

# Original Research

( Check for updates

Seven-day and In-hospital Mortality According to Left and Right Ventricular Dysfunction in Patients With Septic Shock

Sua Kim <sup>(b)</sup>, MD, PhD<sup>1</sup>, Hyeri Seok <sup>(b)</sup>, MD, PhD<sup>2</sup>, Beong Ki Kim <sup>(b)</sup>, MD<sup>3</sup>, Yu Jin Kim <sup>(b)</sup>, MD, PhD<sup>3</sup>, Seung Heon Lee <sup>(b)</sup>, MD, PhD<sup>3</sup>, Je Hyeong Kim <sup>(b)</sup>, MD, PhD<sup>1,3</sup>, and Yong-Hyun Kim <sup>(b)</sup>, MD, PhD<sup>4</sup>

<sup>1</sup>Department of Critical Care Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea

<sup>2</sup>Division of Infectious Disease, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea

<sup>3</sup>Division of Pulmonology, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea

<sup>4</sup>Division of Cardiology, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea

# **AUTHOR'S SUMMARY**

We performed transthoracic echocardiography in patients with septic shock within 48 hours from the diagnosis and 7 days after initial evaluation. In patients who have survived for longer than 7 days, fluctuation of ventricular function was common. Decreased global longitudinal strain (>–16%) at baseline was a significant predictor of 7-day mortality, but it was not associated with the in-hospital mortality of 7-day survivors. Decreased tricuspid annular plane systolic excursion (<16 mm) at follow-up was related to in-hospital mortality of 7-day survivors. Depending on the period of septic shock, dysfunction in each ventricle may affect prognosis of patients differently, therefore, careful interpretation is required.

# ABSTRACT

**Background and Objectives:** The prognostic implications of septic cardiomyopathy have not been clearly demonstrated. We evaluated serial changes in left ventricular (LV) and right ventricular (RV) function in patients with septic shock and their prognostic value on 7-day and in-hospital mortality.

**Methods:** Transthoracic echocardiography was performed within 48 hours of the diagnosis of septic shock and 7 days after the initial evaluation. In addition to traditional echocardiographic parameters, LV and RV function was evaluated using global longitudinal strain (GLS), and tricuspid annular plane systolic excursion (TAPSE).

**Results:** A total of 162 patients (men, 83, 51.5%; 70.7±13.4 years; Acute Physiology and Chronic Health Evaluation [APACHE] II, 30.6±9.2) were enrolled. Initial GLS and TAPSE were -14.9±5.2% and 16.9±5.5 mm, and improved in the follow-up evaluation (GLS, -17.6±4.9%; TAPSE, 19.2±5.4 mm). Seven-day and in-hospital mortality were 24 (14.9%) and 64 (39.8%). Seven-day mortality was significantly associated with initial GLS >–16% (odds ratio [OR], 14.066, 95% confidence interval [CI], 1.178–167.969, p=0.037) and APACHE II score (OR,

OPEN ACCESS

# Received: Mar 3, 2023 Revised: Jun 29, 2023 Accepted: Jul 11, 2023 Published online: Sep 8, 2023

#### Correspondence to Yong-Hyun Kim, MD, PhD

Division of Cardiology, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, 123, Jeokgeum-ro, Danwon-gu, Ansan 15355, Korea.

Email: xkyhx@hanmail.net

# Copyright © 2023. The Korean Society of Cardiology

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https:// creativecommons.org/licenses/by-nc/4.0) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ORCID iDs

Sua Kim 匝

https://orcid.org/0000-0003-3513-7261 Hyeri Seok () https://orcid.org/0000-0002-2032-9538 Beong Ki Kim () https://orcid.org/0000-0003-2009-7658 Yu Jin Kim () https://orcid.org/0000-0002-1823-672X



#### Seung Heon Lee 厄

https://orcid.org/0000-0002-7180-3877 Je Hyeong Kim (D) https://orcid.org/0000-0002-8995-7460 Yong-Hyun Kim (D) https://orcid.org/0000-0003-1376-5128

#### Funding

This study was supported by the Korean Cardiac Research Foundation (Grant No. 201903-05).

#### **Conflict of Interest**

The authors have no financial conflicts of interest.

#### **Data Sharing Statement**

The data generated in this study is available from the corresponding author upon reasonable request.

#### **Author Contributions**

Conceptualization: Kim YH, Kim S; Funding acquisition: Kim S; Methodology: Kim S, Kim JH; Resources: Kim S, Seok H, Kim BK, Kim YJ, Lee SH, Kim JH, Kim YH; Supervision: Kim YH; Validation: Seok H, Kim JH; Writing - original draft: Kim S; Writing - review & editing: Kim S, Seok H, Kim BK, Kim YJ, Lee SH, Kim JH, Kim YH. 1.196, 95% CI, 1.047–1.365, p=0.008). The in-hospital mortality of 7-day survivors was associated with follow-up TAPSE <16 mm (OR, 10.109, 95% CI, 1.640–62.322, p=0.013) and Sequential Organ Failure Assessment score (OR, 1.340, 95% CI, 1.078–1.667, p=0.008). GLS was not associated with in-hospital mortality of 7-day survivors.

**Conclusions:** Fluctuation of both ventricular function was common in septic shock. Sevenday mortality of patients with septic shock was related to GLS, whereas in-hospital mortality of 7-day survivors was related to TAPSE, not to GLS.

Keywords: Sepsis; Shock; Cardiomyopathies; Mortality; Global longitudinal strain

# **INTRODUCTION**

Cardiac dysfunction is common in patients with sepsis and septic shock,<sup>1)2)</sup> and septic cardiomyopathy (SCM) has been studied in terms of its diverse characteristics, the relationship with mortality,<sup>3)</sup> molecular mechanisms of development,<sup>4)</sup> and therapeutic approaches.<sup>5)6)</sup> However, due to the complex pathophysiology of septic shock, a precise definition of SCM is lacking.<sup>7)</sup>

Hemodynamic changes occur sequentially during sepsis; a decrease in systemic vascular resistance reduces cardiac preload, while fluid resuscitation introduces a high volume of crystalloids into the venous system. Vasoactive agents increase vascular resistance in the peripheral circulation.<sup>8)</sup> In the acute stage of septic shock, marked alterations in cardiac preload and afterload occur, potentially influencing the measurements of left ventricular (LV) systolic and diastolic function.<sup>9)</sup> As successful resuscitation from the shock is achieved, these hemodynamic conditions gradually resolve, and perturbations of cardiac preload and afterload stabilize.<sup>10)</sup> The cumulative impact of these various situations complicates the evaluation of the fundamental changes in myocardial function during septic shock.

The high mortality rates in septic shock predominantly occur among patients who do not survive the initial shock. However, the relationship between hemodynamic derangement at the time of presentation and in-hospital mortality in successfully resuscitated patients appears to be less significant. In other words, ventricular dysfunction occurs differently depending on the stage and duration of septic shock, potentially exerting distinct effect on the prognosis.

We performed transthoracic echocardiography (TTE) within 48 hours of the initial presentation in patients with septic shock. A second TTE was performed on the seventh day after the first TTE. We investigated the relationship between ventricular function at the initial TTE evaluation and 7-day mortality, and then explored the association between ventricular function of subsequent TTEs and in-hospital mortality of 7-day survivors.

## **METHODS**

#### **Ethical statement**

This study was approved by Institutional Review Board (IRB) of Korea University Ansan Hospital, Ansan, South Korea (IRB No. 2022A0284) and performed in accordance with the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study.

#### Study population and data collection

Adult patients admitted to the medical intensive care unit (ICU) of our hospital from June 2019 to April 2022 with a diagnosis of septic shock were screened for this study. Sepsis was diagnosed according to the Sepsis-3 definition: patients with infectious disease and Sequential Organ Failure Assessment (SOFA) score  $\geq 2$ , serum lactate level  $\geq 2 \text{ mmol/L}$ , and in need of vasoactive agents despite adequate fluid administration.<sup>11</sup> Patients with coronary artery disease and structural heart disease including valvular heart disease, congenital heart disease, and cardiomyopathies were excluded. Patients with tachycardia (heart rate,  $\geq 140$  beats per minute) and patients with poor echocardiographic images for the analysis were also excluded.

Demographic parameters, medical history, the Charlson comorbidity index, the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the SOFA score, the vasoactiveinotropic score (VIS), cardiac output index, and the systemic vascular resistance index (SVRI) were used to assess the comorbidity of the patients and the severity of the disease, and to measure the hemodynamic condition of the patients.

#### **Echocardiographic evaluation**

An initial TTE was performed within 48 hours from the diagnosis of shock. Follow-up TTE was performed 7 days (±2 days) after the initial study. Echocardiographic images were acquired using a commercially available ultrasound system, VIVID-Q (GE Vingmed Ultrasound AS, Horten, Norway). The offline software ECHO PAC PC (GE Medical Systems, Chicago, IL, USA) was used to analyze the recorded images. Conventional echocardiographic parameters of LV ejection fraction (EF), E/e', maximal blood flow rate of tricuspid valve regurgitation, and tricuspid annular plane systolic excursion (TAPSE) were evaluated. Raw images of the apical 4-chamber, 2-chamber, and long-axis views in each patient were used for global longitudinal strain (GLS) evaluation. Intra- and inter-observer variability for GLS were checked. LV systolic dysfunction was defined as LVEF <50% or GLS >–16% in accordance with the lower margin of the normal range for LV systolic function. The range also presents the overlap area of expected LV systolic function based on Youden indices for LVEF and GLS predicting 7-day mortality. Right ventricular (RV) systolic dysfunction was defined as TAPSE <16 mm based on Youden index predicting hospital mortality.<sup>12</sup>

#### **Statistical analysis**

Continuous variables were expressed as mean±standard deviation or median and interquartile ranges. Categorical variables were expressed as frequencies and percentages. Continuous variables between groups were compared using the independent t-test and Wilcoxon rank-sum test, and continuous variables of the initial and follow-up studies were compared using a paired t-test. Categorical variables were compared using the  $\chi^2$  test. The cumulative survival rates in each group were evaluated using the Kaplan-Meier curve and compared using the log-rank test. Logistic regression analysis was performed to evaluate the impact of cardiac dysfunction on 7-day and in-hospital mortality. In the analysis, a multivariate logistic regression model was employed, incorporating parameters that exhibited significant results in the univariate logistic regression analysis with a p value less than 0.2. Additionally, parameters considered clinically significant were included in the model, irrespective of their significance in the univariate analysis. However, to avoid issues of multicollinearity, parameters that demonstrated a strong correlation with other important parameters were excluded. Statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, NY, USA) and MedCalc version 22 (MedCalc Software, Ostend, Belgium).



## RESULTS

#### Baseline characteristics and cardiac function of the patients with septic shock

In total, 162 patients were enrolled in this study. The mean age of the patients was 70.7±13.4 years, and 83 (51.5%) were men. The APACHE II score was 30.6±9.2. The most common cause of infection was pneumonia (58, 35.8%), followed by urinary tract infections (49, 30.2%). The mean LVEF, GLS, and TAPSE were 55.20±14.13%, -14.90±5.21%, and 16.90±5.54 mm, respectively. GLS was positively related to heart rate, SOFA score, and SVRI. TAPSE was negatively related to heart rate, SOFA score, VIS and SVRI (**Figure 1**). The number of patients with LVEF <50%, GLS >–16%, and TAPSE <16 mm was 50 (31.17%), 74 (54.4%), and 63 (42.9%). Further, 7-day and in-hospital mortality were observed in 24 (14.9%) and 64 (39.8%) patients, respectively (**Table 1**).

