*Original Article*

# Incidence and Outcomes of Sepsis-Related Cardiomyopathy: A Prospective Cohort Study

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***Objective***: To determine the incidence, predictive factors, and prognosis of sepsis-related cardiomyopathy.

***Materials and Methods***: The present study was a prospective cohort study that enrolled adult septic shock patients admitted to the ICU of Siriraj Hospital (Bangkok, Thailand) between October 2013 and November 2014. All the patients were treated following the surviving sepsis campaign international guidelines 2012. Transthoracic echocardiography was performed during day 1, and then again during days 3 to 4 after septic shock diagnosis. Sepsis-related cardiopathy was diagnosed in patients who had left ventricular ejection fraction (LVEF) at less than 50%. The primary outcome was hospital mortality. The present study was registered in the Thai Clinical Trials Registry (TCTR20200818004).

***Results***: Of the 75 patients enrolled, 24 (32%) were diagnosed as having sepsis-related cardiomyopathy, and 51 sepsis with preserved LVEF. Six of the 51 patients (11.8%) in the sepsis with preserved LVEF group, and nine of the 24 patients (37.5%) in the sepsis-related cardiomyopathy group died in the hospital (p=0.009). Multivariate analysis identified a maximum vasopressor dosage greater than 0.08 mcg/kg/minute and requiring renal replacement therapy as predictive factors associated with sepsis-related cardiomyopathy, while cirrhosis was identified as a protective factor. Sepsis-related cardiomyopathy, pneumonia, and requiring vasopressor were predictive factors associated with hospital mortality, while achieving tissue perfusion goals within six hours after resuscitation was a protective factor against in-hospital death.

***Conclusion***: Sepsis-related cardiomyopathy was identified as a significant type of organ dysfunction among the present study sepsis or septic shock patients, and the mortality rate was high.

***Keywords***: Incidence, Outcomes, Sepsis-related cardiomyopathy

Received 23 November 2020 | Revised 3 December 2020 | Accepted 3 December 2020

**J Med Assoc Thai 2021;104(3):497-505**

**Website:** http://www.jmatonline.com

Sepsis and septic shock are clinical syndromes caused by the interaction between the host's immune response and the invading pathogens, which results in systemic inflammation and multi-organ dysfunction[1]. The cardiovascular system is one of the vital organ systems that is affected by sepsis. The proposed pathophysiology is the release of many inflammatory mediators that can cause damage to the myocardium. One of the most important mediators that is released is tumor necrosis factor-α (TNF-α), an inflammatory mediator released from the myocardia during shock via induction by macrophages. Septic shock also releases prostanoids, such as thromboxane and prostacyclin, which alter coronary autoregulation, coronary endothelial function, and intracoronary leukocyte activation. The release of prostanoids also impairs coronary blood flow, potentially leading to global ischemia, particularly in patients at a high risk of coronary artery disease. Furthermore, increasing lactate production, which is associated with tissue hypoxemia during sepsis or septic shock, causes severe metabolic acidosis, which can result in myocardial dysfunction[2,3].

Apart from the pathophysiology of sepsis itself, septic shock resuscitation can play an important role in aggravating sepsis-related cardiomyopathy. An abrupt increase in cardiac preload due to fluid resuscitation and an increase in the afterload due to vasopressor therapy may unmask the impairment of myocardial contractility. Previous studies used cardiac imaging derived from echocardiography to identify a variety of cardiac dysfunctions among sepsis and septic shock patients. The mentioned sepsis-related cardiac dysfunctions included left ventricular (LV) systolic dysfunction, LV diastolic dysfunction, and right ventricular (RV) dysfunction[4-8]. However, the most

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**How to cite this article:**

Chayakul W, Tongyoo S, Permpikul C. Incidence and Outcomes of Sepsis-Related Cardiomyopathy: A Prospective Cohort Study. J Med Assoc Thai 2021;104:497-505.

doi.org/10.35755/jmedassocthai.2021.03.12305

common definition of sepsis-related cardiomyopathy is a left ventricular ejection fraction (LVEF) of less than 50% without evidence of active coronary artery disease, which is typically reversible in seven to ten days[9-11]. The incidence of cardiac dysfunction ranges from 20% to 60% depending on the criteria used and the timing of the diagnosis[12].

