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VOLUME 51 | NUMBER 6 | FREE PAPERS | JUNE 2022

MCI (P) 026/06/2022

A recent observational study conducted in 5 tertiary hospitals in Singapore examined the characteristics, treatment modalities, clinical outcomes and nutrition interventions of critically ill patients with COVID-19 in the intensive care unit.

A large proportion did not receive adequate calories and protein, and late enteral nutrition (more than 36 hours) was associated with higher hospital mortality. High obesity prevalence, as well as frequent usage of neuromuscular blockade, prone therapy and dialysis, had significant implications for the nutrition care of these patients.

More audits should be conducted to refine nutritional interventions and guidelines for this evolving disease.

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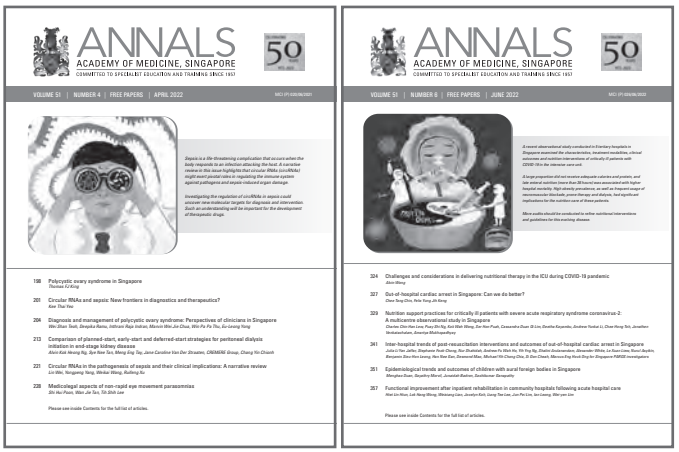
Official Journal of the Academy of Medicine, Singapore



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Printed by Straits Printers (Pte) Ltd

ISSN 0304-4602

MCI (P) 026/06/2022

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ACADEMY OF MEDICINE SINGAPORE

Annals, Academy of Medicine, Singapore

Volume 51 | Number 6 | June 2022

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EDITORIAL

Ann Acad Med Singap 2022;51:324-6
https://doi.org/10.47102/annals-acadmedsg.2022182

Challenges and considerations in delivering nutritional therapy in the ICU during COVID-19 pandemic

Alvin Wong [1,2] *MSc*

Coronavirus disease 2019 (COVID-19) has created unprecedented challenges for healthcare workers in Singapore and across the world. Providing clinical nutrition and metabolic care to patients with COVID-19 has been highly challenging. In this issue of the *Annals*, Lew et al.[1] reported the results of a multicentre retrospective observational study on critically ill patients with COVID-19 in the intensive care unit (ICU). The authors found that more than 25% of these patients lived with obesity and/or diabetes, and a large majority have received neuromuscular blockade (70%), prone therapy (45%) and dialysis (37%). The median ICU and hospital length of stay (LOS) was 11.0 days (interquartile range [IQR] 7.0–21.8) and 31.0 days (IQR 19.3–44.0), respectively, for patients who recovered from COVID-19.[1] In this editorial, we discuss how the results from Lew et al. have implications on nutritional support practices and future research direction in Singapore.

There were significant nutritional concerns observed from the results of the study. Firstly, due to COVID-19, none of the study sites performed nutritional assessment as physical examination for the patients was required.[1] Secondly, refeeding hypophosphataemia, a potentially serious complication, was found in 6% of the cohort. Thirdly, prone therapy was not associated with a higher incidence of high gastric residual volume (GRV) in patients on enteral tube feeding. Fourthly, only 54% of the patients met their minimal goal energy (≥15kcal/kg actual body weight) requirements, and none of the patients met their minimal goal protein (≥1.2g/kg actual body weight) requirements during their ICU stay. Lastly, late enteral nutrition (initiated >36 hours) was associated with higher hospital mortality (adjusted relative risk 9.0, 95% CI 2.3–36.0).

Safety of implementing nutrition support. Before the availability of vaccinations and an adequate supply of personal protective equipment, healthcare professionals were concerned with how to safely insert feeding tubes or determine enteral feed intolerance via the usual methods of gastric residual volumes.[2] The generally used weight-based predictive equations are considered less accurate, while indirect calorimetry—a gold standard for measuring energy needs—was deemed impractical due to the difficulty in ensuring sterility.[2,3]

Nutritional assessment was not considered an essential aspect of nutritional therapy during the pandemic due to the difficulty in performing a physical assessment, as shown by Lew et al.[1] One of the general concerns in the ICU is the determination of caloric and protein requirements of critically ill patients.[2,4] To overcome this, the authors suggested that nutritional screening tools that do not involve physical assessment could be used in the ICU; alternatively, clinicians could focus on risk factors such as age, length of time with minimal intake before initiation of nutritional intervention, and specific metabolic disturbances (e.g. hypokalaemia, hypomagnesaemia and hypophosphataemia).

Obesity, diabetes and metabolic disturbances in COVID-19. The difficulty in assessing the nutritional needs of critically ill patients with obesity is exacerbated during the pandemic. The prevalence of obesity in the study by Lew et al. (54%) was disproportionally higher than the prevalence (10.5%) in Singapore, which is concerning. It is known that for some time, the obesity paradox described by observational data provided some reassurance that patients who are overweight or obese (Class I and II) have better outcomes with lower mortality rates, compared to patients with a normal body mass index.[5]

However, COVID-19 has invalidated this obesity paradox. Obesity increases COVID-19 infection, hospitalisation, the severity of disease, ICU admission and mortality.[6] Similarly for diabetes, a common comorbidity in patients with obesity, where a higher risk of hospitalisation, ICU admission and mortality has also been observed.[6]

Electrolyte and metabolic disturbances should be routinely monitored in ICU patients. Although Lew et al.

[1] Department of Dietetics, Changi General Hospital, Singapore
[2] School of Human Movement and Nutrition Sciences, The University of Queensland, St Lucia, Australia
Correspondence: Mr Alvin Wong, Department of Dietetics, Changi General Hospital, 2 Simei Street 3, Singapore 529889.
Email: alvin_wong@cgh.com.sg

found refeeding hypophosphataemia in only 6% of the patients observed, a recent study reported a higher rate of 36%.[7] Due to the difficulties in providing nutritional therapy for these patients, their risk of refeeding syndrome may increase throughout the ICU stay.

Prone positioning, extracorporeal membrane oxygenation and paralysis in the ICU. During the early periods of the pandemic, basic nutrition principles were extrapolated from existing critical care nutrition guidelines, such as the American Society for Parenteral and Enteral Nutrition (ASPEN) and Society of Critical Care Medicine (SCCM) 2016 guidelines, recommending early gastric feeding with a gradual increase to goal. This included patients who required prone positioning, extracorporeal membrane oxygenation (ECMO), or paralysis by neuromuscular blockade.[8]

Patients with COVID-19 benefit from prone ventilation, which frequently requires the liberal administration of opiate analgesia, leading to gastrointestinal intolerance such as increased gastric residual volumes.[8] Although Lew et al. found no relationship between prone therapy and GRV, several guidelines recommend prokinetics and insertion of post-pyloric tubes.[2] However, there is no consensus on whether GRV should be monitored, at which time points, and at what cut-off values.[2]

Nutritional requirements for the critically ill patient with COVID-19. Only half of the patients observed by Lew et al. received an energy intake of 15kcal/kg/day. This contrasted with the findings by Chen et al.[9] where 75% of the ICU patients received 15–20kcal/kg/day. In this small observational study (n=8), ICU patients were referred to a multidisciplinary team of rehabilitative medicine specialists and allied health professionals (dietitians and occupational/physical/respiratory/speech therapists) for early rehabilitation.

Although the mean Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of both ICU populations were similar, only a quarter of the patients received prone therapy in the study by Chen et al., compared to almost half of the patients examined by Lew et al. This difference had probably led to a lower caloric intake in the latter's patient group since patients on prone therapy may have more feeding disruptions.

Interestingly, the protein intake of patients from both studies was similarly low (<1.2g/kg/day), even though Chen et al. reported a higher caloric intake. This could be due to the choice of tube feeds secondary to fluid restriction, feeding intolerance, non-availability of high protein feeds, or different ICU feeding practices (e.g. Lew et al. reported the use of bolus protein doses but not Chen et al.).

Presently, slow and gradual energy and protein delivery is recommended during the first 5–7 days.[2] However, recommendations for energy and protein prescriptions vary between 20–30kcal/kg/day and 1.2–2.0g protein/kg/day.[2] The recently updated ASPEN/SCCM 2021 guidelines concluded that no significant difference in clinical outcomes was found between patients with higher versus lower levels of energy intake, and limited data were available for protein intake more than the current recommendations.[4]

Non-nutritional calories from propofol and/or dextrose administration should also be considered when evaluating energy delivery.[2] This is supported by another recent Singapore study where patients on continuous renal replacement therapy may receive up to 331kcal from trisodium citrate anticoagulant (which provides substrate intermediates for adenosine triphosphate [ATP] production through Kreb's cycle in the mitochondria).[10]

Nutritional support practices in the ICU and post-ICU. Late initiation of enteral nutrition (>36 hours) has been found by Lew et al.[1] to increase mortality by 9-fold. However, approximately 96% of the patients in the study were initiated on enteral nutrition within 36 hours of ICU admission, in line with existing guidelines (<48 hours).[2] The results would need to be interpreted with caution due to the small sample size for late enteral nutrition.

Limited studies focus on the long-term effects of COVID-19, particularly for critically ill populations. Therefore, while waiting for new evidence to emerge, it is beneficial to focus on improving the nutritional status of patients who may be malnourished to facilitate their post-ICU recovery. Dietary counselling with or without oral nutritional supplements (ONS) has been found to reduce complications and 6-month mortality for patients who are malnourished or at risk of malnutrition.[11] However, unsupervised provision of ONS without targeted education neither benefits the at-risk population[11] nor remains cost-effective as critically ill patients with COVID-19 tend to have extended hospitalisation.

Conclusion. Singapore institutions have performed well in the nutritional management of critically ill patients during the pandemic in terms of early initiation, monitoring and managing complications related to nutritional support. However, more must be done to achieve adequate nutritional intake for patients with long ICU stays. Future research on COVID-19 should focus on the clinical and nutritional outcomes of the

post-ICU patient populations. More multicentre nutrition-related studies involving various institutions are encouraged, to increase the sample size of study populations and advance the quality of clinical nutrition research in Singapore.

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EDITORIAL

Ann Acad Med Singap 2022;51:327-8
https://doi.org/10.47102/annals-acadmedsg.2022184

Out-of-hospital cardiac arrest in Singapore: Can we do better?

Chee Tang Chin [1]*MBChB (Hons)*, Felix Yung Jih Keng [1]*MBBS*

Cardiac arrests are unpredictable events that frequently result in death or significant residual morbidity among survivors. These sudden events affect not only the individual, but are understandably also significant life events and stressors for the family and friends. As such, the impact of cardiac arrests is felt on a societal basis, and significant efforts have been expended to try to improve outcomes.

In this issue of the *Annals*, we have more insight concerning out-of-hospital cardiac arrests (OHCA) in Singapore, specifically with regard to the temporal and inter-hospital trends in the post-resuscitation care provision and patient outcomes. Jaffar et al. observed that rates of advanced post-resuscitation interventions—such as therapeutic temperature management (TTM), emergency percutaneous coronary intervention (PCI), and extracorporeal membrane oxygenation (ECMO)—increased from 2010 to 2018.[1,2] During the same period, the outcomes that they examined also improved significantly. Of particular interest, initial presentation to an academic hospital was associated with improved outcomes when compared to presentation at a non-academic hospital. They therefore concluded that these findings could serve to guide future policies for managing OHCA in Singapore.

Intuitively, it appears unsurprising that more post-resuscitative measures employed would result in better outcomes for OHCA patients. Therefore, given that these advanced therapies are usually based at academic hospitals, it would be logical that outcomes would be better at these centres. Hence, perhaps by making advanced therapiesavailable at all hospitals, outcomes would improve across Singapore.

However, one should be cautious before leaping to these conclusions. As already highlighted by the authors, this dataset lacked individual patient factors that are known to impact OHCA survival.[3] Without more granular data such as the prevalence of comorbidities (e.g. diabetes, known heart failure, renal failure, stroke, etc.), there is likely considerable residual confounding in the models employed by the authors to adjust for outcomes.

Furthermore, as the authors have also mentioned, we are not privy to the decision-making by treating physicians especially with regard to the provision of advanced therapies for different patients. We know that physicians may be more "aggressive" when treating patients whom they feel will likely do better, and vice versa.[4] However, this physician-treatment benefit paradox means that it is difficult to tease out the true value and impact of these advanced therapies. This is especially so when randomised clinical trial data have not shown consistent benefits in OHCA for any of the advanced therapies examined by the authors.

Equally important, we should also not dismiss the potential of these advanced therapies to cause harm. For example, PCI is a common and low-risk procedure when performed in the elective setting. However, PCI becomes considerably more hazardous when performed in a resuscitated patient who may be more prone to bleeding, and yet, has to be anticoagulated and receive antiplatelet drugs for the PCI.[5] Similarly, ECMO has a recognised list of serious complications including bleeding, limb ischaemia and infection.[6] Therefore, we should have a proper understanding of the risks and benefits of these advanced therapies when applied to OHCA patients and tailor treatment appropriately.

Regardless of the considerations discussed above, the observed outcomes reported by Jaffar et al. confirm that OHCA remains a devastating event. Survival to 30 days (throughout the different years and hospitals reported) was generally less than 10%, and not all survivors had good neurological recovery. Although there was a statistically significant improvement in outcomes over time, the absolute increase in improved outcomes over time was, in our opinion, modest.

This is sobering because Singapore has what many would consider an efficient and mature pre-hospital treatment environment. Over time, public awareness of cardiac arrests has increased, as has community involvement in resuscitation efforts. We are particularly impressed by the findings reported in this study that bystander CPR increased significantly from about 20% in 2010 to more than 60% in 2018. Also, as stated

[1] Department of Cardiology, National Heart Centre Singapore, Singapore
Correspondence: Assoc Prof Chee Tang Chin, Department of Cardiology, National Heart Centre Singapore, 5 Hospital Dr, Singapore 169609.
Email: chin.chee.tang@singhealth.com.sg

by the authors, the emergency medical services paramedics in Singapore typically reach the scene of the cardiac arrest in under 10 minutes, and are trained in the use of defibrillators and other aspects of basic life support. Therefore, it is challenging to anticipate what further improvements can be made with regard to pre-hospital treatment of cardiac arrests in Singapore.

Does the answer to improved cardiac arrest outcomes in the future then depend on the hospitals procuring increasingly advanced and sophisticated technologies and techniques for post-resuscitation management? Should all hospitals in Singapore have access to emergency round-the-clock PCI (the reality is that almost all do now), or manage ECMOs in their intensive care units (ICUs)? We are not convinced that this study provides enough justification for this direction. Furthermore, in the context of escalating overall health costs, challenges in recruiting and retaining skilled healthcare professionals, and global economic uncertainties, there must be careful consideration on the most appropriate treatments for this group of patients who have such a guarded prognosis.

So what else could be done to improve outcomes in OHCA? First, we must continue to emphasise the importance of managing modifiable risk factors for cardiac arrest. While cardiac arrests are unpredictable, we do know that many are due to underlying coronary disease. We also now have a wealth of information with regard to reducing the risk of sudden coronary events. Especially pertinent in this aspect is the current drive towards "population health" in Singapore and the direction for the public healthcare clusters to pivot towards primary prevention and greater community engagement.[7] For example, further driving down smoking rates or increasing awareness of blood pressure targets may have a greater impact on overall rates of cardiac arrest and hence outcomes, as compared to equipping the ICU with yet another piece of equipment.

Second, because we cannot totally eliminate cardiac arrests, the public must be continually made aware of the poor outcomes of cardiac arrest highlighted by Jaffar et al. Empowering the public to start the process of advanced care planning early will help cushion the impact to loved ones if and when a cardiac arrest occurs. In the hospitals, we frequently encounter families who are shocked and distressed because the last memories of their loved ones involve invasive tubes and beeping machines.[8] Not all OHCA patients want to be subject to advanced invasive therapies, yet when they are at their most vulnerable, they are not able to express their wishes.

In conclusion, Jaffar et al. have contributed an important study to further our understanding of outcomes and the management of cardiac arrest patients in Singapore. We agree that lessons must be learnt from this, and new paradigms created.

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ORIGINAL ARTICLE

Ann Acad Med Singap 2022;51:329-40
https://doi.org/10.47102/annals-acadmedsg.202231

Nutrition support practices for critically ill patients with severe acute respiratory syndrome coronavirus-2: A multicentre observational study in Singapore

Charles Chin Han Lew [1]*PhD*, Puay Shi Ng [2]*B Nutr Diet (Hons)*, Kok Wah Wong [2]*B Nutr Diet (Hons)*, Ser Hon Puah [3]*MRCP*, Cassandra Duan Qi Lim [4]*MS*, Geetha Kayambu [5]*PhD*, Andrew Yunkai Li [6]*MBBS*, Chee Hong Toh [7]*MS*, Jonathen Venkatachalam [8]*MRCP*, Amartya Mukhopadhyay [9,10]*FRCP*

ABSTRACT

Introduction: To improve the nutritional care and resource allocation of critically ill patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), we described their characteristics, treatment modalities and clinical outcomes, and compared their nutrition interventions against the American Society for Parenteral and Enteral Nutrition (ASPEN) recommendations.

Methods: This was a retrospective observational study conducted in 5 tertiary hospitals in Singapore. Characteristics, treatment modalities, clinical outcomes and nutrition interventions of critically ill patients with SARS-CoV-2 who received enteral and parenteral nutrition were collected between January and May 2020.

Results: Among the 83 critically ill patients with SARS-CoV-2, 22 (28%) were obese, 45 (54%) had hypertension, and 21 (25%) had diabetes. Neuromuscular blockade, prone therapy and dialysis were applied in 70% (58), 47% (39) and 35% (29) of the patients, respectively. Refeeding hypophosphataemia and hospital mortality occurred respectively in 6% (5) and 18% (15) of the critically ill patients with SARS-CoV-2. Late enteral nutrition and cardiovascular comorbidities were associated with higher hospital mortality (adjusted relative risk 9.00, 95% confidence interval [CI] 2.25–35.99; 6.30, 95% CI 1.15–34.40, respectively). Prone therapy was not associated with a higher incidence of high gastric residual volume (≥250mL). The minimum caloric (15kcal/kg) and protein (1.2g/kg) recommendations of ASPEN were achieved in 54% (39) and 0% of the patients, respectively.

Conclusion: The high obesity prevalence and frequent usage of neuromuscular blockade, prone therapy, and dialysis had considerable implications for the nutritional care of critically ill patients with SARS-CoV-2. They also did not receive adequate calories and protein. More audits should be conducted to refine nutritional interventions and guidelines for this ever-evolving disease.

Ann Acad Med Singap 2022;51:329-40

Keywords: COVID-19, critical illness, energy intake, enteral nutrition, nutrition support, protein intake

[1] Dietetics and Nutrition Department, Ng Teng Fong General Hospital, Singapore
[2] Nutrition and Dietetics, Tan Tock Seng Hospital, Singapore
[3] Respiratory and Critical Care Medicine Department, Tan Tock Seng Hospital, Singapore
[4] Dietetics Department, National University Hospital, Singapore
[5] Department of Rehabilitation, National University Hospital, Singapore
[6] Division of Respiratory and Critical Care Medicine, Department of Medicine, National University Hospital, Singapore
[7] Nutrition and Dietetics, Khoo Teck Puat Hospital, Singapore
[8] Respiratory and Critical Care Medicine, Khoo Teck Puat Hospital, Singapore
[9] Research, Innovation and Enterprise, Medical Affairs, Alexandra Hospital, Singapore
[10] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
Correspondence: Dr Charles Chin Han Lew, Dietetics and Nutrition Department, Ng Teng Fong General Hospital, 1 Jurong East Street 21, Singapore 609606.
Email: Charles_lew@nuhs.edu.sg

CLINICAL IMPACT

What is New

- A large proportion of intensive care unit (ICU) COVID-19 patients in Singapore were obese, had diabetes, and received neuromuscular blockade, prone therapy and dialysis.
- Late enteral nutrition (>36 hours) was associated with higher hospital mortality.
- Refeeding hypophosphataemia occurred in 6% of ICU COVID-19 patients.
- Proning was not associated with a higher incidence of high gastric residual volume.

Clinical Implications

- Half and none of ICU COVID-19 patients met their minimal caloric and protein goals, respectively. Therefore, clinicians should pay close attention to the nutrition adequacy of these patients.

INTRODUCTION

Within 3 weeks of the World Health Organization declaring the COVID-19 pandemic on 11 March 2020, the Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) developed a set of nutrition guidelines that addresses issues on nutrition assessment; timing and feeding route; caloric and protein doses; enteral nutrition (EN) formula selection; monitoring; and feeding practices during prone and extracorporeal membrane oxygenation therapies for critically ill patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] Singapore has one of the lowest case fatality rates, and this may be attributed to practices such as early intubation, lung protective ventilatory strategies and good general supportive care.[2]

With an increased number of SARS-CoV-2 patients admitted to intensive care units (ICUs) globally, attention is given to better care, including nutrition. Previous studies have identified barriers in providing nutrition to this vulnerable group, including unpredictable clinical courses and fear of aspiration.[3] In this regard, we recognised that audit of local practices would make clinicians aware of the management gap, if any. There is currently only 1 local study (single-centre case series of 8 patients) that described the nutritional care of SARS-CoV-2 critically ill patients.[4] Therefore, we conducted a multicentred observational study to describe the characteristics, treatment modalities, and clinical outcomes of SARS-CoV-2 critically ill patients; and compare the nutrition support practices of Singapore against the SCCM/ASPEN recommendations.

METHODS

This was a retrospective audit of 5 tertiary hospitals in Singapore. Consecutive patients diagnosed with SARS-CoV-2 (confirmed by reverse-transcriptase–polymerase chain reaction test) and admitted to the ICU between January and May 2020 were screened for eligibility. Patients who were ≥21 years old and received non-volitional nutrition support such as EN and/or parenteral nutrition (PN) in the first 14 days of ICU admission were enrolled. Patients whose sole source of nutrition was peroral in the first 14 days of ICU admission were excluded. All patients were followed up to hospital discharge unless death occurred earlier. The Domain Specific Review Board approved this study (NHG DSRB Ref: 2020/00795), and the requirement of informed consent was waived.

Data collection

All data required were extracted from the electronic medical records of each hospital in a standardised password-protected Excel file. Data were grouped into categories of demographics; anthropometry; comorbidities; disease severity scores (Acute Physiology and Chronic Health Evaluation II [APACHE II], Sequential Organ Failure Assessment [SOFA] and modified Nutrition Risk in Critically Ill score [mNUTRIC][5]); treatment modalities (e.g. extracorporeal membrane oxygenation, dialysis, prone therapy and neuromuscular blockade); nutrition practices (e.g. time from ICU admission to commencement of EN, and malnutrition assessment); caloric and protein intake during exclusive EN and/or PN from ICU admission to a maximum of 14 days unless death occurred earlier (i.e. calories and protein intake contributed by dextrose-containing intravenous fluids, propofol, protein modular and enteral and parenteral formulas); episodes of high gastric residual volume (high-GRV) (≥250mL); duration of mechanical ventilation, ICU and hospital admission in survivors; and ICU and hospital mortality.

To compare our practice (Supplementary Table S1 in online Supplementary Material) with the SCCM/ASPEN recommendations,[1] additional data were collected. Specifically, exposure to early EN (≤36 hours from ICU admission); mean arterial pressure during the initiation of EN; prescription of caloric goal (indirect calorimetry [IC] versus weight-based formula); choice of the enteral and parenteral formula; incidence of diarrhoea (i.e. absence of laxative given 1 day before defecation of ≥3 stools rated as type 6–7 on the Bristol

Stool Scale/day or the utilisation of a rectal tube); measurement of serum triglyceride in patients exposed to propofol and/or PN; and head elevation of at least 10–25º during prone therapy.

Statistical analysis

Normality was assessed by the Shapiro-Wilk test. Data were summarised as mean and standard deviation (SD) (normally distributed continuous data), median and interquartile range (IQR) (non-normally distributed continuous data), or counts and percentages (categorical variables). They were compared using Student's t-test, Mann-Whitney U test, analysis of variance, Kruskal-Wallis H test, or chi-square test, as appropriate. To compare patients' caloric and protein intake from day 1 to day 7 with the SCCM/ASPEN recommendations, one-sample t-tests were carried out. To determine if prone therapy was associated with a higher incidence of high-GRV (≥250mL), episodes of high-GRV and exposure to prone therapy were compared with Student's t-test in all patients. After that, in patients exposed to prone therapy, episodes of high-GRV on prone-day versus non-prone-day were compared with the Wilcoxon signed-rank test. To determine if EN formula containing fibre (EN-Fibre) was worse tolerated compared to fibre-free formula, the median exposure period to EN-Fibre was first determined, and patients below and above the median were classified as "not exposed" and "exposed", respectively. Thereafter, the number of high-GRV episodes and diarrhoea-days per 100 EN days were compared between patients who were "not exposed" and "exposed" using one-way analysis of covariance, adjusting for APACHE and diabetes. Modified Cox regression[6] with backward elimination was used to determine the baseline parameters associated with hospital mortality. Statistical analyses were performed using SPSS Statistics software version 20.0 (IBM Corp, Armonk, US); all tests were two-sided, and P value <0.05 was considered significant. Multiple testing correction was not applied, and P values should be interpreted as exploratory.

RESULTS

Eighty-three patients were enrolled, and their characteristics across the hospitals were generally similar (Table 1). Majority were either overweight (29/80, 36.3%) or obese (22/80, 27.5%) (3 missing data). Most of them had comorbidities such as hypertension (45, 54.2%) and diabetes (21, 25.3%). Disease severity was similar across the hospitals (mean [SD]: APACHE II 19.4 [9.8], SOFA 7.0 [4.5], and mNUTRIC 4.1 [2.0]) except for Hospital B, which had significantly lower APACHE (14.8 [7.7]), SOFA (5.4 [3.3]), and mNUTRIC (3.4 [1.8]) scores.

Treatment modalities such as dialysis, neuromuscular blockade, and prone therapy were common. Across the hospitals, 1 in 3 patients (34.9%) required dialysis with a median duration of 4.0 (IQR 1.5–6.0) days; 7 in 10 patients (69.9%) received neuromuscular blockade with a median duration of 4.0 (IQR 2.0–8.0) days; and 1 in 2 patients (47.0%) received prone therapy with a median duration of 4.0 (IQR 2.0–6.0) days (Table 1). Two patients (2.4%) received extracorporeal membrane oxygenation therapy with a duration of 7 and 14 days, respectively.

Nutrition-related results

At ICU admission, 9 patients (10.8%) were kept on peroral feeding for ≥2 days, and their median EN start time was 4.0 (IQR 4.0–5.5) days (Table 2). Compared to other patients who either received EN or PN (n=74), they had significantly lower disease severity scores (mean [SD]: APACHE II 9.3 [4.1], SOFA 2.8 [2.2], and mNUTRIC 2.9 [1.2]); higher exposure to prone therapy (88.9% vs 41.9%); longer duration of neuromuscular blockade (median [IQR] 7.5 [6.0–9.5] vs 4.0 [2.0–6.0]); and higher mortality (55.6% vs 13.5%).

