

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

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ABSTRACT

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

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

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

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

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

INTRODUCTION

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

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

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

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CLINICAL IMPACT

What is New

- This is the first study in Singapore to the best of our knowledge to characterise the incidence of cardiovascular events (CVEs) among critically ill patients with sepsis, its risk factors and impact on mortality.
- CVEs complicate half of the critically ill patients with sepsis, with 79.4% of patients developing CVEs within the first week of hospitalisation, resulting in longer ICU and hospital length of stay.

Clinical Implications

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

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

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

METHODS

Study design and patient population

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

Definitions

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

The primary outcome was intra-hospital CVEs, defined as any of the following: (1) acute coronary syndrome; (2) type 2 MI; (3) incident AF; (4) new or worsening

heart failure; (5) cerebrovascular accident (CVA); and (6) cardiovascular deaths.

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

Data collection

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

Statistical analysis

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

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

RESULTS

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

Primary outcome: Sepsis and intra-hospital CVEs

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

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

In the multivariate analysis, 3 factors were independently associated with an increased risk of CVEs (adjusted RR [95% CI]): (1) age (1.013 [1.007–1.019]); (2) ethnicity—Malay (1.214 [1.005–1.465]) and Indian (1.240 [1.030–1.494]) when compared to Chinese ethnicity; and (3) comorbidity of ischaemic heart disease (1.317 [1.137–1.527]). Conversely, the occurrence of CVEs was lower (0.688 [0.529–0.895]) in patients who were underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$) when compared to normal BMI ($18.5\text{--}22.9 \text{ kg/m}^2$) 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, $P < 0.001$).

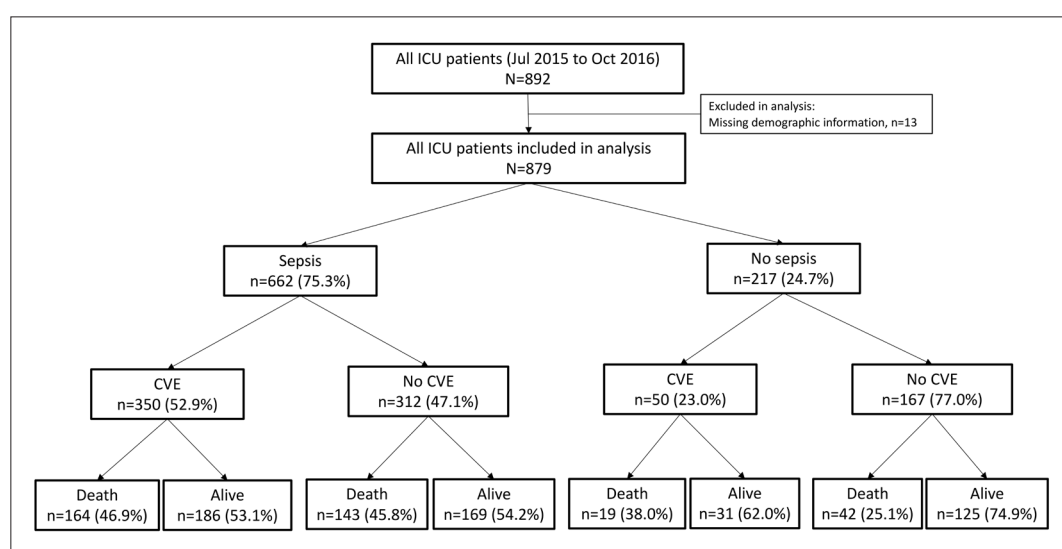


Fig. 1. Flowchart of clinical outcomes of patients admitted to intensive care unit. CVE: cardiovascular event; ICU: intensive care unit.

Table 1. Types of cardiovascular event

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

CVE: cardiovascular event; ICU: intensive care unit

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

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

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

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

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

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

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

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

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

CI: confidence interval; RR: relative risk

^a Further adjusted for sex

and hospital length of stay (median [IQR] 21 [10–42] vs 15 [7–30] days, $P<0.001$). There was no difference in ICU mortality (32.6% vs 34.6%, $P=0.578$) and 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%, $P=0.792$). Multivariate analysis showed that age, pre-existing AF, thrombocytopenia (platelets $<150 \times 10^9/L$), hospital-acquired pneumonia, intra-abdominal infection, and need for mechanical ventilation, vasopressor/inotropic support, cardioversion or renal replacement therapy were independently associated with a higher in-hospital mortality, whereas baseline use of statins was associated with a lower in-hospital mortality (Table 5).

In terms of microbiological results, the majority were found to be culture negative (42.7%), followed by 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 4. Secondary outcomes

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

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

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

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

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

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

likely due to the heterogeneous population and study design, and the use of diverse methodologies to ascertain exposure (CAP) and outcome (CVE). For example, most studies investigated hospitalised patients, some studies were done in the outpatient setting, but very few looked at ICU population; some studies included only

pneumococcal pneumonia; some studies defined MI as the only outcome while others included arrhythmia, heart failure and CVA.^{9-12,16-18}

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

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

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

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

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

which described older age and pre-existing cardiovascular disease as major risk factors for cardiac events. Other risk factors included nursing home residence, chronic kidney disease and greater severity of pneumonia.^{9–12,17} Interestingly, our study found a lower risk of CVEs in patients with chronic lung disease. This is in contrast to a prior publication that reported chronic obstructive pulmonary disease (COPD) as an independent predictor for CVEs.²² In fact, the association between COPD and cardiovascular disease has been well established.²³ We postulate that the discordance seen was because our patients with underlying lung conditions included not only COPD, but asthma, bronchiectasis and other chronic lung diseases, who had chronic symptoms requiring long-term oxygen therapy or had chronic hypercapnia. These patients can rapidly decompensate and develop respiratory failure during an infective exacerbation, but with the appropriate treatment their conditions improved and did not spiral into septic shock and multiorgan failure. This was evidenced by a lower disease severity score and less requirements for organ support in this subgroup. Another possibility was the exclusion of patients with advanced, end-stage lung conditions deemed too sick to benefit from ICU admission, who instead had early 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),²⁴ rather than their cardioprotective effects. Multiple observational studies have demonstrated that prior treatment with statins, antiplatelets and angiotensin-converting enzyme inhibitors were associated with reduced rates of severe sepsis and lower mortality in pneumonia.^{24–29} However,

these findings were not replicated in randomised controlled trials, which were mostly single-centre, with small sample sizes.³⁰ A recent large randomised, 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.

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