Although the previous studies have reported an association between sepsis-related cardiomyopathy and poor septic shock outcome, the results of a meta-analysis did not identify this correlation[13]. In addition, the other types of cardiac dysfunction, apart from LV systolic function, especially LV diastolic dysfunction and RV dysfunction, have not yet been conclusively determined for their predictive value relative to the sepsis or septic shock outcome. Consequently, the present study aimed to identify the incidence and prognostic predictive value of cardiac dysfunction, including LV systolic dysfunction, LV diastolic dysfunction, and RV dysfunction, as determined by transthoracic echocardiography in sepsis and septic shock patients.

## Materials and Methods

The present prospective cohort study was conducted at the medical intensive care unit (ICU) of the Division of Critical Care Medicine, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand between October 1, 2013 and November 30, 2014. The present study was approved by the Siriraj Institutional Review Board (SIRB) before the study commenced (COA no. Si 674/2013). The present study was registered in the Thai Clinical Trials Registry (reg. no. TCTR20200818004). The present study received funding support from the Siriraj Critical Care Research Funding, which played no role in the research study enrollment, analysis, and publication.

The authors enrolled patients aged 18 years or older with a diagnosis of severe sepsis or septic shock according to the Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012[14]. The authors excluded severe sepsis and septic shock patients diagnosed with infective endocarditis, cardiac tamponade, pulmonary embolism, or post-cardiac arrest. Patients with a history of documented myocardial infarction, decompensated heart failure, history of impaired LV systolic function, or had a surface electrocardiogram (ECG) showing a Q wave in two or more consecutive leads were excluded. Patients or those with relatives that declined to participate in the study were also excluded.

After enrollment, the present study patients were resuscitated following the septic shock management guideline. Transthoracic echocardiogram was performed during the first day, and then again during days 3 to 4 after the septic shock diagnosis following a previously described protocol[15,16]. The physician who performed echocardiography was a critical care fellow principal investigator (Chayakul W), who had been trained by certified cardiologists, and who had performed echocardiography on 45 patients under supervision during the 3-month period before the start of the present study. During the training period, the echocardiographic parameters measured included LV end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), LVEF, LV diastolic function, and RV function. Those measurements were all tested for interobserver reliability between the principal investigator and a supervising cardiologist. The continuous variables were compared using the intraclass correlation coefficient (ICC), and the categorical data were compared using the Kappa coefficient. During the pre-study training period, a high correlation (>0.80) of agreement was observed between the fellow and the supervisor for all the evaluated parameters.

LV systolic function was evaluated using the measurement of LVEF by the modified Simpson's method. Patients with an LVEF less than 50% were diagnosed with sepsis-related cardiomyopathy. LV diastolic function was determined in an apical four-chamber view using a pulse wave along the LV to the left atrial axis with the sampling volume at the tip of the mitral valve opening[16]. The maximal flow velocity during early diastole (E wave) and during atrial systole (A wave) were measured, and the E/A ratio was computed. The Tissue Doppler mode was then applied, and pulse wave analysis was performed with the sampling volume at the medial mitral valve annulus. The maximal velocity of its displacement during early diastole (Ea wave) was recorded, and the E/Ea ratio was computed. LV diastolic dysfunction was classified into grade 1 or impaired relaxation (E/A ratio of less than 0.8 Ea of less than 8 cm/second, and E/Ea ratio of less than 8, respectively), grade 2 or pseudonormalization (E/A ratio 0.8 to 1.5, septal Ea of less than 8 cm/second, and E/Ea ratio 9 to 12, respectively), and grade 3 or restrictive to filling pattern (E/A ratio greater than 1.5 septal Ea of less than 8 cm/second, and E/Ea greater than 13, respectively). To determine the RV function, the authors evaluated the morphology of RV in the

parasternal short axis view and apical four-chamber view, together with the measurement of the RV systolic pressure as described in the authors' previous study[15]. The presence of two or more of the following criteria were documented as RV dysfunction, LV-D shape, loss of the LV apical triangle, RV systolic pressure greater than 40 mmHg, and RV:LV end-diastolic area (RVEDA/LVEDA ratio) greater than 0.65. The patients' baseline characteristics, including age, gender, underlying conditions, site of infection, and severity score, as well as resuscitation treatment, including fluid resuscitation volume, vasopressor, and organ support, were recorded. Achieved target tissue perfusion was defined as achievement of mean arterial blood pressure greater than 65 mmHg, with urine flow greater than 0.5 ml/kg/hour for two consecutive hours, or decreased serum lactate greater than 10% from baseline by six hours after diagnosis. Hospital mortality was also recorded.

