Diagnostic value of tissue motion annular displacement in sepsis-induced cardiomyopathy: a single-center retrospective observational study

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Abstract

Background

Currently, there is no formal diagnostic criterion for sepsis-induced cardiomyopathy (SICM). The classic approach has been to use left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) to define SICM. In this regard, tissue motion annular displacement (TMAD) is a novel speckle tracking indicator to quickly assess LV longitudinal systolic function. This study aimed to evaluate the feasibility and application value of TMAD in the diagnosis of SICM in septic patients.

Methods

We conducted a single-center retrospective observational study in sepsis or septic shock patients who underwent echocardiography examination within the first 24h after admission. Basic clinical information and conventional echocardiographic data were collected. Based on speckle tracking echocardiography (STE), GLS and TMAD were respectively performed offline. The correlations between TMAD and other LV systolic function parameters, as well as the diagnostic value of TMAD for SICM, were assessed. Data of 28d and in-hospital mortality were compared between SICM and non-SICM patients.

Results

A total of 143 patients were enrolled in this study. The incidence of SICM according to GLS or TMAD criteria was significantly higher than that according to LVEF criteria (32.9% vs. 18.2%, $p = 0.006$; 38.5% vs. 18.2%, $p < 0.001$). The 28d and in-hospital mortality of SICM patients were significantly higher than the non-SICM patients according to any of the diagnostic criteria (all $p < 0.05$). Significant correlations between TMAD and other LV systolic function echocardiographic parameters, including LVEF, GLS, mitral annular plane systolic excursion (MAPSE), and maximal lateral systolic mitral annular tissue velocity (MA Smax), were detected (all $p < 0.001$). According to the AUROC value, TMADMid had an excellent diagnostic value for SICM (AUROC > 0.9). Compared with LVEF and GLS, TMAD had the highest intra-observer and inter-observer reliability. The mean time for off-line analyses with TMAD was significantly shorter than that with LVEF or GLS ($p < 0.05$).

Conclusion

STE-based TMAD is a feasible, reliable, and time-saving option to assess the LV systolic function. Overall, this approach shows an excellent diagnostic value for SICM in septic patients.

Introduction

Sepsis is defined as a life-threatening organ dysfunction due to a dysregulated immune response to an infection. Moreover, it is the most common cause of organ dysfunction and even death in critically ill patients[1-3]. Sepsis-induced cardiomyopathy (SICM), initially described in the 1980s, is generally defined as an acute and reversible cardiac dysfunction that involves decreased left and/or right ventricular systolic and/or diastolic function, LV dilatation, and absence of acute coronary syndrome[4]. SICM is commonly found in patients with sepsis, especially those with septic shock[5]. Due to the lack of formal diagnostic criteria, the reported incidence of SICM ranges widely from 10% to 70% [6]. Notably, mortality among septic patients with SICM is 2~3 times higher than those without SICM[5,7,8].

Echocardiography is considered the most important method for the diagnosis of SICM. Every patient with unstable hemodynamics is suggested to receive echocardiography examination[9,10]. Left ventricular ejection fraction (LVEF) is the conventional indicator when evaluating LV systolic function. An LVEF onset of less than 50% is often considered as the diagnostic criteria for SICM[11-14]. In this regard, speckle tracking echocardiography (STE) is an angle-independent and semi-automatic method for LV strain measurements[15,16]. STE assesses the cardiac function by tracking the displacement of groups of acoustic greyscale “speckles” frame by frame through the whole myocardium[17]. According to its working principle, STE directly measures the myocardium deformation; therefore, it is less affected by the LV loading conditions and myocardial compliance. Global longitudinal strain (GLS) has demonstrated more sensitivity in the early recognition and diagnosis of SICM[18-20]. Similar to LVEF, there is no formal GLS diagnostic criterion for SICM, but a level of more than -13% is often considered SICM positive[18].

LVEF and GLS measurements require a clear tracing of the endocardium; thus, high-quality echocardiographic imaging is indispensable. However, this is challenging because patients are instructed to take the left lateral decubitus position (the routine ultrasound examination position), which is difficult to achieve for critically ill patients. For instance, patients with unstable hemodynamics, restriction of surgical drainage tubes or organ support devices, such as continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO). Severe cases such as those who have a history of COPD or are receiving respiratory support through mechanical ventilation are prevented from obtaining sharp echocardiographic images.

