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This issue highlights two Singapore studies focused on the impact and mitigation of kidney diseases, in commemoration of World Kidney Day in March.

Patients with chronic kidney disease can benefit from serious illness conversation, following identification of risk factors associated with increased mortality. These include the Charlson Comorbidity Index, serum albumin and recent hospital readmission.

Cardiovascular morbidity and mortality are high among patients with end-stage renal failure. Predictors of death and acute myocardial infarction are examined among those on different modalities of dialysis. Findings show tighter control of cardiovascular risk factors benefits patients on dialysis.

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ANNALS

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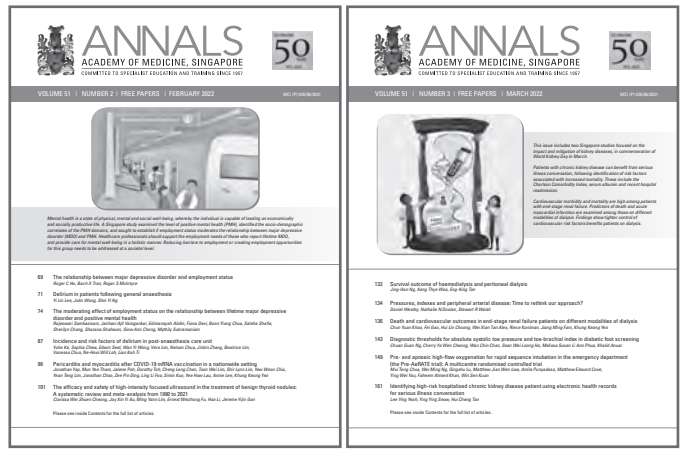

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EDITORIAL

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Survival outcome of haemodialysis and peritoneal dialysis

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End-stage renal disease (ESRD) is a challenging and growing health issue, with number of patients increasing globally. The use of dialysis has greatly improved the survival and life expectancy of ESRD patients. Haemodialysis (HD) and peritoneal dialysis (PD) are 2 broad dialysis modalities used for ESRD. Despite the advancement and proliferation of both modalities over past decades, controversy remains in the comparison of their survival outcomes.[1] Numerous observational studies done have yielded heterogeneous results.[2] Multiple studies, including those from the US, Canada, Northern Europe, Australia and New Zealand, showed that PD conferred a slight survival advantage over HD during the initial years of dialysis.[3] Some postulate that the initial survival advantage of PD is due to better preservation of residual kidney function in the initial phase after dialysis commencement.[4] However, a large Korean study found that mortality among patients aged 55 years and above was higher in PD as compared to HD.[3] Other studies, such as those from Taiwan and Finland, showed similar survival outcomes between the 2 dialysis modalities.[4] However, there is still a paucity of such studies in Southeast Asia.

To address this gap in knowledge, in this issue of the *Annals*, Khoo and colleagues[5] evaluated the mortality and cardiovascular outcomes of HD and PD patients in Singapore. They performed a large retrospective study of approximately 5,000 ESRD patients who started dialysis in Singapore between 2007 and 2012. The authors reported comorbidities and mortality rates of ESRD patients. They identified older age (over 60 years), history of diabetes mellitus, cerebrovascular event, ischaemic heart disease and peripheral vascular disease as risk factors for mortality and acute myocardial infarction in dialysis patients.

They also found a higher mortality rate in the PD group compared to those who received HD, which differed from the findings of many Western studies that showed a superior survival outcome in PD initially. The authors suggested that the differences in their findings may be contributed by the relatively high prevalence of diabetes mellitus (DM) in the Singaporean population (prevalence of DM was 68.5%). The PD solution, which contained glucose, could worsen diabetes control and it is possible that DM patients may be more prone to infections resulting in complications of PD, such as PD peritonitis. Indeed, a recent systematic review showed that the majority of studies, which compared outcomes of diabetic patients on HD and PD, showed a poorer survival with the use of PD.[6] However, the authors of the systematic review noted a high risk of bias as there was significant variability across the studies in terms of DM management, dialysis protocols and patient background. These confounding variables made it difficult to draw definitive conclusions on the superior dialysis modality for DM patients.

It is important to take into account the limitations of observational studies and comparison of the outcomes of dialysis modalities, when interpreting their findings.

Firstly, the nature of observational studies prevents the establishment of causality between the dialysis modality and survival outcome. While randomised controlled trials (RCT) are more appropriate to establish causality, past RCTs have generally been unsuccessful as most ESRD patients valued autonomy in their choice of dialysis modality.[3] As such, comparison between HD and PD have been generally restricted to observational studies.

Secondly, selection bias is an important confounder as the choice of dialysis modality for a patient is often linked to a myriad of factors, including patient lifestyle, medical comorbidities, socio-economic background, resource access and physician inclination. Furthermore, these factors are dynamic and may evolve longitudinally over the course of a patient's disease. Several approaches have been adopted by observational studies to better account for these factors and to reduce selection bias. Selection and streamlining of study cohort is important to improve comparability of the dialysis modalities. For example, a retrospective cohort study by Wong et al. showed that the improved survival outcomes for ESRD patients on PD disappeared when the authors

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restricted the study only to patients deemed eligible for both HD and PD.[7] Statistical models such as propensity score, competing risk and marginal structural models may also be used to study confounding factors of mortality in ESRD patients.[4]

Studies on survival outcomes of dialysis modalities have shown inconsistencies and neither PD nor HD has demonstrated a significant survival outcome advantage over the other. Survival outcomes alone are thus insufficient to guide decision-making on the optimal dialysis treatment for an ESRD patient. Besides emphasis on survival outcomes, it is also important to consider the patient-reported outcomes and quality-of-life measures of each dialysis modality as ESRD patients face significant disease burden.[8] As such, there has been increasing interest in comparing the qualitative outcomes of dialysis modalities. A recent systematic review showed that ESRD patients on PD showed a better health-related quality of life, as compared to patients on HD, based on measurement tools such as Short Form 36 Health Survey Questionnaire (SF-36), EuroQol-5 Dimension (EQ-5D) and Kidney Disease and Quality of Life (KDQOL).[9] Many of the studies included were however limited by the presence of confounders and biases similar to the ones noted in observational studies on survival outcomes. Future large-scale longitudinal prospective studies across different populations to investigate the interactions between the qualitative outcomes (such as quality of social interaction, emotional state and function) and quantitative outcomes (such as mortality, hospitalisation rate and residual renal function) will facilitate a more holistic approach to better identify the optimal dialysis modality for each ESRD patient.

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EDITORIAL

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Pressures, indexes and peripheral arterial disease: Time to rethink our approach?

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Most patients with peripheral arterial disease (PAD) are asymptomatic. Despite the absence of symptoms, these patients have a significantly increased risk of death and adverse vascular events.[1] Early detection of individuals with asymptomatic PAD facilitates prompt introduction of secondary prevention (lifestyle modification, smoking cessation, anti-platelet medications and lipid management). Ankle-brachial pressure index (ABPI) is generally considered the default screening test for PAD. It is relatively simple and non-invasive, with an ABPI less than 0.9 considered diagnostic for PAD. The prevalence of ABPI less than 0.9 among people under 50 years of age with no cardiovascular risk factors is less than 1% and routine PAD screening with ABPI is not recommended.[2] PAD screening with ABPI is reasonable in asymptomatic individuals with at least one atherosclerotic risk factor.[1]

ABPI is an attractive point-of-care option to screen for PAD. However, varying degrees of arterial stiffness may modify or abrogate the ABPI values obtained. This results in false-negative ABPI values that appear in the normal range, but in fact simply reflect vessel calcification in the presence of PAD. Recent interest has focused on the use of toe pressure measurements as an alternative as the hallux digital arteries are thought to be relatively spared from calcification and therefore less prone to false-negative results. However, it is important to point out that toe pressure have not been a useful predictor of limb salvage in patients with critical limb treating ischaemia. Either the absolute systolic toe pressure (ASTP) or the toe-brachial index (TBI) can be used.

In this issue of the *Annals*, Ng et al. reported data from a large Singapore diabetic cohort in which the diagnostic performance of ASTP and TBI were evaluated.[3] Both ASTP and TBI had area under the receiver operating characteristic (ROC) curve values of 0.89 and 0.94, respectively, which are in the range indicating excellent test performance. An ASTP threshold of 95.5mmHg yielded a sensitivity of 0.84 and a specificity of 0.86 for ABPI less than 0.9. Taking approximate values from the data illustrated in Fig. 2 (Ng et al.), 275 of 1,454 screened individuals (19%) had an ASTP less than 95.5mmHg. Based on these data, 190 out of 1,000 diabetics will have PAD. Of these 1,000 diabetics, ASTP less than 95.5mmHg will correctly detect PAD in 160 patients. It will miss PAD in 30 patients who actually have the condition. It will correctly detect the absence of PAD in 697 patients but will incorrectly label 113 patients as having PAD when they are, in fact, PAD-free. With 11% of the hypothetical cohort being false-positive, there may be an argument that an ASTP-positive should be confirmed on another test, such as duplex ultrasound, computed tomography (CT) or magnetic resonance angiography (MRA), before initiating pharmacological interventions with the associated side effects.

Underlying all these calculations is the widely held assumption that an ABPI value less than 0.9 indicates the presence of PAD. However, when ABPI is compared to imaging modalities for the detection of arterial stenosis ≤50%, the results may not support this belief. A recent meta-analysis that pooled results from studies comparing ABPI to an imaging reference standard (duplex ultrasound, CT, MRA or digital subtraction angiography) reported a pooled sensitivity of 61% and a specificity of 92%. If we apply these figures to the hypothetical Singapore diabetic cohort of 1,000 patients, how does ABPI perform? Only 114 patients will be correctly labelled as PAD, the condition will be missed in 76 patients, while another 65 patients will have a false-positive result. TBI was evaluated in the same review. It performed somewhat better in terms of sensitivity (81%) but was less specific (77%).[4]

Clearly, it is unrealistic to suggest that all diabetic patients should be screened regularly for occult PAD with an imaging modality. The current imaging modalities are restricted to symptomatic patients given the use of ionising radiation (CT and invasive angiography),

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contrast-related renal injury (CT, invasive angiography and MRA) and operator-dependency (duplex ultrasound). There is a need for a simple bedside screening test. Novel technologies are beginning to focus more on toe perfusion pressures over the traditional indices, adding another dimension for PAD screening in these patients. The full value of these remains to be seen. As the situation stands, the diagnostic performance of the available bedside tests (ABPI, TBI and ASTP) could use improvement compared to the imaging modalities.

Where to go from here? Perhaps the debate is not whether ASTP is equivalent to ABPI or TBI. Perhaps it is time to utilise all the available data rather than just consider the component parts. Would a combination of ASTP, TBI and ABPI perform better than any component alone? Could they be integrated with other measures such as pulse waveform or velocity acceleration time? Utilising all the available resources is theoretically the most ideal format for providing quantitative evidence of disease. Bedside technology is improving with more data now easily acquired in the clinic. An integrated approach could yield significant improvements in how PAD is investigated and diagnosed, but first the dogma that ABPI less than 0.9 always indicates PAD should be revised.

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ORIGINAL ARTICLE

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Death and cardiovascular outcomes in end-stage renal failure patients on different modalities of dialysis

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ABSTRACT

Introduction: Cardiovascular morbidity and mortality in end-stage renal failure (ESRF) patients are high. We examined the incidence and predictors of death and acute myocardial infarction (AMI) in ESRF patients on different modalities of dialysis.

Methods: Data were obtained from a population-based database (National Registry Disease Offices) in Singapore. The study cohort comprised all adult patients initiated on dialysis between 2007 and 2012 who were closely followed for the development of death and AMI until September 2014. Cox regression methods were used to identify predictors of death and AMI.

Results: Of 5,309 patients, 4,449 were on haemodialysis and 860 on peritoneal dialysis (PD). Mean age of the cohort was 61 (±13) years (44% women), of Chinese (67%), Malay (25%) and Indian (7%) ethnicities. By September 2014, the incidence of all-cause death was 34%; close to a third of the patients died from a cardiovascular cause. Age >60 years and the presence of ischaemic heart disease, diabetes, stroke, peripheral vascular disease and PD were identified as independent predictors of all-cause death. PD patients had lower odds of survival compared to patients on haemodialysis (hazard ratio 1.51, 95% confidence interval 1.35–1.70, $P<0.0001$). Predictors of AMI in this cohort were older age (>60 years) and the presence of ischaemic heart disease, diabetes, stroke, peripheral vascular disease and current/ex-smokers. There were no significant differences in the incidence of AMI between patients on PD and haemodialysis.

Conclusion: The short-term incidence of death and AMI remains high in Singapore. Future studies should investigate the benefits of a tighter control of cardiovascular risk factors among ESRF patients on dialysis.

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Keywords: Acute myocardial infarction, end-stage renal failure, mortality, nephrology

INTRODUCTION

End-stage renal failure (ESRF) is a major cause of morbidity and mortality worldwide, including Asia.[1] In Singapore, incidence of chronic kidney disease (CKD) stage 5 has increased from 383.9 per million population (PMP) in 2010 to 414.8 PMP in 2015. Incidence of patients requiring dialysis has increased in tandem. The age-standardised rate of patients requiring definitive dialysis has increased from 144.7 PMP in 2010 to 185.3 PMP in 2016.[2] Cardiac disease is one of the most important causes of death in these patients. There is a high incidence of acute coronary syndrome (ACS) in patients on chronic dialysis. In a study of 3,374 patients in the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Study Wave II, incidence of ACS was 29/1,000 person-years.[3] Furthermore, patients tend to do worse after an episode of acute myocardial infarction (AMI). Overall mortality after AMI among patients on long-term dialysis in the US was 59% at 1 year and 89.9% sat 5 years.[3]

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CLINICAL IMPACT

What is New

- The short-term incidence of death and acute myocardial infarction (AMI) among patients with end-stage renal failure (ESRF) on dialysis remains high in Singapore.
- Patients on peritoneal dialysis patients harbour a poorer survival outcome compared to those on haemodialysis.

Clinical Implications

- Findings from this population-based study provide quantitative estimates of all-cause death and AMI among ESRF patients in Singapore
- ESRF patients on dialysis may benefit from a tighter control of cardiovascular risk factors.

The predictors of death and AMI on patients newly initiated on dialysis, as well as the impact of different modalities of dialysis on death and AMI outcomes remain an area of uncertainty. Studies have shown conflicting results on the effect of peritoneal dialysis (PD) versus haemodialysis (HD) on clinical outcomes. Population-based studies performed in the US suggest that dialysis modality was not a predictor of adverse cardiovascular outcomes.[4] This is in contrast to most Asian studies where PD has been found to be an independent predictor of adverse clinical outcomes in ESRF patients.[5-7] In Southeast Asia, such data remain limited. The primary aim of this study is to describe the incidence and predictive factors of death and AMI in ESRF patients on different modalities of dialysis in a multiracial Asian society. In addition, difference in outcomes (mortality, AMI) between patients on HD and PD were studied.

METHODS

This study was approved by the SingHealth Centralised Institutional Review Board, with the need for consent waived as anonymised data were used.

Data were obtained from the National Registry Diseases Offices (NRDO) in Singapore. Use of data collected by NRDO has been previously described.[8,9] The NRDO was established in 2001 and contains data on reportable non-communicable diseases in Singapore such as AMI, cancer, stroke and CKD. These data are validated on a regular basis to ensure accuracy. Since 1999, the renal NRDO registry has collected data on patients with CKD stage 5 (defined as patients with serum creatinine ≥10mg/dL or 880μmol/L or initiation on renal replacement therapy). In 2007 and 2009, 2 of the largest hospitals in Singapore contributed listings of patients with estimated glomerular filtration rate (eGFR) <15mL/min (corrected for body surface area [BSA] 1.73m^2). These hospitals account for more than 50% of the new CKD stage 5 cases. By 2010 a subsidiary legislation was put into place, which made it mandatory for the remaining restructured hospitals in Singapore to provide the Registry Office with particulars of patients with advanced CKD using previously determined criteria. There was a broader inclusion of all patients with serum creatinine ≥500μmol/L or eGFR<15mL/min (corrected for BSA 1.73m^2) or those who were started on renal replacement therapy (PD, HD or transplant).

This study included data of all adult patients (age ≥21 years) from 2007 to 2012 with ESRF already on dialysis for at least 3 months. Incident dialysis modality was defined as the dialysis modality after 3 months as patients planned for PD might have been started on HD initially. In addition, this was also to obtain a relatively stable cohort of patients on dialysis as patients with multiple comorbidities may not survive beyond first 3 months of dialysis initiation. This methodology was adopted from the renal NRDO, based on the USRDS methodology. Analysis of outcomes were based on incident dialysis modality. Baseline demographics (ethnicity, age and sex), comorbidities including presence of diabetes mellitus (DM), ischaemic heart disease (IHD), cerebrovascular accident (CVA), peripheral vascular disease (PVD), hypertension and malignancy at time of dialysis initiation were obtained. Data were matched against the Singapore Myocardial Infarction Registry to obtain incidence of AMI post-initiation of dialysis.

Notification of AMI became mandatory for all public hospitals since 2007 and for all private hospitals in Singapore since 2012. This encompasses notifications from all hospitals via the inpatient medical records and cardiac biomarkers, from Ministry of Health's Mediclaim (health insurance) and subvention list, as well as the death registry. The International Classification of Diseases 9th Revision (ICD-9) Clinical Modification code 410 was used as AMI case definition from 2007 to 2011. From 2012 onwards, the ICD-10 American Modification codes I21 and I22 were used.

Death outcomes were evaluated through the National Registry of Births and Deaths. Accurate capture of death records is high as reporting of death is mandatory by law in Singapore within 24 hours of its occurrence.[10]

Statistical analysis

We performed bivariate comparisons between HD and PD with t-test for continuous variables and chi-square test for categorical variables. Continuous variables are reported as a mean with standard deviation (SD).

We constructed univariate and multivariable Cox regression models to assess the risk factors for all-cause death and ACS, respectively.

We excluded 33 patients who were lost to follow-up and those who had continued follow-up in other countries. We also excluded 116 patients who underwent renal transplant as numbers were small and outcomes of transplanted patients are known to be better. All analyses were performed in STATA 13 (StataCorp LLC, College Station, US).

RESULTS

Between 2007 and 2012, 4,449 out of a total of 5,309 patients in the Singapore NRDO renal registry were on haemodialysis and 860 on PD. Mean age was 61 (±13) years and 2,339 (44.1%) were females. There were 3,538 (66.6%) Chinese, 1,313 (24.6%) Malays and 391 (7.4%) Indians.

Majority of the patients had pre-existing hypertension (5,222, 98.4%). There were 3,678 (69.3%) patients with DM and 2,296 (43.3%) had underlying IHD. PVD was present in 764 patients (14.4%), while 1,156 (21.8%) had a history of CVA (Table 1).

All-cause incident mortality was 34% (1,817), of which 35% (640) were cardiovascular related.

Predictive risk factors of mortality included older age more than 60 years (hazard ratio [HR] 2.00, 95% confidence interval [CI] 1.80–2.22, $P<0.0001$), IHD (HR 1.46, 95% CI 1.31–1.61, $P<0.0001$), DM (HR 1.68, 95% CI 1.47–1.91, $P<0.0001$), CVA (HR 1.46, 95% CI 1.31–1.62, $P<0.0001$), PVD (HR 1.77, 95% CI 1.57–1.98, $P<0.0001$), malignancy (HR 1.77, 95% CI 1.51–2.07, $P<0.0001$) and PD (HR 1.51, 95% CI 1.35–1.70, $P<0.0001$) (Table 2). Presence of hypertension (HR 0.44, 95% CI 0.31–0.62, $P<0.0001$) was found to be protective against death. In comparison with patients on HD, PD patients had lower survival rates during follow-up using logrank test ($P<0.0001$) (Fig. 1).

There were 915 patients who developed AMI (5.6/100 person years). Predictive risk factors for AMI include an older age more than 60 years (HR 1.47, 95% CI 1.27–1.69, $P<0.0001$), IHD (HR 2.27, 95% CI 1.97–2.62, $P<0.0001$), DM (HR1.75, 95% CI 1.45–2.10, $P<0.0001$), CVA (HR 1.31, 95% CI 1.13–1.52, $P<0.0001$), PVD (HR 1.55, 95% CI 1.32–1.83, $P<0.0001$) and current/ex-smoker (HR 1.37, 95% CI 1.17–1.61, $P<0.0001$) (Table 3).

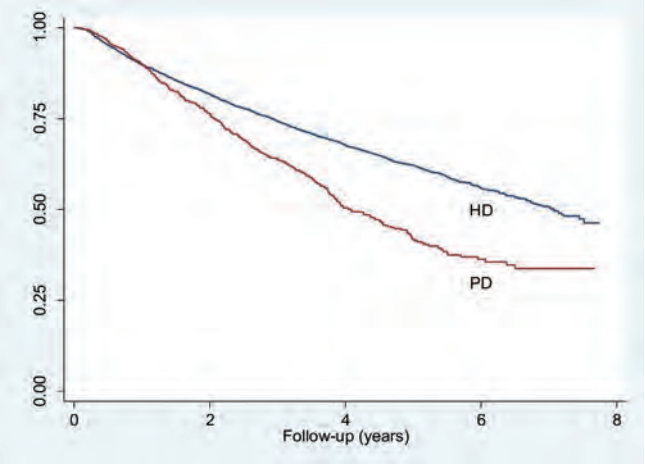


Fig. 1. Kaplan Meier survival curve for patients on haemodialysis (HD) and peritoneal dialysis (PD). Using logrank test, HD patients had significantly higher survival probability compared to PD patients ($P<0.0001$).

DISCUSSION

Despite advances in clinical medicine, mortality rate of ESRF patients in our population-based study remains high.

