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Predictors and outcomes of sepsis-induced cardiomyopathy in critically ill patients

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Background: Sepsis-induced cardiomyopathy (SIC) occurs frequently in critically ill patients, but the clinical features and prognostic impact of SIC on sepsis outcome remain controversial. Here, we investigated the predictors and outcomes of SIC.

Methods: Patients admitted to a single medical intensive care unit from June 2016 to September 2017 were retrospectively reviewed. SIC was diagnosed by ejection fraction (EF) < 50% and ≥ 10% decrease in baseline EF that recovered within 2 weeks.

Results: In total, 342 patients with sepsis met the inclusion criteria, and 49 patients (14.3%) were diagnosed with SIC; the latter were compared with 259 patients whose EF was not deteriorated by sepsis (non-SIC). Low systolic blood pressure and increased left ventricular end-diastolic diameter (LVEDD) were identified as predictors of SIC. SIC and non-SIC patients did not differ significantly in terms of 28-day all-cause mortality (24.5% vs. 26.3%, P = 0.936). Acute Physiology and Chronic Health Evaluation II (APACHE II; hazard ratio [HR], 1.10; 95% confidential interval [CI], 1.02 to 1.18; P = 0.009) and delta neutrophil index (DNI; HR, 1.02; 95% CI, 1.00 to 1.08; P = 0.026) were independent risk factors for 28-day mortality with SIC. DNI, APACHE II, and lactate were identified as risk factors for 28-day mortality in sepsis patients as a whole.

Conclusions: SIC was not associated with increased mortality compared to non-SIC. Low systolic blood pressure and increased LVEDD were predictors of SIC. High APACHE II score and elevated DNI, which reflect sepsis severity, predict 28-day all-cause mortality.

Key Words: APACHE; delta neutrophil index; left; mortality; prognosis; sepsis; ventricular dysfunction

Original Article

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INTRODUCTION

Sepsis is a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection that can result in multiple organ dysfunction via inflammatory cytokines, mitochondria dysfunction, and tissue hypoxia [1]. Due to specific injury of cardiomyocytes, approximately 3.8%–65% of patients with sepsis develop sepsis-induced cardiomyopathy (SIC) [2-7]. SIC has been defined as myocardial dysfunction characterized by decreased ejection fraction (EF) and increased left ventricular end-diastolic diameter (LVEDD) that recovers within 7–10 days [2]. Current understanding of the pathogenesis of SIC is limited, and con-

flicting results remain regarding the prognostic impact of SIC on sepsis outcomes.

Improved understanding of SIC is important for multiple reasons. First, cardiac function is crucial for maintaining hemodynamic stability in patients with septic shock. Second, by understanding the clinical features and predictors of SIC, we can discriminate SIC from other cardiac diseases and avoid unnecessary invasive procedures, such as coronary angiography, a risky procedure in critically ill patients. Thus, we aimed to define clinical predictors of SIC and assess the clinical course and outcome of SIC in patients with sepsis.

KEY MESSAGES

- Sepsis-induced cardiomyopathy (SIC) occurred in 14.3% of intensive care unit patients with sepsis.
- Low systolic blood pressure and increased left ventricular end-diastolic diameter were predictors of SIC.
- High Acute Physiology and Chronic Health Evaluation II and elevated delta neutrophil index were risk factors of 28-day mortality in SIC.

MATERIALS AND METHODS

Study Population

In this study, the medical records of patients who were admitted to the medical intensive care unit (ICU) of Yonsei University College of Medicine from June 2016 to September 2017 were reviewed. A total of 576 adult patients (>18 years old) admitted to the ICU during this period were screened for inclusion (Figure 1). Patients who did not (1) meet the sepsis definition, (2) have baseline transthoracic echocardiography (TTE) data, or (3) undergo TTE within 48 hours after ICU admission were excluded. This study was approved by the Institutional Review Board and Ethics Committee of Severance Hospital (IRB No. 4-2018-0751). The requirement for written informed consent from patients was waived. All methods were performed in accordance with the Declaration of Helsinki.