# Clinical implication of left and right ventricular dysfunction on 7-day mortality in patients with septic shock

When we compared the demographic parameters and TTE results by 7-day mortality, the APACHE II score (29.38±8.70 vs. 39.32±7.70, p<0.001), initial lactic acid level (4.0 [2.7–6.6] vs. 8.9 [5.18–17.08], p=0.001), and VIS (6.98 [0–26.4] vs. 40.1 [15.0–88.0], p=0.001) were significantly higher in 7-day non-survivors than 7-day survivors. GLS (-15.54±5.03% vs. -10.57±4.32%, p<0.001), and TAPSE (17.67±4.87 mm vs. 14.18±4.43 mm, p=0.003) were also significantly different by 7-day mortality. However, in multivariate logistic regression analysis, only LV dysfunction with GLS >–16% was significantly related to 7-day mortality



Figure 1. The relationship of hemodynamic parameters and disease severity scoring systems to (A) GLS and (B) TAPSE in scattered diagram. GLS = global longitudinal strain; SOFA = Sequential Organ Failure Assessment; VIS = vasoactive-inotropic score; SVRI = systemic vascular resistance index; TAPSE = tricuspid annular plane systolic excursion.

Table 1. Baseline characteristics of the patients by 7-day mortality and their evaluation of cardiac function and hemodynamic condition