Cardiovascular mortality plays a significant role in outcomes, but majority of deaths remain non-cardiovascular. This is reflected in a study of ESRF patients on dialysis who underwent transcatheter aortic valve replacement for severe aortic stenosis in Singapore; which shows high mortality rate of 16.7% at 1 year, majority of which were non-cardiovascular.[11] The high mortality rate mirrors that of ESRF patients in the Western population. In the Dialysis Outcomes and Patterns Study involving ESRF patients on dialysis in France, Germany, Italy, Japan, Spain, the UK and the US, 1-year mortality rates were 15.6% in the European countries and 21.7% in the US. These numbers contrast with the 1-year mortality rate of 6.6% observed in Japan. Differences were only partly explained by patient demographic factors and comorbidities.[12]

Patients on PD have increased rates of mortality compared to HD patients in our study. Studies in different countries comparing mortality outcome by different dialysis modalities have shown conflicting results. Our results mirror that of a prior single-centre study conducted in Singapore.[7] This observational study comprised 871 patients newly initiated on dialysis from January 2005 to December 2010. Patients on PD had a higher mortality

Table 1. Baseline clinical characteristics of patients and their modality of dialysis

	Haemodialysis (n=4,449) No. (%)	Peritoneal dialysis (n=860) No. (%)	Total (N=5,309) No. (%)	*P* value
Mean age±SD, years	60±12.9	62±15.3	61±13.3	0.0078
Age >60, years	2,334 (52.9)	525 (61.1)	2,859 (54.2)	<0.0001
Ethnicity				0.0020
Chinese	2,929 (65.8)	609 (70.8)	3,538 (66.6)	
Malay	1,115 (25.1)	192 (22.3)	1,307 (24.6)	
Indian	348 (7.8)	43 (5.0)	391 (7.4)	
Others	57 (1.3)	16 (1.9)	73 (1.4)	
Female	1,882 (42.3)	457 (53.1)	2,339 (44.1)	<0.0001
Diabetes mellitus	3,063 (68.9)	615 (71.5)	3,678 (69.3)	0.12
Ischaemic heart disease	1,908 (42.9)	388 (45.1)	2,296 (43.3)	0.23
Cerebrovascular accident	931 (20.9)	225 (26.2)	1,156 (21.8)	0.0010
Peripheral vascular disease	638 (14.3)	125 (14.5)	763 (14.4)	0.88
Malignancy	329 (7.4)	26 (3.0)	355 (6.7)	<0.0001
Hypertension	4,369 (98.2)	853 (99.2)	5,222 (98.4)	0.037
Have never smoked	2,780 (63.7)	608 (72.0)	3,388 (65.1)	<0.0001

SD: standard deviation

rate compared to patients on HD. Studies in most other Asian countries have yielded similar results. Kim et al. conducted a population-based study involving 32,280 incident dialysis patients with median follow-up of 26.5 months using the Korean Health Insurance Review and Assessment Service database. Mortality rates in PD patients was found to be higher than HD patients.[5] Similarly, a Taiwan study using data from the National Health Insurance Research Database of Taiwan showed worst survival in PD patients compared to HD patients. In this study, a total of 35,664 incident dialysis patients from 1997 to 2007 were studied for a mean follow-up period of 1,265.4±970.8 days. The authors found poorer survival in ESRF patients with DM or cardiovascular disease (CVD) who underwent PD compared to HD. On the other hand, in ESRF patients without DM or CVD, dialysis modality had no impact on survival.[6] Conversely, a small prospective multicentre study conducted by Suzuki et al. in Japan between 2003 and 2008 did not show survival differences between ESRF patients on HD and PD. Prevalence of DM among the patients in this Japanese study was relatively low: 18.1% in PD patients and 27.7% in HD patients. This contrasts with higher rates of DM in other Asian studies. Prevalence of DM in our study was 68.5%. In the single-centre study by Yang et al., 70% of patients had DM[7] and in the Korean study by Kim et al., 62.5% were diabetic.[5] In the Taiwan study, 46.3% of the HD patients and 34.2% of the PD patients had DM.[6]

Findings of poorer outcomes of PD patients in Asian studies contrasts with most Western studies, which show no difference between the 2 modalities or better survival of PD in the initial period of dialysis initiation.[4,13-15] For example, in a study by Mehrota et al. looking at 684,426 patients in the USRDS, there was no difference in mortality between HD and PD patients among incident dialysis patients.[4] Approximately half of the patients in both the HD and PD group had DM. Allan et al. studied incident Medicare patients (99,048 patients on HD and 18,110 patients on PD) from 1994 to 1996 and found PD patients to have better survival outcomes compared to HD patients. The superior outcome of PD might have been contributed by shorter follow-up period of this study. Outcomes were studied were within 2 years of dialysis initiation.[14]

The difference has been thought to be possibly contributed by the increased prevalence of DM in Asian population studied compared to the Western

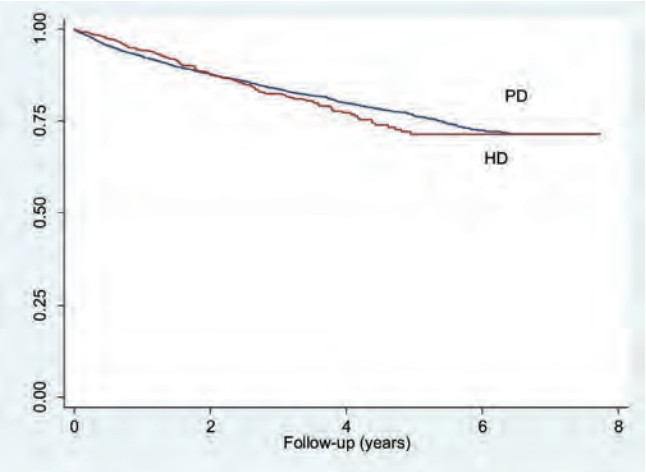
Table 2. Univariate and multivariate analysis of the risk factors for all-cause death

	Unadjusted hazard ratio (95% confidence interval)	*P* value	Adjusted hazard ratio (95% confidence intervals)	*P* value
Age >60 years	2.36 (2.13–2.60)	<0.0001	2.00 (1.80–2.22)	<0.0001
Ethinicity				
Chinese	1		1	
Malay	0.97 (0.87–1.08)	0.39	1.10 (0.99–1.24)	0.085
Indian	0.92 (0.77–1.11)	0.59	0.95 (0.78–1.14)	0.56
Others	1.16 (0.80–1.68)	0.45	1.40 (0.96–2.04)	0.080
Female sex	1.07 (0.98–1.18)	0.14	1.07 (0.96–1.20)	0.21
Comorbidities				
Diabetes mellitus	2.21 (1.97–2.49)	<0.0001	1.68 (1.47–1.91)	<0.0001
Ischaemic heart disease	1.90 (1.73–2.08)	<0.0001	1.46 (1.32–1.61)	<0.0001
Stroke	1.85 (1.67–2.04)	<0.0001	1.46 (1.31–1.62)	<0.0001
Peripheral vascular disease	2.07 (1.85–2.31)	<0.0001	1.77 (1.57–1.98)	<0.0001
Malignancy	1.81 (1.55–2.12)	<0.0001	1.77 (1.51–2.07)	<0.0001
Hypertension	0.78 (0.56–1.09)	0.15	0.44 (0.31–0.62)	<0.0001
Current/ex-smoker	1.14 (1.03–1.25)	0.0090	1.12 (1.00–1.25)	0.056
Dialysis modality				
Haemodialysis			1	
Peritoneal dialysis	1.56 (1.39–1.75)	<0.0001	1.51 (1.35–1.70)	<0.0001

population.[16,17] The glucose load present in PD dialysate is thought to exert a deleterious effect in diabetic patients.[6] In addition, higher levels of atherogenic substances (low-density lipoprotein, serum triglycerides and total cholesterol) have been observed in PD patients compared to patients on HD.[18] Though requiring further validation, these metabolic factors coupled with diabetes may have synergistic effects leading to worse outcomes.

Furthermore, patients selected for PD may be those who are frailer, with cardiac comorbidity.[7] Also, PD patients are reviewed less frequently by medical staff as PD is largely managed at home, when compared to dialysis patients who are reviewed more frequently by medical personnel when they get to dialysis centre. Finally, dialysis efficiency in PD may decline with time, resulting in poorer solute clearance that may contribute to increased mortality.[19]

Increased age and presence of cardiovascular risk factors increased risk of AMI. Dialysis modality (Fig. 2) and racial factors (Table 3) were not observed to have an effect on incidence of AMI in incident dialysis patients.



AMI: acute myocardial infarction

Fig. 2. Kaplan Meier Curve of haemodialysis (HD) and peritoneal dialysis (PD) patients showing probability of remaining free of AMI. Using logrank test, there were no significant differences between the 2 dialysis modalities.

Study limitations

Results of this study must be interpreted in the context of certain limitations. The initial reasons for selecting HD or PD cannot be ascertained in this retrospective

Table 3. Univariate and multivariate analysis of the risk factors for acute myocardial infarction

	Unadjusted hazard ratio (95% confidence interval)	*P* value	Adjusted hazard ratio (95% confidence interval)	*P* value
Age >60years	1.71 (1.49–1.96)	<0.0001	1.47 (1.27–1.69)	<0.0001
Ethnicity				
Chinese	1		1	
Malay	1.14 (0.98–1.32)	0.087	1.15 (0.99–1.35)	0.070
Indian	1.42 (1.13–1.78)	0.020	1.24 (0.99–1.56)	0.064
Others	0.89 (0.48–1.66)	0.71	1.00 (0.53–1.86)	0.99
Female sex	0.91 (0.80–1.04)	0.19	1.09 (0.93–1.28)	0.27
Comorbidities				
Diabetes mellitus	2.67 (2.24–3.18)	<0.0001	1.75 (1.45–2.10)	<0.0001
Ischaemic heart disease	2.96 (2.58–3.39)	<0.0001	2.27 (1.97–2.62)	<0.0001
Stroke	1.71 (1.48–1.98)	<0.0001	1.31 (1.13–1.52)	<0.0001
Peripheral vascular disease	2.11 (1.80–2.47)	<0.0001	1.55 (1.32–1.83)	<0.0001
Malignancy	0.99 (0.75–1.31)	0.96	1.02 (0.77–1.35)	0.91
Hypertension	2.10 (1.00–4.42)	0.050	0.92 (0.43–1.94)	0.82
Current/ex-smoker	1.49 (1.31–1.70)	<0.0001	1.37 (1.17–1.61)	<0.0001
Dialysis modality				
Haemodialysis	1		1	
Peritoneal dialysis	1.05 (0.88–1.26)	0.59	0.99 (0.82–1.18)	0.89

analysis. Traditionally, PD has been thought to have less haemodynamic fluctuations. For example, patients with poor cardiovascular status may have been preferentially chosen by their physicians to undergo PD. Certain variables such as socio-economic circumstances, frailty, nutrition status, blood pressure, left ventricular ejection fraction information and types of HD access (such as arteriovenous fistulae versus dialysis catheter) were not available in our analysis. These may have been important unmeasured co-variates influencing decision for dialysis modality. Crossovers from PD to HD and vice versa were also not considered in our analysis.

CONCLUSION

To our knowledge, this is one of the few studies in Southeast Asia looking at mortality and AMI outcomes in incident dialysis patients at a population-based level. It underscores the high incidence of mortality and ACS in ESRF patients in Singapore despite progress in clinical care, medications and dialysis facilities. PD patients were found to have poorer survival outcomes compared to HD patients. Inherent limitations associated with population-based epidemiological studies limits elucidation of causalities of survival and ACS outcomes. We believe that this study has identified a group of patients in whom more aggressive treatment of underlying risk factors and monitoring may be appropriate, and could serve as a foundation for further studies.

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ORIGINAL ARTICLE

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Diagnostic thresholds for absolute systolic toe pressure and toe-brachial index in diabetic foot screening

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ABSTRACT

Introduction: Identifying peripheral arterial disease (PAD) during diabetic foot screening (DFS) is crucial in reducing the risk of diabetic foot ulcerations and lower limb amputations. Screening assessments commonly used include absolute systolic toe pressure (ASTP) and toe-brachial index (TBI). There is a lack of research defining the threshold values of both assessment methods. We aimed to compare the accuracy of ASTP and TBI and establish optimal threshold values of ASTP and TBI with reference to the internationally accepted ankle-brachial pressure index (ABPI) screening test, for a multiethnic diabetic population in Singapore.

Methods: A retrospective, observational study of DFS results from January 2017 to December 2017 was conducted. Receiver operating characteristic analysis was conducted for ASTP and TBI using the internationally accepted ABPI cut-off value of ≤0.9 to indicate PAD.

Results: A total of 1,454 patients with mean (standard deviation) age of 63.1 (12.4) years old were included. There were 50.8% men and 49.2% women, comprising 69.7% Chinese, 13.5% Indian, 10.1% Malay and 6.7% other ethnicities. Areas under the curve for ASTP and TBI were 0.89 (95% confidence interval [Cl] 0.85–0.94) and 0.94 (95% Cl 0.90–0.98), respectively, and the difference was statistically significant (P<0.001). Derived optimal threshold values to indicate ABPI≤0.9 for ASTP and TBI were <95.5mmHg (specificity 0.86, sensitivity 0.84) and <0.7 (specificity 0.89, sensitivity 0.95), respectively.

Conclusion: ASTP or TBI may be used to detect ABPI-determined PAD in DFS. The optimal threshold values derived from a multiethnic Asian diabetic population were <95.5mmHg for ASTP and <0.7 for TBI.

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Keywords: Ankle-brachial pressure index, diabetes, peripheral arterial disease, sensitivity, specificity

INTRODUCTION

Diabetes mellitus is a global healthcare problem. In Singapore, the rising disease burden of this metabolic condition places considerable strain on the healthcare system, with healthcare costs for diabetes mellitus exceeding 1 billion Singapore dollars a year.[1] An important complication of diabetes is lower limb loss. As diabetic foot ulcers (DFU) have been recognised as a major precursor to lower extremity amputation where almost 3 in 4 amputations were preceded by DFU,[2,3] international guidelines have recommended regular foot assessments to identify and manage DFU risk.[4-7]

Diabetic foot screening (DFS) is performed in Singapore as part of routine diabetic foot assessment. The aim of this assessment is to identify risk factors leading to the development of DFU. This would allow healthcare professionals to intervene accordingly, manage and reduce the risks of DFU. A critical aspect of DFS is to establish if patients have peripheral arterial disease (PAD). Major international guidelines recommend the use of ankle-brachial pressure index (ABPI) at a cut-off value of ≤0.9 to diagnose PAD and stratify diabetic patients in routine foot assessments.[6,8-10]

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CLINICAL IMPACT

What is New

- To the best of our knowledge, this is the first study in Singapore to investigate accuracy and threshold values for absolute systolic toe pressure (ASTP) and toe-brachial index (TBI) to detect ankle-brachial pressure index (ABPI) ≤0.9 in diabetic foot screening (DFS) in a multiethnic diabetic population.

Clinical Implications

- ASTP or TBI may be used to detect ABPI-determined PAD during DFS. The optimal threshold values derived from a multiethnic Asian diabetic population were <95.5mmHg for ASTP and <0.7 for TBI.

In 2019, the Agency for Care Effectiveness, Ministry of Health Singapore, published "Appropriate Care Guide: Foot assessment in people with diabetes".[10] The document provides alignment and a standard at the national level for how DFS should be conducted. Apart from an ABPI≤0.9, the guide recommends the use of absolute systolic toe pressure (ASTP) to detect PAD during routine DFS. ASTP is a measure of microvascular perfusion and has been shown to have excellent inter-rater and intra-rater reliability.[11,12] ASTP is also used to derive the toe-brachial index (TBI), which is another non-invasive vascular assessment tool for identifying PAD. The advantages of ASTP include requiring only a single reading parameter, as well as requiring less equipment and time to perform. In particular, the ASTP does not require the brachial systolic blood pressure to be taken, and as such can be performed quicker than the ABPI or TBI.

Although there is currently no consensus regarding the optimal threshold value of ASTP to detect PAD in routine DFS, published values range from 60mmHg[10,13] to 97mmHg[14] as indicative of PAD. An ASTP value of <60mmHg is recommended by the aforementioned guide to indicate PAD in routine DFS. The guide highlights that further research should be performed to determine a locally derived toe pressure value specifically for DFU risk stratification.[10]

Compared to the well-established ABPI≤0.9 for routine DFS, there is currently a lack of literature defining the diagnostic threshold values for ASTP and TBI, in particular for a multiethnic diabetic population as Singapore. The primary aim of this study was to compare the accuracy of ASTP and TBI with reference to ABPI≤0.9 in DFS of a multiethnic diabetic population. The secondary aim was to establish normative values for ASTP and TBI with reference to ABPI≤0.9.

METHODS

A retrospective, observational study of DFS results from January 2017 to December 2017 was performed at Tan Tock Seng Hospital in Singapore. Ethics approval was obtained from the Domain Specific Review Board (NHG DSRB Reference 2021/00169) prior to study commencement. Data were extracted from consecutive medical records of patients attending their annual outpatient DFS appointments. The inclusion criteria were patients aged ≥21 years old who underwent regular DFS. Patients with incomplete records were excluded. Extracted data included demographic information such as age, sex, ethnicity, diabetes type and self-reported smoking status. Relevant DFS parameters such as the right brachial systolic blood pressure, left brachial systolic blood pressure, right dorsalis pedis systolic blood pressure, right posterior tibial systolic blood pressure and right ASTP were also collected. Only data from the right lower limb were used, to adhere to the assumption of independence of data in statistical analysis. The DFS conducted in the outpatient setting was standardised and performed in accordance to the Tan Tock Seng Hospital podiatry service clinical protocols. Assessments were performed by any 1 of 3 trained podiatry assistants, each with an average practice experience of 4 years.

Ankle-brachial pressure index

The brachial and ankle systolic blood pressures were obtained using a standardised automated blood pressure monitoring device (Dinamap Carescape V100 Monitor, GE Healthcare, Chicago, US). Measurement of the systolic pressure of the brachial artery was performed by placing the cuff around either arm, 3cm above the elbow crease, with the arrow on the cuff indicating the arterial flow aligned to the artery being measured. The systolic pressures of the dorsalis pedis and posterior tibial arteries were measured by positioning the cuff 3cm above the malleoli, with the arrow on the cuff indicating the arterial flow aligned to the dorsalis pedis and posterior tibial arteries, respectively. The ABPI was calculated as the ratio of the higher of the right dorsalis pedis systolic blood pressure or right posterior tibial systolic blood pressure at the ankle, to the higher of the right or left brachial systolic blood pressure.[6,8-10,15,16] For our study, the reference test was defined as ABPI≤0.9 including when

both the right ankle systolic pressures were not detectable. An ABPI of ≤0.9 is well accepted to indicate PAD for routine DFS both internationally and in Singapore.[6,10,16,17]

Absolute systolic toe pressure and toe-brachial index

The ASTP was measured using a standardised automated Doppler device (Smartdop 30EX PPG, Hadeco Inc, Kawasaki, Japan). Measurements were performed by positioning the appropriately sized toe cuff around the hallux and placing the photoplethysmograph probe directly on the apex of the hallux, affixed with an adhesive tape. The TBI was calculated as the ratio of the right ASTP to the higher of the right or left brachial systolic blood pressure.[6]

Statistical methods

The demographic and clinical characteristics of patients were represented as mean and standard deviation for continuous variables and percentages for categorical variables. Normality of ABPI, ASTP and TBI were assessed using quantile-quantile (Q-Q) plots. To examine the diagnostic performance of ASTP and TBI against ABPI-determined PAD (ABPI≤0.9), receiver operating characteristic (ROC) analysis was conducted and area under the curve (AUC) was estimated for ASTP and TBI with 95% confidence interval (CI). The 2 AUCs were compared using DeLong's test for 2 correlated ROC curves. The optimal threshold for ASTP and TBI for detecting ABPI-determined PAD were estimated using Youden's index, and sensitivity and specificity of the threshold were reported with 95% CI. All statistical analyses were performed using R (R Core Team 2021, R Foundation for Statistical Computing, Austria) and pROC package was used for ROC analysis.[18] Statistical significance was fixed at two-sided 5% level for all tests. No a priori sample size calculation was done given the retrospective nature of this study. A post hoc power calculation revealed that our study had a minimum of 80% power to detect the difference between 2 estimated AUCs at two-sided 5% significance level. In general, an AUC of more than 0.9 is considered outstanding, 0.8–0.9 excellent, 0.7–0.8 acceptable and 0.5 suggests no discrimination.[19]

RESULTS

A total of 1,454 patients were included in our study, after excluding patients with data anomalies where TBI=0 or >1.75. There were 50.8% men and 49.2% women and the mean age was 63.1 (standard deviation [SD] 12.4) years. Our study population comprised 69.7% Chinese, 13.5% Indian, 10.1% Malay and 6.7% other ethnicities. A majority of the patients had type 2 diabetes (97%), with the remaining 3% having type 1 diabetes. Additionally, 16.3% of our study population were self-reported smokers.

The mean (SD) ABPI was 1.18 (0.12) with 3.8% of the study cohort indicated to have an ABPI ≤0.9 (Fig. 1). The mean (SD) ASTP was 117.9mmHg (26.7) and the mean (SD) TBI was 0.86 (0.18) (Figs. 2 and 3). The ABPI, ASTP and TBI were normally distributed based on their Q-Q plots, suggesting a good multiethnic representation of the diabetic population attending outpatient DFS in our study.

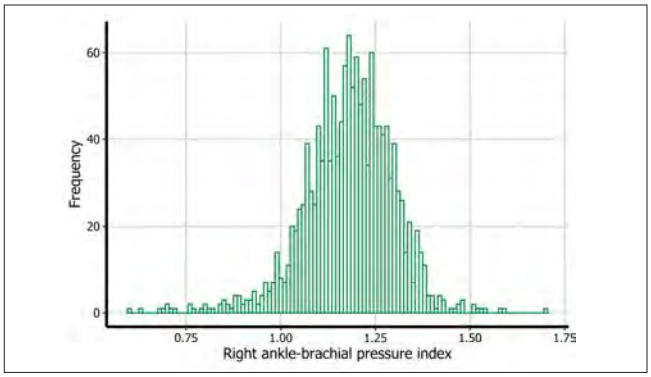

Fig. 1. Distribution of right ankle-brachial pressure index.

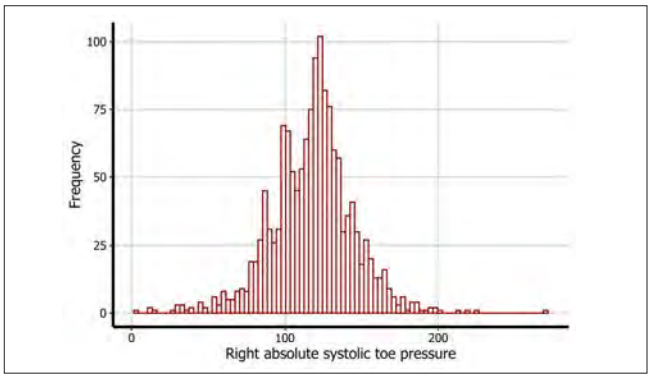

Fig. 2. Distribution of right absolute systolic toe pressure.

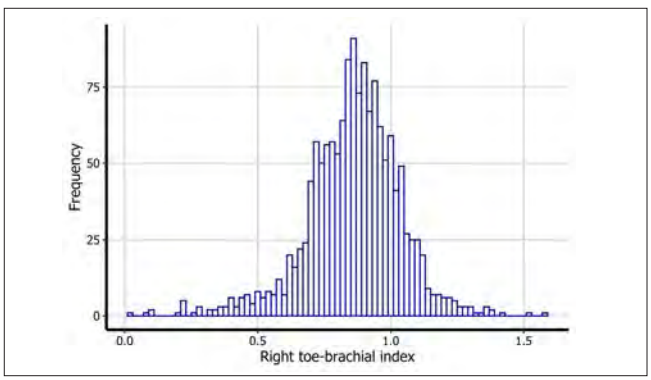

Fig. 3. Distribution of right toe-brachial index.

The ROC curves for right ASTP and right TBI were plotted (Figs. 4 and 5). When right ASTP was evaluated, the AUC was 0.89 (95% CI 0.85–0.94). Based on the Youden index, ASTP threshold value for indicating ABPI≤0.9 was 95.5mmHg with specificity at 0.86 (95% CI 0.84–0.87) and sensitivity at 0.84 (95% CI 0.73–0.93).

Results for right TBI showed an AUC of 0.94 (95% CI 0.90–0.98). Based on the Youden index, TBI threshold value for indicating ABPI≤0.9 was 0.7 with specificity at 0.89 (95% CI 0.88–0.91) and sensitivity at 0.95 (95% CI 0.89–1.00).

AUC differences between Chinese and non-Chinese study participants for both ASTP and TBI were not statistically significant for our study. Further evaluation utilising Delong's test on 2 correlated ROC curves between right ASTP and right TBI yielded a statistically significant difference between them (P<0.001) (Fig. 6).

