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Cardiogenic shock and infection: A lethal combination

Abbreviated title: Cardiogenic shock and infection

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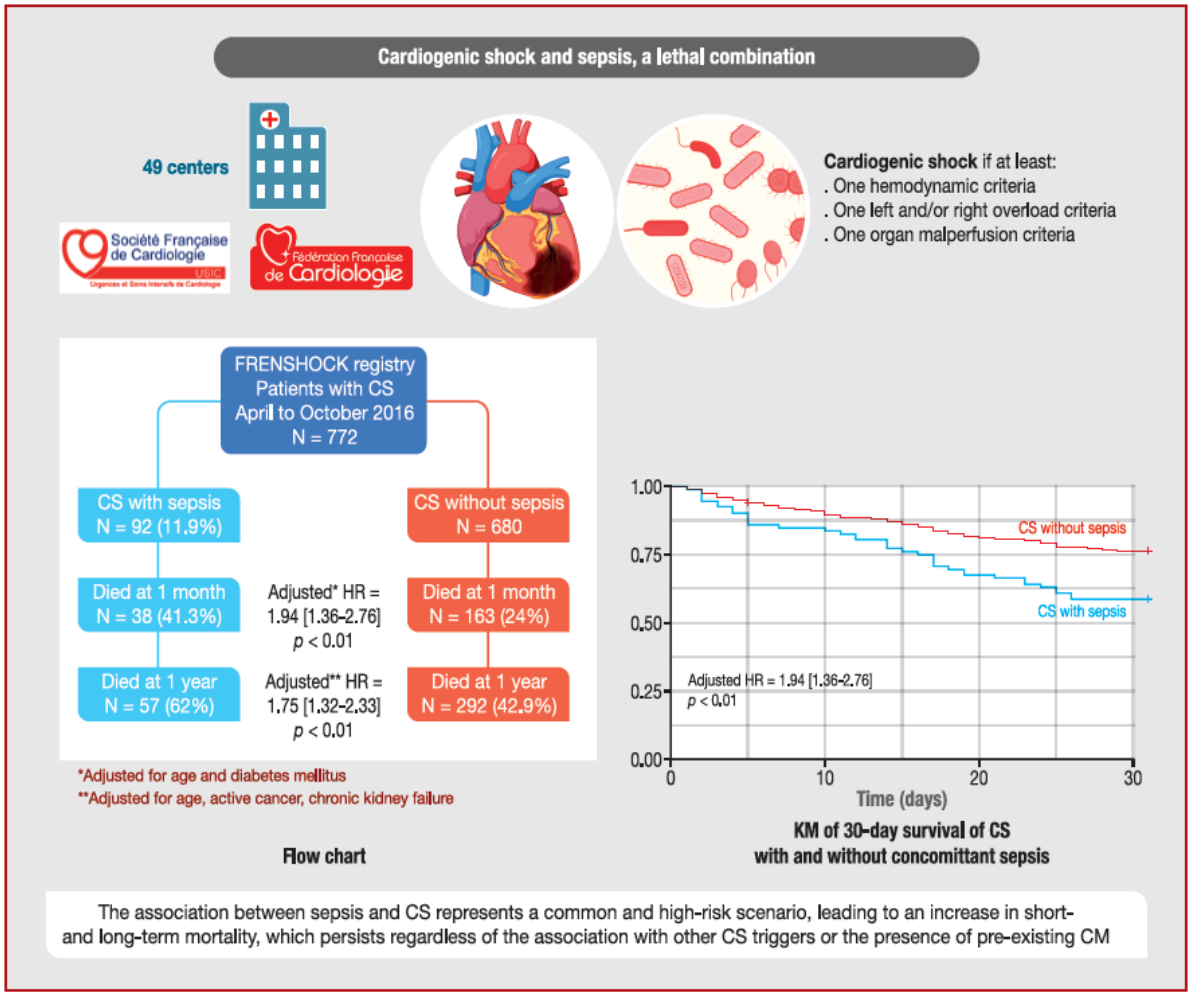
Graphical abstract



Highlights

- Sepsis triggers are frequent, concerning almost 12% of unselected CS cases
- Sepsis trigger can be exclusive (2/3 cases) or associated with other CS triggers
- The other triggers are ischaemia, arrythmias or iatrogenesis
- Sepsis-triggered CS was more profound, with more severe organ dysfunction
- Sepsis-triggered CS required more use of vasopressors/inotropes and organ support
- Sepsis-triggered CS was associated with higher short- and long-term death rates

ABSTRACT

Background: Cardiogenic shock and sepsis are severe haemodynamic states that are frequently present concomitantly, leading to substantial mortality. Despite its frequency and clinical significance, there is a striking lack of literature on the outcomes of combined sepsis and cardiogenic shock.
Methods: FRENSHOCK was a prospective registry including 772 patients with cardiogenic shock from 49 centres. The primary endpoint was 1-month all-cause mortality. Secondary endpoints included heart transplantation, ventricular assistance device and all-cause death rate at 1 year.
Results: Among the 772 patients with cardiogenic shock included, 92 cases were triggered by sepsis (11.9%), displaying more frequent renal and hepatic acute injuries, with lower mean arterial pressure. Patients in the sepsis group required broader use of dobutamine (90.1% vs 81.2%; *P* = 0.16), norepinephrine (72.5% vs 50.8%; *P* < 0.01), renal replacement therapy (29.7% vs 14%; *P* < 0.01), non-invasive ventilation (36.3% vs 24.4%; *P* = 0.09) and invasive ventilation (52.7% vs 35.9%; *P* = 0.02). Sepsis-triggered cardiogenic shock resulted in higher 1-month (41.3% vs 24.0%; adjusted hazard ratio 1.94, 95% confidence interval 1.36–2.76; *P* < 0.01) and 1-year (62.0% vs 42.9%; adjusted hazard ratio 1.75, 95% confidence interval 1.32–2.33; *P* < 0.01) all-cause death rates. No significant difference was found at 1 year for heart transplantation or ventricular assistance device (8.7% vs 10.3%; adjusted odds ratio 0.72, 95% confidence interval 0.32–1.64; *P* = 0.43). In patients with sepsis-triggered cardiogenic shock, neither the presence of a pre-existing cardiomyopathy nor the co-occurrence of other cardiogenic shock triggers had any additional impact on death.
Conclusions: The association between sepsis and cardiogenic shock represents a common high-risk scenario, leading to higher short- and long-term death rates, regardless of the association with other cardiogenic shock triggers or the presence of pre-existing cardiomyopathy.

Keywords:
Cardiogenic shock
Sepsis
Epidemiology
Prognosis
Mortality

1. Abbreviations

aHR	adjusted hazard ratio
aMCS	acute mechanical circulatory support
CICU	cardiac intensive care unit
CS	cardiogenic shock
ECLS	extracorporeal life support
SCAI	Society for Cardiovascular Angiography and Interventions
Sepsis-3	Third International Consensus Definitions for Sepsis and Septic Shock

2. Background

Cardiogenic shock (CS) is a life-threatening condition characterized by systemic hypoperfusion resulting from a primary cardiac dysfunction. Despite advances in its management, the death rate for CS remains high [1].