### Statistical analysis

Continuous variables were presented as the mean ± standard deviation (SD). The unpaired Student's t-test was used to compare continuous variables between groups. Categorical variables were shown as the number and percentage. Comparison of the categorical variables was performed using Fisher's exact test or chi-square test. Receiver operating characteristic (ROC) curve analysis was used to identify the cut-off value of the continuous variables that could significantly predict the outcome. After grouping patients according to the cut-off value derived from ROC curve analysis, univariate analysis was performed to identify the factors that were potentially predictive of sepsis-related cardiomyopathy and hospital mortality. Parameters with a p-value less than 0.1 were included in the multivariate model. Binary logistic regression analysis was employed to identify independent predictive factors of sepsis-related cardiomyopathy and hospital mortality. A p-value of less than 0.05 was recognized as being statistically significant. All the data analyses were performed using PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA).

## Results

Seventy-five patients were enrolled in the present study, 31 were male, and all of them underwent their first echocardiographic examination within the first six to twelve hours after the diagnosis of severe sepsis or septic shock. Only 61 patients underwent a second echocardiographic examination within three to five days. There were 24 patients (32%) who were diagnosed with sepsis-related cardiomyopathy as determined by LVEF of less than 50%. The patients' baseline characteristics compared between the sepsis with preserved LVEF and sepsis-related cardiomyopathy groups are shown in Table 1. The sepsis-related cardiomyopathy patients were older and had a higher Acute Physiology and Chronic Health Evaluation II (APACHE II) severity score compared to those with sepsis with preserved LVEF. The underlying conditions were not significantly different between the two groups, except for a significantly lower proportion of cirrhosis and a higher proportion of patient with history of congestive heart failure with preserved LVEF among those with sepsis-related cardiomyopathy. The leading site of infection was abdominal infection and the lungs (pneumonia), followed by urinary tract infection and skin and soft tissue infection. There were no significant differences in the initial vital signs or baseline laboratory investigations between the groups (Table 1).

The treatments received by the study patients during sepsis or septic shock resuscitation are shown in Table 2. Regarding the fluid resuscitation volume, there was no significant difference in volume resuscitation during the first six hours, the first, second or third day. The sepsis-related cardiomyopathy patients received dopamine and dobutamine in a significantly higher proportion compared to the patients in the preserved LVEF group. The maximum vasopressor dose received during resuscitation showed a trend toward being higher among sepsis-related cardiomyopathy patients compared to preserved LVEF patients ($p>0.05$). The requirement for mechanical ventilator support and renal replacement therapy were significantly higher among the sepsis-related cardiomyopathy patients. The hemodynamic resuscitation goals were achieved in similar proportions in both groups. Six patients (11.8%) in the preserved LVEF group and nine patients (37.5%) in the sepsis-related cardiomyopathy group died in hospital ($p=0.009$) (Table 2).

The echocardiographic findings are shown in Table 3. The initial LVEDV was not different between the two groups, but the LVESV was significantly higher among the sepsis-related cardiomyopathy patients, which resulted in a significantly lower LVEF among the sepsis-related cardiomyopathy patients. However, the initial cardiac index was not different between the two groups. Regarding LV diastolic function, the initial mitral E wave, A wave, and E/A ratio were not different between the groups, but the

**Table 1.** Patients' baseline characteristics compared between preserved and impaired left ventricular systolic function