| Age (gass)         70.7=13.4         70.3=13.5         72.8=13.3         0.461           Male         813 (51.5)         73 (53.3)         10 (4.7)         0.378           Body surface area (m <sup>2</sup> )         1.61+0.17         1.61+0.16         1.64+0.25         0.344           Charlson comorbidity index         4.50-2.00         4.41-2.08         5.12-1.7         0.038           Mean:15D         30.660-9.20         99.318.87.07         83.932-7.7         -         0.001           Mean:10(N1)         31.(22-38)         22.04-25.05         44.132.09         0.001           Vacadity index in |  | All patients (n=162) | Seven-day survivor (n=138) | Seven-day non-survivor (n=24)         | p value |
|---|--|----------------------|----------------------------|---------------------------------------|---------|
| Male         63 (5)         73 (5.3)         10 (4).7)         0.378           Bodyurfice are (m)         1.64:0.27         1.64:0.28         0.44:0.28         0.378           Mean-SD         30.60:-3.20         29.38:-8.70         39.32:7.70         0.001           Median (0k)         31 (23:-38)         20 (22:-36)         44 (33:-40         0.001           Visconctive-Intropic score         0.001         0.001         0.001         0.001           MeanisD         39.50:18.24         0.07-2.09         12.04:35         0.001           MeanisD         39.50:18.24         0.07-2.09         12.04:35         0.001           ManisD         39.50:18.24         0.07-2.09         12.04:35         0.001           ManisD         31.11:17.38         14.81:18.29         31.71:49         0.001           ManisD         0.12:1.58         80.44:1.55         78.93:1.71.49         0.001           ManisD         31.11:17.38         13.12:1.73         31.12:1.49         0.001           ManisD         31.21:40         80.12:1.58         79.53:8         17.14         0.001           ManisD         0.12:1.58         80.44:1.55         79.53:8         17.07:0.8         0.001         0.001         0.001  | Age (years)  | 70.7±13.4            | 70.3±13.5                  | 72.5±13.1                             | 0.461   |
| Body surface area (m <sup>2</sup> )         1.610.17         1.610.16         1.64:0.25         0.344           Charlson connobility index         4.50:2.00         4.41:2.08         5.121.17         0.031           ABC/IE II   | Male   | 83 (51.55)           | 73 (53.3)                  | 10 (41.7)                             | 0.378   |
| Charlson consolidity index         4.50°-2.00         4.41°-2.08         5.1°-1.71, 2         0.088           MACAIE I         .0001           Meastan (DgN)         3.0.6°05.2.00         2.2.38:8.70         3.3.27, 70           SDFA score         9.511.3.74         9.072.2.99         12.043.3.50         0.0.01           Wascattive-Intropic score         .0.001         .0.001         .0.001           Median (DgN)         9.9.0.0.6.24.425)         0.80 (0~56.40)         40.3.13 (1.5-18.9.8)         .0.002           Maan-SD         3.1.17-1.7.38         1.44.55-18.2.9         3.1.77-1.40         .0.002           Maan-SD         29.1.9-95.0.8         3.0.39-37.3.3         3.1.71-1.40         .0.002           Mean-SD         20.1.6-3.40.5         1.0.02-3.8.7         .0.002           Mean-SD         20.1.5.1.5.8         10.042-3.8.5         3.(2.2-4.75)         .0.02           Mean-SD         20.1.5.9         10.042-3.8.5         12.05.8         .0.202 <td>Body surface area (m²)</td> <td>1.61±0.17</td> <td>1.61±0.16</td> <td>1.64±0.25</td> <td>0.344</td>  | Body surface area (m²)   | 1.61±0.17            | 1.61±0.16                  | 1.64±0.25                             | 0.344   |
| APACIE II   | Charlson comorbidity index   | 4.50±2.00            | 4.41±2.08                  | 5.17±1.71                             | 0.038   |
| Maclian (108)         30.00-9.20         29.38-8.70         34.23-7.70           Maclian (108)         31.(23-38)         99.(92-36)         41.(33-40)           SOFA score         9.07-2.99         12.04-3.56         -0.001           Maens5D         29.062-81.24         9.07-2.99         12.04-3.56         -0.001           Maens5D         13.1117.38         14.85.18.97         33.751.49         -0.002           Means5D         13.1117.38         14.85.18.97         33.751.49         -0.001           Means5D         13.1247.38         19.(2-3.65)         32.22-4.75         -0.001           Means5D         13.124.85         19.(2-3.65)         32.22-4.75         -0.001           Maens5D         19.124.85         19.(2-3.85)         32.22-4.75         -0.001           Means5D         18.(2-3.42.5)         19.(2-3.85)         32.22-4.75         -0.001           Means5D         18.(2-1.55)         40.42.15.56         32.22-4.75         -0.001           Means5D         18.(2-1.55)         40.42.15.56         32.22-4.75         -0.001           Means5D         17.00.12.19         15.24.23         91.02.25         -0.001           Means5D         1.01.01.23.21.51.3.30         29.29.02.3         -0.021 <td>APACHE II</td> <td></td> <td></td> <td></td> <td>&lt;0.001</td>   | APACHE II  |                      |                            |                                       | <0.001  |
| median (tok)         31 (23-38)         99 (92-28)         14.(33-44)           Nasoactive-instropic score         0.001           Mean:SD         29.80562.00         9.0792.99         12.04.356         0.001           Mean:SD         29.80562.00         9.090-31.86         88.41:132.98         0.002           Median (tok)         0.002         3.171-1.49         0.002           Mean:SD         12.11:17.38         14.8518.29         3.171-1.49           Median (tok)         7 (4-14)         9 (5-16)         3 (2-4-75)           Hoaghal (angth)         18 (6-34.25)         19 (12-38.5)         3.1251.49           Mean:SD         19 (2-38.5)         3 (225 - 4.75)         0.024           Mean:SD         19 (2-38.5)         3 (225 - 4.75)         0.124           Mean:SD         19 (2-38.5)         3 (225 - 4.75)         0.124           Mean:SD         10 (20 - 28.5)         17 (70.8)         0.254           Mean:SD         10 (20 - 28.5)         17 (70.8)         0.264           Mean:SD         15 (21 - 3.5)         1.20 (2.5 - 3.7)         1.20 (2.5 - 3.7)           Mean:SD         15 (2.6 - 2.5)         1.77 (7.8)         7.23 (1.4 - 1.4 + 1.4)           Mean:SD         15 (2.0 - 2.5) <td< td=""><td>Mean±SD</td><td>30.60±9.20</td><td>29.38±8.70</td><td>39.32±7.70</td><td></td></td<>  | Mean±SD  | 30.60±9.20           | 29.38±8.70                 | 39.32±7.70                            |         |
| SDFA score         9.07-2.99'         12.04-3.56         0.001           Mean.SD         29.90-62.40         20.09-31.86         88.41.132.99         0.00           Mean.SD         0.00 (0-34.25)         6.80 (0-26.40)         0.31.11.12.91         14.85.18.29         3.17.1.49         0.00           Mean.SD         13.11.11.7.38         14.85.18.29         3.17.1.49         0.00 </td <td>Median (IQR)</td> <td>31 (23-38)</td> <td>29 (22-36)</td> <td>41 (33-44)</td> <td></td>   | Median (IQR)   | 31 (23-38)           | 29 (22-36)                 | 41 (33-44)                            |         |
| Vacaactive-instripti score         .0.001           Mean:S0         2.0.06:2.6.40         0.00-31.86         0.81.12.09           Median (108)         0.00 (0: 34.25)         0.58 (0: 02.64.04)         0.002           Mean:S0         3.17.1.17.38         1.4.85:10.8.29.         3.17.1.49           Median (108)         7 (4-14)         9 (5-16)         3 (2-4.75)           Mean:S0         3.17.1.49         .0.002           Mean:S0         18 (0: 34.25)         19 (12-36.5)         3.17.1.49           Mean:S0         19 (2-36.5)         3.17.1.49         .0.001           Mean:S0         18 (0: 34.25)         19 (12-36.5)         3.2.25.4.75           Mean:S0         10.12.15.8         80.44-13.56         78.29-13.80         0.486           Mean:S0         5.18-5.21         5.34-2.96         10.36+8.27         .0.001           Mean:S0         17.005.12.19         18.26:5.77         12.06:10.50         .0.001           Mean:S0         17.005.12.19         18.26:5.77         12.06:10.50         .0.602           Median (108)         5.10 (1.13.8.21)         5.10 (1.33.34.00)         3.76 (0.34+54.10)         .0.238           Meadian (108)         5.20 (1.1.13.8.21)         5.10 (1.33.34.00)         3.76 (0.34+54.10)   | SOFA score   | 9.51±3.24            | 9.07±2.99                  | 12.04±3.56                            | <0.001  |
| Median (IQR)         99.04.62.40         90.02-31.86         80.41.13.9.9           Median (IQR)         0.00 (0-4.4.5)         6.88 (0-58.40)         4D.13 (15.0-88.0)           Median (IQR)         13.111.7.38         14.85:18.29         3.17±1.49           Median (IQR)         7 (4-14)         9 (5-10)         3 (2-4.57)           Median (IQR)         13 (2.44.25)         13 (2.15.6)         0.001           Median (IQR)         13 (2.44.25)         19 (1.2-38.5)         3 (2.4.5.47)           Mendian (IQR)         13 (2.4.4.25)         19 (1.2-38.5)         3 (2.4.5.47)           Mendian (IQR)         13 (2.4.6.7)         10 (2.7.6.8)         17 (7.6.8)         0.1201           Mendian (IQR)         5 (21.6)         28 (20.2)         7 (29.2)         0.400           Median (IQR)         4.3 (2.80-7.5)         4.0 (2.7-6.6)         8.9 (5.15-17.09)         -           Median (IQR)         12 (0.51.2.1)         13 (2.4-19.4)         0.001         -         0.002           Median (IQR)         10 (0.12.3.23         2.3.18+32.83         2.7.97+97.08         -         0.002           Median (IQR)         10.04.12.3         2.3.18+32.83         0.2384.0633         0.314           Median (IQR)         5.00 (1.1.3.82.21)   | Vasoactive-inotropic score   |                      |                            |                                       | 0.001   |
| Median (10R)         9.00 (0=4.25)         6.88 (0=26.40)         40.13 (13.0=88.0)           Median (10R)         13.11-17.38         14.85-18.29         3.17-1.49         0.002           Median (10R)         7 (4-14)         9 (5-16)         3.17-1.49         0.002           Mennar (10R)         18 (9=34.23)         19 (12-38.3)         3.17-1.49         0.001           Mennar (10R)         18 (9=34.23)         19 (12-38.3)         3.17-1.49         0.001           Mennar (10R)         18 (9=34.23)         19 (12-38.3)         3.17-1.49         0.001           Mennar (10R)         18 (9=34.23)         19 (12-38.3)         3.17-1.49         0.496           Mechanical (Vennar (10R)         94 (86.6)         77 (53.6)         17 (00.3)         0.174           Mechanical (Vennar (10R)         4.3 (2.80-7.5)         1.43-3.49         0.86.13-17.00         0.001           Median (10R)         17.00-12.19         18.26-9.77         12.06-10.50         0.001           Meanar (10R)         17.00-12.19         17.77 (7.31-27.69)         7.76 (6.34-54.19         0.001           Median (10R)         5.10 (1.13-82.2)         3.01 (13-3-44.00)         3.65 (0.3-54.19         0.578           Menar (10R)         5.10 (1.13-82.2)         5.10 (1.13-82.10)  | Mean±SD  | 29.90±62.40          | 20.09±31.86                | 88.41±132.99                          |         |
| ICU length of stay (days)         ICU length of stay (days)         0.002           Mean.SD         13.1121.7.38         1.4.85:18.29         3.1721.49           Medina (IQR)         19.12-38.5.08         33.93.73.33         3.1721.49           Medina (IQR)         19.12-38.5.08         33.93.73.33         3.1721.49         0.001           Mean Ibod pressure         80.12-13.58         0.80.44:23.55         78.28:13.60         0.486           Mechanical ventilation         9.4 (58.0)         77 (55.8)         17 (70.8)         0.142           Mean Ibod pressure         33.02.01         7.09.20         0.420         Action (0.86.9.27           Meanical ventilation         9.4 (58.0)         77 (55.8)         17 (70.8)         0.420           Meanical ventilation         9.4 (58.0)         77 (75.8)         0.002         0.002           Meanical (0R)         1.5 4.0 (6.0-25.91)         17.77 (7.91-72.69)         7.23 (1.4-1.9.41)           Median (0R)         1.6 4.0 (6.00-25.91)         17.77 (7.91-72.69)         7.23 (1.4-1.9.41)           Median (0R)         1.8 4.4-1.1         18.1-4.2         2.25 +32.2         0.602           Median (0R)         1.8 (6.12.3)         5.3 (1.4.7.1.94)         0.578         Median (0R)         1.6 (0.0-25.91)         17.77 (   | Median (IQR)   | 9.00 (0-34.25)       | 6.98 (0-26.40)             | 40.13 (15.0-88.0)                     |         |
| Machan (CA)         13.11:17.38         14.85:18.29         3.17:1.49           Hospinal length of stay (days)  | ICU length of stay (days)  | ( )                  |                            |                                       | 0.002   |
| Median (0R)         7 (4-14)         9 (5-16)         3 (2-4-75)           Mean-SD         29.19-36.08         23.03-37.33         3.17-1.49         0.010           Meains (0R)         18 (0-34.25)         19 (12-38.5)         3 (2.9.2-4.75)         0.400         0.486           Median (0R)         94 (58.0)         77 (55.9)         17 (70.8)         0.174           Meana polacement therapy         35 (21.6)         28 (20.2)         7 (23.2)         0.420           Meana polacement therapy         35 (21.6)         28 (20.2)         7 (23.2)         0.420           Meana polacement therapy         4.3 (2.80 - 7.5)         4.0 (2.7 - 6.6)         8.9 (5.15.17.00)           Meana SD         6.18 - 5.21         5.34 - 3.96         0.06 64-8.27         0.001           Meana SD         17.00 - 12.19         18.26 - 9.77         12.06 - 10.50         0.001           Median (0R)         15.40 (6.00 - 25.31)         17.07 (7 - 17.7 (9)         7.23 (1.44 - 13.0)         0.578           Median (0R)         5.10 (1.11 - 38.21)         5.10 (1.31 - 34.00)         3.76 (0.34 - 54.13)         0.578           Median (0R)         6.607 - 0.8 (71.4         8.5 (3.5 - 73.64.13)         0.589         0.590           Typo BNP (ng/m)         6.607 - 0.8 (71.4   | Mean±SD  | 13.11±17.38          | 14.85±18.29                | 3.17±1.49                             |         |
| Hospital length of stay (days)         International constraints  | Median (IQR)   | 7 (4-14)             | 9 (5-16)                   | 3 (2-4.75)                            |         |
| Netian (CR)         29.19-36.08         33.03-37.33         3.17-1.49           Median (CR)         18 (9-34.25)         19 (12-38.5)         3 (2.25.4.75)           Mean blood pressure         80.12-13.58         80.44-13.56         78.29-13.80         0.486           Mechanical ventilation         94 (58.0)         77 (55.9)         17 (70.8)         0.174           Mean blood pressure         80.12-13.58         80.44-13.56         78.29-13.80         0.486           Means SD         6.181-5.21         5.34-3.96         10.086-8.27         -0.001           Mean-SD         6.181-5.21         5.34-3.96         10.086-8.27         -0.001           Mean-SD         17.00-12.19         18.26-9.77         12.06-10.50         -0.001           Median (QR)         16.00 (6.00-25.91)         17.77 (7.91-27.69)         7.23 (1.44-19.44)         -0.578           Median (QR)         5.10 (1.13-38.20)         2.18-32.83         27.97-97.08         -0.578           Median (QR)         5.10 (1.13-38.41.1)         18.1-42.6         2.0.5-32.9.0         0.602           Toponin- (ng/nL)         0.336-11.53         0.259-0.030         0.714           Median (QR)         5.10 (1.13-38.41.21         18.1-42.6         2.0.5-30.5         0.512   | Hospital length of stay (days)   | . ,                  |                            | , , , , , , , , , , , , , , , , , , , | <0.001  |