Seventy-three patients were first exposed to EN in the first 2 days of ICU admission because most of them were mechanically ventilated (67, 91.8%) during this period. The caloric and protein intake of these patients are shown in Figs. 1 and 2. Standard, diabetes-specific, and high-protein renal enteral formulas were commonly prescribed (Fig. S1 in Supplementary Material). Two patients (2.4%) received PN, of whom 1 also received EN. In both cases, PN was given for 1 day. No patients had a nasojejunal tube inserted. Refeeding hypophosphataemia was present in 5 patients (6.0%) (Table 1).

Enteral feeding intolerance was determined by the incidence of high-GRV and diarrhoea (Table 1). High GRV incidences mostly occurred in the first 4 days of ICU admission (Fig. S2 in Supplementary Material). High-GRV was also not associated with exposure to EN-Fibre after adjusting for APACHE and diabetes ($F(1,69)=0.406$, $P=0.526$). As for diarrhoea, there were 5.8 diarrhoea-days per 100 ICU days across the hospitals, and exposure to EN-Fibre is associated with lower mean diarrhoea-days per 100 EN days, ($F(1,69)=4.373$, $P=0.040$, adjusted for APACHE and diabetes).

Prone therapy is frequently carried out in the first 5 days of ICU admission (Fig. S2 in Supplementary Material). Compared to patients receiving EN without prone therapy (37), patients with EN and prone therapy

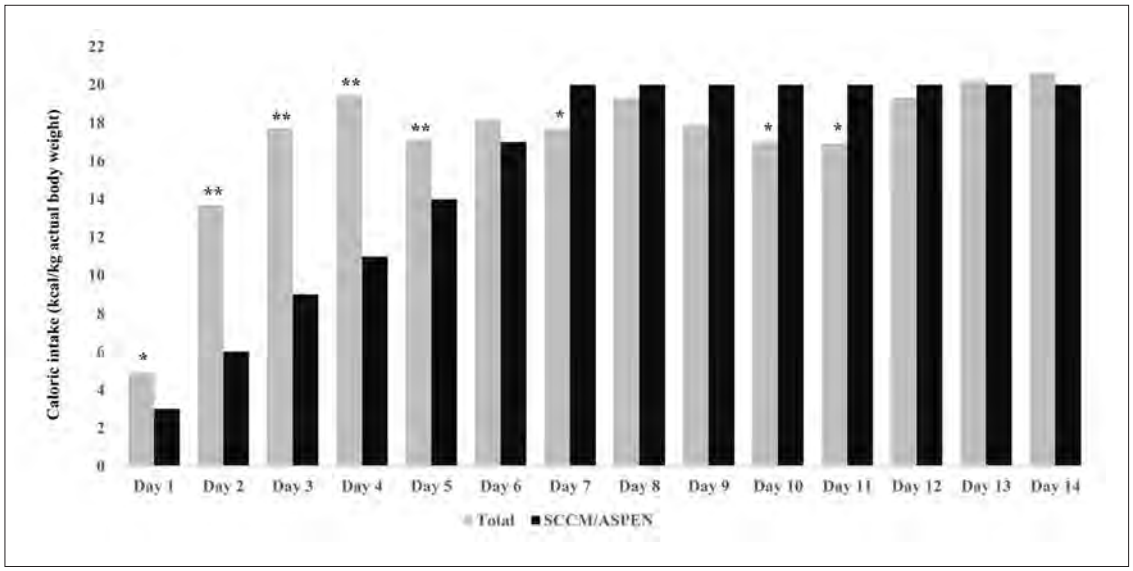

Fig. 1. Caloric intake of patients over 14 days.
SCCM/ASPEN: Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition
* P<0.05, ** P<0.001

had significantly higher episodes of high-GRV (median [IQR]: 0 [0] vs 0 [0–2], P=0.031). In patients with EN and prone therapy (n=36), the episodes of high-GRV on proned and non-proned days were similar (median [IQR]: 0 [0–0.1] vs 0 [0], P=0.113).

In the modified Cox regression, cardiovascular comorbidities—i.e. congestive heart failure, myocardial infarction and angina (adjusted relative risk [RR]: 9.00, 95% CI 2.25–35.99, P=0.002)—and late enteral feeding (>36 hours upon ICU admission) (adjusted RR 6.30, 95% CI 1.15–34.40, P=0.034) were significantly associated with hospital mortality. Other parameters such as sex, APACHE II, admission source, hypertension, neurological comorbidities, renal disease, and oncological comorbidities were not significantly associated with hospital mortality.

Comparison with the SCCM/ASPEN COVID-19 recommendations

Among the 8 domains of the SCCM/ASPEN COVID-19 recommendations, the nutritional practices in Singapore were not in line with half of them. Specifically, these were in areas of baseline malnutrition assessment; achievement of caloric and protein targets; choice of EN formula used in the initial phase of critical illness; and monitoring (Table 3).

DISCUSSION

In this multicentre observational study, critically ill patients with SARS-CoV-2 had similar characteristics and clinical outcomes across multiple hospitals. They also received comparable treatment modalities and nutrition support, suggesting that the cohort was a good representation of such patients in Singapore. The characteristics and treatment modalities used in these patients posed unique nutrition support challenges as 1 in 3 were obese, had diabetes and received dialysis; 1 in 2 received prone therapy; and 7 in 10 received neuromuscular blockade. These have considerable implications for caloric and protein dosing as well as EN formula choice that the ASPEN/SCCM guidelines have not comprehensively addressed.

Nutrition assessment

All participating sites did not assess baseline nutritional status because their routine assessment tool is the Subjective Global Assessment that requires a nutrition-focused physical examination. Of note, malnutrition diagnosed by the Subjective Global Assessment was associated with higher mortality risk in both non-SARS-CoV-2[1] and SARS-CoV-2[7] critically ill patients. To minimise physical contact and the risk of nosocomial transmission, nutrition screening tools that do not require physical examination could be used to quantify malnutrition risk. Nutrition Risk Screening 2002 score ≥3 was associated with higher mortality risk in one prospective study (N=285)[7] but not in another retrospective study (N=286).[8]

In the absence of a validated nutrition screening/assessment tool that has good prognostic value and can be conducted without physical assessment, the utility of baseline nutrition screening/assessment can be questioned. We lack robust evidence showing that higher

Table 1. Characteristics, clinical outcomes, treatment modalities, feeding practices and enteral feeding intolerances

Parameters	All (N=83)	Hospital A (n=21)	Hospital B (n=35)	Hospital C (n=10)	Hospital D (n=14)	Hospital E (n=3)	*P*
Age, mean (SD), years	58.0 (12.7)	56.1 (13.5)	59.6 (14.3)	60.0 (8.8)	54.6 (9.7)	65.7 (8.7)	0.513
Male, no. (%)	63 (75.9)	15 (71.4)	28 (80.0)	7 (70.0)	10 (71.4)	3 (100)	0.764
Ethnicity, no. (%)							0.346
Chinese	51 (61.4)	12 (57.1)	23 (65.7)	5 (50.0)	8 (57.1)	2 (100)	
Malay	11 (13.3)	1 (4.8)	3 (8.6)	4 (40.0)	3 (21.4)	0	
Indian	10 (12.0)	4 (19.0)	5 (14.3)	0	1 (7.1)	0	
Others	11 (13.8)	4 (19.0)	4 (11.4)	1 (10.0)	2 (14.3)	0	
Weight, mean (SD), kg	74.4 (15.4)	72.4 (13.5)	72.0 (16.3)	78.8 (12.3)	77.6 (17.4)	85.1 (17.7)	0.406
BMI, mean (SD), kg/m^2 [a]	27.1 (5.0)	27.0 (4.3)	26.4 (5.9)	28.1 (2.8)	27.7 (5.1)	29.4 (6.1)	0.777
25.0–29.9	29 (36.3)	6 (33.3)	14 (40.0)	6 (60.0)	3 (21.4)	0	0.270
>30.0	22 (27.5)	4 (22.2)	8 (22.9)	3 (30.0)	5 (35.7)	2 (66.7)	0.487
Admission, no. (%)							
ED	26 (31.3)	14 (66.7)*	5 (14.3)	2 (20.0)	4 (28.6)	1 (33.3)	0.001
HD	3 (3.6)	0	0	0	3 (21.4)*	0	0.004
Ward	44 (53.0)	5 (23.8)*	22 (62.9)	8 (80.0)	7 (50.0)	2 (66.7)	0.019
Other hospitals	10 (12.0)	8 (9.5)	8 (22.9)	0	0	0	0.104
Comorbidities, no. (%)							
Diabetes	21 (25.3)	4 (19.0)	4 (22.9)	5 (50.0)	4 (28.6)	0	0.187
Hypertension	45 (54.2)	12 (57.1)	17 (48.6)	8 (80.0)	7 (50.0)	1 (33.3)	0.430
Cardiological	6 (7.2)	1 (4.8)	4 (11.4)	0	1 (7.1)	1 (33.3)	0.388
Neurological	4 (4.8)	2 (9.5)	1 (2.9)	1 (10.0)	0	0	0.600
Renal	8 (9.6)	1 (4.8)	3 (8.6)	2 (20.0)	2 (14.3)	0	0.641
Cancer	5 (6.0)	3 (14.3)	1 (2.9)	1 (10.0)	0	0	0.340
Disease severity scores, mean (SD)							
APAPCHE II	19.4 (9.8)	21.2 (11.6)	14.8 (7.7)*	24.6 (6.7)	25.4 (9.1)	15.3 (4.9)	0.001
SOFA	7.0 (4.5)	6.3 (5.1)	5.4 (3.3)*	8.4 (2.7)	10.5 (5.3)	8.7 (1.2)	0.003
mNUTRIC	4.1 (2.0)	4.0 (1.9)	3.4 (1.8)*	5.9 (1.8)	5.1 (1.8)	4.3 (2.3)	0.002

Table 1. Characteristics, clinical outcomes, treatment modalities, feeding practices and enteral feeding intolerances (Cont'd)

Parameters	All (N=83)	Hospital A (n=21)	Hospital B (n=35)	Hospital C (n=10)	Hospital D (n=14)	Hospital E (n=3)	*P*
Dialysis, no. (%)	29 (34.9)	7 (33.3)	12 (34.3)	2 (20.0)	8 (57.1)	0	0.226
Median (IQR), days	4.0 (1.5, 6.0)	1.0 (1.0, 10.0)	3.0 (2.0, 6.0)	3.0 (2.0, NA)	5.0 (1.8, 7.0)	NA	0.855
Neuromuscular blockade, no. (%)	58 (69.9)	11 (52.4)	429 (82.9)	3 (30.0)*	12 (85.7)	3 (100)	0.004
Median (IQR), days	4.0 (2.0, 8.0)	2.0 (2.0, 4.0)	6.0 (4.0, 8.0)	3.0 (1.0, NA)	3.0 (3.0, 4.0)	2.0 (1.0, NA)	0.056
Prone (%)	39 (47.0)	4 (19.0)	21 (60.0)*	4 (40.0)	9 (64.3)*	1 (33.3)	0.026
Median (IQR), days	4.0 (2.0, 6.0)	4.5 (2.5, 8.0)	6.0 (3.5, 7.0)	3.5 (2.0, 6.5)	3.0 (2.0, 3.5)	2.0 (2.0, 2.0)	0.079
Head elevated <10º, no. (%)	5 (12.8)	1 (25)	3 (14.3)	0	0	1 (100)*	0.032
Feeding practices							
Start of EN, no. (SD), hour	11.5 (10.2)	11.8 (11.8)	14.2 (10.4)	10.7 (7.2)	7.7 (9.5)	6.7 (2.1)	0.345
Early feeding, no. (%)[b]	70/73 (95.9)	19/20 (95.0)	24/26 (92.3)	10/10 (100)	14/14 (100)	3/3 (100)	0.506
MAP<65, no. (%)	3/73 (4.1)	20/20 (100)	2/26 (7.7)	10/10 (100)	1/14 (7.1)	0/3 (0)	0.628
Peroral ≥2 days, no. (%)	9/83 (10.8)	1/21 (4.8)	8/35 (22.9)	0	0	0	0.054
Parenteral nutrition, no. (%)	2/83 (2.4)	0	2/35 (5.7)	0	0	0	0.590
Feeding intolerance							
High-GRV, episodes/100 feeding days	7.7	17.4*	7.2	1.2	3.1	0.0	<0.001
Diarrhoea							
Patients, no. (%)	35 (42.2)	7 (33.3)	19 (54.3)	0	9 (64.3)*	0	0.005
Days/100 ICU days	5.8	8.5	5.4	0	30.8*	0	<0.001
Clinical outcomes							
RH, no. (%)	5 (6.0)	1 (4.8)	3 (8.6)	0	1 (7.1)	0	0.857
ICU mortality, no. (%)	15 (18.1)	2 (9.5)	10 (28.6)	0	3 (21.4)	0	0.158
Hosp mortality, no. (%)	15 (18.1)	2 (9.5)	10 (28.6)	0	3 (21.4)	0	0.158
ICU-LOS of survivors, median (IQR), days	11.0 (7.0, 21.8)	8.0 (6.0, 11.0)*	18.0 (8.0, 31.0)	8.5 (5.0, 15.0)	14.0 (11, 32.0)	19.0 (13.0, NA)	0.027
Hosp-LOS of survivors, median (IQR), days	31.0 (19.3, 44.0)	23.0 (17.0, 37.0)	31.0 (19.5, 67.0)	30.5 (15.0, 41.5)	39.0 (29.0, 48.0)	31.0 (17.0, NA)	0.119
MV of survivors, median (IQR), days	9.0 (5.0, 15.0)	7.0 (3.0, 10.0)	11.0 (5.5, 25.5)*	7.5 (3.0, 11.3)	12.0 (9.0, 15.0)*	10.0 (8.0, NA)	0.039
Tracheostomy, no. (%)	11 (13.3)	2 (9.5)	5 (14.3)	0	4 (28.2)	0	0.274

APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II; BMI: body mass index; ED: emergency department; EN: enteral nutrition; GRV: gastric residual volume; HD: high dependency ward; Hosp: hospital; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay; MAP: mean arterial pressure (mmHg); mNUTRIC: modified Nutrition Risk in Critically Ill; MV: mechanical ventilation; NA: not available; RH: refeeding hypophosphataemia defined as serum phosphate <0.65 within 72 hours of feeding; SD: standard deviation; SOFA: Sequential Organ Failure Assessment

[a] 3 missing data

[b] Enteral nutrition started within 36 hours of admission to the intensive care unit

* $P<0.05$

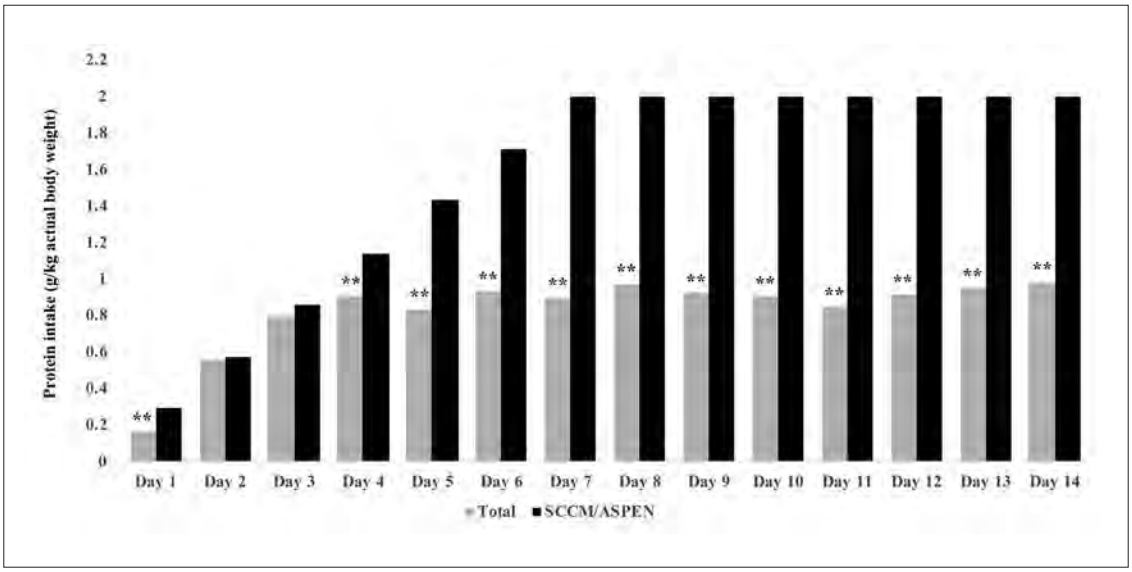

Fig. 2. Protein intake of patients over 14 days.
SCCM/ASPEN: Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition
** P<0.001

caloric intake or more timely nutritional interventions can modify the poor clinical outcomes associated with baseline malnutrition.[9] Furthermore, since well-nourished patients with severe illness can deplete their stores rapidly, early nutrition provision is essential regardless of baseline nutrition status. Perhaps the role of nutrition assessment should focus on identifying patients who may be harmed by rapid escalation of nutrition. This will include quantifying the risk of refeeding hypophosphataemia—6% in this study and 15% in another.[10] In patients with hypophosphataemia, caloric restriction was demonstrated to reduce long-term mortality risk.[11] The National Institute of Health and Care Excellence guidelines[12] are commonly used to assess the risk of refeeding hypophosphataemia but require information such as diet and weight history—a challenging prospect to obtain from critically ill patients. Instead, one could focus on risk factors that do not rely on history taking such as the presence of hypokalaemia, hypophosphataemia and hypomagnesaemia; use of diuretics; and old age before the initiation of nutrition support,[13,14] and provide protocolised caloric restriction to high-risk patients.[11]

Timing and feeding route

In patients receiving peroral feeding, we did not measure caloric and protein intake from food. Many of them received awake prone therapy, and may potentially suffer from dyspnoea, anosmia and ageusia, which may lead to poor oral intake.[15] EN was started on day 4 of ICU admission in most of these patients. Although they had significantly lower disease severity, their mortality rate was significantly higher than patients first exposed to EN in the initial 2 days of ICU admission. It is possible that early EN modulates immune responses, opposes dysbiosis, and maintains gut integrity.[16] Although this is consistent with previous meta-analysis,[17] our results should be interpreted with caution due to the small number of patients who received late EN (n=3).

Caloric dose

In this study, caloric goals were not established by IC as this technique may increase the healthcare providers' exposure to COVID-19. Furthermore, the use of IC lacks robust benefits for the heterogenous ICU population. A recent meta-analysis reported that IC-guided nutrition support resulted in an absolute mortality risk reduction of about 5.5%.[18] Since 3 and 7 in 10 patients in our study were obese and received neuromuscular blockade, respectively, IC may be especially applicable to this population where estimating energy expenditure can be challenging.[19-21] In addition, SARS-CoV-2 critically ill patients did not appear to have a uniform course of energy expenditure during their ICU admission; some patients had normal metabolism[22] whereas others had hypermetabolism[23,24] after week 3 and onwards in the ICU. Preliminary data suggest that the resolution of infection may reduce energy demand, and the cessation of isolation may be an important clinical landmark to re-evaluate energy

Table 2. Characteristics, treatment modalities, and clinical outcomes of patients who were placed on enteral nutrition versus peroral feeding in the first 2 days of intensive care unit admission

Parameters	All (N=83)	Enteral nutrition (n=74)	Peroral (n=9)	*P*
Age, no. (SD), years	58.0 (12.7)	57.8 (12.5)	61.2 (14.6)	0.444
BMI (SD), kg/m^2 [a]	27.1 (5.0)	27.3 (5.0)	25.3 (5.4)	0.250
Comorbidities, no. (%)				
Diabetes	21 (25.3)	19 (25.7)	2 (22.2)	1.000
Hypertension	45 (54.2)	40 (54.1)	5 (55.6)	1.000
Cardiological	6 (7.2)	7 (9.5)	0	1.000
Neurological	4 (4.8)	3 (4.1)	1 (11.1)	0.374
Renal	8 (9.6)	7 (9.5)	1 (11.1)	1.000
Cancer	5 (6.0)	5 (6.8)	0	1.000
Disease severity				
APAPCHE II	19.4 (9.8)	20.7 (9.6)	9.3 (4.1)	<0.001
SOFA	7.0 (4.5)	7.5 (4.4)	2.8 (2.2)	<0.001
mNUTRIC	4.1 (2.0)	4.3 (2.1)	2.9 (1.2)	0.008
Clinical outcomes				
ICU mortality, no. (%)	15 (18.1)	10 (13.5)	5 (55.6)	0.008
Hosp mortality, no. (%)	15 (18.1)	10 (13.5)	5 (55.6)	0.008
ICU-LOS of survivors (IQR), days	11.0 (7.0, 21.8)	11.0 (7.0, 20.8)	22.0 (10.5, 30.5)	0.292
Hosp-LOS of survivors (IQR), days	31.0 (19.3, 44.0)	31.0 (19.3, 43.5)	53.5 (23.0, 92.3)	0.225
MV of survivors (IQR), days	9.0 (5.0, 15.0)	9.0 (5.0, 15.0)	11.5 (4.0, 24.3)	0.870
Dialysis, no. (%)	29 (34.9)	24 (32.4)	5 (55.6)	0.266
Median (IQR), days	4.0 (1.5, 6.0)	3.5 (1.3, 6.8)	5.0 (2.0, 6.0)	0.889
Neuromuscular blockade (%)	58 (69.9)	50 (67.6)	8 (88.9)	0.266
Median (IQR), days	4.0 (2.0, 8.0)	4.0 (2.0, 6.0)	7.5 (6.0, 9.5)	0.008
Prone, no. (%)	39 (47.0)	31 (41.9)	8 (88.9)	0.011
Median (IQR), days	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)	6.0 (4.5, 7.0)	0.079

APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II; BMI: body mass index; EN: enteral nutrition; Hosp: hospital; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay; MV: mechanical ventilation; mNUTRIC: modified Nutrition Risk in Critically Ill; SD: standard deviation; SOFA: Sequential Organ Failure Assessment
[a] 3 missing data

demands.[22] In the above circumstances, healthcare providers can adopt a set of practical guidance for using IC in SARS-CoV-2 critically ill patients[25] so that appropriate caloric goals can be set for nutrition support.

The minimum caloric recommendation of SCCM/ASPEN was only met by 1 in 2 patients in this study. Of note, a recent review[26] and a newer version of the ASPEN guidelines[27] state that current evidence precludes precise recommendations on the optimal caloric intake, and the latter should be based on clinical judgment. That said, insufficient micronutrients intake resulting from hypocaloric feeding should not be managed by high-dose supplementation.[28] Nevertheless, caloric intake may be improved by feeding protocols developed by a multidisciplinary team.[9] For instance, the protocol can stipulate that EN can be safely started as soon as patients

Table 3. Nutrition recommendations of SCCM/ASPEN for critically ill patients with COVID-19 and the nutritional practice in Singapore

	SCCM/ASPEN recommendation	Nutritional practice in Singapore
	Assessment	
1	Perform nutrition assessment with minimal physical contact, and establish the risk of refeeding syndrome as well as the route and dose of nutrition support.	• Malnutrition assessment was not performed at baseline across the hospitals.
	Timing and finding route	
2	Initiate enteral nutrition within 36 hours of ICU admission or as soon as patient achieved adequate resuscitation (sustained mean arterial pressure of ≥65mmHg).	• Most patients (95.9%) received early EN, and their mean arterial pressure was >65mmHg when started on EN.
3	Start early parenteral nutrition in patients with sepsis or shock requiring escalating or multiple vasopressors or rising lactate levels.	• Two patients received parenteral nutrition. One started on day 2 and the other on day 5 of ICU admission.
4	Prioritise continuous gastric feeding and use prokinetic agents to manage EFI. If EFI persists, consider bedside placement of post-pyloric tube.	• Continuous gastric feeding was carried out in all patients on EN.
	Caloric and protein doses	
5	Use weight-based equations to estimate energy requirements.	• Caloric goals were estimated by weight-based equations, and IC was not used.
6	Initiate low-dose enteral nutrition and gradually advance to caloric goal (15–20kcal/kg ABW) over the first week of critical illness.	• In the first 14 days of ICU admission, the mean caloric intakes across the hospitals were similar (Supplementary Table S1). • Caloric intake in the first 5 days was significantly higher than recommendations, whereas it was significantly lower on day 7 (Fig. 1). • By day 14, the mean (SD) caloric intake was 20.6 (6.9) kcal/kg ABW, and 54% of the patients received ≥15kcal/kg ABW.
7	Initiate low-dose enteral nutrition and gradually advance to protein goal (1.2–2.0g protein/kg ABW) over the first week of critical illness.	• In the first 14 days of ICU admission, the mean protein intakes across the hospitals were similar (Supplementary Table S1). • On most days (except for day 2 and day 3), protein intake was significantly lower than recommendations (Fig. 2). • By day 14, the mean (SD) protein intake was 0.98 (0.34) g/kg ABW, and no patients received ≥1.2g protein/kg ABW.
8	If parenteral nutrition is necessary, conservative dextrose content and volume should be used in the early phase of critical illness.	• In the patient who received early parenteral nutrition, dextrose contributed to 37% of the total caloric content.
	Formula selection	
9	Use standard high protein (≥20% protein) polymeric isosmotic enteral formula at the early phase of critical illness, and at a later phase, consider adding fibre in the absence of significant gastrointestinal dysfunction.	• None of the hospitals used standard high protein (>20%) polymeric isosmotic enteral formula (Supplementary Fig. S1). • One in 4 received formulas containing fibre on the first week of EN feeding.
10	If parenteral nutrition is used, limit the use of pure soybean lipid emulsions and use mixed lipid emulsions instead.	• None of the hospitals used pure soybean lipid emulsion for parenteral nutrition.
	Monitoring	
11	To monitor feeding tolerance, use parameters such as stool frequency and flatulence, and avoid using gastric residual volume.	• All hospitals routinely checked gastric residual volume and stool frequency.
12	In patients on parenteral nutrition and/or propofol, monitor serum triglyceride levels early in their course of therapy to help distinguish secondary haemophagocytic histiocytosis from propofol-related hypertriglyceridaemia.	• Serum triglyceride was measured in 30.6% (n=15) of the patients who received propofol or parenteral nutrition, and the mean (SD) was 2.29 (1.24) mmol/L.

Table 3. Nutrition recommendations of SCCM/ASPEN for critically ill patients with COVID-19 and the nutritional practice in Singapore (Cont'd)

	SCCM/ASPEN recommendation	Nutritional practice in Singapore
	Feeding in the prone position	
13	Although the provision of enteral nutrition during prone positioning is not associated with increased risk of gastrointestinal or pulmonary complications, the head of the bed should be elevated to at least 10–25º to decrease the risk of aspiration of gastric content, facial oedema, and intra-abdominal hypertension.	• Most patients' head was elevated >10º (Table 2).
	Nutrition therapy during extracorporeal membrane oxygenation	
14	Consider early trophic enteral feeding and gradually increase to goal over the first week of critical illness.	• One of 2 patients received trophic enteral feeding.
15	Monitoring for enteral feeding intolerance closely.	• Gastric residual volume and stool frequency were monitored.

