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Original Research

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

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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,

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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. Seven-day 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,[1)2)] and septic cardiomyopathy (SCM) has been studied in terms of its diverse characteristics, the relationship with mortality,[3)] molecular mechanisms of development,[4)] and therapeutic approaches.[5)6)] However, due to the complex pathophysiology of septic shock, a precise definition of SCM is lacking.[7)]

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.[8)] 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.[9)] As successful resuscitation from the shock is achieved, these hemodynamic conditions gradually resolve, and perturbations of cardiac preload and afterload stabilize.[10)] 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.

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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 ≥2, serum lactate level ≥2 mmol/L, and in need of vasoactive agents despite adequate fluid administration.[11] 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, ≥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 vasoactive-inotropic 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 mortaltiy.[12]

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 χ^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).

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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

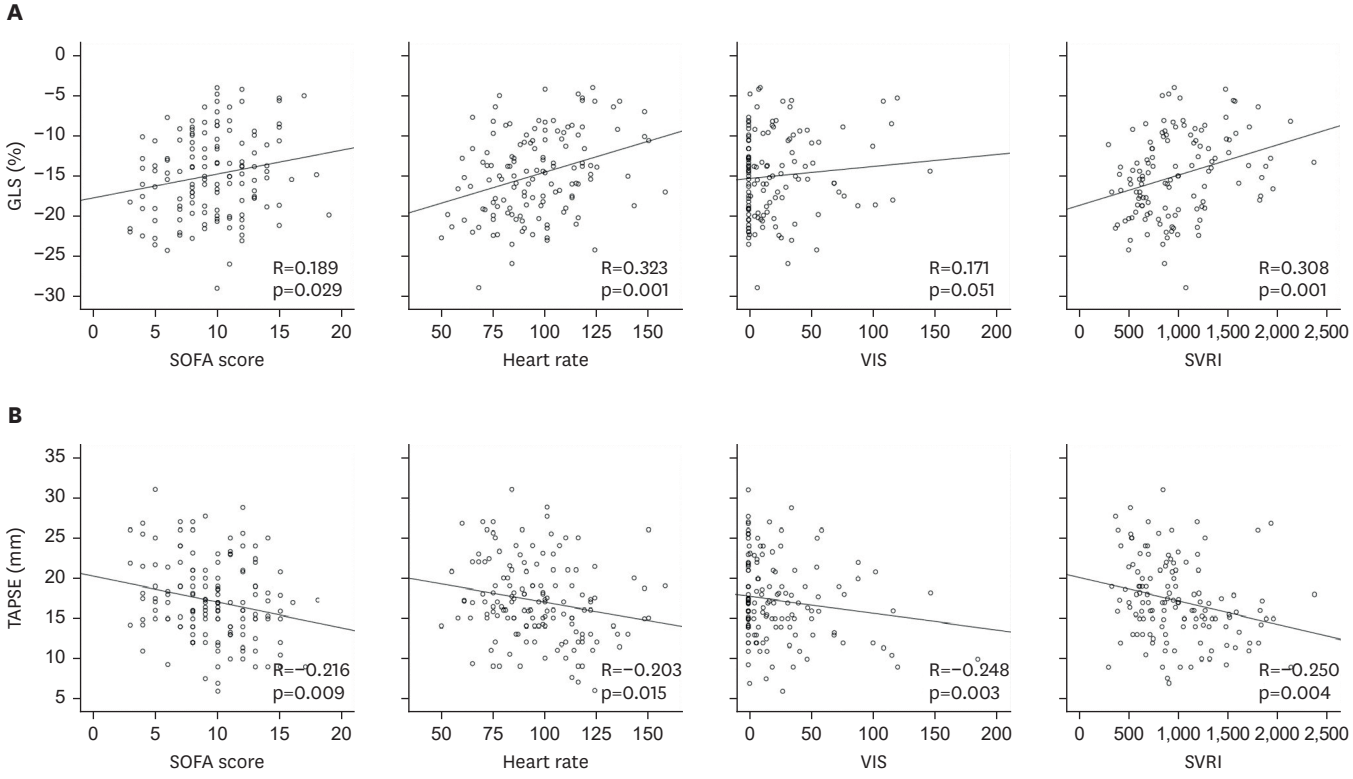

Figure 1. The relationship of hemodynamic parameters and disease severity scoring systems to (A) GLS and (B) TAPSE in scattered diagram.
GLS = global longitudinal strain; SOFA = Sequential Organ Failure Assessment; VIS = vasoactive-inotropic score; SVRI = systemic vascular resistance index; TAPSE = tricuspid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

