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

Sharlene Ho1 MRCP (UK), Hwee Pin Phua2 BS, Wei-Yen Lim2 PhD, Niranjana Mahalingam3 MBBS, Guan Hao Chester Tan4, Ser Hon Puah1 MRCP (UK), Jin Wen Sennen Lew1 MRCP (UK)

ABSTRACT

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

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

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

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

INTRODUCTION

Sepsis is defined as “life-threatening organ dysfunction caused by a dysregulated host immune response to infection”.1 It is one of the most common conditions afflicting intensive care unit (ICU) patients, causing a high mortality rate. An estimated 48.9 million incident cases of sepsis and 11 million sepsis-related deaths were reported worldwide in 2017, accounting for almost 20% of all global deaths.2 In addition to the high mortality risk, sepsis patients were found to have higher cardiovascular complications such as myocardial infarction (MI),3-5 heart failure,3,6,7 new onset atrial fibrillation (AF) and stroke.5,8 Systemic inflammation and cytokine storm during sepsis is thought to trigger endothelial dysfunction, procoagulant response, atheroma instability, and myocardial dysfunction that contributes to cardiovascular complications.3,9

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

1 Department of Respiratory and Critical Care Medicine, Tan Tock Seng Hospital, Singapore
2 Department of Clinical Epidemiology, Office of Clinical Epidemiology, Analytics, and Knowledge (OCEAN), Tan Tock Seng Hospital, Singapore
3 Department of General Medicine, Tan Tock Seng Hospital, Singapore
4 Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Correspondence: Sharlene Ho, Department of Respiratory and Critical Care Medicine, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.

Email: sharlene_ho@ttsh.com.sg

References

1. Roman SA, Bernardi E, de Lemos JA, et al. Severe sepsis and septic shock. Circulation. 2004;110(22):3279-3292
2. World Health Organization. Global mortality estimates for 2017. World Health Organization. 2018
3. Kotsianidis K, Brinkman K, Crowson K, et al. The prevalence and clinical impact of cardiovascular complications in sepsis. Crit Care. 2018;22(1):151
4. Zeeb H, Bluhmki E, Cannegieter SC, et al. The global burden of sepsis-related mortality in intensive care units in a 70-country sample: a multinational observational study. Lancet Infect Dis. 2016;16(3):305-312
5. Vincent JL, Haase DW, Suter PM, et al. An international study of 30-day mortality for patients with severe sepsis and septic shock. Crit Care Med. 1998;26(4):1839-1846
6. Vincent JL, Suter PM, Haase DW, et al. Mortality in septic shock depends on the time to effective antibiotic therapy. Intensive Care Med. 1998;24(7):683-689
7. Vincent JL, de Mendonça A, Canete J, et al. Definition and diagnosis of sepsis: third international consensus definitions for sepsis and septicaemia (Sepsis-3).crit Care. 2016;20(5):214
8. Vincent JL, Obertegger T, de Mendonça A. Sepsis: definition and diagnosis. Crit Care. 2016;20(1):214
9. Vincent JL, de Mendonça A, Suter PM, et al. Sepsis: definitions of infection and infection-related conditions. Crit Care. 2016;20(1):214
10. Vincent JL, de Mendonça A, Suter PM, et al. Sepsis: definitions of infection and infection-related conditions. Crit Care. 2016;20(1):214
11. Vincent JL, de Mendonça A, Suter PM, et al. Sepsis: definitions of infection and infection-related conditions. Crit Care. 2016;20(1):214
12. Vincent JL, de Mendonça A, Suter PM, et al. Sepsis: definitions of infection and infection-related conditions. Crit Care. 2016;20(1):214

https://doi.org/10.47102/annals-acadmedsg.202220
We aim to describe the occurrence of intra-hospital cardiovascular events (CVEs) among critically ill patients with sepsis, the risk factors for CVEs, and the association of CVEs with in-hospital mortality in these patients.