ABW: actual body weight; EFI: enteral feeding intolerance; EN: enteral nutrition; IC: indirect calorimetry; ICU: intensive care unit; SD: standard deviation

achieved haemodynamic stability, and in patients who are on neuromuscular blockade and do not have severe gastrointestinal dysfunction.[26]

Protein dose

No patient met the minimal protein recommendation in this study. This is especially concerning since 1 in 3 received dialysis, and such therapy depletes protein.[29] Furthermore, the mean duration of mechanical ventilation could be >10 days in some centres; when combined with neuromuscular blockade and steroid use, these can pose as risk factors for ICU-acquired weakness.[30] Therefore, more efforts should be made to meet protein goals, especially when a recent meta-analysis showed that higher protein provision significantly attenuates muscle loss.[31] Nevertheless, all hospitals in this study provide additional protein given in boluses; this method of protein provision has the potential to benefit muscle health if targets are achieved. There is recent evidence that bolus provision of protein may attenuate muscle catabolism better than continuous feeding.[32]

Formula selection

One-third of the patients in this cohort have type 2 diabetes mellitus, and since a low carbohydrate EN formula may improve glycaemic control,[33] 23% of the patients received diabetes-specific EN formula. Of note, all diabetes-specific formulas used in this study contain fibre, and providing such EN formula at the initial stage of critical illness is not in line with the SCCM/ASPEN guidelines.[1] However, we did not observe EN intolerances in patients who received diabetes-specific EN formula (containing fibre), but noted a significantly lower incidence of diarrhoea. This is congruent with a recent systematic review demonstrating that EN formula containing fibre is associated with a significantly lower incidence of diarrhoea.[34]

Monitoring

All the included hospitals did not adopt the recommendation of omitting GRV measurement. Of note, there is evidence[35,36] that consistently demonstrated that high-GRV is a surrogate marker for delayed gastric emptying. Therefore, this parameter should be monitored to determine whether complex investigations or therapeutic interventions (e.g. prokinetic agents) are warranted.[35] Our data suggest that GRV can be routinely monitored during the initial phase of ICU admission, albeit less frequently or discontinued at a later phase because the frequency of high-GRV appeared to be heightened during the first 4 days of EN, an observation that coheres with large international data.[37] A large proportion of patients received prone therapy when high-GRV is a common concern.[1] However, our study does not support this. In our study, patients who received prone therapy had a significantly higher incidence of high-GRV than patients who were never proned. However, this could be explained by higher disease severity and not prone therapy per se. The poor association between prone therapy and high-GRV is further discussed in a recent review.[26]

Besides high-GRV, diarrhoea may be a sign of EN intolerance. There is a paucity of data on the prevalence of diarrhoea in SARS-CoV-2 critically ill patients since most studies included non-critically ill patients and the pooled prevalence was 53.3%.[38] Although the diarrhoea prevalence in our study is similar to the meta-analysis,[38] it is considerably higher than reported in an ICU-specific

study (15%).[39] Similar to the latter, a limitation of our study is that we did not collect data about antibiotic exposure.

Serum triglycerides levels were not routinely monitored in patients who received propofol and PN in all included hospitals. Although hypertriglyceridaemia may not necessarily be associated with the dose and duration of propofol provided to SARS-CoV-2 critically ill patients, the incidence of hypertriglyceridaemia was as high as 1 in 2 patients.[40] Therefore, the guideline about serum triglyceride monitoring should be adopted to reduce the risk associated with hypertriglyceridaemia.

CONCLUSION

In this observational study of critically ill patients with SARS-CoV-2, we identified several aspects of nutrition that require further attention. With the long duration of mechanical ventilation and frequent usage of dialysis in such patients, more focus should be placed on increasing protein adequacy. Our observation also demonstrated that prone therapy and usage of EN-containing fibre may not be associated with EN feeding intolerances. Finally, the high prevalence of obesity and exposure to neuromuscular blockade prompt more studies about the role of indirect calorimetry in SARS-CoV-2 critically ill patients.

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ORIGINAL ARTICLE

Ann Acad Med Singap 2022;51:341-50
https://doi.org/10.47102/annals-acadmedsg.2021498

Inter-hospital trends of post-resuscitation interventions and outcomes of out-of-hospital cardiac arrest in Singapore

Julia Li Yan Jaffar [1]*MBBCh BAO*, Stephanie Fook-Chong [2]*MSc*, Nur Shahidah [3]*BA*, Andrew Fu Wah Ho [2,3]*MPH*, Yih Yng Ng [4,5]*MPH*, Shalini Arulanandam [6]*MBA*, Alexander White [7]*JD,MPH*, Le Xuan Liew [7]*BSc*, Nurul Asyikin [7]*BSc*, Benjamin Sieu-Hon Leong [8]*MMed*, Han Nee Gan [9]*MRCSEd*, Desmond Mao [10]*MMed*, Michael Yih Chong Chia [4]*MBBS*, Si Oon Cheah [11]*MRCSEd*, Marcus Eng Hock Ong [3,12]*MPH* for Singapore PAROS investigators

ABSTRACT

Introduction: Hospital-based resuscitation interventions, such as therapeutic temperature management (TTM), emergency percutaneous coronary intervention (PCI) and extracorporeal membrane oxygenation (ECMO) can improve outcomes in out-of-hospital cardiac arrest (OHCA). We investigated post-resuscitation interventions and hospital characteristics on OHCA outcomes across public hospitals in Singapore over a 9-year period.

Methods: This was a prospective cohort study of all OHCA cases that presented to 6 hospitals in Singapore from 2010 to 2018. Data were extracted from the Pan-Asian Resuscitation Outcomes Study Clinical Research Network (PAROS CRN) registry. We excluded patients younger than 18 years or were dead on arrival at the emergency department. The outcomes were 30-day survival post-arrest, survival to admission, and neurological outcome.

Results: The study analysed 17,735 cases. There was an increasing rate of provision of TTM, emergency PCI and ECMO (P<0.001) in hospitals, and a positive trend of survival outcomes (P<0.001). Relative to hospital F, hospitals B and C had lower provision rates of TTM (≤5.2%). ECMO rate was consistently <1% in all hospitals except hospital F. Hospitals A, B, C, E had <6.5% rates of provision of emergency PCI. Relative to hospital F, OHCA cases from hospitals A, B and C had lower odds of 30-day survival (adjusted odds ratio [aOR]<1; P<0.05 for hospitals A–C) and lower odds of good neurological outcomes (aOR<1; P<0.05 for hospitals A–C). OHCA cases from academic hospitals had higher odds ratio (OR) of 30-day survival (OR 1.3, 95% CI 1.1–1.5) than cases from hospitals without an academic status.

Conclusion: Post-resuscitation interventions for OHCA increased across all hospitals in Singapore from 2010 to 2018, correlating with survival rates. The academic status of hospitals was associated with improved survival.

Ann Acad Med Singap 2022;51:341-50

Keywords: Out-of-hospital cardiac arrest, percutaneous coronary intervention, post-resuscitation care, resuscitation, targeted temperature management

[1] Ministry of Health Holdings, Singapore
[2] Pre-hospital & Emergency Research Centre, Duke-NUS Medical School, Singapore
[3] Department of Emergency Medicine, Singapore General Hospital, Singapore
[4] Emergency Department, Tan Tock Seng Hospital, Singapore
[5] Home Team Medical Services, Ministry of Home Affairs, Singapore
[6] Emergency Medical Services Department, Singapore Civil Defence Force, Singapore
[7] Unit for Pre-hospital Emergency Care, Singapore General Hospital, Singapore
[8] Emergency Medicine Department, National University Hospital, Singapore
[9] Accident & Emergency, Changi General Hospital, Singapore
[10] Department of Acute and Emergency Care, Khoo Teck Puat Hospital, Singapore
[11] Emergency Medicine Department, Ng Teng Fong General Hospital, Singapore
[12] Health Services & Systems Research, Duke-NUS Medical School, Singapore
Correspondence: Dr Julia Li Yan Jaffar, Department of Emergency Medicine, Singapore General Hospital, Outram Road, Singapore 169608.
Email: julia.jaffar@mohh.com.sg

CLINICAL IMPACT

What is New

- This is the first study to the best of our knowledge to describe trends in post-resuscitation interventions and out-of-hospital cardiac arrest (OHCA) outcomes across public hospitals in Singapore over a 9-year period.
- Post-resuscitation interventions for OHCA increased across public hospitals, correlating with survival rates.
- OHCA cases from academic hospitals reported higher 30-day survival (odds ratio 1.3, 95% confidence interval 1.1–1.5).

Clinical Implications

- Findings of the present study may guide policies for OHCA management in future.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) have notoriously been a medical issue with high morbidity and mortality.[1] It is a multifaceted problem with a multitude of aetiologies,[2] and as such various factors influence the outcome of OHCA patients.

The management of OHCA can generally be outlined by the "Chain of Survival", a framework that includes pre-hospital and hospital-based management for increasing survival from sudden cardiac arrest.[3] Each step in the chain is crucial in optimising survival.[4] Non-modifiable pre-hospital factors that affect outcomes include age and sex.[5] Modifiable pre-hospital factors that are well-established to affect survival outcomes include cause of arrest, ambulance response timings, presence of bystander cardiopulmonary resuscitation (CPR) and pre-hospital defibrillation.[6-8] In Singapore, there have been efforts to improve countrywide pre-hospital management in recent years.[9] The rates of pre-hospital CPR and return of spontaneous circulation have improved greatly.[10]

The fifth link—post-resuscitation care—in the Chain of Survival is largely based in hospitals and includes advanced treatments such as therapeutic temperature management (TTM),[11] extracorporeal membrane oxygenation (ECMO)[12,13] and percutaneous coronary intervention (PCI).[14-16] There are advocates for TTM and ECMO to be commenced as early as possible in OHCA management, even in emergency department (ED) settings where appropriate.[17,18] Recently, there has been an international interest in hospital management of OHCA patients in cardiac arrest centres, similar to the concept of management of stroke patients in acute stroke units.[19] Studies from Denmark,[20] the US,[21] Britain[22] and Australia[23] suggest significantly better survival to hospital discharge with a cardiac arrest centre model. Such centres are defined as institutions that have the following facilities available round-the-clock[24]: (1) intensive care, including mechanical ventilation and TTM; (2) acute cardiac care including PCI; (3) radiology service with computed tomography availability; and (4) delayed, multimodality and standardised neuroprognostication.

Hospital characteristics such as number of beds, years in operation, and teaching status are also known to affect survival outcomes.[25] In the context of Singapore, Tan et al.[26] showed stark differences in survival outcomes among government hospitals and suggested that academic status and hospital bed number correlated with better survival to discharge. An academic hospital is defined by the presence of a medical school directly affiliated to it. Apart from the aforementioned study in 2019, there is a paucity of local studies that focus on the quality of hospital-based interventions in OHCA. The current study aimed to glean insights into hospital-based factors associated with better OHCA survival outcomes in Singapore. We aimed to investigate trends in post-resuscitation interventions and OHCA outcomes across public hospitals in Singapore over a 9-year period. We hypothesised that inter-hospital differences in intervention rates (of TTM, ECMO and PCI) and hospital characteristics correlate with differences in survival outcomes.

METHODS

This was a prospective, nationwide, multicentre cohort study of consecutive OHCA cases presenting to Singapore government restructured hospitals from 2010 to 2018. Data were extracted from the Singapore cohort of the Pan-Asian Resuscitation Outcomes Study Clinical Research Network (PAROS CRN) registry, an international registry of OHCA in the Asia-Pacific region.[27] The registry included all OHCA cases that were either conveyed by emergency medical services (EMS) or had presented to EDs. The registry excluded patients who were immediately pronounced dead, for whom resuscitation was not attempted; or were associated with decapitation, rigor mortis, dependent lividity or existing "do not attempt resuscitation'' orders. We further excluded patients who were younger than 18 years, found to be dead on arrival, and non-EMS cases.

We reviewed pre-hospital characteristics such as age, sex, presence of bystander CPR, pre-hospital defibrillation, cause of arrest, and ambulance response timings to look for trends over the years and between hospitals.

Data were collected from ambulance case reports and discharge summaries from wards, EDs and intensive care units (ICUs). The primary outcome was 30-day survival, defined as either discharged alive or remained alive in hospital on the 30th day post-arrest, whichever occured first. Secondary outcomes included survival to hospital admission and survival with favourable neurological outcome, defined as Glasgow-Pittsburgh Cerebral Performance Categories (CPC) score ≤2 at either hospital discharge, or on the 30th day post-arrest if patient remained in hospital for longer than 30 days. Patients who were transferred to the nearest hospital for any intervention would be tallied under the hospital that they were first conveyed to.

Study setting

Singapore is a Southeast Asian country with a population of 5,905,527. As of the year 2021, its population density is 8,358 people per km^2, with a median age of 42.4 years.[28] Pre-hospital EMS is provided by the Singapore Civil Defence Force (SCDF), a uniformed government agency that operates a publicly funded fire-fighting, rescue and emergency medical service. As of 2018, it has 65 ambulances at its disposal.[29] Paramedics are trained in basic life support, 12-lead electrocardiography, automated external defibrillator usage, and adrenaline administration. SCDF operates through a centralised phone dispatch, with a tiered system after a phone triage. In scenarios of OHCA, SCDF conveys patients to a public hospital that is nearest to the incident location. In 2018, SCDF responded to 82% of life-threatening cases within 8 minutes.[30]

In 2010, there were 6 adult acute restructured hospitals in Singapore (labelled Hospitals A-F in the current study), equipped with 6,686 beds with an occupancy rate of 343,332 (78.5%).[31] There were 7 private hospitals in Singapore; however, they did not receive OHCA cases from EMS or handle post-OHCA patients. There was also a paediatric restructured hospital that did not manage adult OHCA patients. By 2018, an additional government restructured hospital was in operation, but it was excluded from the current study as it had limited temporal data. All hospitals had the capacity to offer TTM, whereas only 5 of the 6 hospitals (B–F) provided 24-hour emergency PCI services. Hospital F was the only hospital with ECMO capability on-site, but all the other hospitals were able to transfer patients there for ECMO. All hospitals involved had readily available intensive care, computed tomography services with radiological interpretation, and multidisciplinary management for neuroprognostication. The current study was approved by the SingHealth Centralised Institutional Review Board (CIRB 2013/604/C and 2018/2937) and Domain Specific Review Board (C/10/545 and 2013/00929).

Statistical analysis

Characteristics of OHCA cases over consecutive calendar years were presented as mean (standard deviation) for continuous data and as count (%) for categorical data. For each hospital and for all hospitals combined, the yearly trends of hospital interventions and survival outcomes were explored graphically and tested for a linear trend by Mantel-Haenszel test. Similarly, OHCA characteristics of cases were summarised for each hospital and tabulated for comparison purpose.

Logistic regression was used to investigate the effect of hospital, time (in years), and interaction of time and hospital on the survival outcomes, with adjustment for pre-hospital factors. If the interaction time was not significant, it was removed from the regression model. The logistic regression was then repeated with adjustment for pre-hospital factors known to influence survival, namely, age, sex, witnessed arrest, bystander CPR, first arrest rhythm, pre-hospital defibrillation and cause of arrest. Response time was not adjusted for as SCDF conveys patients to the nearest hospitals independent of pre-hospital diagnosis. For the odds ratio (OR) of survival outcome from logistic regression, hospitals were compared against Hospital F, the oldest and largest restructured hospital in Singapore.

We attempted to explain inter-hospital differences in 30-day survival by examining hospital characteristics reported to be influential in the literature.[25] Hospital characteristics investigated were 24-hour access to PCI, academic status of hospitals, OHCA patient volume >4,000 cases a year, and years in operation (>20). The effect of each hospital characteristic on 30-day survival was analysed with univariate logistic regression.

Lastly, in the subgroup of OHCA who survived to hospital admission, the effect of each hospital intervention on 30-day survival was analysed by univariate logistic regression. All analyses were performed with SPSS Statistics software version 26.0 (IBM Corp, Armonk, US), where $P<0.05$ was considered as statistically significant.

RESULTS

Description of patient characteristics

A total of 18,359 cases were extracted from the PAROS CRN registry. Of these, 17,735 cases qualified for analysis (Fig. 1). From year 2010 to 2018, there was an increase of 4.6 years in the mean age of patients with OHCA, while the proportion who were of male sex remained stable (Table 1). Bystander CPR increased throughout the years from 225 (21.6%) to 1,683 (61.6%) cases. The proportion of witnessed arrest remained stable, as did defibrillation prior to ED and the cause of arrest. There was no significant difference in major pre-hospital patient characteristics (age, sex, first arrest rhythm, cause of arrest and bystander CPR) between hospitals (Supplementary Table S1 in online Supplementary Material).

Graphical exploratory analysis of hospital-based interventions over the years by hospitals

There was a growing provision of hospital-based interventions (Fig. 2A). Hospitals B and C showed lower provision rates of TTM (number of patients with TTM employed out of the total number of OHCA cases per hospital) across all years (≤5.2%) compared to other hospitals. All hospitals except F had an ECMO rate of <1% over the study period 2010–2018. Hospitals A, B, C and E had ≤6.5% yearly rates of emergency PCI; however, hospital E had a steady increase in emergency PCI provision rate from 2% to an estimated 6.1% over the years studied.

Graphical exploratory analysis of survival outcomes over the years by hospitals

There was a significant positive trend (P<0.001) for all 3 outcomes over the years (Fig. 2B). Hospitals A, B and C had rates below 25% over the years for survival to admission (Fig. 2B, P value not significant for linear trend). Hospital E had low rates of yearly survival to admission (below 25%) but rates improved linearly over the years (P<0.001).

Although hospitals B, C, D and E had a linear positive trend in 30-day survival (B: P=0.015; C: P=0.045; D: P<0.001; E: P<0.001; Fig. 2B), hospitals A, B and C had lower rates of 30-day survival (all below 7.1% for any year) compared to the other hospitals.

Hospitals A, B and C had lower rates of good neurological outcome (below 4.2% for any year). A linear positive trend in good CPC was reflected in hospitals B, D and E (B: P=0.015; D: P<0.001; E: P<0.001).

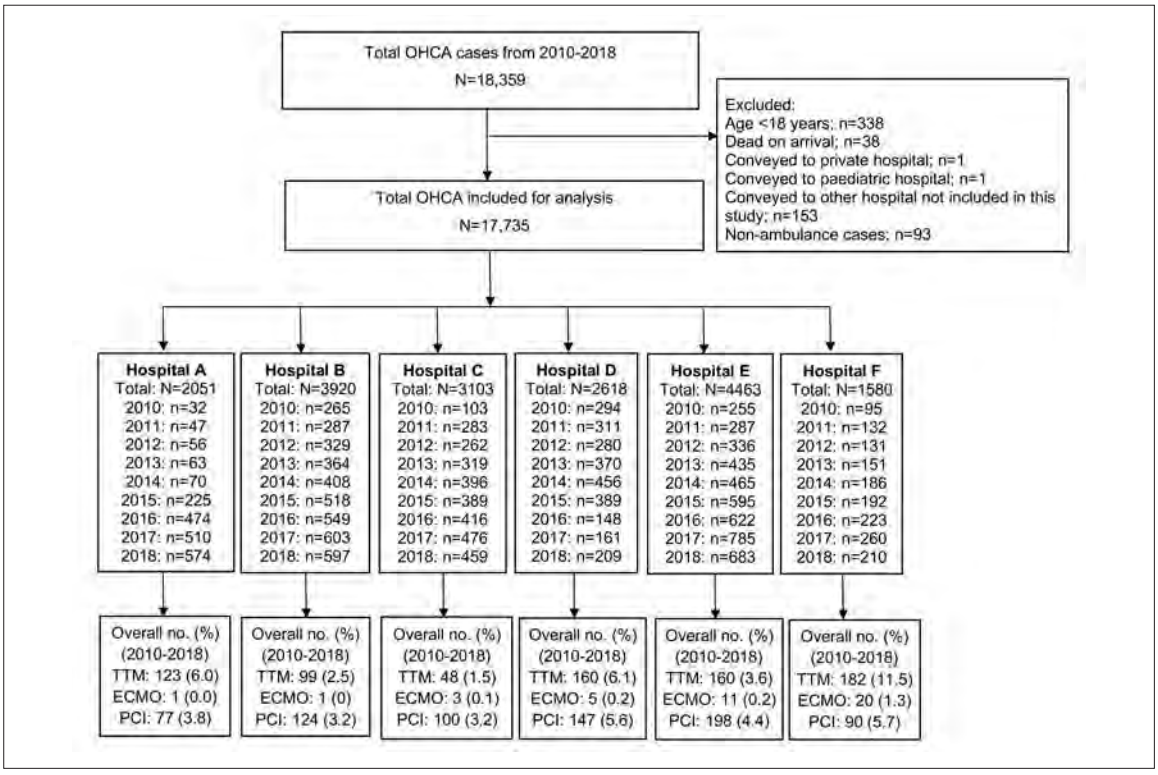

Fig. 1. Patient flowchart by hospital and outcomes
ECMO: extracorporeal membrane oxygenation; PCI: percutaneous coronary intervention; OHCA: out-of-hospital cardiac arrest; TTM: therapeutic temperature management

Logistic regression assessing effect of each hospital and time on survival outcomes

For any given hospital, the odds of any survival outcome increased over the years as seen in Model 2 (Table 2; $P<0.05$ for all outcomes). For each additional year, adjusted odds ratio (aOR) was 1.04 for survival to admission, 1.12 for 30-day survival, and 1.16 for CPC 1 or 2.

However, at any given year, hospitals A, B and C when compared to F had lower odds of survival to discharge (Model 2). Compared to hospital F, the 3 hospitals decreased in odds of approximately 25–35% (aOR 0.67–0.76; $P<0.05$ for A, B and C), and had lower 30-day survival with decreased odds of approximately 30–40% (aOR 0.61–0.68; $P<0.05$ for A, B and C). These hospitals had lower odds of good neurological outcome with decreased odds of 30–35% (aOR 0.65–0.71; $P<0.05$ for A, B and C).

Logistic regression assessing effect of hospital characteristics on 30-day survival

Hospitals D, E and F with academic status had 30% higher odds of 30-day survival (Table 3) as compared to hospitals A, B and C without academic status. The OR was 1.3 (95% confidence interval [CI] 1.1–1.5).

At the hospital level, 24-hour access to PCI did not confer a higher OR for 30-day survival (0.97, 95% CI 0.78–1.20). Academic status of hospitals was also found to be the only significant hospital characteristic that affected 30-day survival.

Logistic regression assessing effect of hospital interventions on 30-day survival in cohort of patients who survived to hospital admission

Among patients who survived to admission, those who underwent TTM and PCI show improved 30-day survival where ORs were 1.96 (95% CI 1.64–2.34) and 3.95 (95% CI 3.31–4.71), respectively (Table 4).

DISCUSSION

The present study of OHCA over a 9-year period reinforces current observational evidence in the literature that there is a difference in the provision of interventions and OHCA outcomes between hospitals.[32] Our primary outcome, 30-day survival, had a similar maximum rate of 14.2% when compared with Møller et al.[33] (13.8%). However, there was a vastly different minimum survival rate in our study (0%) as compared to their study (8.5%) which could be attributed to their selection of patients with only cardiac causes of OHCA.

Table 1. Characteristics of out-of-hospital cardiac arrest cases in Singapore over a 9-year period from 2010 to 2018

Characteristics	2010 n=1044	2011 n=1347	2012 n=1394	2013 n=1702	2014 n=1984	2015 n=2308	2016 n=2432	2017 n=2795	2018 n=2732
Age, mean (SD), years	64.4 (16.2)	64.7 (16.0)	65.6 (16.7)	67.0 (16.4)	67.0 (16.6)	66.7 (16.4)	67.5 (16.9)	68.9 (16.6)	69.0 (17.1)
Male sex, no. (%)	677 (64.8)	935 (67.9)	916 (68.1)	1106 (65.1)	1279 (64.6)	1505 (65.3)	1549 (63.8)	1743 (62.5)	1857 (64.4)
Witnessed cardiac arrest									
Bystander, no. (%)	382 (36.6)	93 (51.6)	18 (45.0)	797 (46.9)	977 (49.4)	1130 (49.0)	1129 (46.5)	1388 (49.7)	1080 (39.5)
EMS/private ambulance, no. (%)	78 (7.5)	112 (8.3)	119 (8.5)	137 (8.1)	154 (7.8)	214 (9.3)	246 (10.1)	254 (9.1)	385 (10.4)
Bystander CPR, no. (%)	225 (21.6)	291 (21.6)	460 (33.0)	727 (42.8)	1002 (50.6)	1247 (54.1)	1379 (56.8)	1679 (60.2)	1683 (61.6)
Pre-hospital defibrillation, no. (%)	239 (22.9)	322 (23.9)	364 (26.1)	420 (24.7)	558 (28.2)	642 (27.9)	632 (26.0)	649 (23.3)	646 (23.6)
Cause of arrest									
Presumed cardiac, no. (%)	769 (73.7)	1053 (78.2)	994 (71.3)	1159 (68.1)	1367 (69.0)	1537 (66.6)	1653 (68.0)	1807 (64.7)	1887 (69.1)
Respiratory, no. (%)	97 (9.3)	74 (5.5)	116 (8.3)	89 (5.2)	81 (4.1)	99 (4.3)	96 (3.9)	87 (3.1)	104 (3.8)
Trauma, no. (%)	28 (2.7)	45 (3.3)	32 (2.3)	53 (3.1)	56 (2.8)	96 (4.2)	96 (3.9)	96 (3.4)	91 (3.3)
Initial shockable rhythm, no. (%)	200 (22.2)	249 (18.5)	280 (20.0)	299 (17.5)	345 (17.4)	377 (16.3)	428 (17.6)	419 (15.0)	436 (15.9)

CPR: cardiopulmonary resuscitation; EMS: emergency medical services; SD: standard deviation

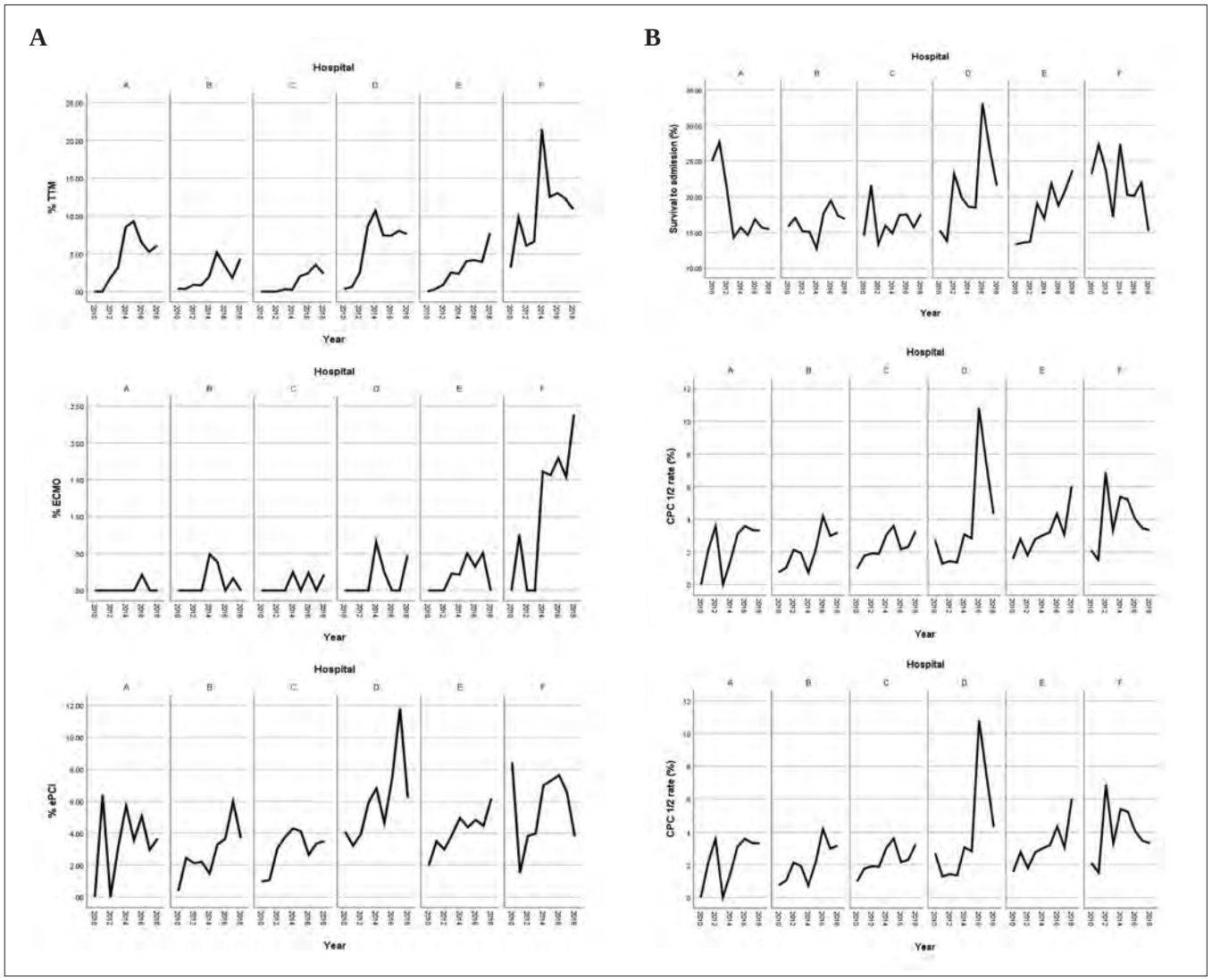

Fig. 2. (A) Inter-hospital temporal trends of hospital-based interventions. (B) Inter-hospital temporal trends in survival outcomes
CPC: cerebral performance category; ECMO: extracorporeal membrane oxygenation; PCI: percutaneous coronary intervention; TTM: therapeutic temperature management

The data showed an encouraging trend towards improving provision of hospital-based interventions across all hospitals in Singapore. This correlated with the improvement in survival for patients with OHCA. Patients who received TTM or PCI were associated with better outcomes. Although our data showed no significant improved survival in patients who underwent ECMO, the number of cases that received ECMO was minimal (n=45, across 9 years).