Many patients diagnosed with CS exhibit signs indicative of sepsis. Indeed, approximately 15–20% of patients with shock in cardiac intensive care units (CICUs) in the USA have CS with concomitant sepsis or CS-vasodilatory shock [2].

Sepsis is also a life-threatening organ dysfunction, caused by an unregulated host response, with septic shock being its most severe manifestation [3]. These two conditions are also associated with significant mortality and morbidity worldwide [4]. The haemodynamic cardiovascular profile of sepsis is complex and dynamic, and combines different levels of alterations in preload, afterload and often cardiac contractility, sometimes leading to ventriculoarterial uncoupling [5]. The management of sepsis involves early recognition, timely administration of antibiotics, fluid resuscitation and haemodynamic optimization using vasopressors and inotropes as recommended [6]. Recent studies have suggested some potential links between CS and sepsis. Indeed, on the one hand, the presence of sepsis may contribute to the development of CS as an initial trigger [7], such as in patients with pre-existing chronic heart failure, or sepsis may even worsen CS severity [8]. In addition, septic shock can also induce CS, such as in sepsis-induced cardiomyopathy [9-11], sometimes needing acute mechanical circulatory support (aMCS) [12]. On the other hand, CS may increase the risk of sepsis [13] or may lead to the development of sepsis and septic shock [14]. However, the underlying mechanisms that drive these associations are not well understood.

Regarding sepsis leading to sepsis-induced cardiomyopathy and CS, many possible mechanisms have been suggested, such as the effect on the myocardium of proinflammatory cytokines, dysfunctional nitric oxide synthase or mitochondria, sympathetic hyperactivation and, finally, coronary microcirculatory disorders, such as endothelial dysfunction and glycocalyx degradation, leading to ischaemia and capillary leaks, and resulting in myocardial oedema [9, 15].

Regarding CS leading to septic shock, impairment of immune function during CS may favour sepsis [16]; another mechanism may be intestinal ischaemia, favouring translocation of bacteria/endotoxins into the bloodstream, leading to profound hypoperfusion and a vicious circle phenomenon [14].

Despite the frequent prevalence and clinical relevance of this association, there is limited literature available on the short- and long-term outcomes of mixed sepsis-CS [2, 17].

Our purpose is to provide an overview of the clinical presentation, management and outcomes of patients with CS and sepsis, based on the FRENSHOCK registry, a large cohort of miscellaneous cases of CS.

3. Methods

3.1. Patient population

As reported previously [1, 18, 19], FRENSHOCK is a prospective observational multicentre survey that was conducted between April and October 2016, including 772 patients admitted for CS to an intensive care unit/CICU in France from various types of institutions (primary to tertiary centres, university and non-university, public and private hospitals).

All adult patients (aged ≥ 18 years) with CS were included prospectively if they met at least one criterion from each of the following three components: (1) low cardiac output: low systolic blood pressure < 90 mmHg and/or the need for maintenance with vasopressors/inotropes and/or a low cardiac index < 2.2 L/min/m²; (2) left and/or right heart filling pressure elevation, defined by clinical signs, radiology, blood tests, echocardiography or signs of invasive haemodynamic overload; and (3) signs of organ malperfusion, which could be clinical (oliguria, confusion, pale and/or cold extremities, mottled skin) and/or biological (lactate > 2 mmol/L, metabolic acidosis, renal failure, liver insufficiency).

For each patient, investigators had to specify one to three CS triggers among the following: sepsis; ischaemia (type 1 or 2 acute myocardial infarction); mechanical complications (valvular injury,

ventricular septal defect); ventricular and supraventricular arrhythmia; severe bradycardia; iatrogenesis (medication induced); and non-observance of previous medication. Patients could therefore have one or several co-existing CS triggers. The diagnosis of sepsis was based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [3]. Those who had sepsis as the only trigger were defined as having exclusively sepsis-triggered CS, whereas those whose sepsis was associated with other concomitant triggers (ischaemia, ventricular arrhythmia, etc.) were defined as having non-exclusively sepsis-triggered CS.

3.2. Data collection

The protocol for data collection has been published previously [1, 18, 19]. Briefly, the data collected included the patient's medical history, past treatments and management of CS during hospitalization, including fluid administration and the use of antibiotics, inotropes/vasopressors, mechanical ventilation, renal replacement therapy and aMCS. Additionally, various clinical, biological and echocardiographic variables were recorded at admission and after 24 hours.

3.3 Outcomes

All-cause mortality, heart transplantation and ventricular assist devices were assessed at 1 month and 1 year. The primary endpoint was 1-month all-cause death rate. Secondary endpoints included 1-year all-cause death rate and 1-year need for heart transplantation or a ventricular assist device.

3.4. Ethics

The study was conducted in accordance with the Helsinki declaration and French law. Written consent was obtained for all patients. Recorded data and their storage were approved by the CCTIRS (*Comité consultatif pour le traitement de l'information en matière de recherche dans le domaine de la santé*; French Health Research Data Processing Advisory Committee; n° 15.897) and the CNIL (*Commission nationale de l'informatique et des libertés*; French Data Protection Agency; n° DR-2016-109). The trial was registered at ClinicalTrials.gov (Identifier:NCT02703038).

3.5. Statistical analysis

Continuous variables are reported as means ± standard deviations or medians (interquartile ranges), as appropriate. Categorical variables are described as frequencies and percentages. Comparisons were made using the Mann-Whitney non-parametric test for continuous variables, and Fisher's exact test for categorical variables. Paired data were analysed with the Wilcoxon signed-rank test. To identify independent predictors for each outcome, we employed a multivariable stepwise logistic regression approach. Initially, univariate logistic regression analyses assessed the association of all baseline characteristics with each primary and secondary outcome. Subsequently, based on their statistical significance in the univariate analyses, and their clinical relevance, a backward reduction process was applied to include only characteristics with $P \leq 0.05$ in the multivariable models for adjusted outcome analyses. The variance inflation factor was used to ensure the absence of multicollinearity among variables. The primary outcome of all-cause death rate was assessed using Kaplan-Meier time-to-event analysis, and Cox proportional hazards models were used to determine the adjusted hazard ratio (aHR), 95% confidence interval (CI) and *P* value. Secondary outcomes (heart transplantation, ventricular assist device and further composites) are reported as their adjusted odds ratio and 95% CI by multivariable logistic regression, as we did not have the exact temporal data needed to develop a Cox model. The main analysis was a comparison between patients with sepsis-triggered and non-sepsis-triggered CS. Further analyses were conducted examining the primary and secondary outcomes in the sepsis-triggered group: (1) between patients with sepsis as the exclusive trigger for CS and those with other coexisting triggers; and (2) between patients with sepsis as the exclusive trigger for CS without a history of chronic cardiomyopathy and other sepsis-triggered cases of CS.