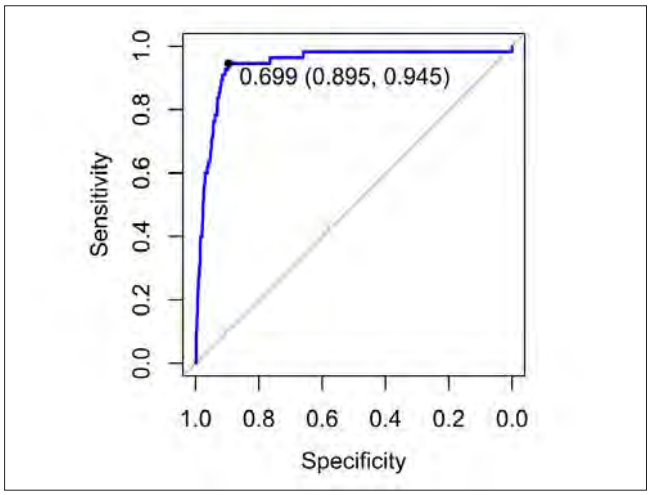

Fig. 5. ROC curve for detecting ABPI≤0.9 using TBI. Based on the Youden index, the optimal TBI threshold is 0.7 with specificity at 0.90 and sensitivity at 0.95.
ABPI: ankle-brachial pressure index; ROC: receiver operating characteristic; TBI: toe-brachial index

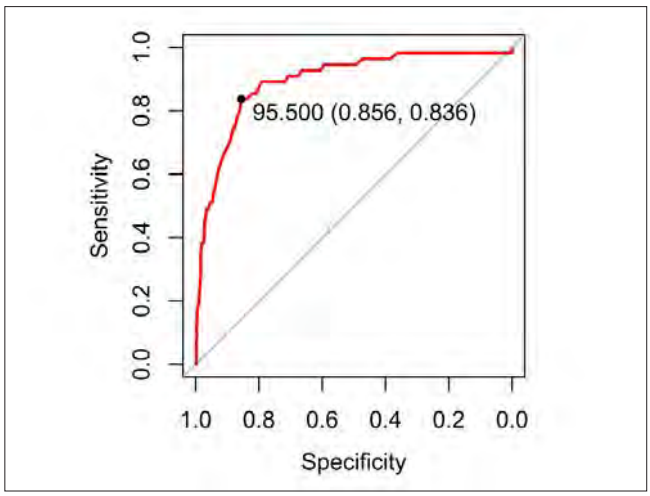

Fig. 4. ROC curve for detecting ABPI≤0.9 using ASTP. Based on the Youden index, the optimal ASTP threshold is 95.5mmHg with specificity at 0.86 and sensitivity at 0.84.
ABPI: ankle-brachial pressure index; ASTP: absolute systolic toe pressure; ROC: receiver operating characteristic

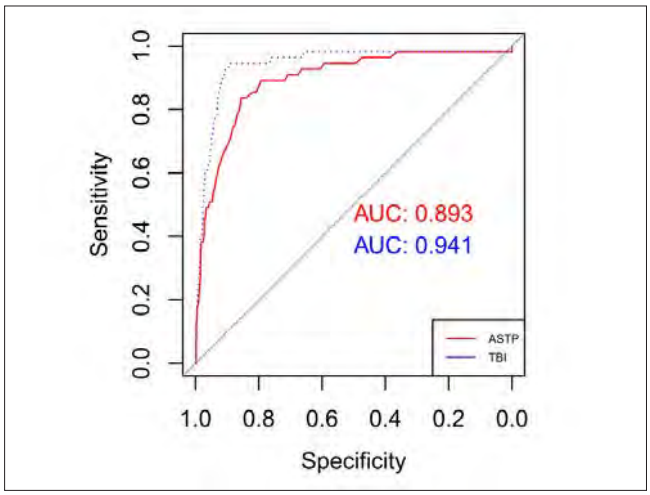

Fig. 6. Comparison of ROC curves for detecting ABPI≤0.9 between ASTP and TBI. The AUCs are 0.89 and 0.94 for ASTP and TBI, respectively (P<0.001, Delong's test).
ABPI: ankle-brachial pressure index; ASTP: absolute systolic toe pressure; AUC: area under the curve; ROC: receiver operating characteristic; TBI: toe-brachial index

DISCUSSION

ASTP and TBI yielded AUCs in the excellent and outstanding categories of 0.8–0.9 and >0.9, respectively. These results supported the use of ASTP or TBI as alternative measurements to ABPI≤0.9 to indicate PAD for risk stratification in routine DFS in Singapore. Although the difference in AUCs between ASTP and TBI was statistically significant in favour of TBI, ASTP could be considered for implementation in screening services due to its excellent AUC value and single parameter measurement characteristic. ASTP is easier to perform and time-saving as brachial systolic blood pressure measurement is not needed when compared to TBI. Time constraints have been reported to be a major deterrent to performing vascular assessments in practice.[20,21] In Singapore where the prevalence of diabetes is one of the highest in the world,[1] an accurate, time-saving and efficient measurement is needed to allow screening for ABPI-determined PAD during DFS that can also be performed on a large scale.

The indicative threshold value of TBI at 0.7 (specificity 0.89, sensitivity 0.95) for detecting an ABPI≤0.9 is in agreement with some of the internationally reported

threshold values and guideline recommendations of TBI<0.7 to be indicative of PAD.[16] Our results provided further evidence to support TBI<0.7 as the optimal threshold in indicating ABPI-determined PAD in routine DFS in a multiethnic diabetic population such as Singapore.

The derived indicative threshold value of ASTP at 95.5mmHg (specificity 0.86, sensitivity 0.84) for indicating ABPI≤0.9 is about 50% higher than the current recommended value of 60mmHg.[10] The current threshold of ASTP<60mmHg may be under-diagnosing many patients who may benefit from earlier detection and intervention during routine DFS. As the results of this study are consistent with previously reported threshold values of 97mmHg to be indicative of PAD,[14] the current recommendation of ASTP<60mmHg for indicating ABPI-determined PAD in DFS in Singapore needs to be reconsidered as more data and evidence become available.

One limitation of our study was the potential for measurement errors as only single readings were performed for each parameter. To minimise this, all readings were performed by 3 trained podiatry assistants. The accuracy of ABPI was another limitation. Although ABPI≤0.9 is considered the accepted standard in assessing PAD in routine DFS, limitations have been reported regarding its reduced accuracy in the presence of medial arterial calcification. However, ABPI is still the de facto standard recommended by international guidelines and is commonly used worldwide for routine DFS. Future studies may consider investigating how ABPI, TBI and ASTP compare with each other using colour duplex sonography as the reference test to overcome the limitation of ABPI. ROC analysis may be used to further investigate the optimal threshold value for indicating PAD for ABPI, TBI and ASTP, with colour duplex sonography as the reference standard, in a multiethnic diabetic population in Singapore.

CONCLUSION

Our study showed that ASTP or TBI may be used to detect ABPI-determined PAD in DFS. The optimal threshold values derived from a multiethnic Asian diabetic population were <0.7 for TBI and <95.5mmHg for ASTP. ASTP is an effective and efficient single measurement modality that may be used as an alternative to the well-established ABPI in DFS.

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ORIGINAL ARTICLE

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Pre- and apnoeic high-flow oxygenation for rapid sequence intubation in the emergency department (the Pre-AeRATE trial): A multicentre randomised controlled trial

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ABSTRACT

Introduction: Evidence regarding the efficacy of high-flow nasal cannula (HFNC) oxygenation for preoxygenation and apnoeic oxygenation is conflicting. Our objective is to evaluate whether HFNC oxygenation for preoxygenation and apnoeic oxygenation maintains higher oxygen saturation (SpO_2) during rapid sequence intubation (RSI) in ED patients compared to usual care.

Methods: This was a multicentre, open-label, randomised controlled trial in adult ED patients requiring RSI. Patients were randomly assigned 1:1 to either intervention (HFNC oxygenation at 60L/min) group or control (non-rebreather mask for preoxygenation and nasal prongs of at least 15L/min oxygen flow for apnoeic oxygenation) group. Primary outcome was lowest SpO_2 during the first intubation attempt. Secondary outcomes included incidence of SpO_2 falling below 90% and safe apnoea time.

Results: One hundred and ninety patients were included, with 97 in the intervention and 93 in the control group. Median lowest SpO_2 during the first intubation attempt was 100% in both groups. Incidence of SpO_2 falling below 90% was lower in the intervention group (15.5%) compared to the control group (22.6%) (adjusted relative risk=0.68, 95% confidence interval [CI] 0.37–1.25). Post hoc quantile regression analysis showed that the first quartile of lowest SpO_2 during the first intubation attempt was greater by 5.46% (95% CI 1.48–9.45%, *P*=0.007) in the intervention group.

Conclusions: Use of HFNC for preoxygenation and apnoeic oxygenation, when compared to usual care, did not improve lowest SpO_2 during the first intubation attempt but may prolong safe apnoea time.

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Keywords: Airway management, apnoeic oxygenation, high-flow nasal oxygenation, preoxygenation, rapid sequence intubation

INTRODUCTION

Critically ill patients in the emergency department (ED) have shorter safe apnoea times due to physiological distress from decreased cardiac output, increased shunting and reduced pulmonary reserves.[1] Hypoxia is a commonly encountered adverse event during rapid sequence intubation (RSI)[2] and is associated with cardiac arrest, neurological injury and death.[3] Therefore,

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CLINICAL IMPACT

What is New

- To our knowledge, this is the first randomised controlled trial in the emergency department in Singapore evaluating high-flow nasal cannula (HFNC) oxygenation for preoxygenation and apnoeic oxygenation in patients who required rapid sequence intubation.
- Our study showed that HFNC may prolong safe apnoea time.

Clinical Implications

- Patients with challenging intubation may benefit from the longer safe apnoea time provided by HFNC during preoxygenation and apnoeic oxygenation.

there is significant interest in prolonging safe apnoea time without hypoxia or bag-valve-mask (BVM) ventilation,[4,5] as the latter may cause aspiration risk in unfasted ED patients, unlike for most patients in intensive care units (ICUs). Existing strategies for preoxygenation include the use of high-flow face mask (HFFM),[6] such as the non-rebreather mask (NRM) or via well-fitting BVM without additional positive pressure for those with higher degree of respiratory compromise. Apnoeic oxygenation is commonly delivered through application of standard nasal cannula (NC) at 15L/min.[7-10]

Systematic reviews of apnoeic oxygenation in both ICU and ED settings suggest reduction in incidence of hypoxaemia.[5,11] However, these reviews included heterogenous studies with different apnoeic oxygenation strategies (high-flow nasal cannula [HFNC] versus standard NC at 15L/min) and have differing controls (no intervention, BVM, non-invasive ventilation [NIV] or no control at all).[5,11] Using HFNC for preoxygenation and apnoeic oxygenation in RSI may offer potential advantages over standard NC. These include better patient tolerance and generation of small amounts of positive end-expiratory pressure.[12] HFNC oxygenation during intubation has been studied in randomised trials,[13,14] and observational studies in ICUs[15,16] and EDs.[17,18] However, its role and effectiveness are still actively debated,[19-21] with inconsistent evidence regarding its efficacy compared to NIV,[22,23] HFFM[23,24] or BVM,[14] and whether it is best utilised in conjunction with NIV.[25] Importantly, there has been no randomised controlled trial in the ED that evaluates the use of HFNC for preoxygenation and apnoeic oxygenation in RSI. Little is known about its efficacy in preventing hypoxia in ED patients during the peri-intubation period.

In our trial, we aimed to evaluate if HFNC use at 60L/min for preoxygenation and apnoeic oxygenation will maintain higher oxygen saturation (SpO_2) for ED patients during RSI, compared to the usual care of preoxygenation with NRM and standard NC with at least 15L/min of oxygen flow for apnoeic oxygenation.

METHODS

Study design and setting

In this Pre- and Apnoeic high flow oxygenation for RApid sequence intubation in The Emergency department (Pre-AeRATE) study, an open-label, randomised, controlled trial, we enrolled adult patients who required RSI in EDs of the National University Hospital and Ng Teng Fong General Hospital in Singapore. Each ED receives over 110,000 attendances annually and performs 12–20 RSIs monthly. Pre-AeRATE was registered with ClinicalTrials.gov (NCT03396094). Ethics approval for waiver of consent at enrolment and delayed informed consent was obtained from the institutional ethics review board (DSRB reference number 2017/00348) in accordance with the Singapore regulations for clinical trials under emergency situations.[26]

Subjects were randomised at 1:1 ratio into intervention and control groups, stratified by study site, with variable blocks of 4 and 6 via a web-based randomisation service generated by an independent statistician. Allocation concealment was maintained until completion of randomisation. Blinding of the ED team and patient was not possible due to the intervention. Clinicians in the admitting ICUs were blinded to the study allocation. The full protocol for this study was published elsewhere.[27]

Selection of participants

Inclusion criteria were patients aged ≥21 years requiring RSI due to any condition. The following were excluded: active "do-not-resuscitate" orders; crash, awake or delayed sequence intubations; requiring non-invasive positive pressure ventilation; cardiac arrest; suspicion or confirmed diagnosis of base of skull fractures or severe facial trauma that precluded placement of NC; pregnant women; and those incarcerated.

Interventions

The intervention group using HFNC received 60L/min of warm and humidified oxygen at 37°C and fraction

of inspired oxygen (FiO_2) of more than 0.90 using the AIRVO 2 Humidifier with Integrated Flow Generator (Fisher & Paykel Healthcare Ltd, Auckland, New Zealand) during preoxygenation and apnoeic oxygenation phases. Control group was managed with usual care by preoxygenating using only NRM at flush rate, and then given at least 15L/min of non-humidified and non-heated oxygen from wall supply via NC for apnoeic oxygenation. Flush rate used for NRM preoxygenation reduces leak around the mask margins and is non-inferior to BVM, which is the other recommended modality.[28]

After ≥3 minutes of preoxygenation, induction medications were administered based on treating physician's discretion, and apnoeic oxygenation commenced as per allocation. Intubation was attempted after 30–60 seconds, depending on the paralytic agent. End of intubation was defined as correct placement of endotracheal tube with confirmation using quantitative end-tidal carbon dioxide ($ETCO_2$) monitoring.

Measurements and outcomes

Vital signs and airway features were assessed prior to preoxygenation. The primary endpoint was lowest SpO_2 during the first intubation attempt, defined as time taken from administration of paralytic agent until quantitative $ETCO_2$ was detected post-intubation if successful, or until the start of the second attempt if failed. The primary outcome analysis was restricted to the first intubation attempt as clinicians may deviate from initial treatment allocation based on their discretion after the first attempt. SpO_2 was measured using the pulse oximeters, Philips Intellivue MP30 Patient Monitor (Royal Philips, Amsterdam, the Netherlands) and Zoll R Series defibrillator (Zoll Medical Corporation, Chelmsford, US) at 2 different areas in the upper extremities. A research coordinator, nurse or clinician not involved in the intubation recorded the lowest SpO_2 and other variables collected during the attempts. Patients were monitored for peri-intubation adverse events (AEs) such as aspiration, arrhythmia and cardiac arrest during intubation or within 5 minutes after intubation. Main secondary outcomes were incidence of SpO_2 falling below 90% and safe apnoea time during intubation (duration of apnoea where SpO_2 remains ≥90% and censored at the time of successful intubation). Other secondary outcomes included number of intubation attempts, time (from induction) to successful intubation, peri-intubation AE, and various post-intubation clinical outcomes.

Sample size calculation

Based on our preliminary data (unpublished) and a previous study,[24] we anticipated a standard deviation of 14% in the lowest SpO_2. Enrolment of 184 patients (92 patients in each control and intervention groups) would provide statistical power of 80% (two-sided α of 0.05) to detect a 6% difference in lowest SpO_2,[15] allowing for a 5% dropout.

Data analyses

Analyses of baseline and efficacy data were performed with the intention-to-treat (ITT) population, stratified or adjusted for study site for outcome variables. Supplementary analyses of efficacy data were performed with the per-protocol (PP) population, comprising randomised patients who received FiO_2 of at least 0.70 during preoxygenation and apnoeic oxygenation with no major protocol deviation. This FiO_2 value was chosen as it is the minimum acceptable level to be comparable with that delivered by NRM.[29] Frequency and proportion of patients with any peri-intubation AE were summarised in the "as-treated" population, that is, according to actual approaches of preoxygenation and apnoeic oxygenation received.

Since distribution of lowest SpO_2 was highly skewed as observed in similar studies,[15,24] a stratified Mann-Whitney U test (namely the van Elteren test) was used to compare lowest SpO_2 between treatment groups. Post hoc analysis with quantile regression of lowest SpO_2 was performed with adjustment for covariates, selected backward stepwise into the final adjusted model.[30]

The Cochran-Mantel-Haenszel test was used to compare risk of SpO_2 below 90% between groups. The common relative risk (RR) was estimated with its 95% confidence interval (CI) by the Mantel-Haenszel method. Safe apnoea time during intubation and time to successful intubation were compared using the stratified log-rank test. The hazard ratios (HR) of SpO_2 falling below 90% and successful intubation were estimated from the Cox proportional hazards model. All analyses were performed using SAS 9.4 (SAS Institute, Cary, US) and $P<0.05$ indicated statistical significance.

RESULTS

From May 2018 to December 2019, a total of 518 patients were screened and 192 eligible patients were randomised, with 97 assigned to intervention group and 95 to control group. All intervention patients and 93 patients in the control group were included in ITT

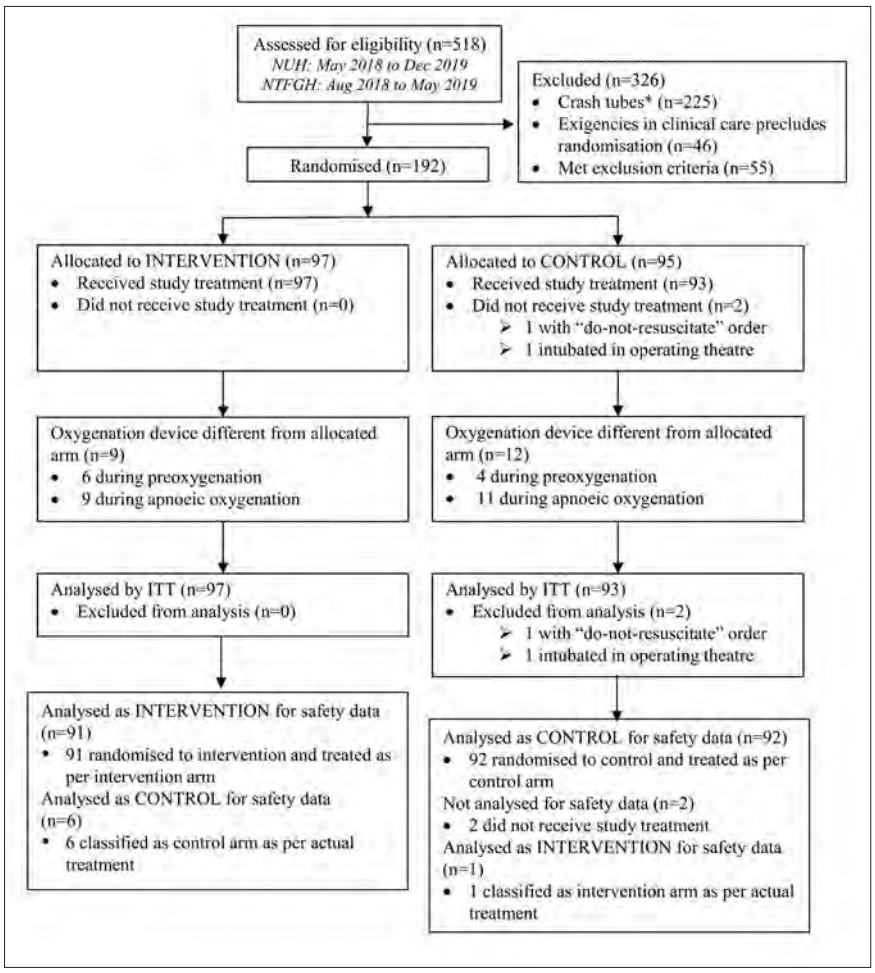

Fig 1. Flowchart illustrating patient enrolment, randomisation and treatment allocation.

ITT: intention-to-treat; NUH: National University Hospital; NTFGH: Ng Teng Fong General Hospital
*Refers to patients who were unconscious and apnoeic

analysis (Fig. 1). In the control group, 2 patients were excluded from data analysis as 1 had a "do-not-resuscitate" order established after randomisation and the other was intubated in the operating room.

Characteristics of study subjects

Overall, there was a predominance of males (124/190, 65.3%) with a mean age of 61.1 years (standard deviation [SD] 15.1) and mean estimated weight of 64.6kg (SD 14.0) (Table 1 and online Supplementary Table 1). The top 3 indications for intubation were non-traumatic intracranial, subarachnoid and subdural haemorrhages (57/190, 30.0%); shock states (28/190, 14.7%); and seizures (23/190, 12.1%).

Most patients were assessed to have no potential airway difficulty (121/190, 63.7%). A great proportion (176/190, 92.6%) were intubated using the C-MAC (Karl Storz, Tuttlingen, Germany) video laryngoscope; 20 patients (10.6%) had Grade 3 or 4 laryngeal view by the Cormack-Lehane classification. Most received NRM before randomisation (intervention 52/97 [53.6%] and control 44/93 [47.8%]; see online Supplementary Table 2) as part of prehospital care. Full data relating to the study procedure and treatment are summarised in the online Supplementary Tables 2 and 3.

Outcomes

Lowest SpO_2 was maintained at 100% during the first intubation attempt in more than half of the patients in both groups. There was no statistical difference in the lowest SpO_2 recorded during the first intubation attempt between the intervention (median SpO_2 100%, interquartile range [IQR] 96.0–100%) and control groups (median SpO_2 100%, IQR 91.0–100%)

Table 1. Demographics, baseline characteristics and airway features

	Intervention (n=97)	Control (n=93)	Total (N=190)
Demographics and baseline characteristics			
Age, mean (SD), years	60.4 (15.4)	61.9 (14.7)	61.1 (15.1)
Sex, male, no. (%)	59 (60.8)	65 (69.9)	124 (65.3)
Body mass index, mean (SD), kg/m^2	23.4 (4.0)	24.5 (4.7)	24.0 (4.4)
Indication for intubation, no. (%)			
Asthma/COPD	2 (2.1)	1 (1.1)	3 (1.6)
Fluid overload, cardiac/renal	4 (4.1)	5 (5.4)	9 (4.7)
Gastrointestinal bleed	6 (6.2)	6 (6.5)	12 (6.3)
ICH/SAH/SDH (non-traumatic)	34 (35.1)	23 (24.7)	57 (30.0)
Pneumonia	10 (10.3)	7 (7.5)	17 (8.9)
Shock states			
Cardiogenic	1 (1.0)	6 (6.5)	7 (3.7)
Septic	6 (6.2)	13 (14.0)	19 (10.0)
Hypovolaemic	0 (0)	2 (2.2)	2 (1.1)
Seizures	11 (11.3)	12 (12.9)	23 (12.1)
Trauma	7 (7.2)	5 (5.4)	12 (6.3)
Others	16 (16.5)	13 (14.0)	29 (15.3)
Glasgow Coma Scale, median (Q1, Q3)	7 (6, 14)	10 (6, 14)	8 (6, 14)
Vasopressor use, no. (%)	7 (7.2)	13 (14.0)	20 (10.5)
Abnormal chest X-ray findings, no. (%)	41 (42.3)	42 (46.2)	83 (44.1)
Airway features			
Potential airway difficulty, no. (%)			
Reduced neck mobility or in cervical collar	11 (11.3)	11 (11.8)	22 (11.6)
Airway obstruction	2 (2.1)	1 (1.1)	3 (1.6)
Facial trauma	2 (2.1)	1 (1.1)	3 (1.6)
Blood or vomitus in airway	17 (17.5)	13 (14.0)	30 (15.8)
Others	11 (11.3)	12 (12.9)	23 (12.1)
None	61 (62.9)	60 (64.5)	121 (63.7)
Mallampati score, no. (%)			
Class 1	9 (9.3)	6 (6.5)	15 (7.9)
Class 2	14 (14.4)	14 (15.1)	28 (14.7)
Class 3	11 (11.3)	16 (17.2)	27 (14.2)
Class 4	6 (6.2)	6 (6.5)	12 (6.3)
Not assessed	57 (58.8)	51 (54.8)	108 (56.8)

Table 1. Demographics, baseline characteristics and airway features (Cont'd)

	Intervention (n=97)	Control (n=93)	Total (N=190)
Mouth opening, no. (%)			
Normal (≥3 fingerbreadths)	45 (46.4)	36 (38.7)	81 (42.6)
Reduced (1 or 2 fingerbreadths)	25 (25.8)	32 (34.4)	57 (30.0)
Not assessed	27 (27.8)	25 (26.9)	52 (27.4)
Thyromental distance (fingerbreadth), no. (%)			
1	3 (3.1)	1 (1.1)	4 (2.1)
2	33 (34.0)	37 (39.8)	70 (36.8)
3	38 (39.2)	41 (44.1)	79 (41.6)
≥4	2 (2.1)	2 (2.2)	4 (2.1)
Not assessed	21 (21.6)	12 (12.9)	33 (17.4)
Cormack-Lehane classification of laryngeal view, no. (%)			
Grade 1	50 (51.5)	52 (56.5)	102 (54.0)
Grade 2	36 (37.1)	31 (33.7)	67 (35.4)
Grade 3	8 (8.2)	9 (9.8)	17 (9.0)
Grade 4	3 (3.1)	0 (0)	3 (1.6)
Type of laryngoscope, no. (%)			
Direct	9 (9.3)	5 (5.4)	14 (7.4)
Video	88 (90.7)	88 (94.6)	176 (92.6)

COPD: chronic obstructive pulmonary disease; ICH: intracranial haemorrhage; Q1: 25th percentile; Q3: 75th percentile; SAH: subarachnoid haemorrhage; SDH: subdural haemorrhage
Additional baseline demographics are presented in online Supplementary Table 1.