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

	All patients (n=162)	Seven-day survivor (n=138)	Seven-day non-survivor (n=24)	p value
Age (years)	70.7±13.4	70.3±13.5	72.5±13.1	0.461
Male	83 (51.55)	73 (53.3)	10 (41.7)	0.378
Body surface area (m^2)	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	5.17±1.71	0.038
APACHE II				<0.001
Mean±SD	30.60±9.20	29.38±8.70	39.32±7.70	
Median (IQR)	31 (23–38)	29 (22–36)	41 (33–44)	
SOFA score	9.51±3.24	9.07±2.99	12.04±3.56	<0.001
Vasoactive-inotropic score				0.001
Mean±SD	29.90±62.40	20.09±31.86	88.41±132.99	
Median (IQR)	9.00 (0–34.25)	6.98 (0–26.40)	40.13 (15.0–88.0)	
ICU length of stay (days)				0.002
Mean±SD	13.11±17.38	14.85±18.29	3.17±1.49	
Median (IQR)	7 (4–14)	9 (5–16)	3 (2–4.75)	
Hospital length of stay (days)				<0.001
Mean±SD	29.19±36.08	33.93±37.33	3.17±1.49	
Median (IQR)	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 (55.8)	17 (70.8)	0.174
Renal replacement therapy	35 (21.6)	28 (20.2)	7 (29.2)	0.420
Lactic acid				0.001
Mean±SD	6.18±5.21	5.34±3.96	10.86±8.27	
Median (IQR)	4.3 (2.80–7.55)	4.0 (2.7–6.6)	8.9 (5.15–17.08)	
C-reactive protein (mg/dL)				0.002
Mean±SD	17.00±12.19	18.26±9.77	12.06±10.50	
Median (IQR)	16.40 (6.00–25.91)	17.77 (7.91–27.69)	7.23 (1.44–19.44)	
Procalcitonin (ng/mL)				0.578
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	22.5±32.9	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	6,565.5±8,841.5	6,883.8±7,907.1	0.919
Cause of infection				0.238
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				0.054
Mean±SD	55.20±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)	
E/e'	13.23±13.84	12.05±5.35	12.27±4.97	0.869
GLS				<0.001
Mean±SD	−14.90±5.21	−15.54±5.03	−10.57±4.32	
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±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%	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	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/m^2)	3.06±2.10	2.97±0.98	2.53±1.09	0.207
Systemic vascular resistance (dynes sec/cm^5)	1,556.23±650.98	1,537.12±646.94	1,714.79±597.49	0.088
Systemic vascular resistance index (dynes sec/cm^5m^2)	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)	

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; SOFA = Sequential Organ Failure Assessment; TAPSE = tricuspid annular plane systolic excursion.

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Table 2. Univariate and multivariate logistic regression analysis for 7-day mortality in patients with septic shock

	Univariate logistic regression analysis			Multivariate 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 ≤–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. ≥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**).