In terms of hospital characteristics, only academic status of hospitals showed a significant correlation with better 30-day survival, whereas 24-hour access to PCI, years in operation, number of beds, and OHCA patient volume were not significant factors. It should be noted that patients who had been transferred to the nearest hospital for any intervention would be tallied under the hospital they were first conveyed to.

Academic hospitals overseas have been reported to have a lower mortality rate from its medical and surgical interventions.[34] Academic hospitals were more likely to utilise contemporary technologies.[35] Hospitals without an academic status might have been less likely to offer the same level of guideline-directed care.[36] ED care in academic hospitals was associated with more effective CPR and earlier PCI commencement, which could have contributed to improved survival.[37] However, our study did not examine the quality of resuscitative efforts in ED to discern if quality had any effect on survival outcomes.

As opposed to the landmark Singapore study in 2019,[26] our data did not find that bed capacity was a significant

Table 2. Unadjusted and adjusted survival outcomes for out-of-hospital cardiac arrest by hospital

Survival to admission	Model 1 Adjusted OR[a] (95% CI)	Model 2 Adjusted OR[b] (95% CI)
Year	1.03 (1.01–1.05)	1.04 (1.03–1.06)
Hospital A	0.68 (0.58–0.81)	0.67 (0.56–0.81)
Hospital B	0.73 (0.63–0.85)	0.76 (0.65–0.89)
Hospital C	0.73 (0.63–0.85)	0.72 (0.61–0.85)
Hospital D	0.94 (0.80–1.10)	0.90 (0.76–1.06)
Hospital E	0.86 (0.75–0.99)	0.92 (0.78–1.07)
Hospital F	Reference	
30-day survival		
Year	1.09 (1.06–1.13)	1.12 (1.08–1.16)
Hospital A	0.66 (0.49–0.88)	0.67 (0.49–0.93)
Hospital B	0.59 (0.45–0.76)	0.68 (0.51–0.91)
Hospital C	0.62 (0.47–0.81)	0.61 (0.45–0.82)
Hospital D	0.85 (0.65–1.11)	0.82 (0.61–1.11)
Hospital E	0.79 (0.62–1.01)	0.90 (0.68–1.117)
Hospital F	Reference	
CPC scores 1 or 2		
Year	1.13 (1.09–1.18)	1.16 (1.11–1.22)
Hospital A	0.65 (0.46–0.93)	0.68 (0.45–1.01)
Hospital B	0.58 (0.42–0.80)	0.71 (0.50–1.02)
Hospital C	0.61 (0.44–0.86)	0.65 (0.45–0.94)
Hospital D	0.90 (0.64–1.26)	0.88 (0.61–1.28)
Hospital E	0.84 (0.63–1.14)	1.01 (0.72–1.41)
Hospital F	Reference	

CI: confidence interval; CPC: cerebral performance category; OR: odds ratio

[a] Adjusted for year, hospital

[b] Adjusted for year, hospital, age, sex, cause of arrest (cardiac/respiratory/traumatic/others), witnessed arrest, bystander cardiopulmonary resuscitation, first arrest rhythm (shockable/unshockable) and pre-hospital defibrillation

factor associated with better survival to discharge. However, the data showed that OHCA patient volumes correlated inversely with survival outcomes, in contrast to other studies.[38] This could imply that hospital volume and capacity have a complex relationship that includes an optimal level of function, beyond which quality may be compromised.

A 24-hour PCI access is considered an important criterion for cardiac arrest centres.[24] However, our study

Table 3. Association between hospital characteristics and 30-day survival for out-of-hospital cardiac arrest

Hospital characteristic	No. of hospitals	Hospitals	With hospital characteristics[a]		Without hospital characteristics[b]		Unadjusted OR[c] (95% CI)
			No. of OHCA cases	30-day survival, no. (%)	No. of OHCA cases	30-day survival, no. (%)	
24h PCI capability	5	B, C, D, E, F	15684	735 (4.7)	2051	99 (4.8)	0.97 (0.78–1.20)
Years in operation (>20 years)	4	B, D, E, F	12581	610 (4.8)	5154	224 (4.3)	1.12 (0.96–1.31)
Academic status	3	D, E, F	8661	460 (5.3)	9074	374 (4.1)	**1.30 (1.13–1.50)**
Bed number (≥1,000 beds)	4	B, D, E, F	12581	610 (4.8)	5154	224 (4.3)	1.12 (0.96–1.31)
OHCA patient volume (>40 patients/month)	3	A, B, E	10434	479 (4.6)	7031	355 (4.9)	0.94 (0.82–1.08)

CI: confidence interval; OHCA: out-of-hospital cardiac arrest; OR: odds ratio; PCI: percutaneous coronary intervention

[a] OHCA cases sent to hospitals with the hospital characteristic indicated in that row

[b] OHCA cases sent to hospitals without the hospital characteristic indicated in that row

[c] Odds ratio is reported for odds of 30-day survival for group with hospital characteristics versus the reference group without respective hospital characteristics

Table 4. Association between interventions and 30-day survival for out-of-hospital cardiac arrest in the cohort of patients who survived to hospital admission

Hospital intervention type	With intervention	Without intervention	30-day survival, no. (%)		Unadjusted OR[b] (95% CI)
	No. of cases[a]	No. of cases[a]	In group with intervention	In group without intervention	
TTM	718	2503	263 (36.6)	571 (22.8)	1.96 (1.64–2.34)
ECMO	25	3196	5 (20)	829 (25.9)	0.71 (0.27–1.91)
PCI	732	2489	355 (48.5)	479 (19.2)	3.95 (3.31–4.71)

CI: confidence interval; ECMO: extracorporeal membrane oxygenation; PCI: percutaneous coronary intervention; OR: odds ratio; TTM: therapeutic temperature management

[a] Out of the number of patients that survived to admission

[b] Not corrected for pre-hospital factors

suggested that 24-hour PCI alone did not confer improved survival. This may be because 1 hospital in our study did not have 24-hour PCI service, making it difficult to ascertain significance. Although a sizable proportion of the study population had a labelled "presumed cardiac cause" of arrest (66.6–78.2% from year 2010 to 2018 [Table 1]), the data did not specify if the causes were structural, arrhythmic, or ischaemic. Therefore, we were unable to determine which cases in the study qualified for PCI. It has been shown that for patients who were successfully resuscitated post-cardiac arrest without an ST-segment elevation myocardial infarction, emergency angiography did not have better outcomes than delayed angiography.[39] Furthermore, post-resuscitation care is a complex, multidisciplinary effort not dependent on a single therapy. Due to the limitations of our data, we were unable to quantify other aspects of post-resuscitation care, such as quality of intensive care, compliance with post-resuscitation bundles, availability of neuroprognostication, rehabilitation, and other essential elements of care.

Given the strong correlation of survival with academic status of hospitals, the study suggests that patients with OHCA might benefit from EMS conveyance to academic hospitals with a focus on providing excellent, multidisciplinary, post-resuscitation care. However, a change in pre-hospital transport policies faces logistical challenges such as increased travel and turnaround time for ambulances; overcrowding of receiving hospitals; and resultant increased demand of ICU capacity.

The data reflected OHCA outcomes of Singapore hospitals over a period. While it may not be clear as to which factors directly influenced these trends, the data offer an opportunity for Singapore hospitals to review their practices and operations. There is much work to be done before OHCA management can be perfected within our hospitals. Further inquiry into cases of suboptimal OHCA management should be conducted in the pursuit of quality improvement, where information should also be interpreted with data on quality of ED resuscitation and door-to-intervention time.

Limitations

The current study has several limitations. Despite correcting for confounding pre-hospital factors, certain factors were not accounted for. Data on CPR quality in the pre-hospital and ED setting were not available in this study. Other factors such as renal function and comorbidities were also not available. Given the geographically determined catchment area for each hospital, there could be differences in socioeconomic factors (such as income, ethnicity, age, etc.) in each region. This could have introduced bias into the demographics of patients presenting to each hospital.

We were limited by a lack of data on many other individual patient characteristics (e.g. comorbidities, baseline functioning, prognosis and prior preferences). Without in-depth comprehension of the patient population at hand, we were unable to interpret the data optimally in an appropriate context. Clinically, the holistic view of each patient may be very different, and individual physician decision-making affects a patient's eligibility for each intervention. In practice, patients deemed too ill to benefit from an intervention may not be selected.[40] Hence, the observed superior survival rate of patients who received interventions may have been inflated.

Hospital-based factors such as treatment policy changes over time. Infrastructure limitations and workforce changes could have influenced intervention trends within each hospital.

CONCLUSION

Post-resuscitation interventions for OHCA increased across all hospitals in Singapore over a 9-year period, correlating with survival rates. Only academic status of hospitals was associated with improved survival. The findings of this study may have policy implications for the management of OHCA in future. Future research involving simulation modelling may study how different pre-hospital transport policies impact OHCA outcomes.

Disclosure

Prof Marcus Ong reports funding from ZOLL Medical Corporation for a study related to mechanical cardiopulmonary resuscitation devices; grants from the Laerdal Foundation, Laerdal Medical, and Ramsey Social Justice Foundation for funding of the Pan-Asian Resuscitation Outcomes Study; an advisory relationship with Global Healthcare SG, a commercial entity that manufactures cooling devices; and funding from Laerdal Medical on an observation programme to their Community CPR Training Centre Research Program in Norway. Prof Ong has a licensing agreement and patent filed (Application no: 13/047,348) with ZOLL Medical Corporation for a study titled "Method of predicting acute cardiopulmonary events and survivability of a patient".

Funding

This study was funded by the National Medical Research Council, Clinician Scientist Awards, Singapore (NMRC/CSA/024/2010, NMRC/CSA/0049/2013 and NMRC/CSA-SI/0014/2017) and Ministry of Health, Health Services Research Grant, Singapore (HSRG/0021/2012).

Group information

The Singapore PAROS investigators are listed in Appendix of the Supplementary Material in the online version of this article.

Acknowledgements

The authors thank Ms Pek Pin Pin and the late Ms Susan Yap of Department of Emergency Medicine, Singapore General Hospital; Ms Nurul Asyikin, Ms Liew Le Xuan, Ms Noor Azuin and Ms Joann Poh of Unit for Pre-hospital Emergency Care, Singapore General Hospital; Ms Woo Kai Lee of Department of Cardiology, National University Heart Centre Singapore; and Ms Charlene Ong formerly of Accident & Emergency, Changi General Hospital for their contributions and support t o the Singapore OHCA registry.

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ORIGINAL ARTICLE

Ann Acad Med Singap 2022;51:351-6
https://doi.org/10.47102/annals-acadmedsg.2021319

Epidemiological trends and outcomes of children with aural foreign bodies in Singapore

Menghao Duan [1]*MBBS*, Gayathry Morvil [1]*MBBS*, Junaidah Badron [1,2]*MMED (Paediatrics)*, Sashikumar Ganapathy [1,2]*MRCPCH (UK)*

ABSTRACT

Introduction: Aural foreign bodies (FBs) are a common presenting complaint in emergency departments (EDs) worldwide. This study aims to describe trends and outcomes of aural FBs in the paediatric population, presenting to a tertiary hospital in Singapore.

Methods: A retrospective review of medical records was conducted of all children 0–16 years old with aural FBs who presented to KK Women's and Children's Hospital ED from 2013 to 2017. Clinical data that were collected include patient demographics, type of FB, ear compartment and laterality of FB, symptoms, duration of impaction, mode of removal, outcome in ED, and final disposition.

Results: There were a total of 1,003 cases. The largest age group consisted of 53.7% preschool children of 0–6 years. Males (61.7%) were more common than females (38.3%). FBs were predominantly organic materials (25.6%), followed by beads and stones (15.2%). Most FBs were found in the right ear (56.6%). The majority of patients were asymptomatic (62%). Symptoms observed included ear pain (20.1%), itch (4.8%) and bleeding (3.2%). FBs were removed by instruments (36.6%), suctioning (15.4%), syringing (8.2%), or a combination of methods (13.7%). In the ED, 73.9% of patients had an attempt at removal, among which 78.4% of FBs were successfully removed, 5.9% required specialist review, and 15.7% were unsuccessful.

Conclusion: The majority of paediatric aural FBs can be successfully removed in the ED. Emergency physicians should be trained and equipped with the relevant skills to remove aural FBs.

Ann Acad Med Singap 2022;51:351-6

Keywords: Aural, ear, emergency medicine, foreign body, paediatrics

INTRODUCTION

Aural foreign bodies (FBs) commonly present to the emergency department (ED) worldwide. Children represent the majority of the population, believed to be due to their inquisitive minds and experimental nature.[1] Aetiologies for aural FBs include accidental or intentional insertion of FBs into body orifices, ear irritation caused by rhinitis or otalgia, and habitual cleaning of the ear with cotton buds.[2] Certain pre-existing medical conditions such as hyperkinetic disorders and psychological developmental disorders also place children at a higher risk of FB insertion.[3]

In the past decade, aural FBs continue to be a public health concern, driving up healthcare expenditure and causing significant morbidity.[4] Insertion of FBs in the upper aerodigestive tracts has been identified as a common childhood injury, alongside drowning, falls and poisoning.[5] These adverse effects impose significant financial burden on the socio-economic system. Healthcare costs based on procedures for FB extraction and length of hospitalisation incurred up to 50.8 million euros per year in a pan-European survey.[4]

There have been studies in countries worldwide reporting the epidemiology of FB but only few from Southeast Asia.[6] In Malaysia, Chiun et al. reported the age distribution, clinical features and types of FB encountered over 4 years in a single tertiary hospital.[7] There are differences in the 2 study outcomes and recommendations for FB removal. Such differences may also be noted when comparing developed and developing countries. Research done in developed countries has identified several factors contributing

[1] Department of Emergency Medicine, KK Women's and Children's Hospital, Singapore
[2] Paediatric Academic Clinical Programme, Duke-NUS Medical School, Singapore
Correspondence: Dr Menghao Duan, Department of Emergency Medicine, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: menghao.duan@mohh.com.sg
This article was first published online on 3 June 2022 at annals.edu.sg

CLINICAL IMPACT

What is New

- This study describes epidemiological trends and outcomes of aural foreign bodies (FBs) in a paediatric population in Singapore.
- The majority of paediatric aural FBs were successfully managed by the ED physician and did not require specialist referral.

Clinical Implications

- The study identifies clinical factors contributing to successful aural FB removal in children.
- Training ED physicians to remove aural FBs and anticipate difficult removal is recommended.

to unsuccessful removal.[8,9] In such cases, early referral to the specialists for potential removal under general anaesthesia should be considered.[10] However, resource-poor regions may grapple with the lack of appropriate instruments and a poorly established referral system to the specialists. This presents a unique set of challenges to reduce complications associated with aural FB extraction, and emphasises the need for proficiency of primary care doctors.[11]

The management for aural FB in paediatric patients remains a challenge for many physicians, given the varying levels of experience. While most FBs have a benign course, several cautionary tales of progression to severe complications have been reported.[12] The external ear canal is a small, enclosed and sensitive space where any form of instrumentation or procedure may be challenging. Complications arise as a result of prolonged FB impaction or repeated attempts at removal.[8] These complications include, but are not limited to, canal abrasions, haematomas, tympanic membrane injuries, otitis media or externa, and mastoiditis.[12]

This study aimed to describe trends and outcomes of aural foreign bodies in the paediatric population, presenting to a tertiary hospital in Singapore. We recorded the characteristics of the patients and FBs commonly encountered in our practice. By comparing our results with other studies, we aim to identify potential areas of improvement to reduce disease morbidity and mortality.

METHODS

A retrospective study was conducted on paediatric patients aged under 16 years old, presenting to the ED of KK Women's and Children's Hospital for aural FBs, over 4 years from 2013 to 2017. The KK Women's and Children's Hospital is one of 2 tertiary paediatric centres in Singapore's public sector. We included all patients diagnosed with aural FBs according to the International Classification of Diseases, Ninth Revision (ICD-9) Codes 931, 38010, 3849 and 7847. The search criteria were also expanded to include any diagnosis with the keywords "foreign bodies", "ear canal", "tympanic membrane" and/or "pinna". Patients with FBs in the respiratory and gastrointestinal tracts were excluded.

Each patient was assigned a unique identification number, and clinical notes of all relevant patients were retrieved anonymously via the Sunrise Clinical Manager (SCM) electronic medical record software. Patient information included age, race and sex. Data surrounding the ED attendance including types of FB, ear laterality, ear compartment, duration of impaction, symptoms, mode of removal, outcome in the ED, and final disposition were collected. Patients who had an onward referral to ear, nose and throat (ENT) specialists had further data obtained on their complications and treatments.

Following data collection, patients were grouped according to the removal attempts in the ED. The relationship between clinical factors and FB removal attempt was examined using the chi-square test of independence. A P value of <0.05 indicated statistical significance. FBs were categorised into 13 classes based on materials. Results were presented using simple descriptive analysis, as proportions in tables.

The study was approved by the SingHealth Institutional Review Board. The requirement for informed consent was waived due to the use of anonymised data and the low feasibility of retrospectively obtaining consent from a large number of patients.

RESULTS

There were a total of 1,003 paediatric cases over the 4-year period. The largest age group consisted of 539 (53.7%) preschool children aged 0 to 6 years. The remainder included 407 (40.6%) children aged 7 to 12 years and 57 (5.7%) above 12 years. The median age was 5.8 (interquartile range 4.3–7.8) years. The cohort constituted of 619 (61.7%) males and 384 (38.3%) females, with a male-to-female sex ratio of 1.6:1.

The most common objects were organic materials (25.6%), including paper, cotton bud, tissue and erasers, followed by beads and stones (15.2%), inorganic material (12.1%), as well as toys (9.8%) (Table 1). There were 31 cases involving insects and 11 cases involving button batteries. More than half (568, 56.6%) of the

Table 1. Types of aural foreign bodies

No.	Type of foreign bodies	No. of patients	%
1	Organic material: paper/cotton bud/tissue/ sand/eraser/cloth/glass	257	25.6
2	Inorganic bead/sequin/stone	153	15.2
3	Inorganic material: plastic/styrofoam/ blue tack/sponge/foam	122	12.1
4	Inorganic toy: crayon/sticker/magnet/toy	98	9.8
5	Organic food/plant/seed	98	9.8
6	Pencil lead/pen	75	7.5
7	Earring	64	6.4
8	Playdough/plasticine	36	3.6
9	Organic: insect	31	3.1
10	Metals: metal foil	22	2.2
11	Button battery	11	1.1
12	Others: artificial turf/earpiece/hairpin/ thermometer	9	0.9
13	Tooth/hair	7	0.7
14	Unspecified	20	2.0
	Total	1003	100

FBs were found in the right ear, 380 (37.8%) in the left ear and 55 (5.5%) had bilateral involvement. Most FBs (926, 92.3%) were predominantly lodged in the external auditory canal and could be seen on direct visualisation.

A total of 622 (62%) patients remained asymptomatic. Among those who experienced symptoms, the most frequent presenting complaint was ear pain or discomfort (209/1003, 20.1%). Some patients presented with ear pruritus (48/1003, 4.8%), bleeding (32/1003, 3.2%), hearing loss (13/1003, 1.3%) and tinnitus (2/1003, 0.2%). The duration of impaction varied from hours to several days, although 445 (44.5%) patients presented within 24 hours of witnessed FB insertion or onset of symptoms.

The mode of removal (Table 2) depended on the type and location of the FBs; 367 (36.6%) FBs were removed with the use of instruments. The instruments were a combination of alligator forceps, Jobson Horne probe, 90-degree hook and Tilley's forceps. Other methods utilised in the ED included suctioning (155/1003, 15.4%), syringing (82/1003, 8.2%), and a combination of different methods (137/1003, 13.7%).

Of the 1,003 patients (Fig. 1), 741 (73.9%) had an attempt at removal in the ED. No attempt was made for 231 (23%) patients, who consequently required a referral

Table 2. Mode of removal of aural foreign bodies

Mode of removal	No. of patients	%
Instruments		
Alligator forceps	165	16.5
Jobson Horne probe	83	8.2
90-degree hook	27	2.7
Tilley's forceps	92	9.2
Suctioning	155	15.4
Syringing or flushing	82	8.2
Combination of methods	137	13.7
Unspecified	31	3.1
No attempt	231	23.0

to the outpatient ENT clinic. Thirty-one patients (3.1%) had unspecified data on removal attempt. A comparison table was drawn between patients who had an attempt at FB removal in the ED and those with no attempt made (Table 3). Chi-square independence test showed that between the 2 groups, age (P=0.003), sex (P=0.012) and types of FBs (P<0.001) differed significantly.

Among those who had attempts at removal, 581 (78.4%) FBs were successfully removed by the emergency physician in the ED, without sedation or general anaesthesia. Forty-four (5.9%) patients required a consult with ENT physicians and had the FBs removed by them on the same day of the ED visit. These consisted of patients who were referred directly to ENT without any prior attempt at removal. There were 116 (15.7%) patients with unsuccessful removal in the ED and they were given an ENT appointment for the next working day. A myriad of factors contributed to the unsuccessful attempts—patient factors (20/116, 16.9%), physician factors (10/116, 8.5%), nature of FB (24/116, 20.8%), or a combination of the above.

More than half or 576 (57.4%) of the patients were discharged from the ED with no follow-up appointment. A total of 410 (40.9%) were referred to the outpatient ENT clinic for further management. Of note, 12 patients required admission for examination and extraction of the FB under general anaesthesia. Two of them had impacted button batteries, and 4 involved organic food including plants and seeds. These objects are known to cause severe complications and warrant immediate ENT referral at the ED.

DISCUSSION

Our patient demographics consisted predominantly of children aged 0–6 years old and males. The most

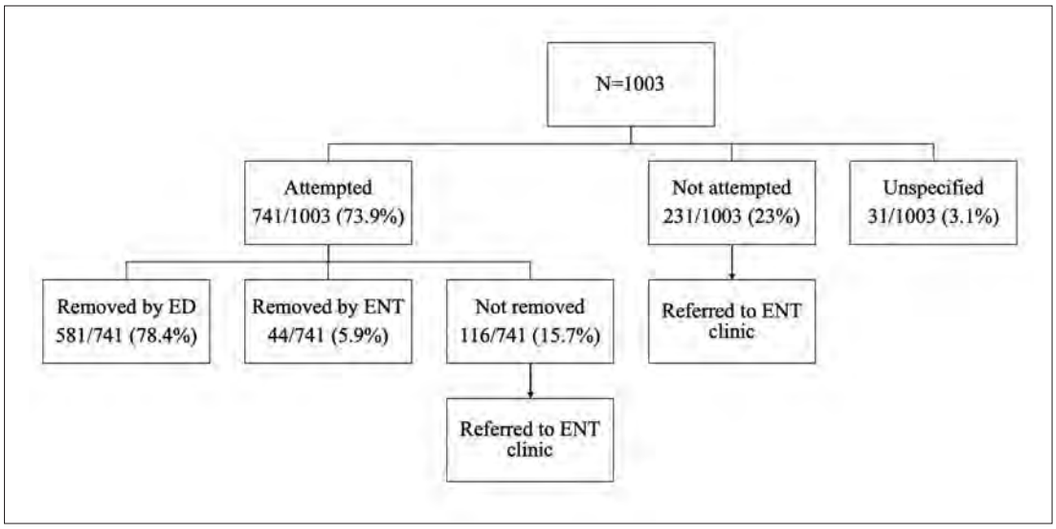

Fig. 1. Flowchart of all patients from presentation to emergency department, attempted/not attempted removal of aural foreign bodies, and final disposition.
ED: emergency department; ENT: ear, nose and throat

common type of FBs was organic materials. The majority of FBs were found in the right ear, most patients remained asymptomatic, and presented within 24 hours to the ED. The removal of FB was done with instruments, suctioning or syringing.

Of the 1,003 patients, 73.9% had an attempt at FB removal in the ED and among those attempted, 78.4% were successfully removed by ED physicians. More than half of the patients were discharged from the ED.