(Table 2 and Fig. 2). Comparison of lowest SpO_2 between the 2 groups using the stratified Mann-Whitney U test provided *P* values of 0.138 and 0.061 in ITT and PP populations, respectively (Table 2). A post hoc quantile regression analysis of the first quartile of lowest SpO_2 (adjusted for indication for intubation, potential airway difficulty and baseline SpO_2) estimated a difference of 5.5% (95% CI 1.5–9.5%, *P*=0.007) in first quartile between the 2 groups (online Supplementary Table 4). Outcomes were comparable between groups with respect to number of intubation attempts and time to successful intubation. Most patients were successfully intubated at first attempt (intervention group 80/97 [82.5%] versus control group 78/93 [83.9%]). Median time from induction to successful intubation was 3.0 minutes in the intervention group and 3.5 minutes in the control group (Table 2). Treatment in intervention group reduced the risk of SpO_2 falling below 90% by at least 30% during the first intubation attempt and any attempt (adjusted RRs 0.55, *P*=0.084; 0.52, *P*=0.057 in first and any attempt in the PP population; and adjusted RRs 0.68, *P*=0.213; 0.65, *P*=0.156 in first and any attempt in the ITT population). Median safe apnoea time was prolonged by 3.0 minutes in the intervention group (10 minutes) compared to the control group (7 minutes), with HR of SpO_2 falling below 90% = 0.57 (95% CI 0.28–1.12, *P*=0.104).

Incidences of ventilator-associated pneumonia and aspiration pneumonia were comparable between both groups (22.6% vs 22.7%). The treatment in the intervention group did not affect other clinical outcomes (Table 3). Seventeen (18.5%) patients in the intervention group and 13 (13.3%) patients in the control group experienced peri-intubation AE (Table 3).

DISCUSSION

In our cohort, SpO_2 was maintained at 100% in more than 50% of patients in both groups. Use of HFNC compared with routine care did not show any statistically

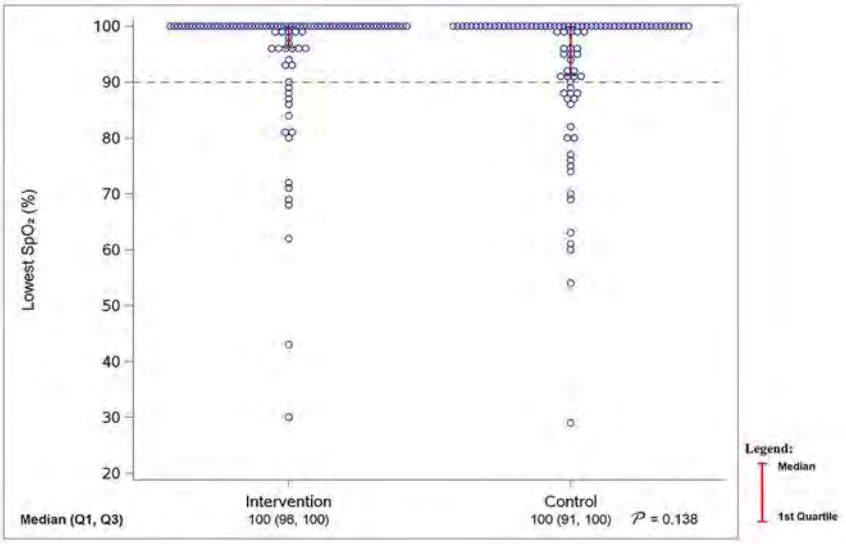

Fig. 2. Lowest SpO_2 during first intubation attempt.
SpO_2: oxygen saturation; Q1: 25th percentile; Q3: 75th percentile

significant difference in oxygenation during the first and subsequent intubation attempts. These observations could be due to the result of better physiological reserves in our cohort, which largely comprised patients with neurological emergencies. However, in our post hoc analysis, patients having lowest SpO_2 of below 95% with usual care were expected to have their lowest SpO_2 improved by an average of 5% if they were managed with HFNC (P=0.032 from Mann-Whitney U test in this subgroup). This is clinically important as the oxygen dissociation curve has a steep gradient below 90% and patients can reach critical hypoxic state in a span of seconds.[31] After adjustment for significant covariates using quantile regression analysis, the first quartile of lowest SpO_2 achieved during the first intubation attempt was greater by 5.5% (95% CI 1.5–9.5%, P=0.007) in the intervention group compared to the control group. This is consistent with a recent network meta-analysis, which showed that HFNC or NIV was better than conventional oxygen therapy for preoxygenation in ICU, at least in terms of lowest SpO_2 achieved.[32] Our study results add to the evidence by examining peri-intubation HFNC in ED patients.

An acceptable alternative strategy to optimise SpO_2 for intubation is through positive pressure ventilation using NIV.[4] Although NIV may be superior to conventional oxygenation therapy in preoxygenation, its use may be limited if patients are obtunded, have emesis or are unable to tolerate face masks.[22,33] Unlike NIV, HFNC allows apnoeic oxygenation during intubation without additional maneuvers. Studies comparing HFNC versus NIV have yielded inconsistent results. In the largest study to-date (n=313), neither modality reduced risk of severe hypoxia during intubation,[34] though there seems to be potential synergistic benefit in combining NIV with HFNC.[25] Nevertheless, combining the use of both NIV and HFNC has its problems of inadequate mask seal due to obstruction from the HFNC nasal cannula, as well as increase in procedural complexity and healthcare costs due to using 2 oxygen delivery devices. This may not be adequate given current dearth in evidence for this oxygenation method.

Our study showed that HFNC was safe compared to our usual care. The intervention patients had lower median pre-intubation Glasgow Coma Scale (7 [IQR 6–14]) compared to controls (10 [IQR 6–14]). However, we did not observe significant increase in aspiration risk and other adverse events. The safety of HFNC use in RSI was replicated in other existing literature.[14] Pending availability of more evidence, HFNC can be considered as a useful alternative in selected patients with contraindications to NIV, given its safety profile and better tolerance.

Apart from optimising preoxygenation, apnoeic oxygenation is a strategy that can prevent peri-intubation desaturation. Physiologically during apnoea, the much higher solubility of carbon dioxide in blood compared to oxygen allows oxygen to move more readily from alveoli into the bloodstream. This creates a sub-atmospheric alveolar pressure, allowing passive flow of oxygen from the pharynx to alveoli. Despite this rationale, previous randomised controlled trials in the ED and ICU did not demonstrate significant benefit

Table 2. Study outcomes at intubation

Characteristic	Intention-to-treat analysis		Per-protocol analysis	
	Intervention (n=97)	Control (n=93)	Intervention (n=86)	Control (n=91)
Lowest SpO_2 during first attempt, %				
Median (Q1, Q3)	100.0 (96.0, 100.0)	100.0 (91.0, 100.0)	100.0 (99.0, 100.0)	100.0 (91.0, 100.0)
Median diff (95% CI) [*P* value]	0 (0–4.0) [0.138[a]]		0 (0–1.0) [0.061[a]]	
Lowest SpO_2 during all intubation attempts, %				
Median (Q1, Q3)	100.0 (96.0, 100.0)	100.0 (90.5, 100.0)	100.0 (99.0, 100.0)	100.0 (91.0, 100.0)
Median diff (95% CI) [*P* value]	0 (0–4.0) [0.072[a]]		0 (0–2.5) [0.029[a]]	
Change in SpO_2 from baseline to end of preoxygenation, %				
Median (Q1, Q3)	0.5 (0, 3.5)	1.0 (0, 5.0)	0 (0, 3.0)	1.0 (0, 5.0)
Median diff (95% CI) [*P* value]	-0.5 (-2.0–1.0) [0.633[a]]		-1.0 (-2.0–1.0) [0.500[a]]	
Change in SpO_2 from end of preoxygenation to the lowest SpO_2 during all intubation attempts, %				
Median (Q1, Q3)	0 (-2.0, 0)	0 (-8.0, 0)	0 (-1.0, 0)	0 (-6.0, 0)
Median diff (95% CI) [*P* value]	0 (0–1.0) [0.094[a]]		0 (0–0.5) [0.029[a]]	
Number of intubation attempts, no. (%)				
1	80 (82.5)	78 (83.9)	72 (83.7)	76 (83.5)
2	14 (14.4)	9 (9.7)	11 (12.8)	9 (9.9)
≥3	3 (3.1)	6 (6.5)	3 (3.5)	6 (6.6)
P value	0.439[b]		0.648[b]	
Incidence of SpO_2 <90%, no. (%)				
At first attempt	15 (15.5)	21 (22.6)	10 (11.6)	19 (20.9)
Adj RR (95% CI) [*P* value]	0.68 (0.37–1.25) [0.213]		0.55 (0.27–1.10) [0.084]	
At any attempt	15 (15.5)	22 (23.7)	10 (11.6)	20 (22.0)
Adj RR (95% CI) [*P* value]	0.65 (0.36–1.19) [0.156]		0.52 (0.26–1.04) [0.057]	
Safe apnoea time, min				
Median (95% CI)	10.0 (8.0–U)	7.0 (5.5–12.0)	11.0 (8.0–U)	7.0 (6.0–12.0)
HR (95% CI)	0.57 (0.28–1.12)		0.48 (0.22–1.05)	
P value	0.082[c]	0.104[d]	0.050[c]	0.066[d]
Time to successful intubation, min				
Median (95% CI)	3.0 (3.0–4.0)	3.5 (3.0–4.0)	3.0 (3.0–4.0)	3.0 (3.0–4.0)
HR (95% CI)	0.98 (0.73–1.30)		1.00 (0.74–1.34)	
P value	0.842[c]	0.866[d]	0.940[c]	0.983[d]

Adj RR: adjusted relative risk; CI: confidence interval; HR: hazard ratio; Median diff: median difference; U: unable to be estimated; Q1: 25th percentile; Q3: 75th percentile; SD: standard deviation; SpO_2: oxygen saturation

[a] *P* value from van Elteren test

[b] *P* value from chi-squared test or Fisher's Exact test if more appropriate

[c] *P* value from stratified log-rank test

[d] *P* value from chi-squared test of hazard ratio

Table 3. Clinical outcomes and adverse events

Characteristic	Intervention	Control	Effect size (95% CI)	*P* value
Clinical outcomes (intention-to-treat population)				
	n=97	**n=93**	**Adj RR (95% CI)**	
Ventilator associated pneumonia and aspiration pneumonia, no. (%)	21 (22.6)	20 (22.7)	0.99 (0.58–1.70)	0.984[a]
Acute respiratory distress syndrome, no. (%)	3 (3.2)	5 (5.7)	0.58 (0.14–2.32)	0.431[a]
Mortality in ICU, no. (%)	14 (15.4)	11 (13.3)	1.17 (0.56–2.42)	0.682[a]
Mortality on discharge, no. (%)	24 (25.8)	21 (23.9)	1.08 (0.65–1.79)	0.770[a]
Died in ED	1 (1.1)	4 (4.5)		
Died on discharge	23 (24.7)	17 (19.3)		
Number of ventilated days			**Median diff (95% CI)**	0.381[b]
Median (Q1, Q3)	2.0 (1.0, 5.0)	2.0 (1.0, 5.0)	0 (-1.0, 1.0)	
Length of stay in ICU, days				
Median (Q1, Q3)	4.0 (2.0, 7.0)	3.0 (2.0, 8.0)	1.0 (-1.0, 2.0)	0.615[b]
Highest SOFA score				
Median (Q1, Q3)	7.0 (5.0, 10.0)	8.0 (6.0, 11.0)	-1.0 (-2.0, 0)	0.112[b]
Adverse events (as-treated population)				
	n=92	**n=98**	**Adj RR (95% CI)**	
Patients with any peri-intubation adverse events	17 (18.5)	13 (13.3)	1.39 (0.72, 2.71)	0.426[b]
Type of peri-intubation adverse events[d]				
Aspiration	1 (1.1)	0 (0)	NA	0.484[c]
Bradycardia	2 (2.2)	3 (3.1)	0.71 (0.12, 4.15)	1.000[c]
Cardiac arrest	3 (3.3)	1 (1.0)	3.20 (0.34, 30.17)	0.356[c]
Cardiac arrhythmia	0 (0)	3 (3.1)	NA	0.247[c]
Hypertension	4 (4.3)	5 (5.1)	0.85 (0.24, 3.08)	1.000[c]
Hypotension	4 (4.3)	3 (3.1)	1.42 (0.33, 6.18)	0.714[c]
Oropharynx or dental trauma	0 (0)	2 (2.0)	NA	0.498[c]
Regurgitation	0 (0)	0 (0)	NA	1.000[c]
Tachycardia	4 (4.3)	2 (2.0)	2.13 (0.40, 11.36)	0.433[c]
Others	0 (0)	0 (0)	NA	1.000[c]
Action taken to study treatment				
Continued with allocated group	15 (16.3)	13 (13.3)		
Changed to other oxygenation techniques	1 (1.1)	0 (0)		
Adverse events caused patient to be discontinued from study	0	0		

Adj RR: adjusted relative risk; CI: confidence interval; ED: emergency department; ICU: intensive care unit; median diff: median difference; NA: not available; Q1: 25th percentile; Q3: 75th percentile; SOFA: Sequential Organ Failure Assessment

[a] *P* value from van Elteren test

[b] *P* value from Cochran-Mantel-Haenszel test

[c] For number of events <10, Fisher's Exact test was used instead of Cochran-Mantel-Haenszel test

[d] Peri-intubation adverse events (occurring during or within 5 minutes after intubation) were defined as: bradycardia (defined as heart rate <60 beats per minute or decrease by >20%); tachycardia (defined as heart rate >100 beats per minute or increase by >20%); hypotension (defined as systolic blood pressure <90mmHg or decrease by >20%); hypertension (defined as systolic blood pressure >140mmHg or increase by >20%)

in improving lowest SpO_2 during intubation.[8,35] These negative findings could be a result of study procedural limitations. In both studies, oxygen flow at 15L/min was delivered through standard NC that are not designed for such flows. Additionally, a flow of at least 30L/min is necessary before positive airway pressures could be generated.[36] By using an HFNC device that can deliver up to 60L/min of high-flow oxygenation and that is specifically designed for this purpose, we were able to overcome these limitations. We showed a lower risk of SpO_2 falling below 90% in the intervention group at the first and any attempt, and safe apnoea time was prolonged by at least 3 minutes (Table 1). Despite lack of statistical significance, this could be clinically significant for 2 reasons. First, an SpO_2 of 90% represents the beginning of the steep down-sloping gradient of the oxygen dissociation curve, whereby small changes in the arterial partial pressure of oxygen (PaO_2) result in large changes in haemoglobin oxygen binding capacity.[37] Second, an ill average-sized adult could reach an SpO_2 of less than 60% in under 2 minutes once SpO_2 drops to 90%.[31] Hence, prolonging safe apnoea time is of utmost importance.

Pre-AeRATE has several strengths. First, this is the only randomised controlled trial to-date evaluating HFNC use for RSI in ED, in Singapore. Second, to our knowledge, this is also the largest trial (190 patients analysed) comparing HFNC with standard oxygen therapy during the peri-intubation period in any clinical setting, in Singapore.[13,14,24,38,39] Third, we conducted a post hoc analysis employing a quantile regression analysis as an endpoint due to the skewed distribution in such studies and in our cohort (Fig. 2), where a minority would experience much greater desaturation.[40] This allowed us to generate a hypothesis on the usefulness of HFNC on these patients in extremis. Despite similar decrease in median SpO_2 between the intervention and control arms, safe apnoeic time was noted to be prolonged by HFNC use. Fourth, this pragmatic trial reflects real-world conditions, and shows the plausibility of using HFNC for a time-sensitive procedure in ED and in patients with high aspiration risk, such as trauma with bloody airways and depressed consciousness.

Limitations

This trial has its limitations. First, the time-sensitive nature of RSI precluded measurements of PaO_2 in our protocol, thereby rendering stratification of severity based on hypoxaemia impossible. SpO_2 was used as an endpoint instead, as it is a ubiquitous non-invasive clinical parameter that allows better external validity. Second, it was impracticable to blind patients and ED clinical staff due to the nature of the intervention. However, objective measurements of SpO_2 by 2 separate devices and blinding of the ICU teams to study allocation made biasing of results unlikely. Third, consecutive recruitment was not possible due to clinicians focusing on resuscitation in the fast-paced ED environment.

Fourth, although we included patients requiring RSI due to any indication, our eventual cohort comprised 42.1% of neurological conditions (intracranial haemorrhage and seizures) and may under-represent those with predominantly cardiorespiratory compromise, who could provide greater physiological insight. As this trial was designed to be pragmatic, we did not specify strict inclusion criteria due to indications for intubation. The observation of more than 50% of patients in each treatment group maintaining SpO_2 at 100% during the first intubation attempt may be attributed to better cardiorespiratory reserves and low risk of desaturation in patients with predominant neurological conditions. By performing post hoc regression analysis of the first quartile of lowest SpO_2, we were able to evaluate the treatment effect on patients in physiological extremis who had higher desaturation risk (compared to the general study population). Although the intervention group comprised a slightly higher proportion of neurological conditions by chance, this difference was not statistically significant. Lastly, given our primary endpoint was to evaluate the lowest SpO_2 achieved, the study was not powered to make meaningful conclusions regarding patient-oriented outcomes such as mortality or length of ICU stay. Future studies should focus on such endpoints, other long-term outcomes and evaluate the cost-effectiveness of using HFNC during the peri-intubation period.

CONCLUSION

We found that HFNC use for preoxygenation and apnoeic oxygenation, when compared to usual care, did not show improvement in lowest median SpO_2 achieved during the first intubation attempt. However, such HFNC use may prolong safe apnoea time. Our study showed that patients without neurological indications for intubation were likely to desaturate faster, or have a more challenging intubation, and may benefit from the longer apnoea time that HFNC provides.

Disclosure

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Trial registration

ClinicalTrials.gov (NCT03396094). Registered on 10 January 2018.

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ORIGINAL ARTICLE

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Identifying high-risk hospitalised chronic kidney disease patient using electronic health records for serious illness conversation

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ABSTRACT

Introduction: This study aimed to identify risk factors that are associated with increased mortality that could prompt a serious illness conversation (SIC) among patients with chronic kidney disease (CKD).

Methods: The electronic health records of adult CKD patients admitted between August 2018 and February 2020 were retrospectively reviewed to identify CKD patients with >1 hospitalisation and length of hospital stay ≥4 days. Outcome measures were mortality and the duration of hospitalisation. We also assessed the utility of the Cohen's model to predict 6-month mortality among CKD patients.

Results: A total of 442 patients (mean age 68.6 years) with median follow-up of 15.3 months were identified. The mean (standard deviation) Charlson Comorbidity Index [CCI] was 6.8±2.0 with 48.4% on chronic dialysis. The overall mortality rate until August 2020 was 36.7%. Mortality was associated with age (hazard ratio [HR] 1.51, 95% confidence interval [CI] 1.29–1.77), CCI≥7 (1.58, 1.08–2.30), lower serum albumin (1.09, 1.06–1.11), readmission within 30-day (1.96, 1.43–2.68) and CKD non-dialysis (1.52, 1.04–2.17).

Subgroup analysis of the patients within first 6-month from index admission revealed longer hospitalisation stay for those who died (CKD-non dialysis: 5.5; CKD-dialysis: 8.0 versus 4 days for those survived, $P<0.001$). The Cohen's model demonstrated reasonable predictive ability to discriminate 6-month mortality (area under the curve 0.81, 95% CI 0.75–0.87). Only 24 (5.4%) CKD patients completed advanced care planning.

Conclusion: CCI, serum albumin and recent hospital readmission could identify CKD patients at higher risk of mortality who could benefit from a serious illness conversation.

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Keyword: Charlson comorbidity index, chronic kidney disease, dialysis, hospitalisation, mortality

INTRODUCTION

In-hospital cardiopulmonary resuscitation (CPR) for chronic kidney disease (CKD) patients is shown to have lower survival[1] and a higher proportion of survivors on maintenance haemodialysis were discharged to skilled nursing facilities.[2] Despite that, haemodialysis patients still preferred CPR during cardiac arrest[3] and there are lower do-not-resuscitate orders for the critically ill end-stage kidney disease patients.[4] Notably, there have been discordant views towards end-of-life care among patients, relatives and healthcare professionals locally.[5] Timely engagement of high-risk patients and their families in serious illness conversation (SIC) would better prepare for the inevitable trajectory and outcome. Facilitating concordance in end-of-life care and respecting patients' wishes should hence be our goal,[6] instead of focusing on life extension associated with lower family satisfaction.[7]

Living Matters adopted from Respecting Choices model was implemented for advance care planning (ACP) in Singapore almost a decade ago.[9] A retrospective study of ACP done between January 2011 and December 2015 in Singapore found that the median time between ACP completion and death was 7.27 months (95% confidence interval [CI] 6.35–8.18), with 63.2% of the participants completing ACP within only 3 months prior to death.[9] In addition, among individuals with chronic illness, almost 1 in 3 opted for CPR and

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CLINICAL IMPACT

What is New

- This study highlights use of the Charlson Comorbidity Index, serum albumin and 30-day readmission to prompt serious illness conversation among chronic kidney disease patients in Singapore.

Clinical Implications

- The study supports the use of poor prognosis factors to trigger discussions with patients and family to improve their end-of-life preparedness.

life-sustaining treatment even though the likelihood of survival was low. In a semi-structured interview with CKD stage 4–5 patients, care partners and healthcare professionals had discordant views during ACP discussion.[10,11] One of the challenges in implementing ACP is shifting the paradigm from life prolongation to maximum quality of life[12] without jeopardising care.

A population study from Singapore Eastern Regional Health System in 2016 showed that CKD was the most prevalent condition (31.9%) in healthcare utilisation.[13] A systematic review by Tonelli et al.[14] showed that CKD patients have higher mortality especially from cardiovascular cause. However, information regarding hospitalised Singapore CKD patients at high risk of mortality and utility of SIC is limited.

Using our hospital's electronic health records, we conducted a retrospective cohort study of CKD patients who were admitted from Aug 2018 to February 2020. The primary objective was to identify adverse factors associated with inpatient mortality in CKD patients. Secondary objectives were assessing the length of stay within 6-month of index admission stratified to dialysis status and mortality, and the utility of Cohen's 6-month haemodialysis mortality predictor[15] for hospitalised CKD patients. The study was approved by SingHealth Centralised Institutional Review Board with waiver of informed consent (CIRB Ref 2020/2103).

METHODS

Study design and subjects

This was a retrospective cohort study of CKD patients admitted to Sengkang General Hospital from August 2018 to February 2020. All cases in the study have been followed up for at least 6 months, last follow-up date was 31 August 2020 or date of patient's death. Clinical data were extracted from SingHealth's Electronic Health Records system, using the Electronic Health Intelligence System, which is an enterprise data repository that integrates information from multiple sources, including administrative, clinical and ancillary.

