guidance on mask-wearing. GINA defers to individual countries and regions for localised health advice regarding hygiene strategies and personal protective equipment.[5]

Notably, GINA states that many countries have seen a reduction in asthma exacerbations and influenza-related illness, which may be partly due to mask-wearing and other COVID-19-related measures.[5] In the UK, a large cohort study was done to analyse a database of an estimated 10 million patients, comparing pre-lockdown and post-lockdown records. The analysis found that exacerbation rates among asthma patients were reduced by 0.196 episode per person-year, which represents about 20 episodes for every 100 asthma patients per year.[47] In terms of admission rates, a Hong Kong study compared admission rates in 2020 against baseline data from 2015 to 2019 and found a decrease in admissions for asthma exacerbations by 53.2%.[48] This trend is likely to be a true reduction in exacerbations rather than a reluctance to initiate face-to-face provider contact or healthcare system avoidance during the pandemic.[49] In a study that included exacerbations not resulting in a visit to a healthcare provider but were reported remotely, there was a 40% decrease in asthma exacerbations with the onset of the COVID-19 pandemic.[49] While these effects are likely to be multifactorial, the findings suggest that existing practices may be beneficial for asthma patients. Significant reduction in inappropriate attendances to emergency departments during the COVID-19 pandemic was also reported in a study from Singapore, highlighting some of the unexpected beneficial knock-on effects from the pandemic.[50]

Concerns of increased risks of adverse effects of mask-wearing in patients with chronic respiratory diseases are also largely unfounded. In an evidence review by Alberta Health Services, the health authority for the Canadian province of Alberta, the risks of wearing a face mask were not found to be increased for those with chronic respiratory disease.[46] A recent study also noted that mask-wearing does not affect oxygen saturation levels in both asthma and non-asthma patients, with oxygen saturation levels reported to be between 93% and 100% among the study participants, and averaging 98% for people with asthma.[51]

In view of the current available evidence, it is important that patients with asthma continue to wear masks and adhere to stricter standards of protective measures against COVID-19, as the benefits are very likely to outweigh any potential harms. Some patients, such as those with severe asthma who may feel it is difficult to breathe while wearing a face mask, should continue to stay home or avoid public places as much as possible.

Role of telemedicine in the management of asthma

Clinical question: Is there a role for telemedicine in managing asthma patients during the COVID-19 pandemic?

Key messages:

1. Telemedicine is a useful option for providing patient care that is more convenient while reducing in-person visits, but many barriers may prevent successful implementation.
2. Healthcare providers should continually improve on the delivery of asthma care using new models of care. A combination of telemedicine and in-person visits may be employed.

In the face of the COVID-19 pandemic, telemedicine, which is defined as the "remote delivery of health care services and clinical information using telecommunications technology", has offered a safer and effective alternative for patients to continue to receive care remotely without the need to leave their homes.[52] Telemedicine has increasingly been used to care for patients with asthma and allergies in response to the pandemic.[52] However, this concept is not new and has been used with favourable outcomes for patients with asthma even before the pandemic. Telemedicine has been shown to improve quality of life while improving medication adherence and decreasing the use of healthcare resources.[52] In the first systematic review and meta-analysis of telemedicine that investigated the effects of telemedicine activities in asthma patients, results from 22 studies showed that a combination of different telemedicine approaches led to significant improvements in asthma control and quality of life in adult asthma patients when compared with usual care.[53]

Patients also appear to report high satisfaction with telemedicine, although this finding was based on data from an allergy and immunology practice in New York instead of from asthma patients only.[54] In this study, data provided by 4 physicians on 518 patient visits by children and adults from 13 April to 8 May 2020, including 290 telemedicine encounters, were analysed.[54] Among the 177 patients who completed the follow-up telephone survey, 97% were satisfied with their virtual visit, and 77% found the appointment as satisfactory as an in-person visit.[54] Despite the high patient satisfaction, there might still be a preference for in-person consultations. The most important factor that led to a preference for in-person visits was the desire for a more personal interaction, which was cited by 45.3% of patients. Moreover, when treating physicians were asked to assess the patient encounters, 42.4% of the encounters were deemed to be incomplete, although there was no elaboration of what was lacking in these encounters.[54]

Overall, telemedicine serves as a useful option for providing patient care that is more convenient while reducing in-person visits. Despite the potential benefits, many barriers may prevent successful implementation. These may include a lack of access to the required technology, complexity in billing and documentation, and difficulties in conducting a thorough physical examination.[55] In Singapore, there is a lack of telemedicine integration into the hospital information technology ecosystem, and its use may add to the physician administrative load.[56]

In the current climate, telemedicine is likely to continue to expand and play an important role in providing care to patients remotely to complement in-person visits. Healthcare providers should continue to build on current experience and improve on the delivery of asthma care using a combination of telemedicine and in-person visits.

DISCUSSION

This review summarises the recommendations from the various professional bodies on the management of asthma during the COVID-19 pandemic and provides additional information from the literature to justify the recommendations.

In general, healthcare professionals should continue to manage asthma according to accepted asthma guidelines and recommendations. Key themes are highlighted in Fig. 1. In summary, the key points are:

1. Patients with well-controlled, mild-to-moderate asthma are unlikely to be at increased risk of acquiring COVID-19 or having worse outcomes from COVID-19. However, a subset of patients with poorly controlled asthma may be at increased risk of COVID-19-related death.
2. All patients with asthma, even those with severe asthma as well as those treated with biologic therapy, should receive COVID-19 vaccination. Other vaccinations, such as those for influenza and pneumococcal disease, should also continue to be part of the routine care for asthma patients.
3. At-home administration of asthma biologics can be considered for selected patients to reduce the risk of getting infected with SARS-CoV-2, but this should be balanced against the benefits of in-office administration.
4. Spirometry can be performed unless there is a suspicion of COVID-19. When spirometry is

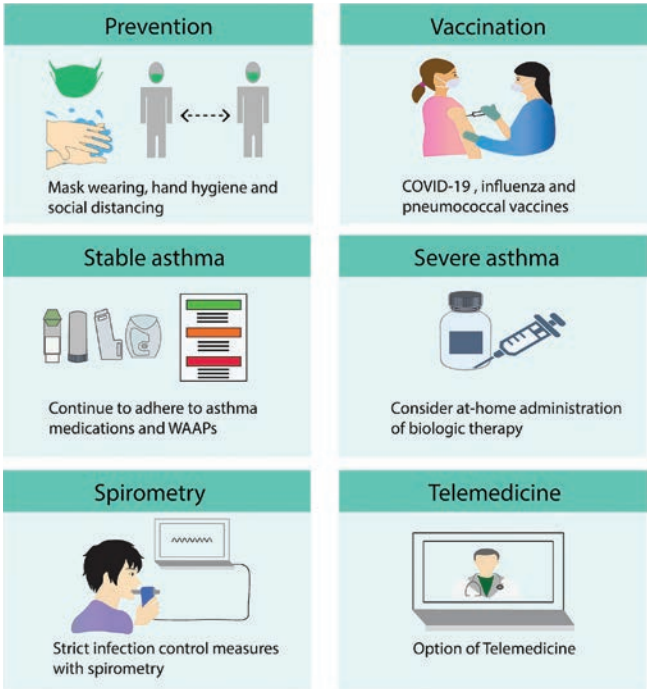

Fig. 1. Key themes in asthma management.
WAAPs: written asthma action plans

performed, strict infection control procedures as previously recommended should be adhered to.

5. As with the general population, measures to reduce the spread of COVID-19 are recommended. These include screening for COVID-19 and isolating suspicious cases, as well as general measures such as mask-wearing, personal hygiene, social distancing and testing of selected high-risk persons who are otherwise asymptomatic.
6. Mask-wearing and other measures to reduce transmission risk should continue for patients with asthma as these precautions may reduce the risk of asthma exacerbations and are unlikely to cause any adverse effects.
7. Telemedicine is a useful option for providing asthma care. It may be convenient and reduces in-person visits and could be used to complement in-person visits.