| Median (QR)         18 (3-34.95)         19 (12-38.5)         3 (2.25-4.75)           Mean blood pressure         80.12-13.58         80.444-13.56         78.29-13.80         0.486           Mean blood pressure         94 (58.0)         77 (55.8)         17 (70.8)         0.174           Rena replacement therapy         35 (21.6)         28 (30.2)         7 (25.2)         0.400           Median (QR)         6.184.5.21         5.344.396         10.064.6.27         0.001           Mean-SD         6.102 (280-7.55)         4.0 (27.76.6)         89.5 (51.51.70.8)         7           Mean-SD         17.00-12.19         18.2649.77         12.06-10.50         0.001           Mean-SD         16.40 (6.00-25.01)         17.77 (7.91-27.6)         7.32 (1.44-19.44)         0.578           Median (QR)         5.10 (1.1-38.21)         5.10 (1.3.3-34.00)         3.76 (0.34-54.18)         0.578           Median (QR)         5.10 (1.1-38.21)         5.10 (1.3.3-34.00)         3.76 (0.34-54.18)         0.502           Troporin-(trig/mL)         0.3302-1080         0.3452-1153         0.2592-0.603         0.714           Median (QR)         5.8 (35.8)         5 (38.7)         5 (20.8)         0.919           Urinary tract infection         49 (30.2)         42 (30.7) <td>Mean±SD</td> <td>29.19±36.08</td> <td>33.93±37.33</td> <td>3.17±1.49</td> <td></td>   | Mean±SD  | 29.19±36.08          | 33.93±37.33                | 3.17±1.49                             |         |
| Mean block pressure         80.12+13.5g <sup>2</sup> 80.44+13.5g <sup>2</sup> 78.29+13.80 <sup>2</sup> 0.446           Mechanicul ventilation         94 (58.0)         77 (55.8)         17 (70.8)         0.176           Mean replacement therapy         35 (21.6)         28 (20.2)         7 (25.8)         17 (70.8)         0.420           Mean replacement therapy         35 (21.6)         28 (20.2)         7 (25.2)         0.420           Mean replacement therapy         35 (21.6)         28 (20.2)         7 (25.2)         0.420           Mean replacement therapy         35 (21.6)         28 (40.7.6.6)         8.9 (5.15-17.0.8)         0.002           Mean-SD         17.07 (0.12.7.9)         18.266.9.7         12.0.661.0.5.0         0.002           Mean-SD         16.40 (6.00-25.01)         17.77 (7.91-27.69)         7.33 (1.44-13.44)         0.414-13.45           Mean-SD         18.391         5.10 (1.13-38.21)         5.10 (1.13-38.21)         0.402         0.602           Toposini-T (ng/nL)         0.301-1080         0.345+1.13         0.225+3.29         0.602           Toposini-T (ng/nL)         0.302-0.67         59.632+7.13         0.288.91.79.70.8         0.231           Pneumonia         S8 (35.8)         53 (38.7)         5 (20.8)         0.231      <   | Median (IQR)   | 18 (9-34.25)         | 19 (12-38.5)               | 3 (2.25-4.75)                         |         |
| Mechanical ventilation         94 (58.0)         77 (55.8)         17 (70.8)         0.174           Renal replacement therapy         35 (21.6)         28 (20.2)         7 (29.2)         0.420           Meclian (10R)         6.18±5.21         5.34±3.96         10.0616.8.77         0.001           Meclian (10R)         4.3 (2.80-7.55)         4.0 (2.7-6.6)         8.9 (51.51-7.08)         -           C-reactive protein (mg/dL)         0.001         18.06±9.77         12.06±10.50         -           MeansD         17.00-12.19         18.26±9.77         12.06±10.50         -           Median (0R)         16.40 (6.00-25.91)         17.77 (7.9.1-27.69)         7.23 (1.44-19.44)         -           Procalcitorin (mg/mL)         18.84±1.1         18.1+42.6         22.5±3.9         0.602           Median (0R)         5.10 (1.11-38.21)         5.10 (1.3-3=40.00)         3.76 (0.34-54.18)         -           CRMB (ng/mL)         18.84±1.1         18.1+42.6         22.5±3.9         0.602           Troponin (10g/mL)         6.607 0-28.671.4         6.565.58.84.1.5         6.883.87.97.1         0.919           Cause of infection         91 (30.2)         42 (30.7)         7 (22.2)         11.71         41.87.7           MenarSD         55 (20-14.13  | Mean blood pressure  | 80.12±13.58          | 80.44±13.56                | 78.29±13.80                           | 0.486   |
| Renal replacement therapy         35 (21.6)         28 (20.2)         7 (29.2)         0.400           Lactic acid         0.001           Mean-SD         6.18±5.21         5.34±3.96         10.86±8.27           Median (QR)         4.3 (2.80~7.55)         4.0 (2.7-6.6)         8.2 (5.15-17.08)           Creactive protein (mg/dL)         0.002         0.002         0.002           Mean-SD         17.00:12.19         18.26±9.77         12.06±10.50           Procatictonin (ng/mL)         0.502         7.77 (7.91-27.08)         0.002           Mean-SD         23.91±33.39         23.18±32.83         27.97=0.70.68         0.602           Median (QR)         5.10 (1.11-38.21)         5.10 (1.13-34.00)         3.76 (0.34-54.18)         0.502           Mean-SD         0.330:1.060         0.345:1.153         0.259:0.603         0.714           NT pro BNP (pg/mL)         6.607.02:6.71.4         6.65:55:8.841.5         6.883.82+9.07.1         0.919           Urinary tract infection         49 (30.2)         42 (130.7)         7 (29.2)         1           Urinary tract infection         49 (30.2)         42 (14.0)         28 (43.67.07         7 (29.2)           Urinary tract infection         49 (20.2)         26 (19.0)         8 (34.2)         0   | Mechanical ventilation   | 94 (58.0)            | 77 (55.8)                  | 17 (70.8)                             | 0.174   |
| Lactic add         Control         Control         Control         Output         Output <tho< td=""><td>Renal replacement therapy</td><td>35 (21.6)</td><td>28 (20.2)</td><td>7 (29.2)</td><td>0.420</td></tho<>   | Renal replacement therapy  | 35 (21.6)            | 28 (20.2)                  | 7 (29.2)                              | 0.420   |
| Median (QR)         6.18+5.21         5.34+3.96         10.86+8.27           Median (QR)         4.3 (2.80-7.55)         4.0 (2.7-6.6)         8.9 (5.15-17.08)           Creactive protein (mg/dL)         0.002           Median (QR)         17.00+12.19         18.26=9.77         12.06±10.50           Median (QR)         16.40 (6.00-25.91)         17.77 (7.91-27.68)         7.23 (1.44-13.44)           Procalcitonin (ng/mL)         23.91±32.39         23.18±32.83         27.97±97.08           Median (QR)         5.10 (1.11-38.21)         5.10 (1.33-34.00)         3.76 (0.34-54.18)           CK-ME (ng/mL)         0.3091.080         0.345±1.153         0.2590.603         0.714           NT pro DNP (og/mL)         6.607.0±8.671.4         6.565.5±8.841.5         6.883.8±7.907.1         0.919           Cause of infection         94 (30.2)         42 (30.7)         7 (29.2)         0.238           Urinary tract infection         34 (21.0)         26 (19.0)         8 (33.3)         0.042           VEDV (mL)         59.00.902.06 7         59.6317.81         60.87±8.61         0.442           VEDV (mL)         59.00.902.06 7         59.6317.91         0.18.90         0.280           UFEDV (mL)         59.00.902.06 7         59.6317.81         60.87±8.61   | Lactic acid  |                      |                            | ( )                                   | 0.001   |
| Median (1QR)         4.3 (2.80-7.55)         4.0 (2.7-6.6)         8.9 (5.15-17.08)           C-reactive protein (mg/dL)         12.06±10.50         0.002           Mean-SD         17.00±12.19         18.26±9.77         12.06±10.50           Median (1QR)         16.40 (6.00-25.91)         17.77 (7.91-27.69)         7.23 (1.4-19.44)           Procalcitonin (ng/mL)         23.91±33.39         23.18±32.83         27.97±97.08         0.578           Median (1QR)         5.10 (1.11-38.21)         5.10 (1.13-34.94)         3.76 (0.34-54.18)         0.255±0.603         0.714           Troponin-t (mg/mL)         0.330±0.800         0.345±1.153         0.255±0.603         0.714           Typ os NP (og/mL)         6,607.0±8,671.4         6,565.5±8,841.5         6,883.8±7,907.1         0.919           Cause of infection         94 (30.2)         42 (30.7)         7 (29.2)         1           Urinary tract infection         34 (21.0)         26 (13.0)         8 (33.3)         0.042           Other         20 (12.3)         16 (11.7)         4 (16.7)         0.842           UV mL)         59.00±0.67         59.63±17.81         60.87±2.861         0.842           UV mL)         59.00±0.67         59.63±17.81         60.87±2.861         0.842   | Mean±SD  | 6.18±5.21            | 5.34±3.96                  | 10.86±8.27                            |         |
| C-reactive protein (mg/dL)         0.002           Mean=SD         17.00=12.19         18.26=9.77         12.06±10.50           Median (QR)         16.40 (6.00=25.91)         17.77 (7.91=27.69)         7.23 (1.44=19.44)           Procatitonin (ng/mL)         5.10 (1.11=38.21)         5.10 (1.33=34.00)         3.76 (0.34=54.18)           CK-MB (ng/mL)         0.330±1.080         0.345±1.153         0.259±0.603         0.714           Troponin* (ng/mL)         0.330±1.080         0.345±1.153         0.259±0.603         0.714           NT pro BNP (pg/mL)         6.607.0±8,671.4         6.555.5±8,841.5         6.883.8±7,907.1         0.919           Cusse of infection         94 (30.2)         42 (30.7)         7 (29.2)         1           Intraabdominal infection         34 (21.0)         26 (13.0)         8 (33.3)         0           VE EV (mL)         55.0012.0.67         55.6317.81         60.8712.8.61         0.842           VE EV (mL)         55.0012.0.67         55.8.247.53         50.032.4.25=6.3.87)         50.6317.8.61         0.842           VE EV (mL)         55.0012.0.67         55.8.615.35         50.50 (34.25=6.3.87)         56.432.2.42         48.2321.8.44         Median (0(R)         55.201.4.13         56.4321.2.42         48.2321.8.44         Median (0(R)  | Median (IOR)   | 4.3 (2.80-7.55)      | 4.0 (2.7-6.6)              | 8.9 (5.15-17.08)                      |         |
| Maar, SD         17,00;12,19         18,26:9,77         12,06:10.50           Median (1QR)         16,40 (6.00-25.91)         17.77 (7.91-27.69)         7.23 (1.44-19.44)           Procalcitomin (ng/mL)         0.578         0.578           Mean,SD         23,91:33,39         23,18:32,83         27.979.97.08           Median (1QR)         5.10 (1.11-38.21)         5.10 (1.33-34.00)         3.76 (0.34-50.81)           CK-MB (ng/mL)         0.330:1.080         0.345:1.153         0.259:0.603         0.714           Np ros NP (ng/mL)         6,607.0:6,671.4         6,555.5:8,841.5         6,833.8:7,907.1         0.919           Cause of infection         0.238         0.239:0.603         0.714         0.239           Pneumonia         58 (35.8)         53 (38.7)         5 (20.8)         0.238           Urinary tract infection         49 (30.2)         42 (30.7)         7 (29.2)         1           Intraabdominal infection         34 (21.0)         26 (19.0)         8 (33.3)         0.054           Median (1QR)         55.20:14.13         56.43:12.42         48.23:18.43         0.056           Median (1QR)         55.20:14.13         56.43:12.42         48.23:18.44         0.056           Median (1QR)         55.20:14.13         56.43:12   | C-reactive protein (mg/dL)   |                      |                            |                                       | 0.002   |
| Median (IQR)         16.40 (6.00-25.91)         17.77 (7.91-27.69)         7.23 (1.44-19.44)           Procalitorin (ng/mL)   | Mean±SD  | 17.00±12.19          | 18.26±9.77                 | 12.06±10.50                           |         |
| Procalcitonin (ng/mL)         0   | Median (IQR)   | 16.40 (6.00-25.91)   | 17.77 (7.91-27.69)         | 7.23 (1.44-19.44)                     |         |
| Mean±SD         23.91±33.39         23.18±32.83         27.97±97.08           Median (IQR)         5.10 (1.11-38.21)         5.10 (1.33-34.00)         3.76 (0.34-54.18)           CK-MB (ng/mL)         18.8±41.1         18.1±42.6         22.552.9         0.602           Troponin-t (ng/mL)         0.330±1.080         0.345±1.153         0.259±0.603         0.714           NT pro BNP (pg/mL)         6.607.0±8.671.4         6.555±8.841.5         6.883.8±7,907.1         0.919           Cause of infection         0.238         53 (38.7)         5 (20.8)         0.238           Pneumonia         58 (35.8)         53 (38.7)         5 (20.8)         0.238           Urinary tract infection         49 (30.2)         42 (30.7)         7 (29.2)         1           Intraabdominal infection         34 (21.0)         26 (19.0)         8 (33.3)         0           V EDV (mL)         59.00±2.067         59.63±17.81         6.87±8.61         0.482           V EDV (mL)         27.11±13.96         26.78±13.04         31.09±18.00         0.280           LVEF         0.55         50.50 (34.25-63.87)         50.63         50.50 (34.25-63.87)         50.63           Kedian (IQR)         55.20±14.13         56.43±12.42         48.23±18.44         Median (IQR  | Procalcitonin (ng/mL)  | . ,                  |                            |                                       | 0.578   |
| Median (IQR) $5.10 (1.11-38.21)$ $5.10 (1.33-34.00)$ $3.76 (0.34-54.18)$ CK-MB (ng/mL) $18.8\pm41.1$ $18.1\pm42.6$ $22.5\pm32.9$ $0.602$ Droponit- (ing/mL) $0.330\pm1.080$ $0.345\pm1.153$ $0.259\pm0.603$ $0.714$ NT pro BNP (pg/mL) $6.607.0\pm8.671.4$ $6.565.5\pm8.841.5$ $6.883.8\pm7.907.1$ $0.919$ Cause of Infection $0.330\pm1.080$ $0.345\pm1.153$ $0.259\pm0.603$ $0.714$ Drawonia $58 (35.8)$ $53 (38.7)$ $5 (20.8)$ $0.339$ Urinary tract infection $49 (30.2)$ $42 (30.7)$ $7 (29.2)$ Intraabdominal infection $34 (21.0)$ $26 (19.0)$ $8 (33.3)$ Other $20 (12.3)$ $16 (11.7)$ $4 (16.7)$ UV EV (mL) $25.00\pm20.67$ $59.63\pm17.81$ $60.87\pm28.61$ $0.482$ UV EV (mL) $27.1\pm13.96$ $26.78\pm3.04$ $31.09\pm18.00$ $0.280$ UFF $52.00\pm14.13$ $56.43\pm12.42$ $48.23\pm18.44$ $0.056$ Mean±SD $55.20\pm14.13$ $56.43\pm12.42$ $48.23\pm18.44$ $0.056$ Median (IQR) $55.20\pm14.13$ $56.43\pm12.42$ $48.23\pm18.44$ $0.001$ Mean±SD $-14.90\pm5.21$ $-15.54\pm5.03$ $-10.57\pm4.32$ $0.001$ Mean±SD $16.90\pm5.24$ $10.06-19.00$ $15.90 (12.10-19.50)$ $9.30 (7.70-13.70)$ TRVmax (m/sec) $2.73\pm0.47$ $2.72\pm0.47$ $2.78\pm0.44$ $0.596$ GAS $16.90\pm5.54$ $17.67\pm4.87$ $14.18\pm4.43$ Median (IQR) $17.00 (14.00-20.00)$ $17.00 (14.22-21.00)$ $15.00 (15.50-76.01)$  | Mean±SD  | 23.91±33.39          | 23.18±32.83                | 27.97±97.08                           |         |