The International Classification of Disease-10 (ICD-10) codes used for identifying patients were N 185 CKD stage 5, N189 CKD unspecified, T827 AVF infection, T 828 Dialysis AVF stenosis/ thrombosis, T856 PD catheter obstruction, T8571 PD associated peritonitis and I 978 HD associated hypotension. Only admissions to our hospital were captured. Based on a retrospective study at the Singapore General Hospital, the average length of hospital stay was 4.6 days.[28] We hence decided to choose patients who had more than 1 admission from August 2018 to February 2020 and with any of the stays being 4 days or more. The former would serve as a trigger for SIC while the latter provided an adequate period to broach SIC while addressing the clinical issues.

Main outcome was inpatient mortality until end of follow-up. Other outcomes were length of stay within 6 months from index admission, high dependency and/ or intensive care unit (HD/ICU) admission and advance care planning (ACP) documentation.

Variables noted were:

- Patient demographics and laboratory results: age, sex, ethnicity, dialysis status and serum albumin
- Medical comorbidities
- Readmission within 30 days

Medical comorbidities identified were those for Charlson Comorbidity Index (CCI) scoring. These diseases were extracted using ICD-10 codes of the discharge diagnoses and problem list compiled from all admissions. We calculated the age-adjusted CCI using MdCal.

Primary analysis was to determine the factors associated with inpatient mortality. Secondary analysis was to assess the length of stay of all hospitalisations within the 6-month from index admission stratified according to the survival outcome and dialysis status. Subsequently, we used Cohen's 6-month haemodialysis mortality predictor calculator to assess the correlation with 6-month mortality in our study cohort. The variables used for age and serum albumin were based on index admission. The diagnosis of dementia and peripheral vascular disease were based on the discharge diagnosis and problem list within 6 months from the index admission. The "surprise question" was "Would I be surprised if this patient were to die within the next 12 months?". A "no" response to the question was applied if the patients had extent of care and resuscitation status documented within 6 months from the index admission.

Statistical analysis

Continuous variables were presented as mean and standard deviation for normally distributed data and median and interquartile range (IQR) for non-normally distributed data. Categorical variables were presented as number and percentage. Univariate and multivariable Cox regression analyses were performed to evaluate the risk factors associated with mortality. Kaplan-Meier survival function was used to compare the patients with CCI≥7 versus <7.[37] Length of stay for all hospitalisations at 6-month follow-up from index admission was stratified to dialysis status and mortality using Kruskal-Wallis test. Receiver operating characteristic analysis was performed to evaluate the association with Cohen's 6-month haemodialysis mortality predictor.

RESULTS

A total of 3,301 admissions from August 2018 to February 2020 with the diagnosis of CKD were extracted from our institution's Electronic Health Records. After excluding cases with only 1 admission, hospitalisation less than 4 days and incomplete data, 442 patients were included in the analysis (Fig. 1). Inpatient mortality outcome was collected up to August 2020. Median follow-up for the whole cohort was 15.3 months (IQR 8.1–20.1). The mean age was 68.6±13.6 years, 51.8 % were male, 65.6 % were Chinese, mean CCI was 6.8±2, median serum albumin was 34g/L (IQR 30.0–37.3), 45.7% had admission to HD/ICU, 48.4% were on chronic dialysis (haemodialysis or peritoneal dialysis) and 47.3% were readmitted within 30 days (Table 1).

Overall inpatient mortality outcome

The overall inpatient mortality rate was 36.7%. Univariate Cox regression showed that increasing age, CCI≥7, lower serum albumin, readmission within 30 days and CKD non-dialysis were associated with higher risk of mortality, $P<0.05$ (Fig. 2 and Table 2). On multivariable Cox regression, all these variables remained statistically significant factors for risk of mortality after adjustment for sex, ethnicity and HD/ICU admission. For every 10-year increase in age, the adjusted risk of mortality increases by 51%. The adjusted mortality risk for patients with CCI≥7 was 1.58 (95% CI 1.08–2.30) compared to those with CCI<7. Patients in the 30-day readmission group were also observed to have a higher risk mortality (HR 1.96,95% CI 1.43–2.68). Each 1g/L increment in serum albumin was associated with a lower mortality risk (HR 0.92, 95% CI 0.90–0.94). Chronic dialysis patients were also observed to have a lower risk of mortality (HR 0.66, 95% CI 0.46–0.96) compared to CKD non-dialysis patients (Table 2).

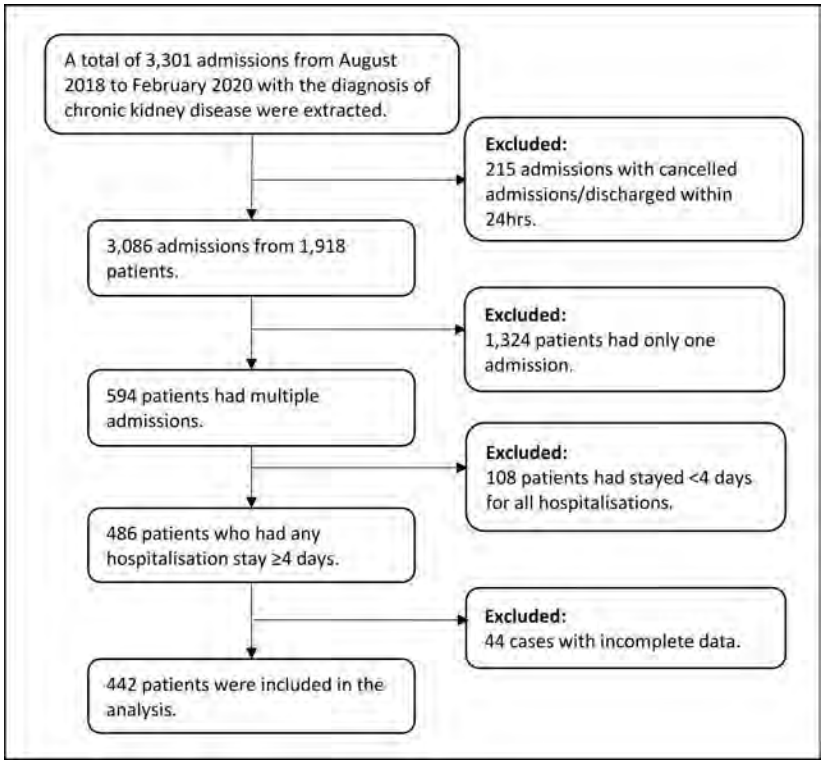

Fig. 1. Patient selection criteria.

Table 1. Characteristics of patients included in the study, stratified by survival status at the end of study period

	Overall N=442	**Survived** n=280	**Died** n=162
Age, mean (SD), years	68.6 (13.6)	65.4 (13.2)	74.2 (12.3)
Male sex, %	51.8	52.9	50.0
Chinese ethnicity, %	65.6	63.6	69.1
Charlson Comorbidity Index, mean (SD)	6.8 (2.0)	6.2 (1.8)	7.8 (2.0)
Serum albumin, g/L (IQR)	34.0 (30.0–37.3)	35.0 (32.0–38.0)	32.0 (27.0–36.0)
Chronic dialysis, %	48.4	54.6	37.7
High dependency/ICU, %	45.7	45	46.9
Readmission within 30 days, %	47.3	43.6	53.7
Follow-up, months (IQR)	15.3 (8.1–20.1).	18.8 (14.9–21.6)	6.9 (2.6–11.5)

ICU: intensive care unit IQR: interquartile range; SD: standard deviation

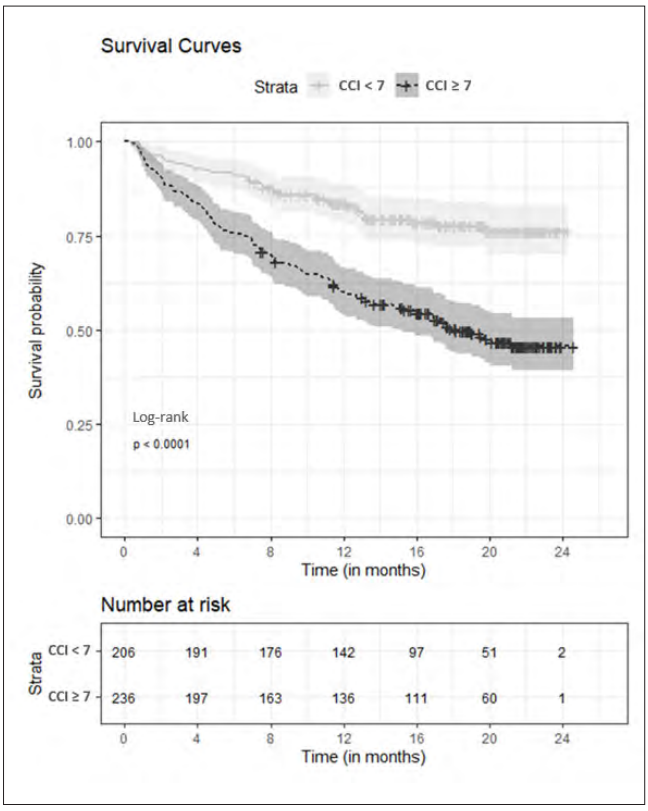

Fig. 2. Kaplan-Meier survival functions for patients with CCI<7 and CCI≥7.

ACP documentation

Only 24 out of 442 (5.4%) patients had completed ACP between August 2018 and February 2020. Among this group, mean age was 72.3 years and CCI was 7.9. Twelve (50%) were chronic dialysis patients and 10 had prior HD/ICU admission. A total of 11 (45.8%) patients who completed ACP had died by the end of August 2020, in contrast to 151 out of 162 (93.2%) patients who died without ACP completion. We do not have the data for ACP referral and incomplete ACP.

Subgroup analysis

Length of stay and high dependency/ICU admission at 6 months

We decided to look at the length of stay for all hospitalisations at 6-month from the index admission as the median follow-up time for those who died was 6.9 months. Patients were stratified according to their dialysis status and survival outcome (Table 3). There were a total of 75 deaths (17.0%) out of the 442 patients within 6 months from the index admission.

Kruskal-Wallis test showed that there were statistically significant differences in the median length of stay between the different groups of patients, $P<0.001$ (Table 3). Dunn's test with Bonferroni Correction showed that the length of stay for those who died at 6-month was statistically significantly longer (CKD-non dialysis: 5.5 days; CKD-dialysis: 8.0 days) as compared to those who survived (4.0 days), regardless of dialysis status (Table 3). No statistically significant differences in the median ICU/HD days were observed among groups, $P=0.122$ (Table 3).

Utility of Cohen's 6-month haemodialysis mortality predictor

We applied Cohen's haemodialysis mortality predictor to our study cohort, correlating it to the chance of survival at 6 months from index admission. The association with predicted mortality probability was high, irrespective of their dialysis status. The C-statistic was 0.81 (95% CI 0.75–0.87) (Fig. 3).

Table 2. Univariate and multivariable Cox regression model with mortality as the outcome variable

	Univariate				Multivariable			
	P value	Unadjusted HR	95% CI		*P* value	Adjusted HR	95% CI	
			Lower	Upper			Lower	Upper
Age (every 10-year increase)	<0.001	1.57	1.38	1.79	<0.001	1.51	1.29	1.77
Sex								
Female	reference				reference			
Male	0.482	0.90	0.66	1.22	0.984	1.00	0.73	1.38
Ethnicity	0.377				0.618			
Chinese	reference				reference			
Malay	0.575	0.90	0.61	1.31	0.275	1.25	0.84	1.88
Indian	0.202	0.63	0.31	1.28	0.645	0.84	0.41	1.74
Others	0.208	0.61	0.29	1.31	0.528	1.29	0.58	2.88
CCI								
<7 (n=206)	reference				reference			
≥7 (n=236)	<0.001	2.71	1.91	3.85	0.018	1.58	1.08	2.30
Serum albumin (g/L) (every unit increase)	<0.001	0.92	0.90	0.94	<0.001	0.92	0.90	0.94
Chronic dialysis								
No	reference				reference			
Yes	0.001	0.55	0.40	0.76	0.028	0.66	0.46	0.96
Readmission within 30 days								
No	reference				reference			
Yes	0.001	1.71	1.25	2.33	<0.001	1.96	1.43	2.68
HD/ICU utilisation								
No	reference				reference			
Yes	0.876	1.03	0.75	1.40	0.031	1.48	1.04	2.11

CCI: Charlson Comorbidity Index; CI: confidence interval; HD/ICU: high dependency/intensive care unit; HR: hazard ratio

Table 3. Total in-hospital stay and high dependency/ICU admission at 6-month follow-up

	Survived		Died		*P* value
	Non-dialysis (n=178)	Dialysis (n=189)	Non-dialysis (n=50)	Dialysis (n=25)	
Cumulative LOS, days[a]	2,891	4,754	1,317	1,117	
Total number of admissions	500	598	172	70	
Average number of admissions per index case	2.8	3.2	3.4	2.8	
LOS, mean (SD), days	5.8 (6.8)	8.0 (12.8)	7.7 (7.8)	16.0 (24.0)	
LOS, median (IQR)	4.0 (2.0–6.0)	4.0 (2.0–9.0)	5.5 (3.0–9.0)	8.0 (3.5–15.3)	
Mean rank of LOS, days	626.5	661.0	755.4	857.9	<0.001
HD/ICU admissions					
Total days	121	296	56	117	
Total number of admissions	57	113	14	28	
Average number of admissions per index case	0.3	0.6	0.3	1.1	
HD/ICU, mean (SD), days	2.1 (1.6)	2.6 (2.7)	4.0 (4.8)	4.2 (4.8)	
HD/ICU, median (IQR), days	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.8–4.0)	2.0 (1.0–4.8)	
Mean rank of HD/ICU, days	97.8	103.9	126.4	124.7	0.122

HD/ICU: high dependency/intensive care unit; IQR: interquartile range; LOS: length of stay
[a] The total length of stay in each admission within the first 6 months from index admission

DISCUSSION

CKD has a significant impact on global health with regards to morbidity and mortality.[16] Data from the chronic renal insufficiency cohort demonstrated that high hospital utilisation was associated with a trajectory towards mortality among CKD patients.[17] Risk of fatal hospitalisation is known to be higher in dialysis and CKD compared to non-CKD admissions.[18] With all this in mind, timely discussion to explore the goals of care with patients and families is important since shared decision making is crucial to align the subsequent care plans. Achieving concordance in goals of care will reduce decisional burden when confronting uncertainties, while honouring the patients' wishes.

End-stage kidney disease patients were more likely to receive active treatment and ICU admission compared to patients with other major organ diseases.[4] Such dissociation between the intensity of care despite high mortality among CKD patients occurs because of overly optimistic outcome prognostication[19] and higher perceived life expectancy[20] by dialysis patients. A substantial proportion of patients (45.7%) required HD/ICU utilisation in our cohort. However, this might be an over-representation because dialysis patients who need vasopressor support or non-invasive ventilation are admitted to our HD unit for dialysis.

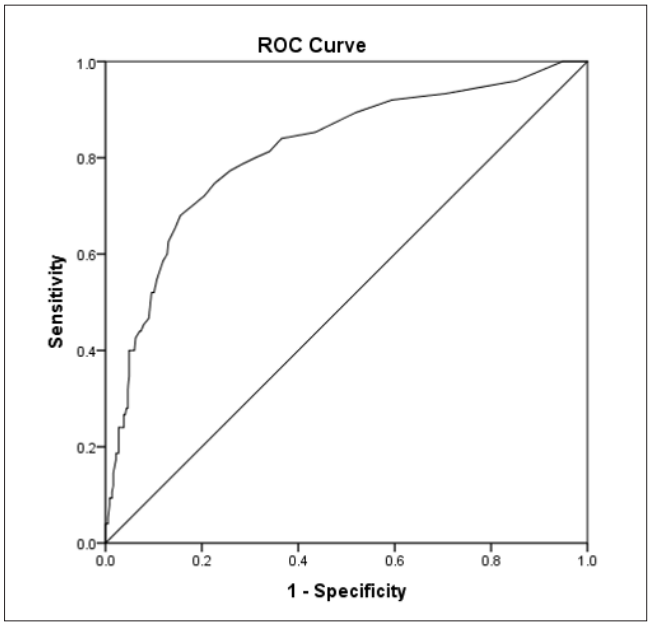

Fig. 3. ROC curve to evaluate the performance of the Cohen's haemodialysis mortality predictor.[a]
ROC: receiver operating characteristic
[a] Diagonal segments are produced by ties

Despite significant mortality (36.7%) in our cohort study of hospitalised CKD patients, completion of ACP was low (5.4%). However, a survey conducted among

community-dwelling Singaporeans revealed willingness to discuss ACP in particular those of older age, with life-threatening illness and with ACP knowledge.[38] The dissonance between expectation and reality prompted us to study factors associated with mortality. If we were able to identify patients at high risk of early mortality, we could then initiate SIC such as ACP as part of clinical care. Local experience has shown that 90% of ACP was completed in the acute hospital setting,[9] hence our choice of studying an inpatient cohort. We looked at well-established mortality factors such as age, CCI,[21-23] serum albumin,[24,25] readmission[17,18] and ICU admission.[26,27]

Based on our hospital's electronic health records, we found that higher CCI, hypoalbuminemia, readmission within 30 days, and CKD non-dialysis patients had higher in-patient mortality. There have been conflicting studies on CCI and mortality outcome in CKD patients, some reporting an association[21,22] but others not.[29] The heterogeneity in study populations, setting and duration of follow-up could explain the different findings. Nonetheless, a study from Korea demonstrated that for maintenance haemodialysis patients, CCI predicted mortality, especially for scores ≥7.[38] The CCI score in our study was based on the cumulative diagnoses made throughout the study period, and therefore reflected cumulative burden of disease. In this context, we found a parallel between CCI score and mortality, in particular when comparing the score of ≥7 to lower. We felt that the cumulative CCI calculation when the patients were admitted with new events had better prognostic value than a single time point for the CCI score. We also noted that median serum albumin was low for our cohort at 34.0 g/L (IQR 30.0–37.3). Nonetheless, the degree of hypoalbuminemia remained significantly associated with mortality, which was consistent with other studies.[24]

Readmission within 30 days has been widely used to assess quality of healthcare delivery and cost. In our study, we also found an association with mortality. A study from Alberta, Canada shown that chronic dialysis patients had longer hospitalisation stays and were more likely to receive HD/ICU care.[30] In our cohort, the median follow-up for those who died was 6.9 months (IQR 2.6–11.5). In order to standardise the comparison for hospitalisation stay and survival, we decided to assess total in-hospital stay and death within 6 months from index admission. In this sub-group, mortality rate was 17%. Patients who died, regardless of dialysis status, had longer length of stay than those who survived. However, HD/ICU utilisation was not significantly different between the groups. Given these patients with higher mortality risk, timely discussion on goals and end-of-life care is critical.

Various risk stratification tools[29,31] have been studied to predict survival in CKD patients. One of the readily accessible online calculators is the Cohen's 6-month mortality on haemodialysis derived from prevalent community dialysis patients.[15] Our population included non-dialysis CKD in an acute hospital setting, while the calculator was derived from an ambulatory chronic haemodialysis setting. Nonetheless, our study demonstrated Cohen's model has reasonable predictive ability to discriminate 6-month mortality in CKD patients. The variables used in the calculator were age, serum albumin, whether the patient had dementia, and whether he/she had peripheral vascular disease. Compared to the cohorts used in Cohen's study,[15] our population was older (mean age 68 compared to 61) and a high proportion had low serum albumin <35g/L (normal range 40–51 g/L). There was significant deviation in the survival estimate for those >80 years old and those with albumin <30g/L (data not shown). The calculator also has a question asking if the clinician would be surprised if the patient died in the next 12 months. There might be a bias since we entered a "no" in response to the "surprise question" for those with documented resuscitation and extent of care plan. Establishment of such plans presumably may indicate anticipation of deterioration in a critically ill patient. The "surprise question" itself to identify patients near end-of-life should not be used in isolation.[32] Despite that, 6-month mortality on haemodialysis predictor[15] has shown its applicability in hospitalised CKD patients in our study. The utility has to be contextualised and further validation studies are required.

There were many limitations to our study. Data were retrieved only from our hospital's electronic health records, with no case note review to validate the information retrieved from the system. Since medical comorbidities were based on discharge diagnoses and problem lists, CCI could be incomplete. CKD patients may also have been missed out if the diagnosis was not coded. All events (death and admissions) were limited to those that occurred within our hospital. In addition, for the mortality outcomes, it was not possible to follow up all participants for the same amount of time after index admission. Information such as functional status[33] and frailty,[34-36] which are important factors and can enhance accuracy of mortality prediction, was not included due to incomplete data entry.

In conclusion, use of electronic health records might serve as a readily accessible tool to trigger SIC such as ACP. Hospitalised CKD patients who have readmission

within 30 days, CCI≥7 and lower serum albumin are at higher risk of mortality. The CCI score derived from the medical history and admitting diagnosis has better reflection on the cumulative burden of disease, therefore providing more precise information for the disease trajectory than the baseline CCI. Further studies have to be done to validate the utility of Cohen's 6-month mortality predictor in the acutely hospitalised CKD/dialysis population.

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REVIEW ARTICLE

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Determinants of emergency department utilisation by older adults in Singapore: A systematic review

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ABSTRACT

Introduction: Adults aged ≥60 years contribute to disproportionately higher visits to the emergency departments (ED). We performed a systematic review to examine the reasons why older persons visit the ED in Singapore.

Methods: We searched Medline, Embase and Scopus from January 2000 to December 2021 for studies reporting on ED utilisation by older adults in Singapore, and included studies that investigated determinants of ED utilisation. Statistically significant determinants and their effect sizes were extracted. Determinants of ED utilisation were organised using Andersen and Newman's model. Quality of studies was evaluated using Newcastle Ottawa Scale and Critical Appraisal Skills Programme.

Results: The search yielded 138 articles, of which 7 were used for analysis. Among the significant individual determinants were predisposing (staying in public rental housing, religiosity, loneliness, poorer coping), enabling (caregiver distress from behavioural and psychological symptoms of dementia) and health factors (multimorbidity in patients with dementia, frailty, primary care visit in last 6 months, better treatment adherence). The 7 included studies are of moderate quality and none of them employed conceptual frameworks to organise determinants of ED utilisation.

Conclusion: The major determinants of ED utilisation by older adults in Singapore were largely individual factors. Evaluation of societal determinants of ED utilisation was lacking in the included studies. There is a need for a more holistic examination of determinants of ED utilisation locally based on conceptual models of health seeking behaviours.

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Keywords: Aged, elderly, emergency medical services, healthcare utilisation, health services

INTRODUCTION

Older adults in Singapore contribute to a disproportionately higher number of visits to the emergency department (ED), mirroring trends around the world.[1,2] For instance, hospital admissions among those aged ≥65 years have been on the rise from 2018 to 2020, contributing a growing burden to ED services over the last decade.[3] In 2014, the rise in acute hospital admissions led to a hospital bed crunch, where bed occupancy rates increased to 87%.[4] Singapore has an ageing population, and it is projected that by 2035, the proportion of Singaporeans ≥65 years will be 32%.[5]

Compared to younger patients, older patients tend to have more complex healthcare needs requiring extensive investigations. They are also more likely to be hospitalised and have multiple comorbidities that require management beyond the scope of primary care physicians (PCPs).[6] Visiting the ED is not without risk for older patients, as they are more susceptible to hospitalisation and adverse events when compared to younger patients.[7]

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CLINICAL IMPACT

What is New

- Major determinants of ED utilisation by older adults in Singapore were individual factors such as the type of residence, religiosity, sense of loneliness, coping mechanisms, and health factors. Evaluation of societal determinants of ED utilisation was lacking in the included studies.

Clinical Implications

- There is a need for a more holistic examination of determinants of ED utilisation locally based on conceptual models of health seeking behaviours.