Definitions of Variables

The sepsis-3 definition was applied in patients with sepsis and septic shock [1]. Sepsis was defined by an increase in Sequential Organ Failure Assessment (SOFA) score of ≥2 points due to infection. Infection was defined as detection of microorganisms in culture or as radiologic or clinical manifestations suggesting infection despite negative culture results [8]. Septic shock was defined as sepsis with persistent hypotension re-

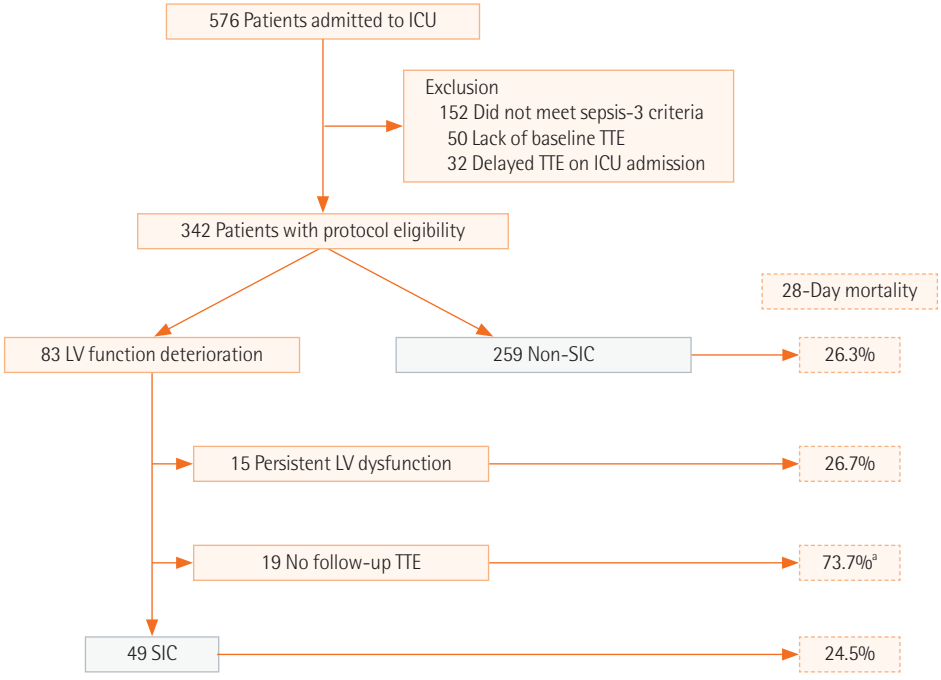

Figure 1. Patient recruitment flowchart. ICU: intensive care unit; TTE: transthoracic echocardiography; LV: left ventricle; SIC: sepsis-induced cardiomyopathy. [a]Patients without follow-up TTE showed poor mortality outcome. Lack of follow-up TTE in this group was due to several reasons: eight patients (42.1%) died within 72 hours after ICU admission, end-of-life decisions were made for six patients (31.6%), two patients were transferred to other hospitals, and three patients (15.8%) recovered from sepsis.

quiring vasopressor drugs to maintain mean arterial pressure ≥65 mm Hg accompanied with serum lactate level >2 mmol/L despite adequate volume resuscitation. Left ventricular function deterioration was defined as EF <50% and ≥10% decrease in baseline EF. Among patients with left ventricular function deterioration, those whose EF recovered to the baseline level within 2 weeks were defined as having SIC [7,9,10].

Data Collection

Demographic data (age, sex, body weight, height, pre-existing comorbidities), vital signs, laboratory findings, echocardiographic findings, and clinical findings (presence of acute kidney injury, acute respiratory distress syndrome, and use of mechanical ventilation) were collected. Laboratory tests were performed within 24 hours of ICU admission, and SOFA and Acute Physiology and Chronic Health Evaluation (APACHE) II scores were evaluated at ICU admission. The delta neutrophil index (DNI) was assessed using an automated blood cell analyzer (ADVIA 120; Siemens, Forchheim, Germany) and calculated using the following formula: (neutrophil subfraction+eosinophil subfraction measured in the myeloperoxidase channel)–(polymorphonuclear subfraction measured in nuclear lobularity channel) [11,12]. If there was no contraindication, TTE was routinely performed by a cardiologist at the time of ICU admission. There was no fixed schedule for follow up TTE, but in the majority of patients it was performed 1–2 weeks after ICU admission, especially when cardiac function deteriorated during ICU admission.