In our population, the highest incidence of aural FB was in preschool children aged 0–6 years. It was consistently observed that most aural FB cases arise from this age group, and the rate of incidence decreases as age increases.[11,13] This is postulated to be the age where children are most active and exploratory in nature. They are driven by general curiosity and a whim to insert FBs into their body orifices, usually with household objects. Adult supervision is crucial during this period and educational advice should be provided opportunistically to all caregivers.

Organic materials were the most common type of aural FBs, consisting of paper, cotton bud and tissue fragments. Similarly, these objects were also reported to be of the highest incidence in Ireland,[10] and were also common in Papua New Guinea[13] and Nigeria.[11] Small inorganic objects such as beads and stones were the next most common FBs. These objects are easily available in the household and are likely to be inserted into the ear by unsupervised children.[14]

Aural FBs were found to be predominantly lodged in the external auditory canal (EAC). The EAC is divided into cartilaginous and bony portions, which are lateral and medial, respectively. The osseous passage is very vascular and is lined with a sensitive thin layer of skin. As a result, trauma to this area causes bleeding and pain. Most FBs were inserted superficially and lodged in the lateral aspect of the ear canal, which may explain why most patients remained asymptomatic.[15] In a separate study at the Pediatric Hospital of Turin,[16] a retrospective analysis of 100 aural FB cases in children aged 0–12 years found a significant proportion presenting with hearing loss, ear fullness and otalgia.[16] These symptoms were relatively rare in our population.

FBs lodged in the ear for a prolonged period often result in inflammatory reactions, sensitising the EAC and causing oedema, hence making the removal process more challenging. In the Children's Hospital of Wisconsin, FBs removed between 24 hours and 1 week had a lower success rate compared to those who presented within a shorter period.[8] It was encouraging that the majority of our patients presented within 24 hours from the onset. However, while caregivers should be advised to seek treatment at the earliest time possible, Kumar suggested in his study that most ENT FBs do not require immediate removal and instead, can be undertaken the next day in a more ideal environment.[17]

The majority of aural FBs in our study were successfully removed in the ED. All FBs were assessed by the attending ED physician before deciding to attempt removal. We reported a 78% success rate among those deemed suitable for an attempt, an improved result compared to the previous Singapore study, which

Table 3. Comparison of attempted versus non-attempted foreign bodies

N=1003	Attempted n=741 (73.9%)		Non-attempted n=231 (23%)		*P* value
Age, years, no. (%)					0.003
0–6	405	54.7	147	63.4	
7–12	305	41.1	68	29.6	
>12	31	4.2	16	7.0	
Sex, no. (%)					0.012
Male	494	66.6	133	57.7	
Female	247	33.4	98	42.3	
Types of foreign bodies, no. (%)					<0.001
Organic	173	23.3	91	39.4	
Inorganic[a]	369	49.8	71	30.9	
Fruit/plant/seed, insect	92	12.4	20	8.5	
Battery	5	0.7	2	0.7	
Others[b]	68	9.1	16	7.1	
Unspecified	34	4.7	31	13.4	
Ear compartment, no. (%)					-
External auditory canal	719	97	166	71.8	
Middle ear	0	0	57	24.7	
Unspecified	22	3.0	8	3.5	
Duration of impaction, days, no. (%)					0.261
<1	330	44.5	117	50.7	
2–7	115	15.5	33	14.1	
>7	296	40.0	81	35.2	

[a] Inorganic material: plastic/styrofoam/blue tack/sponge/foam, bead/sequin/stone, toy, crayon/sticker/magnet, pencil, playdough/plasticine
[b] Others: earring, metal, tooth/hair, artificial turf/earpiece/hairpin/thermometer

recorded a success rate of 53%.[6] The discrepancy between the 2 studies done at a decade-long interval could suggest improved skills and competency of the ED physicians. Our result is comparable to the Gupta et al. study in Australia, which reported a 72% success rate.[18] The researchers also concluded that most aural FB cases can be managed in the ED setting. Several other studies shared poorer success rates: 53% in the US[19] and 7% in Ireland,[10] with both recommending an early referral to the specialists.

To have all FBs in children referred to the ENT specialist for management is not practical nor economically feasible. In our study, a small, selected group of patients (23%) was referred to ENT without an attempt in ED. Aural FB should be triaged based on its type and location to optimise the chances of successful retrieval and lower complication rates, while avoiding unnecessary referrals. Smooth spherical objects were less graspable and had the worst outcomes, as shown by Dimuzio et al.[19] Multiple attempts were also associated with lower success rates according to Schulze et al., as children became increasingly uncooperative.[8]

Among the few patients who required direct admission for examination and extraction under anaesthesia by ENT, 2 had impacted button batteries and 4 had plants and seeds. These objects are notorious for developing severe complications and warrant a more cautious management with urgent ENT review. Batteries can cause liquefactive necrosis of the ear epithelium from the leakage of its alkaline contents. Vegetative matter

may expand on contact with moisture and lead to high pressures in the enclosed ear canal space.[20] Fortunately, our patients received timely treatment and made good recovery. Live insects in the ear should also be killed by submersion to relieve patient symptoms prior to removal with instruments or irrigation.[21]

An area for further research could potentially include the competency and confidence of ED physicians in FB removal, as well as the equipment and resource available in the ED to support these procedures. While it is widely agreed that specialist opinion should be sought whenever there is anticipated difficulty, most straightforward cases can be effectively managed by the ED physician.

Limitations

Limitations of this study included possible incomplete or inadequate documentation and data. This was despite best efforts made to capture all data surrounding visits to the ED for the topic of interest. Significant types of data requested by the reviewers were not available, including sedation rates, seniority of operators, proportion of children with autism spectrum disorder or developmental delay. These were factors that could have contributed to FB removal outcomes. There was also a lack of information on follow-up ENT visits, resulting in limited data on complications that may have developed from the ED removal attempt. Cost analysis comparing resource utilisation in the ED and ENT outpatient clinics in the management of aural FB was not possible due to insufficient data.

CONCLUSION

Aural FBs remain a common occurrence, particularly among young and unsupervised children. Appropriate education to responsible caregivers is a primary intervention to reduce FB incidence. Our centre demonstrated a 78.4% success rate of attempted aural FB removal, and an overall 58% success rate among all patients presenting to ED with aural FBs. Training ED physicians to become better equipped with the relevant skill set and experience, as well as recognising situations where difficult removal is anticipated, could help in striking a balance between specialist resource allocation and ensuring good patient outcomes.

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ORIGINAL ARTICLE

Ann Acad Med Singap 2022;51:357-69
https://doi.org/10.47102/annals-acadmedsg.2021507

Functional improvement after inpatient rehabilitation in community hospitals following acute hospital care

Htet Lin Htun [1]*MPH*, Lok Hang Wong [1]*MPH*, Weixiang Lian [1]*BSc*, Jocelyn Koh [2]*MMed*, Liang Tee Lee [3]*MMed*, Jun Pei Lim [4]*MMed*, Ian Leong [4,5]*MMed*, Wei-yen Lim [1]*PhD*

ABSTRACT

Introduction: There are limited studies exploring functional improvement in relation to characteristics of patients who, following acute hospital care, receive inpatient rehabilitation in community hospitals. We evaluated the association of acute hospital admission-related factors with functional improvement on community hospital discharge.

Methods: We conducted a retrospective cohort study among patients who were transferred to community hospitals within 14-day post-discharge from acute hospital between 2016 and 2018. Modified Barthel Index (MBI) on a 100-point ordinal scale was used to assess functional status on admission to and discharge from the community hospital. We categorised MBI into 6 bands: 0–24, 25–49, 50–74, 75–90, 91–99 and 100. Multivariable logistic regression models were constructed to determine factors associated with categorical improvement in functional status, defined as an increase in at least one MBI band between admission and discharge.

Results: A total of 5,641 patients (median age 77 years, interquartile range 69–84; 44.2% men) were included for analysis. After adjusting for potential confounders, factors associated with functional improvement were younger age, a higher MBI on admission, and musculoskeletal diagnosis for the acute hospital admission episode. In contrast, a history of dementia or stroke; lower estimated glomerular filtration rate; abnormal serum albumin or anaemia measured during the acute hospital episode; and diagnoses of stroke, cardiac disease, malignancy, falls or pneumonia; and other chronic respiratory diseases were associated with lower odds of functional improvement.

Conclusion: Clinicians may want to take into account the presence of these high-risk factors in their patients when planning rehabilitation programmes, in order to maximise the likelihood of functional improvement.

Ann Acad Med Singap 2022;51:357-69

Keywords: Barthel Index, community hospitals, functional status, inpatients, rehabilitation, risk factors

INTRODUCTION

Early inpatient rehabilitation therapy has been known to have beneficial impact on physical function and mobility, psychological status and cognitive function of patients following an acute medical event requiring hospitalisation.[1] Following an acute hospital care, those who have been identified to have potential for functional improvements are often transferred to a community hospital or rehabilitation unit for physical therapy and rehabilitation. Patients typically go through a series of multidisciplinary therapeutic interventions. These interventions aim to restore their functional capability, activities of daily living (ADL) and cognitive function,[2,3] with the overall objective of improving quality of life and reducing complications arising from their disability. Appropriate level of medical stability, significant level

[1] Department of Preventive and Population Medicine, Office of Clinical Epidemiology, Analytics, and Knowledge, Tan Tock Seng Hospital, Singapore
[2] Ang Mo Kio - Thye Hua Kwan Hospital, Singapore
[3] Ren Ci Community Hospital, Singapore
[4] Department of Geriatric Medicine, Tan Tock Seng Hospital, Singapore
[5] Department of Continuing and Community Care, Tan Tock Seng Hospital, Singapore
Correspondence: Dr Wei-yen Lim, Department of Preventive and Population Medicine, Office of Clinical Epidemiology, Analytics, and Knowledge, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: weiyen_lim@ttsh.com.sg

CLINICAL IMPACT

What is New

- Our study identified the determinants of functional improvement in patients who were transferred from an acute hospital to community hospital for inpatient rehabilitation.
- Patient factors such as age, comorbidities, psychotropic medication use, laboratory parameters, and the principal reason for admission to acute hospital were associated with functional improvement during extended care at the community hospital.

Clinical Implications

- Factors associated with the high and low odds of functional improvement may support healthcare professionals in the planning of personalised rehabilitation programmes with the aim of achieving the best possible functional improvement in patients.

of functional disability and capability to learn in patients are important criteria for the development of a rehabilitation plan.[4]

In Singapore, inpatient rehabilitation service is offered in acute care hospitals and community hospitals. There are currently 9 community hospitals in operation providing medical, nursing and rehabilitation care.[5] The majority of patients in the community hospitals are transferred from an acute hospital after treatment and stabilisation of their condition. The additional stay in the community hospital is intended to reduce post-illness disability and functional impairment, so as to optimise their ability to perform ADL and function within the home environment. Rehabilitative care including physical, occupational and speech therapies are conducted by trained professionals, and individualised to the specific needs of each patient.

Literature on the benefits of inpatient rehabilitation in relation to functional status after an acute event has typically looked at outcomes in persons with a certain disease condition such as stroke or spinal injuries.[4,6-8] However, many patients receiving care in community hospitals have multiple comorbidities or are extremely frail. In some cases, their decline in functional impairment may possibly be due to deconditioning rather than a direct consequence of the event that caused their admission. Furthermore, this topic has not been well-explored in Asian countries. We were thus motivated to evaluate rehabilitation outcomes in a group of patients who were discharged from an acute hospital for inpatient rehabilitation therapy in community hospitals. This article describes the factors from acute hospital admission that are associated with functional improvement at the point of discharge from community hospital.

METHODS

Study design, setting and population

We conducted a retrospective closed cohort study among patients hospitalised in Tan Tock Seng Hospital (TTSH) in Singapore, a 1,700-bed acute care tertiary hospital. The patients were discharged to one of 2 affiliated community hospitals: a 370-bed community hospital A, or 472-bed community hospital B. Study participants were selected based on the following eligibility criteria:

(1) patients discharged from TTSH between January 2016 and December 2018; and

(2) patients transferred subsequently to either community hospital A or B within 14 days of discharge from TTSH.

Outcome measurement

The Modified Barthel Index (MBI),[9,10] a 100-point ordinal scale for the assessment of a patient's functional state, was determined within 48 hours of admission and at discharge. MBI assesses 5 subcategories for each of the 10 ADL comprising personal hygiene, feeding, bathing, toileting, stair climbing, dressing, bladder control, bowel control, ambulation and transfers. In the absence of established MBI cut-off scores, we selected the MBI bands used by the Ministry of Health Singapore.[11] Patients were categorised into 6 bands: total dependency (score of 0–24), severe dependency (25–49), moderate dependency (50–74), mild dependency (75–90), minimal dependency (91–99) and independent (100).[11] Taking the first recorded MBI score at admission and the last MBI score on discharge, improvement in MBI was defined as an increase in a minimum of 1 MBI band on discharge from the community hospital. We excluded 14 patients who had an MBI of 100 on admission to the community hospital.

Explanatory variables

Data recorded during the acute hospital care episode that could potentially be associated with functional improvement were extracted for the study. All data were electronically extracted from the electronic medical records of the hospital in a standardised fashion. We included the following variables: age (<65, 65–74, 75–84, ≥85 years), sex, ethnicity, type of residential accommodation (rental flat versus non-rental flat)

as a surrogate index for social status, prescribed psychotropic medications (i.e. psychotherapeutics, anxiolytics/sedatives/hypnotics, anticonvulsants and/or antiparkinsonian medication),[12] Hospital Frailty Risk Score (low risk <5, intermediate risk 5–15, and high risk >15)[13] and Charlson's Comorbidity Index (CCI).[14] Additionally, the last available values of the laboratory parameters during the acute hospital stay were also extracted; the following laboratory variables were included: serum albumin (normal ≥35g/L, mild hypoalbuminaemia 25–34g/L, marked hypoalbuminaemia <25g/L),[15] blood urea (low <2.5mmol/L in men and <2.0mmol/L in women, normal 2.5–7.5mmol/L in men and 2.0–6.5mmol/L in women, and high >7.5mmol/L in men and >6.5mmol/L in women), anaemia assessed by haemoglobin (normal ≥13g/dL in men and ≥12g/dL in women, mild anaemia 10.0–12.9g/dL in men and 10.0–11.9g/dL in women, and moderate to severe anaemia <10.0g/dL in men and women),[16] serum sodium (hypernatraemia ≥145mmol/L, normal 135–144mmol/L, mild hyponatraemia 130–134mmol/L, and moderate to severe hyponatraemia <130mmol/L), estimated glomerular filtration rates (eGFRs) calculated from serum creatinine using Chronic Kidney Disease Epidemiology Collaboration equation and categorised by levels of eGFR (≥60, 30–59, and <30mL/min/1.73m^2),[17] red blood cell (RBC) count, platelets, white blood cell (WBC) count, as well as neutrophil, and lymphocyte counts (<1.5 and ≥1.5 x 10^9/L) as a marker of nutritional status.[18-20] Based on electronically extracted principal discharge diagnosis during acute hospital care, we further categorised the patients into 8 distinct groups: (1) injuries/fractures, (2) stroke, (3) musculoskeletal (e.g. spondylopathies and arthrosis/arthritis such as knee arthrosis, gouty arthritis, rheumatoid arthritis and dorsalgia), (4) cardiac conditions, (5) malignancy/palliative conditions, (6) falls (without fractures), (7) acute exacerbation of chronic obstructive pulmonary disease (AE-COPD)/pneumonia/lower respiratory tract infections (LRTIs), and (8) other infections; and the remaining patients as others.

Statistical analysis

Characteristics of patients were described with frequencies and percentages, or median values and interquartile ranges (IQRs) as appropriate. The differences in characteristics were compared using chi-square test or Mann-Whitney U test. Multivariable logistic regression analysis was performed to assess the determinants associated with functional outcome improvement. Explanatory variables that were significantly different between the groups that improved MBI bands and that did not, and variables that were judged as clinically important by clinicians (age, sex, race, MBI on admission, frailty and comorbidities) were selected to be included in the multivariable models. We assessed variables for correlation, and excluded highly correlated variables (RBC count and blood urea were excluded due to correlation with haemoglobin and eGFR, respectively). Four nested multivariable regression models were developed, with improvement in MBI band as an outcome variable and the following variables as predictors: demographics, MBI score on admission and principal discharge condition in model 1, addition of the Hospital Frailty Risk Score category and pre-existing comorbidities in model 2, addition of overall psychotropic medication use and number of medication prescribed on discharge in model 3, and final addition of laboratory test results in model 4. As supplementary analysis, we further performed a logistic regression stratified by principal discharge condition (including injuries/fractures, stroke, musculoskeletal disorders, AE-COPD/pneumonia/LRTIs, other infections and others considering the number of participants in each category) using explanatory variables from model 4. All reported *P* values were two-tailed, with an α level of 0.05. All statistical analyses were conducted using R version 4.0.2 (RStudio Team, Vienna, Austria).

The study was approved with waiver of informed consent by Domain Specific Review Board of the National Healthcare Group, Singapore (reference ID: 2021/00404).

RESULTS

Characteristics of study population

From 2016 to 2018, a total of 5,641 patients aged 23–111 years (median age 77, IQR 69–84) were included for analysis (Fig. 1). Fig. 2 illustrates the distribution of absolute MBI score on admission to and discharge from community hospital stratified by disease condition. Improvement in MBI score at discharge was seen most among patients who underwent rehabilitation for musculoskeletal disorders and injuries/fractures. The demographic and clinical characteristics of the study population are shown in Table 1. Nearly half (n=2,831, 50.2%) had improvement in their MBI band. Those who improved tended to be younger (median age 76 years, IQR 68–83 vs 79 years, IQR 71–86; *P*<0.001), women (58.6% vs 53.1%; *P*<0.001), had a higher MBI score on admission (median 58, IQR 43.5–67 vs 50, IQR 26–61; *P*<0.001), a longer length of stay in the

Table 1. Characteristics of patients and risk factors of improvement in MBI band

Characteristics	Total (N=5641)	Improvement by at least 1 MBI band		*P*
		No (n=2810)	Yes (n=2831)	
Demographics				
Age, median (IQR), years	77 (69.0–84.0)	79 (71.0–86.0)	76 (68.0–83.0)	<0.001
Age category, no. (%)				<0.001
<65 years	784 (13.9)	341 (12.1)	443 (15.6)	
65–74 years	1461 (25.9)	643 (22.9)	818 (28.9)	
75–84 years	2019 (35.8)	1004 (35.7)	1015 (35.9)	
≥85 years	1377 (24.4)	822 (29.3)	555 (19.6)	
Sex, no. (%)				<0.001
Male	2492 (44.2)	1319 (46.9)	1173 (41.4)	
Female	3149 (55.8)	1491 (53.1)	1658 (58.6)	
Ethnicity, no. (%)				0.059
Chinese	4812 (85.3)	2364 (84.1)	2448 (86.5)	
Malay	305 (5.4)	157 (5.6)	148 (5.2)	
Indian	324 (5.7)	176 (6.3)	148 (5.2)	
Others	200 (3.5)	113 (4.0)	87 (3.1)	
Reside in rental flat, no. (%)	596 (10.6)	271 (9.6)	325 (11.5)	0.025
Details of hospital admission				
MBI score on admission, median (IQR)	53 (35–65)	50 (26–61)	58 (43.5–67)	<0.001
MBI score on admission category, no. (%)				<0.001
0–24	927 (16.4)	653 (23.2)	274 (9.7)	
25–49	1524 (27.0)	721 (25.7)	803 (28.4)	
50–74	2603 (46.1)	1162 (41.4)	1441 (50.9)	
75–90	532 (9.4)	240 (8.5)	292 (10.3)	
91–99	55 (1.0)	34 (1.2)	21 (0.7)	
Diagnosis at discharge from acute care hospital				<0.001
Injuries and fractures	1944 (34.5)	834 (29.7)	1110 (39.2)	
Stroke	717 (12.7)	430 (15.3)	287 (10.1)	
Musculoskeletal conditions	567 (10.1)	130 (4.6)	437 (15.4)	
Cardiac conditions	178 (3.2)	111 (4.0)	67 (2.4)	
Malignancy and palliative conditions	155 (2.7)	87 (3.1)	68 (2.4)	
Falls	161 (2.9)	95 (3.4)	66 (2.3)	
AE-COPD, pneumonia and other LRTIs	522 (9.3)	287 (10.2)	235 (8.3)	
Other infections	857 (15.2)	509 (18.1)	348 (12.3)	
Others	540 (9.6)	327 (11.6)	213 (7.5)	
Community hospital length of stay, median (IQR), days	29 (18–43)	25 (14–40)	32 (23–46)	<0.001

Table 1. Characteristics of patients and risk factors of improvement in MBI band (Cont'd)

Characteristics	Total	Improvement by at least 1 MBI band		*P*
	(N=5641)	No (n=2810)	Yes (n=2831)	
Comorbidities				
Frailty Risk Score, median (IQR)	9.4 (4.7–15.5)	10.8 (6.0–17.4)	8.1 (3.7–13.8)	<0.001
Frailty Risk Score category, no. (%)				<0.001
Low risk (<5)	1484 (26.3)	576 (20.5)	908 (32.1)	
Intermediate risk (5–15)	2666 (47.3)	1332 (47.4)	1334 (47.1)	
High risk (>15)	1491 (26.4)	902 (32.1)	589 (20.8)	
CCI, median (IQR)	3 (1.0–5.0)	3 (2.0–5.0)	2 (0.0–4.0)	<0.001
CCI category, no. (%)				<0.001
Fair (≤5)	4557 (80.8)	2110 (75.1)	2447 (86.4)	
Poor (>5)	1084 (19.2)	700 (24.9)	384 (13.6)	
Patients with the following comorbidity, no. (%)				
Dementia	910 (16.1)	628 (22.3)	282 (10.0)	<0.001
Chronic pulmonary disease	680 (12.1)	341 (12.1)	339 (12.0)	0.853
Chronic liver disease	349 (6.2)	203 (7.2)	146 (5.2)	0.001
Diabetes mellitus	2546 (45.1)	1381 (49.1)	1165 (41.2)	<0.001
Renal disease	1482 (26.3)	903 (32.1)	579 (20.5)	<0.001
Tumour	561 (9.9)	304 (10.8)	257 (9.1)	0.029
Stroke	1862 (33.0)	1108 (39.4)	754 (26.6)	<0.001
Congestive heart failure/myocardial infarct	1219 (21.6)	737 (26.2)	482 (17.0)	<0.001
Medications prescribed, no. (%)				
Overall psychotropic medications usea	2693 (47.7)	1462 (52.0)	1231 (43.5)	<0.001
Use of following medications				
Psychotherapeutics	1339 (23.7)	781 (27.8)	558 (19.7)	<0.001
Anxiolytics/sedatives/hypnotics	715 (12.7)	394 (14.0)	321 (11.3)	0.002
Anticonvulsants	1631 (28.9)	877 (31.2)	754 (26.6)	<0.001
Antiparkinsonians	58 (1.0)	29 (1.0)	29 (1.0)	0.977
Medications on discharge, no. (%)				0.010
<9	1326 (23.5)	614 (21.9)	712 (25.2)	
9–11	1617 (28.7)	834 (29.7)	783 (27.7)	
12–14	1466 (26.0)	720 (25.6)	746 (26.4)	
>14	1232 (21.8)	642 (22.8)	590 (20.8)	
Laboratory parameters, no. (%)				
eGFR				<0.001
≥60mL/min/1.73m^2	3968 (70.3)	1829 (65.1)	2139 (75.6)	
30–59mL/min/1.73m^2	1180 (20.9)	644 (22.9)	536 (18.9)	

Table 1. Characteristics of patients and risk factors of improvement in MBI band (Cont'd)

Characteristics	Total	Improvement by at least 1 MBI band		*P*
	(N=5641)	No (n=2810)	Yes (n=2831)	
<30mL/min/1.73m^2	451 (8.0)	319 (11.4)	132 (4.7)	
Unknown	42 (0.7)	18 (0.6)	24 (0.8)	
Albumin				<0.001
Normal	1143 (20.3)	504 (17.9)	639 (22.6)	
Mild hypoalbuminaemia	2451 (43.4)	1318 (46.9)	1133 (40.0)	
Marked hypoalbuminaemia	651 (11.5)	427 (15.2)	224 (7.9)	
Unknown	1396 (24.7)	561 (20.0)	835 (29.5)	
Urea				<0.001
Low	179 (3.2)	98 (3.5)	81 (2.9)	
Normal	3766 (66.8)	1728 (61.5)	2038 (72.0)	
High	1582 (28.0)	943 (33.6)	639 (22.6)	
Unknown	114 (2.0)	41 (1.5)	73 (2.6)	
Haemoglobin				<0.001
Normal	1262 (22.4)	586 (20.9)	676 (23.9)	
Mild anaemia	2860 (50.7)	1363 (48.5)	1497 (52.9)	
Moderate to severe anaemia	1490 (26.4)	847 (30.1)	643 (22.7)	
Unknown	29 (0.5)	14 (0.5)	15 (0.5)	
Sodium				<0.001
Normal	3772 (66.9)	1857 (66.1)	1915 (67.6)	
Mild hyponatraemia	1219 (21.6)	619 (22.0)	600 (21.2)	
Moderate to severe hyponatraemia	150 (2.7)	93 (3.3)	57 (2.0)	
Hypernatraemia	43 (0.8)	31 (1.1)	12 (0.4)	
Unknown	457 (8.1)	210 (7.5)	247 (8.7)	
RBC (10^{12}/L),[b] median (IQR)	3.7 (3.3–4.2)	3.7 (3.3–4.1)	3.8 (3.4–4.2)	<0.001
WBC (10^9/L),[c] median (IQR)	8.2 (6.6–9.9)	8.2 (6.6–10.0)	8.2 (6.6–9.9)	0.699
Lymphocytes (10^9/L),[c] median (IQR)	1.4 (1.0–1.8)	1.4 (1.0–1.8)	1.4 (1.1–1.9)	0.012
Lymphocytes (10^9/L) category, no. (%)				0.101
<1.5	2990 (53.0)	1529 (54.4)	1461 (51.6)	
≥1.5	2620 (46.4)	1265 (45.0)	1355 (47.9)	
Unknown	31 (0.5)	16 (0.6)	15 (0.5)	
Neutrophils (10^9/L),[c] median (IQR)	5.7 (4.3–7.3)	5.7 (4.3–7.4)	5.6 (4.3–7.3)	0.676
Neutrophil-to-lymphocyte ratio,[c] median (IQR)	4.0 (2.7–6.0)	4.0 (2.8–6.1)	4.0 (2.7–5.8)	0.101
Platelets (10^9/L),[c] median (IQR)	287.0 (221.0–375.0)	285.0 (218.0–373.0)	289.0 (223.0–377.0)	0.127

AE-COPD: acute exacerbation of chronic obstructive pulmonary disease; CCI: Charlson's Comorbidity Index; eGFR: estimated glomerular filtration rate; IQR: interquartile range; LRTIs: lower respiratory tract infections; MBI: Modified Barthel Index; RBC: red blood cells; WBC: white blood cells

[a] Includes the use of psychotherapeutics, anxiolytics/sedatives/hypnotics, anticonvulsants, and/or antiparkinsonians

[b] n (%) missing = 34 (0.6)

[c] n (%) missing = 31 (0.5)

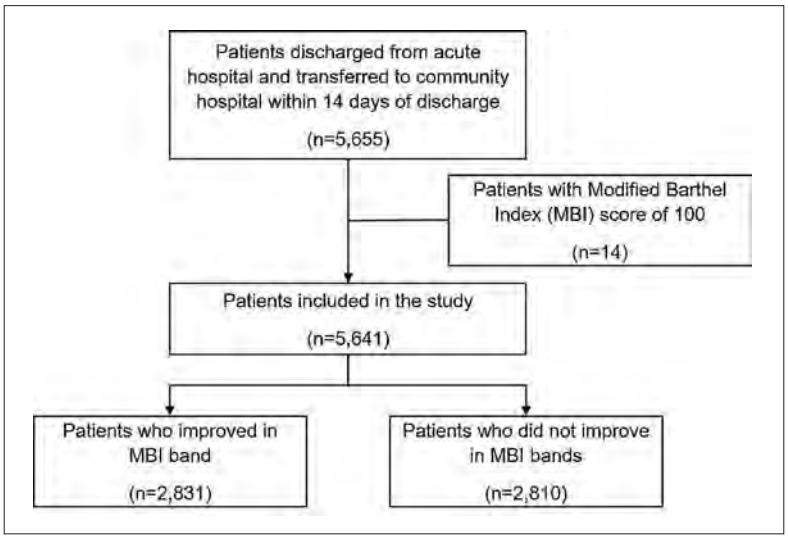

Fig. 1. Participants flow diagram for the study.