There is limited evidence of whether the standards of asthma care have changed during the pandemic. There is significant variation across countries and care settings in how the pandemic has impacted the management of different non-communicable diseases.[57] Services may be disrupted owing to resource diversion and disruption to healthcare delivery. However, various alternative strategies, including systems for triaging patients and the increased use of telemedicine, have helped to ensure that patients continue to receive appropriate treatment.[57] As many countries have seen a reduction in asthma exacerbations and influenza-related illness without an increase in asthma mortality, it is unlikely that the quality of care has declined significantly during this period. Nevertheless, defining quality of care is complex, hence it is important that practices based on the best available evidence are implemented, highlighting the importance of continual timely review of the literature.

This review has some limitations that need to be considered. The objective of the review was to summarise recommendations by professional bodies and provide additional information beyond the recommendation statements, supplemented by a literature search. Thus, a rigorous, systematic search of the literature was not conducted, and the quality of the evidence was not appraised. Nevertheless, it is reassuring that the professional bodies have a high level of agreement in their recommendations, even though the recommendations may be based on different supporting literature, and are mostly based on expert opinion. In addition, the most relevant source was referenced for each topic of interest for the purpose of this review. Several aspects of asthma management were also not discussed and may warrant a further review of the literature. These may include COVID-19's impact on asthma comorbidities, asthma complications such as viral/bacterial pneumonia and pneumothorax, and asthma triggers such as exposure to cleaning and disinfectants that may be used with increased frequency for surface cleaning. Nevertheless, some topics, such as the management of concomitant allergic rhinitis, were already discussed in the previous review.[3]

CONCLUSION

Our understanding of how asthma may be affected by COVID-19 continues to evolve. While previous recommendations were largely based on expert opinion, the tremendous amount of literature published since the pandemic first emerged 2 years ago has helped guide respiratory professional bodies to update their recommendations. This study provides a timely review of the various recommendations and can be used to guide healthcare professionals in managing asthma patients as the world prepares for a future with COVID-19 becoming endemic. The long-term consequences of COVID-19 infection in asthma patients and the ripple effects of COVID-19 remain uncertain and deserve ongoing study.

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COMMENTARY

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Low-dose computerised tomography screening for lung cancer in Singapore: Practical challenges of identifying participants

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INTRODUCTION

In March 2022, the European Commission on cancer screening suggested the inclusion of low-dose computerised tomography (LDCT) for lung cancer, targeted at current and former smokers.[1] The aim of LDCT screening is to increase early detection, decrease diagnoses at metastatic stage of the disease and improve overall 5-year survival.[2] Both China and the US recommend screening with LDCT for lung cancer detection. Currently, the Ministry of Health (MOH) in Singapore recommends individual-level use of LDCT to screen for lung cancer in high-risk populations,[3] in line with the College of Radiologists' recommendations.[4] This policy ought to be reconsidered for population-level screening based on improving prognosis, catering for the unmet need and cost-effectiveness analysis. The key to all this is identifying the right participants.

Lung cancer has traditionally been classified into 2 major categories: non-small cell lung cancer (NSCLC), which is more common and usually associated with smoking; and small cell lung cancer, which is more aggressive and has worse survival rates. Clinical benefit evidence from adequately powered studies such as the National Lung Screening Trial (NLST) in the US and the Dutch-Belgian Randomized Lung Cancer Screening Trial (Nederlands–Leuvens Longkanker Screenings Onderzoek [NELSON]) show screening for lung cancer with LDCT to have a mortality benefit.[5,6] The main reason for this is "stage shift" in diagnosis with increases in early-stage (I–II) and decreases in late-stage (III–IV) lung cancer incidence.

Stage IV diagnosis: Singapore compared with other countries

The stage at diagnosis is an important prognostic factor in explaining international differences in cancer survival and early detection of cancer improves prognosis. The majority of patients in Singapore (>60%) are diagnosed with advanced (or metastatic) NSCLC, which is higher than international comparative statistics (Fig. 1).

The reason for late diagnosis can be attributed primarily to symptoms being non-specific or more likely asymptomatic. In the US, the 5-year survival rate for early-stage lung cancer was 57% compared with 5% for stage IV disease.[7]

An effective national screening programme may contribute to early detection. The Lung Cancer Policy Model-Asia estimated a 3.8% mortality reduction and 8,118 life-years gained in Singapore through the implementation of LDCT using age and smoking history screening eligibility criteria recommended by the U.S. Centers for Medicare & Medicaid Services.[10] While this appears promising, there are several questions about the practical challenges associated with the implementation of LDCT screening—most notably, how will the healthcare system in Singapore identify and invite high-risk individuals to a national screening programme?

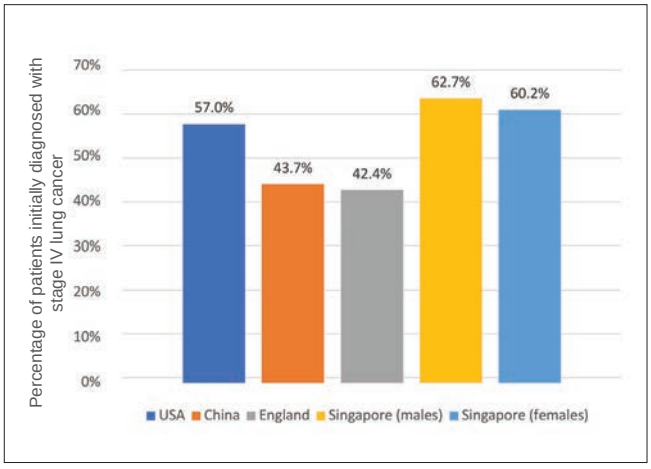

Fig. 1. Percentage of patients diagnosed with American Joint Committee on Cancer (AJCC) stage IV non-small cell lung cancer (NSCLC) in the US,[7] China[2] and England,[8] compared with Singapore.[9]
Superscript numbers: Refer to REFERENCES

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Identifying participants

In the literature, modelling studies focus on smoking history to identify eligible patients for screening, but the definition varies. For example, patient screening eligibility is based upon: "at least 30 pack-years of smoking", "a maximum of 15 years since quitting", "20-40 pack-years of smoking" or "between 10 and 20 years since quitting smoking".[6,11-13] Risk prediction models also vary with baseline characteristics of age, sex and smoking status[14] or age, smoking history, education, coexisting diagnosis of chronic obstructive pulmonary disorder, family history of lung cancer, and body mass index.[15] The absence of a solitary data source in Singapore that collects the required variables or risk factors discussed above makes it difficult to identify and offer screening to eligible individuals at "high risk" based on pack-years. A strategy based on smoking history would suffice in Singapore. Some possible recruitment strategies in Singapore could be:

- Invite all individuals aged 55–74 years to consider their lung cancer risk and screening eligibility with or without completing a self-administered prostate, lung, colorectal and ovarian (PLCO) cancer screening questionnaire ($PLCO_{m2012}$) on an annual basis. This would be a large-scale population-based screening but could be inefficient, as invitations would be sent to never-smokers or smokers who would be eventually deemed ineligible.
- Most general practices in Singapore now use some form of patient management system that could potentially be used to identify a target population to invite for screening, based on age and smoking history. This approach would be more focused but will however depend on the access to these patient management systems and on accurate smoking status being captured and updated.
- Targeted case finding where general practitioners conduct a lung cancer risk assessment on individuals who are aged over 55 years and are current or former smokers. The general practitioner will then refer those eligible to go for LDCT screening. The disadvantage of this approach would be that not all eligible individuals aged over 55 years will visit a general practitioner. Also, not all general practitioners may be motivated enough to conduct the lung cancer risk assessment for eligible individuals.