Statistical Analysis

The primary endpoint was 28-day all-cause mortality of SIC. The secondary endpoint was to identify predictors of SIC development and risk factors for 28-day all-cause mortality in patients with SIC. Factors contributing to the incidence of SIC were also analyzed. Continuous variables were analyzed using Student t-test or Mann-Whitney U-test; categorical variables were analyzed using the chi-squared distribution and Fisher's exact test. A logistic regression model was used to identify variables contributing to the development of SIC. Cox proportional hazards regression analyses were conducted to assess the relationships between variables and 28-day all-cause mortality. Area under the curve of receiver operating characteristic curves was used to identify the effect of major variables in multivariate Cox proportional hazards regression analysis ($P<0.05$) on 28-day all-cause mortality. Cumulative time-to-event distribution (survival) was estimated using Kaplan-Meier survival curves, and differences in survival between groups were assessed using the log-rank test. In all cases, P-values <0.05 were considered statistically significant. Statistical analyses were performed using R statistical software ver. 3.5.1 (R Foundation, Vienna, Austria).

RESULTS

Baseline Characteristics of Study Population

A total of 342 patients met the study eligibility criteria. Of these, 83 showed left ventricular function deterioration compared to baseline TTE. Among these, 49 patients had an EF that recovered to the baseline value and were categorized as SIC. Fifteen patients with persistently decreased EF in follow-up TTE and 19 patients without follow-up TTE were excluded (Figure 1). A total of 259 patients whose EF did not deteriorate with sepsis were categorized as the non-SIC group.

Baseline characteristics of 49 SIC and 259 non-SIC patients with sepsis are shown in Table 1. There was no significant difference between SIC and non-SIC patients in terms of age, sex, and body mass index. APACHE II and SOFA scores also did not significantly differ between SIC and non-SIC patients. Underlying heart failure was more frequent in SIC patients (8.2% vs. 1.5%, P=0.029), but the incidence of other comorbidities, including coronary artery disease, was not significantly different between the groups. On ICU admission, systolic blood pressure was significantly lower in patients with SIC (83.9±18.3 vs. 91.1±22.9, P=0.039). There was no significant difference in vasopressor and inotrope use between SIC and non-SIC patients. Primary site of infection was not significantly different between SIC and non-SIC patients. Both C-reactive protein and serum bilirubin levels were higher (192.4±134.2 vs. 137.5±110.6, P=0.002; 1.2±1.4 vs. 2.1±4.1, P=0.008, respectively), whereas serum albumin levels were lower (2.4±0.5 vs. 2.5±0.5, P=0.032) in SIC patients than in non-SIC patients.

Echocardiographic findings and cardiac biomarkers are shown in Table 2. LVEDD and left ventricular end-systolic diameter (LVESD) were significantly increased in SIC patients (49.6±6.0 vs. 43.4±6.3, P<0.001; 39.5±6.4 vs. 28.7±4.8, P<0.001, respectively). N-terminal pro b-type natriuretic peptide (NT-proBNP; pg/ml) and troponin-T (pg/ml) were significantly higher in SIC patients (19,911.2±18,194.9 vs. 7,940.3±13,613.9, P<0.001; 278.9±492.7 vs. 104.8±178.4, P=0.019, respectively), but creatine kinase (CK) and creatine kinase-muscle/brain (CK-MB) levels were not significantly different between SIC and non-SIC patients.