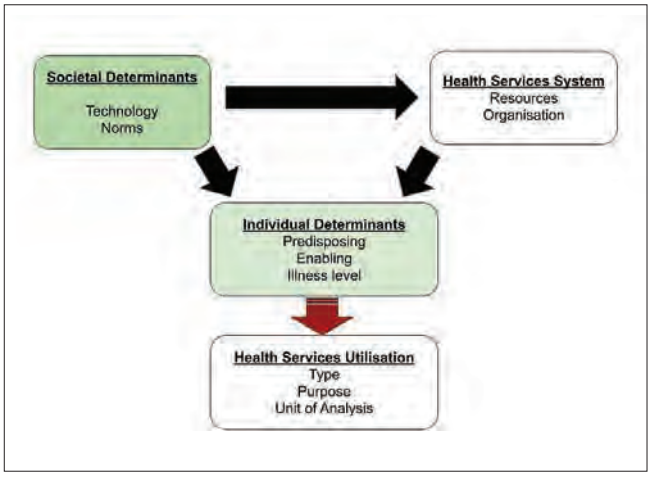

Fig. 1. Andersen and Newman's model of healthcare utilisation. (Reproduced with permission from *The Milbank Quarterly*.)

Upon discharge from the ED, older patients harbour increased risks of poorer outcomes, resulting in a reduction in community mobility that may not improve subsequently.[8]

With population ageing, increased life expectancy, and the projected increase in healthcare utilisation by older adults in Singapore,[9] it is imperative to understand the various determinants driving ED utilisation by older adults. Hence through this systematic review, we aimed to identify the determinants of ED utilisation by older adults in Singapore, adopting Andersen and Newman's model for a more holistic view of these determinants.

In a systematic review by McCusker et al. in 2003,[10] Andersen's behavioural model was modified to study the determinants of ED utilisation. However, Andersen and Newman proposed a newer model in 2005,[11] as shown in Fig. 1. Factors influencing ED utilisation are broadly categorised into societal and individual determinants in Andersen and Newman's model. Both determinants influence the infrastructure of health services provided within the country. Societal determinants include technology and social norms, whereas individual determinants include predisposing, enabling and health factors.[11] Predisposing factors are patient socio-demographic characteristics that can incline or deter a patient from utilising healthcare. Enabling factors encompass the influence of family and community, with examples including marital status, living conditions and geographical accessibility to PCPs or EDs. Health factors can be divided into perceived (subjective) need or evaluated (objective) need.

METHODS

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] It is registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021253770). Ethical approval was not required as all data used were derived from aggregated public sources and contained no individually identifying information.

Search strategy

The search strategy was developed in consultation with a medical information specialist (senior librarian at National University of Singapore). Three bibliographic databases were searched from 1 January 2000 to 31 December 2021: Medline, Embase and Scopus. Medical Subject Headings (MeSH) terms used included "aged", "health services for the aged", "health services accessibility", "emergency service, hospital" and "emergency medical services". Emtree subject headings used were "aged", "hospital", "emergency health service", "emergency medicine" and "emergency ward". "Singapore" was included in all searches. The full search strategy is available under Supplementary Materials in the online version of this article. References of relevant sources were hand-searched to identify additional relevant articles. Articles were exported to Endnote X9 (Clarivate Analytics, Philadelphia, US) for screening.

Selection criteria

Studies evaluating one or more determinants of ED utilisation by older adults in Singapore are included. The study will be included as long as one of the study participants is older than 60 years. The United Nations defines older adults as those at and above 60 years,[13] while Singapore defines it at 65 years and above.[14] As we have limited studies on our research question, we have utilised the age threshold specified by the United Nations

to capture a larger study population. We posit that there is unlikely to be major differences to the determinants of utilisation between the age of 60 and 65 years. The studies should indicate that older adults have sought care at the ED.

Studies that evaluated determinants of healthcare utilisation in other contexts such as urgent care centres or primary care clinics that are open beyond office hours were excluded. Papers that only studied presenting complaints, revisits or frequent visits were also excluded. Revisits, frequent and inappropriate visits were excluded as these are only a proportion of the patients that visit the ED, while our study focuses on determinants of any visit. Non-English papers were not included.

Data extraction

The following study characteristics were identified and extracted from the included studies: (1) author and year, (2) study design, (3) study population, (4) sample size and sampling methods, (5) outcome variable(s), (6) data source for outcome(s), (7) individual determinants, (8) societal determinants, and (9) data source for determinants. The determinants examined were classified according to societal determinants and individual determinants. The statistically significant determinants of ED utilisation were identified in the studies, together with their effect size.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was validated and used for evaluating the quality of the included studies.[15] A modified version of the scale was adopted and modified for cross-sectional studies as the original NOS only includes assessment of the quality of cohort and case-control studies.[16] This modified scale was used by a prior study with similar criteria of assessment—selection, comparability and outcomes of study.[16] Modifications were also made to the assessment criteria to suit the context of our study.

For the randomised controlled trial included in our study (Ong 2018),[17] the Critical Appraisal Skills Programme (CASP) tool was used.[18] The CASP aims to review the reliability and applicability of findings published in studies, and provides checklists for different study designs.[18] The CASP randomised controlled trial checklist was last updated in 2010 taking into consideration the CONSORT 2010 guidelines.[18] The CASP assessment of the randomised controlled trial is included in the Supplementary Materials of the online article. Two reviewers (XRT and PPP) independently appraised the included studies, with disagreements resolved in consultation with a third reviewer (FJS). The original and modified NOS are included in the Supplementary Material.

RESULTS

Literature retrieval

The search and selection process is displayed in a PRISMA flow chart[12] in Fig. 2. The database search yielded a total of 134 articles, and an additional 4 articles were identified from hand searching and additional sources. After removal of duplicates, 113 articles were screened for their eligibility through titles and abstracts, and 14 articles shortlisted for full-text screening. Upon full-text screening, 7 papers were excluded as they only measured determinants of frequent admission (n=2), only measured determinants for inappropriate attendances (n=1) and only measured determinants for readmission (n=4). Finally, 7 papers were identified and included in our review.[17,19–24]

Characteristics of included studies

The characteristics of included studies are presented in Table 1.

Demographics of older adults

In the included studies, the majority of older adults studied were aged 60 and above. Data from the Singapore Longitudinal Ageing Study [25] were used in 1 study while data from the Well-being of the Singapore Elderly study were used in 2 studies.[24] The Singapore Longitudinal Ageing Study provides a large database of community-dwelling older adults for gerontology research purposes from 2003 to 2020 while the Well-being of the Singapore Elderly investigates depression and dementia among older adults nationwide over 3 years. However, the Singapore Longitudinal Ageing Study only included Chinese patients in Ng et al.'s study.[19] Older adults residing within the regional healthcare systems—Singapore Health Services[17,22] and National Healthcare Group[21]—were being studied. Other subpopulations that were studied included persons with dementia (PWD), older adults living alone and those residing in public rental housing.

Measurements of ED utilisation

Most of the included studies (4 out of 7) measured ED utilisation dichotomously, while 2 studies reported the frequency of ED visits. In the study by Ng et al.,[19] hospitalisations in the past year were used as an indicator of ED utilisation, assuming that majority of older adults who were hospitalised came in through the ED. ED utilisation was measured over a period ranging from 3 to 12 months in the included studies. Two studies used the

Table 1. Characteristics of included studies

Author (year)	Design of study	Study population	Sample size and sampling methods	Outcome variable(s)	Data source for outcome	Individual determinants	Societal determinants	Data source for determinants
Ge et al.[21] (2020)	Cross-sectional study	Community-dwelling older adults aged ≥60 years	701 Random selection within eligible household using Kish grid	Healthcare utilisation, including emergency department visits	Administrative database	Frailty		Questionnaire
Lau et al.[23] (2021)	Cross-sectional study	Singaporean residents aged ≥60 years	399 caregiver-PWD dyads Disproportionate stratified sampling	Emergency service utilisation and hospital admission	Questionnaire from Well-being of the Singapore Elderly (WiSE) study	Caregiver distress from BPSD Caregiver psychiatric comorbidity Caregiver burden Multimorbidity and severity of dementia among PWD Household composition and income of PWD		Administrative database
Ng et al.[19] (2009)	Cross-sectional study	Community-living Chinese elderly aged ≥65 years	1281	Hospitalisations (≥1) in past year	Questionnaire from Singapore Longitudinal Ageing study	Successful ageing		Questionnaire
Ong et al.[17] (2018)	Randomised controlled trial	Older adults aged ≥65, living alone, experienced fall in last 6 months	162 elderly Random sampling for 90 to receive telephone follow-up and 72 to receive MAPS	Number of emergency department visits	Telephone interview	Telephone follow-up	MAPS	Questionnaire
Seng et al.[22] (2019)	Retrospective cohort study	Patients under care of SingHealth Regional Health System	10400 elderly staying in public rental housing	Number of emergency department visits	Administrative database	Socio-demographics (age, gender, ethnicity, type of housing) Comorbidities		Administrative database
Vaingankar et al.[24] (2017)	Cross-sectional study as part of WiSE	Singapore residents aged ≥60 years	2102 Random selection with disproportionate stratified sampling	Service utilisation in past 3 months, including emergency room visits	Interviewer administered survey	Frailty Socio-demographics		Interviewer administered survey

Table 1. Characteristics of included studies (Cont'd)

Author (year)	Design of study	Study population	Sample size and sampling methods	Outcome variable(s)	Data source for outcome	Individual determinants	Societal determinants	Data source for determinants
Wee et al.[20] (2019)	Cross-sectional study	Residents aged ≥60 years living in public rental housing	928	Emergency room visit in past 6 months	Interviewer administered standardised questionnaire	Socio-demographics Family make-up Health status and physical disabilities/limitations Health behaviours Social network and isolation Psychological health and stressors Income sources and perception of financial adequacy Medication adherence Quality of life		Interviewer administered standardised questionnaire

BPSD: Behavioural and psychological symptoms of dementia; MAPS: Medical Alert Protection System; PWD: patients with dementia; WiSE: Well-being of the Singapore Elderly

Client Service Receipt Inventory[27] to collect information regarding healthcare utilisation.[23,24] Five out of 7 studies reported their utilisation through questionnaires, surveys or interviews.[17,19,21,23,24] The other 2 studies sourced ED utilisation through administrative databases.[20,22]

Measurement of determinants

Validated scales and checklists were used to evaluate various determinants. Across 2 studies,[23,24] psychiatric morbidity was evaluated using the Self-Reported Questionnaire.[28] Caregiver distress was evaluated using the Neuropsychiatric Inventory Questionnaire.[23,29] Loneliness was evaluated with UCLA 3-item loneliness scale, while Partners in Health scale was used to evaluate self-management, coping and adherence to treatment in Wee 2019's study.[20,30,31] The Partners in Health scale aims to determine how well community-dwelling older adults manage their chronic conditions.[30] Frailty was evaluated using Fried's frailty phenotype[32] and FRAIL scale[33] in 2 different studies.[21,24]

In the study by Ng et al.,[19] successful ageing was associated with lower frequency of hospitalisation. Successful ageing was measured using the following factors: age, sex, type of residence, education level, engagement in physical activities and exercise, presence of religious and spiritual beliefs, and nutritional risk.

None of the studies included conceptual frameworks for organising the determinants of ED utilisation. All the studies conducted multivariate analysis to determine the statistical significance of the examined determinants and ED utilisation. Table 2 provided a summary of determinants that were found to be statistically significant.

Predisposing factors

Predisposing factors are socio-demographic factors that can increase a person's risk utilising healthcare.

Residing in a public rental housing was a significant determinant of ED utilisation in Singapore (odds ratio [OR] 2.4, confidence interval [CI] 2.12–2.74). In Wee et al., loneliness (adjusted OR [aOR] 1.96, 95% CI 1.13–3.43) and poorer coping (aOR 1.72, 95% CI 1.01–3.03) were associated with higher rates of ED visits among older adults living in public rental housing, evaluated with UCLA 3-item loneliness scale and Partners in Health scale, respectively. Among the same sub-population, religiosity is associated with lower ED utilisation (aOR 0.43, 95% CI 0.24–0.76).[20]

Enabling factors

Enabling factors are family and community resources that encourage or impede a person's access to healthcare.

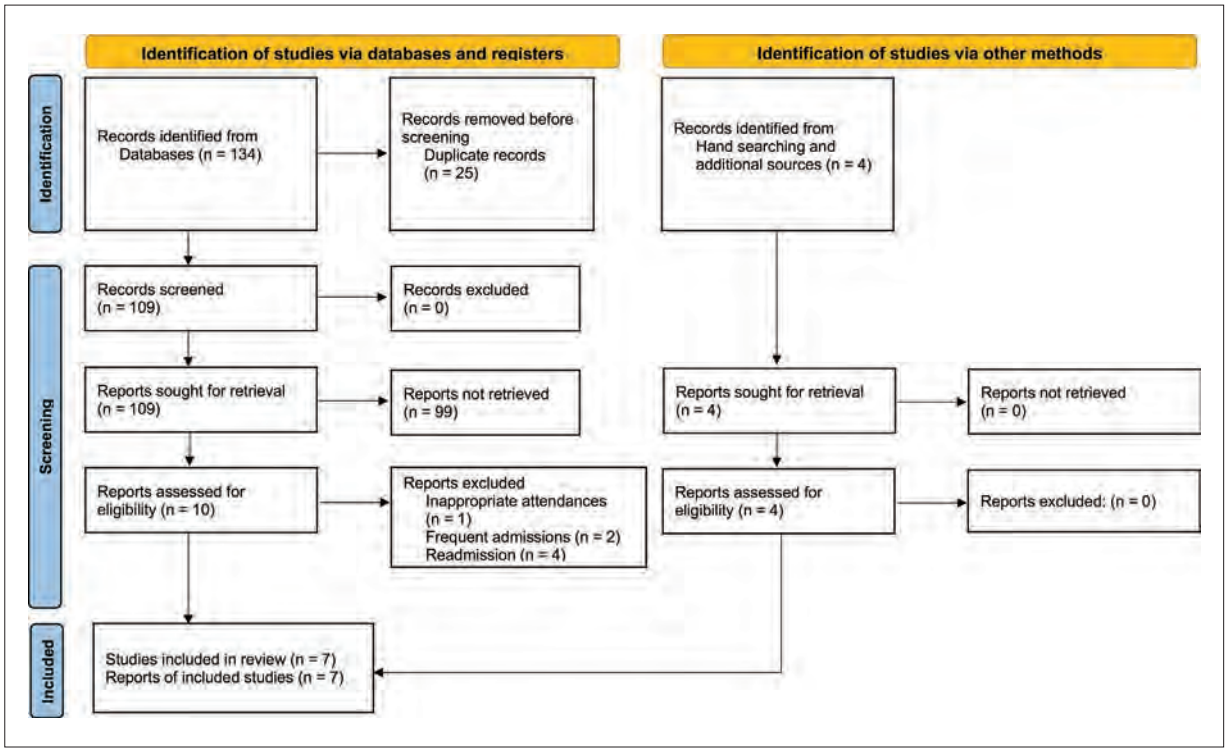

Fig. 2. PRISMA flow diagram.

Caregiver distress from those looking after elderly with behavioural and psychological symptoms of dementia, increased the likelihood of ED visits (OR 1.1, 95% CI 1.0–1.1, *P*=0.003).

Health factors

Health factors can be divided into perceived need (subjective) and evaluated need (objective). Frailty was a significant determinant of ED utilisation (incidence rate ratio 3.1, 95% CI 1.1–8.1). This was assessed using the 5-item FRAIL scale consisting of fatigue, resistance, ambulation, illnesses and loss of weight.[33] In addition, better adherence to treatment (aOR 2.23, 95% CI 1.29–3.83), and presence of multimorbidity among PWD (OR 4.3, 95% CI 1.6–11.3, *P*=0.004) were associated with ED utilisation. Having visited a PCP in the last 6 months for a routine review was a protective factor against ED use (aOR 0.46, 95% CI 0.27–0.80).

Quality assessment of studies

The studies assessed by NOS are shown in Table 3. A maximum of 5 stars can be given for selection and a maximum of 2 stars for comparability. A maximum of 1 star can be given for the quality of the outcome assessment in the original NOS, but 2 stars in the modified NOS.

DISCUSSION

To our knowledge, this is the first systematic review that is being conducted in Singapore to investigate the determinants of ED utilisation among older adults.

Our study found that residing in a public rental housing, religiosity, loneliness and poorer coping and caregiver distress were predisposing factors towards ED utilisation. Health factors that were significantly associated with the rate of ED utilisation included frailty,[34] multimorbidity among PWD, visitation of PCP in the last 6 months and adherence to treatment.

Older adults living in public rental housing were found to have a higher utilisation of the ED.[20,35] In Singapore, the ownership of housing is typically representative of the socio-economic status (SES) of a person.[20] Public rental housing is usually resided by people who are unable to afford ownership of the property, thus reflecting their lower SES.[36] Housing status by itself has been found to be associated with a higher rate of ED utilisation.[37,38] These older adults may neglect their personal well-being from inflexibility in managing their priorities,[22,38] hence leading to over-utilisation of ED services when they face complications from their disease.[22] For instance, they are found to only visit their health practitioners when they experience symptoms such as pain.[39] This possibly indicates that they do not

Table 2. Determinants of ED utilisation[a]

	Individual determinants		
Author (year)	**Predisposing factors (effect size)**	**Enabling factors (effect size)**	**Health factors (effect size)**
Ge et al.[21] (2020)			Frailty (IRR 3.1, 95% CI 1.1–8.1)
Lau et al.[23] (2021)		Caregiver distress from BPSD (OR 1.1, 95% CI 1.0–1.1, *P*=0.003)	PWD with multimorbidity (OR 4.3, 95% CI 1.6–11.3, *P*=0.004)
Seng et al.[22] (2019)	Staying in public rental housing (OR 2.4, CI 2.12–2.74)		
Wee et al.[20] (2019)	Religiosity (aOR 0.43, 95% CI 0.24–0.76) Loneliness (aOR 1.96, 95% CI 1.13–3.43) Poorer coping (aOR 1.72, 95% CI 1.01–3.03)		Visited a PCP in last 6 months for routine review (aOR 0.46, 95% CI 0.27–0.80) Better adherence (aOR 2.23, 95% CI 1.29–3.83)

aOR: adjusted odds ratio; BPSD: behavioural and psychological symptoms of dementia; CI: confidence interval; IRR: incidence rate ratio; OR: odds ratio; PCP: primary care physician; PWD: persons with dementia.
[a] Only statistically significant determinants are included
Superscript numbers: Refer to REFERENCES

Table 3. Quality assessment of included studies with modified Newcastle-Ottawa Scale

Author (year)	**Selection**	**Comparability**	**Outcome**
Ge et al.[21] (2020)	*****	**	**
Lau et al.[23] (2021)	***	-	*
Ng et al.[19] (2009)	****	**	*
Seng et al.[22] (2019)	****	**	*
Vaingankar et al.[24] (2017)	****	*	*
Wee et al.[20] (2019)	*****	*	*

comply with their follow-up visits as seen by the lower frequency of specialist outpatient clinic visits among this group.[22] Consequently, older adults with lower SES are also associated with poorer outcomes following an ED visit,[40] which may lead to more costs being incurred in the form of hospital bills and lost work days. Additionally, Chan et al. proposed that their health beliefs, health literacy and perceived need influence their ED utilisation.[41]

Religious and spiritual beliefs are part of the "social structure" under predisposing factors,[11] which is hypothesised to influence health care utilisation.[42] Religion can shape an individual's health beliefs as the sanctity of life is respected across all religions.[43] This potentially influences ED utilisation[44] through enhancement of their perseverance and coping skills.[20] However, the findings may not truly reflect how religious someone is in predisposing them to healthcare utilisation; an amalgamation of influences[44] such as the presence of religious communities and social support[20] are also enabling factors in ED utilisation.

Presence of caregiver distress increased the likelihood of visitation to the ED by PWD, which is congruent with the literature in other countries.[45,46] Caregivers for PWD face a greater amount of stress among other chronic conditions.[47] Caring for their loved ones more than 40 hours a week, physical strain and aiding in healthcare tasks are found to increase the likelihood of an ED visitation by PWD.[48] In 2010, 74% of regular caregivers were also employed, indicating their need to take on multiple responsibilities within the family.[49] The caregiver burden is expected to worsen as the social structure of families evolve, with smaller families and rise in dual-income families.[50] Sending their loved ones to the ED could provide a respite from their long hours of care for their elderly relatives when they are no longer able to manage by themselves. There is an opportunity for clinicians in the ED to provide these caregivers with adequate emotional support and ensure continuity of care within the community, which will hopefully reduce ED utilisation among this population.[48]

Surprisingly, better adherence to treatment was associated with higher rates of ED utilisation among older adults residing in public rental housing.[20] Wee et al. hypothesised that among this lower income population, they are perhaps disengaged with their PCPs and turn to the ED for care instead.[51] This was consistent with a Taiwanese study investigating ED utilisation among

people with intellectual disability, where patients who were compliant with their medication regime had a higher number of ED visits.[52] Another hypothesis to explain this phenomenon is the prompt identification of acute complications of their chronic diseases, where they would immediately seek treatment at the ED. Recent visits in the last 6 months to their PCP was protective against ED utilisation. This shows that by ensuring that the older patients are compliant with their routine follow-up visits, the number of ED visits can be potentially reduced.

Outside Singapore, geographical distance and availability of transport is an important predictor of ED utilisation as living in a rural area versus an urbanised area will determine their accessibility to healthcare institutions.[53,54] In Singapore, the average amount of time taken for an ambulance to reach a patient ranged from 7 to 15 minutes, with another 20 to 40 minutes to arrive at the ED.[55] This is in contrast to the US, where ambulances can take more than 14 minutes to arrive in rural areas.[56] Given the relatively small geographical area of 728.3km^2 [57] and organisation of the 3 regional health systems in Singapore (Singapore Health Services, National University Health System and National Healthcare Group), with each serving different regions of the city state,[58] the impact of geographical distance on healthcare utilisation is minimal. Additionally, due to the proximity and ease of access to primary care in Singapore,[22] enabling factors would play a less prominent role in predicting ED utilisation as compared to other countries.[59]

In the included studies, no conceptual frameworks were used to organise determinants for ED utilisation. According to Boudreaux et al.,[60] health behaviour research in the context of emergency care should be grounded in conceptual models. Adopting these conceptual frameworks help provide a holistic overview of the various influencers of health sub-care utilisation. Hence, future studies in Singapore should incorporate conceptual frameworks to better understand ED utilisation. This would also enable a core set of common variables or indicators to be assessed across studies, allowing for comparison over time and population sub-groups. The Andersen and Newman's model can also be modified according to our Singapore healthcare system in future studies.

Our study has various limitations. We excluded non-English articles in our study but there were minimal non-English articles in our search, and hence the impact of this exclusion is small. The societal determinants (technology and norms) and enabling factors in Andersen and Newman's model were not thoroughly investigated in the included studies. Additionally, this model was developed in the US against the context of their healthcare system, which differs from our healthcare system in Singapore. This could provide a less comprehensive picture of the various factors influencing ED utilisation here. Future studies can look at the development of a similar model in the context of our healthcare system. The majority of the studies included were cross-sectional studies. The main limitation of cross-sectional studies is the inability to study causality or determine the temporal sequence of events. The Singapore Longitudinal Ageing Study in Ng et al.'s study[19,25] included only Chinese patients. Hence, there is presence of selection bias as well.

CONCLUSION

The major determinants of ED utilisation by older adults in Singapore based on the Andersen and Newman's model included (1) predisposing and enabling factors such as the type of residence, religiosity, sense of loneliness and coping mechanisms, and (2) health factors such as frailty,[34] comorbidities, recent visitation of PCPs and adherence to treatment. Evaluation of societal determinants of ED utilisation was lacking in the included studies of this review. Given the greying population in Singapore and disproportionate use of healthcare resources among this population, there is a need for a more holistic examination of determinants of ED utilisation locally based on conceptual models of health seeking behaviours.