All tests were two-tailed. A value of $P \leq 0.05$ was accepted as statistically significant. To address the issue of multiple testing, *P* values were adjusted with the Benjamini-Hochberg false discovery rate method, and reported with raw and corrected values. All *P* values presented in the text are the corrected ones, unless otherwise stated. Analyses were performed using R software, version 4.1.2 (R Core Team [2021]. R Foundation for Statistical Computing, Vienna, Austria).

4. Results

4.1. Baseline characteristics

As illustrated in Fig. 1, a total of 772 patients with CS were enrolled from 49 different medical centres. Among this cohort, 92 patients were identified with concurrent sepsis, accounting for 11.9% of the total sample, and their characteristics are delineated in Table 1. Comparison between the two groups revealed no significant disparities in age, sex distribution or prevalence of cardiovascular risk factors. The distribution of cardiac disease history was evenly balanced between the groups (64.1% vs 55.1% *P* = 0.31), irrespective of the specific cardiomyopathy subtype. Notably, the severity of cardiac ailments, as indicated by the prevalence of previously implanted implantable cardioverter-defibrillators, was similar between the sepsis and non-sepsis cohorts (15.2% vs 16.6%; *P* = 0.97). Additionally, there were no discernible differences in the prevalence of associated co-morbidities, such as peripheral artery disease, chronic kidney disease and chronic obstructive pulmonary disease. However, patients in the sepsis group exhibited a trend towards a higher incidence of active cancer (14.1% vs 5.6%; *P* = 0.02). Baseline drug therapy, encompassing antithrombotic agents, antiarrhythmics and medications for heart failure, was consistent across both groups.

Among the 92 patients in the sepsis group, 61 (66.3%) presented with infection as the sole trigger, whereas the remaining 31 patients displayed a combination of other concurrent triggers, including ischaemia (16.3%), supraventricular tachycardia (6.5%), iatrogenesis (6.5%) and recurrent supraventricular tachycardia (6.5%) (Table A.1).

4.2. CS presentation and evolution at 24 hours according to sepsis and non-sepsis groups

Patients in the sepsis group presented with a lower mean arterial pressure at baseline compared with those in the non-sepsis group (70.2 vs 75.5 mmHg; *P* = 0.03), along with a lower diastolic blood pressure (59.4 vs 63.7 mmHg; *P* = 0.049), although lactate concentrations were not significantly different between the two groups (Table 2). Cardiac arrests were predominantly observed in the non-sepsis group (2.2% vs 11.3%; *P* = 0.02). Notably, organ dysfunction was more pronounced in the sepsis group, with a higher incidence of acute liver injury compared with the non-sepsis cohort, as evidenced by a decreased prothrombin time (50.0% vs 60.0%; *P* = 0.02) and a trend towards higher creatinine concentrations (150.0 vs 131.0 µmol/L; raw *P* = 0.03, corrected *P* = 0.13). There were no significant differences observed in systolic or diastolic right ventricular and left ventricular function between the two groups. Matched data analysis revealed that only patients in the non-sepsis group

demonstrated a notable improvement in systolic blood pressure, lactate concentration, creatinine concentration and left ventricular ejection fraction at 24 hours (Table A.2).

4.3. In-hospital management according to sepsis and non-sepsis groups

Dobutamine was the most frequently used inotrope (90.1% vs 81.2%; *P* = 0.16), and norepinephrine (72.5% vs 50.8%; *P* < 0.01) was used more frequently in the sepsis group, whereas no significant differences were observed for levosimendan and epinephrine (Table 3). The presence of sepsis also resulted in a higher utilization of invasive ventilation (52.7% vs 35.9%; *P* = 0.02). There was no disparity in the overall utilization of aMCS (13.0% vs 18.2%; *P* = 0.49), whereas sepsis was associated with a greater need for acute renal replacement therapy (29.7% vs 14.0%; *P* < 0.01).

4.4. Short and long-term outcomes

The combination of CS and sepsis led to a notable increase in 1-month (41.3% vs 24.0%; aHR 1.94, 95% CI 1.36–2.76; *P* < 0.01) and 1-year (62.0% vs 42.9%; aHR 1.75, 95% CI 1.32–2.33; *P* < 0.01) all-cause death rates, as illustrated in Fig. 2. Conversely, there was no significant disparity observed at 1 year for heart transplantation or ventricular assist device between the two groups (8.7% vs 10.3%; adjusted odds ratio 0.72, 95% CI 0.32–1.64; *P* = 0.69).

4.5. Exclusively and non-exclusively sepsis-triggered CS, with and without past cardiomyopathy

Among the 92 patients with CS in the sepsis group, 61 cases were solely triggered by sepsis (66.3%). The concurrent presence of other CS triggers did not influence the all-cause death rate at 1 month (42.6% vs 38.7%; aHR 1.13, 95% CI 0.57–2.26; *P* = 0.89) or at 1 year (65.6% vs 54.8%; aHR 1.29, 95% CI 0.72–2.31; *P* = 0.67) (Fig. 3). Additionally, the existence of a pre-existing cardiomyopathy did not impact death rates at 1 month (aHR 1.16, 95% CI 0.57–2.36; *P* = 0.89) and at 1 year (aHR 1.13, 95% CI 0.6–2.11; *P* = 0.89) for sepsis-triggered CS (Fig. 4).

5. Discussion

In this post-hoc analysis of a large prospective observational multicentre registry of miscellaneous patients with CS managed in routine practice in primary, secondary and tertiary centres, 11.9% were triggered by sepsis, resulting in a higher all-cause mortality rate at 1 month and 1 year. This increase

in mortality was observed regardless of whether sepsis was the sole trigger of CS or not, and independent of the presence of a history of chronic cardiomyopathy.

Sepsis is a common trigger for CS and has been associated with worse outcomes in critically ill patients [20]. Our results showed that patients with sepsis-triggered CS had significantly higher short-term mortality rates compared with those without sepsis. Specifically, the 1-month death rate was 41.3% in the sepsis group compared with 24% in the non-sepsis group, with a 1-month adjusted HR of 1.94 (95% CI 1.36–2.76; $P < 0.01$). This result is consistent with previous studies that have shown that sepsis is a major contributor to death in critically ill patients [4], particularly those with chronic cardiomyopathy [21] or hospitalized for acute heart failure [22], via exacerbation of pre-existing cardiac conditions [8] or a true sepsis-induced cardiomyopathy [11]. In our study, neither having sepsis as the exclusive CS trigger nor having an antecedent of chronic cardiomyopathy had any impact on death rates at 1 month and 1 year, reinforcing again that sepsis is a strong and independent predictive factor for death in CS. It is noteworthy that, despite this heavy burden, most scores intended for the stratification of the severity of CS (CardShock, Cardiogenic Shock Score, IABP-SHOCKII) do not consider the presence of concurrent sepsis. The Society for Cardiovascular Angiography and Interventions (SCAI) SHOCK stage classification [23] seems to perform better than the Sequential Organ Failure Assessment (SOFA) cardiovascular subscore for death risk stratification in patients in the CICU with sepsis and concomitant cardiovascular disease or mixed sepsis-CS [2].