Table 1. Baseline characteristics of patients

Variable	Total (n=308)	SIC (n=49)	Non-SIC (n=259)	P-value
Age (yr)	64.6±14.5	65.1±11.2	64.6±15.0	0.772
Male sex	195 (63.3)	32 (65.3)	163 (62.9)	0.877
BMI (kg/m^2)	22.2±4.3	22.4±3.9	22.2±4.4	0.782
APACHE II	24.9±8.8	26.4±9.3	24.6±8.6	0.209
SOFA	9.4±3.2	9.7±3.2	9.3±3.2	0.378
Comorbidity				
Hypertension	159 (51.6)	25 (51.0)	134 (51.7)	1.000
Diabetes mellitus	108 (35.1)	17 (34.7)	91 (35.1)	1.000
Chronic kidney disease	67 (21.8)	11 (22.4)	56 (21.6)	1.000
Liver cirrhosis	25 (8.1)	2 (4.1)	23 (8.9)	0.399
Chronic liver disease	29 (9.4)	1 (2.0)	28 (10.8)	0.097
Cancer	83 (26.9)	16 (32.7)	67 (25.9)	0.420
Heart failure	8 (2.6)	4 (8.2)	4 (1.5)	0.029
Coronary artery disease	30 (9.7)	7 (14.3)	23 (8.9)	0.364
Cerebrovascular disease	42 (13.6)	6 (12.2)	36 (13.9)	0.934
Charlson comorbidity index	2.8±2.2	3.2±2.1	2.8±2.2	0.231
Acute kidney injury	73 (23.7)	14 (28.6)	59 (22.8)	0.490
ARDS	28 (9.1)	8 (16.3)	20 (7.7)	0.099
Septic shock	295 (95.8)	49 (100.0)	246 (95.0)	0.224
Blood culture (+)	113 (36.7)	22 (44.9)	91 (35.1)	0.255
Mechanical ventilation	200 (64.9)	36 (73.5)	164 (63.3)	0.229
Vital sign on admission				
SBP (mm Hg)	90.0±22.3	83.9±18.3	91.1±22.8	0.039
MAP (mm Hg)	66.7±15.4	64.3±15.3	67.1±15.4	0.249
HR (bpm)	103.0±27.9	109.6±28.9	101.7±27.6	0.071
Use of vasopressor and inotrope				
None	13 (4.2)	0	15 (5.1)	0.224
Norepinephrine	262 (85.1)	44 (89.8)	247 (84.3)	0.420
Dobutamine	3 (0.9)	2 (4.1)	1 (0.4)	0.105
Primary focus of infection				0.507
Pulmonary	155 (50.3)	29 (59.2)	126 (48.6)	
GI tract	43 (14.0)	3 (6.1)	40 (15.4)	
Urogenital	35 (11.4)	7 (14.3)	28 (10.8)	
Pancreatobiliary	25 (8.1)	2 (4.1)	23 (8.9)	
Soft tissue/bone	17 (5.5)	4 (8.2)	13 (5.0)	
Liver	9 (2.9)	1 (2.0)	8 (3.1)	
Kidney	6 (1.9)	1 (2.0)	5 (1.9)	
Miscellaneous	18 (5.8)	2 (4.1)	16 (6.2)	

(*Continued to the next page*)

Predictors of SIC

Univariate logistic regression analyses for predictors of SIC revealed that low systolic blood pressure, hypoalbuminemia, elevated NT-proBNP, troponin-T, and increased LVEDD were major covariates ($P<0.05$). Multivariate logistic regression analysis revealed that low systolic blood pressure upon ICU

Table 1. Continued

Variable	Total (n=308)	SIC (n=49)	Non-SIC (n=259)	P-value
Laboratory parameter				
WBC (10^3/μl)	15.1±10.4	12.9±10.3	15.5±10.4	0.117
Platelet (10^3/μl)	159.2±120.4	162.6±139.1	158.5±116.8	0.831
Serum albumin (g/dl)	2.5±0.5	2.4±0.5	2.5±0.5	0.032
Serum bilirubin (mg/dl)	2.0±3.8	1.2±1.4	2.1±4.1	0.008
Serum creatinine (mg/dl)	2.1±1.9	2.0±1.8	2.1±2.0	0.757
Lactate (mmol/L)	4.0±4.1	3.8±3.4	4.0±4.3	0.826
CRP	146.3±116.2	192.4±134.2	137.5±110.6	0.002
Procalcitonin (ng/ml)	17.5±33.0	23.9±35.5	16.2±32.4	0.135
DNI (%)	11.0±15.1	13.9±18.9	10.5±14.2	0.224

Values are presented as mean±standard deviation or number (%).
SIC: sepsis-induced cardiomyopathy; BMI: body mass index; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; ARDS: acute respiratory distress syndrome; SBP: systolic blood pressure; MAP: mean arterial pressure; HR: heart rate; GI: gastrointestinal; WBC: white blood cell; CRP: C-reactive protein; DNI: delta neutrophil index.