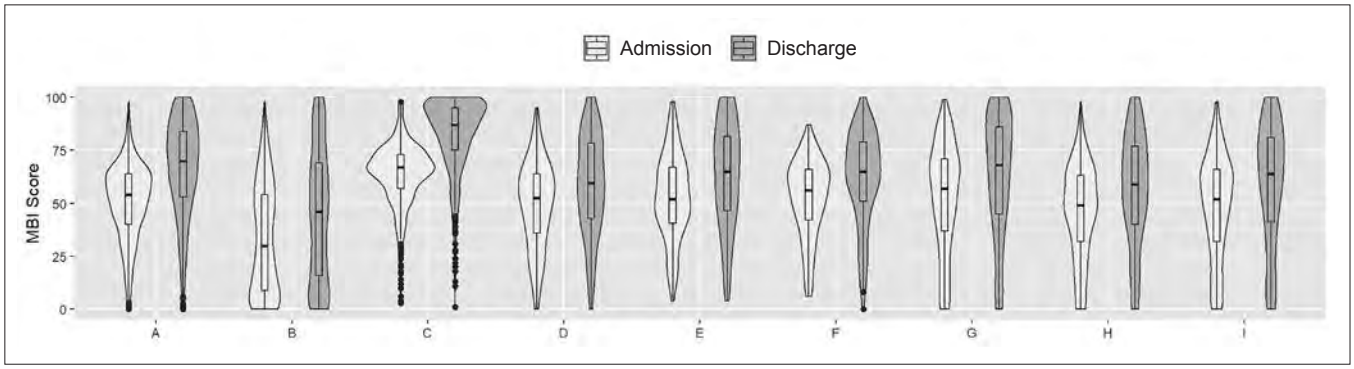

Fig. 2. Distribution of Modified Barthel Index on admission to and discharge from community hospital, stratified by admitting disease condition. (A) Injuries and fractures, (B) stroke, (C) musculoskeletal conditions, (D) cardiac conditions, (E) malignancy and palliative conditions, (F) falls, (G) acute exacerbation of chronic obstructive pulmonary disease, pneumonia and other lower respiratory tract infections, (H) other infections, and (I) others.

community hospital (median 32 days, IQR 23–46 vs 25 days, IQR 14–40; *P*<0.001), were less frail (median Frailty Risk Score 8.1, IQR 3.7–13.8 vs 10.8, IQR 6.0–17.4; *P*<0.001) and had fewer comorbidities (median CCI 2, IQR 0–4 vs 3, IQR 2–5; *P*<0.001). They had lower use of psychotropic medications (43.5% vs 52.0%, *P*<0.001), higher eGFR (≥60mL/min/1.73m^2: 75.6% vs 65.1%, *P*<0.001). Among this group, there was a higher proportion of those with normal level of albumin (22.6% vs 17.9%, *P*<0.001), blood urea (72.0% vs 61.5%, *P*<0.001), haemoglobin (23.9% vs 20.9%, *P*<0.001) and sodium levels (67.6% vs 66.1%, *P*<0.001), in addition to a higher RBC count (median 3.8, IQR 3.4–4.2 vs 3.7, IQR 3.3–4.1, *P*<0.001). Notably, a significantly higher proportion of patients whose discharge diagnosis at the acute hospital was musculoskeletal conditions had improved while those with other conditions did not.

Multivariable analysis

In multivariable regression analyses, age (65–74 years, odds ratio [OR] 0.97, 95% confidence interval [CI] 0.80–1.18; 75–84 years, OR 0.82, 95% CI 0.68–0.99; and ≥85 years, OR 0.63, 95% CI 0.51–0.78; with reference to <65 years), a history of dementia (OR 0.53, 95% CI 0.45–0.64), stroke (OR 0.72, 95% CI 0.62–0.84), psychotropic medication use during the acute hospital stay (OR 0.85, 95% CI 0.75–0.96), lower eGFR (30–59mL/min/1.73m^2 [OR 0.86, 95% CI 0.73–1.02], and <30mL/min/1.73m^2 [OR 0.48, 95% CI 0.36–0.63]), hypoalbuminaemia (mild [OR 0.80, 95% CI 0.69–0.94] and marked [OR 0.63, 95% CI 0.50–0.80]), and moderate to severe anaemia (OR 0.81, 95% CI 0.68–0.97) were associated with lower odds of improvement. However, higher MBI on admission (25–49 [OR 2.30, 95% CI 1.90–2.79], 50–74 [OR 1.83, 95% CI 1.51–2.21] and 75–90 [OR 1.20–2.01]

Table 2. Multivariable logistic regression analysis of epidemiological and clinical risk factors associated with functional improvement

Characteristics	Model 1		Model 2		Model 3		Model 4 (Final model)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Demographics								
Age category								
<65 years	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
65–74 years	0.88 (0.73–1.05)		0.94 (0.78–1.14)		0.93 (0.77–1.13)		0.97 (0.80–1.18)	
75–84 years	0.71 (0.59–0.85)		0.79 (0.66–0.95)		0.78 (0.65–0.94)		0.82 (0.68–0.99)	
≥85 years	0.48 (0.40–0.59)		0.60 (0.49–0.74)		0.58 (0.47–0.71)		0.63 (0.51–0.78)	
Female	1.11 (0.98–1.24)	0.090	1.05 (0.93–1.19)	0.396	1.05 (0.93–1.18)	0.434	1.09 (0.96–1.23)	0.185
Ethnicity								
Chinese	Reference	0.033	Reference	0.165	Reference	0.199	Reference	0.217
Malay	0.81 (0.63–1.04)		0.85 (0.66–1.09)		0.83 (0.65–1.07)		0.87 (0.67–1.12)	
Indian	0.76 (0.60–0.97)		0.80 (0.62–1.02)		0.82 (0.64–1.04)		0.79 (0.61–1.01)	
Others	0.81 (0.60–1.09)		0.88 (0.65–1.20)		0.89 (0.66–1.21)		0.94 (0.69–1.28)	
Details of hospital admission								
MBI score on admission category								
0–24	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
25–49	2.38 (1.98–2.85)		2.20 (1.83–2.65)		2.21 (1.84–2.67)		2.30 (1.90–2.79)	
50–74	2.23 (1.88–2.66)		1.80 (1.51–2.16)		1.79 (1.49–2.14)		1.83 (1.51–2.21)	
75–90	2.03 (1.60–2.57)		1.51 (1.18–1.93)		1.49 (1.16–1.91)		1.55 (1.20–2.01)	
91–99	0.89 (0.49–1.60)		0.62 (0.34–1.12)		0.59 (0.32–1.07)		0.64 (0.35–1.17)	
Diagnosis at discharge from acute care hospital								
Injuries and fractures	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
Stroke	0.60 (0.50–0.73)		0.75 (0.60–0.94)		0.73 (0.58–0.92)		0.70 (0.55–0.88)	
Musculoskeletal conditions	2.12 (1.69–2.65)		1.87 (1.48–2.37)		1.90 (1.50–2.41)		2.06 (1.61–2.64)	
Cardiac conditions	0.48 (0.35–0.67)		0.63 (0.45–0.89)		0.63 (0.44–0.88)		0.64 (0.45–0.91)	
Malignancy and palliative conditions	0.55 (0.39–0.76)		0.54 (0.36–0.79)		0.52 (0.35–0.78)		0.57 (0.38–0.85)	
Falls	0.55 (0.39–0.77)		0.65 (0.46–0.91)		0.64 (0.45–0.90)		0.57 (0.40–0.81)	
AE-COPD, pneumonia and other LRTIs	0.70 (0.57–0.85)		0.78 (0.63–0.97)		0.78 (0.63–0.97)		0.81 (0.65–1.01)	

Table 2. Multivariable logistic regression analysis of epidemiological and clinical risk factors associated with functional improvement (Cont'd)

Characteristics	Model 1		Model 2		Model 3		Model 4 (Final model)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Other infections	0.51 (0.43–0.61)		0.62 (0.52–0.74)		0.62 (0.52–0.74)		0.66 (0.54–0.79)	
Others	0.50 (0.41–0.61)		0.53 (0.43–0.66)		0.53 (0.43–0.66)		0.55 (0.44–0.68)	
Comorbidities								
Frailty Risk Score category								
Low risk (<5)	-		Reference	0.058	Reference	0.175	Reference	0.270
Intermediate risk (5–15)	-		0.89 (0.76–1.03)		0.91 (0.78–1.06)		0.94 (0.80–1.10)	
High risk (>15)	-		0.80 (0.67–0.96)		0.84 (0.70–1.01)		0.86 (0.71–1.04)	
Patients with the following comorbidity								
Dementia	-		0.54 (0.45–0.64)	<0.001	0.54 (0.46–0.65)	<0.001	0.53 (0.45–0.64)	<0.001
Chronic liver disease	-		0.86 (0.68–1.08)	0.192	0.85 (0.67–1.07)	0.174	0.86 (0.68–1.09)	0.217
Diabetes mellitus	-		0.85 (0.75–0.96)	0.008	0.87 (0.77–0.99)	0.032	0.89 (0.78–1.01)	0.071
Renal disease	-		0.76 (0.66–0.87)	<0.001	0.76 (0.66–0.87)	<0.001	1.01 (0.84–1.20)	0.933
Tumour	-		0.95 (0.77–1.18)	0.658	0.96 (0.78–1.19)	0.714	1.08 (0.87–1.35)	0.487
Stroke	-		0.75 (0.64–0.86)	<0.001	0.75 (0.65–0.87)	<0.001	0.72 (0.6–0.84)	<0.001
Congestive heart failure/myocardial infarct	-		0.81 (0.7–0.94)	0.005	0.82 (0.71–0.96)	0.013	0.92 (0.79–1.08)	0.294
Medications prescribed								
Overall psychotropic medications use	-		-		0.87 (0.77–0.98)	0.023	0.85 (0.75–0.96)	0.009
No. of medication on discharge								
<9	-		-		Reference	0.024	Reference	0.132
9–11	-		-		0.81 (0.69–0.94)		0.83 (0.71–0.98)	
12–14	-		-		0.91 (0.77–1.08)		0.95 (0.80 –1.13)	
>14	-		-		0.80 (0.67–0.96)		0.89 (0.74–1.08)	
Length of stay in community hospital	-		-		-		1.01 (1.01–1.01)	<0.001
Laboratory parameters								
eGFR								
≥60mL/min/1.73m^2	-		-		-		Reference	<0.001
30–59mL/min/1.73m^2	-		-		-		0.86 (0.73–1.02)	

Table 2. Multivariable logistic regression analysis of epidemiological and clinical risk factors associated with functional improvement (Cont'd)

Characteristics	Model 1		Model 2		Model 3		Model 4 (Final model)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
<30mL/min/1.73m^2	-		-		-		0.48 (0.36–0.63)	
Unknown	-		-		-		0.59 (0.25–1.38)	
Albumin								
Normal	-		-		-		Reference	0.001
Mild hypoalbuminaemia	-		-		-		0.80 (0.69–0.94)	
Marked hypoalbuminaemia	-		-		-		0.63 (0.50–0.80)	
Unknown	-		-		-		0.89 (0.75–1.07)	
Haemoglobin								
Normal	-		-		-		Reference	0.038
Mild anaemia	-		-		-		0.99 (0.85–1.16)	
Moderate to severe anaemia	-		-		-		0.81 (0.68–0.97)	
Unknown	-		-		-		1.54 (0.31–7.71)	
Sodium								
Normal	-		-		-		Reference	0.013
Mild hyponatraemia	-		-		-		1.01 (0.88–1.16)	
Moderate/severe hyponatraemia	-		-		-		0.64 (0.45–0.93)	
Hypernatraemia	-		-		-		0.56 (0.27–1.14)	
Unknown	-		-		-		1.24 (0.99–1.55)	
Lymphocytes (10^9/L) category								
<1.5	-		-		-		Reference	0.550
≥1.5	-		-		-		0.94 (0.84–1.06)	
Unknown	-		-		-		0.70 (0.15–3.14)	
Model assessment								
Log likelihood	-3642.4		-3569.1		-3560.7		-3464.5	
Likelihood-ratio test *P* value	-		<0.001		0.002		<0.001	
Area under receiver operating curve	0.6701		0.6936		0.6961		0.7240	

AE-COPD: acute exacerbation of chronic obstructive pulmonary disease; CI: confidence interval; eGFR: estimated glomerular filtration rate; LRTIs: lower respiratory tract infections; MBI: Modified Barthel Index; OR: odds ratio

The community hospital that the patient was admitted to was additionally adjusted in all the models (data not shown).

with 0–24 as reference) and longer length of stay at the community hospital (OR 1.01, 95% CI 1.01–1.01) were associated with improvement. Compared with patients admitted for injuries and fractures, patients admitted to community hospital for stroke (OR 0.70, 95% CI 0.55–0.88), cardiac conditions (OR 0.64, 95% CI 0.45–0.91), malignancy/palliative care (OR 0.57, 95% CI 0.38–0.85), falls (OR 0.57, 95% CI 0.40–0.81), AE-COPD/pneumonia/LRTIs (OR 0.81, 95% CI 0.65–1.01), other infections (OR 0.66, 95% CI 0.54–0.79), and all others (OR 0.55, 95% CI 0.44–0.68) were less likely to show improvement in the MBI band. In contrast, patients admitted for musculoskeletal disorders (OR 2.06, 95% CI 1.61–2.64) were more likely to improve (Table 2). Our final model (model 4) achieved an area under the receiver operating curve of 72.4% (fair predictive value).

Stratified analyses showed that history of dementia, history of stroke, psychotropic medication use, eGFR <60mL/min/1.73m^2 and Malay ethnicity were associated with a lower odds of improvement in patients who were admitted to the acute hospital with injuries/fractures. A history of dementia was also associated with lower odds of improvement among those admitted for stroke and other infections. A history of stroke was also associated with lower odds of improvement among those admitted for musculoskeletal conditions (Supplementary Table S1 in online Supplementary Material).

DISCUSSION

In this 3-year retrospective cohort study, we found that half (50.2%) of all patients discharged to a community hospital showed an improvement in MBI band after rehabilitation. Age determined functional improvement significantly in our study. This is consistent with a German study that reported a decrease in relative improvement on MBI scale with increasing age among stroke patients.[21] A similar association was found in a study that assessed the functional capacity using the Functional Independence Measure (FIM).[22]

We found that patients with musculoskeletal conditions had double the odds of improvement during their stay at the community hospital compared to patients admitted to the acute hospital for injuries. This is consistent with a study by Cook et al.[23] The study suggested that long-stay home care patients suffering from musculoskeletal disorders who received physiotherapy and occupational therapy had significantly increased odds of functional improvement.[23] Patients discharged with malignancy, falls, pneumonia and stroke had lower likelihood of improvement. This is consistent with a study conducted in 4 community hospitals in Singapore where the median rehabilitation effectiveness was lower in stroke, pneumonia, cancer and falls patients than in patients admitted for fractures.[24] Nonetheless, many studies have showed that physical and psychosocial rehabilitation can improve symptom control, minimise disability, reduce recurrence of events, facilitate recovery and psychological well-being, and improve quality of life among patients in those groups.[25-28]

The presence of comorbidities has an effect on the potential for functional improvement. Patients with a CCI score of >3 had a statistically significant lower odds of functional improvement by 16% compared to those with scores of ≤3 (results not shown), after adjustment. We observed that having dementia reduced the overall odds of improvement by nearly 50%. An Italian study conducted among elderly patients who were admitted to a rehabilitation unit after acute care hospitalisation reported that dementia was a significant determinant of mobility impairment (OR 3.45, 95% CI 2.39–4.37).[29] Similarly, a higher improvement in cognitive and motor subscales of FIM at discharge in post-hip fractured individuals aged ≥65 years without dementia compared to those with dementia was highlighted in a study performed in Australian public hospitals.[30] One possible reason for the lower rehabilitation effectiveness in dementia patients is a comparatively poorer adherence to the rehabilitation plan, or inability to perform rehabilitation exercises properly.[31] It is important that motor ability and cognitive function are taken into consideration when designing rehabilitation plans. Our study, likewise, found that patients with a pre-existing history of stroke were less likely to improve—a finding consistent with previous studies.[32] Furthermore, patients with severe stroke have been reported to show slower functional recovery compared to those with moderately severe stroke.[33,34]

Psychotropic medication use during acute hospital stay was associated with lower odds of improvement in our study. This is similar to findings in a study among elderly hip fracture patients, which revealed that lower total and motor FIM gains were observed in psychotropic drug users.[35]

Our finding of a significant dose-response relationship between eGFR and functional improvement agreed with observations made in a UK study, which described the correlation between eGFR at admission and improvement in Barthel Index score during rehabilitation.[36] Serum albumin collected at admission[37,38] or after rehabilitation[39] among elderly stroke patients was previously reported as a predictor of functional outcome assessed by the Barthel Index. Consistent with these findings, our results suggested a dose-response relationship between

low serum albumin and the likelihood of functional improvement. We further observed that anaemia was a significant predictor of functional outcome. Chan and Ganasekaran suggested that anaemia could reduce rehabilitation efficacy and affect functional outcomes.[40] Furthermore, anaemic patients were found to encounter more complications compared to non-anaemic stroke patients who required a longer period of stay in the rehabilitation unit.[40,41]

Similar to our findings among patients with principal diagnosis of injury/fracture, a Singapore study on rehabilitation effectiveness and rehabilitation efficiency in stroke patients showed that Malay ethnicity was an independent predictor of poorer rehabilitation outcomes.[42] It is not clear why this should be so, but it may reflect residual confounding of biological factors that are associated with poorer improvement.

This study highlights that patient factors such as the presence of dementia; presence of markers of frailty such as anaemia and hypoalbuminaemia, and pre-existing conditions should be considered by physiotherapists and rehabilitation physicians when designing rehabilitation programmes. In addition, the reason for admission to the acute hospital is also important, and should be taken into account when developing personalised rehabilitation plan. It is possible that patients with multiple factors associated with lower odds of improvement will benefit from customised therapy that optimises the intensity or length of physiotherapy. Intervention studies are needed to establish this.

The strength of our study lies in the use of pragmatic evidence from a real-world setting in which patients with varying types of underlying conditions requiring community hospital stay and physical rehabilitation are included. MBI was assessed by trained healthcare professionals from community hospitals, thus minimising potential measurement error and outcome misclassification. Limitations include the use of MBI cut-offs that are not standardised. As our study population only comprises patients who received hospital-based rehabilitation, our findings may not be generalisable to individuals receiving home- or community-based rehabilitation programmes. We were unable to obtain potentially important social determinants of functional improvement, such as the availability of family and social support or being socially isolated. Indeed, social factors have been reported to be associated with functional decline among community-dwelling elderly.[43] The functional status data of patients prior to acute hospital admission was also not available. Therefore, we cannot assess the extent of functional improvement to premorbid status as a consequence of rehabilitation in the community hospital.

In summary, we demonstrated that certain patient medical factors in relation to medical history and laboratory parameters, as well as the principal reason for admission to acute hospital were associated with functional improvement during the community hospital stay for extended care. Therapists may consider the presence of these high-risk factors in their patients when planning rehabilitation programmes, in order to maximise the likelihood of functional improvement and prevent complications arising from their disability.

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COMMENTARY

Ann Acad Med Singap 2022;51:370-2
https://doi.org/10.47102/annals-acadmedsg.2021461

Congenital cytomegalovirus infection: Advocating for screening and education

Ching Yee Chan [1]*FAMS*, Liying Yang [2]*FAMS*, Jiun Fong Thong [3]*FAMS*

Cytomegalovirus (CMV) infection is the leading non-genetic cause of congenital neurosensory hearing loss in children, accounting for 21% of cases of hearing loss at birth and 25% of deafness at age 4 years.[1] It can also give rise to other serious sequelae such as cerebral palsy, cognitive impairment, seizures and visual impairment.[2] CMV infection in children and adults is frequently either asymptomatic or gives rise to non-specific symptoms such as malaise and pharyngitis.[2] Infected pregnant patients are therefore often unaware of the infection, which leads to missed opportunities for diagnosis of congenital CMV (cCMV) and interventions for the fetus and infant.

Despite the potential harm, awareness of cCMV infection is low among women of reproductive age. A 2012 Singapore study by Lim et al. evaluating the awareness of pregnant women in Singapore about cCMV infection found that only 20% knew of the virus and that none of the participants had been informed about CMV by their obstetrician.[3]

The birth prevalence of cCMV infection is approximately 0.4–6%.[4] This is higher than Down syndrome, for which screening has been offered as a standard part of antenatal care for decades, and also higher than inborn errors of metabolism, for which all neonates in Singapore are offered screening under the National Newborn Screening Programme. Despite this, cCMV screening is currently neither routinely offered in pregnancy nor in newborns, except in selected states in the US and Canada.

Screening for cCMV infection in pregnancy may be performed using CMV immunoglobulin (Ig) M and IgG antibodies as well as IgG avidity testing. This will identify 4 groups of women.

The first group consists of women who have never been infected (IgM and IgG negative), and who are at risk of primary infection. Primary CMV infection in pregnancy is associated with the highest risk (30–35%) of transplacental infection.[5] These women would benefit from antenatal educational interventions aimed at primary prevention of CMV infection.

CMV is transmitted via bodily fluids such as saliva, urine and blood. As infected children may secrete the virus in their urine and saliva for 24 months,[6] having a child in nursery is a major risk factor for primary maternal CMV infection during pregnancy. Hygiene counselling, which includes attention to hand-washing after contact with urine or saliva, avoiding sharing of food and drinks with young children, and not kissing them on or near the mouth, appears to be effective in preventing CMV infection in pregnancy.[7] These recommendations are simple and 98% of mothers in Singapore who were surveyed felt it was easy to adopt them.[3] They are also recommended by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, as well as the French National College of Obstetricians and Gynaecologists.

The second group would be those who are IgM negative and IgG positive, indicating a past infection. While these women have only a 0.51% chance of reactivation of CMV, or infection with a different strain of virus during pregnancy, non-primary infections make up the majority of maternal infections during pregnancy due to the relatively high seroprevalence rates in both developing and developed countries.[5] Asymptomatic babies of these patients may be screened for cCMV within the first 21 days of life as positive tests beyond this window cannot differentiate between congenital and acquired infections. This has been traditionally done using urine culture, but salivary polymerase chain reaction (PCR) is an alternative technique that is highly sensitive, specific and more easily performed.[8] Babies who test positive should undergo intensified follow-up screening as 10–12% of asymptomatic neonates may develop delayed, progressive hearing loss, and a smaller proportion may develop visual or neurodevelopmental disabilities.

The third group of women who test positive for both IgM and IgG may have avidity testing done to determine timing of infection, as IgM antibodies can persist for several months after infection. A high IgG avidity would indicate past infection, whereas a low IgG avidity is highly suggestive of a recent primary infection and a

[1] Department of Otolaryngology, KK Women's and Children's Hospital, Singapore
[2] Department of Obstetrics and Gynaecology, Singapore General Hospital, Singapore
[3] Department of Otorhinolarygology-Head & Neck Surgery, Singapore General Hospital, Singapore
Correspondence: Dr Ching Yee Chan, Department of Otolaryngology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: chan.ching.yee@singhealth.com.sg

fetus at risk of cCMV. The patients in the latter group should be offered amniocentesis for PCR amplification of CMV DNA to diagnose fetal CMV infection.[6] This is recommended to be done 7–8 weeks after maternal infection, and after 21 weeks when fetal urine output accounts for the majority of amniotic fluid volume. Ville et al. have also recently demonstrated that chorionic villus sampling for viral DNA PCR at 13–14 weeks has good positive predictive values of 100% and negative predictive value of 91%, which may enable earlier diagnosis of fetal infection.[5] Patients with positive amniocentesis results can be followed up with serial ultrasound scans with or without fetal therapy. Ultrasound scans will enable detection of signs such as ventriculomegaly, microcephaly, echogenic bowel, hydrops and intrauterine growth restriction, which can inform fetal prognosis.

The fourth group of women are those who test positive for IgM but negative for IgG. While this may suggest a recent active primary infection, it may also be a false positive, hence IgG will need to be repeated in 10–14 days. If this turns positive, IgG avidity testing can be done to confirm recent primary infection.

When should maternal screening be done? The timing is important. Recent evidence suggests that all long-term sequelae (hearing loss and neurodevelopmental delay) develop in fetuses infected in the first trimester.[9] Screening should therefore be done by 14 weeks of gestation to detect these women who have the highest risk of having an affected neonate.[5]

From a purely practical standpoint, an opportune time for CMV screening would be at the time of the routine antenatal bloods at around 11–14 weeks. Earlier screening at the time of the booking visit has also been advocated,[5] as this not only enables earlier detection of infection occurring in the peri-conceptional period and start of the first trimester, but also early hygiene counselling of susceptible women. However, this will mean that patients will need to be re-screened at the end of the first trimester so as not to miss late first trimester infections. Further studies to compare the feasibility, acceptability and cost-effectiveness of the various screening protocols will be beneficial.

Resistance to CMV screening may be partly due to historical reasons, as fetal CMV infection used to be challenging to diagnose because of poor serological assays and difficulty in differentiating between recent and old infections. This is however no longer the case. Maternal infection can be sensitively and reliably diagnosed with CMV serology and avidity testing.[10,11] A positive IgM and IgG with a low IgG avidity indicates infection in the preceding 3 months with a sensitivity and specificity of over 90%,[12] while amniocentesis for fetal infection has a 100% specificity and 85–95% sensitivity to detect fetal infection.

Some have proposed routine ultrasound scans be used to screen for CMV infection. These have however been reported to be able to identify only 26% of infected fetus that developed long-term sequelae, in contrast to targeted ultrasound performed after known fetal infection, which has a high sensitivity (91%) and negative predictive value (96%) for predicting long-term complications.[13] This approach also precludes primary prevention with hygiene education, and early initiation of treatment for secondary prevention of CMV infection.