METHODS

Study design and patient population

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

Definitions

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

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

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

Statistical analysis

Continuous variables were reported as mean and standard deviation (SD), or median and interquartile range (IQR) where distributions were skewed. For categorical variables, frequencies and percentages were reported. The differences between the 2 groups of patients with CVEs and without CVEs were assessed with Student’s t-test or Mann-Whitney U test for continuous variables, and Pearson’s chi-square test or Fisher’s Exact test for categorical variables. Multivariable modified Poisson regression was used to identify factors associated with intra-hospital CVEs and in-hospital mortality, and results were presented as relative risk (RR) with a 95% confidence interval (CI). This approach was chosen...
since odds ratio estimated using logistic regression may significantly overestimate RR when the outcome is common. Variables with non-missing values and having a significant univariate test result were considered as candidates in the multivariable analysis. Correlations of the estimated coefficients for these candidate variables were examined to assess for possible multicollinearity. Clinical expert knowledge was also used to guide variables selection in the final model to account for clinically important predictors as well as potential confounding factors. All statistical tests were two-sided, and $P<0.05$ was considered statistically significant. Analyses were performed using Stata version 14.0 (StataCorp, College Station, US).

RESULTS

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

Primary outcome: Sepsis and intra-hospital CVEs

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

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

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

Secondary outcomes

The majority of patients (79.4%) developed CVEs early within the first week of hospital admission (Supplementary Fig. S1 in the online version of this article). Compared to sepsis patients without CVEs, sepsis patients with CVEs had a longer ICU length of stay (median [IQR] of 6 [3–12] vs 4 [2–9] days, $P<0.001$).
Table 1. Types of cardiovascular event

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

CVE: cardiovascular event; ICU: intensive care unit

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

| All patients with sepsis n=662 | Patients with sepsis and CVE n=350 | Patients with sepsis and no CVE n=312 | P value |
|--------------------------------|------------------------------------|----------------------------------------|---------|
| Age, median (IQR), years       | 70 (60–78)                         | 72 (62–79)                             | 68 (56–77) | <0.001 |
| Male, no. (%)                  | 422 (63.7)                         | 219 (62.6)                             | 203 (65.1) | 0.505  |
| Ethnicity, no. (%)             |                                    |                                        |          | 0.063  |
| Chinese                        | 462 (69.8)                         | 232 (66.3)                             | 230 (73.7) |         |
| Malay                          | 92 (13.9)                          | 56 (16.0)                              | 36 (11.5)  |         |
| Indian                         | 75 (11.3)                          | 47 (13.4)                              | 28 (9.0)   |         |
| Others                         | 33 (5.0)                           | 15 (4.3)                               | 18 (5.8)   |         |
| Smoking status, no. (%), n=444 |                                    |                                        |           | 0.482  |
| Smoker                         | 126 (28.4)                         | 66 (27.6)                              | 60 (29.3)  |         |
| Ex-smoker                      | 110 (24.8)                         | 55 (23.0)                              | 55 (26.8)  |         |
| Non-smoker                     | 208 (46.8)                         | 118 (49.4)                             | 90 (43.9)  |         |
| Comorbidities, no. (%)         |                                    |                                        |           |         |
| Diabetes mellitus              | 303 (45.8)                         | 185 (52.9)                             | 118 (37.8)  | <0.001 |
| Hypertension                   | 436 (65.9)                         | 247 (70.6)                             | 189 (60.6)  | 0.007  |
| Hyperlipidaemia                | 338 (51.1)                         | 205 (58.6)                             | 133 (42.6)  | <0.001 |
| Ischaemic heart disease        | 163 (24.6)                         | 114 (32.6)                             | 49 (15.7)   | <0.001 |
| Heart failure                  | 64 (9.7)                           | 41 (11.7)                              | 23 (7.4)    | 0.059  |
| Atrial fibrillation            | 65 (9.8)                           | 31 (8.9)                               | 34 (10.9)   | 0.379  |
| Other arrhythmias              | 11 (1.7)                           | 7 (2.0)                                | 4 (1.3)     | 0.553  |
| Valvular heart disease         | 16 (2.4)                           | 10 (2.9)                               | 6 (1.9)     | 0.435  |
| Cerebrovascular accident       | 98 (14.8)                          | 56 (16.0)                              | 42 (13.5)   | 0.359  |
Table 2. Characteristics of patients with sepsis, with or without cardiovascular events (Cont’d)