Of note, patients with sepsis-triggered CS had more severe initial clinical and laboratory variables, including lower blood pressure, and a higher incidence of acute kidney and liver injuries, which are well-known indicators of critical and severe state [24, 25]. Organ support therapies, such as assisted ventilation (invasive and non-invasive) and acute renal replacement therapy, were also required more frequently in the sepsis group.

Our data shed light on the complexity of managing patients with CS and concomitant sepsis, illustrated by a poorer 24-hour recovery in the sepsis group in terms of clinical and biological variables. Indeed, although rapid fluid resuscitation is the cornerstone of septic shock management, patients with sepsis-triggered CS had more signs of left and right congestion, limiting usual fluid management for sepsis-associated vasoplegia and hypotension. This is consistent with past studies that have shown that patients with sepsis often present with fluid overload as a result of capillary leaks and vasodilation [26]. Fluid overload and its persistence are strongly associated with a higher death rate in patients with

sepsis [27], and patients with sepsis as a trigger for CS will usually require diuretics for decongestion. Conversely, if the sepsis is not properly controlled, the same patient might progress to septic shock requiring fluid resuscitation because of the relative hypovolaemia induced by the vasoplegic shock. Thus, the optimal approach to fluid therapy in patients with sepsis with concurrent CS remains controversial [28], and further studies are needed to determine the optimal timing and volume of fluid resuscitation in this high-risk population.

Besides, whereas sepsis is known to impair microcirculation and tissue oxygen extraction [10], patients in the sepsis-triggered group required more extensive use of dobutamine, the effect of which on microcirculation remains a matter of debate, as it may worsen tissue hypoxia by increasing oxygen demand without improving oxygen delivery [29]. There is mounting evidence that inotropic agents, such as dobutamine, may not improve outcomes in septic shock, and may even be harmful in certain patients [30], with some studies (still highly debated) showing that beta-blockers may have beneficial effects in sepsis and septic shock [31, 32].

Levosimendan – used in only seven patients in the sepsis group (8.6%) – may be a potential therapeutic alternative based on its anti-inflammatory properties, microcirculation improvement and associated effect on cardiac output [17]. However, it has not demonstrated substantial efficacy in reducing organ dysfunction or mortality in sepsis, and is not currently recommended [33].

In the context of sepsis, the management of aMCS becomes even more challenging because of the complexity of the underlying pathophysiology. Our study showed that among the 13 patients in the sepsis-triggered CS group, 12 were supported with extracorporeal life support (ECLS) and one with the Impella® device (Abiomed, Danvers, MA, USA). The use of ECLS for isolated sepsis without severe left ventricular depression is a matter of debate, with disappointing results reported in the literature [34]. Indeed, whereas ECLS represents a very effective circulatory support in the setting of CS [35], resulting mainly from a drop in cardiac output, its benefit in the context of vasoplegic shock as observed in sepsis is highly questionable. However, it has been suggested that ECLS may be more effective in patients with sepsis-associated cardiac dysfunction [12]. Other devices, such as Impella®, may offer an alternative option for circulatory support in patients with CS and sepsis, with the limitation that this device does not allow oxygenation, which is often compromised in patients with sepsis. The decision to initiate aMCS should be based on the severity of the CS and the presence of cardiac dysfunction, as well as the potential benefits and risks associated with the selected device.

Additionally, our study revealed that sepsis-triggered CS was also associated with worse long-term outcomes, as illustrated by an increased 1-year all-cause death rate (adjusted HR 1.75, 95% CI 1.32–2.33; $P < 0.01$). This finding is important, as previous studies have suggested that sepsis may lead to persistent organ dysfunction and impaired long-term survival (postsepsis syndrome) [36, 37]. Indeed, long-term survival largely relies on the severity of sepsis and the degree of organ dysfunction [38]. Although we have accounted for all-cause deaths, there is emerging evidence that sepsis may be associated with an increased risk of long-term cardiovascular events [39], potentially as a result of persistent inflammation [40], persistent dyslipidaemia [41] and accelerated vascular senescence [42]. This highlights the need for continued follow-up of sepsis survivors beyond the acute phase, with a focus on assessing and managing long-term cardiovascular risk.

5.1. Study limitations

Because there is still no consensus definition [9], we were unable to differentiate CS with sepsis-induced cardiomyopathy from other forms of CS based on the available data, and therefore we cannot formally establish their specific prognoses. Although we used Sepsis-3 criteria [3] for patient grouping, we were unable to distinguish between sepsis and septic shock. Unfortunately, our dataset lacks comprehensive information regarding the specific type of sepsis, microbiological results and details of the initial inflammatory response and infection variables (such as white blood cell count, temperature, antimicrobial therapy and identified pathogens). This limitation hinders a more nuanced understanding of the characteristics and management of sepsis in the context of CS. Secondly, the diagnosis of sepsis was based on the Sepsis-3 criteria, and was reported as such by the investigators, but without detailed information on the diagnostic or therapeutic modalities employed for sepsis management, such as duration and type of antibiotics. This lack of granularity in the data may limit the interpretation of sepsis-related outcomes and the assessment of treatment effectiveness.

Although the decision to use all-cause death rate as the primary outcome was intentional, and reflects the daily reality of the many co-morbidities associated with heart failure, future studies could also examine specific cardiovascular outcomes to determine any differences from all-cause deaths. Additionally, we acknowledge the importance of understanding the potential impact of sepsis on care decisions, such as temporary contraindications for heart transplantation or left ventricular assist device placement, and the potential influence of sepsis-associated multiorgan failure on withdrawal decisions.

Therefore, the inclusion of cause-specific death data in future studies could provide valuable insights into these aspects of patient care.

As previously reported [1], the FRENSHOCK registry involves risks of selection bias related to non-consecutive inclusions or exclusion of the most severe cases, with specific inclusion and exclusion criteria limiting the applicability to all patients with CS. We were unable to use the SCAI SHOCK stage classification given that it was not yet available at the time of our study.

6. Conclusions

The association between sepsis and CS represents a common and high-risk scenario, leading to an increase in short- and long-term deaths, which persists, regardless of the association with other CS triggers or the presence of pre-existing cardiomyopathy. Acute management is challenging because of the overlap of conflicting phenomena related to vascular filling and the use of inotropes/vasopressors, highlighting the crucial need for large clinical trials to improve patient outcomes.

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Disclosure of interest

The authors declare that they have no competing interest.