Is there effective treatment for secondary prevention of cCMV infection or tertiary prevention of cCMV sequlae? A recent randomised trial looking at the efficacy of high-dose oral valaciclovir (8g/day) showed a 71% reduction in congenital infection in women with primary infection between -3 and 12 weeks gestation.[14] In addition, a phase II trial of oral valaciclovir reported a significantly higher chance of delivering an asymptomatic neonate versus the untreated group.[15] Hyperimmunoglobulin (HIG) may also be effective if started early after maternal infection; a non-randomised study by Kagan et al. where HIG was started at an average of 10 days after maternal infection reported a 7.5% risk of fetal transmission with high-dose HIG (200UI/kg) versus 35% in untreated women.[16] Even so, the safety and efficacy of HIG needs further evaluation as 2 other randomised studies where treatment was initiated later did not show any benefit and 1 reported an increase in prematurity in the treated group.[17,18]

Another concern raised about screening is related to the unpredictability of the postnatal course. While it is true that this can result in parental anxiety and may lead to the termination of pregnancies in which the fetuses might not have developed long-term sequelae, this uncertainty is a common feature of many prenatally diagnosed conditions and is not unique to cCMV infection. We are of the opinion that patients and their partners would benefit from the autonomy and knowledge to make informed decisions about their pregnancies. Indeed, the 2012 study by Lim et al. showed that the majority of mothers would like to be given the option of receiving prenatal CMV serologic screening, and most would choose it if it was offered by their obstetrician.[3]

The cost-effectiveness of universal screening has been explored in a previous study, which suggested that universal screening would be cost-effective if prevention of fetal transmission was 30% effective and the primary

CMV incidence was ≥0.82%.[19] The incidence of primary CMV infection in Singapore is currently not known and would be an important area for further study. However, with valaciclovir appearing to reduce the risk of transmission by >70%, universal screening is likely to be cost-effective even at a lower incidence of primary CMV infection. Screening of asymptomatic infants with cCMV also allows for early diagnosis of affected children; this can lower the costs currently incurred working up infants and children with delayed onset disabilities, reduce the stress and anxiety caused by an unknown diagnosis, and indirectly affect future reproductive decision-making by excluding genetic causes.

Finally, vaccine development has been proposed as a more effective way for CMV prevention. There are currently several vaccine candidates, including a messenger RNA vaccine that is undergoing phase II trials.[20] CMV screening, however, remains an important step to reduce fetal morbidity from cCMV infection while a safe and efficient vaccine is being developed.

In conclusion, there is a dire need to improve awareness of CMV in the medical community and couples of reproductive age, and to consider introducing screening for cCMV in pregnancy and newborns. Similar to Down syndrome screening, parents should have the opportunity to make an informed choice on whether they wish to proceed with testing. Mothers should not find out retrospectively about cCMV, nor should they feel guilty knowing it could have been prevented.

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Ann Acad Med Singap 2022;51:373-5
https://doi.org/10.47102/annals-acadmedsg.2021459

Attitude towards screening for congenital cytomegalovirus infection in newborns in Singapore

Dear Editor,

Cytomegalovirus (CMV) infection is the most common congenital infection.[1] A systematic review that included 77 studies from 36 countries reported that the overall prevalence of CMV was 0.67% in their newborn population.[1] Among newborns with CMV, it was estimated that 15–20% will suffer from potentially deleterious effects including permanent sensorineural hearing loss, intrauterine growth restriction, visual impairment, cerebral palsy and seizure disorders.[2] In fact, congenital CMV (cCMV) is the leading cause of non-genetic sensorineural hearing loss worldwide.[3] While some infected newborns have obvious symptoms, the majority (90%) are asymptomatic, making detection difficult without screening. Asymptomatic newborns remain at risk from long-term sequelae.[4]

Prevalence of cCMV infection in Singapore is unknown,[1] with little publicity about the infection and its complications. A Singapore study reported that only 20% of women who attended a specialist obstetrics and gynaecology clinic in Singapore were aware of CMV and none of their physicians had informed them about it.[5]

Intrauterine CMV infection may occur as primary infection during pregnancy, a reactivation of a previous infection, or an infection caused by a different CMV strain.[6] The transmission risk to the fetus is much higher with primary infection compared with non-primary infection (30–35% versus 1.1–1.7%).[6] Despite this, two-thirds of infection in infants are caused by non-primary maternal infections due to high CMV seroprevalence in adults.[6] In one study, 87% of pregnant women in Singapore was found to be seropositive.[7]

To date, there is no available vaccine for CMV.[8] Infection control measures remain the mainstay to reduce CMV prevalence. In 2015, the International Congenital Cytomegalovirus Recommendations Group convened and recommended consideration to be given for universal neonatal cCMV screening to facilitate early detection and intervention for sensorineural hearing loss and developmental delay.[9] Serologic or virologic CMV screening during antenatal and/or neonatal periods is offered in parts of Europe, the US and Australia.[1,9] However, screening is not discussed nor routinely offered in Asian countries including Singapore.[1] As such, the aim of our study was to evaluate the awareness and attitude of the public towards cCMV infection and neonatal screening. Information gathered can be used to understand the factors that may guide decision-making if screening was to be implemented.

A questionnaire study was performed between May 2019 and June 2020, on adults of reproductive age attending Otorhinolaryngology, Obstetrics and Gynaecology, and Neonatal and Developmental Medicine clinics at the Singapore General Hospital. The questionnaire was self-administered and anonymous, and structured such that participants would be educated on cCMV infection and newborn screening while being assessed (Appendix A in online Supplementary Material). Data collected were analysed using SPSS Statistics version 25 (IBM Corp, Armonk, US). A P value of <0.05 was considered significant.

A total of 709 responses were collected. None of the questionnaires were excluded because of incomplete entry. Despite good awareness of congenital infections (81.4%), there was low awareness of cCMV prevalence (15.7%) and cCMV screening (10.2%). Only 7.4% were aware that diagnosis can only be made before the first 3 weeks of life. There was a significant correlation between the respondent's level of education and awareness of congenital infections. Participants with tertiary education qualification (n=542) were more likely to be aware of congenital infections than those with primary (n=8, odds ratio [OR] 3.95, 95% confidence interval [CI] 1.099–14.286, P=0.036) or secondary education (n=62, OR 4.525, 95% CI 2.703–7.576, P<0.001).

Few participants (13.7%) were cognisant that babies with cCMV can be asymptomatic at birth. The proportions of respondents who were aware of cCMV causing progressive hearing loss, visual impairment, developmental delay and seizures were 15.6%, 15.6%, 16.7% and 14.4%, respectively. Majority were keen for universal newborn cCMV screening to be offered (589/659, 89.4%). Demographics of participants and their attitude towards cCMV testing are shown in Appendix B in online Supplementary Material. On multivariate analysis, no significant correlation was found between the respondents' demographics and their attitude towards screening. The reasons for being keen or against cCMV screening are shown in Fig. 1. Notably, some participants commented that they still did not know what cCMV was at the end of the questionnaire.

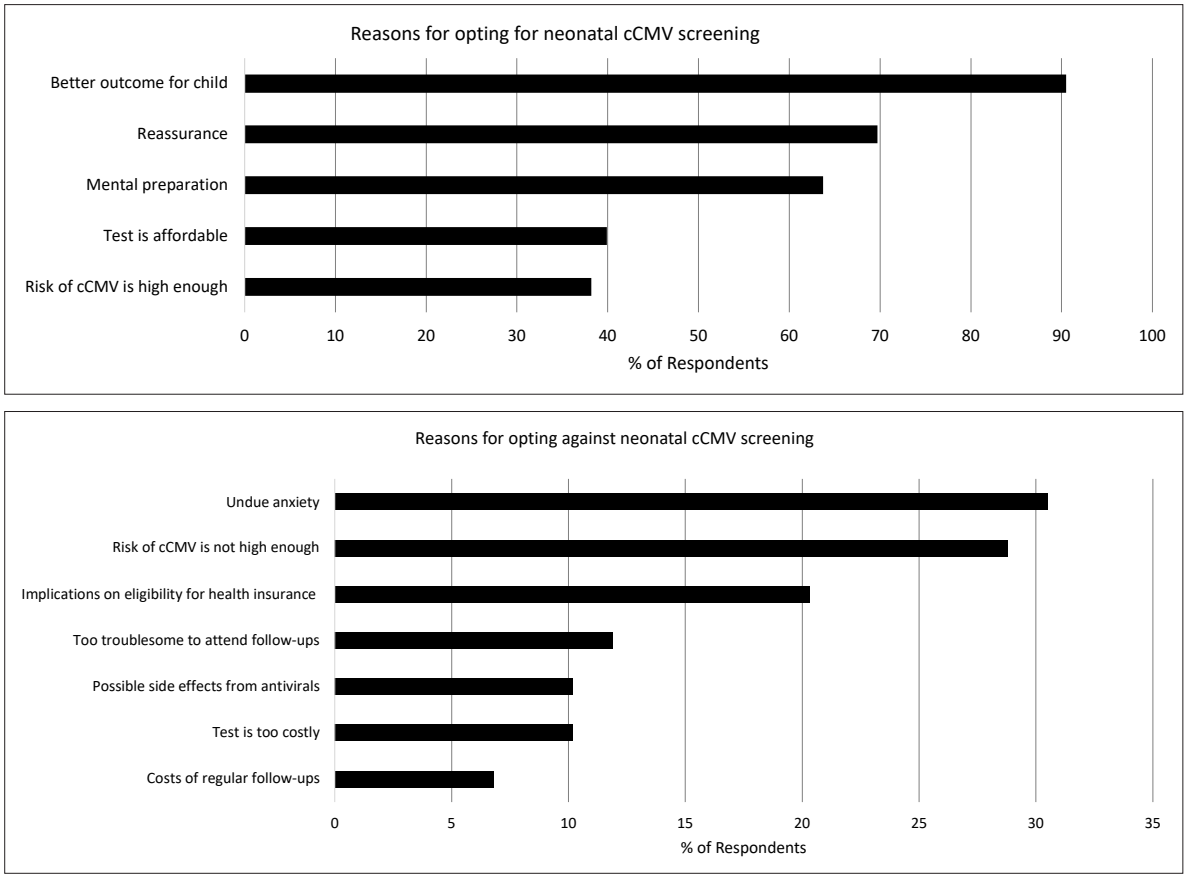

Fig. 1 Reasons for opting for and against neonatal congenital CMV (cCMV) screening.

From our study, it is apparent that awareness of CMV infection and its implications on infected newborns is low among the surveyed public. This is despite CMV being the most common congenital infection. As a priority, public education is of paramount importance. Primary prevention for seronegative mothers through infection control measures is simple and cost-effective.[9] Antenatal counselling of pregnant women attending outpatient clinics provides further opportunity to reduce mother-to-child CMV transmission. Simple hygiene precautions include not sharing food, drinks and utensils with young children; avoiding contact with saliva when kissing a child; and washing hands thoroughly after changing diapers, feeding a child or wiping a child's nose or saliva. These simple measures also help to prevent reinfection with a new CMV strain.

However, these measures have little impact on maternal CMV reactivation during pregnancy. Hence, in tandem with primary prevention, screening for cCMV should be considered to allow early detection and intervention. Having a known diagnosis also helps to minimise unnecessary investigations should the child develop symptoms in the future. Majority of respondents in our study were keen to be given the option of newborn cCMV screening. Since few respondents were concerned about the cost of screening, it was unsurprising that we found no significant correlation between combined family income and attitude towards screening.

Trials are currently ongoing to assess the risks and benefits of antiviral treatment in asymptomatic, mildly symptomatic or isolated sensorineural hearing loss.[9] Assuming a modest benefit of antiviral treatment, studies have shown cCMV screening to be cost-effective.[10] Targeted screening for newborns of seropositive mothers is also a consideration. Screening using salivary CMV polymerase chain reaction (PCR) can be studied as part of a comprehensive newborn screening programme. Collecting saliva from newborns is easier than collecting urine. In addition, salivary PCR testing has been shown to be possibly more sensitive compared to urinary PCR.[9] Akin to genetic testing, adequate counselling on the implications of cCMV testing for the child and family is important prior to testing.

Until a vaccine becomes available, the importance of primary prevention through infection control measures and public education cannot be over-emphasised.

Secondary prevention with prenatal serologic screening for seroconversion coupled with immunoglobulin G avidity testing is another consideration. Ultimately, primary, secondary and tertiary prevention measures should be considered and implemented in tandem so that the outcome of newborns can be improved.

Acknowledgements

We would like to express our special thanks to the participants of this survey, SSN Sharon Yam of the Neonatal and Developmental clinic, Sister Chun Yan Yu of the Obstetrics and Gynaecology clinic, and the staff at the Otorhinolaryngology clinic, Singapore General Hospital for their help in administering the questionnaires in their respective clinics.

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Eugene Ren Jie Lim [1]*MBBS*, Selina Kah Ying Ho [1]*MMed*, Daisy Kwai Lin Chan [2]*MMed*, Tze Tein Yong [1]*FRCOG*, Jiun Fong Thong [1]*FAMS*

[1] Department of Otorhinolaryngology-Head and Neck Surgery, Singapore General Hospital, Singapore
[2] Department of Neonatal & Developmental Medicine, Singapore General Hospital, Singapore
[3] Department of Obstetrics & Gynaecology, Singapore General Hospital, Singapore

Correspondence: Dr Jiun Fong Thong, Department of Otorhinolaryngology Head and Neck Surgery, Singapore General Hospital, Level 5 Academia, 20 College Road, Singapore 169856.
Email: thong.jiun.fong@singhealth.com.sg

Ann Acad Med Singap 2022;51:376-7
https://doi.org/10.47102/annals-acadmedsg.2022106

Neuralgic amyotrophy in COVID-19 infection and after vaccination

Dear Editor,

Various neurological manifestations associated with coronavirus disease 2019 (COVID-19) have been described,[1] conditions which left a significant proportion of patients with permanent disability. Continued vigilance is crucial with emergence of new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants that cause the disease. Vaccination against COVID-19 remains the key strategy to reduce disease severity and transmission.[2] However, the novel mRNA technology and reports of neurological adverse effects raise concerns about COVID-19 vaccine safety, especially since multiple doses are needed to combat the waning immunity of such vaccines.[3]

Neuralgic amyotrophy (NA), or Parsonage-Turner syndrome/brachial neuritis, is characterised by male predisposition, severe pain and limb weakness in the 3rd to 7th decade of life.[4] It has rarely been reported in COVID-19 infections or within 6 weeks of vaccination.[5] Hypothesised causes focus on immune-mediated processes,[3] although the underlying pathophysiology remains unclear. With the COVID-19 pandemic, the challenge lies in differentiating the trigger for NA in vaccinated individuals who develop breakthrough COVID-19 infections. Comparisons of disease characteristics in COVID-19 patients with those occurring after COVID-19 vaccinations may shed some light, but such data are lacking. We illustrate a case and review the literature by searching PubMed, Embase and Google Scholar from 1 December 2019 to 30 November 2021 using the following keywords: "Parsonage-Turner Syndrome", "brachial plexopathy", "brachial neuritis", "brachial plexitis", "neuralgic amyotrophy", "SARS-CoV-2" and "COVID-19". We analysed cases with confirmed COVID-19 (World Health Organization guidelines)[6] occurring in symptomatic individuals and in those presenting within 6 weeks of COVID-19 vaccination (time frame conventionally used to study vaccine-related adverse events).[7] Cases with inadequate data, unclear temporality and non-English reports were excluded. The study was approved by the Singapore Health Services institutional review board (CIRB 2020/2410), and waiver of consent was granted.

A 34-year-old healthy man presented on day 4 of symptomatic COVID-19 with a 3-day history of shoulder pain, weakness and numbness of the left upper limb. There was no trauma, recent neck manipulation nor other constitutional symptoms. He had received the Moderna mRNA-1273 vaccines on 3 and 24 July 2021, approximately 4 months prior to his presentation.

Clinical examination revealed diminished left biceps reflex, weakness of the left shoulder, elbow, wrist and finger movements (Medical Research Council [MRC] scale grade 3), as well as patchy numbness of the left arm, forearm and anatomical snuffbox, raising the suspicion of NA. There was no winging of the scapula.

Investigations including full blood count, serum electrolytes, liver enzymes, erythrocyte sedimentation rate, C-reactive protein and chest X-ray were unremarkable. A contrast-enhanced magnetic resonance imaging (MRI) of the brachial plexus (Figs. 1A and 1B), performed on day 3 of neurological symptoms, showed increased signal along the course of the distal trunks and divisions of the left brachial plexus, consistent with the clinical suspicion. MRI cervical spine showed mild spondylosis.

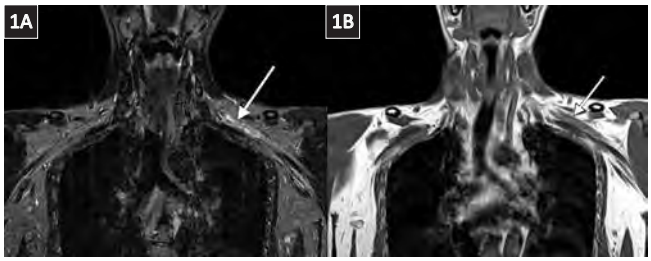

Fig. 1. (A) Magnetic resonance imaging (MRI) of brachial plexus coronal short tau inversion recovery (STIR) sequence shows mildly increased signal along the course of the distal trunks and divisions of the left brachial plexus (white arrow). (B) MRI of coronal T1 sequence shows partial effacement of intervening fat planes between the nerves (white arrow), indicating inflammation in all trunks, divisions and cords of the brachial plexus.

He improved remarkably on day 13 with conservative management. Pain and numbness resolved, while motor power improved to approximately MRC grade 4 across all ranges of motion. Unfortunately, he defaulted his outpatient follow-up.

Our literature search yielded 12 cases of NA in patients with COVID-19 infection—8 critical and 4 mild (Supplementary Table S1 in online Supplementary Material)—and 8 after COVID-19 vaccinations—6 Pfizer-BioNTech BNT162b2, 2 Moderna mRNA-1273, and 3 after first dose (Supplementary Table S2). Both groups share similar demographics, clinical features and anatomical involvement (Table S3). Common to both groups is a greater predisposition for middle-aged males (median age 52 years in COVID-19 patients versus 49.5 years in those after recent vaccination), main clinical

manifestations of pain and weakness, and predominant involvement of the brachial plexus (Tables S1 and S2).

The median latency of NA was longer in COVID-19 patients than in those after recent vaccination (21 vs 8 days, *P*=0.02) and may be explained by difficulty in confirming the diagnosis in critically ill COVID-19 patients in whom symptoms may not be apparent while intubated. Persistent shoulder pain and limb weakness after recovery from critical COVID-19 should raise suspicion of NA. Our patient had mild symptomatic COVID-19 and a short latency of 2 days. His 2-dose COVID-19 vaccination was completed about 4 months prior. The temporal relationship to COVID-19 infection and the short latency period suggested either a para-infectious mechanism or direct neuroinvasion.[8] Among 246 NA cases unrelated to COVID-19 infection nor vaccination, majority occurred 1–7 days after a postulated antecedent event; 65.3% of cases that followed infection similarly occurred in this time interval.[9] Unlike the majority with involvement of the upper/middle trunks, our patient had features suggestive of pan-brachial plexopathy.

Sensorimotor axonal involvement is commonly seen in electrodiagnostic studies in both groups.[9] Of those with brachial plexus involvement, COVID-19 patients appear to have a predilection for the upper/middle trunk (Table S1) while those recently immunised with COVID-19 vaccines seemed to predominantly involve the lower trunk (Table S2). In addition, 3/12 COVID-19 patients had bilateral brachial plexus involvement, while none with recent vaccination had bilateral involvement. These differences were however not significant, likely due to the small number of patients in this review and the patchy nature of brachial plexus inflammation.

MRI neurography/brachial plexus is a sensitive imaging modality to diagnose NA early, as shown by the positive imaging findings in our patient on day 3 of neurological symptoms. This is useful in patients who cannot undergo electrodiagnostic testing due to COVID-19 infection control measures; in those who present early before sufficient time has passed for denervation to appear on electrodiagnostic tests; and to exclude other musculoskeletal pathologies. MRI features may include neurogenic muscle oedema, muscle atrophy and fatty infiltration.[10]

Treatment outcomes were similar in both groups, regardless of corticosteroid effect. Notably, complete recovery was observed in only a minority of patients, possibly due to the short follow-up period (Table S3). As recovery is often protracted in NA, studies bearing data from longer term follow-up will be helpful. Currently, there is no conclusive evidence of the superiority of corticosteroid use in treatment of NA.

Our study was limited by the small number of patients and incomplete outcome data. Therefore, the absence of significant differences in demographics or NA characteristics between COVID-19 patients and those with recent COVID-19 vaccination may be difficult to conclude.

NA may rarely occur early in mild COVID-19 and after recent vaccination. The presence of shoulder pain and limb weakness should prompt suspicion for NA, to perform further evaluation with early MRI and subsequent electrodiagnostic studies.

Availability of data and materials

All anonymised data relevant to the study in the article and Supplementary Material are available upon reasonable request.

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Gee Jin Ng [*1]*MRCP*, Yi Rong Chiew [*1]*MRCP*, Yongyao Kong [1]*MRCP*, Jasmine Shimin Koh [1]*MRCP*

[1] Department of Neurology, National Neuroscience Institute, Singapore
* Joint first authors

Correspondence: Dr Gee Jin Ng, Department of Neurology, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: ng.gee.jin@singhealth.com.sg

Ann Acad Med Singap 2022;51:378-80
https://doi.org/10.47102/annals-acadmedsg.202216

Perception of disease, well-being and financial burden by patients with chronic hepatitis B: A self-reported assessment

Dear Editor,

Chronic hepatitis B (CHB) infection affects approximately 248 million individuals in the world[1] and 3.6% of the Singapore population.[2] Given the natural history of CHB, regular surveillance with blood tests is necessary to ensure early detection of complications such as cirrhosis and hepatocellular carcinoma in patients. Our study aimed to evaluate patients' perception of CHB, general and emotional well-being, and financial burden as a result of CHB.

A survey was conducted among 520 patients with CHB who have been followed up at Singapore General Hospital in a hepatitis B virtual monitoring study.[3] There were 194 patients who were on treatment (OT) and 326 patients not on treatment (N-OT) for CHB at the time of the survey. All survey participants were stable and chronically infected with hepatitis B virus without evidence of hepatocellular carcinoma or decompensated liver disease. Patient consent was obtained and the study was approved by SingHealth Centralised Institutional Review Board (IRB reference CIRB 2013/474/E and 2014/830/E).

The survey utilised a questionnaire on patient demographics, socioeconomic status, experience with care, health status, health beliefs and non-medical cost of care (in terms of time spent, financial burden, loss in productivity for patient and caregiver) (Appendix in Supplementary Material in the online version of this article). In the section on caregivers, patients answered on behalf of their caregiver. The survey was conducted in both English and Mandarin.

The majority (61.1%) of the 520 patients surveyed were >55 years old. Chinese ethnicity made up the majority (97.3%) of the respondents.

Knowledge and perception of the disease. There were 77.5% of patients who rated regular blood tests as very important, and the proportion did not vary between the OT and N-OT groups (78.8% versus 76.6%, P=0.57). However, in the follow-up question regarding respondents' understanding of the purpose of blood tests, a significant number were not sure of its purpose and implications. Although a majority of patients in both groups were aware that the blood tests were done in relation to hepatitis B, 40.2% of patients in the OT group and 31.9% in the N-OT group had the perception that blood tests were done to "check if I still have hepatitis B", reflecting their false understanding that there is a curative intent with treatment and follow-up for CHB. Only 40.2% in the OT group and 76.9% in the N-OT group selected the correct option for purpose of monitoring for the development of liver complications from CHB.

General health and well-being. When respondents were asked to rate their general health as excellent/very good/good/fair/poor, most rated their general health as good, very good or excellent, although a significant 22.4% of patients rated their general health as fair or poor. This was similar in both the OT and N-OT groups (22.7% versus 22.1%, P=0.88).

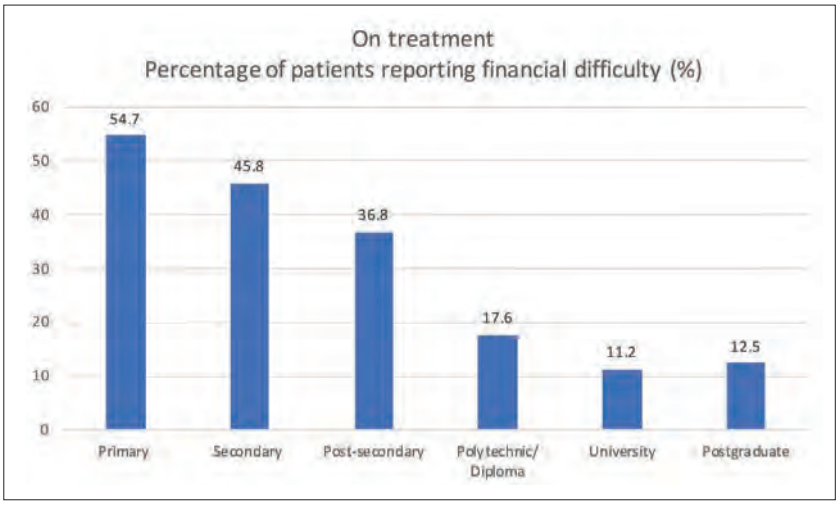
General financial status. Financial status was ranked from A to D as:

A. After paying the bills, you still have enough money for special things that you want
B. You have enough money to pay the bills, but little spare money to buy extra or special things
C. You have money to pay the bills, but only because you have to cut back on things
D. You are having difficulty paying the bills, no matter what you do

In the present study, we defined financial difficulty as ranks C or D. The percentage of respondents reporting financial difficulty was significantly higher in the OT group than the N-OT group (38.7% vs 19.4%, P<0.001). This showed that treatment for CHB had an impact on patients' financial burden (Figs. 1A and 1B).