| Characteristic                          | All patients with sepsis n=662 | Patients with sepsis and CVE n=350 | Patients with sepsis and no CVE n=312 | P value |
|----------------------------------------|---------------------------------|------------------------------------|----------------------------------------|---------|
| Peripheral vascular disease            | 55 (8.3)                        | 38 (10.9)                          | 17 (5.5)                               | 0.012   |
| Chronic lung disease                   | 137 (20.7)                      | 60 (17.1)                          | 77 (24.7)                              | 0.017   |
| Chronic kidney disease                 | 133 (20.1)                      | 83 (23.7)                          | 50 (16.0)                              | 0.014   |
| Chronic liver disease                  | 50 (7.6)                        | 20 (5.7)                           | 30 (9.6)                               | 0.058   |
| Cancer                                 | 83 (12.5)                       | 38 (10.9)                          | 45 (14.4)                              | 0.167   |
| Dementia                               | 24 (3.6)                        | 16 (4.6)                           | 8 (2.6)                                | 0.168   |
| Charlson Comorbidity Index, median (IQR) | 2 (1–4)                        | 2 (1–4)                            | 2 (1–4)                                | 0.030   |
| BMI, no. (%)                           |                                 |                                    |                                        | 0.008   |
| Underweight (<18.5kg/m²)               | 94 (14.2)                       | 35 (10.0)                          | 59 (18.9)                              |         |
| Normal (18.5–22.9kg/m²)                | 305 (46.1)                      | 174 (49.7)                         | 131 (42.0)                             |         |
| Overweight (23.0–27.4kg/m²)            | 159 (24.0)                      | 83 (23.7)                          | 76 (24.4)                              |         |
| Obese (≥27.5kg/m²)                     | 104 (15.7)                      | 58 (16.6)                          | 46 (14.7)                              |         |
| Premorbid ADL, no. (%), n=661          |                                 |                                    |                                        | 0.037   |
| Independent                            | 566 (85.6)                      | 305 (87.1)                         | 261 (83.9)                             |         |
| Assisted                               | 83 (12.6)                       | 43 (12.3)                          | 40 (12.9)                              |         |
| Dependent                              | 12 (1.8)                        | 2 (0.6)                            | 10 (3.2)                               |         |
| Premorbid ambulatory status, no. (%), n=661 |                                 |                                    |                                        | 0.036   |
| Independent                            | 471 (71.3)                      | 244 (69.6)                         | 227 (73.0)                             |         |
| Using walking aid/assisted             | 144 (21.8)                      | 84 (24.0)                          | 60 (19.3)                              |         |
| Chairbound                             | 37 (5.6)                        | 21 (6.0)                           | 16 (5.1)                               |         |
| Bedbound                               | 9 (1.4)                         | 1 (0.3)                            | 8 (2.6)                                |         |
| APACHE II score, mean (SD)             | 29.4 (7.2)                      | 30.2 (6.8)                         | 28.5 (7.5)                             | 0.003   |
| SOFA score, mean (SD)                  | 8.3 (3.6)                       | 8.6 (3.5)                          | 7.9 (3.6)                              | 0.028   |
| Laboratory investigation at point of ICU admission |                                 |                                    |                                        |         |
| WBC >12x10⁹/L or <4 x10⁹/L, no. (%)    | 435 (65.7)                      | 231 (66.0)                         | 204 (65.4)                             | 0.868   |
| Thrombocytopenia (platelets <150 x10⁹/L), no. (%) | 157 (23.7)                      | 80 (22.9)                          | 77 (24.7)                              | 0.582   |
| Anaemia Hb <8g/dL, no. (%)             | 59 (8.9)                        | 37 (10.6)                          | 22 (7.1)                               | 0.113   |
| CRP (mg/L), median (IQR), n=637        | 102.7 (34.8–204.4)              | 101.4 (32.7–213.6)                 | 103.2 (38.4–192.5)                     | 0.856   |
| CRP categorical, no. (%)               |                                 |                                    |                                        | 0.829   |
| CRP <10mg/L                            | 59 (9.3)                        | 34 (9.9)                           | 25 (8.5)                               |         |
| CRP 10–100mg/L                         | 254 (39.9)                      | 136 (39.7)                         | 118 (40.1)                             |         |
| CRP >100mg/L                           | 324 (50.9)                      | 173 (50.4)                         | 151 (51.4)                             |         |
| Procalcitonin (ng/mL), median (IQR), n=642 | 2.6 (0.5–14.0)                 | 3.8 (0.7–19.2)                     | 1.5 (0.4–10.6)                         | <0.001  |
| Procalcitonin ≥0.5ng/mL, no. (n=642)   | 483 (75.2)                      | 275 (79.9)                         | 208 (69.8)                             | 0.003   |
| Lactate (mmol/L), median (IQR), n=506  | 2.6 (1.5–5.3)                   | 2.7 (1.6–5.5)                      | 2.4 (1.4–4.9)                          | 0.100   |
| Lactate ≥2mmol/L, no. (%) n=506        | 310 (61.3)                      | 181 (63.7)                         | 129 (58.1)                             | 0.197   |
Table 2. Characteristics of patients with sepsis, with or without cardiovascular events (Cont’d)