| Ck-MB (ng/mL)         18,8±41.1         18,1±42.6         22,5±32.9         0.602           Tropoint-(ng/mL)         0.330±1.080         0.345±1.153         0.259±0.603         0.714           Np ro BNP (pg/mL)         6,607.0±8,671.4         6,565.5±8,841.5         6,883.8±7,907.1         0.919           Cause of infection         0.238         0.029         0.238         0.259±0.603         0.714           Viriary tract infection         49 (30.2)         42 (30.7)         7 (29.2)         1         0.238           Uriary tract infection         34 (21.0)         26 (19.0)         8 (33.3)         0.01er         0.012.3)         16 (11.7)         4 (16.7)           LV EDV (mL)         27.11±13.96         26.78±13.04         31.09±18.00         0.280           UV EFV         0.054         0.054         0.054         0.054           Mean±SD         55.0±14.13         56.43±12.42         48.23±18.44         0.054           Median (QR)         15.00 (10.60-19.00)         15.05 (10.21.0-19.50)         50.50 (30 (27.7-13.70)         0.669           Median (QR)         15.00 (10.60-19.00)         15.00 (12.10-19.50)         9.30 (7.70-13.70)         0.003           Mean±SD         -14.902.5.21         -15.54±5.03         -10.57±4.32         0.00  | Median (IOR)   | 5.10 (1.11-38.21)    | 5.10 (1.33-34.00)          | 3.76 (0.34-54.18)                     |         |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $  | CK-MB (ng/mL)  | 18.8±41.1            | 18.1±42.6                  | 22.5±32.9                             | 0.602   |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $  | Troponin-t (ng/mL)   | 0.330±1.080          | 0.345±1.153                | 0.259±0.603                           | 0.714   |
| Cause of infection0.238Pneumonia58 (35.8)53 (38.7)5 (20.8)Uriary tract infection49 (30.2)42 (30.7)7 (29.2)Intraabdominal infection34 (21.0)26 (19.0)8 (33.3)Other20 (12.3)16 (11.7)4 (16.7)VEDV (mL)55.00-20.6755.63+17.8160.87±28.610.842LV ESV (mL)27.11±13.9626.78±13.0431.09±18.000.280LVEF0.5520.50 (34.25-63.87)0.5540.647Mean=SD55.20±14.1356.43±12.4248.23±18.440.054Median (IQR)58.40 (45.00-65.15)58.8 (47.59-65.65)50.50 (34.25-63.87)0.001Median (IQR)15.00 (10.60-19.00)15.90 (12.10-19.50)9.30 (7.70-13.70)7TRVmax (m/sec)2.73±0.472.72±0.472.78±0.440.596Aps116.90±5.5417.67±4.8714.18±4.430.003Median (IQR)17.00 (14.00-20.80)17.00 (14.22-21.00)15.00 (0.65-17.40)LVF <50%   | NT pro BNP (pg/mL)   | 6,607.0±8,671.4      | 6,565.5±8,841.5            | 6,883.8±7,907.1                       | 0.919   |
| Pneumonia         58 (35.8)         53 (38.7)         5 (20.8)           Urinary tract infection         49 (30.2)         42 (30.7)         7 (29.2)           Intraabdominal infection         34 (21.0)         26 (19.0)         8 (33.3)           Other         20 (12.3)         16 (11.7)         4 (16.7)           LV EDV (mL)         59.00±20.67         59.63±17.81         60.87±28.61         0.842           LV ESV (mL)         27.11±13.96         26.78±13.04         31.09±18.00         0.280           LVEF         0.552.02±14.13         56.43±12.42         48.23±18.44         Median (IQR)         58.40 (45.00-65.15)         58.8 (47.59-65.65)         50.50 (34.25-63.87)         E669           GLS         -         -         -0.051         -0.0574.432         -0.011           Median (IQR)         15.00 (10.60-19.00)         15.90 (12.10-19.50)         9.30 (7.70-13.70)         -           TRVmax (m/sec)         2.73±0.47         2.72±0.47         2.72±0.47         2.72±0.47         -         0.003           Median (IQR)         15.00 (10.60-19.00)         15.00 (10.422-21.00)         15.00 (0.65-17.40)         -         0.003           Median (IQR)         17.00 (14.00-20.80)         17.00 (14.22-21.00)         15.00 (0.65-17.40)         -  | Cause of infection   |                      |                            |                                       | 0.238   |
| $\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$  | Pneumonia  | 58 (35.8)            | 53 (38.7)                  | 5 (20.8)                              |         |
| $\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$  | Urinary tract infection  | 49 (30.2)            | 42 (30.7)                  | 7 (29.2)                              |         |
| $\begin{array}{ c c c c c c c c c c c c c c c c c c c$  | Intraabdominal infection   | 34 (21.0)            | 26 (19.0)                  | 8 (33.3)                              |         |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $  | Other  | 20 (12.3)            | 16 (11.7)                  | 4 (16.7)                              |         |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $  | LV EDV (mL)  | 59.00±20.67          | 59.63±17.81                | 60.87±28.61                           | 0.842   |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $  | LV ESV (mL)  | 27.11±13.96          | 26.78±13.04                | 31.09±18.00                           | 0.280   |
| $\begin{array}{llllllllllllllllllllllllllllllllllll$  | LVEF   |                      |                            |                                       | 0.054   |
| Median (IQR) $58.40 (45.00-65.15)$ $58.8 (47.59-65.65)$ $50.50 (34.25-63.87)$ E/e' $13.23\pm13.84$ $12.05\pm5.35$ $12.27\pm4.97$ $0.869$ GLS $-14.90\pm5.21$ $-15.54\pm5.03$ $-10.57\pm4.32$ $0.001$ Median (IQR) $15.00 (10.60-19.00)$ $15.90 (12.10-19.50)$ $9.30 (7.70-13.70)$ TRVmax (m/sec) $2.73\pm0.47$ $2.72\pm0.47$ $2.78\pm0.44$ $0.596$ TAPSE (mm) $0.001$ $17.00 (14.00-20.80)$ $17.00 (14.22-21.00)$ $15.00 (9.65-17.40)$ LVEF \$50% $50 (31.17)$ $40 (29.0)$ $10 (41.7)$ $0.224$ GLS >-16% $74 (54.4)$ $57 (48.7)$ $17 (89.5)$ $0.001$ Cardiac output (L/min) $4.92\pm3.65$ $4.75\pm1.66$ $4.11\pm1.70$ $0.901$ Cardiac output (L/min/m²) $3.06\pm2.10$ $2.97\pm0.98$ $2.53\pm1.09$ $0.207$ Systemic vascular resistance (dynes sec/cm <sup>5</sup> ) $1,556.23\pm650.88$ $1,537.12\pm646.94$ $1,714.79\pm597.49$ $0.088$ Systemic vascular resistance (dynes sec/cm <sup>5</sup> m²) $2.493.62\pm1.076.98$ $2.434.61\pm1.072.59$ $2.822.1\pm1.064.88$ $0.116$ 7-day mortality $24 (14.9)$ $0 (0)$ $24 (100.0)$ $24 (100.0)$ $24 (100.0)$ Hospital mortality $64 (39.8)$ $41 (29.7)$ $24 (100.0)$ $24 (100.0)$  | Mean±SD  | 55.20±14.13          | 56.43±12.42                | 48.23±18.44                           |         |
| E/e'13.23±13.8412.05±5.3512.27±4.970.869GLS<  | Median (IQR)   | 58.40 (45.00-65.15)  | 58.8 (47.59-65.65)         | 50.50 (34.25-63.87)                   |         |
| GLS $< -14.90\pm5.21$ $-15.54\pm5.03$ $-10.57\pm4.32$ $< 0.001$ Median (IQR)15.00 (10.60-19.00)15.90 (12.10-19.50)9.30 (7.70-13.70) $< 12.78\pm0.44$ 0.596TAPse (mm) $2.73\pm0.47$ $2.72\pm0.47$ $2.78\pm0.44$ 0.596Median (IQR)16.90\pm5.5417.67\pm4.8714.18\pm4.43Median (IQR)17.00 (14.00-20.80)17.00 (14.22-21.00)15.00 (9.65-17.40)LVEF <50%   | E/e'   | 13.23±13.84          | 12.05±5.35                 | 12.27±4.97                            | 0.869   |
| Mean±SD $-14.90\pm5.21$ $-15.54\pm5.03$ $-10.57\pm4.32$ Median (IQR)15.00 (10.60-19.00)15.90 (12.10-19.50)9.30 (7.70-13.70)TRVmax (m/sec) $2.73\pm0.47$ $2.72\pm0.47$ $2.78\pm0.44$ $0.596$ TAPSE (mm)0.003Mean±SD16.90±5.5417.67±4.8714.18±4.43Median (IQR)17.00 (14.00-20.80)17.00 (14.22-21.00)15.00 (9.65-17.40)LVEF <50%50 (31.17)40 (29.0)10 (41.7)0.224GLS >-16%74 (54.4)57 (48.7)17 (89.5)0.001Cardiac output (L/min)4.92±3.654.75±1.664.11±1.700.091Cardiac output (L/min/m²)3.06±2.102.97±0.982.53±1.090.207Systemic vascular resistance (dynes sec/cm⁵)1,556.23±650.981,537.12±646.941,714.79±597.490.088Systemic vascular resistance index (dynes sec/cm⁵)2.493.62±1.076.982.434.611±1.072.592.826.21±1.064.880.116Ca-day mortality24 (14.9)0.0024 (100.0)24 (100.0)24 (100.0)24 (100.0)Bospital mortality64 (39.8)41 (29.7)24 (100.0)24 (100.0)24 (100.0)  | GLS  |                      |                            |                                       | <0.001  |
| Median (IQR)         15.00 (10.60-19.00)         15.90 (12.10-19.50)         9.30 (7.70-13.70)           TRVmax (m/sec)         2.73±0.47         2.72±0.47         2.78±0.44         0.596           TAPSE (mm)         0.003           Mean±SD         16.90±5.54         17.67±4.87         14.18±4.43           Median (IQR)         17.00 (14.00-20.80)         17.00 (14.22-21.00)         15.00 (9.65-17.40)           LVEF <50%   | Mean±SD  | -14.90±5.21          | -15.54±5.03                | $-10.57 \pm 4.32$                     |         |
| TRVmax (m/sec)       2.73±0.47       2.72±0.47       2.78±0.44       0.596         TAPSE (mm)       0.003         Mean±SD       16.90±5.54       17.67±4.87       14.18±4.43         Median (IQR)       17.00 (14.00-20.80)       17.00 (14.22-21.00)       15.00 (9.65-17.40)         LVEF <50%  | Median (IQR)   | 15.00 (10.60-19.00)  | 15.90 (12.10-19.50)        | 9.30 (7.70-13.70)                     |         |
| TAPSE (m)       0.003         Mean±SD       16.90±5.54       17.67±4.87       14.18±4.43         Median (IQR)       17.00 (14.00-20.80)       17.00 (14.22-21.00)       15.00 (9.65-17.40)         LVEF <50%  | TRVmax (m/sec)   | 2.73±0.47            | 2.72±0.47                  | 2.78±0.44                             | 0.596   |
| Mean±SD<br>Median (IQR)         16.90±5.54         17.67±4.87         14.18±4.43           Median (IQR)         17.00 (14.00-20.80)         17.00 (14.22-21.00)         15.00 (9.65-17.40)           LVEF <50%  | TAPSE (mm)   |                      |                            |                                       | 0.003   |
| Median (IQR)         17.00 (14.00-20.80)         17.00 (14.22-21.00)         15.00 (9.65-17.40)           LVEF <50%   | Mean±SD  | 16.90±5.54           | 17.67±4.87                 | $14.18 \pm 4.43$                      |         |
| LVEF <50%         50 (31.17)         40 (29.0)         10 (41.7)         0.224           GLS >-16%         74 (54.4)         57 (48.7)         17 (89.5)         0.001           TAPSE <16 mm   | Median (IQR)   | 17.00 (14.00-20.80)  | 17.00 (14.22-21.00)        | 15.00 (9.65-17.40)                    |         |
| GLS >-16%         74 (54.4)         57 (48.7)         17 (89.5)         0.001           TAPSE <16 mm  | LVEF <50%  | 50 (31.17)           | 40 (29.0)                  | 10 (41.7)                             | 0.224   |
| TAPSE <16 mm       63 (42.9)       48 (38.4)       15 (68.2)       0.011         Cardiac output (L/min)       4.92±3.65       4.75±1.66       4.11±1.70       0.091         Cardiac output index (L/min/m²)       3.06±2.10       2.97±0.98       2.53±1.09       0.207         Systemic vascular resistance (dynes sec/cm⁵)       1,556.23±650.98       1,537.12±646.94       1,714.79±597.49       0.088         Systemic vascular resistance index (dynes sec/cm⁵m²)       2,493.62±1,076.98       2,434.611±1,072.59       2,826.21±1,064.88       0.116         7-day mortality       24 (14.9)       0 (0)       24 (100.0)       24         28-day mortality       53 (32.9)       29 (21.0)       24 (100.0)       41 (29.7)         Hospital mortality       64 (39.8)       41 (29.7)       24 (100.0)       41 (20.0)  | GLS >-16%  | 74 (54.4)            | 57 (48.7)                  | 17 (89.5)                             | 0.001   |
| Cardiac output (L/min)         4.92±3.65         4.75±1.66         4.11±1.70         0.091           Cardiac output index (L/min/m²)         3.06±2.10         2.97±0.98         2.53±1.09         0.207           Systemic vascular resistance (dynes sec/cm <sup>5</sup> )         1,556.23±650.98         1,537.12±646.94         1,714.79±597.49         0.088           Systemic vascular resistance index (dynes sec/cm <sup>5</sup> m²)         2,493.62±1,076.98         2,434.611±1,072.59         2,826.21±1,064.88         0.116           7-day mortality         24 (14.9)         0 (0)         24 (100.0)         28           28-day mortality         53 (32.9)         29 (21.0)         24 (100.0)         41 (29.7)         24 (100.0)  | TAPSE <16 mm   | 63 (42.9)            | 48 (38.4)                  | 15 (68.2)                             | 0.011   |
| Cardiac output index (L/min/m <sup>2</sup> )         3.06±2.10         2.97±0.88         2.53±1.09         0.207           Systemic vascular resistance (dynes sec/cm <sup>5</sup> )         1,556.23±650.98         1,537.12±646.94         1,714.79±597.49         0.088           Systemic vascular resistance index (dynes sec/cm <sup>5</sup> m <sup>2</sup> )         2,493.62±1,076.98         2,434.611±1,072.59         2,826.21±1,064.88         0.116           7-day mortality         24 (14.9)         0 (0)         24 (100.0)           28-day mortality         53 (32.9)         29 (21.0)         24 (100.0)           Hospital mortality         64 (39.8)         41 (29.7)         24 (100.0)   | Cardiac output (L/min)   | 4.92±3.65            | 4.75±1.66                  | 4.11±1.70                             | 0.091   |
| Systemic vascular resistance (dynes sec/cm <sup>5</sup> )         1,556.23±650.98         1,537.12±646.94         1,714.79±597.49         0.088           Systemic vascular resistance index (dynes sec/cm <sup>5</sup> m <sup>2</sup> )         2,493.62±1,076.98         2,434.611±1,072.59         2,826.21±1,064.88         0.116           7-day mortality         24 (14.9)         0 (0)         24 (100.0)           28-day mortality         53 (32.9)         29 (21.0)         24 (100.0)           Hospital mortality         64 (39.8)         41 (29.7)         24 (100.0)  | Cardiac output index (L/min/m <sup>2</sup> )                                   | 3.06±2.10            | 2.97±0.98                  | 2.53±1.09                             | 0.207   |
| Systemic vascular resistance index (dynes sec/cm <sup>s</sup> m <sup>2</sup> )         2,493.62±1,076.98         2,434.611±1,072.59         2,826.21±1,064.88         0.116           7-day mortality         24 (14.9)         0 (0)         24 (100.0)           28-day mortality         53 (32.9)         29 (21.0)         24 (100.0)           Hospital mortality         64 (39.8)         41 (29.7)         24 (100.0)  | Systemic vascular resistance (dvnes sec/cm <sup>5</sup> )                      | 1,556.23±650.98      | $1,537.12\pm646.94$        | 1,714.79±597.49                       | 0.088   |
| 7-day mortality     24 (14.9)     0 (0)     24 (100.0)       28-day mortality     53 (32.9)     29 (21.0)     24 (100.0)       Hospital mortality     64 (39.8)     41 (29.7)     24 (100.0)  | Systemic vascular resistance index (dvnes sec/cm <sup>5</sup> m <sup>2</sup> ) | 2,493.62±1.076.98    | 2,434.611±1.072.59         | 2,826.21±1.064.88                     | 0.116   |
| 28-day mortality     53 (32.9)     29 (21.0)     24 (100.0)       Hospital mortality     64 (39.8)     41 (29.7)     24 (100.0)   | 7-day mortality  | 24 (14.9)            | 0 (0)                      | 24 (100.0)                            |         |
| Hospital mortality 64 (39.8) 41 (29.7) 24 (100.0)   | 28-day mortality   | 53 (32.9)            | 29 (21.0)                  | 24 (100.0)                            |         |
|   | Hospital mortality   | 64 (39.8)            | 41 (29.7)                  | 24 (100.0)                            |         |