Table 2. Echocardiographic parameters and cardiac biomarkers of patients

Echocardiographic parameter	SIC (n=49)		Non-SIC (n=259)		P-value
	Individual	Value	Individual	Value	
Ejection fraction (%)	49	34.3±8.4	259	64.7±7.5	<0.001
LVEDD (mm)	46	49.6±6.0	248	43.4±6.3	<0.001
LVESD (mm)	46	39.5±6.4	248	28.7±4.8	<0.001
Mitral E/e' ratio	36	12.9±5.5	198	12.0±4.3	0.341
FAC (%)	7	25.3±5.3	17	24.0±8.7	0.712
Cardiac biomarker					
NT-proBNP (pg/ml)	46	19,911.2±18,194.9	233	7,940.3±13,613.9	<0.001
CK (IU/L)	49	341.7±491.8	245	635.9±3,711.8	0.235
CK-MB (ng/ml)	49	8.0±12.8	252	11.9±60.3	0.357
Troponin-T (pg/ml)	48	278.9±492.7	230	104.8±178.4	0.019

Values are presented as mean±standard deviation.
SIC: sepsis-induced cardiomyopathy; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; E: early mitral inflow velocity; e': mitral annular early diastolic velocity; FAC: fractional area change; NT-proBNP: N-terminal pro b-type natriuretic peptide; CK: creatine kinase; CK-MB: creatine kinase-muscle/brain.

admission and increased LVEDD were independent risk factors for the development of SIC (Table 3).

Outcomes of SIC

There was no significant difference between SIC patients and non-SIC patients in 28-day all-cause mortality (24.5% vs. 26.3%, P=0.936), length of ICU stay in days (15.4±13.8 vs. 12.4±20.2, P=0.249), ICU mortality (26.5% vs. 24.3%, P=0.882), and in-hospital mortality (36.7% vs 36.7%, P=1.000) (Table 4). Among 31 patients who survived in the hospital, 25 were discharged home and six were transferred to another hospital. Cause of death for those who died in the hospital were as follows: primary infection-related multiple organ failure (n=10), respiratory failure (n=3), end of life decision (n=4), sudden cardiac arrest (n=1).

SIC patients were divided into survivors and non-survivors according to 28-day all-cause mortality, as shown in Table 5. Non-survivors showed higher APACHE II (32.1±8.3 vs. 24.4±8.9, P=0.012) and SOFA scores (11.7±3.3 and 9.1±3.0, P=0.015) than survivors. Non-survivors showed significantly lower platelet counts (54.0; interquartile range [IQR], 29.0–138.5 vs. 155.0; IQR, 76.0–271.0; P=0.024) and higher DNI (26.1; IQR, 3.0–45.9 vs. 3.2; IQR, 1.1–9.5; P=0.049) than survivors. Regarding vital signs on admission, non-survivors showed a higher heart rate

Table 3. Logistic regression analyses for predictors of sepsis induced cardiomyopathy

Variable	HR (95% CI)	P-value
Univariate logistic regression analysis		
Age	0.99 (0.97–1.02)	0.714
Male sex	0.73 (0.31–1.70)	0.460
Diabetes mellitus	0.59 (0.25–1.38)	0.221
Heart failure	4.79 (0.29–78.86)	0.273
Systolic blood pressure	0.98 (0.96–1.00)	0.027
Heart rate	1.00 (0.98–1.01)	0.748
CRP	1.00 (1.00–1.01)	0.088
Procalcitonin	1.01 (0.99–1.02)	0.357
DNI	1.00 (0.97–1.02)	0.821
Lactate	0.93 (0.83–1.05)	0.264
Albumin	0.43 (0.20–0.94)	0.035
Blood culture (+)	1.28 (0.57–2.87)	0.553
NT-proBNP/1000	1.03 (1.01–1.06)	0.001
Troponin T/10	1.03 (1.01–1.06)	0.007
LVEDD	1.19 (1.09–1.28)	<0.001
E/e'	1.05 (0.97–1.14)	0.195
Multivariate logistic regression analysis		
Systolic blood pressure	0.96 (0.93–0.99)	0.007
Albumin	0.38 (0.14–1.07)	0.066
NT-proBNP/1000	1.04 (0.99–1.04)	0.296
Troponin T/10	1.01 (1.00–1.03)	0.068
LVEDD	1.24 (1.13–1.37)	<0.001

HR: hazard ratio; CI: confidential interval; CRP: c-reactive protein; DNI: delta neutrophil index; NT-proBNP: N-terminal pro b-type natriuretic peptide; LVEDD: left ventricular end-diastolic diameter; E: early mitral inflow velocity; e': mitral annular early diastolic velocity.