Currently, LDCT screening is widely available in the private healthcare setting in Singapore, suggesting that there is an unmet need. However, the risks of screening include false-positive results leading to follow-up tests and surgeries that are not needed; and overdiagnosis of cancer cases that may never cause a problem, which again leads to unnecessary treatment. Evaluation of the long-term costs and benefits of vying screening strategies, known as a Health Technology Assessment (HTA), is needed for policymakers within MOH to make recommendations with confidence. Whether validation of the NLST and NELSON trial results for a Singapore population as part of the HTA is needed requires deliberation among clinicians and policymakers.

Implementation of the lung cancer screening programme

Key elements of the programme include customising the inclusion criteria, training of general practitioners and radiologists, targeted recruitment strategy for eligible high-risk participants, integration with existing smoking cessation programmes, and continued research to analyse the uptake and impact of LDCT screening. The successful implementation of a targeted lung cancer screening programme would achieve a stage shift to an increase in stage I/II cancer detection, improved overall prognosis and decreased mortality over time. A recent retrospective audit in a single hospital of Singapore patients (N=126) showed that 85.4% of those presenting at an advanced stage would have benefited from an LDCT based on NLST criteria.[16] However, a trade-off needs to be acknowledged, in that this proposed targeted high-risk screening approach will probably not capture the subpopulation of East Asian non-smoking lung adenocarcinoma cancers.[16,17] Non-smokers represented a third of patients (33.3%) diagnosed with lung cancer in the hospital audit.[16] Apart from smoking, additional risk factors in Asian populations have been described, including a positive family history[18] and environmental carcinogen signatures,[19] which may need further research as a distinct cohort from the high-risk smoking population. Furthermore, in clinical practice, the Lung Imaging Reporting and Data System (Lung-RADS) classification system of nodules is based on the NLST high-risk smoking population.[20] Therefore, if LDCT screening is extended to a low-smoking population cohort, classification and management of lung nodules is also an area for future research.

CONCLUSION

Singapore has a strong smoking cessation and tobacco control public health programme. A national synchronised LDCT screening for lung cancer programme would be complementary. The aim of early intervention and reduction in mortality in high-risk patients would bring

Singapore in line with other countries. Without such a national programme that adheres to predefined principles, ad hoc and discretionary screening of current and former smokers is likely to continue in private healthcare settings. Singapore has the resources necessary to implement a national lung cancer screening programme and a clear incentive to do so from a public health perspective.

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Childhood interstitial lung disease: The end of a diagnostic odyssey

Dear Editor,

Childhood interstitial lung disease is a heterogeneous group of rare disorders featuring pulmonary interstitial remodelling and diffuse parenchymal infiltrates on imaging.[1] Incidence is estimated at 0.13–16.2 cases/100,000 children per year.[1] *ABCA3* (ATP-Binding Cassette, Subfamily A, Member 3) (OMIM #601615) is expressed in alveolar type II cells involved in pulmonary surfactant production,[2] thus attributed to surfactant metabolism dysfunction-3 (OMIM# 610921).[3] Differences in variant frequency and disease phenotype were reported in different ethnic groups, with Asians uniquely identified with homozygous c.4909+1G>A/c.4909+1G>A variants within an American cohort,[4] whereas a Japanese cohort demonstrated 6 novel variants.[5] This may result in different prognostication and outcomes. We report what is likely the first case of childhood interstitial lung disease in a Southeast Asian child with deleterious compound heterozygous *ABCA3* variants, with consideration for early genetic testing when progression is refractory to treatment.

Our patient was a term boy, born via spontaneous vertex delivery with a birth weight of 2.99kg. Antenatally, apart from an episode of maternal H1N1 infection during the 2nd trimester, there were no other complications. The father (41-year-old) and mother (35-year-old) were unrelated with no significant medical or family concerns. They had a healthy 6-year-old daughter.

The patient was born vigorous with Apgar scores of 7 and 8 at 1st and 5th minute. At 1st hour of life, he developed respiratory distress and required non-invasive ventilation (NIV). Intravenous penicillin and gentamicin were started. He was intubated by day 2. Chest X-ray showed left retrocardiac and upper lobe consolidation. Echocardiogram showed a structurally normal heart. He received 2 doses of endotracheal surfactant due to radiographic concerns for term respiratory distress syndrome (RDS), and showed transient improvement. Intravenous clarithromycin was added, and a short course of intravenous dexamethasone, oral spironolactone and hydrochlorothiazide were attempted.

He was extubated on day 9 to NIV, but required re-intubation on day 11. Blood gases showed type 2 respiratory failure. Intravenous ceftriaxone was commenced as tracheal secretion culture grew *Enterobacter cloacae*. On day 22, the third dose of surfactant was attempted as a "rescue dose", but to no avail.

On day 26 of life, he was referred to our unit. He required high ventilatory support, with an oxygenation index of 22. Repeated chest X-ray showed diffuse bilateral ground-glass opacities (Grade IV), resembling neonatal respiratory distress syndrome. Repeated echocardiogram showed pulmonary hypertension that responded to inhaled nitric oxide. Investigations included bronchoscopy that showed no malacic airways, bronchoalveolar lavage for cytology that was negative for PAS staining, and serological blood tests that included parvovirus IgM positive and IgG negative, and negative for herpes simplex virus IgM, Epstein-Barr virus IgM, cytomegalovirus and varicella zoster IgM. High-resolution computed tomography of the thorax (non-contrasted) (Fig. 1) showed diffused ground glass changes in upper lobes and interstitial thickening; while middle and lower lobes (especially over the left side) showed consolidative changes and reduced lung volume, interlobular septal thickening and bronchial dilatations. The overall impression was extensive lung damage with fibrosis and scarring. Lung biopsy was not pursued due to significant risks of complication.

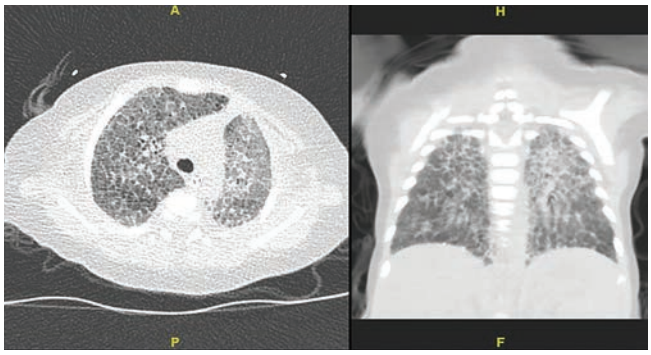

Fig. 1. High-resolution computed tomorgraphy of the thorax (non-contrasted). Axial and coronal views show ground glass changes and interstitial thickening in upper, middle and lower lobes (especially over the left side).

Treatments attempted included: intravenous immunoglobulin (0.4g/kg/dose for 2 days), intravenous methylprednisolone pulse therapy (20mg/kg/day, 5-day courses on a monthly basis), hydroxychloroquine (5mg/kg/day) and azithromycin (7mg/kg/dose every other day), with no sustainable improvement. Parents were not keen for tracheostomy. Lung transplantation was not feasible due to resource limitations.

Subsequent genetic testing with whole exome sequencing revealed compound heterozygous variants

of c.3364G>A p.(Glu1122Lys) and c.737C>T p.(Pro246Leu). Both were present in the Single Nucleotide Polymorphism database (dbSNP) as rs1233043384 and rs144653790, respectively. A previous study reported the c.737C>T variant together with c.1450del in an infant with neonatal respiratory distress syndrome,[6] with the c.737C>T variant being classified as "likely pathogenic".[7] Although both of our variants found were reported in dbSNP, almost all of the pathogenicity prediction programmes in the VarSome platform predicted the c.737C>T and c.3364G>A variants as deleterious by 94.4% (17 out of 18 programmes) and 94.7% (18 out of 19 programmes), respectively.[8] Therefore, both are predicted to be classified as "likely pathogenic".