| Characteristics | Preserved LVEF ≥50% (n=51); n (%) | Impaired LVEF <50% (n=24); n (%) | p-value |
|---|---|---|---|
| Age (years); mean±SD | 65.8±16.5 | 73.1±17.4 | 0.082 |
| Age ≥65 years | 26 (51.0) | 18 (75.0) | 0.049 |
| Sex: male | 20 (39.2) | 11 (45.8) | 0.591 |
| Body mass index (kg/m$^2$); mean±SD | 23.3±4.3 | 22.0±4.0 | 0.213 |
| APACHE II score; mean±SD | 22.3±5.6 | 25.7±6.7 | 0.028 |
| APACHE II score ≥20 | 31 (60.8) | 20 (83.3) | 0.051 |
| Underlying conditions | | | |
| Hypertension | 31 (60.8) | 12 (50.0) | 0.378 |
| Diabetes mellitus | 14 (27.5) | 6 (25.0) | 0.832 |
| Cirrhosis | 13 (25.5) | 1 (4.2) | 0.027 |
| Immunosuppressive drugs | 8 (15.7) | 4 (16.7) | 0.914 |
| Cerebrovascular disease | 8 (15.7) | 6 (25.0) | 0.334 |
| Congestive heart failure with preserved LVEF | 6 (11.8) | 8 (33.3) | 0.025 |
| Site of infection | | | |
| Intra-abdominal infection | 16 (31.4) | 4 (16.7) | 0.179 |
| Pneumonia | 12 (23.5) | 5 (20.8) | 0.795 |
| Urinary tract infection | 9 (17.6) | 8 (33.3) | 0.130 |
| Skin and soft tissue infection | 4 (7.8) | 1 (4.2) | 0.277 |
| Hemoculture positive | 7 (13.7) | 6 (25.0) | 0.298 |
| Initial vital signs; mean±SD | | | |
| Temperature (°C) | 37.8±1.2 | 38.1±1.1 | 0.327 |
| Heart rate (per minute) | 101.9±27.1 | 107.7±26.6 | 0.393 |
| Mean arterial blood pressure (mmHg) | 57.1±8.0 | 57.7±11.2 | 0.802 |
| Respiratory rate (per minute) | 26.6±5.9 | 27.5±6.5 | 0.541 |
| Initial investigations; mean±SD | | | |
| White blood cell count (per microliter) | 16,783.3±11,560.7 | 14,082.9±7,737.1 | 0.303 |
| Hematocrit (%) | 32.7±8.5 | 33.0±7.4 | 0.906 |
| Platelet count (per microliter) | 192,354.0±111,333.4 | 164,375.8±100,328.9 | 0.299 |
| Arterial pH | 7.31±0.12 | 7.34±0.18 | 0.631 |
| $PaO_2$ | 112.9±50.2 | 128.4±60.5 | 0.474 |
| $PaCO_2$ | 27.5±7.3 | 25.6±12.0 | 0.622 |
| Serum creatinine (mg/dL) | 2.14±1.73 | 2.30±1.56 | 0.701 |

LVEF=left ventricular ejection fraction; APACHE II score=Acute Physiology and Chronic Health Evaluation score; $PaO_2$=partial pressure of oxygen; $PaCO_2$=partial pressure of carbon dioxide; mg/dL=milligram per deciliter; SD=standard deviation

A $p<0.05$ indicates statistical significance

Ea wave was significantly lower in the sepsis-related cardiomyopathy group. The E/Ea ratio was also significantly higher among those with sepsis-related cardiomyopathy. Overall, LV diastolic dysfunction occurred in a higher proportion (15/24, 62.5%) in the sepsis-related cardiomyopathy group compared to in the sepsis with preserved LVEF group (18/51, 35.3%) (p=0.03). The initial echocardiography identified RV dysfunction in comparable proportions between the sepsis patients with cardiomyopathy and those with preserved LVEF (Table 3).

Follow-up echocardiography during the third to fifth day after sepsis or septic shock resuscitation was performed in 61 patients, including 44 in the preserved LVEF group, and 17 in the cardiomyopathy group. The findings showed significant differences in LV systolic and diastolic function between the sepsis-related cardiomyopathy group and sepsis with preserved LVEF group, which was similar to the outcome from the initial echocardiographic findings.

**Table 2.** Treatment that patients received during septic shock therapy and hospital outcome compared between preserved and impaired left ventricular systolic function