Table 4. Outcome of sepsis induced cardiomyopathy

Variable	Total (n=308)	SIC (n=49)	Non-SIC (n=259)	P-value
28-Day mortality	80 (26.0)	12 (24.5)	68 (26.3)	0.936
In-hospital mortality	113 (36.7)	18 (36.7)	95 (36.7)	1.000
ICU mortality	76 (24.7)	13 (26.5)	63 (24.3)	0.882
Length of ICU stay (day)	13.2±19.3	15.4±13.8	12.7±20.2	0.249

Values are presented as number (%) or mean±standard deviation.
SIC: sepsis-induced cardiomyopathy; ICU: intensive care unit.

than survivors (134.3±25.8 vs. 101.5±25.2, P<0.001). Cox hazard proportional regression analysis for 28-day mortality in SIC patients revealed that APACHE II (hazard ratio [HR], 1.10; 95% confidential interval [CI], 1.02 to 1.18; P=0.009) and DNI (HR, 1.02; 95% CI, 1.00 to 1.08; P=0.026) were independent risk factors, while TEE parameters and cardiac biomarkers did not show statistically significant correlations with 28-day mortality. Cox hazard proportional regression analysis for 28-day mortality in sepsis patients as a whole revealed that APACHE II (HR, 1.04; 95% CI, 1.01 to 1.07; P=0.004), DNI (HR, 1.02; 95% CI, 1.00 to 1.03; P=0.044), and lactate (HR, 1.07; 95% CI, 1.02 to 1.13; P=0.007) were independent risk factors (Table 6). These variables are known to represent sepsis severity [12-14]. This suggests that sepsis severity, rather than TTE parameters and cardiac biomarkers, has the most important effect on SIC mortality.

Using the definition of SIC delineated in this study, patients with reversible LV function deterioration due to sepsis were compared with non-SIC patients. Of 83 patients who showed LV function deterioration, 15 patients with persistent LV dysfunction in follow-up TTE and 19 patients without follow-up TTE were excluded. The mortality outcomes of these two excluded groups are shown in Figure 1. While patients with persistent LV dysfunction revealed similar mortality outcomes as SIC and non-SIC patients, the group of patients without follow-up TTE showed a significantly poorer mortality outcome (28-day mortality, 73.7%). Follow-up TTE data were not available within 14 days from the first TTE in this group of patients for the following reasons. Eight patients (42.1%) died within 72 hours after ICU admission, end-of-life decisions were made for six patients (31.6%) mostly due to terminal underlying diseases (e.g., cancer), two patients were transferred to other hospitals, and three patients (15.8%) recovered from sepsis.

DISCUSSION

In this study, we demonstrated the clinical features, predictors, and survival outcomes of SIC. Low systolic blood pressure and increased LVEDD were revealed to be independent predictors of SIC. There was no significant difference between SIC and sepsis patients as a whole in terms of 28-day all-cause mortality. However, high APACHE II scores and DNI, which reflect sepsis severity, were independent risk factors for 28-day all-cause mortality in SIC patients.

To define SIC, we used a definition commonly applied in previous studies [2,7,10]. In these studies, the inclusion of pre-existing cardiac diseases was controversial. In some studies, patients with pre-existing cardiac disease were excluded to reduce false-positive errors in detecting SIC [4,5,10,15-17]. However, those with pre-existing cardiac disease should be included and evaluated if this condition alters the risk of SIC

Table 5. Baseline characteristics of sepsis-induced cardiomyopathy patients according to 28-day all-cause mortality