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Telepalliative care during the pandemic: Lessons for the future

Dear Editor,

Mok et al. gave hope for cautious optimism for the acceptance of telemedicine for palliative care—which will be referred to as "telepalliative care" in this article—during the COVID-19 pandemic.[1] Properly organised, telepalliative care can save time, provide flexibility, improve access for patients[2,3] and possibly reduce the need for hospitalisations. Telepalliative care adoption should continue and be increased to meet the growing needs of an ageing population. It is foreseeable that there may be an increasing demand for palliative intervention arising from better management of illnesses that prolong lifespans, though not necessarily "healthspans", i.e. the length of healthy years.[4] This article outlines some of the concerns and benefits of telepalliative care (Table 1).

Table 1. Concerns and benefits of telepalliative care

Concerns and mitigation measures
Concern: Loss of human touch and connection Mitigation: Caregivers/relatives to step in
Concern: Consent and privacy Mitigation: Telepalliative team to be aware of regulations and to implement clear and consistent guidance for practice
Concern: Standards of care and appropriate patient selection Mitigation: Appraisal of needs, patient's wishes, advance care planning, and specialist palliative physicians to provide guidance
Concern: Trust Mitigation: Incremental adoption, blending with in-person care, and willingness to revert to in-person care
Benefits
Harnessing technology in an increasingly technology-savvy Singapore to enhance access and efficiency, thus saving time and cost
Possible reduction in inappropriate care and hospitalisations through enhanced access for clarifications on expectations and goals

Understandably, many lament the loss of a human connection when care is delivered through an audiovisual medium as it fails to capture the nuances of body language. Touching, which instantly conveys support and compassion is fundamental to human thriving.[5,6] "Skin hunger", which is our innate need for human touch, can become an unmet need. Touch is one missing element of care during the pandemic, such as for patients who may be apprehensive about going out in public due to concerns ranging from severe weight loss approaching disfigurement, emaciation and/or odours. Some patients may require external devices that are connected to their persons, which can hamper venturing out and engaging with people outside the palliative care environment. However, caregivers physically close to the patient should be encouraged to fill a "high touch"[1] role, that is, one that provides personal attention and interaction.

Consent for telemedicine, besides being regulated by the Singapore Medical Council,[7] is required under the Personal Data Protection Act, as outlined in its recently updated advisory guidelines for photography, video and audio recordings in October 2021.[8] This may demonstrate heightened awareness for consent and privacy, given that palliative care patients are particularly vulnerable. It is plausible that these patients can be pressured or feel less entitled to assert their right of refusal when telepalliative care is offered. The consequences of saying no, which may be construed to mean less or no care in spite of this not necessarily being the case, may compel them to say yes to telepalliative care. Consent issues can be made more challenging when caregivers, whom patients may depend on to facilitate the telepalliative care process, express preferences that patients feel unable to object to. The patient's final decision therefore should always be sought independently to ensure voluntariness that is free from undue pressure. For patients without mental capacity, the doctor shall make the final decision based on the patient's best interests after considering the views of others involved in the patient's welfare.[9] The palliative team also has the responsibility to safeguard the privacy concerns of the patient and the security of audiovisual recordings. In spite of this, a major concern and dilemma is the possibility that a wholly informed consent from the patient may not in fact be fully obtained, which could happen in situations where patients are not fully aware or able to fully understand. Solutions, such as a written medical order made in advance and in a period of lucidity by the patient, are needed to resolve this problem.

Standards in telemedicine must meet equivalence of the in-person consultation, and limitations that may affect the quality of care in relation to the specific circumstances should be recognised.[7] There are several questions that doctors and the palliative care team should examine. What are the acceptable limitations in the

context of telepalliative care? Regulatory scrutiny over the use of controlled drugs such as opioids, especially for non-specialist practitioners outside of institutionalised settings can be both concerning and discouraging. A challenge that presents in an in-person setting may not be mitigated but in fact exacerbated in the telepalliative setting. Specialist palliative physicians should lead to establishing standards and mentorship for non-specialist practitioners who are keen to develop in this area of practice. This will help build their competence, confidence and the much-needed sense of security.

The World Health Organization defines palliative care as "an approach that improves the quality of life of patients (adults and children) and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual."[10] Some doctors may interpret elements in this, such as in making a "correct assessment", too literally. This may lead to a convoluted hospital journey of investigations, fluid infusion, artificial nutrition and antibiotic escalation, at the stage when needs are clearly palliative and no longer curative. Few among us would choose aggressive treatment at end of life, though it is unfortunate that patients may be subjected to such a treatment. It is key to learn the difference between doing things "to" patients as opposed to "for" patients.

Anecdotal evidence suggests that demands from families, their lack of death literacy, coupled with doctors' fear of complaints often make the route of aggressive interventions easier to navigate, rather than one of restraint and moderation. The main issue may be the absence of clear advance planning, which ideally should have been ongoing when a life-threatening diagnosis is made or as a person ages. A realistic appraisal of the needed care and its correct siting will help reduce hospitalisations and conserve resources at the acute care hospitals for complex care, which admittedly can also occur with a palliative route.

Admission for dying is inappropriate when dying with comfort and support is an attainable goal outside of the acute care hospital. Telepalliative care, blended with in-person care outside the acute hospital setting can be part of the solution to minimise inappropriate admissions. Telepalliative care delivery can help to meet the goals of care, clarify expectations and augment support throughout the patient's journey. Requesting stepped-up telepalliative care, only when necessary, incurs minimum added cost.

Telepalliative care can amplify the difficulties that stem from a lack of trust and confidence. The perception of patients that telepalliative care is undertaken for convenience and cost savings at the expense of patient welfare must be dispelled by a willingness to revert to an in-person encounter if needed.

Moving forward, telepalliative care adoption may need to be incremental to win acceptance as an established future norm. Therefore, at the very least, the initial encounter must be an in-person encounter. Subsequently, "blended care" comprising online/telepalliative and offline/in-person care shall be determined by the patient's clinical and non-clinical needs, and with guidance if necessary, from specialist palliative physicians.

Finally, there is hope that technical challenges for the elderly, currently often perceived as a barrier, will diminish over time. The increasing penetration of information technology in Singapore may facilitate the narrowing of the "digital divide"—the gap in access to technology by different demographic, regional, socio-economic and other groups—in years to come. Some may even prefer the unique nature of intimacy that the digital age renders, which facilitates focused attention and listening with individuals' own design of care within the comfort of their homes.[11]

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LETTER TO THE EDITOR

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Evaluation of a health screening protocol for recovered COVID-19 patients before "return-to-play" and strenuous physical activity

Dear Editor,

We conducted a prospective, single-centre cohort study to develop guidance for military personnel returning to strenuous activities following SARS-CoV-2 infection. The patients underwent a clinical review followed by a protocol to screen for cardiac, respiratory, haematological, endocrine/renal and neurological complications after recovery from infection.

Both the study and screening protocol were developed in consultation with Headquarters Medical Corps, Singapore Armed Forces and physicians at National University Hospital, Singapore. The protocol was developed based on evidence available in August 2020.

The patients who underwent the clinical review were Singapore military personnel infected with SARS-CoV-2 from February to September 2020. The "entry review" was performed for all patients at the start of the protocol, where signs and symptoms of sequelae after recovery from SARS-CoV-2 infection were assessed. This was repeated 6 months later at the "exit review". Following the entry review, individuals were excused from duties involving strenuous physical activity for 6 months, up to the date of their exit review. Before the planned appointment date for the exit review, individuals underwent a comprehensive screening for subclinical abnormalities. Individuals with no abnormalities on their exit review were returned to their premorbid level of physical activity within their job scope. Individuals with abnormalities continued to be excused from physical activity until further workup ordered by the attending physician was completed.

In March 2021, 25 patients (96% male sex) completed the screening protocol at a median interval of 203 days (interquartile range [IQR] 176–277) after the first positive polymerase chain reaction (PCR) test during the acute illness episode. The mean age was 23 years old (range 17–49). Severity of infection was determined in accordance with the National Institutes of Health clinical spectrum of SARS-CoV-2 infection.[1]

A majority of 22 patients (88%) experienced asymptomatic to mild infection. Two (8%) experienced moderate infection due to lower respiratory tract involvement without desaturation below oxygen saturation of 94%. One (4%) experienced critical illness due to bilateral pneumonia complicated by type 1 respiratory failure, requiring high-flow nasal cannula oxygen therapy in the intensive care unit.

Of the 25 patients, 7 (28%) had completely normal investigation results (Table 1). All abnormal cardiac screening results were either incidental or artefactual. This low prevalence of true cardiac-related complications due to coronavirus disease 2019 (COVID-19) was also seen in other real-world studies that operationalise a screening protocol for return-to-play.[2,3] Only 1 patient had an abnormal chest X-ray that was deemed to be artefactual after computed tomography of the chest. Other investigations were largely unremarkable. Electrolyte and creatinine levels remained normal within our cohort, and none had significant neurological complications.

In screening for haematological complications, our study showed that 11 patients (44%) had non-negative (10 indeterminate, 1 positive) anticardiolipin immunoglobulin M (IgM) antibodies. None of these individuals had signs or symptoms of arterial or venous thrombosis or thromboembolism. We rechecked their anticardiolipin antibodies 4–5 months later to check for resolution and all of them demonstrated declining titres, suggesting that the phenomenon was transient, with no apparent clinical significance. We suggest that findings of isolated, transiently abnormal anticardiolipin IgM following SARS-CoV-2 infection are probably not useful in predicting future thromboembolic events. This has been demonstrated in other contemporary studies.[4]

Our study did not uncover any cardiac or respiratory abnormalities attributable to SARS-CoV-2 infection and none of our patients experienced long-lasting effects or complications after their acute disease course. Although this study examined a small sample size of COVID-19 patients, extensive and advanced investigations were organised for all patients so as to rule out subclinical complications. Our study suggests that organisations can be prudent in the use of specialised investigations for persons with asymptomatic or mild COVID-19 disease.

There is a need to balance safe return to physical activity against the risk of sequelae following acute COVID-19 infection. Return-to-play protocols should tailor the extent of clinical investigations to an individual's baseline characteristics and disease severity, and be balanced against a gradual and phased return to physical

Table 1. Results of first-line screening investigations at the exit review[a]

	Time of test from date of infection, median (IQR), days	Abnormal screening investigations, no. (%) N=25
Cardiac investigations		
12-lead electrocardiogram	203 (194–223)	1 (4)
Troponin T, ng/L	203 (195–223)	0
Treadmill electrocardiography	203 (195–223)	4 (16)
Resting transthoracic echocardiogram	203 (195–223)	4 (16)
Overall first-line cardiac investigations		
Any abnormal tests		7 (28)
2 abnormal tests		**2 (8)**
1 abnormal test		**5 (20)**
Respiratory investigations		
Chest X-ray	203 (194–223)	1 (4)
Haematological investigations		
D-dimer, μg/mL	203 (195–223)	0
Lupus anticoagulant	203 (195–223)	0
Anticardiolipin IgM, MPL	203 (195–223)	Indeterminate: 10 (40) Positive: 1 (4)
Anticardiolipin IgG, GPL	203 (195–223)	0
Anti-beta-2-glycoprotein IgM, SMU	203 (195–223)	0
Anti-beta-2-glycoprotein IgG, SGU	203 (195–223)	0
Endocrine/renal investigations		
Serum sodium, mmol/L	203 (195–223)	0
Serum potassium, mmol/L	203 (195–223)	0
Serum creatinine, μmol/L	203 (195–223)	1 (4)
Lipid panel, mmol/L	203 (195–223)	6 (24)
Glycated haemoglobin, %	203 (195–223)	2 (8) 1 with known type 2 diabetes mellitus
Neuropsychiatric investigation		
Symptom screen and full neurological examination	203 (194–223)	0

IgG: immunoglobulin G; IgM: immunoglobulin M; IQR: interquartile range
[a] Exit review was conducted 6 months after the entry review. Entry review was undertaken when individuals have recovered from acute COVID-19 infection and returned to the workplace.

activity.[5] There have been several "return to physical activity" consensus guidelines[6-9] built on expert opinion, but few published studies on real-world experience using a screening protocol.[3] All patients in our study were able to return safely to premorbid activity levels regardless of their initial disease severity.

Our study demonstrated that individuals may remain well 6–10 months after an acute SARS-CoV-2 infection. It is not clear whether there is COVID-19-related morbidity and mortality beyond this time frame. Further research is required to better inform clinicians of the long-term sequelae of SARS-CoV-2 infection.

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LETTER TO THE EDITOR

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Acute hypercapnic respiratory failure in thyroid storm and the role of plasma exchange

Dear Editor,

Thyroid storm is a life-threatening condition due to excessive release of thyroid hormone. Cardiovascular, gastrointestinal and neurological manifestations have been described.[1] Acute respiratory failure as the initial presentation of a thyrotoxic crisis may occur due to pre-existing cardiopulmonary disease. Management is supportive, with medications aimed at inhibiting synthesis and release of thyroid hormone. In this article, we discuss a patient with thyroid storm who presented with decompensated hypercapnic respiratory failure.

Case presentation. A 61-year-old man presented to the emergency department for severe respiratory distress of acute onset. He was a chronic smoker with known Graves' disease, for which he had defaulted follow-up. He had no prior history of chronic lung disease. On arrival, his temperature was 36.6°C, blood pressure 142/86mmHg, heart rate 226 beats/min, respiratory rate 28 breaths/min and oxygen saturation 96% on room air. Physical examination was significant for tachypnoea, respiratory distress, confusion, exophthalmos, a diffuse goitre, proximal weakness and hand tremors. Lungs were clear without wheeze. Arterial blood gas done on 4L/min nasal oxygen showed pH of 7.23, partial pressure of carbon dioxide ($PaCO_2$) 57mmHg, partial pressure of oxygen (PaO_2) 201.1mmHg, base excess -4.9mmol/L and bicarbonate 20.1mmol/L. Lactate was 4.4mmol/L. He was presumptively treated for exacerbation of chronic obstructive pulmonary disease (COPD) with bronchodilators and non-invasive ventilation (NIV). However, he did not tolerate NIV—repeat blood gas showed pH of 7.112, $PaCO_2$ 75.9mmHg and PaO_2 145.8mmHg on expiratory positive airway pressure (EPAP) 5cmH_2O, inspiratory positive airway pressure (IPAP) 20cmH_2O and fraction of inspired oxygen (FiO_2) 0.5. He was intubated for worsening hypercapnic respiratory failure and was admitted to the intensive care unit.

Laboratory tests revealed thyrotoxicosis, mixed respiratory and metabolic acidosis, and raised transaminases (Table 1). Electrocardiogram showed atrial fibrillation with rapid ventricular response. Chest X-ray showed clear lung fields. COVID-19 polymerase chain reaction test result was negative. Further history was notable for weight loss, heat intolerance, diarrhoea and painful eyes over the past 6 months, with tremors and palpitations noted over the past few weeks. His lactic acidosis resolved following intravenous hydration. However, he remained persistently hypercapnic. Capnography and ventilator mechanics were not suggestive of bronchospasm. He was diagnosed with thyroid storm following a Burch-Wartofsky Point Scale score of 95 points. He was commenced on intravenous hydrocortisone 100mg 4 times a day, oral cholestyramine 4g 3 times a day, and Lugol's iodine and lithium 400mg 2 times a day. Liver transaminases continued to rise on day 2 of admission to levels exceeding 10 times upper limit of normal (Table 1), for which autoimmune and infective studies returned unyielding. With elevated bilirubin levels, there was concern for impending acute liver failure and therefore, conventional anti-thyroid medications were contraindicated. With multiple organ involvement, he was deemed to require urgent control of thyrotoxicosis. Hence, decision was made for initiation of therapeutic plasma exchange (TPE) as a bridge to emergency thyroidectomy. He underwent 2 cycles of TPE through a right femoral venous catheter on days 2 and 3 of admission. Fresh frozen plasma (FFP) was used as exchange fluid, with 1 plasma volume exchanged per session. There was marked clinical and biochemical improvement. He was extubated and his liver transaminases normalised. His therapeutic options were reconsidered, and he was started on carbimazole 10mg every morning. He tolerated treatment, allowing thyroidectomy to be deferred pending further evaluation. At this time of writing, he has been scheduled for spirometry to exclude COPD.

Discussion. The pathophysiology of hypercapnic respiratory failure in thyroid storm has been rarely discussed in existing literature. At steady state, the volume of carbon dioxide (CO_2) eliminated per minute is equal to that produced by the body. This relationship is illustrated by the equation: $VA = K \times VCO_2 / PaCO_2$, where VA represents alveolar ventilation, K represents a constant (0.863), and VCO_2 represents CO_2 production.[2]

In thyrotoxicosis, muscle mass and strength may be decreased by approximately 20% and 40%, respectively.[3] It is theorised that thyrotoxic myopathy arises from damage to the motor end plates.[4] Functional weakness of the diaphragm has also been described in active Graves' disease.[5] As weak muscles require more energy relative to their maximum energy consumption

Table 1. Serial laboratory values of a patient with thyroid storm who received plasmapheresis on days 2 and 3 of admission

Serial laboratory values / Day	Admission	Day 1	Day 2 #1 TPE	Day 3 SBT #2 TPE	Day 4	Day 5	Day 6 carbimazole 10mg OM started	Day 19	Reference values
Full blood count									
Haemoglobin (g/dL)	13.4			10.9	10.2	10.6	10.7		11.5–15
TW (10^9/L)	13.4			19.8	20.8	18.1	11.4		4.0–10.0
Platelets (10^9/L)	280			152	146	164	188		150–450
Thyroid function									
Free triiodothyronine (pmol/L)	32.8		25.4	9.7	7.9	5.3	7.1	6.3	3.2–5.3
Free thyroxine (pmol/L)	69.7		51.7	53.0	35.2	35.4	29.4	12.7	10.0–20.0
TSH (mU/L)	<0.010					<0.010		<0.010	0.400–4.00
Liver function									
Total protein (g/L)	57		53	54	51	50	47	69	62–82
Albumin (g/L)	34		31	31	30	28	27	39	37–51
Total bilirubin (μmoles/L)	56		46	33	28	40	40	22	5.0–30.0
Alkaline phosphatase (U/L)	198		186	129	88	107	98	163	32–103
ALT (U/L)	617		784	614	217	137	80	24	10–55
AST (U/L)	851		1088	470	95	40	46	26	10–45
Arterial blood gas									
pH	7.112	7.274	7.361	7.402	Extubated				7.35–7.45
$PaCO_2$ (mmHg)	75.9	62.5	51.8	50.7					38.9
PaO_2 (mmHg)	145.8	102.2	93.1	70.2					69.3
Base excess (mmol/L)	-7.2	0.4	2.5	5.2					
Renal panel									
Urea (mmol/L)	6.4	9.3	12.2	14.6	14.4	11.1	7.4		2.8–7.7
Sodium (mmol/L)	140	146	147	148	147	147	142		135–145
Potassium (mmol/L)	5.2	4.1	3.4	4.2	4.2	38	3.6		3.5–5.3
Chloride (mmol/L)	103	103	109	111	109	110	108		96–108
Bicarbonate (mmol/L)	20.9	25.1	29.8	31.8	34.0	32.4	27.0		19–31
Creatinine (μmol/L)	50	71	71	49	37	37	33		65–125
Lactate (mmol/L)	6.7	3.2	1.8						0.50–2.20

ALT: alanine transaminase; AST: aspartate transaminase; OM: every morning; SBT: spontaneous breathing trial; TPE: therapeutic plasma exchange; TSH: thyroid stimulating hormone; TW: total white cell count

to achieve a set amount of work, the balance between energy demand and supply weighs in favour of the former, resulting in fatigue. When fatigued, respiratory muscles fail to generate adequate mean tidal pressures, with resultant decreases in both tidal volumes and minute ventilation, reducing the ventilatory capacity of the respiration system (reduced VA). Other causes of respiratory muscle weakness in thyroid storm include rhabdomyolysis and thyrotoxic periodic paralysis—the latter encountered more frequently in Asian population. A normal creatine kinase level and absence of hypokalaemia suggest against these 2 causes in our patient. As a metabolic end product, CO_2 production increases in thyrotoxic states. Increased CO_2 production gives rise to excessive ventilatory demand (increased VCO_2) which, in the setting of compromised ventilatory capacity, can result in acute hypercapnic respiratory failure.

TPE as a treatment modality in thyroid storm was first described by Ashkar in 1970.[6] Its use has been reported in patients who had contraindications for or were refractory to conventional medical therapy. Thyroid-binding globulin and bound thyroid hormones are removed with plasma during TPE. FFP contains albumin, which contributes new binding sites for circulating thyroid hormone.[7] In recent literature, TPE has been described in clinical settings, including methimazole-induced agranulocytosis,[8] preparation for surgery, postoperative thyroid storm, and type II amiodarone-induced thyrotoxicosis.[9] TPE remains at Grade 2C for treatment of thyroid storm according to the American Society for Apheresis.[10] Given sparsity of data, knowledge gaps still exist regarding optimal timing and frequency of TPE in the management of thyroid storm.

In conclusion, our case highlights that acute hypercapnic respiratory failure can be the initial presentation of untreated thyrotoxicosis even in the absence of known lung disease. As such occurrences are rare, initial misdiagnosis is possible. Prompt recognition and differentiation from more frequently encountered aetiologies of respiratory failure are important given the unique management of thyroid storm. Furthermore, unlike prior case reports, early use of TPE in our patient ultimately obviated the need for emergency thyroidectomy. We hope that our case contributes to the growing pool of clinical evidence supporting TPE as a potentially life-saving modality for thyroid storm patients who are not candidates for conventional treatment.

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Intravascular large B-cell lymphoma associated with sudden stridor arising from thyroid mucormycosis and concomitant bacterial infection

Dear Editor,

Mucormycosis is a life-threatening fungal infection that mainly affects immunocompromised patients. It typically has low prevalence, but fatality rate is as high as 50%.

We present a patient with intravascular lymphoma with secondary bacterial infection and invasive mucormycosis involving the thyroid gland, who experienced good outcomes following surgical decompression and prolonged intravenous antibiotics.

A 65-year-old man with diabetes and intravascular large B-cell lymphoma (IVLBCL) who had undergone 3 cycles of rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin) and prednisolone (R-CHOP) presented with sudden stridor due to bilateral vocal cord palsy.

Computed tomography scan revealed thyroid gland liquefaction with enlargement. Ultrasound showed that the entire gland was replaced by avascular heterogeneous content. He was clinically euthyroid and thyroid autoantibodies were negative. Tracheostomy was performed for prolonged intubation, and thyroid isthmusectomy was performed to obtain histology and culture samples.

Intraoperatively, necrotic yellowish serous material was seen upon exposure of the thyroid gland (Fig. 1A). Bilateral thyroid lobes were ischaemic with necrotic cricoid and tracheal cartilages but there was no frank pus. As the overall tracheal cartilage framework was deemed stable, resection of these necrotic cartilages was withheld. The thyroid isthmus biopsy showed necrotic tissue only, while cultures and bacterial, fungal and *hsp65* gene sequencing were negative.