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Figure legends

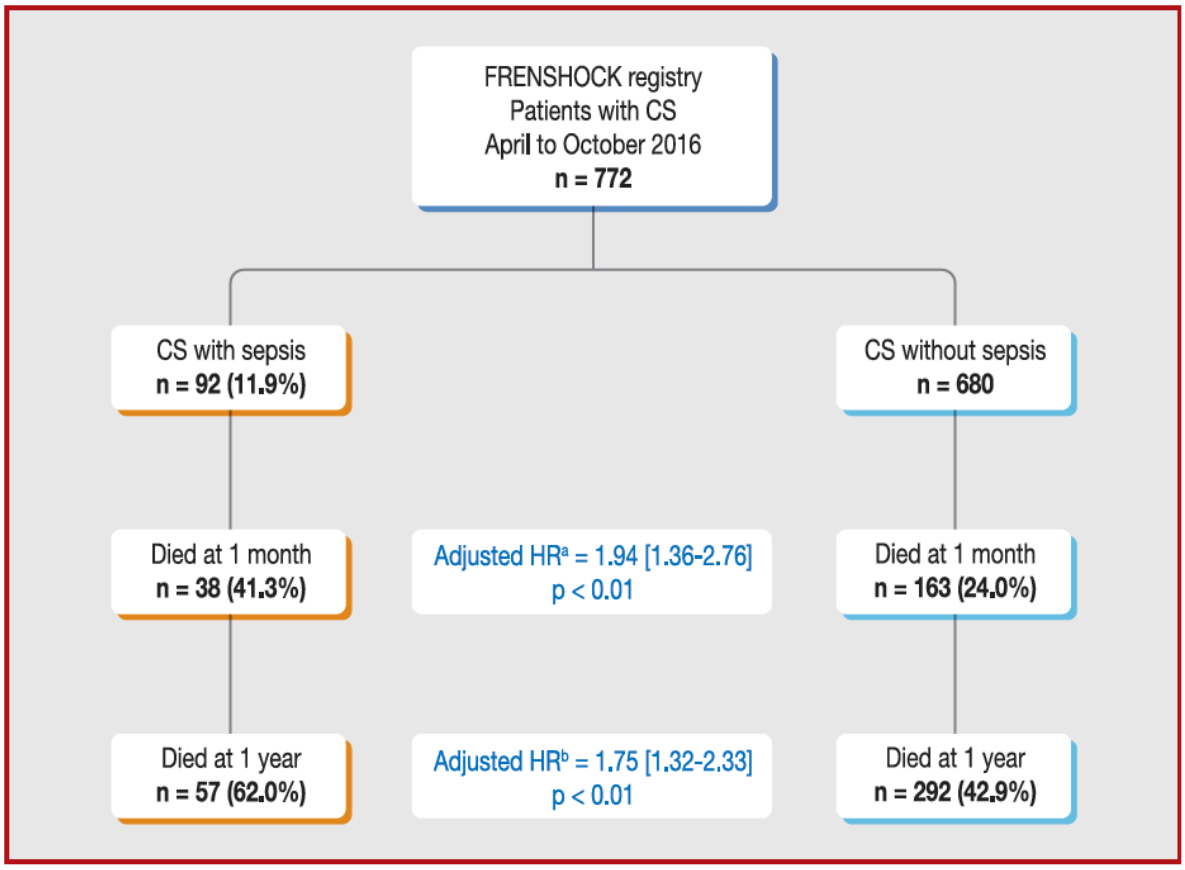


Fig. 1. Study flow chart. Each adjusted outcome analysis included significant characteristics found as independent predictive factors in multivariable analyses and used as fixed covariates. CS: cardiogenic shock; HR: hazard ratio.

[a] Adjusted for age and diabetes mellitus.

[b] Adjusted for age, active cancer and chronic kidney failure.

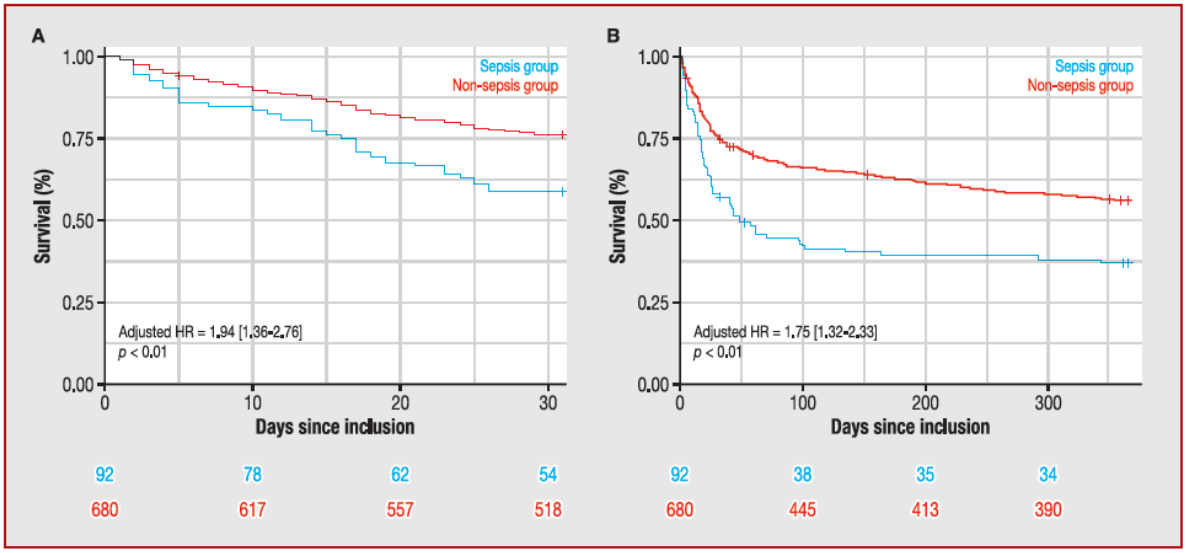


Fig. 2. Short- and long-term mortality outcomes after cardiogenic shock (CS) comparing sepsis-triggered and other patients with CS. A. One-month overall mortality. B. One-year mortality. The cumulative incidences of 1-year and 1-month mortality were estimated using the Kaplan-Meier method; hazard ratios (HRs) and 95% confidence intervals were estimated using Cox regression models. According to significant characteristics found as independent predictive factors in multivariable analyses, 1-month mortality was adjusted for age and diabetes mellitus, and 1-year mortality was adjusted for age, active cancer and chronic kidney disease.