Characteristics	Survivor (n=37)	Non-survivor (n=12)	P-value
Age (yr)	65.0±11.2	65.3±11.7	0.935
Male sex	24 (64.9)	8 (66.7)	1.000
BMI (kg/m^2)	22.3±3.8	22.6±4.3	0.837
APACHE II	24.4±8.9	32.1±8.3	0.012
SOFA	9.1±3.0	11.7±3.3	0.015
Charlson comorbidity index	3.0 (2.0–4.0)	3.0 (2.0–4.5)	0.715
Acute kidney injury	10 (27.0)	4 (33.3)	0.721
ARDS	8 (21.6)	0	0.173
Mechanical ventilation	25 (67.6)	11 (91.7)	0.142
Blood culture (+)	16 (43.2)	6 (50.0)	0.940
Vital sign on admission			
Systolic blood pressure (mm Hg)	83.7±18.5	84.7±18.3	0.876
Mean arterial pressure (mm Hg)	64.8±15.1	63.1±16.7	0.746
Heart rate (bpm)	101.5±25.2	134.3±25.8	<0.001
Use of vasopressor			
Norepinephrine	32 (86.5)	12 (100.0)	0.427
Dobutamine	2 (5.4)	0	1.000
Laboratory parameter			
WBC (10^3/μl)	10.3 (7.0–17.1)	9.4 (3.0–14.7)	0.429
Platelet (10^3/μl)	155.0 (76.0–271.0)	54.0 (29.0–138.5)	0.024
Serum albumin (g/dl)	2.4±0.6	2.4±0.5	0.872
Serum bilirubin (mg/dl)	0.7 (0.4–1.1)	1.0 (0.4–1.9)	0.470
Serum creatinine (mg/dl)	1.3 (0.9–1.9)	2.0 (1.2–3.6)	0.212
Lactate (mmol/L)	2.5 (1.6–3.8)	4.0 (2.0–7.6)	0.089
CRP	179.1 (100.7–257.4)	185.9 (49.5–343.2)	1.000
Procalcitonin (ng/ml)	5.1 (1.3–30.3)	5.6 (0.8–40.6)	0.917
DNI (%)	3.2 (1.1–9.5)	26.1 (3.0–45.9)	0.049
Echocardiographic finding			
Ejection fraction (%)	34.9±8.7	32.6±7.5	0.410
LVEDD (mm)	50.2±5.1 (n=35)	47.6±8.1 (n=11)	0.339
LVESD (mm)	39.7±5.8 (n=35)	39.1±8.2 (n=11)	0.800
Mitral E/e' ratio	12.9±4.8 (n=31)	13.2±10.0 (n=5)	0.943
Cardiac biomarker			
NT-proBNP (pg/ml)	11,983.0 (7,514.5–30,442.0) (n=35)	22,073.0 (3,705.5–35,000.0) (n=11)	0.857
CK (IU/L)	76.0 (35.0–331.0)	171.0 (59.0–688.0)	0.231
CK-MB (ng/ml)	4.2 (2.0–7.2)	2.1 (1.5–5.3)	0.236
Troponin-T (pg/ml)	156.0 (47.0–318.0)	108.0 (62.5–304.0) (n=11)	0.980

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
BMI: body mass index; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; ARDS: acute respiratory distress syndrome; WBC: white blood cell; CRP: C-reactive protein; DNI: delta neutrophil index; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; E: early mitral inflow velocity; e': mitral annular early diastolic velocity; NT-proBNP: N-terminal pro b-type natriuretic peptide; CK: creatine kinase; CK-MB: creatine kinase-muscle/brain.

Table 6. Cox proportional hazard regression analysis for 28-day mortality in SIC patients and sepsis patients as a whole

Variable	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
SIC patient				
APACHE II	1.08 (1.02–1.14)	0.006	1.10 (1.02–1.18)	0.009
DNI	1.03 (0.01–2.21)	0.027	1.02 (1.00–1.08)	0.026
Lactate	1.12 (1.01–1.24)	0.036	1.12 (0.74–1.07)	0.210
EF	0.97 (0.91–1.04)	0.381		
LVEDD	0.94 (0.85–1.04)	0.231		
Sepsis patients as a whole				
APACHE II	1.06 (1.03–1.09)	<0.001	1.04 (1.01–1.07)	0.004
DNI	1.03 (0.01–1.04)	<0.001	1.02 (1.00–1.03)	0.044
Lactate	1.12 (1.07–1.16)	<0.001	1.07 (1.02–1.13)	0.007
EF	1.01 (0.99–1.03)	0.321		
LVEDD	0.96 (0.93–0.98)	0.008	0.97 (0.93–1.01)	0.118
SIC	0.89 (0.0.48–1.65)	0.723	0.88 (0.43–1.74)	0.688

SIC: sepsis-induced cardiomyopathy; HR: hazard ratio; CI: confidential interval; APACHE: Acute Physiology and Chronic Health Evaluation; DNI: delta neutrophil index; EF: ejection fraction; LVEDD: left ventricular end-diastolic diameter.

development and survival. Our study revealed that neither heart failure nor coronary artery disease was a risk factor for SIC development or mortality.