| Treatment | Preserved LVEF ≥50% (n=51); n (%) | Impaired LVEF <50% (n=24); n (%) | p-value |
|---|---|---|---|
| Fluid resuscitation (mL); mean±SD | | | |
| Volume received within 6 hours | 2,727.7±1,006.0 | 2,864.7±1,092.4 | 0.599 |
| Volume received during 1st day | 4,860.3±1,565.8 | 5,371.1±1,624.8 | 0.227 |
| Volume received during 2nd day | 1,775.3±1,239.8 | 1,208.1±1,266.7 | 0.222 |
| Volume received during 3rd day | 1,171.9±1,038.7 | 1,754.9±1,073.3 | 0.066 |
| Vasopressors | | | |
| Norepinephrine | 35 (68.6) | 15 (62.5) | 0.772 |
| Adrenaline | 4 (7.8) | 3 (12.5) | 0.518 |
| Dopamine | 1 (2.0) | 4 (16.7) | 0.017 |
| Dobutamine | 1 (2.0) | 4 (16.7) | 0.017 |
| Maximum dose vasopressors (mcg/kg/minute); mean±SD | 0.11±0.10 | 0.18±0.15 | 0.068 |
| Maximum dose vasopressors ≥0.08 (mcg/kg/minute) | 16 (31.4) | 13 (54.2) | 0.059 |
| Mechanical ventilator | 9 (17.6) | 12 (50.0) | 0.004 |
| Renal replacement therapy | 3 (5.9) | 5 (20.8) | 0.050 |
| Achieved tissue perfusion goal within 6 hours | 31 (60.8) | 14 (58.3) | 0.840 |
| Hospital mortality | 6 (11.8) | 9 (37.5) | 0.009 |

LVEF=left ventricular ejection fraction; SD=standard deviation

A p<0.05 indicates statistical significance

**Table 3.** Echocardiographic findings at initial septic shock diagnosis, and at follow-up 96 to 120 hours later

| Echocardiographic findings | Initial echocardiography; mean±SD | | p-value | Follow-up echocardiography; mean±SD | | p-value |
|---|---|---|---|---|---|---|
| | Preserved LVEF ≥50% (n=51) | Impaired LVEF <50% (n=24) | | Preserved LVEF ≥50% (n=44) | Impaired LVEF <50% (n=17) | |
| LV systolic function | | | | | | |
| LVEDV (mL) | 56.6±22.6 | 59.8±37.1 | 0.662 | 61.3±19.6 | 64.4±31.7 | 0.687 |
| LVESV (mL) | 25.6±11.4 | 38.2±32.8 | 0.025 | 27.3±12.9 | 38.9±28.1 | 0.037 |
| LVSV (mL) | 31.0±12.0 | 21.6±7.6 | 0.001 | 34.0±11.7 | 25.3±9.0 | 0.001 |
| LVEF (%) | 54.7±5.4 | 38.1±7.2 | <0.001 | 58.7±10.2 | 40.2±10.8 | <0.001 |
| Cardiac index | 2.73±0.94 | 2.72±0.88 | 0.969 | 2.73±0.82 | 2.35±0.55 | 0.059 |
| LV diastolic function | | | | | | |
| E wave | 91.8±29.5 | 91.8±32.7 | 0.991 | 98.2±28.5 | 87.5±28.1 | 0.222 |
| A wave | 89.5±18.1 | 80.5±29.5 | 0.200 | 86.7±20.9 | 86.1±22.7 | 0.931 |
| E/A ratio | 1.02±0.47 | 1.07±0.50 | 0.706 | 1.04±0.33 | 1.11±0.57 | 0.607 |
| Ea wave | 10.8±4.3 | 8.3±3.5 | 0.011 | 10.1±2.7 | 7.4±4.0 | 0.017 |
| E/Ea ratio | 9.8±3.9 | 12.5±7.0 | 0.055 | 9.5±3.2 | 13.2±6.5 | 0.013 |
| LV diastolic dysfunction; n (%) | 18 (35.3) | 15 (62.5) | 0.027 | 10 (23.3) | 12 (70.5) | 0.014 |
| Right ventricular dysfunction; n (%) | 10 (19.6) | 7 (29.2) | 0.356 | 3 (7.1) | 6 (35.3) | 0.006 |

LVEF=left ventricular ejection fraction; LV=left ventricular; LVEDV=left ventricular end-diastolic volume; LVESV=left ventricular end-systolic volume; LVSV=left ventricular stroke volume; E wave=maximal flow velocity during early diastole; A wave=maximal flow velocity during atrial systole; Ea wave=maximal velocity of the displacement of sampling volume at the medial mitral valve annulus during early diastole; SD=standard deviation

A p<0.05 indicates statistical significance

However, RV dysfunction was found in a significantly higher proportion of sepsis-related cardiomyopathy patients [3/44 (7.1%) versus 6/17 (35.3), p=0.006] (Table 3).