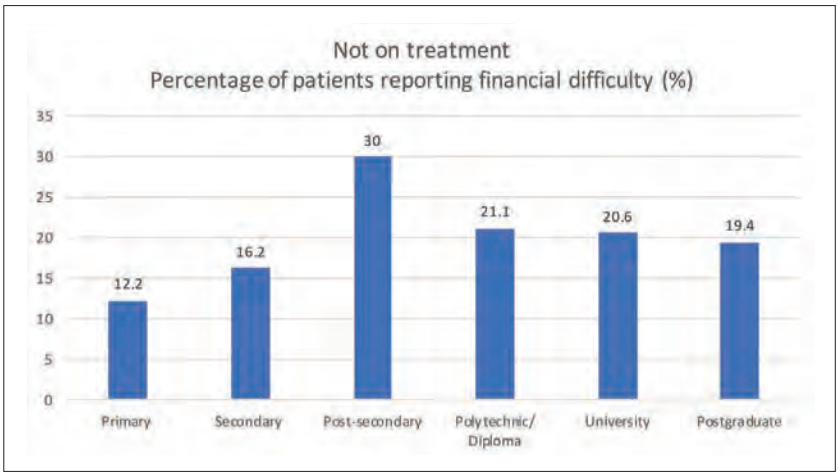
We further analysed the financial impact of CHB in the OT and N-OT groups based on the educational background of patients. In the OT group, financial difficulty was significantly higher in the group with secondary school or below education compared to the group with above secondary school education (49.6% vs 20.0%, P<0.001). Whereas in the N-OT group, there was no significant difference in financial difficulty between the 2 education groups, (14.9% vs 22.5%, P=0.089). In Singapore, the average number of years of education by adults >25 years old are 10.9 years and 11.7 years for female and male sex, respectively, corresponding to the completion of secondary school.[4]

To the best of our knowledge, the present study is one of the few to assess the perception of CHB and disease



On treatment group	Total	Secondary school and below[a]	Post-secondary school and above[b]	*P* value
	n=193[c]	n=123	n=70	
Financial difficulty, no. (%)	75 (38.9)	61 (49.6)	14 (20.0)	<0.001

Fig. 1A. Self-reported financial difficulty (rank C and rank D) by education level in group on treatment for chronic hepatitis B.
[a] Includes secondary school, primary school and below
[b] Includes post-secondary (non-tertiary, general or vocational), polytechnic, university and postgraduate
[c] Only 193 patients of the OT group completed this section of the questionnaire



Not on treatment group	Total	Secondary school and below[a]	Post-secondary school and above[b]	*P* value
	n=325[c]	n=134	n=191	
Financial difficulty, no. (%)	63 (19.4)	20 (14.9)	43 (22.5)	0.089

Fig. 1B. Self-reported financial difficulty (rank C and rank D) by education level in group not on treatment for chronic hepatitis B.
[a] Includes secondary school, primary school and below
[b] Includes post-secondary (non-tertiary, general or vocational), polytechnic, university and postgraduate
[c] Only 325 patients of the N-OT group completed this section of the questionnaire

burden from a patient's point of view. A recent study on the knowledge of chronic liver diseases in Singapore showed that the public's overall knowledge about CHB, although better compared to hepatitis C, is still suboptimal.[5] Despite 77.5% of patients rating the need for regular follow-up and blood tests as very important, a proportion of them did not fully understand the rationale of regular follow-up, blood tests and scans. In this aspect, patient education could focus on the natural history of CHB and reasons for regular blood tests and follow-up clinic visits. Such education, if constrained by time in the clinic, may be augmented by nurse-led initiatives or via virtual education platforms.[3]

Treatment for CHB posed a financial burden for patients, and for patients with lower educational levels. A lower education level is in turn often associated with lower income. Currently, government or private insurance does not cover outpatient expenses for CHB. For this group of patients, the use of generic medications has reduced treatment costs.

In conclusion, there is room for improvement of patients' understanding of CHB and the need for follow-up clinic visits. CHB was significantly more of a financial burden in patients with lower educational levels as compared to patients from higher educational levels.

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Ruojun Ding *[1]*MRCP*, Gayathry Morvil *[1]*MBBS*, Boon-Bee George Goh [1,2]*MRCP*, Thinesh Lee Krishnamoorthy [1,2]*MRCP*, Pei-Yuh Chia [4]*BScN*, Hiang-Keat Tan [1,2]*MRCP*, Victoria Sze-Min Ekstrom [1,2]*MRCP*, Chang-Chuen Mark Cheah [1,2]*MRCP*, Jin-Yang Terence Tan [1,2]*MRCP*, Pek-Siang Edmund Teo [3]*MSc*, Pik-Eu Jason Chang [1,2]*MRCP*, Chee-Kiat Tan [1,2]*MRCP*, Xiaohui Xin [3]*MA*, Wan-Cheng Chow [1,2]*MRCP*, Rajneesh Kumar [1,2]*MRCP*

[1] Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore
[2] Duke-NUS Medical School, Singapore
[3] Health Services Research Unit, Research Office, Singapore General Hospital, Singapore
[4] Department of Nursing, Singapore General Hospital, Singapore

Correspondence: Rajneesh Kumar, Department of Gastroenterology and Hepatology, Singapore General Hospital, Outram Rd, Singapore 169608.
Email: rajneesh.kumar@singhealth.com.sg
* Joint first authors

Ann Acad Med Singap 2022;51:381-3
https://doi.org/10.47102/annals-acadmedsg.2021470

Safe time interval for screening estimated glomerular filtration rate prior to gadolinium-enhanced MRI scan

Dear Editor,

Magnetic resonance imaging (MRI) contrast media are commonly used in medical imaging and are usually gadolinium-based contrast agents (GBCAs). They can be divided into 3 groups. Group I consists of compounds with linear molecular structures. Group II consists of compounds with macrocyclic molecular structures. Group III currently includes only gadoxetate disodium, which is a new generation GBCA with a linear molecular structure and partial biliary excretion.[1]

Nephrogenic systemic fibrosis (NSF) is associated with the use of GBCAs. NSF is a systemic fibrosing condition involving various organs, particularly the skin. It is potentially fatal, particularly in patients with significant renal impairment.[2] Screening for impaired renal function in patients prior to performing a contrast-enhanced MRI scan is therefore important to guide and determine suitability for contrast administration. This is usually done using the estimated glomerular filtration rate (eGFR). While eGFR as a surrogate measure for renal function has limitations, its use as a rapid point-of-care test (POCT) is adequate in most clinical settings, including for contrast administration.[3,4]

There are several established international guidelines on timing of eGFR for patients requiring GBCA administration. In Singapore, the American College of Radiology (ACR) guidelines are used and appear to be the most stringent in terms of the recommended time of eGFR testing.[5] For example, for outpatients with chronic kidney disease (CKD) stage 3a renal impairment based on the Kidney Disease: Improving Global Outcomes criteria (eGFR 45–59mL/min/1.73m^2), ACR recommends an eGFR measured within 6 weeks of the MRI study. For outpatients with stage 3b renal impairment (eGFR 30–44mL/min/1.73m^2), ACR recommends eGFR obtained within 2 days of the MRI study. For patients with eGFR <30mL/min/1.73m^2, contrast is to be avoided.

However, group I GBCAs, associated with the highest risk of NSF, are virtually not used in clinical practice in Singapore. There is evidence that risk of unconfounded NSF in groups II and III GBCAs is almost negligible in patients with eGFR ≥30mL/min/1.73m^2.[3,6] Based on this, the latest available ACR guidelines at the time of our study may potentially result in repeated eGFR testing in the interval between eGFR screening and GBCA administration.

We sought to establish if a longer time interval between eGFR screening and GBCA administration than that proposed by the ACR guidelines would be safe in clinical routine, in an outpatient setting. We also sought to identify risk factors that may lead to worsening of eGFR. These factors can help to identify patients who would likely still require eGFR testing on the day of the MRI scan.

We reviewed all outpatients who presented to the radiology department from 1 November 2019 to 31 June 2020 for a contrast-enhanced MRI scan and underwent POCT for eGFR ($eGFR_{POCT}$) based on the ACR guidelines. Prior eGFR result ($eGFR_{prior}$) and same-day $eGFR_{POCT}$ were compared. The time interval between $eGFR_{prior}$ and $eGFR_{POCT}$ was divided into <3 months, 3–6 months and >6 months. Patients were grouped according to $eGFR_{prior}$ into Group A (eGFR ≥60mL/min/1.73m^2), Group B (eGFR 45–59mL/min/1.73m^2) and Group C (eGFR <45mL/min/1.73m^2), reflecting the criteria for eGFR testing based on the ACR guidelines.

A total of 472 patients were reviewed. There were 394 patients in Group A, 45 patients in Group B and 33 patients in Group C. Prior to POCT for contrast administration, there were 33 patients with at least one $eGFR_{prior}$ result within <3 months, 210 patients with at least one $eGFR_{prior}$ result 3–6 months, and 442 patients with at least one $eGFR_{prior}$ result ≥6 months. We compared the median $eGFR_{POCT}$ and $eGFR_{prior}$ based on CKD stage recorded prior to MRI scan. There were no significant differences between median $eGFR_{POCT}$ and $eGFR_{prior}$ at all time intervals prior to POCT for all 3 groups of patients (Table 1). No patient had documented NSF.

However, there were 42 patients with a significant drop in eGFR (decrease from most recent $eGFR_{prior}$ to $eGFR_{POCT}$) of at least one CKD stage to that of CKD stage 3a or worse (<60mL/min/1.73m^2) prior to MRI scan. The drop in eGFR did not appear to be significantly associated with established risk factors based on the Choyke questionnaire: diabetes (P=0.75), pre-existing renal impairment (P=0.07), hypertension (P=0.76) and gout (P=0.36).

Out of these 42 patients, 38 had a significant drop in eGFR up to that of CKD stage 3b. However, as their eGFR remained ≥30mL/min/1.73m^2, these patients still proceeded with GBCA administration for MRI scan, and the impact on workflow was minimal. Four patients had a drop in eGFR resulting in CKD stage 4 or 5 (eGFR <30mL/min/1.73m^2) and were unable to proceed with GBCA administration. Review of medical records for these 4 patients revealed that 1 had recent prolonged hospitalisation for urosepsis, 2 already had a borderline baseline eGFR of 30mL/min/1.73m^2 (hence a drop of a single unit in eGFR resulted in a worse CKD stage), while 1 was on hydroxyurea, which is known to cause falsely elevated serum creatinine due to interference with the POCT cartridge system. Repeat eGFR testing performed 2 days after POCT did not show significant change from $eGFR_{prior}$. Therefore, we conclude that in our study population, only 1 out of 472 patients had a significant drop in eGFR to a level where contrast could not be administered.

Based on our findings, we propose that the time interval between contrast-enhanced MRI and eGFR can be lengthened up to 6 months regardless of the degree of renal impairment, as we found no significant difference between median $eGFR_{POCT}$ and $eGFR_{prior}$ across all time points. Furthermore, we suggest that in deciding whether POCT of eGFR is required, additional factors that may contribute to acute-on-chronic renal injury—such as infection; cancer; or trauma and surgery related to the kidneys and urinary tract—should be considered, as these factors are more likely to be associated with progression of renal impairment.[5,7-9]

While we recognise that findings based on our study population may not be generalised to all patients with varying degrees of renal impairment, our proposal would simplify clinical workflows and save healthcare costs by reducing the need for POCT. Larger studies to determine the precise safe time interval between eGFR screening and MRI scan are needed.

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Table 1. Patients classified into 3 groups (A, B and C) based on $eGFR_{prior}$. Median $eGFR_{POCT}$ and $eGFR_{prior}$ were compared for each group stratified by time interval between the 2 readings. In all 3 groups, differences in median eGFR values did not present any significant difference, regardless of time interval from point-of-care test.

Group	Time interval between $eGFR_{POCT}$ and $eGFR_{prior}$	No. of patients in group	No. of patients with progression in CKD stage (%)	Median $eGFR_{prior}$ mL/min/1.73m^2 (IQR)	Median $eGFR_{POCT}$ mL/min/1.73m^2 (IQR)	*P* value
Group A ($eGFR_{prior}$ >60mL/min/1.73m^2)	<3 months	4	0	100 (92–119)	117 (92–157)	0.144
	3–6 months	167	12 (3.0)	85 (75–102)	85 (71–101)	0.350
	>6 months	223	12 (3.0)	87 (76–100)	88 (76–102)	0.327
Group B ($eGFR_{prior}$ 45–59mL/min/1.73m^2)	<3 months	8	4 (8.9)	50 (45–59)	45 (39–55)	0.067
	3–6 months	21	6 (13.3)	52 (49–57)	51 (44–61)	0.658
	>6 months	16	4 (8.9)	54 (48–57)	51 (43–55)	0.379
Group C ($eGFR_{prior}$ <45mL/min/1.73m^2)	<3 months	23	4 (12.1)	38 (34–41)	38 (31–42)	0.671
	3–6 months	6	0	43 (38–43)	40 (36–46)	0.750
	>6 months	4	0	42 (40–43)	36 (31–43)	0.144

CKD: chronic kidney disease; eGFR: estimated glomerular filtration; IQR: interquartile range; POCT: point-of-care test; prior: prior eGFR result

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Pearlyn Mei Ping Wong [1]*MD*, Jared Jue Ying Yeo [1]*MBBS*, Gek Hsiang Lim [3]*MSc*, Martin Weng Chin H'ng [1]*FRCR*, Chau Hung Lee [1]*FRCR*, Cher Heng Tan [1]*FRCR*

[1] Department of Diagnostic Imaging, Tan Tock Seng Hospital, Singapore
[2] Department of Diagnostic Imaging, Singapore General Hospital, Singapore
[3] Singapore General Hospital, Singapore
[4] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Correspondence: Dr Pearlyn Mei Ping Wong, Department of Diagnostic Imaging, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433. Email: pearlyn.wong@mohh.com.sg

Ann Acad Med Singap 2022;51:384-5
https://doi.org/10.47102/annals-acadmedsg.2021475

Palliative dialysis in hospice: A paradox or promising answer?

Dear Editor,

End-stage renal disease (ESRD) patients have higher mortality, hospital admissions and invasive procedures towards the end of life.[1] However, many of them (82%) prioritise minimising suffering over life prolongation. Although twice as many patients prefer dying at home and inpatient hospice (65%) compared to hospital (27%), hospice utilisation remains lower for dialysis patients (20%) compared to those with cancer (55%) and heart failure (39%).[2] For patients continuing dialysis until death, hospice usage plummets further (18% versus 58%).[3]

Dialysis seemingly contravenes traditional hospice tenets of prioritising comfort over life prolongation. The dilemma of withdrawing dialysis to enter hospice, or continue dialysis but forgo hospice, is a disservice to patients who are seeking a transition to comfort-driven care, yet would benefit symptomatically, psychologically and prognostically from dialysis.

We describe a case of a patient on peritoneal dialysis (PD) with concomitant malignancy, who restarted PD in an inpatient hospice after initial dialysis withdrawal.

The patient was a 78-year-old man with lung adenocarcinoma with metastases to brain and pleura. He was on PD for ESRD secondary to diabetic kidney disease.

Seventeen days into second-line chemotherapy, he was admitted to hospital for delirium and functional decline. Considering the rapid deterioration, his oncologist advised for best supportive care and gave a prognosis of 3 months. He concurrently developed recurrent intradialytic hypotension, rendering PD unsafe. A goals-of-care discussion was conducted with his wife, and PD was withdrawn. Unfortunately, the patient's delirium prevented his participation in this discussion.

He was transferred to our inpatient hospice, where his haemodynamics and confusion significantly improved. He could communicate his wishes coherently and consistently. He desired to continue PD until medically contraindicated, while shifting care goals towards prioritising comfort, as he was cognisant of the limited prognosis portended by his incurable malignancy. After discussion with his oncologist, nephrologist and palliative care physician, we restarted PD in our inpatient hospice.

We worked closely with the hospital's nephrology team for PD regime adjustments and practical guidance. We enlisted the expertise of his wife who was previously trained, to carry out PD. He was transited to twice-weekly PD of 1.5% dextrose solution with total therapy volume of 8 litres over eight hours with no last fill volume. We did not carry out blood investigations for monitoring, but sought to be symptom-guided.

He successfully underwent 2 PD sessions. On the third session, he developed hypotension with drowsiness, and PD was aborted. On the fourth session, he developed distressing abdominal pain, and after discussion, the therapeutic burden was deemed intolerable. PD was formally withdrawn, with transition to full comfort care, and the patient demised comfortably 4 days later.

Renal palliative care is gaining attention, but still underdeveloped.[4] The protracted journey from early disease to ESRD is fraught with both physical symptoms and psychological distress. Early advance care planning is imperative to navigate care goals when life-limiting illnesses, either related to or independent of ESRD, arise. In the latter, many adopt an "all-or-nothing" approach where dialysis and palliation are mutually exclusive. The concept of palliative dialysis, though lacking a uniform definition, is summarised by Axelsson et al. as being focused on quality of life over achieving medical parameters.[5]

As alluded to, palliative dialysis in hospice may be suitable for patients with a poor, yet reasonable prognosis, owing to other life-limiting illnesses. It provides a bridge between dialysis and withdrawal, when both are suboptimal—the former becoming burdensome, while the latter undesirable for several reasons: expected severe symptoms,[6] predictably short prognosis,[2] and ethical struggles (12% of patients being unsure or believing it akin to suicide).[7]

Evidence supporting hospice dialysis is promising, with better outcomes shown in dialysis patients receiving hospice services than those without.[3] ESRD hospice enrolments also occur regrettably late in the disease course,[8] and lengthening the admission duration by virtue of a longer prognosis on dialysis will allow patients and families to further benefit from hospice care.

We restarted PD in hospice for various reasons in an endeavour to maximise quality, without compromising

quantity, of life. Firstly, balancing the certainty of death in days to short weeks without dialysis, with the less certain trajectory of cancer. Secondly, normalised haemodynamics permitted PD to proceed. Thirdly, the patient's improved cognition allowed him to meaningfully enjoy the lengthened time. Lastly, his expressed wishes to continue PD while pursuing comfort-driven care, which aligns with hospice philosophy.

Several challenges arose in this undertaking. The inpatient hospice setting lacked on-site nephrologists for dialysis regime and medication adjustments, and dialysis nurses with practical expertise. This was circumvented by strong collaboration with the hospital's nephrology team who availed themselves for off-site consultation.

With palliative dialysis, clear objectives and limits should be discussed early with patients and family. In this case description, severe distress during PD meant treatment burden outweighed the benefits. Symptomatic hypotension also precluded safe dialysis provision. Other considerations include patients' requests and dialysis access dysfunction that cannot be resolved by conservative management.

The role of dialysis in a hospice remains fairly uncharted territory, as there is no clear framework for patient selection and metrics to guide management. Additionally, there are limited specific funding mechanisms for dialysis patients in hospice care. Dialysis is health-resource intense, and many voluntary welfare organisations in Singapore supporting haemodialysis require adherence to dialysis prescription so they could achieve acceptable medical parameters, to justify the use of donor funding for financial aid. In this patient, existing PD supplies from his home helped to circumvent the issues of potential additional costs. Therefore, a concerted effort involving hospices re-evaluating workflows, legislation for funding, and greater acceptance by medical practitioners and the palliative care community is needed to provide dialysis-dependent ESRD patients with better end-of-life care when facing the inevitable.

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Yun Ying Ho [1]*MBBS*, Tricia Sek Hwee Yung [2]*MRCP*, Yong Pey See [3]*MMed (Internal Medicine)*, Mervyn Koh [1]*FAMS*

[1]Dover Park Hospice, Singapore
[2]Department of Palliative Medicine, Tan Tock Seng Hospital, Singapore
[3]Department of Renal Medicine, Tan Tock Seng Hospital, Singapore

Correspondence: Dr Yun Ying Ho, Dover Park Hospice, 10 Jalan Tan Tock Seng, Singapore 308436.
Email: yunying.ho@mohh.com.sg

Ann Acad Med Singap 2022;51:386-7
https://doi.org/10.47102/annals-academedsg.2022122

Cause of vaginal spotting in an older woman

A 77-year-old Chinese woman with a past medical history of Sjogren's syndrome, nodular goitre and right-sided neck lymphadenopathy, presented to the gynaecological service for per-vaginal spotting. On clinical examination, she was noted to have a cervical polyp. A polypectomy was performed and the specimen was sent for histological examination.

The specimen consisted of multiple small fragments of pale tissue measuring 1.2cm in maximum dimension.

The polypoid pieces of tissue contained a dense infiltrate in the submucosal stroma (Figs. 1A and 1B). The stroma is composed of sheets of cells of uniform appearance with a moderate amount of cytoplasm, slightly eccentrically placed round and ovoid nuclei—many with small nucleoli—and occasional nuclear pseudoinclusions (Fig. 1B). Small lymphocytes were interspersed. The infiltrate percolated around residual endocervical glands and the surface endocervical mucosa that was focally attenuated. No gland formation, keratin, pigment or mucin production was seen. Immunohistochemical stains for HMB-45, MNF-116 and CD20 were negative.

Which is the most likely diagnosis?

A. Invasive squamous carcinoma of the cervix
B. Invasive adenocarcinoma of the cervix
C. Florid cervicitis
D. Marginal zone B cell lymphoma
E. Spread from an endometrioid endometrial carcinoma

Additional immunohistochemical staining subsequently performed showed positivity for CD38, CD138 and lambda light chain restriction (Fig. 3). CD3 confirms scattered interspersed small lymphocytes.

Results of the previous neck lymph node biopsy were not known at the time of the cervical biopsy, but subsequent information revealed that a nodal marginal zone B cell lymphoma with plasmacytic differentiation had been previously diagnosed, with tumour cells immunopositive for CD38 and CD138, and which demonstrated lambda light chain restriction.

Discussion. The commonest primary tumours of the cervix are squamous cell carcinoma with its variants, and adenocarcinoma.[1-3] The most common haematopoietic neoplasm involving the cervix, whether primary or secondary, is diffuse large B-cell lymphoma.[4]

Secondary involvement of the cervix represents less than 0.3% of all cervical malignancies.[1] The most

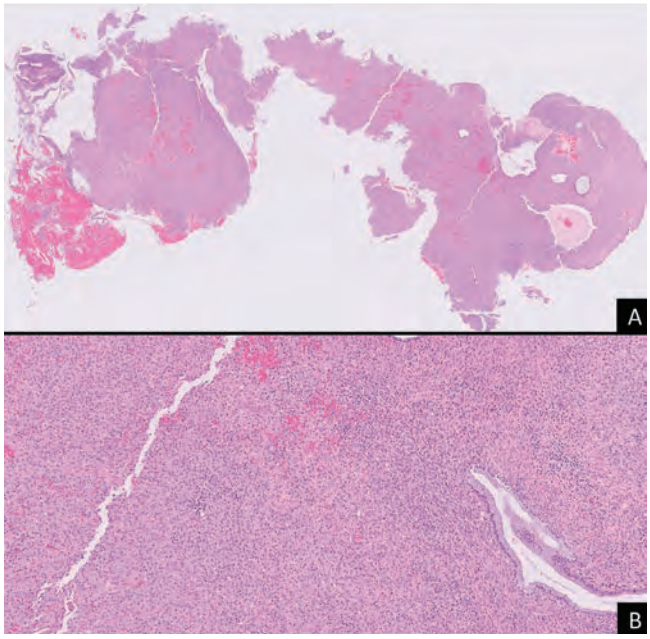

Fig. 1. (A) Polypoid pieces of tissue with residual endocervical glands (haematoxylin and eosin [H&E], 2x magnification). (B) The infiltrate composed of sheets of cells in the submucosal stroma (H&E, 10x magnification).

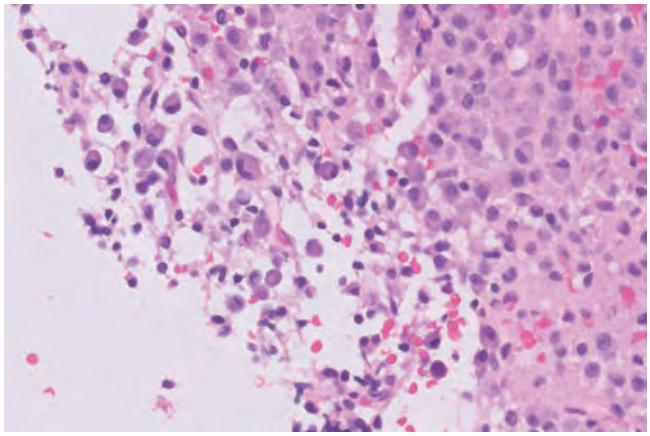

Fig. 2. The cells show a uniform appearance with a moderate amount of cytoplasm, slightly eccentrically placed round and ovoid nuclei, and occasional nuclear pseudoinclusions (H&E, magnification 40x).

Answer: D

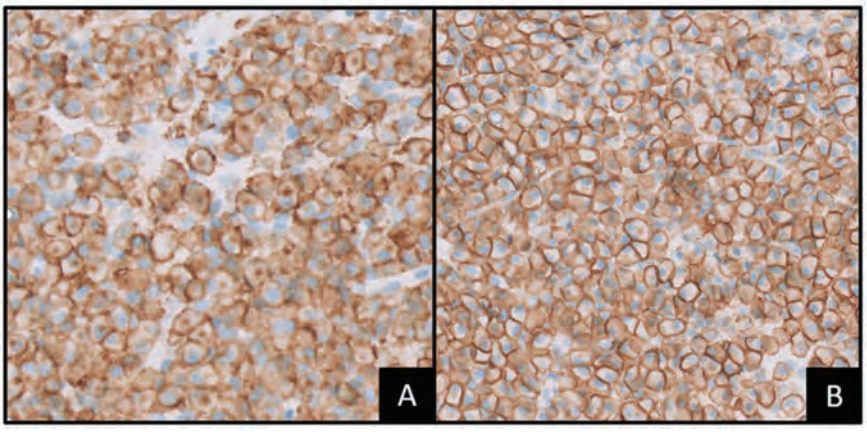

Fig. 3. (A) CD38 and (B) CD138 immunohistochemical stains showing diffuse positivity (40x magnification).

common secondary tumour is endometrial carcinoma by direct contiguous spread, followed by metastases from carcinomas of ovarian (42.1%), gastrointestinal tract (19.8%) and breast (4.5%) origins.[2,3]

Only 6% of cervical metastases are of haematopoietic origin, of which 75% are diffuse large-cell B cell lymphoma, followed by non-Hodgkin lymphoma (10%) and chronic lymphocytic leukaemia (3%).[4] Cervical involvement in multiorgan disease is more common than a primary lymphoma of the cervix, and hence one should consider the possibility of metastasis when encountering a lymphoproliferative neoplasm in the cervix. The cervix is also the most common location in the female genital tract in which lymphoma may arise.[5]

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Logaswari M [1]*MBBS*, Inny Busmanis [1]*FRCPA*

[1]Department of Anatomical Pathology, Singapore General Hospital, Singapore

Correspondence: Dr Logaswari M, Department of Anatomical Pathology, Singapore General Hospital, 21 College Road, Singapore S792413
Email: logaswari.m@mohh.com.sg

Acknowledgement

The Editorial Board of the *Annals*, Academy of Medicine, Singapore gratefully acknowledges the generous support of

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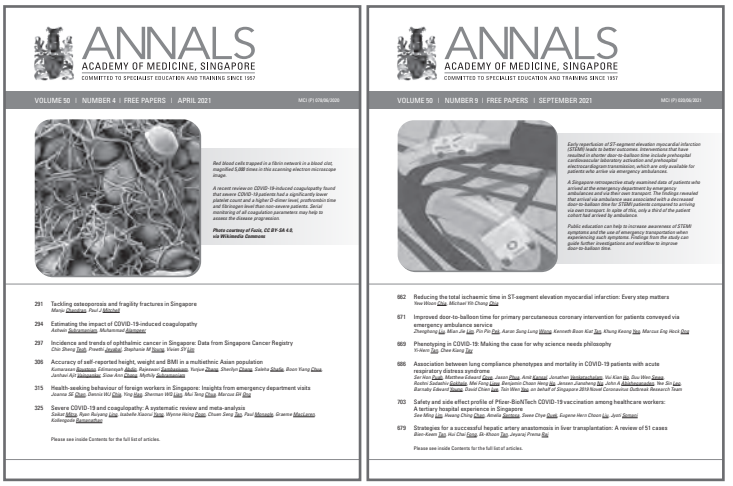

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