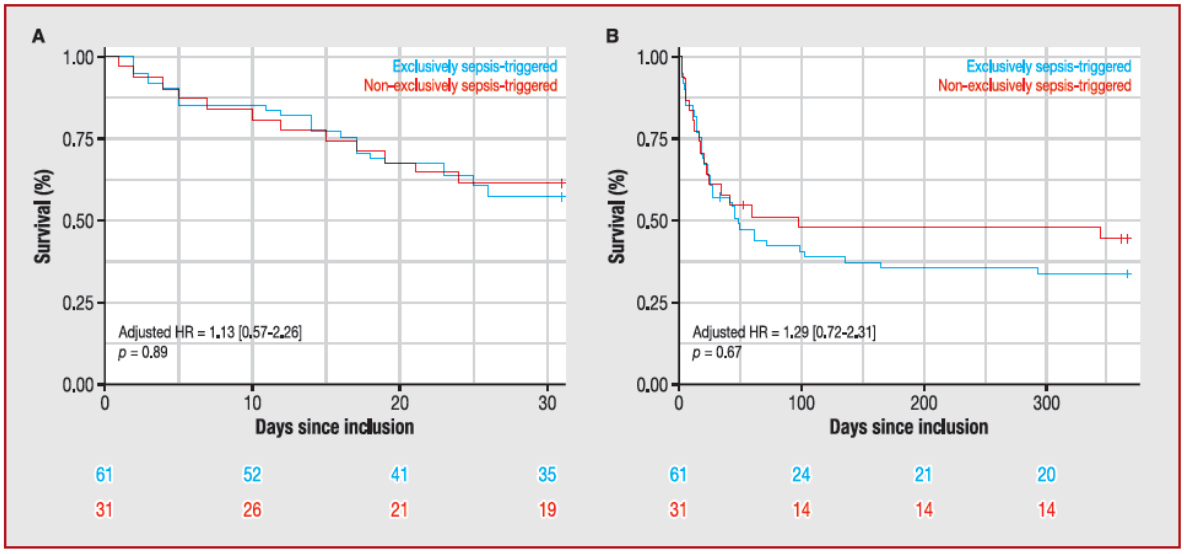


Fig. 3. Short- and long-term mortality outcomes after cardiogenic shock (CS) based on the exclusive or non-exclusive sepsis trigger. A. One-month overall mortality. B. One-year mortality. The cumulative

incidences of 1-year and 1-month mortality were estimated using the Kaplan-Meier method; hazard ratios (HRs) and 95% confidence intervals were estimated using Cox regression models. According to significant characteristics found as independent predictive factors in multivariable analyses, 1-month mortality was adjusted for age and diabetes mellitus, and 1-year mortality was adjusted for age, active cancer and chronic kidney disease.

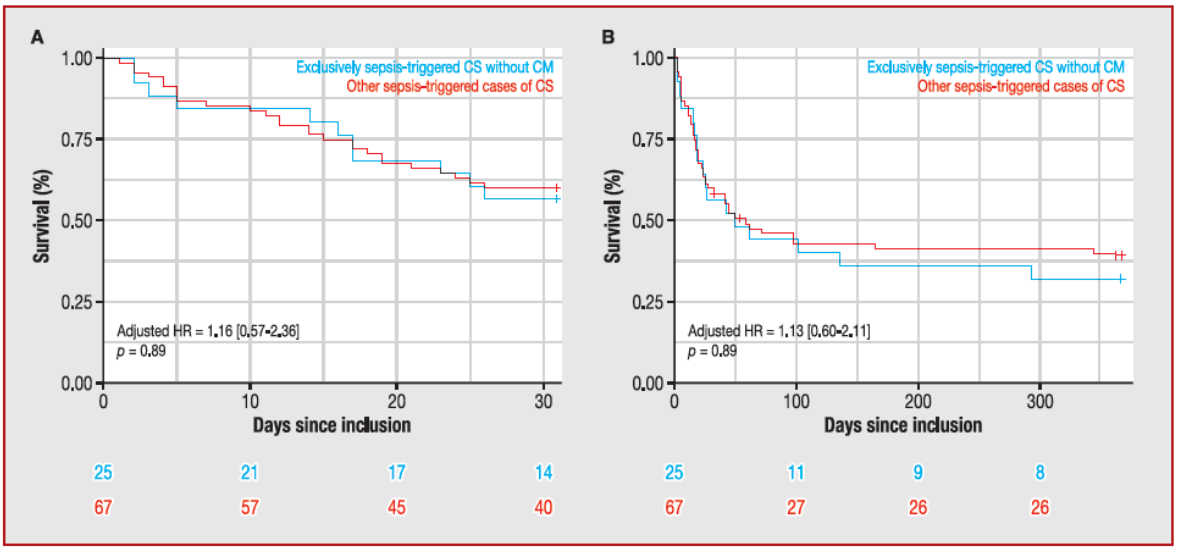
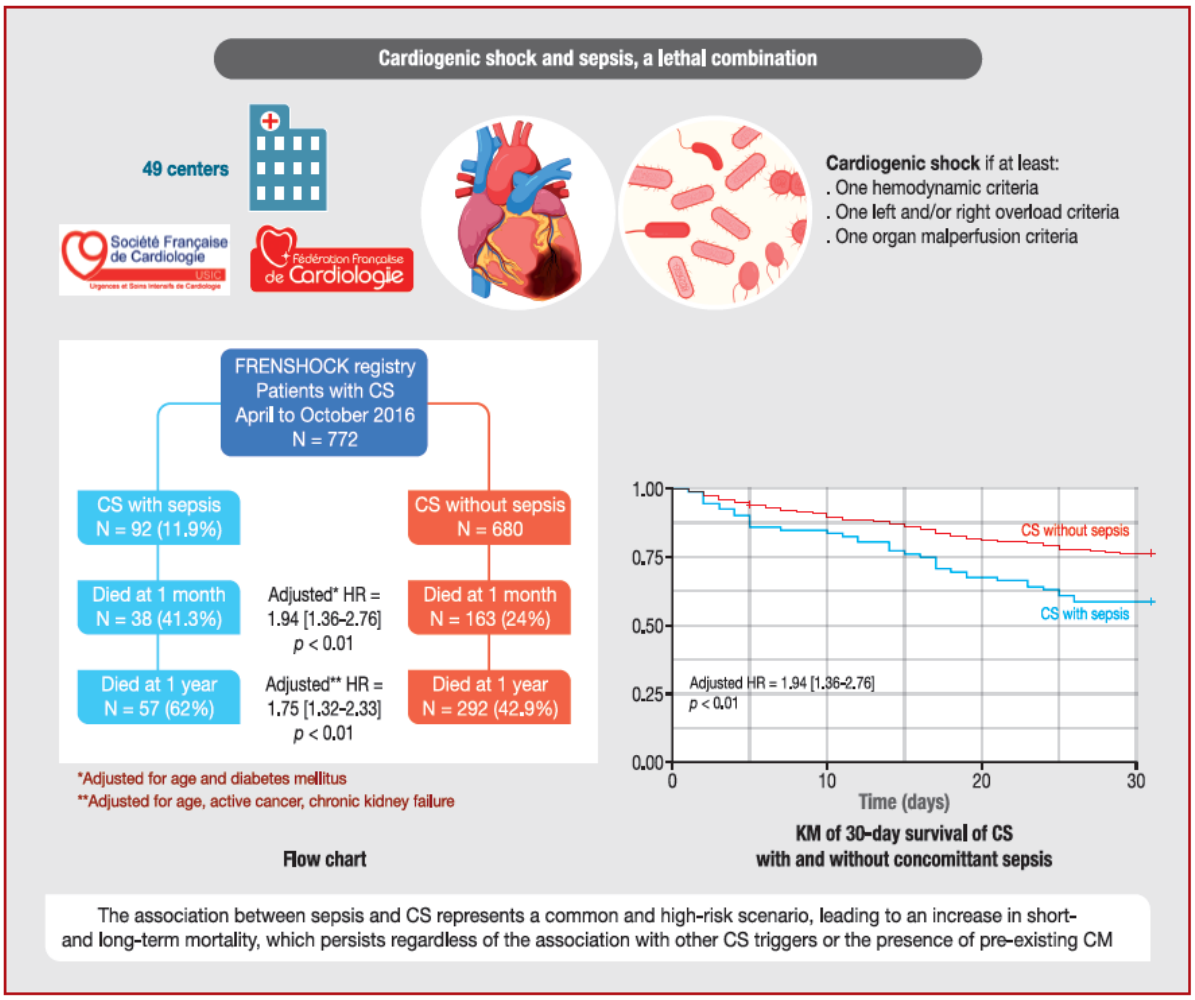


Fig. 4. Short- and long-term mortality outcomes after cardiogenic shock (CS) based on the exclusive or non-exclusive sepsis trigger and history of cardiomyopathy (CM). A. One-month overall mortality. B. One-year mortality. The cumulative incidences of 1-year and 1-month mortality were estimated using the Kaplan-Meier method; hazard ratios (HRs) and 95% confidence intervals were estimated using Cox regression models. According to significant characteristics found as independent predictive factors in multivariable analyses, 1-month mortality was adjusted for age and diabetes mellitus, and 1-year mortality was adjusted for age, active cancer and chronic kidney disease.