This case was consistent with neonatal respiratory failure due to surfactant deficiency. A further parental genetic study by polymerase chain reaction and sequencing of the *ABCA3* gene revealed that the mother carries the c.737C>T variant whereas the father carries the c.3364G>A variant, indicating the variant was on opposite alleles, and confirming the segregation of variants. These results facilitated genetic counselling, future reproductive options, and ending the diagnostic odyssey.

Due to irrecoverable poor lung function, palliative care was pursued. At day 83 of life, the patient was extubated to high settings of bilevel positive airway pressure. Home care was untenable due to high NIV requirements. Life-sustaining support was withdrawn at 11 months old, and he succumbed peacefully.

ABCA3 variants leading to neonatal respiratory failure were mostly reported in Caucasians.[9] The Han and Zhuang populations in Japan and China, respectively, were reported to have a carrier rate of 1.3%, lower than the US.[9] With 2 *ABCA3* variants, pulmonary phenotype varies for disease prognosis.[4] Role of hydroxychloroquine, corticosteroids, macrolides, azathioprine, cyclophosphamide and colchicine remained uncertain.[10] Lung transplantation was the next treatment option, but requires high expertise and facilities. The 5-year survival rate of 50% from lung transplant[1] was not acceptable for the parents.

There are some limitations in the present study. Firstly, the association between our findings of the variants and poor prognosis requires additional cases to support the above findings. Secondly, a robust functional study is needed to prove the negative impact of these variants on the gene/protein function. Lastly, lung biopsy may still be considered to prove the variants' pathogenicity.

To the authors' best knowledge, this is the first reported child with likely deleterious compound heterozygous variants in Southeast Asia. Diagnosis can be made based on clinical features of RDS, imaging and genetics analysis without lung biopsy, in accordance with both European protocols and the American Thoracic Society Clinical Practice Guideline.[1] Genetic testing can assist in prognostication, decision-making, and future family planning.

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Clinical characteristics of macrolide-resistant *Mycoplasma pneumoniae* infections among hospitalised children in Singapore

Dear Editor,

Mycoplasma pneumoniae has become the leading cause of paediatric community-acquired pneumonia in countries where pneumococcal vaccination is included in the national immunisation programme, including Singapore.[1] *M. pneumoniae* is intrinsically resistant to beta-lactams due to the absence of cell walls. Macrolides, tetracyclines, and fluoroquinolones are used to treat *M. pneumoniae* infections, and macrolides are recommended in children, due to the potential adverse effects of tetracyclines and fluoroquinolones. Macrolide-resistant *M. pneumoniae* (MRMP) isolates were first observed in 2001.[2] The prevalence of MRMP worldwide varies from 0.2% in Europe to 90% in East Asia.[3] In Singapore, the prevalence of MRMP in hospitalised children was 13% in 2017.[4] Studies in Asia have reported increased disease severity in persons infected with MRMP,[5] while others have not detected differences in the clinical course in persons with MRMP versus those with macrolide-susceptible *M. pneumoniae* (MSMP) infections.[6] We compare differences between hospitalised children with MSMP and those with MRMP infections.

From July 2019 to February 2020, patients younger than 16 years in KK Women's and Children's Hospital, Singapore, who tested positive for *M. pneumoniae* by polymerase chain reaction on nasopharyngeal or throat swab samples, were screened for inclusion. Assessment of genotypic macrolide resistance was done as previously described.[4] Sequencing was performed retrospectively; thus, the results of genotypic macrolide resistance were not known at the time of treatment. Electronic medical records of patients with *M. pneumoniae* infection were retrospectively reviewed after informed consent was obtained. Demographic and clinical data were collected and matched to the results of genotypic macrolide-resistance testing. Comparisons between binary groups were analysed using chi-square or Fisher's Exact test for categorical variables, and Mann-Whitney U test for continuous variables. All *P* values were two-tailed and differences were considered statistically significant at <0.05.

Between July 2019 and February 2020, 170 patients with *M. pneumoniae* infection consented to participate in this study. Thirty-one patients (18.2%) had *M. pneumoniae* strains for which no readable sequence was obtained; they were not included in further analysis. Of the remaining 139 patients, 125 (90%) had *M. pneumoniae* strains that had the wild-type sequence and were presumed to be macrolide-susceptible, and 14 (10%) patients had strains with mutations conferring macrolide resistance. The A2063G point mutation accounted for all 14 *M. pneumoniae* strains with macrolide resistance.

There were no differences in demographics, presenting symptoms, clinical examination or haematological parameters at presentation (Table 1). A higher median C-reactive protein was observed in children with MRMP infections, although this was not statistically significant. Pneumonia constituted the clinical diagnosis in 86 (68.8%) and 11 (78.6%) hospitalised children with MSMP and MRMP infections, respectively (*P*=0.09). Children younger than 5 years were significantly more likely to have *M. pneumoniae* with viral co-infections compared to children older than 5 years (odds ratio [OR] 3.3, confidence interval [CI] 1.5–7.1, *P*=0.002).

All 139 children with MSMP or MRMP infections received treatment with clarithromycin. The median total duration of fever in children with MRMP infection was significantly longer compared to those with MSMP infection (9.0 vs 7.0 days, *P*=0.047). Despite the fact that clinicians were unaware of the presence of macrolide resistance, the odds of antibiotics switched from macrolide to fluoroquinolone or tetracycline in children with MRMP infections was 8.2 that of children with MSMP infections (CI 1.6–41.7, *P*=0.02). Children with MRMP infection who had a switch of antibiotic therapy had a significantly longer median duration of fever during hospitalisation (median 12.0 days, range 6.0–21.0) compared to children with MRMP infection who remained on macrolide therapy (median 1.0 day, range 0–5.0) (*P*=0.005). Eleven (78.5%) children with MRMP infections remained on macrolide therapy, and all defervesced and were discharged.

Pleural effusions were significantly more frequent in children with MRMP infections compared to those with MSMP infections (OR 4.4, CI 1.4–13.9, *P*=0.01), and required more frequent chest drain insertions (*P*=0.048). There were no significant differences between children

Table 1. Demographics, clinical characteristics, treatment and outcomes of children with macrolide-susceptible and macrolide-resistant *Mycoplasma pneumoniae* infections

	MSMP No. (%) (n=125)	**MRMP No. (%) (n=14)**	***P* value**
Sex			0.78
Male	62 (49.6)	8 (57.1)	
Female	63 (50.4)	6 (42.8)	
Ethnicity			0.81
Chinese	82 (65.5)	10 (71.4)	
Malay	23 (18.4)	2 (14.3)	
Indian	11 (8.8)	2 (14.3)	
Caucasian	2 (1.6)	0	
Others	7	0	
Age, median (range), year	4.4 (0.1–14.6)	4.4 (1.1–11.5)	0.88
Overseas travel in preceding 4 weeks	21 (16.8)	4 (28.6)	0.28
Sick household contacts	64 (51.2)	8 (57.1)	0.78
Underlying conditions			
Asthma	8 (6.4)	3 (21.4)	0.08
Global developmental delay	6 (4.8)	0	1.00
Prior treatment with antibiotic	46 (37.0)	2 (14.0)	0.14
Beta-lactam	41 (89.1)	2 (100)	
Macrolide	2 (4.3)	0	
Unknown	3 (6.5)	0	
Presenting symptoms			
Fever	117 (93.6)	14 (100)	1.00
Maximum temperature, median (range), °C	39.0 (38.0–41.8)	39.8 (38.0–40.6)	0.11
Cough	124 (99.2)	14 (100)	1.00
Rhinorrhoea	30 (24.0)	1 (7.1)	0.19
Shortness of breath	54 (43.2)	7 (50.0)	0.78
Sore throat	122 (97.6)	14 (100)	1.00
Rash	6 (4.8)	0	1.00
Respiratory examination			
Tachypnoea	67 (53.6)	7 (50.0)	1.00
Pulse oximetry reading <95%	28 (22.4)	3 (21.4)	1.00
Crepitations	61 (48.8)	8 (57.1)	0.59
Rhonchi	32 (25.6)	2 (14.3)	0.52
Investigations			
Chest radiograph performed	115 (92)	13 (93)	
Focal consolidation	77 (67.0)	10 (77.0)	0.37