Values are presented as number (%) or mean±SD and median (interqurtile range [IQR]). APACHE = Acute Physiology and Chronic Health Evaluation; EDV = end diastolic volume; ESV = end systolic volume; GLS = global longitudinal strain; ICU = intensive care unit; LV = left ventricular; LVEF = left ventricular ejection fraction; SD = standard deviation; SDFA = Sequential Organ Failure Assessment; TAPSE = tricuspid annular plane systolic excursion.

| Table 2. Univariate and mu | ltivariate logistic regre   | ssion analysis for 7-day m   | nortality in patients with septic sl  | hock |
|----------------------------|-----------------------------|------------------------------|---------------------------------------|------|
|                            | ter var late togiotio rogio | cononi analyono non 7 alay n | ion tailing in patientie man copie of |      |

| 6                          | 0 ,      | , , ,                     |          |           |                         |          |
|----------------------------|----------|---------------------------|----------|-----------|-------------------------|----------|
|                            | Univaria | ate logistic regression a | Inalysis | Multivari | ate logistic regression | analysis |
|                            | OR       | 95% CI                    | p value  | OR        | 95% CI                  | p value  |
| Age                        | 1.013    | 0.979-1.048               | 0.459    | 0.952     | 0.880-1.030             | 0.219    |
| Sex                        | 1.572    | 0.654-3.782               | 0.312    | 10.988    | 1.537-78.559            | 0.017    |
| Charlson comorbidity index | 1.196    | 0.969-1.476               | 0.095    | 1.194     | 0.721-1.977             | 0.491    |
| APACHE II                  | 1.161    | 1.078-1.250               | <0.001   | 1.196     | 1.047-1.365             | 0.008    |
| Initial SOFA score         | 1.366    | 1.164-1.602               | <0.001   | 1.282     | 0.941-1.746             | 0.115    |
| Vasoactive-inotropic score | 1.016    | 1.006-1.025               | 0.001    |           |                         |          |
| Lactic acid                | 1.171    | 1.079-1.272               | <0.001   |           |                         |          |
| E/e'                       | 1.015    | 0.930-1.109               | 0.734    |           |                         |          |
| LVEF <50%                  | 1.615    | 0.821-3.180               | 0.165    | 0.759     | 0.100-5.743             | 0.789    |
| GLS >-16%                  | 8.947    | 1.978-40.476              | 0.004    | 14.066    | 1.178-167.969           | 0.037    |
| TAPSE <16 mm               | 3.437    | 1.307-9.039               | 0.012    | 2.083     | 0.393-11.036            | 0.389    |
| SVRI                       | 1.000    | 1.000-1.001               | 0.121    |           |                         |          |
| Cardiac output             | 0.768    | 0.563-1.047               | 0.095    | 0.944     | 0.797-1.119             | 0.508    |

APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction; OR = odds ratio; SOFA = sequential organ failure assessment; SVRI = systemic vascular resistance index; TAPSE = tricuspid annular plane systolic excursion.

(odds ratio [OR], 14.066, 95% confidence interval [CI], 1.178–167.969, p=0.037) among echocardiographic parameters with an APACHE II score (OR, 1.196, 95% CI, 1.047–1.365, p=0.008) (**Table 2**).

# Change of left and right ventricular function and its clinical implication on in-hospital mortality in 7-day survivors from septic shock

Among 7-day survivors, the requirement for vasoactive and inotropic agents was significantly reduced at the follow-up period. LVEF (55.64±12.74% vs. 61.05±8.29%, p<0.001), GLS (-15.58±4.77% vs. -17.26±4.45%, p=0.005), and TAPSE (17.61±4.87 mm vs. 19.16±5.35 mm, p=0.006) were all improved in comparison to those of initial evaluation (**Table 3**, **Supplementary Figure 1**).

Different from the relationship between initial GLS and 7-day mortality of all patients, GLS >–16% was not related to in-hospital mortality of 7-day survivors in both initial and follow-up study (initial GLS >–16%, OR, 1.743, 95% CI, 0.778–3.905, p=0.177; follow-up GLS >–16%, OR, 2.000, 95% CI, 0.746–5.363, p=0.168). Instead, follow-up TAPSE <16 mm was a significant parameter for in-hospital mortality in 7-day survivors (initial TAPSE <16 mm, OR, 1.710, 95% CI, 0.788–3.712, p=0.175; follow-up TAPSE <16 mm, OR, 5.647, 95% CI, 2.115–15.074, p=0.001) in univariate analysis. Consistently in multivariate logistic regression analysis, TAPSE <16 mm at the follow-up study was significantly associated with in-hospital mortality of 7-day survivors (OR, 10.109, 95% CI, 1.640–62.322, p=0.013) with follow-up SOFA score (OR, 1.340, 95% CI, 1.078–1.667, p=0.008) (**Table 4**).

The Kaplan-Meier curve of all patients demonstrated a significant difference in cumulative survival based on initial GLS (>–16% vs. GLS  $\leq$ –16%) with a p value of 0.031 from log-rank test. Similarly, a significant difference was observed based on initial TAPSE (<16 mm vs.  $\geq$ 16 mm) with a p value of 0.006. However, when evaluating only the 7-day survivors, the Kaplan-Meier curves did not show a significant difference based on initial LV or RV dysfunction (p=0.479 and 0.169, respectively). In 7-day survivors, the cumulative survival based only on follow-up RV dysfunction was significantly different (p<0.001) (**Figure 2**).