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

	Initial evaluation				Follow-up evaluation				p value*
	Seven-day survivor (n=138)	Survivor (n=91)	Non-survivor (n=41)	p value	Seven-day survivor (n=138)	Survivor (n=91)	Non-survivor (n=41)	p value	
LV EDV (mL)	61.69±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
LV ESV (mL)	28.20±13.93	26.67±11.80	27.03±15.77	0.883	25.85±14.57	26.08±15.36	24.53±12.38	0.651	0.078
LVEF (%)	55.64±12.74	57.40±11.89	54.13±13.48	0.159	61.05±8.29	60.91±8.30	61.94±8.56	0.598	<0.001
E/e'	12.06±5.33	12.19±5.64	11.71±4.60	0.659	11.77±5.22	11.97±5.66	11.08±3.11	0.346	0.433
GLS (%)	−15.58±4.77	−16.12±5.00	−14.24±4.94	0.064	−17.26±4.45	−16.96±4.22	−17.59±5.20	0.569	0.005
TRVmax (m/sec)	2.75±0.45	2.72±0.45	2.71±0.53	0.861	2.70±0.49	2.68±0.45	2.79±0.57	0.323	0.372
TAPSE (mm)	17.61±4.87	18.60±4.72	15.55±4.57	0.001	19.16±5.35	19.89±5.04	16.94±5.29	0.015	0.006
CO (L/min)	5.35±4.64	5.31±4.51	4.49±1.66	0.271	3.06±2.10	4.81±1.51	4.93±1.67	0.749	0.308
COI (L/min/m^2)	3.29±2.64	3.26±2.56	2.88±1.07	0.388	2.99±0.91	2.98±0.88	3.05±0.96	0.739	0.325
SVR (dynes sec/cm^5)				0.946				0.558	0.008
Mean±SD	1,511.95±599.77	1,525.89±649.6	1,534.48±684.74		1,232.96±637.66	1,247.90±609.20	1,369.28±982.60		
Median (IQR)	1,429.63 (1,081.34–1,828.76)	1,432.86 (1,112.06–1,795.21)	1,426.40 (971.19–1,945.91)		1,141.33 (722.13–1,381.88)	1,157.25 (931.28–1,358.16)	1,107.28 (819.35–1,581.79)		
SVRI (dynes sec/cm^{5}m^2)				0.831				0.781	0.007
Mean±SD	2,434.61±1,072.59	2,448.13±1,069.48	2,036.42±1,055.98		2,059.79±1,134.83	2,036.42±1,055.98	2,131.46±1,388.45		
Median (IQR)	2,240.80 (1,724.12–2,752.68)	2,237.07 (1,839.22–2,679.47)	2,244.54 (1,497.06–2,877.50)		1,832.93 (1,358.97–2,329.81)	1,878.65 (1,497.84–2,325.99)	1,832.93 (1,278.82–2,653.03)		
VIS				0.035				0.002	<0.001
Mean±SD	18.94±29.14	15.61±26.08	30.56±40.93		4.18±15.18	1.38±4.76	11.33±26.62		
Median (IQR)	6.98 (0.00–26.43)	6.72 (0.00–19.83)	10.71 (0.00–55.47)		0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–10.97)		

Values are presented as mean±SD or median (interquartile range [IQR]).
CO = cardiac output; COI = cardiac output index; EDV = end diastolic volume; ESV = end systolic volume; GLS = global longitudinal strain; LV = left ventricular; LVEF = left ventricular ejection fraction; SD = standard deviation; SVR = systemic vascular resistance; SVRI = systemic vascular resistance index; TAPSE = tricuspid annular plane systolic excursion; VIS = vasoactive-inotropic score.
*The p value for the comparison of initial study and follow-up evaluation of all 7-day survivors using paired t-test.