Post-procedure, he had persistent sepsis. A multidisciplinary team involving otorhinolaryngology, infectious diseases and endocrinology determined the thyroid necrosis to be the likely nidus for infection and total thyroidectomy was performed. Histology revealed extensively necrotic thyroid tissue with sheets of large cells, suggestive of necrotic tumour tissue with therapy effects. Within necrotic areas, dense neutrophilic infiltrates with foreign body giant cell reaction were also noted, raising the possibility of concomitant secondary infection. Immunohistochemical staining for B-cell lymphoma markers were negative on the extensively necrotic tissue. Intraoperative cultures grew *Klebsiella* and *Proteus*. Gomori methenamine silver (GMS) stain was performed only after review of histology for multidisciplinary meeting. This showed broad (5–25µm), pleomorphic, ribbon-like, pauci-septate hyphae with tendency for right-angle-branching, in keeping with Mucorales. Areas suggestive of angioinvasion (Fig. 1B) were also seen, revealing the concomitant cause for acute thyroid necrosis. Due to extensive necrosis, ghost outlines of pale stained *Mucor* hyphae were initially missed on haematoxylin and eosin (HE) stain. This emphasises the importance of performing GMS stain on necrotic tissue for their identification. Although uncertain whether

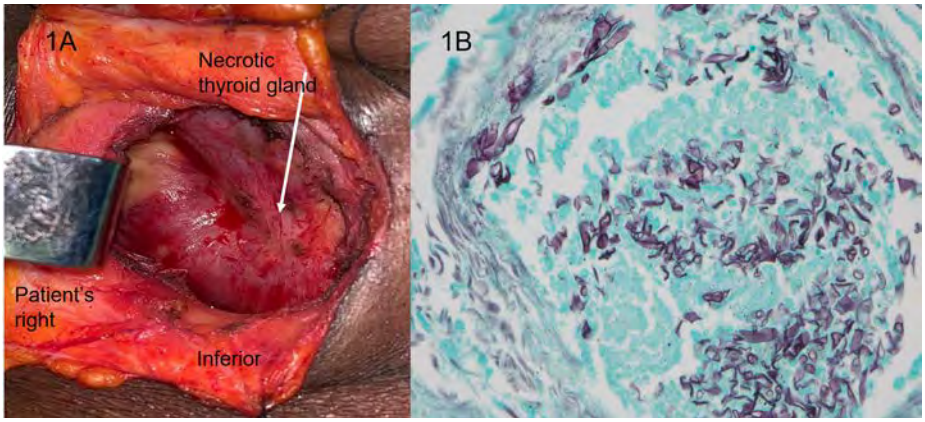

Fig. 1A. Intraoperative photo showing the necrotic thyroid gland (arrow), with the retractor placed on patient's right.
Fig. 1B. Grocott methenamine silver stain showing extensively necrotic tissue from thyroid parenchyma with likely vessel wall with invasive fungal elements featuring pleomorphic, ribbon-like, pauci-septate hyphae with the tendency for right-angle-branching, in keeping with Mucorales.

mucormycosis may merely be a contaminant, this is unlikely, in view of angioinvasion noted within the thyroid parenchyma and localisation within the central necrotic areas.

Postoperatively, patient's fever lysed and wound healed. Prolonged courses of intravenous piperacillin/tazobactam and meropenem were administered until inflammatory markers trended downwards. Nasoendoscopy performed 1 month postoperatively showed mobile vocal cords bilaterally. He was successfully decannulated 2.5 months later. During his follow-up, he did not encounter airway complications such as subglottic stenosis. Unfortunately, he succumbed to lymphoma relapse 2 years later.

Acute suppurative thyroiditis is rare due to the gland capsule, high iodide content, rich blood supply, and extensive lymphatic drainage. Potential risk factors include pre-existing thyroid disease, congenital anomalies and immunosupression.[1] Treatment consists of antibiotics, drainage, and partial or total thyroidectomy.

Our patient had IVLBCL with likely thyroid gland involvement. IVLBCL is a rare variant of diffuse large B-cell lymphoma. It is characterised by malignant lymphoid proliferation within blood vessels but without circulating neoplastic cells.[2] This often poses a diagnostic challenge. Additionally, it is aggressive and may involve any organ.[3] Although immunohistochemical staining for lymphoma in our patient was negative, this may be explained by extensive tumour necrosis and 3 cycles of anti-CD20/rituximab before resection. The rapid progression and necrosis after commencing chemotherapy was consistent with tumour lysis syndrome of IVLBCL involving the entire thyroid gland,[4] which subsequently got infected secondary to his immunosuppressed state.

Acute invasive mucormycosis is extremely rare in the thyroid gland but is associated with high mortality. Most reported cases had thyroid involvement in the context of disseminated infection while isolated thyroid involvement is rare.[5] To the best of our knowledge, there are 12 reported cases involving the thyroid gland, of which only 2 are isolated within the gland.

The first patient is a 79-year-old man with chronic lymphocytic leukemia who underwent ibrutinib 2 months prior to presentation of a rapidly progressive neck mass and dysphonia. Imaging and biopsy revealed extensive necrotic thyroid with sternocleidomastoid invasion.[5] He underwent surgical debridement and prolonged course of liposomal amphotericin-B and Posaconazole. The disease was eradicated successfully; however, left vocal cord palsy persisted.

The second patient was a 52-year-old man on long-term immunosuppressant for renal allograft transplant.[6] He presented acutely with fever and neck swelling. This progressed to hoarseness and right vocal cord palsy within 4 days, and stridor with bilateral cord palsy within another 6 hours. A tracheostomy was planned for, but he succumbed to cardiac arrest. Post-mortem examination revealed thyroid gland mucormycosis with severe angioinvasion.

These cases illustrate the rapidity invasive mucormycosis progresses and the potential for upper airway compromise due to vocal cord palsy from thyroid gland involvement. However, the diagnosis of mucormycosis is often only established post-mortem.[7] The gold standard for diagnosis is still tissue biopsy. Mucorales grow within 1–7 days on most fungal culture media. However, culture has low sensitivity of 50% due to the friable nature of fungal hyphae. Evidence of thyroid gland liquefaction post-chemotherapy should raise suspicion about possible lymphoma involvement or opportunistic infections. Hence, evaluation with special stains for invasive fungal infections should be considered in immunocompromised hosts. Current treatment guidelines recommend a combination of antifungal therapy, surgical debridement, and correction of risk factors.[8] In our patient, rapid improvement was seen following thyroidectomy, with resolution at confirmation of mucormycosis.

Current literature has shown 2 other case reports of vocal cord paralysis resulting from acute suppurative thyroiditis. Bukvic reported a 75-year-old patient with resolution of thyroid abscess after surgical drainage and intravenous antibiotics. However, right vocal cord paralysis persisted.[9] Additionally, Boyd reported a 41-year-old patient with resolution of thyroid abscess and left vocal cord paralysis following intravenous antibiotics and drainage.[10]

In our patient, total thyroidectomy, instead of drainage, was performed to remove the nidus of infection and relieve compression. Resolution of bilateral cord paralysis with successful decannulation suggests that early surgical intervention to obtain source control could potentially reverse cord paralysis.

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LETTER TO THE EDITOR

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Change in hepatitis B virus DNA status in patients receiving chronic immunosuppressive therapy for moderate-to-severe skin disease

Dear Editor,

Hepatitis B virus (HBV) infection poses a global health burden. Clinically, patients may present with chronic HBV infection, occult HBV infection, and fulminant hepatic failure. In 2010, the hepatitis B surface antigen (HBsAg) seroprevalence in Singapore was 3.6%.[1]

Patients with dermatological conditions receive prolonged corticosteroid and other immunosuppressive therapy for moderate-severe skin diseases. All patients with chronic HBV infection are at risk of HBV reactivation. The 2015 American Gastroenterological Association Institute Guidelines indicate that patients subjected to prolonged courses (greater than 4 weeks) of moderate to high dose (at least 10mg prednisolone daily equivalent being moderate dose, and greater than 20mg prednisolone daily equivalent being high dose) may lead to HBV reactivation in 1–10% of patients.[2] There are no Singapore data on the outcome of chronic hepatitis B patients receiving oral or topical steroid and/or other immunosuppressive therapy for skin conditions.

We conducted a retrospective study from 2016 to 2020 of 25 patients from the dermatology outpatient clinic at the National University Hospital, a Singapore tertiary hospital. This study was approved by the NHG Domain Specific Review Board.

The inclusion criteria were: patients above 21 years old, possessing dermatological conditions that required them to be on chronic systemic immunosuppression for more than 3 months, having had either resolved or chronic HBV infection. Treatment with topical clobetasol ointment for bullous pemphigoid, which has been shown to be equivalent to systemic steroids, was also included.[3] The exclusion criteria included: previous or concomitant biologic therapy at the point of recruitment, pre-existing chronic liver disease with evidence of cirrhosis, haematological malignancy, immunodeficiency syndromes, pregnancy or breastfeeding, ongoing active systemic infection, previous stem cell or solid organ transplant, and known hepatocellular carcinoma.

Resolved infection was defined as the presence of positive anti-hepatitis B core antibody (anti-HBc total Ab) with negative HBsAg, while chronic HBV infection was defined as a state where HBsAg was positive, with positive anti-HBc total antibody.

For patients with chronic HBV infection, reactivation was defined to have occurred when any one of the following is fulfilled: (1) ≥2 log (100-fold) increase in HBV DNA compared to the baseline; (2) HBV DNA ≥3 log (1,000) IU/mL in those with baseline undetected HBV DNA; or (3) HBV DNA ≥4 log (10,000) IU/mL, if the baseline level unavailable. For patients with resolved HBV infection, the criteria used are detection of HBV DNA or development of HBsAg (reverse seroconversion).

Hepatitis flare was defined as an event with abrupt rise of alanine aminotransferase (ALT) levels to >5 times the upper limit of normal during chronic HBV infection. Chronic oral steroid use was defined as the use of prednisolone at least 20mg once daily, or 0.5mg/kg/day, whichever dose was lower, for at least 3 months. Low-dose oral steroid use was defined as prednisolone use of 0.5mg/kg/day and less.

The mean age of the subjects was 74.1 years old; 16 were male (64%) and 9 (36%) were female. Fifteen patients had bullous pemphigoid, 4 had endogenous eczema, 2 had pemphigus, 1 had chronic plaque psoriasis, and 1 had chronic actinic dermatitis (Table 1). The mean duration of patients having dermatological disease was 4.0 years. Eighteen patients (72%) had used systemic steroids. The types of non-steroid immunosuppressants used were azathioprine, methotrexate, cyclosporine and rituximab. There were 2 patients on cyclosporine, 6 patients on azathioprine (5 receiving a dose of 50mg daily, and 1 patient on 25mg daily), 2 patients on methotrexate (dosage ranging from 2.5mg once a week to 15mg once a week), and 1 patient was given 2 doses rituximab after being recruited (at the point of recruitment only having received oral prednisolone).

The lowest initial prednisolone dose used was 7.5mg once daily, while the highest initial dose was 30mg once daily (0.5mg/kg/day). The prednisolone doses at the initiation of therapy tended to be low (≤0.5mg/kg/day).

The mean duration of follow-up among 25 patients was 30.8 months. Four patients with chronic HBV infection had detectable HBV DNA on the first visit. All received therapeutic antivirals and had undetectable HBV DNA levels with treatment. The 21 remaining patients had resolved HBV infection; none had detectable HBV DNA at initial assessment. Seven were started on antivirals (6 for prophylaxis and 1 after reactivation occurred). Of the 6 started on prophylactic antivirals, 4 were maintained on high-dose steroids >20mg/day for at least 4 weeks (range 4–16 weeks), and 2 were

maintained on moderate-dose steroids >10mg/day for at least 4 weeks.

In comparison, of the 14 patients with resolved HBV infection who did not receive prophylactic antivirals, 1 received clobetasol ointment (equivalent to systemic oral steroids),[3] 12 received either high/moderate-dose steroids for durations less than 4 weeks, and 1 patient (patient A) received high-dose steroids for 7 weeks and moderate doses for 12 weeks. She had not been given prophylactic antivirals and reactivated after 22 months of chronic steroid therapy.

Due to lower costs, telbivudine (n=5) was the most common antiviral agent used, followed by lamivudine (n=3) and entecavir (n=3). Among the 21 with resolved HBV infection, there were no cases of hepatitis flare.

There were 2 cases of hepatitis B reactivation (Patients A and B). Patient A had used 7 weeks of high-dose steroids at 20mg/day, 12 weeks of moderate- to high-dose steroids (10–20mg/day) in her lifetime, and was on low-dose prednisolone 3mg/day when she reactivated. At that time of reactivation, she had already been on this low maintenance dose for at least 9 months and received 22 months of chronic steroid therapy. She received a total of 20 months telbivudine therapy, but had HBV DNA become undetectable by 4 months of antiviral therapy.

Patient B received 27 months of chronic steroid therapy at the time of reactivation. She demonstrated a reverse seroconversion from HBsAg negative to HBsAg positive. She had used 7 weeks of high-dose steroids at least 20mg/day, 13 weeks of moderate- to high-dose steroids, and was on low-dose prednisolone 3mg/day when she reactivated (on this low dose for 2 years prior to reactivation). Patient B elected not to receive antivirals. Without antivirals, her HBV DNA levels became undetectable 11 months after the point of detection.

Existing guidelines by major liver societies suggest that patients with chronic HBV infection and patients with resolved HBV infection should be treated similarly.[2,4-6] Antiviral prophylaxis should be started before and continued well after cessation of immunosuppression, 12 to 18 months if rituximab is used and 6 to 12 months for other immunosuppressive agents.[7] The European Association for the Study of the Liver and American Association for the Study of Liver Diseases recommend that patients should be continued on biochemical monitoring for hepatitis B reactivation that may occur post-antiviral withdrawal.[4,5]

The strengths of this study include longitudinal follow-up of patients over at least 4 years with careful surveillance of hepatitis serologies and documentation of their treatment modalities. The exclusion of patients with any underlying cirrhotic disease or pre-existing liver dysfunction mirrors real-world practice where the use of potent immunosuppressant therapy tends to be restricted in such patients.

Our study shows that the majority of patients with moderate-to-severe skin disease with resolved HBV infection remain well without antiviral treatment while on chronic immunosuppression. Nonetheless, patients should be risk-stratified so that those at higher risk of hepatitis B reactivation receive antiviral prophylaxis.

Table 1. Demographics, hepatitis serologies, treatment and surveillance patterns in 25 patients with anti-HBc total positive at first screen

Parameter	Overall (N=25) No. (%)
Demographic	
Mean age at diagnosis, years	74.1 (median 75, range 51–94)
Sex	
Male	16 (64)
Female	9 (36)
Duration of disease	
Mean duration of disease, years	4.0 (median 5, range 1–17)
Indication for treatment	
Bullous pemphigoid	15 (60)
Endogenous eczema/atopic dermatitis	4 (16)
Pemphigus vegetans/oral pemphigus vulgaris	2 (8)
Chronic plaque psoriasis	1 (4)

Table 1. Demographics, hepatitis serologies, treatment and surveillance patterns in 25 patients with anti-HBc total positive at first screen (Cont'd)

Parameter	Overall (N=25) No. (%)
Chronic actinic dermatitis	1 (4)
Asteatotic eczema	2 (8)
Hepatitis serologies at initial assessment	
Anti HBc-total positive	25 (100)
HBsAg positive (chronic HBV infection)	4 (16)
HBsAg negative (resolved HBV infection)	21 (84)
HBV DNA detected (in patients with chronic HBV infection)	4 out of 4 (100)
Laboratory surveillance patterns	
Three-monthly HBV DNA check	17 (68)
Six monthly HBV DNA check	3 (12)
Lost to follow-up/unchecked	5 (20)
ALT normal at diagnosis	24 (96)
ALT abnormal at diagnosis	1 (4)
Number of cases with ALT abnormality during subsequent follow-up	0
Abnormal liver function tests due to HBV reactivation	0
Outcomes	
Number of hepatitis flares	0
Virological suppression with antiviral treatment in patients with chronic HBV infection	4 out of 4 (100)
Reactivation of HBV in patients with resolved HBV infection [a]	2 out of 21 (9.5)
Antiviral therapy	
Number on antivirals	11 (44)
Number of patients with chronic HBV infection on antivirals	4/4 (100)
Number of patients with resolved HBV infection on antivirals	For prophylaxis: 6/21 (33.3%), 1/21 subsequently reactivated and was given antivirals
Telbivudine	5/11 (45.4)
Lamivudine	3/11 (27.3)
Entecavir	3/11 (27.3)
Types of immunosuppressive therapy	
Oral steroid only	18 (including 1 patient with topical clobetasol ointment used) (72%)
Oral steroid + non-steroid immunosuppressants	6 (24)
Non-steroid immunosuppressants only	1 (4)
Types of non-steroid immunosuppressants	
Number of patients who received azathioprine	6
Number of patients who received methotrexate	2
Number of patients who received cyclosporine	2
Number of patients who received rituximab [b]	1

ALT: alanine aminotransferase; HBc: hepatitis B core; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus
[a] These 2 patients were not previously on antivirals prior to reactivation
[b] The patient used rituximab only after recruitment (with inclusion criteria being no previous/concomitant biologic use at time of recruitment)

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Unusual biliary gem: Cause of acute obstructive suppurative cholangitis and pancreatitis in a patient with Billroth II anastomosis

A 72-year-old man with a 10-year history of subtotal gastrectomy with Billroth II anastomosis and laparoscopic cholecystectomy presented with abdominal pain, high fever and altered mental status. His blood pressure was 94/50mmHg, heart rate 136bpm and body temperature 39.4°C. Laboratory examination revealed the following: white blood cell count 16,200/μL; aspartate aminotransferase 418IU/L; alanine aminotransferase 160IU/L; alkaline phosphatase 3,137U/L; total bilirubin 4.1mg/dL; and serum lipase 1,131U/L. A computed tomography scan revealed dilatation of the common bile duct (CBD), obstructed by an object containing a hyperdense string-shaped component at distal CBD (Fig. 1). Magnetic resonance cholangiopancreatography showed a hypodense object in the distal third portion of the CBD (Fig. 2). Considering the above findings, the patient was diagnosed with acute obstructive suppurative cholangitis (AOSC) and pancreatitis.

Which patient-related factor might be responsible for the biliary tract stone?

A. Age
B. Male sex
C. History of subtotal gastrectomy with Billroth II anastomosis
D. History of laparoscopic cholecystectomy
E. Accidental ingestion of a foreign object

Endoscopic retrograde cholangiopancreatography revealed a surgical clip embedded in a 10mm CBD stone (Fig. 3). The patient was diagnosed with AOSC and pancreatitis due to a surgical clip embedded in a CBD stone. The patient underwent endoscopic sphincterotomy with the use of a forward-viewing gastroscope (GIF-Q260J, Olympus Medical Systems, Japan) and inverted sphincterotome (Billroth II sphincterotome; Cook Medical LLC, US) (Fig. 4). We successfully eliminated the choledocholithiasis and extracted the embedded surgical clip (Fig. 5). The patient had complete improvement of his condition with no adverse events.

Post-cholecystectomy clip migration (PCCM), defined as the migration of metallic clips into the CBD where the clips may act as a nidus for stone formation, is one of the rare post-cholecystectomy complications.[1] Clinically, CBD stones caused by PCCM have the same risk as stone impaction and resulting AOSC. The treatment for CBD stones embedding metallic clips is similar to that for regular CBD stones, such as conventional sphincterotomy and balloon/basket-assisted stone extraction.[1] If patients with choledocholithiasis had a previous gastrectomy with Billroth II anastomosis, CBD stones were retracted with a forward-viewing gastroscope and an inverted sphincterotome.[2]

The exact pathogenesis of PCCM remains unknown; however, several hypotheses have been proposed.[3] One possible underlying mechanism is when a surgical clip falls off an inverted cystic duct and then migrates into the CBD.[2] A large number of clips used intraoperatively or incorrect clip placements may also induce PCCM.[4]

Clip migration can be partly prevented by using fewer surgical clips and ensuring their proper placement away from the cystic duct and the CBD junction, or by using absorbable clips.[4] In our case, one of the clips at the post-cholecystectomy site might have migrated into the CBD (Fig. 3). There were clips placed outside the CBD from the patient's history of gastrectomy. Those clips were not related to the PCCM.

The time interval between laparoscopic cholecystectomy and the occurrence of PCCM-induced complication varies from 11 days to 20 years, with a median interval of 26 months.[5] Physicians should be aware of the fact that PCCM can cause severe cholangitis and pancreatitis, even decades after a surgery. PCCM-induced cholangitis and/or pancreatitis can be considered as a differential diagnosis in patients with a remote history of laparoscopic cholecystectomy presenting with abdominal pain and fever.

In summary, PCCM can cause severe cholangitis and pancreatitis when clips function as a nidus for biliary tract stones decades after laparoscopic cholecystectomy. Surgeons should note that a smaller number and correct placement of clips can prevent PCCM after laparoscopic cholecystectomy.

Answer: D

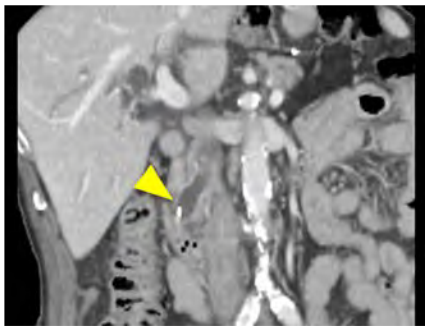

Fig. 1. A computed tomography scan showing a string-shaped hyperdense object (arrow) in the distal portion of the common bile duct.

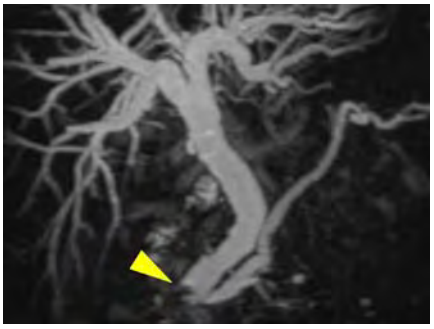

Fig. 2. Magnetic resonance cholangiopancreatography of an obstructing hypodense object (arrow) in the distal portion of the CBD.

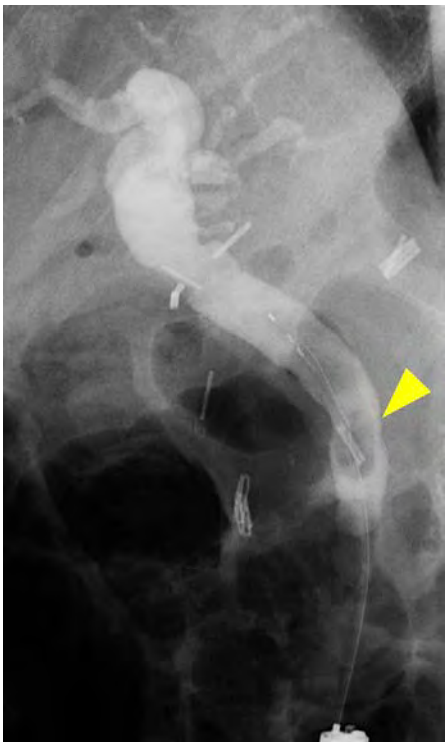

Fig. 3. Endoscopic retrograde cholangiopancreatography showing a 10mm filling defect with a hyperdense metal-like object (arrow) in the distal portion of the CBD.

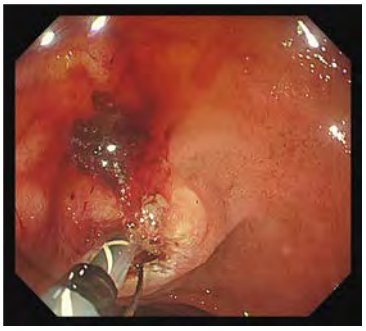

Fig. 4. Inverted sphincterotomy carried out with the use of a forward viewing gastroscope and an inverted sphincterotome.

Fig. 5. The removed surgical clip embedded in a common bile duct stone.

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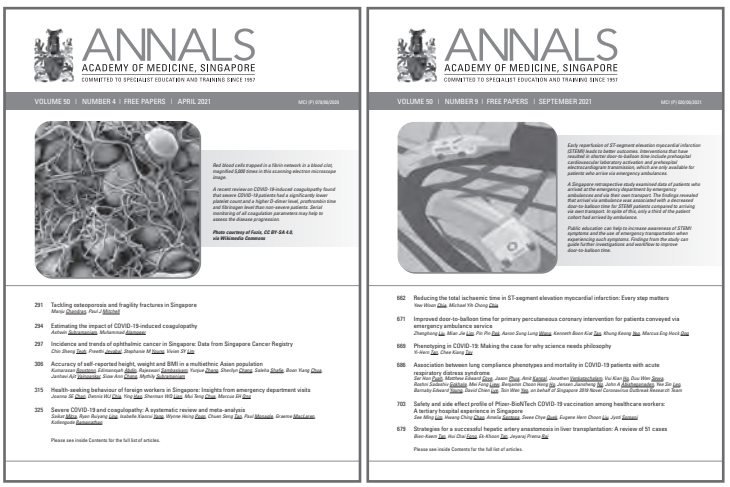

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