|  |  | Initial evalua                                       | tion   |              |  | Follow-up eval  | uation  |               |                      |
|--|--|--|--|--------------|--|---|---|---------------|----------------------|
|  | Seven-day survivor<br>(n=138)                        | Survivor (n=91)                                      | Non-survivor (n=41)                                  | p value      | Seven-day survivor<br>(n=138)                        | Survivor (n=91)   | Non-survivor (n=41)   | p value       | p value <sup>*</sup> |
| .V EDV (mL)  | $61.69 \pm 18.83$                                    | 60.44±16.17  | 57.70±21.31  | 0.467        | 62.91±17.62  | 61.83±6.57  | 63.46±22.09   | 0.700         | 0.372                |
| .V ESV (mL)  | $28.20 \pm 13.93$                                    | $26.67 \pm 11.80$                                    | 27.03±15.77  | 0.883        | $25.85 \pm 14.57$                                    | $26.08 \pm 15.36$   | $24.53 \pm 12.38$   | 0.651         | 0.078                |
| .VEF (%)   | $55.64 \pm 12.74$                                    | 57.40±11.89  | $54.13 \pm 13.48$                                    | 0.159        | $61.05\pm 8.29$                                      | 60.91±8.30  | $61.94 \pm 8.56$  | 0.598         | <0.001               |
| :/e,   | $12.06 \pm 5.33$                                     | $12.19\pm 5.64$                                      | $11.71 \pm 4.60$                                     | 0.659        | $11.77 \pm 5.22$                                     | $11.97 \pm 5.66$  | $11.08 \pm 3.11$  | 0.346         | 0.433                |
| (%) ST5  | $-15.58 \pm 4.77$                                    | $-16.12\pm5.00$                                      | $-14.24 \pm 4.94$                                    | 0.064        | $-17.26 \pm 4.45$                                    | $-16.96 \pm 4.22$   | $-17.59\pm 5.20$  | 0.569         | 0.005                |
| -RVmax (m/sec)                                     | $2.75\pm0.45$  | 2.72±0.45  | $2.71 \pm 0.53$                                      | 0.861        | 2.70±0.49  | 2.68±0.45   | 2.79±0.57   | 0.323         | 0.372                |
| APSE (mm)  | $17.61 \pm 4.87$                                     | 18.60±4.72   | $15.55 \pm 4.57$                                     | 0.001        | $19.16 \pm 5.35$                                     | $19.89 \pm 5.04$  | $16.94 \pm 5.29$  | 0.015         | 0.006                |
| co (L/min)   | $5.35 \pm 4.64$                                      | $5.31 \pm 4.51$                                      | 4.49±1.66  | 0.271        | 3.06±2.10  | $4.81 \pm 1.51$   | 4.93±1.67   | 0.749         | 0.308                |
| 201 (L/min/m <sup>2</sup> )                        | $3.29\pm 2.64$                                       | $3.26 \pm 2.56$                                      | $2.88 \pm 1.07$                                      | 0.388        | 2.99±0.91  | 2.98±0.88   | 3.05±0.96   | 0.739         | 0.325                |
| WR (dynes sec/cm <sup>5</sup> )                    |  |  |  | 0.946        |  |   |   | 0.558         | 0.008                |
| Mean±SD  | $1,511.95\pm599.77$                                  | $1,525.89\pm 649.6$                                  | $1,534.48\pm 684.74$                                 |              | $1,232.96\pm 637.66$                                 | $1,247.90\pm609.20$   | $1,369.28\pm 982.60$  |               |                      |
| Median (IQR)                                       | 1,429.63<br>(1,081.34-1,828.76)                      | 1,432.86<br>(1,112.06-1,795.21)                      | 1,426.40<br>(971.19-1,945.91)                        |              | 1,141.33<br>(722.13-1,381.88)                        | 1,157.25<br>(931.28-1,358.16)   | 1,107.28<br>(819.35-1,581.79)   |               |                      |
| WRI (dynes sec/cm <sup>5</sup> m <sup>2</sup> )    |  |  |  | 0.831        |  |   |   | 0.781         | 0.007                |
| Mean≟SD<br>Median (IQR)                            | 2,434.61±1,072.59<br>2,240.80<br>(1,724.12-2,752.68) | 2,448.13±1,069.48<br>2,237.07<br>(1,839.22-2,679.47) | 2,036.42±1,055.98<br>2,244.54<br>(1,497.06-2,877.50) |              | 2,059.79±1,134.83<br>1,832.93<br>(1,358.97-2,329.81) | $\begin{array}{c} 2,036.42\pm1,055.98\\ 1,878.65\\ (1,497.84-2,325.99) \end{array}$ | $\begin{array}{c} 2,131.46\pm1,388.45\\ 1,832.93\\ (1,278.82-2,653.03) \end{array}$ |               |                      |
| SI   |  |  |  | 0.035        |  |   |   | 0.002         | <0.001               |
| Mean±SD<br>Median (IQR)                            | 18.94±29.14<br>6.98 (0.00−26.43)                     | $15.61\pm26.08$<br>6.72 (0.00-19.83)                 | 30.56±40.93<br>10.71 (0.00−55.47)                    |              | 4.18±15.18<br>0.00 (0.00−0.00)                       | 1.38±4.76<br>0.00 (0.00−0.00)   | 11.33±26.62<br>0.00 (0.00-10.97)  |               |                      |
| /alues are presented as<br>20 = cardiac output; CC | s mean±SD or median (<br>)1 = cardiac output inde    | interquartile range [IQI<br>ex; EDV = end diastolic  | R]).<br>volume; ESV = end syst                       | olic volume; | GLS = global longitudin:                             | al strain; LV = left vent   | ricular; LVEF = left ventr  | icular ejecti | on fraction;         |

|      | eje                               | SC            |
|------|-----------------------------------|---------------|
|      | lar                               | pido          |
|      | icu                               | otro          |
|      | entr                              | -in           |
|      | Ę                                 | tive          |
|      | =<br>=                            | oac           |
|      | Ш                                 | vas           |
|      | Z                                 | s<br>S        |
|      | lar                               | ž             |
|      | ricu                              | ion           |
|      | ent                               | Surs          |
|      | ff <                              | exo           |
|      | =                                 | olic          |
|      | $\geq$                            | yst           |
|      | ain;                              | Je            |
|      | strä                              | olaı          |
|      | nal                               | lar           |
|      | ipn                               | nuc           |
|      | ngit                              | d ar          |
|      | [ lo                              | spi           |
|      | oba                               | ricu          |
|      | 50                                | =             |
|      | ĽS                                | PSE           |
|      | G                                 | Ā             |
|      | me                                | lex;          |
|      | volt                              | ш.            |
|      | [ic                               | nce           |
|      | /stc                              | ista          |
|      | d s)                              | resi          |
|      | = en                              | ılar          |
|      | Š                                 | SCU           |
|      | ш.                                | C Va          |
|      | me                                | , mi          |
| ÷    | volt                              | yste          |
| ₫.   | i.                                | S<br>II       |
| ge   | astc                              | VRI           |
| ran  | di                                | e; S          |
| tile | enc                               | anc           |
| uar  | $^{\scriptscriptstyle \parallel}$ | sist          |
| erq  |                                   | ŗ             |
| (Int | jex;                              | ula           |
| lan  | in                                | asc           |
| nea  | tpu!                              | .⊆            |
| orn  | out                               | tem           |
| SD   | liac                              | syst          |
| an±  | arc                               | 1             |
| me   | =                                 | SVI           |
| as   | S                                 | ;uo           |
| ted  | ùt;                               | <i>i</i> iati |
| sen  | utp                               | dev           |
| pre  | ac c                              | ard           |
| are  | rdi                               | nd            |
| es : | = ca                              | sta           |

ore. SD = standard deviation; SVM = systemme vascurante resistance, over - opportune for the comparison of initial study and follow-up evaluation of all 7-day survivors using paired t-test.

Table 3. Comparison of initial and follow-up evaluation of the cardiac function and hemodynamic condition of 7-day survivors by in-hospital mortality





**Figure 2.** Kaplan-Meier curves for the in-hospital mortality by GLS  $\leq$  -16% and  $\geq$ -16% and by TAPSE  $\geq$ 16 mm and <16 mm in initial and follow-up TTE; (A, B) the curves of all patients evaluated by initial TTE evaluation; (C, D) curves of 7-day survivors by initial TTE evaluation; (E, F) curves of 7-day survivors by follow-up TTE evaluation.

GLS = global longitudinal strain; LV = left ventricular; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TTE = transthoracic echocardiography.

#### Impact of Septic Cardiomyopathy on Mortality

| Table 4. Univariate and multiva | riate logistic regressic | on analysis for in-hospital ( | mortality in 7-day surviyors o | f patients with septic shock |
|---------------------------------|--------------------------|-------------------------------|--------------------------------|------------------------------|
|                                 |                          | in analysis for in hospital   | moreater in r aay bar more o   |                              |

|                            | Univariate logistic regression analysis |              | Multivaria | Multivariate logistic regression analysis |              |         |
|----------------------------|---|--------------|------------|---|--------------|---------|
|                            | OR                                      | 95% CI       | p value    | OR  | 95% CI       | p value |
| Age                        | 1.008                                   | 0.980-1.036  | 0.593      | 0.985                                     | 0.919-1.054  | 0.653   |
| Sex                        | 0.958                                   | 0.461-1.991  | 0.907      | 1.896                                     | 0.298-12.420 | 0.505   |
| Charlson comorbidity index | 1.229                                   | 1.025-1.475  | 0.026      | 1.056                                     | 0.621-1.794  | 0.841   |
| APACHE II                  | 1.100                                   | 1.045-1.157  | <0.001     | 1.340                                     | 0.992-1.308  | 0.066   |
| Follow-up SOFA score       | 1.404                                   | 1.214-1.624  | <0.001     | 1.340                                     | 1.078-1.667  | 0.008   |
| Cause of infection         |   |              | 0.002      |   |              | 0.480   |
| Pneumonia                  | -                                       | -            | -          | -   | -            | -       |
| Urinary tract infection    | 0.176                                   | 0.060-0.519  | 0.002      | 0.396                                     | 0.051-3.107  | 0.378   |
| Intra-abdominal infection  | 0.237                                   | 0.072-0.784  | 0.018      | 0.084                                     | 0.003-2.349  | 0.145   |
| Others                     | 1.304                                   | 0.425-3.999  | 0.642      | 0.423                                     | 0.028-6.412  | 0.535   |
| Initial EF <50%            | 1.907                                   | 0.617-5.890  | 0.262      |   |              |         |
| Initial GLS <–16%          | 1.743                                   | 0.778-3.905  | 0.177      |   |              |         |
| Initial TAPSE <16 mm       | 1.710                                   | 0.788-3.712  | 0.175      |   |              |         |
| Follow-up SVRI             | 1.000                                   | 1.000-1.001  | 0.777      |   |              |         |
| Follow-up COI              | 0.926                                   | 0.500-1.716  | 0.807      |   |              |         |
| Follow-up EF <50%          | 0.344                                   | 0.041-2.895  | 0.326      |   |              |         |
| Follow-up GLS <-16%        | 2.000                                   | 0.746-5.363  | 0.168      | 0.511                                     | 0.081-3.219  | 0.474   |
| Follow-up TAPSE <16 mm     | 5.647                                   | 2.115-15.074 | 0.001      | 10.109                                    | 1.640-62.322 | 0.013   |

APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; COI = cardiac output index; EF = ejection fraction; GLS = global longitudinal strain; OR = odds ratio; SOFA = Sequential Organ Failure Assessment; SVRI = systemic vascular resistance index; TAPSE = tricuspid annular plane systolic excursion.

## DISCUSSION

In our study on patients with septic shock, we used TTE to perform serial evaluations of cardiac function within 48 hours of the diagnosis of septic shock and after 7 days from the initial cardiac evaluation. Cardiac dysfunction was common in both the RV and LV, related to severity index of the disease and hemodynamic parameters, and quickly recovered in 7-day survivors. Regarding mortality outcomes, LV systolic dysfunction during the initial evaluation was significantly related to 7-day mortality. However, in the 7-day survivors, LV systolic dysfunction did not demonstrate a significant association with in-hospital mortality. Instead, RV dysfunction at the follow-up evaluation was related to in-hospital mortality in these 7-day survivors.