**Table 4.** Univariate and multivariate analysis to identify predictive factors independently associated with impaired left ventricular systolic dysfunction (LVEF <50%) among sepsis and septic shock patients

| Factors | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | RR | 95% CI | p-value | aRR | 95% CI | p-value |
| Age ≥65 years | 1.37 | 1.01 to 1.84 | 0.049 | 2.08 | 0.49 to 8.88 | 0.322 |
| APACHE II score ≥20 | 1.37 | 1.03 to 1.82 | 0.051 | 1.51 | 0.34 to 6.76 | 0.590 |
| Congestive heart failure with preserved LVEF | 1.72 | 0.92 to 3.21 | 0.025 | 2.62 | 0.59 to 11.62 | 0.207 |
| Cirrhosis | 0.67 | 0.53 to 0.86 | 0.027 | 0.10 | 0.01 to 0.91 | 0.048 |
| Maximum dose vasopressors ≥0.08 mcg/kg/minute | 1.38 | 0.96 to 1.99 | 0.059 | 3.86 | 1.18 to 12.63 | 0.026 |
| Mechanical ventilator | 1.82 | 1.09 to 3.03 | 0.004 | 1.22 | 0.29 to 5.08 | 0.787 |
| Renal replacement therapy | 1.91 | 0.77 to 4.73 | 0.050 | 8.42 | 1.05 to 67.54 | 0.045 |

LVEF=left ventricular ejection fraction; RR=relative risk; CI=confidence interval; aRR=adjusted risk ratio; APACHE II score=Acute Physiology and Chronic Health Evaluation score

Factors with a p<0.1 in univariate analysis were included in the multivariate analysis

A p<0.05 indicates statistical significance in the multivariate analysis

**Table 5.** Univariate and multivariate analysis to identify predictive factors independently associated with hospital mortality among sepsis and septic shock patients

| Factors | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | RR | 95% CI | p-value | aRR | 95% CI | p-value |
| APACHE II score ≥20 | 1.32 | 1.09 to 1.60 | 0.019 | 2.88 | 0.25 to 33.51 | 0.398 |
| Congestive heart failure with preserved LVEF | 1.49 | 0.94 to 2.38 | 0.018 | 5.37 | 0.97 to 29.87 | 0.055 |
| Pneumonia | 1.31 | 0.90 to 1.89 | 0.073 | 5.90 | 1.02 to 34.25 | 0.048 |
| Left ventricular systolic dysfunction (LVEF <50%) | 1.14 | 1.02 to 1.96 | 0.009 | 5.18 | 1.16 to 23.15 | 0.031 |
| Right ventricular dysfunction | 1.31 | 0.90 to 1.89 | 0.073 | 2.22 | 0.49 to 10.01 | 0.299 |
| Receiving vasopressor | 1.24 | 1.02 to 1.52 | 0.066 | 11.90 | 1.46 to 96.91 | 0.021 |
| Achieved tissue perfusion goals within 6 hours | 0.81 | 0.62 to 1.05 | 0.077 | 0.15 | 0.03 to 0.78 | 0.024 |
| Mechanical ventilator | 1.56 | 1.06 to 2.28 | 0.002 | 1.39 | 0.24 to 7.95 | 0.711 |
| Renal replacement therapy | 1.67 | 0.83 to 3.37 | 0.025 | 1.45 | 0.15 to 13.79 | 0.747 |

RR=relative risk; CI=confidence interval; aRR=adjusted risk ratio; APACHE II score=Acute Physiology and Chronic Health Evaluation score; LVEF=left ventricular ejection fraction

Factors with a p<0.1 in the univariate analysis were included in the multivariate analysis

A p<0.05 indicates statistical significance in the multivariate analysis

To identify the predictive factors independently associated with sepsis-related cardiomyopathy, a multivariate analysis model that included all the clinical parameters for which the univariate analysis had shown a potential significant difference between the preserved LVEF and sepsis-related cardiomyopathy patients with p<0.1 was performed (Table 4). Receiving a maximum vasopressor dosage of 0.08 mcg/kg/minute or more and requiring renal replacement therapy were identified as the independent predictive factors associated with sepsis-related cardiomyopathy, while underlying cirrhosis was a protective factor against sepsis-related cardiomyopathy.