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

ACEI: angiotensin-converting enzyme inhibitor; ADL: activities of daily living; APACHE II: Acute Physiology and Chronic Health Evaluation II; ARB: angiotensin receptor blocker; BMI: body mass index; BNP: brain natriuretic peptide; CRP: C-reactive protein; CVE: cardiovascular event; Hb: haemoglobin; ICU: intensive care unit; IQR: interquartile range; NIV: non-invasive ventilation; SD: standard deviation; SOFA: Sequential Organ Failure Assessment; Trop I: troponin I; WBC: white blood cell
and hospital length of stay (median [IQR] 21 [10–42] vs 15 [7–30] days, \( P < 0.001 \)). There was no difference in ICU mortality (32.6% vs 34.6%, \( P = 0.578 \)) and in-hospital mortality (46.4% vs 46.9%, \( P = 0.792 \)) between the 2 groups (Table 4).

Clinical characteristics of sepsis patients according to in-hospital mortality are represented in Supplementary Table S1. There was no difference in CVE occurrence among patients who died and those who survived (53.4% vs 52.4%, \( P = 0.792 \)) between the 2 groups (Table 4).

In terms of microbiological results, the majority were found to be culture negative (42.7%), followed by gram-negative bacteria (37.3%) and gram-positive bacteria (16.6%) (Supplementary Table S2).

**DISCUSSION**

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

| Table 3. Factors associated with cardiovascular events among sepsis patients: univariate and multivariable analysis |
|---------------------------------------------------|---------------------------------------------------|------------------|------------------|
| **Univariate regression** | **Multivariable regression (final model)** | **Univariate regression** | **Multivariable regression (final model)** |
| RR | 95% CI | \( P \) value | Adjusted RR | 95% CI | \( P \) value |
| Age | 1.012 | 1.007–1.018 | <0.001 | 1.013 | 1.007–1.019 | <0.001 |
| Ethnicity | | | | | | |
| Chinese | Reference | | | | | |
| Malay | 1.212 | 1.005–1.462 | 0.044 | 1.214 | 1.005–1.465 | 0.044 |
| Indian | 1.248 | 1.025–1.520 | 0.028 | 1.240 | 1.030–1.494 | 0.023 |
| Others | 0.905 | 0.616–1.330 | 0.612 | 1.029 | 0.692–1.531 | 0.886 |
| Body mass index | | | | | | |
| Normal (18.5–22.9kg/m\(^2\)) | Reference | | | | | |
| Underweight (<18.5kg/m\(^2\)) | 0.653 | 0.493–0.864 | 0.003 | 0.688 | 0.529–0.895 | 0.005 |
| Overweight (23.0–27.4kg/m\(^2\)) | 0.915 | 0.766–1.093 | 0.328 | 0.867 | 0.729–1.031 | 0.106 |
| Obese (≥27.5kg/m\(^2\)) | 0.978 | 0.803–1.191 | 0.821 | 0.960 | 0.785–1.174 | 0.690 |
| Charlson Comorbidity Index | 1.035 | 1.004–1.068 | 0.027 | - | - | - |
| Diabetes mellitus | 1.328 | 1.150–1.534 | <0.001 | 1.155 | 0.988–1.352 | 0.071 |
| Hypertension | 1.243 | 1.054–1.465 | 0.010 | 0.900 | 0.746–1.087 | 0.274 |
| Hyperlipidaemia | 1.355 | 1.168–1.572 | <0.001 | 1.104 | 0.929–1.312 | 0.259 |
| Ischaemic heart disease | 1.479 | 1.290–1.696 | <0.001 | 1.317 | 1.137–1.527 | <0.001 |
| Heart failure | 1.240 | 1.016–1.513 | 0.035 | - | - | - |
| Peripheral vascular disease | 1.344 | 1.108–1.630 | 0.003 | - | - | - |
| Chronic lung disease | 0.793 | 0.646–0.973 | 0.026 | 0.733 | 0.598–0.899 | 0.003 |
| Chronic kidney disease | 1.236 | 1.057–1.446 | 0.008 | - | - | - |