Cardiac dysfunction is a common manifestation of sepsis. Although the precise mechanism of myocardial injury at the cellular level has not been completely elucidated, various pathways of dysregulated host responses influencing cardiomyocytes have been confirmed.<sup>13)14)</sup> Nitric oxide and reactive oxygen species involved in calcium handling, mitochondrial dysfunction of cardiomyocytes, 15)16) or perturbation of coronary microvasculature caused deleterious effects on cardiac function.<sup>17)</sup> Moreover, the characteristics of the distributive shock of sepsis—decreased LV afterload and preload with low systemic vascular resistance and venous return—directly influence LV systolic function. Vasoactive agents and fluid resuscitation with large amounts of fluid also change loading conditions and interfere with accurate measurement of LV function.<sup>9)</sup> Therefore, variable results of the relationship between LV systolic function and the prognosis of patients with sepsis have been reported. With advanced parameters evaluating LV function, GLS more accurately differentiated LV dysfunction in sepsis<sup>18-20)</sup> and resulted in a more consistent relationship between LV systolic function and patient mortality than LVEF.<sup>21-23</sup> Compared to LV, there were fewer evaluations concerning RV for the diagnosis of SCM. However, RV is independent of systemic afterload; RV afterload is decided by pulmonary circulation, not systemic circulation, and the RV free wall is more compliant with the preload than LV.<sup>24</sup>) Therefore, the assessment of RV function in relation to patient prognosis appears reasonable and has yielded positive results.<sup>25-27)</sup>

In comparison to previous reports, we observed more pronounced cardiac dysfunction in both the RV and LV. However, our study population had a higher mean age and a greater severity of illness, as evidenced by higher APACHE II and SOFA scores. Considering that cardiac function is influenced by age, comorbidities, and loading condition, cardiac parameters should be more cautiously interpreted. Our study population, elderly patients in acute stage of septic shock with several comorbidities, GLS more sensitively differentiated LV systolic dysfunction than LVEF. Finally, in the follow-up study performed in 7-day survivors, LV and RV function were significantly improved (**Table 3**).

In patients with septic shock, the 7-day mortality predominantly develops in patients who did not survive the initial presentation of shock. Therefore, the strong relationship between parameters such as lactic acid level, VIS, or initial SOFA score and 7-day mortality was predictable. In addition, LV systolic dysfunction with GLS >–16% was significantly related to 7-day mortality, whereas RV dysfunction was not in our study. Because LV systolic function is more directly related to the hemodynamic condition of septic shock than RV function, LV dysfunction at initial evaluation might reflect the severity of septic shock more accurately and show a significant association with the 7-day mortality of patients with septic shock. In contrast, RV has a larger volume, a thinner free wall, a smaller muscle mass compared to LV, and is coupled to the low-pressure and high-compliance pulmonary system.<sup>24)</sup> As a result, RV function was not directly influenced by the hemodynamic changes associated with distributed shock in sepsis and demonstrates a weaker association with 7-day mortality than LV function in this study.

In the follow-up TTE results, RV dysfunction with TAPSE <16 mm was related to the inhospital mortality of 7-day survivors from septic shock. This finding is consistent with previous studies that have reported the relationship of RV dysfunction and short-term mortality in septic shock.<sup>7</sup> Similar findings have been observed in heart failure or cardiogenic shock where biventricular dysfunction is associated with a worse prognosis.<sup>28)29)</sup> However, in our analysis of 7-day survivors from septic shock, LV dysfunction with GLS >-16% in followup study did not show a significant relationship with the in-hospital mortality. Furthermore, as shown in Kaplan-Meier curves in Figure 2, both LV and RV dysfunction identified during initial evaluation did not exhibit significant differences in 7-day survival (log rank, p=0.479 for LV dysfunction and p=0.169 for RV dysfunction). We think that this difference could be attributed to the different time point at which the TTE evaluations were conducted. Although there was a strong correlation between initial and follow-up TTE results, the clinical implication of cardiac dysfunction at a particular point may not remain consistent throughout the course of septic shock. Considering that most of previous studies assessed the relationship between the acute phase TTE results and relatively longer-term outcomes such as 28-day mortality or in-hospital mortality, our research has obvious advantages over previous studies. Higher disease severity and age in our study could potentially explain higher 7-day mortality compared to the previous study. Adoption of different cutoff value of GLS for LV dysfunction also seems to have contributed the disparity from other studies.<sup>21)23)</sup>

Although we excluded patients with structural heart disease, we did not have information on previous cardiac function in all the patients. Patients with undiagnosed cardiac dysfunction could be included in this study. We may have missed patients with less severe shock who recovered quickly from the condition because we only enrolled patients who were admitted to the ICU. This could be the reason for the higher disease severity indicated by the APACHE II score and SOFA score in our patients. In addition, we excluded patients with tachycardia.

Tachycardia may be a more severe form of the disease. We cannot repudiate the possibility of a selection bias. Finally, RV dysfunction can be exaggerated when a patient has a poor pulmonary function, which is followed by increased pulmonary vascular resistance. The poor outcome of patients with RV dysfunction could be augmented by respiratory failure and mechanical ventilation due to lower TAPSE.

We serially evaluated myocardial function and assessed the prognostic implication of SCM on 7-day and in-hospital mortality, considering the characteristics of hemodynamic changes in patients with septic shock. GLS was a good prognostic marker for 7-day mortality in this study, but the relationship between GLS and mortality over an extended period of longer than a week may require more evidence. Instead, for 7-day survivors, TAPSE may be a good prognostic marker, irrespective of LV function. To interpret the relationship between cardiac dysfunction and the prognosis of septic shock, a cautious approach is needed considering the stage of septic shock.

# ACKNOWLEDGMENTS

We would like to acknowledge the contribution of the sonographers who performed the echocardiographic evaluation of the patients; Seon-ju Woo, Hyeon-mi Kim, and Hye-joo Kim.

# SUPPLEMENTARY MATERIAL

#### **Supplementary Figure 1**

(A) GLS and (B) TAPSE of baseline and follow-up study in 7-day survivors in terms of inhospital mortality; TAPSE was significantly different in both baseline and follow-up study between survivor and non-survivor, however, GLS was not different in both evaluations in 7-day survivors with septic shock.

Click here to view

# REFERENCES

- Pulido JN, Afessa B, Masaki M, et al. Clinical spectrum, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock. *Mayo Clin Proc* 2012;87:620-8.
   PUBMED | CROSSREF
- Charpentier J, Luyt CE, Fulla Y, et al. Brain natriuretic peptide: a marker of myocardial dysfunction and prognosis during severe sepsis. *Crit Care Med* 2004;32:660-5.
   PUBMED | CROSSREF
- Ehrman RR, Sullivan AN, Favot MJ, et al. Pathophysiology, echocardiographic evaluation, biomarker findings, and prognostic implications of septic cardiomyopathy: a review of the literature. *Crit Care* 2018;22:112.
   PUBMED | CROSSREF
- Martin L, Derwall M, Al Zoubi S, et al. The septic heart: current understanding of molecular mechanisms and clinical implications. *Chest* 2019;155:427-37.
   PUBMED | CROSSREF
- Lee MT, Jung SY, Baek MS, Shin J, Kim WY. Early vitamin C, hydrocortisone, and thiamine treatment for septic cardiomyopathy: a propensity score analysis. *J Pers Med* 2021;11:610.
   PUBMED | CROSSREF

- Bréchot N, Hajage D, Kimmoun A, et al. Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study. *Lancet* 2020;396:545-52.
   PUBMED | CROSSREF
- Hollenberg SM, Singer M. Pathophysiology of sepsis-induced cardiomyopathy. *Nat Rev Cardiol* 2021;18:424-34.
   PUBMED | CROSSREF
- De Backer D, Cecconi M, Lipman J, et al. Challenges in the management of septic shock: a narrative review. *Intensive Care Med* 2019;45:420-33.
- Kakihana Y, Ito T, Nakahara M, Yamaguchi K, Yasuda T. Sepsis-induced myocardial dysfunction: pathophysiology and management. *J Intensive Care* 2016;4:22.
   PUBMED | CROSSREF
- 10. Malbrain ML, Van Regenmortel N, Saugel B, et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. *Ann Intensive Care* 2018;8:66.

PUBMED | CROSSREF

- Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315:801-10.
   PUBMED | CROSSREF
- Ruopp MD, Perkins NJ, Whitcomb BW, Schisterman EF. Youden Index and optimal cut-point estimated from observations affected by a lower limit of detection. *Biom J* 2008;50:419-30.
   PUBMED | CROSSREF
- Smith LM, Yoza BK, Hoth JJ, McCall CE, Vachharajani V. SIRT1 mediates septic cardiomyopathy in a murine model of polymicrobial sepsis. *Shock* 2020;54:96-101.
   PUBMED | CROSSREF
- Boyd JH, Mathur S, Wang Y, Bateman RM, Walley KR. Toll-like receptor stimulation in cardiomyoctes decreases contractility and initiates an NF-κB dependent inflammatory response. *Cardiovasc Res* 2006;72:384-93.
   PUBMED | CROSSREF
- Haileselassie B, Mukherjee R, Joshi AU, et al. Drp1/Fis1 interaction mediates mitochondrial dysfunction in septic cardiomyopathy. *J Mol Cell Cardiol* 2019;130:160-9.
- 16. Zanotti-Cavazzoni SL, Hollenberg SM. Cardiac dysfunction in severe sepsis and septic shock. *Curr Opin Crit Care* 2009;15:392-7.

#### PUBMED | CROSSREF

- 17. Ince C, Mayeux PR, Nguyen T, et al. The endothelium in sepsis. *Shock* 2016;45:259-70. PUBMED | CROSSREF
- Bazalgette F, Roger C, Louart B, et al. Prognostic value and time course evolution left ventricular global longitudinal strain in septic shock: an exploratory prospective study. *J Clin Monit Comput* 2021;35:1501-10.
   PUBMED | CROSSREF
- Ng PY, Sin WC, Ng AK, Chan WM. Speckle tracking echocardiography in patients with septic shock: a case control study (SPECKSS). *Crit Care* 2016;20:145.
   PUBMED | CROSSREF
- Zhang HM, Wang XT, Zhang LN, et al. Left ventricular longitudinal systolic function in septic shock patients with normal ejection fraction: a case-control study. *Chin Med J (Engl)* 2017;130:1169-74.
   PUBMED | CROSSREF
- Chang WT, Lee WH, Lee WT, et al. Left ventricular global longitudinal strain is independently associated with mortality in septic shock patients. *Intensive Care Med* 2015;41:1791-9.
   PUBMED | CROSSREF
- 22. Sanfilippo F, Corredor C, Fletcher N, et al. Left ventricular systolic function evaluated by strain echocardiography and relationship with mortality in patients with severe sepsis or septic shock: a systematic review and meta-analysis. *Crit Care* 2018;22:183. PUBMED | CROSSREF
- Hai PD, Binh NT, Hien NV, et al. Prognostic role of left ventricular systolic function measured by speckle tracking echocardiography in septic shock. *BioMed Res Int* 2020;2020:7927353.
   PUBMED | CROSSREF
- Sanz J, Sánchez-Quintana D, Bossone E, Bogaard HJ, Naeije R. Anatomy, function, and dysfunction of the right ventricle: JACC state-of-the-art review. J Am Coll Cardiol 2019;73:1463-82.
   PUBMED | CROSSREF

- Lanspa MJ, Cirulis MM, Wiley BM, et al. Right ventricular dysfunction in early sepsis and septic shock. *Chest* 2021;159:1055-63.
   PUBMED | CROSSREF
- 26. Singh RK, Kumar S, Nadig S, et al. Right heart in septic shock: prospective observational study. *J Intensive Care* 2016;4:38.

PUBMED | CROSSREF

- 27. Vallabhajosyula S, Shankar A, Vojjini R, et al. Impact of right ventricular dysfunction on short-term and long-term mortality in sepsis: a meta-analysis of 1,373 patients. *Chest* 2021;159:2254-63.
  PUBMED | CROSSREF
- 28. Carluccio E, Biagioli P, Alunni G, et al. Prognostic value of right ventricular dysfunction in heart failure with reduced ejection fraction: superiority of longitudinal strain over tricuspid annular plane systolic excursion. *Circ Cardiovasc Imaging* 2018;11:e006894.
  PUBMED | CROSSREF
- van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation* 2017;136:e232-68.
   PUBMED | CROSSREF