Regarding the predictive factors associated with in-hospital mortality, multivariate analysis that included all the clinical parameters for which the univariate analysis had shown a potential significant difference between survivors and non-survivors with a p<0.1 was performed (Table 5). Pneumonia, requiring vasopressor, and LV systolic dysfunction were identified as the independent predictive factors associated with hospital mortality, while achieving tissue perfusion goals within six hours after resuscitation was a protective factor against in-hospital death.

## Discussion

In the present prospective observational study

revealed that transthoracic echocardiography identified impaired LV systolic function (LVEF of less than 50%) in 32% of sepsis or septic shock patients. Moreover, the incidences of LV diastolic dysfunction and RV dysfunction were significantly higher among sepsis with impaired LVEF patients than in preserved LV systolic function patients. Receiving a high dosage of vasopressor and requiring renal replacement therapy were independent predictors associated with sepsis-related cardiopathy, while underlying cirrhosis was a protective factor. The present study also identified sepsis-related cardiomyopathy, pneumonia, and requiring vasopressor as independent predictive factors associated with in-hospital mortality. Achieving tissue perfusion goals within six hours after resuscitation was identified as a protective factor for in-hospital death among the enrolled sepsis or septic shock patients.

The overall results of the present study were in some ways parallel to those from the previous studies that used either transthoracic or transesophageal echocardiography to detect impairment of the LV systolic function[4-6]. Most studies of impaired LVEF among severe sepsis or septic shock patients used a cut-off point less than 45% to 50%, reported an incidence that ranged from 16% to 60%[4-6,10,11]. The incidence of impaired LVEF among the authors' enrolled sepsis or septic shock patients was 32%. Previous studies also reported a high incidence of LV diastolic dysfunction, with a range of 33% to 83%[7,17]. In the present study, 33 patients (44%) were diagnosed with LV diastolic dysfunction, with significantly higher proportion among those patients who had impaired LVEF than in the preserved LVEF group (62.5% versus 35.3%, p=0.03). Concerning RV dysfunction, a few studies reported the incidence of RV dysfunction at a rate that ranged from 31% to 72% depending on the method used to determine the RV function[8,18]. In the present study, RV dysfunction was diagnosed in 17 patients (22.7%), a significantly higher incidence than in the patients who had impaired LVEF.

Regarding the predictive factors associated with sepsis-related cardiomyopathy, previous studies identified several factors, including older age, higher lactate on admission, history of congestive heart failure, and higher APACHE II score, as independent predictors[10,11]. However, the present study multivariate analysis did not identify older age, history of congestive heart failure, or higher APACHE II score, as predictive factors for sepsis-related cardiomyopathy. Interestingly, the present study identified receiving high dosage of vasopressor and requiring renal replacement therapy as independent predictors associated with sepsis-related cardiopathy. These results could reflect the septic shock severity. The more severe patient who did not respond to fluid resuscitation to restore cardiac output and blood pressure, then required a higher vasopressor dose, as well as the development of organ failure. Furthermore, a higher dose of vasopressor could increase systemic vascular resistance and LV afterload. In a setting where LV myocardium is suppressed by several inflammatory mediators, the blood flow ejected from the left ventricle is decreased. An increase in LVESV results in a decreased LVEF. If this process progressed, the accumulation of blood volume in the left ventricle increased the LVEDV, as well as the LV end-diastolic pressure and RV afterload. This causes the LV diastolic dysfunction and RV dysfunction detected in a significant proportion among the present study sepsis or septic shock patients. On the other hand, cirrhosis was identified as a protective factor against sepsis-related cardiomyopathy. It has been well documented that cirrhosis is associated with low systemic vascular resistance and low LV afterload, which facilitates maintenance of the stroke volume and cardiac output, even under the condition of myocardial suppression during sepsis[19]. However, this observation requires further investigation to confirm this preventive effect.

Concerning the impact of sepsis-related cardiomyopathy and the prognosis of severe sepsis and septic shock patients, most previous studies did not identify a correlation between LV systolic function and mortality outcome[6,7,13]. However, the present study multivariate analyses revealed that a LVEF of less than 50%, pneumonia, and receiving vasopressor as independent predictive factors associated with in-hospital death. However, there was no significant association between LV diastolic dysfunction and RV dysfunction related to in-hospital mortality (Table 5). Additionally, achieving tissue perfusion goals within six hours was identified as a protective factor for in-hospital death among the present study enrolled septic shock patients[20].