Recently, several studies have indicated differences in the pathophysiology of SIC and stress-induced cardiomyopathy, also known as Takotsubo cardiomyopathy, in which sepsis is the source of stress [7,9,10]. Endotoxins, inflammatory cytokines, and nitric oxides are major contributors to the development of SIC [18,19]. In contrast, elevated catecholamine release is a key contributor to the development of Takotsubo cardiomyopathy [20]. However, it is difficult to distinguish these two diseases based on clinical parameters. Previous studies that distinguished SIC and Takotsubo cardiomyopathy used the criterion of typical apical ballooning in TTE. However, Takotsubo cardiomyopathy has both apical ballooning type and atypical type, which are difficult to discriminate from SIC based on TTE findings [20,21]. Thus, we proposed that SIC is a syndrome characterized by reversible LV dysfunction and includes Takotsubo cardiomyopathy caused by sepsis. Endotoxins, inflammatory cytokines, nitric oxides, and catecholamine are all considered associated with SIC development.

Echocardiography revealed that LVEDD was significantly higher in SIC patients than in non-SIC patients. Diastolic ventricle size increased to compensate for decreased systolic contractility. After fluid resuscitation, stroke volume can recover while EF is temporarily decreased due to increased LVEDD. Based on this pathophysiology, the importance of diastolic dysfunction rather than systolic function has been emphasized recently with reports of correlation between a lower e', higher E/e' ratio, and mortality in sepsis patients [19,22]. However, in this study, the LVEDD and E/e' ratio did not show significant differences between survivors and non-survivors. This might be due to missing TTE parameters, especially in non-survivors.

In this study, low systolic blood pressure upon ICU admission and increased LVEDD were considered predictors of SIC development. Low systolic blood pressure resulting in inadequate coronary blood flow has been proposed as a mechanism of SIC based on animal studies [23]. Dilated LVEDD is diastolic compliance to decreased systolic function [19]. The predictors of SIC identified in this study are discrepant from those previously identified, probably due to the small sample size of each study and the use of discordant definitions [7,10,24].

In SIC patients, tachycardia on ICU admission was significantly more common among non-survivors than survivors. This is explained by adapting to insufficient diastolic filling to increase stroke volume. In the Cox proportional hazard regression analysis of 28-day mortality, APACHE II score and DNI were revealed as independent risk factors for mortality in SIC patients. Both APACHE II and DNI are markers of sepsis severity. DNI is a novel biomarker that reflects the number of circulating granulocytes in blood and correlates with sepsis severity in critically ill patients [11,12,25,26]. This suggests that sepsis severity has a greater effect on SIC prognosis than TEE parameters and cardiac biomarkers.

Among the 83 patients who showed LV dysfunction, 19 had no follow-up TTE. This group of patients showed significantly poorer mortality outcome, suggesting that the cardiac function of these 19 patients deteriorated due to sepsis and they usually did not recover, resulting in mortality. This may imply that this group of patients had the same pathophysiology as patients with SIC development and poor outcome. Due to the small number of these patients, the characteristics of persistent LV dysfunction could not be analyzed in detail in this group with no follow-up TTE. Further studies should be performed to clarify the characteristics of these patients.

This study had several limitations. First, detailed information regarding fluid resuscitation and vasopressor initiation were not available. These factors strongly affect sepsis patient prognosis. However, the study was performed in a single ICU of a tertiary university hospital in which sepsis management, including fluid resuscitation and vasopressor initiation, was generally performed according to the more recent sepsis-3

guidelines. Second, baseline TTE and TTE within 48 hours were not available in 8.7% of the initial population. This selection bias may have influenced the final results. Third, TTE parameters were not documented equally among patients and laboratory data. For example, inflammatory cytokines and catecholamines were not available due to the retrospective nature of this study. Lastly, this was a single center, retrospective study, which could affect the generalizability of results. Further prospective studies are needed to validate the results of this study.

In conclusion, this study identified predictors and outcome of SIC with inclusion of pre-existing cardiac diseases and Takotsubo cardiomyopathy. We found that low systolic blood pressure and dilated LVEDD were SIC predictors. The prognosis of SIC was affected by sepsis severity rather than cardiac function. Reversible SIC does not increase mortality risk compared to non-SIC. Further studies are needed on sepsis patients with persistent LV dysfunction and on patients whose LV function could not be restored, resulting in death.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Conceptualization: MJS, MSP. Data curation, Formal analysis, & Methodology: all authors. Project administration, Visualization, & Writing–original draft: MJS, MSP. Writing–review & editing: all authors.

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