Central illustration. Cardiogenic shock and sepsis: A lethal combination. CM: cardiomyopathy; CS: cardiogenic shock; HR: hazard ratio; KM: Kaplan-Meier analysis.

Table 1

Baseline characteristics of the FRENSHOCK population, comparing patients with sepsis-triggered versus non-sepsis-triggered cardiogenic shock.

	Overall population	Sepsis group	Non-sepsis group	Raw *P* value	Corrected *P* value
	(*n* = 772)	(*n* = 92)	(*n* = 680)		
Age (years)	65.7 ± 14.9	65.4 ± 14.8	65.7 ± 14.9	0.64	0.85
Male sex	552 (71.5)	65 (70.7)	487 (71.6)	0.90	0.98
Body mass index (kg/m^2)	25.8 ± 5.5 (*n* = 744)	25.2 ± 5.8 (*n* = 91)	25.9 ± 5.5 (*n* = 653)	0.12	0.31
Risk factors					
Diabetes mellitus	217 (28.2) (*n* = 770)	26 (28.3)	191 (28.2) (*n* = 678)	1.00	1.00
Hypertension	364 (47.2) (*n* = 771)	40 (43.5)	324 (47.7) (*n* = 679)	0.50	0.75
Dyslipidaemia	277 (35.9) (*n* = 771)	35 (38.0)	242 (35.6) (*n* = 679)	0.65	0.86
Current smoker	206 (27.8) (*n* = 740)	22 (25.9) (*n* = 85)	184 (28.1) (*n* = 655)	0.80	0.93
Medical history					
Peripheral artery disease	91 (11.8) (*n* = 771)	5 (16.3)	76 (11.2) (*n* = 679)	0.17	0.40
Chronic kidney disease	164 (21.3) (*n* = 771)	23 (25.0)	141 (20.8) (*n* = 679)	0.34	0.61
COPD	50 (6.5) (*n* = 771)	9 (9.8)	41 (6.0) (*n* = 679)	0.18	0.40
ICD	127 (16.5) (*n* = 771)	14 (15.2)	113 (16.6) (*n* = 679)	0.88	0.97
Active cancer	51 (6.6) (*n* = 771)	13 (14.1)	38 (5.6) (*n* = 679)	< 0.01	0.02
Stroke	62 (8.0) (*n* = 771)	7 (7.6)	55 (8.1) (*n* = 679)	1.00	1.00

History of cardiac disease					
All causes	433 (56.2) (*n* = 771)	59 (64.1)	374 (55.1) (*n* = 679)	0.12	0.31
Ischaemic	230 (29.8) (*n* = 771)	31 (33.4)	199 (29.3) (*n* = 679)	0.40	0.67
Hypertrophic	11 (1.4) (*n* = 771)	1 (1.1)	10 (1.5) (*n* = 679)	1.00	1.00
Toxic	34 (4.4) (*n* = 771)	2 (2.2)	32 (4.7) (*n* = 679)	0.42	0.68
Dilated	78 (10.1) (*n* = 771)	6 (6.5)	72 (10.6) (*n* = 679)	0.27	0.51
Valvular	65 (8.4) (*n* = 771)	11 (12.0)	54 (8.0) (*n* = 679)	0.23	0.47
Hypertensive	24 (3.1) (*n* = 771)	5 (5.4)	19 (2.8) (*n* = 679)	0.19	0.41
Previous medications					
Aspirin	288 (37.4) (*n* = 770)	36 (39.1)	252 (37.2) (*n* = 678)	0.73	0.89
Vitamin K antagonist	165 (21.4) (*n* = 770)	27 (29.3)	138 (20.4) (*n* = 678)	0.058	0.19
Direct oral anticoagulant	56 (7.3) (*n* = 770)	3 (3.3)	53 (7.8) (*n* = 678)	0.14	0.35
ACE inhibitors	292 (37.9) (*n* = 770)	40 (43.5)	252 (37.2) (*n* = 678)	0.25	0.49
Sacubitril/valsartan	18 (2.5) (*n* = 727)	0 (0.0) (*n* = 90)	18 (2.8) (*n* = 637)	0.15	0.37
Beta-blockers	316 (41.0) (*n* = 770)	39 (42.4)	277 (40.9) (*n* = 678)	0.82	0.93
Statins	286 (37.1) (*n* = 770)	39 (42.4)	247 (36.4) (*n* = 678)	0.30	0.54
Loop diuretics	376 (48.8) (*n* = 770)	45 (48.9)	331 (48.8) (*n* = 678)	1.00	1.00
Aldosterone antagonist	108 (14.0) (*n* = 770)	15 (16.3)	93 (13.7) (*n* = 678)	0.52	0.76
Amiodarone	132 (17.6) (*n* = 752)	16 (17.4)	116 (17.6) (*n* = 660)	1.00	1.00

Data are expressed as mean ± standard deviation or number (%). ACE: angiotensin-converting enzyme; COPD: chronic obstructive pulmonary disease; ICD: implantable cardioverter-defibrillator.

Table 2

Clinical, echocardiographic and biological initial presentation, comparing patients with sepsis-triggered versus non-sepsis-triggered cardiogenic shock.