Table 1. Demographics, clinical characteristics, treatment and outcomes of children with macrolide-susceptible and macrolide-resistant *Mycoplasma pneumoniae* infections (Cont'd)

	MSMP No. (%) (n=125)	**MRMP No. (%) (n=14)**	***P* value**
Multifocal consolidation	17 (14.8)	3 (23.1)	
Peribronchial thickening	15 (13.0)	0	
CRP, mg/L, median (range)	25.4 (1.0–163.8)	69.2 (4.3–282.0)	0.15
Viral co-infection	120 (96)	14 (100)	
Mycoplasma pneumoniae with 1 viral co-infection	32 (26.7)	7 (50.0)	0.21
Mycoplasma pneumoniae with 2 viral co-infections	7 (5.8)	1 (7.1)	
Clinical diagnosis			
Pneumonia	86 (68.8)	11 (78.6)	0.09
Bronchitis	27 (21.6)	0	
Upper respiratory tract infection	12 (9.6)	3 (21.4)	
Total duration of fever, median (range), days	7.0 (0–16)	9.0 (4–28)	**0.047**
Antibiotic switched from macrolide to fluoroquinolone/tetracycline	4 (3.2)	3 (21.4)	**0.02**
Pleural effusion	23 (18.4)	7 (50)	**0.01**
Chest drain inserted	0	2 (28.5)	**0.048**
Oxygen supplementation	44 (35.2)	6 (42.9)	0.57
Non-invasive ventilation	2 (1.6)	1 (7.1)	0.28
Length of hospitalisation, median (range), days	2.0 (1–15.0)	2.5 (1–22.0)	0.57

CRP: C-reactive protein; MRMP: macrolide-resistant *Mycoplasma pneumoniae*; MSMP: macrolide-susceptible *Mycoplasma pneumoniae*

with MSMP and MRMP infections in terms of the need for oxygen supplementation, non-invasive ventilatory support or length of hospitalisation.

These findings add to the growing literature that reports a prolonged clinical course and more complications in MRMP infections.[5,7] Delayed effective antimicrobial treatment for *M. pneumoniae* has been postulated to be related to an immune response, which may lead to prolonged or extrapulmonary disease.[8] It is crucial to note that the majority of children with MRMP infections (78.6%) eventually became afebrile even when receiving macrolide therapy. Clinical response to macrolides in MRMP infections has been described, although the duration of illness tends to be longer.[9] The usefulness of macrolide treatment in children with MRMP infection is unclear, but there may be anti-inflammatory effects due to the inhibition of cytokine production, including interleukin-8.[7]

The prevalence of MRMP isolates sampled between July 2019 and February 2020 was 10% in our study, which did not differ significantly from the prevalence of 13% in an earlier cohort in Singapore studied between 2013 and 2014.[4] With relatively low prevalence rates, macrolides remain a suitable first-line antimicrobial for community-acquired pneumonia in children with suspected *M. pneumoniae* infection.

The lack of distinguishing clinical features among children with infections by MRMP and MSMP has also been described in other comparative studies.[10] Until the time when molecular tests for macrolide resistance in *M. pneumoniae* become available on a real-time basis, clinicians will have to rely on the clinical course of the patient and a setting's prevalence of MRMP to guide decisions on switching antimicrobial therapy for children with *M. pneumoniae* infections. Persistent fever despite macrolide therapy and the presence of pleural effusions in children with *M. pneumoniae* infections are factors that may alert clinicians to the presence of macrolide resistance.

Our study involved hospitalised children in a single centre, and macrolide resistance rates may not reflect those of the wider community. The number of children

with MRMP infection was also small, limiting the power of the study.

In conclusion, a longer duration of fever and higher rates of pleural effusions were found in children with MRMP infections compared to those with MSMP infections. The prevalence of MRMP isolates remains low in children in Singapore despite the high rates reported in East Asia, and macrolides remain a suitable first-line antibiotic for children with suspected *M. pneumoniae* infection.

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LETTER TO THE EDITOR

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Child passenger safety awareness training for healthcare professionals in Singapore

Dear Editor,

Road traffic injuries are a preventable cause of childhood morbidity and mortality.[1,2] Use of age-appropriate child car seats (CCS) lowers the risk of injury and death by about 82% and 28%, respectively.[3-5] In Singapore, although the Road Traffic Act states that CCS use is mandatory,[6] many children presenting to paediatric emergency departments are unrestrained at the time of the road traffic accident.[7,8]

In a retrospective cohort of over 2,000 Singapore children with road traffic injuries, more than half were unrestrained, with non-compliance to CCS greatest at infancy.[7] In a subsequent qualitative study,[9] parents of young children cited lack of knowledge on the importance of CCS, and inadequate installation skills as barriers to CCS use; parental suggestions to improve CCS compliance from birth included the hospital as a "crucial touch point" for opportunistic education and assistance with installation.[9] In a local cross-sectional study of parents in a tertiary hospital neonatal unit, a significant proportion thought cradling the baby or using a baby carrier was a safe alternative to a CCS, while only 41% of those planning to return home via a motor vehicle intended to use a CCS.[10] This apparent gap in parental knowledge and skills may be addressed by providing information and guidance during the postnatal discharge of newborn infants from the hospital and at the hospital emergency department. Healthcare professionals also need "train the trainer" education to teach parents the requisite knowledge and skills for the safe use of child car restraints.

Therefore, the injury prevention group in KK Women's and Children's Hospital (KKH) implemented training for healthcare staff to provide effective patient and family education on CCSs, with the long-term aim of shifting the emphasis upstream—from managing road traffic injuries in children, to preventing road traffic injuries through the correct use of CCSs for children in passenger cars. In this pilot study, we aim to examine the awareness and skill sets of healthcare staff before and after receiving online child passenger safety training.

KKH is an 830-bed tertiary hospital in Singapore. Approximately 12,000 well babies are born each year in the hospital, and it had an annual emergency department volume of approximately 150,000 patients prior to the COVID-19 outbreak. From 21 to 25 June 2021, we conducted Child Passenger Safety training for healthcare staff including nurses and doctors from the Emergency Department, Neonatology, and Obstetrics. This consisted of 3 standalone 2-hour online sessions, training a total of 727 persons. The didactic component was taught by a US-certified Child Passenger Safety instructor and the interactive component facilitated by paediatric emergency physicians and a hospital physiotherapist. The course content included the following aspects of child passenger safety relevant to patient and family education: (1) how a CCS protects a child, (2) choosing a CCS for various aged children, (3) answering parents' frequently asked questions and where to find resources, (4) modelling and advocating for best-practice child passenger safety in one's family and community, and (5) identifying obvious CCS mistakes.

We administered a pre- and post-intervention anonymous survey as an online form prior to training ("pre-course"), and following each training session ("post-course"). The survey included competency-based questions with self-reported familiarity scores, and "true/false" knowledge-based questions. Participants were encouraged to complete the survey immediately after training, with 2 months (until 25 August 2021) after training to complete the post-course survey. Data were analysed with SPSS Statistics software version 26.0 (IBM Corp, Armonk, US), using the Wilcoxon rank sum test for continuous variables and the Pearson's chi-square test for categorical variables. The institutional review board granted exemption from ethics review (reference number 2020/2473).