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

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

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

|                  | Univariate regression | Multivariable regression (final model)* |
|------------------|-----------------------|----------------------------------------|
|                  | RR   | 95% CI    | P value | Adjusted RR | 95% CI    | P value |
| Age              | 1.016 | 1.010–1.023 | <0.001  | 1.013       | 1.007–1.020 | <0.001  |
| Pre-existing atrial fibrillation | 1.337 | 1.075–1.662 | 0.009   | 1.268       | 1.021–1.575 | 0.031   |
| Chronic lung disease | 0.728 | 0.572–0.926 | 0.010   | -           | -          | -       |
| APACHE II score  | 0.728 | 0.572–0.926 | 0.010   | -           | -          | -       |
| SOFA score       | 1.053 | 1.041–1.064 | <0.001  | -           | -          | -       |
| Ventilatory support | -    | -          | -       | -           | -          | -       |
| No ventilatory support | Reference | Reference | Reference | Reference | Reference | Reference |
| Mechanical ventilation (with/without NIV) | 2.899 | 1.296–6.482 | 0.010   | 2.906       | 1.354–6.238 | 0.006   |
| NIV only         | 0.728 | 0.572–0.926 | 0.010   | -           | -          | -       |
| Vasopressor/inotropic support | 3.554 | 2.539–4.976 | <0.001  | 2.891       | 2.039–4.100 | <0.001  |
| Packed cell transfusion | 1.264 | 1.074–1.488 | 0.005   | -           | -          | -       |
| Cardioversion    | 1.648 | 1.337–2.032 | <0.001  | 1.409       | 1.119–1.775 | 0.004   |
| Renal replacement therapy | 1.340 | 1.138–1.579 | <0.001  | 1.212       | 1.035–1.418 | 0.017   |
| Thrombocytopenia (platelets <150 x10⁹/L) | 1.672 | 1.434–1.949 | <0.001  | 1.317       | 1.140–1.522 | <0.001  |
| Anaemia (Hb <8g/dL) | 1.315 | 1.046–1.654 | 0.019   | -           | -          | -       |
| Baseline medication: use of statins | 0.843 | 0.715–0.995 | 0.043   | 0.825       | 0.705–0.966 | 0.017   |
| Community-acquired pneumonia | 0.714 | 0.607–0.840 | <0.001  | -           | -          | -       |
| Hospital-acquired pneumonia | 1.428 | 1.209–1.686 | <0.001  | 1.311       | 1.034–1.662 | 0.025   |
| Intra-abdominal infection | 1.400 | 1.147–1.710 | 0.001   | 1.408       | 1.116–1.775 | 0.004   |

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

* Further adjusted by sex and ethnicity. APACHE II and SOFA scores were not included as candidates in the multivariable analysis as they were correlated with other independent variables considered in the model.
more integrative approach by evaluating cardiac complications as a combined clinical outcome rather than separate entities. We investigated the settings of sepsis as a whole and among ICU patients where there is paucity of data. These characteristics distinguished our analysis from previous publications.