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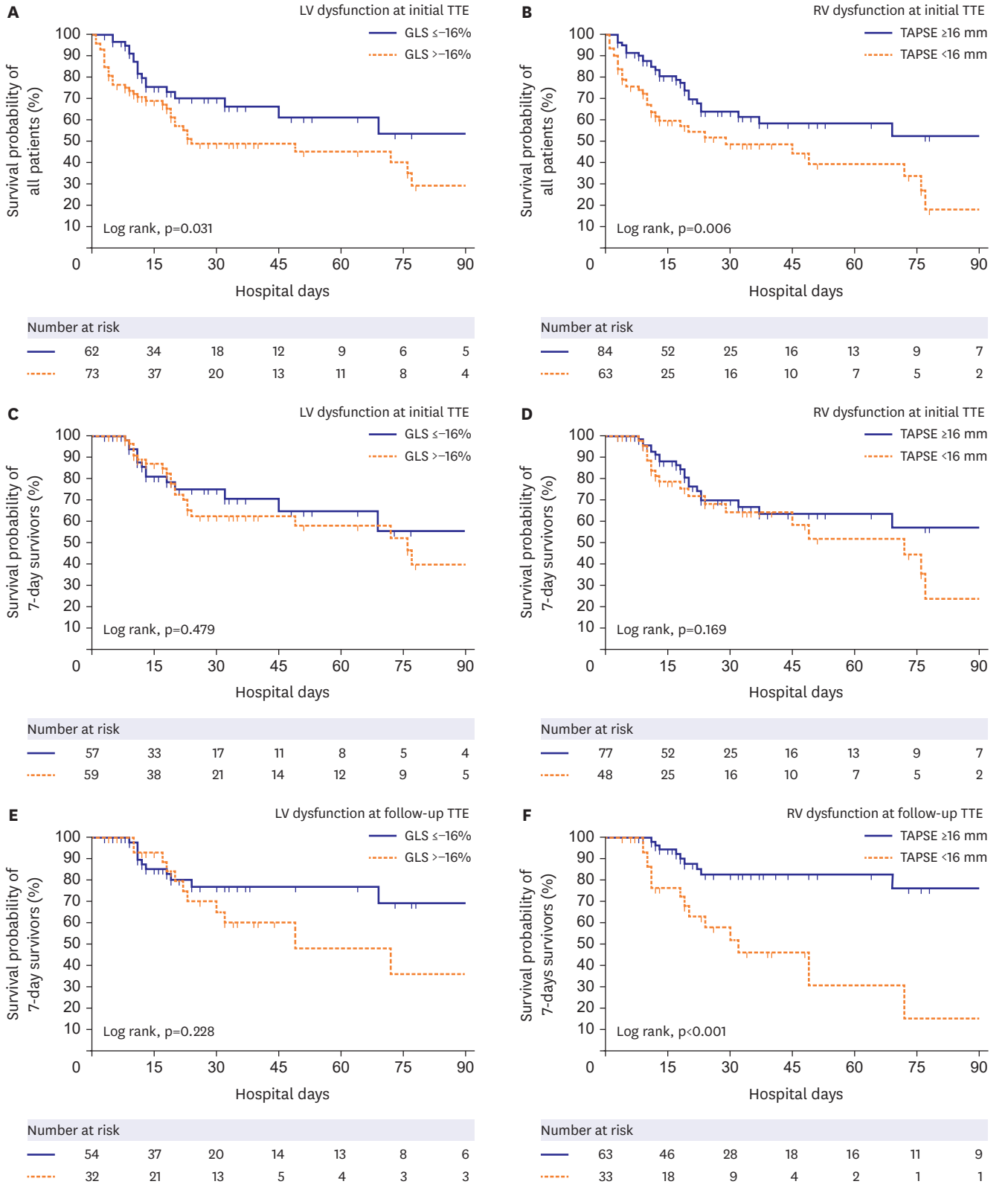

Figure 2. Kaplan-Meier curves for the in-hospital mortality by GLS ≤–16% and >–16% and by TAPSE ≥16 mm and <16 mm in initial and follow-up TTE; (A, B) the curves of all patients evaluated by initial TTE evaluation; (C, D) curves of 7-day survivors by initial TTE evaluation; (E, F) curves of 7-day survivors by follow-up TTE evaluation.
GLS = global longitudinal strain; LV = left ventricular; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TTE = transthoracic echocardiography.

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Table 4. Univariate and multivariate logistic regression analysis for in-hospital mortality in 7-day survivors of patients with septic shock

	Univariate logistic regression analysis			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.[13)14)] 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.[17)] 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.[9)] 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[18-20)] and resulted in a more consistent relationship between LV systolic function and patient mortality than LVEF.[21-23)] 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.[24)] Therefore, the assessment of RV function in relation to patient prognosis appears reasonable and has yielded positive results.[25-27)]

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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.[24] 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 in-hospital 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.[7] Similar findings have been observed in heart failure or cardiogenic shock where biventricular dysfunction is associated with a worse prognosis.[28][29] However, in our analysis of 7-day survivors from septic shock, LV dysfunction with GLS >–16% in follow-up 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.[21][23]

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.

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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.

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SUPPLEMENTARY MATERIAL

Supplementary Figure 1

(A) GLS and (B) TAPSE of baseline and follow-up study in 7-day survivors in terms of in-hospital 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.

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