The survey response rate was 93.6% (755/807) for the pre-course survey and 81.3% (591/727) for the post-course survey. Most of the post-course survey respondents (84.4%, 499/591) completed the post-course survey immediately after training, while 15.5% (92/591) completed the post-course survey up to 2 months later. The 755 pre-course survey respondents had a median age of 35 years (range 18–74); 95.6% (722/755) were female and 4.4% (33/755) were male. The 591 post-course survey respondents had a median age of 35 years (range 19–74 years); 96.2% (569/591) were female, and 3.7% (22/591) were male. With respect to their area of work, for pre-course

Table 1. Results of pre- and post-intervention surveys. (A) Median familiarity score for each competency dimension with interquartile range in parentheses (1 = "not familiar", 5 = "very familiar"). (B) Percentage scoring correct answer on "true/false statement" knowledge questions.

A. Competency dimensions	**Pre-course median score**	**Post-course median score**	***P* value**
1. Where to find reliable information on child car seats	2 (1–3)	4 (4–5)	<0.001
2. How to select an age-appropriate child car seat	2 (1–3)	4 (4–5)	<0.001
3. When to transition the child to the next stage of child car seat	2 (1–3)	4 (4–5)	<0.001
4. Where to obtain a child car seat	3 (1–4)	4 (4–5)	<0.001
5. How to install the child car seat in the car	2 (1–3)	4 (4–5)	<0.001
6. How to buckle a child in the car seat	3 (1–4)	4 (4–5)	<0.001
7. Whether the car seat should face forwards or backwards	3 (1–4)	4 (4–5)	<0.001
8. How to find a taxi/private hire vehicle with child car seats	2 (1–3)	4 (4–5)	<0.001
9. How to encourage a crying infant to stay in the car seat	2 (1–3)	4 (4–5)	<0.001
10. Your overall familiarity with child car seats	2 (1–3)	4 (4–5)	<0.001
B. Knowledge questions (Correct answer in parentheses)	**Pre-course correct answers**	**Post-course correct answers**	***P* value**
1. Singapore has a legal requirement to use a child car seat in cars and private hire vehicles. (True)	95.8%	94.1%	0.159
2. Child car seats are effective in protecting children in the event of an accident. (True)	99.6%	99.8%	0.445
3. Since I grew up without a child car seat, my child need not have one. (False)	90.6%	91.5%	0.548
4. Even if I drive safely, other drivers may not. (True)	94.7%	95.4%	0.541
5. Even a short trip carries the risk of a serious road traffic accident. (True)	99.2%	99.0%	0.669
6. Second-hand child car seats are only safe before the expiry date and if accident-free. (True)	49.3%	69.4%	<0.001
7. Babywear/baby carrier is NOT a substitute for a child car seat. (True)	93.2%	95.4%	0.088
8. Child car seats when used appropriately are safe for an infant's breathing and infant's spine. (True)	94.7%	97.6%	0.007
9. If practical, it is better not to use the car seat as a seat for the child when they're not in the car. (True)	65.3%	79.0%	<0.001
10. Premature babies should not be placed in a child car seat. (False)	64.2%	81.2%	<0.001
11. An infant's harness should be snug, at shoulder level or just below the shoulder, in a rear-facing car seat. (True)	82.3%	92.0%	<0.001
12. It is all right to place a swaddled baby in a car seat and/or place bolsters/pillows around them. (False)	72.7%	77.3%	0.053
13. It is all right for a newborn infant to look small compared to the car seat. (True)	55.6%	74.8%	<0.001
14. If the infant appears fragile, this is the reason why the child car seat should be used. (True)	56.6%	78.2%	<0.001
15. Children should ride in rear-facing car seats until age 2 or older. If their seat's height/weight limit allow, they should remain rear-facing until age 4 or older. (True)	75.5%	92.0%	<0.001
16. You can place a rear-facing car seat in the front of a car with a passenger airbag. (False)	65.8%	77.7%	<0.001
17. Children should remain in a harnessed car seat (rather than a booster seat where the adult seat belt goes in front of the child's body) until age 5 or older. If their seat's height/weight limit allow, they should remain in that seat longer. (True)	78.7%	87.1%	<0.001
18. Children 5 years and above should travel in a booster seat until about 1.35–1.45 metres tall. (True)	79.5%	87.5%	<0.001
19. A 6-year-old can sit in the front passenger seat. (False)	69.9%	84.8%	<0.001
20. Children can use an adult seat belt only when the seat belt fits (lap belt across upper thighs and shoulder belt across the chest) without a booster seat. (True)	71.0%	68.4%	0.296

survey respondents, 73.0% (551/755) were from the Neonatal Intensive Care Unit, Nursery, and Delivery Suite; 22.8% (172/755) from Children's Emergency, and 4.2% (32/755) from the Paediatric Wards. For post-course survey respondents, 79.0% (467/591) were from the Neonatal Intensive Care Unit, Nursery, and Delivery Suite; 17.4% (103/591) from Children's Emergency, and 3.6% (21/591) from the Paediatric Wards. The survey respondents' professional roles were as follows. For pre-course survey respondents, 89.4% (675/755) were nurses, 9.4% (71/755) doctors, and 1.2% (9/755) allied health. For post-course survey respondents, 91.2% (539/591) were nurses, 7.6% (45/591) doctors, and 1.2% (7/591) allied health. Only 4.4% (33/755) of pre-course survey respondents had previously attended teaching on child car restraints.

The first part of the survey comprised 10 competency-based questions on child passenger safety, rating respondents' familiarity on a 5-point scale, 1 being "not familiar", and 5 being "very familiar". Table 1 shows a significant improvement in the median self-assessed familiarity score for all 10 competency dimensions pre- to post-course.

The second part of the survey comprised 20 "true/false statement" knowledge-based questions testing key aspects of course content, with 17/20 questions showing an increase in the percentage of correct answers following training (statistically significant increase in 12/20 questions). The greatest knowledge increments were shown in these true statements "If the infant appears fragile, this is the reason why the child car seat should be used" (+21.6%), and "Second-hand child car seats are only safe before the expiry date and if accident-free" (+20.1%). When results were stratified by respondents' areas of work, those working in the Children's Emergency scored a higher percentage of correct answers than colleagues from other parts of the hospital on 13/20 knowledge-based questions.

This is to our knowledge the first Singapore study to specifically evaluate the awareness and skill sets of healthcare professionals in a tertiary children's hospital, before and after receiving training in child passenger safety. Less than 5% of respondents reported having previously attended teaching on child car restraints, reflecting the need for greater knowledge in healthcare workers who have the opportunity to provide CCS education to parents and families. We found that across all 10 competency dimensions, the average self-assessed familiarity score increased following training. For knowledge-based "true/false" questions, most (17/20) questions showed an increase in the percentage of correct answers following training, with 3/20 questions having a marginal decrease in the percentage of correct answers. For question 20, this may be due to difficulty interpreting the lengthy question. The higher scores for knowledge-based questions in respondents working in the Children's Emergency may possibly be related to encountering child injuries from road accidents, although this will need further study to ascertain. Taken together, these suggest that course respondents' sense of self-efficacy in knowledge and skill sets increased with training, broadly translating into increased knowledge in the immediate and short-to-medium term post-training period.

We recognise that this study was designed to assess knowledge and familiarity with child passenger safety skill sets, rather than to test actual skills in correct child car seat instruction and use. We only assessed immediate to short-medium term knowledge gains and were not able to assess knowledge attrition. To maximise the gains in healthcare professionals' knowledge and skill sets, hands-on CCS training of selected hospital staff and refresher training with car seat clinics to evaluate and maintain their skills, are part of an ongoing multipronged approach encompassing multiple aspects of injury prevention.

In conclusion, our pilot study supports the feasibility of online training for mass educational outreach to healthcare professionals in child passenger safety. These findings may provide better understanding for future interdisciplinary child road safety and injury prevention efforts in Singapore.