	Overall population	Sepsis group	Non-sepsis group	Raw *P* value	Corrected *P* value
	(*n* = 772)	(*n* = 92)	(*n* = 680)		
Clinical presentation at admission					
SBP (mmHg)	101.2 ± 25.2 (*n* = 770)	98.5 ± 26.7 (*n* = 91)	101.6 ± 24.9 (*n* = 679)	0.10	0.28
DBP (mmHg)	63.2 ± 17.4 (*n* = 769)	59.4 ± 17.4 (*n* = 91)	63.7 ± 17.4 (*n* = 678)	0.01	0.049
MBP (mmHg)	74.9 ± 18.3 (*n* = 767)	70.2 ± 17.5 (*n* = 91)	75.5 ± 18.4 (*n* = 676)	< 0.01	0.03
Sinus rhythm	399 (52.0) (*n* = 768)	50 (55.6) (*n* = 90)	349 (51.5) (*n* = 678)	0.50	0.75
Left heart failure	554 (71.9) (*n* = 770)	74 (81.3) (*n* = 91)	480 (70.7) (*n* = 679)	0.03	0.13
Right heart failure	377 (49.1) (*n* = 768)	56 (61.5) (*n* = 91)	321 (47.4) (*n* = 677)	0.01	0.049
Mottling	256 (38.8) (*n* = 660)	34 (44.7) (*n* = 76)	222 (38.0) (*n* = 584)	0.26	0.50
Cardiac arrest	79 (10.2) (*n* = 771)	2 (2.2)	77 (11.3) (*n* = 679)	< 0.01	0.02
Blood tests at admission					
Creatinine (µmol/L)	133.0 (96.0–190.0) (*n* = 761)	150.0 (107.8–208.8)	131.0 (94.0–186.0) (*n* = 669)	0.03	0.13
Bilirubin (mg/L)	16.0 (9.0–29.0) (*n* = 544)	14.0 (9.0–26.0) (*n* = 69)	16.0 (9.5–29.0) (*n* = 475)	0.44	0.70
Haemoglobin (g/dL)	12.6 (11.0–14.0) (*n* = 754)	12.0 (10.0–13.0) (*n* = 90)	13.0 (11.0–14.0) (*n* = 664)	< 0.01	< 0.01

Arterial blood lactates (mmol/L)	3.0 (2.0–4.7) (*n* = 684)	3.0 (2.0–5.5) (*n* = 83)	3.0 (2.0–4.3) (*n* = 601)	0.19	0.41
PT (%)	59.0 (37.0–77.0) (*n* = 731)	50.0 (28.0–67.3) (*n* = 88)	60.0 (38.0–78.0) (*n* = 643)	< 0.01	0.02
NT-proBNP (pg/mL)	9276.5 (4057.8–22,702.5) (*n* = 224)	10,900.0 (5373.5–29,900.0) (*n* = 31)	8840.0 (3599.0–21,455.0) (*n* = 193)	0.17	0.40
BNP (pg/mL)	1150.0 (476.8–2757.3) (*n* = 264)	1343.0 (532.8–2800.0) (*n* = 34)	1144.5 (470.0–2742.0) (*n* = 230)	0.76	0.89
CRP (mg/L)	28.0 (9.0–69.0) (*n* = 406)	77.0 (28.0–182.0) (*n* = 65)	24.0 (8.0–56.0) (*n* = 341)	0.50	0.75
Baseline echocardiography					
LVEF (%)	26.3 ± 13.4 (*n* = 763)	26.8 ± 12.6	26.2 ± 13.5 (*n* = 671)	0.50	0.75
TAPSE (mm)	13.0 (10.0–16.0) (*n* = 259)	14.0 (10.0–16.0) (*n* = 33)	13.0 (10.0–16.0) (*n* = 226)	0.60	0.82
PSVtdi (cm/s)	8.0 (6.0–11.0) (*n* = 206)	9.5 (6.3–12.0) (*n* = 26)	8.0 (6.0–10.0) (*n* = 180)	0.18	0.40
E/A ratio	2.0 (1.1–2.8) (*n* = 90)	2.45 (1.2–3.4) (*n* = 17)	1.8 (1.0–2.7) (*n* = 73)	0.24	0.48
E/e' ratio	11.7 (7.4–15.6) (*n* = 117)	13.5 (6.3–16.8) (*n* = 23)	11.7 (7.6–15.5) (*n* = 94)	0.87	0.97
Severe mitral regurgitation	107 (14.6) (*n* = 733)	13 (14.8) (*n* = 88)	94 (14.6) (*n* = 645)	1.00	1.00
Severe aortic stenosis	36 (4.7) (*n* = 759)	6 (6.7) (*n* = 90)	30 (4.5) (*n* = 669)	0.42	0.68

Data are expressed as mean ± standard deviation, number (%) or median (interquartile range). BNP*:* brain natriuretic peptide*;* CRP*:* C-reactive protein*;* DBP*:* diastolic blood pressure*;* LVEF*:* left ventricular ejection fraction*;* MBP*:* mean blood pressure*;* NT-proBNP*:* N-terminal prohormone of brain natriuretic peptide*;* PSVtdi*:* peak systolic velocity tissue Doppler imaging*;* PT*:* prothrombin time*;* SBP*:* systolic blood pressure*;* TAPSE*:* tricuspid annular plane systolic excursion.

Table 3

In-hospital management, comparing patients with sepsis-triggered versus non-sepsis-triggered cardiogenic shock.

	Overall population	Sepsis group	Non-sepsis group	Raw *P* value	Corrected *P* value
	(*n* = 772)	(*n* = 92)	(*n* = 680)		
Medications used					
Dobutamine	632 (82.3) (*n* = 768)	82 (90.1) (*n* = 91)	550 (81.2) (*n* = 677)	0.04	0.16
Norepinephrine	410 (53.4) (*n* = 768)	66 (72.5) (*n* = 91)	344 (50.8) (*n* = 677)	< 0.01	< 0.01
Epinephrine	95 (12.4) (*n* = 768)	14 (15.4) (*n* = 91)	81 (12.0) (*n* = 677)	0.40	0.67
Levosimendan	57 (7.4) (*n* = 768)	7 (8.6) (*n* = 91)	50 (7.4) (*n* = 677)	0.83	0.93
Loop diuretics	467 (67.4) (*n* = 693)	47 (58.8) (*n* = 80)	420 (68.5) (*n* = 613)	0.10	0.28
Thiazide diuretics	27 (4.0) (*n* = 682)	6 (7.5) (*n* = 80)	21 (3.5) (*n* = 602)	0.12	0.31
Aldosterone antagonist	91 (13.1) (*n* = 693)	9 (11.3) (*n* = 80)	82 (13.4) (*n* = 613)	0.73	0.89
Respiratory support					
Non-invasive	198 (25.8) (*n* = 768)	33 (36.3) (*n* = 91)	165 (24.4) (*n* = 677)	0.02	0.09
Invasive	291 (37.9) (*n* = 768)	48 (52.7) (*n* = 91)	243 (35.9) (*n* = 677)	< 0.01	0.02
Short-term mechanical circulatory support					
Overall	135 (17.6) (*n* = 769)	12 (13.0)	123 (18.2) (*n* = 677)	0.25	0.49

IABP	48 (6.3) (*n* = 768)	0 (0.0)	48 (7.1) (*n* = 676)	< 0.01	0.02
Impella® device	26 (3.4) (*n* = 768)	1 (1.1)	25 (3.7) (*n* = 676)	0.35	0.65
ECLS	85 (11.1) (*n* = 769)	11 (12.0)	74 (10.9) (*n* = 677)	0.72	0.89
Renal replacement therapy	122 (15.8) (*n* = 771)	27 (29.7) (*n* = 91)	95 (14.0)	< 0.01	< 0.01
Data are expressed as number (%). ECLS: extracorporeal life support; IABP: intra-aortic balloon pump.					