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

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

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

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

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

CONCLUSION

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

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
2. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395:200-11.
3. Merx MW, Weber C. Sepsis and the heart. Circulation 2007;116:793-802.
4. Smilowitz NR, Gupta N, Guo Y, et al. Comparison of outcomes of patients with sepsis with versus without acute myocardial infarction and comparison of invasive versus noninvasive management of the patients with infarction. Am J Cardiol 2016;117:1065-71.
5. Smeeth L, Thomas SL, Hall AJ, et al. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med 2004;351:2611-8.
6. Beesley SJ, Weber G, Sarge T, et al. Septic Cardiomyopathy. Crit Care Med 2018;46:625-34.
7. Sato R, Kuriyama A, Takada T, et al. Prevalence and risk factors of sepsis-induced cardiomyopathy: A retrospective cohort study. Medicine (Baltimore) 2016;95:e5031.
8. Walkey AJ, Wiener RS, Ghobrial JM, et al. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. JAMA 2011;306:2248-54.
9. Di Pasquale M, Henchi S, Vanoni N, et al. Cardiovascular complications in patients with community-acquired pneumonia. Community Acquir Infect 2017;4:23-31.
10. Corrales-Medina VF, Musher DM, Wells GA, et al. Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. Circulation 2012;125:773-81.
11. Cilli A, Cakin O, Aksoy E, et al. Acute cardiac events in severe community-acquired pneumonia: A multicenter study. Clin Respir J 2018;12:2212-9.
12. Violi F, Cangemi R, Falcone M, et al. Cardiovascular Complications and Short-term Mortality Risk in Community-Acquired Pneumonia [published correction appears in Clin Infect Dis 2017;65:1431-3]. Clin Infect Dis 2017;64:1486-93.
13. Thygensen K, Alperi JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018) [published correction appears in Circulation 2018;138:e652]. Circulation 2018;138:e618-51.
14. McKee PA, Castelli WP, McNamara PM, et al. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285:1441-6.
15. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159:702-6.
16. Corrales-Medina VF, Musher DM, Shachkina S, et al. Acute pneumonia and the cardiovascular system. Lancet 2013;381:496-505.
17. Griffin AT, Wiemken TL, Arnold FW. Risk factors for cardiovascular events in hospitalized patients with community-acquired pneumonia. Int J Infect Dis 2013;17:e1125-9.
18. Musher DM, Rueda AM, Kaka AS, et al. The association between pneumococcal pneumonia and acute cardiac events. Clin Infect Dis 2007;45:158-65.
19. Musher DM, Abers MS, Corrales-Medina VF. Acute Infection and Myocardial Infarction. N Engl J Med 2019;380:171-6.
20. Joffre J, Hellman J, Ince C, et al. Endothelial Responses in Sepsis. Clin Infect Dis 2017;65:1431-3 [published correction appears in Clin Infect Dis 2017;64:1486-93].
21. Kakihana Y, Ito T, Nakahara M, et al. Sepsis-induced myocardial dysfunction: pathophysiology and management. J Intensive Care 2016;4:22.
22. Mandal P, Chalmers JD, Choudhury G, et al. Vascular complications are associated with poor outcome in community-acquired pneumonia. QJM 2011;104:489-95.
23. Rabe KF, Hurst JR, Suiissa S. Cardiovascular disease and COPD: dangerous liaisons? [published correction appears in Eur Respir Rev 2018;27:180057]. Eur Respir Rev 2018;27:180057.
24. Nakashima B, Restrepo MI, Anzueto A, et al. The Potential Role of Statins in Pneumonia. Cur Respir Med Rev 2010;6:155-61.
25. Almog Y, Shefer A, Novack V, et al. Prior statin therapy is associated with a decreased rate of severe sepsis. Circulation 2004;110:880-5.
26. Hackam DG, Mandani M, Li P, et al. Statins and sepsis in patients with cardiovascular disease: A population-based cohort analysis. Lancet 2006;367:413-8.
27. Mortensen EM, Pugh MJ, Copeland LA, et al. Impact of statins and angiotensin-converting enzyme inhibitors on mortality of subjects hospitalised with pneumonia. Eur Respir J 2008;31:611-7.
28. Wu A, Good C, Downs JR, et al. The association of cardioprotective medications with pneumonia-related outcomes. PLoS One 2014;9:e85797.
29. Ouyang Y, Wang Y, Liu B, et al. Effects of antiplatelet therapy on the mortality rate of patients with sepsis: A meta-analysis. J Crit Care 2019;50:162-8.
30. Pertzov B, Eliakim-Raz N, Atamna H, et al. Hydroxymethylglutaryl-CoA reductase inhibitors (statins) for the treatment of sepsis in adults - A systematic review and meta-analysis. Clin Microbiol Infect 2019;25:280-9.
31. Eisen DP, Leder K, Woods RL, et al. Effect of aspirin on deaths associated with sepsis in healthy older people (ANTISEPSIS): a randomised, double-blind, placebo-controlled primary prevention trial. Lancet Respir Med 2021;9:186-95.