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Tragus pressure-guided removal of airway devices for safe emergence from sedation: A randomised controlled trial

Dear Editor,

Emergence from anaesthesia and deep sedation is the transition from unconsciousness to the return of awareness and airway reflexes. The chief patterns of unsafe recovery include sudden unpredictable emergence or delayed return of airway tone and reflex with risk of airway obstruction.[1] Agitation includes straining, sitting up, screaming or shouting. Even with supraglottic airway (SGA) use, coughing and expulsion of airway secretions can occur in 14–19% of patients.[2]

Emergence is more predictable when guided by surrogate measures of anaesthetic depth evaluated by processed cortical electroencephalography (EEG) analysis, such as the bispectral index monitoring system (Covidien-Medtronic, Boulder, US) or SedLine (Masimo Corp, Irvine, US);[3] or volatile anaesthetic concentration measurements of end-expiratory gas analysis. However, these require specialised equipment that is largely limited to the operating theatre (OT) environment. These technologies are less consistently employed when patients are sedated or anaesthetised in resource-limited settings, or in locations outside the OT and in post-anaesthesia care units (PACU) where patients recover with airway devices in situ until they can maintain their airway patency unassisted.

A randomised controlled trial was conducted to evaluate the use of a novel technique utilising pressure on the tragus—a fleshy prominence in front of the ear canal—to guide emergence. The tragus pressure technique (Fig. 1) encompasses the application of 3–5 seconds of pressure at 10–30 newtons on the tragus, calibrated by staff pre-trained with using weighing scales to apply optimal non-nociceptive pressure on the tragus.

Tragus pressure application is postulated to stimulate neuro-humoral outflow, thalamo-cortical projections and the reticular activating system.[4-6] This might produce arousal to wakefulness without resulting in sudden emergence, thus guiding and smoothening the process of emergence, removal of airway devices, and safe recovery. The application of tragus (TG) pressure (acupuncture points TG1 and TG2) with counterpressure at the intertragal notch and antitragus (AT) (acupuncture points AT1, AT2 and AT3) shown in Fig. 1 is known to stimulate airway and autonomic responses.[7,8] This pressure application might have triggers on the projections to the solitary nucleus, which is in turn part of the complex neural circuitry that contributes to arousal to hypercarbia.[7] We evaluated the facilitation of emergence from anaesthesia and deep sedation through the application of tragus pressure in this randomised controlled study.

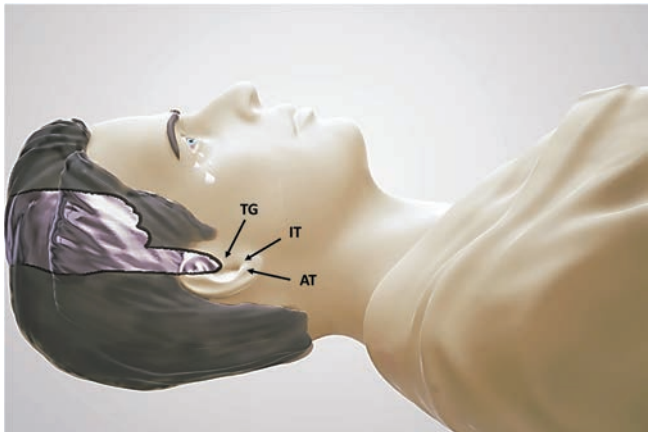

Fig. 1. Application of pressure on the tragus with a steady pressure at 10–30N for 3–5 seconds and releasing the pressure is postulated to trigger tragus (TG) (includes acupuncture points TG1 and TG2), intertragus (IT) notch and antitragus (AT) (includes acupuncture points ATI, AT2 and AT3). Stimulation of these points corresponds to the activation of neuronal outflows from the brain stem to the cortex. Image demonstrates signs of emergence to tragus pressure application: pupillary dilatation, conjunctival injection, eye opening and tears. Other signs (not shown) include the presence of grimacing, tight closure of eyelids/lifting of eyebrows, swallowing movements and gentle motor movements in extremities (shrugging of shoulders/movement of fingers).

Approval was obtained from the institution's ethics review committee (NHG Domain Specific Review Board DSRB Ref: 2017/00071), and the study was registered with ClinicalTrials.gov (ID: NCT04331756) prior to the commencement of the study. All patients who had consented and signed a written informed consent were included in the study.

The primary outcome that the study aimed to explore was the reduction of incidence of airway events (airway obstruction, laryngospasm and negative pressure pulmonary oedema) or patient-deterioration, that necessitated manoeuvres to maintain airway patency. Power calculation based on an anticipated airway event reduction to <5% showed a sample size of 500 with 250 in each arm (tragus and control). The secondary outcomes included the assessment of predicted time-to-emergence, emergence profile and evaluation of the usefulness of

tragus pressure in minimising agitation from rapid, uncontrolled sudden emergence. Sudden emergence was identified by the occurrence of thrashing, biting on the airway devices, lip or tongue, or dislodgement of intravenous and arterial/central venous lines. Block randomisation was achieved through segments of 100 each, with allocation concealment ensured until the arrival of patients in PACU (online Supplementary Fig. S1 for consort diagram**)**. Statistical analysis was performed using SPSS Statistics version 25.0 (IBM Corp, Armonk, US). Univariate analyses (chi-square and Fisher's Exact tests) were used to identify differences between groups.

Results. All patients aged from 21 to 65 years scheduled for short surgical procedures under general anaesthesia with SGA were eligible for the study. A total of 371 patients were recruited and randomised into tragus (n=182) and control (n=189) groups. A total of 272 patients were included for analysis (tragus n=140, control n=132) due to dropouts from changes in anaesthetic technique such as the conversion of SGA to tracheal intubation, patient awakening prior to arrival or waking up immediately on arrival in PACU, before data collection could commence.

Study data **(**online Supplementary Table S1**)** revealed a lower incidence of uncontrolled emergence with patient flailing (2.6% for tragus versus 8.3% for controls) and biting on the airway device (23.4% for tragus vs 32.8% for control). The mean time-to-emergence was comparable (tragus 11min 29s vs control 12min 42s).

A subgroup analysis was performed by stratification of patients according to anaesthetic depth based on the last recorded end-tidal volatile anaesthetic concentrations before leaving the OT. Patients with lighter anaesthetic planes (minimum alveolar concentration [MAC] <0.3) had an increased incidence of adverse events during emergence at PACU in the control group such as biting (37.5% control group vs 18.2% in tragus group), and flailing (12.5% control group vs 0.0% in tragus group). There were no incidences of airway complications (airway obstruction and desaturation to <95%) in the tragus pressure group, suggesting the safety of the technique. Further data collection was ceased as no new patterns emerged.

Discussion. The different stages of anaesthesia and recovery were first described in unpremedicated, spontaneously breathing patients receiving diethyl ether as an inhaled anaesthetic. These stages are not elicitable in the originally described sequences with modern balanced anaesthesia. Advanced monitoring equipment, mathematical modelling of target-controlled infusions and use of end-tidal anaesthetic gas concentrations are all limited to the intraoperative measurement of anaesthetic depth. With increasing proportion of general anaesthetics being provided with SGA, more scientific and predictable ways of emergence are needed for bedside assessment of anaesthetic depth in PACU, and for recovery of patients and SGA removal.

We identified tragus pressure as a simple, predictable intervention to guide smooth emergence from anaesthesia, while potentially minimising the risks of rapid emergence. The tragus pressure-guided emergence technique is easily reproducible, safe and inexpensive. It stratifies patients into non-reactive and reactive phases. Reactive phase features the occurrence of pupillary dilation, facial grimace, contraction of orbicularis oculi, eye opening or gentle motor movements such as shrugging of shoulders or fine movements in hand as a response to tragus pressure application (Fig. 1). This reactive phase is a predictable component of impending emergence from anaesthesia, an indication of an optimal plane for SGA removal (without laryngospasm). It is also a primer of anticipated emergence necessitating closer monitoring by attending staff. This predictability is particularly vital in resource limited settings (compromised nurse-patient ratios), clinical environments with very rapid turnover such as PACU and remote locations for anaesthesia and deep sedations (dental, endoscopy and radiology), where expertise in airway management is scarce.