From the results of the present study, the authors support the early resuscitation of sepsis or septic shock patients with fluid therapy and early vasopressor, along with optimized antibiotic therapy and effective drainage, if needed, until the patient achieves target tissue perfusion. Transthoracic echocardiography, which was shown to be an accurate method for evaluating LV systolic function

among non-cardiologist physicians that underwent a short training program, should be used to help assist septic shock resuscitation[21]. Aggressive high-dose vasopressor administration should be avoided, especially among patients with impaired LV systolic function. To improve tissue perfusion among those who had impair LV systolic function, LV diastolic dysfunction and RV dysfunction, fluid responsive test should be performed to prevent complication from fluid overload. Inotropes, including dobutamine and milrinone, should be considered for improving tissue perfusion, however, the efficacy of inotropes still needs to be conclusively established.

The present study has some limitations. First, the authors enrolled only 75 patients, so the study may have lacked sufficient statistical power to identify all the clinical parameters that could have statistically significant differences and associations. More specifically, there may be more parameters that might significantly predict sepsis-related cardiomyopathy, but they could not be identified in the present study. This may be the reason that the authors did not detect any difference in fluid resuscitation volume between the preserved and impaired LV systolic function groups. Second, the authors excluded the patients with a history of documented myocardial infarction, decompensated heart failure, impaired LV systolic function, or their surface ECG showed a Q wave in two or more consecutive leads, so the findings of the present study may not be generalized to these subgroups of patients. Third, the follow-up echocardiography was performed during ICU admission, and all the procedures were performed during 96 to 120 hours after the first examination. However, 14 patients did not undergo follow-up echocardiography. Of those, eight patients died before, while six patients were discharged from the ICU before the repeated echocardiography was performed. This may explain why the authors were unable to detect any improvement in LV systolic function among the sepsis-related cardiomyopathy patients. Fourth and last, dobutamine was prescribed in only five enrolled patients, so the authors were unable to identify any association between dobutamine use and sepsis-related cardiomyopathy, and between dobutamine use and the outcomes. Further study is needed in a larger population receiving inotropic agents and having long-term follow-up echocardiography.

## Conclusion

Severe sepsis and septic shock can result in both LV and RV dysfunction. Risk factors for impaired LVEF include receiving a high dosage of vasopressor and requiring renal replacement therapy, while underlying cirrhosis is a protective factor. The present study also identified sepsis-related cardiomyopathy, pneumonia, and requiring vasopressor as the independent predictive factors associated with in-hospital mortality. Achieving tissue perfusion goals within six hours after resuscitation was identified as a protective factor for in-hospital death among the enrolled sepsis or septic shock patients.

## What is already known on this topic?

Sepsis-related cardiomyopathy is a significant complication among sepsis and septic shock patients. However, its incidence, precipitating factors, and impact on septic shock outcome were inconclusive.

## What this study adds?

This study reported an incidence of sepsis-related cardiomyopathy in about 32% of sepsis or septic shock patients. The independent predictive factors of sepsis-related cardiopathy included receiving a high dosage of vasopressor, and requiring renal replacement therapy, while underlying cirrhosis was a protective factor. In addition, sepsis-related cardiomyopathy, together with pneumonia, and requiring vasopressor were the independent predictive factors associated with in-hospital mortality. The rapid restoration of tissue perfusion goals within six hours was a protective factor for in-hospital death among the authors' patients.

## Acknowledgement

The authors thank Mr. Kevin P Jones for language editing and Mr. Suthipol Udompanturak for statistics advice.

## Authors' contributions

Surat Tongyoo developed the study protocol, performed the data analyses, and prepared the draft manuscript. Watcharin Chayakul developed the study protocol, enrolled the participants, and performed the data collection. Chairat Permpikul contributed to the data analyses and manuscript drafting. All the authors read and approved the final manuscript.

## Conflicts of interest

The authors have each completed the International Committee of Medical Journal Editors Form for the Uniform Disclosure of Potential Conflicts of Interest. The authors have no competing interests to declare, or any real or perceived financial interests in any product

or commodity mentioned in the present paper.

## Data sharing statement

All datasets generated or analyzed as part of the current study are available by contacting the corresponding author and upon reasonable request and with permission from the Siriraj Institutional Review Board (SIRB).

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