Further studies exploring processed EEG documentation of smooth emergence could ascertain wider application of tragus pressure technique in the safe monitoring of patients recovering from deep sedation in out-of-theatre settings.

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A man with bark-like skin

A 65-year-old Chinese man was admitted for evaluation of chronic anaemia. He had a history of hypertension and chronic kidney disease, and his regular medications were nifedipine and losartan. He was a retired cleaner who lived with friends and had no contact with his family.

He was referred to the Dermatology clinic for thick, brown and tree bark-like scaling on his legs extending from below the knees down to the dorsal feet. On rubbing with alcohol swabs, the scales came off, but only very slightly. According to the patient, his legs had looked like this for the past 1 year (Figs. 1A and 2). He reported occasional mild itch, but denied scratching or applying anything in particular to his legs. He had no personal or family history of atopy. Apart from the leg lesions, which were the most dramatic, he also had some mild brown scaling over the axillae and abdomen, and had elongated untrimmed toenails. The rest of his skin and mucosae were unremarkable and he had no palpable lymph nodes. Skin scrapings did not reveal any scabies mites. He admitted to avoiding washing his legs while showering.

He was advised to shower with chlorhexidine soap and apply urea cream thrice daily. He was instructed to gently rub off loose scales in the shower. He was also referred to a podiatry specialist to assist with toenail trimming. Two days later, a dramatic improvement was seen in the skin condition of his legs (Fig. 1B). The axillary and abdominal lesions had completely cleared. At subsequent follow-up 1 month later, the skin on his legs continued to improve (Fig. 1C).

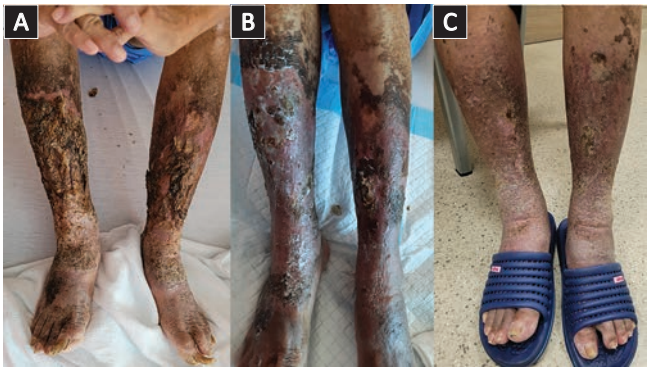

Fig. 1. Serial pictures of the shin. (A) At presentation, (B) 2 days post-urea cream and showering with chlorhexidine soap, and (C) at 1-month follow-up. Note the toenails as well.

Fig. 2. Close-up of left shin showing tree bark-like skin morphology of dermatitis neglecta, at presentation.

What is your diagnosis?

A. Epidermodysplasia verruciformis
B. Crusted scabies
C. Pellagra
D. Terra firma-forme dermatosis
E. Dermatitis neglecta

Epidermodysplasia verruciformis (EV) is a rare inherited disorder, associated with increased susceptibility to human papillomavirus infections. An acquired form of EV occasionally develops in the immunocompromised. The condition presents with multiple giant verrucous cutaneous horns, plane warts and pityriasis versicolor-like lesions. These are difficult to eradicate completely, and skin cancers can develop from these lesions.[1] Although our patient had warty tree-bark-like plaques on the shins, these lesions improved quickly with keratolytic moisturisers and cleansing.

Crusted scabies presents with thick, yellowish crusted scales, and burrows predominantly at typical sites such as hands, feet and genitals. Scrapings for scabies are generally teeming with mites, which were not seen in our patient.

Sharply demarcated, thick and brown plaques over sun-exposed sites can be seen in pellagra. Points against

Answer: E

pellagra in our patient included absence of involvement at other sun-exposed sites, absence of glossitis or stomatitis or other mucosal symptoms, absence of any other history suggestive of malnutrition or malabsorption, and rapid improvement with mere soap, water and urea cream.

Terra firma-forme dermatosis (TFFD) can morphologically resemble our patient's lesions. Lesions of TFFD are not removable upon washing with soap and water. However, they can be completely rubbed off with isopropyl alcohol. [2] This was not the case in our patient.

Dermatitis neglecta (DN) is a condition that results from inadequate frictional cleansing leading to accumulation of corneocytes, sebum and sweat ultimately resulting in hyperpigmented patches or verrucous plaques.[3] DN was first described by Poskitt et al. in 1995.[4] It has no gender predilection, affects all ages, and is frequently underdiagnosed. Clinically, there are asymptomatic hyperkeratotic plaques with cornflake-like scales. Inadequate cleansing and improper hygiene in an area of immobility, pain, hyperaesthesia, prior trauma, and surgery leading to inadequate exfoliation of skin are the commonly reported inciting factors.[3] There are also reports of DN in patients with psychiatric conditions, including depression and schizophrenia, or related to religious beliefs.[5]

DN has been reported at a variety of body sites[3,6,7] and at all ages.[8] It is suggested that DN should be kept in mind in the differential diagnosis of all hyperpigmented localised lesions, especially in those with a background of disability. There are many similarities between DN and TFFD. In TFFD, the distinguishing features are the presence of adequate hygiene, unresponsiveness of the hyperpigmented patch to soap water swabbing, but successful removal of lesions by alcohol swabbing.[2,3] On dermoscopy, larger polygonal scales are more suggestive of TFFD, while DN is characterised by more irregularly distributed cornflake-like scales. On histopathology, TFFD shows more prominent papillomatosis, acanthosis and compact orthohyperkeratosis, while DN shows basketweave hyperkeratosis and diminished rete pegs.[6] Other differential diagnoses depending on the site of lesions would include confluent and reticulated papillomatosis of Gougerot and Carteaud, pityriasis versicolor, verrucous epidermal naevi, acanthosis nigricans, frictional hyperkeratosis, atopic dirty neck, pemphigus foliaceus, Darier's disease and several forms of ichthyosis.[3,9]

Our patient had no psychiatric issues, but poor social support could have contributed to his condition. His serum zinc level was low, which was replaced. He was also advised to undergo a varicose vein scan in view of the possibility of chronic venous insufficiency and stasis dermatitis contributing to his condition.

Often patients are alarmed by the appearance of their skin, which leads to further avoidance of washing the area, thus ultimately worsening the problem and resulting in a vicious cycle. This was probably the case in our patient. Interestingly, a case of DN was reported involving the face, where the patient was in fact washing her face 12–15 times a day, but not drying her face after washing.[10] Hence, adequate education of patients on how to cleanse the skin is important.

DN is a relatively common but under-reported entity. Greater awareness of this condition can spare patients from unnecessary and invasive investigations.

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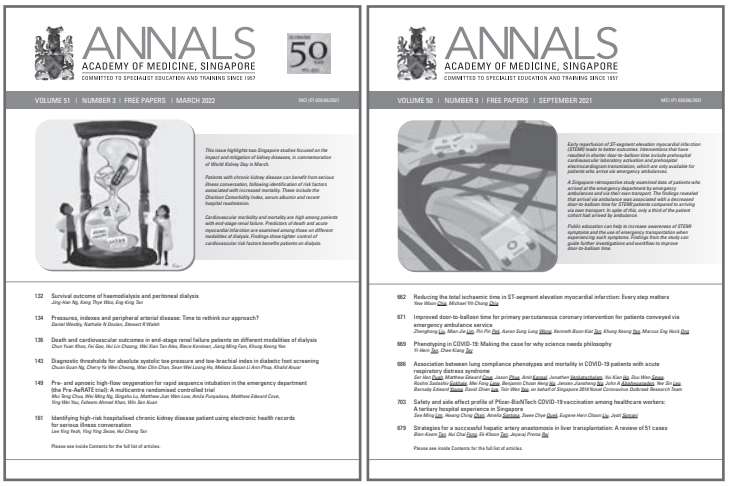

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