Tissue motion annular displacement (TMAD) is a novel speckle tracking indicator that quickly assesses the LV longitudinal systolic function[21-23]. According to the TMAD working principle, the only measurement requirement is to track the displacement of the mitral annulus and the apex of the left ventricle instead of the whole LV endocardium. Therefore, there are fewer exigencies in the quality of the echocardiographic image, which can be performed more quickly by eliminating the need of tracing and adjusting the endocardium[21,24,25]. TMAD has become a valuable tool to evaluate cardiovascular diseases; in particular, to perform early diagnosis and assessment of therapeutic efficacy[26,27]. However, the application of TMAD in SICM is rarely reported. Considering the above, we inferred that this relatively simple index may also be useful for the assessment of LV longitudinal systolic function in septic

patients. This study aimed to evaluate the feasibility and the application value of TMAD in the diagnosis of SICM in septic patients.

Method

Study population

A single-center retrospective observational study was conducted in Zhongshan Hospital Fudan University. Patients who were admitted to the surgical intensive care unit (SICU) from March 2019 to July 2021 and met the following criteria were enrolled as study subjects: (1) age ≥ 18 years; (2) diagnosis of sepsis or septic shock; (3) underwent echocardiography examination within the first 24h after admission to SICU. Those who met any of the following criteria were excluded: (1) poor echocardiographic image quality or incomplete echocardiographic data; (2) incomplete clinical data; (3) history of valvular heart disease; (4) history of congestive heart failure (CHF); (5) holder of cardiac implanted device; (6) atrial fibrillation; (7) refusal to participate in the study; (8) further reasons that implied unsuitability. This project was approved by the Ethics Committee of the Zhongshan Hospital Fudan University (Approval No: B2021-501R). All participants signed informed consent.

Clinical and laboratory data collection

Basic, clinical, and laboratory data from all participants were collected within the first 24 hours after admission to SICU. Basic information from all participants was collected from the electronic medical record system, including age, gender, body mass index (BMI), comorbidity, medication history, septic source, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and the Sequential Organ Failure Assessment (SOFA) score. Clinical information comprised heart rate, mean arterial pressure, central venous pressure (CVP), and net fluid balance. Laboratory data included hemoglobin, bilirubin, serum albumin, creatinine clearance, blood urea nitrogen, cardiac troponin T (cTnT), N-terminal pro brain natriuretic peptide (NT-proBNP), creatine kinase-MB (CK-MB), lactate, and arterial blood gases.

Conventional Echocardiographic data

All conventional echocardiography examinations in our study were conducted using a CX50 CompactXtreme Ultrasound System (Philips, MA, USA) with a 1–5 MHz-phased array transducer. The recorded parameters included: left atrial dimension, LV end-systolic and end-diastolic volume (LVESV / LVEDV), left ventricular ejection fraction (LVEF), velocity-time integral of LV outflow tract (LVOT VTI), stroke volume (SV), cardiac output (CO), early (E) and late (A) diastolic trans-mitral inflow velocity, early (e') and late (a') lateral diastolic mitral annular tissue velocity, maximal lateral systolic mitral annular tissue velocity (MA Smax), mitral annular plane systolic excursion (MAPSE), tricuspid annular plane systolic excursion (TAPSE), pulmonary arterial systolic pressure (PASP), inferior vena cava (IVC) diameter, and IVC variation. LV volumes and LVEF were calculated by the modified biplanar Simpson method. E and A velocities were measured using pulsed wave (PW) Doppler at the tip of the mitral valve, and e' and

a’ tissue velocities were measured using PW tissue Doppler in the apical four-chamber view. E/A ratio and E/e’ ratios were calculated. LVEF < 50% was considered as a kind of SICM diagnostic criteria[13,14].

Speckle tracking echocardiographic data

STE analysis was performed offline and averaged by two independent investigators who were trained by an echocardiography software engineer. During the echocardiographic analysis, the investigators were blinded to the patients’ clinical conditions. STE analysis was performed by the QLAB software, version 9.0 (Philips Healthcare, MA, USA).

GLS

To distinguish the different phases of the cardiac cycle, the opening and closing times of the mitral and aortic valves were derived from the electrocardiograph. For GLS evaluation, the semi-automated CMQ package of the QLAB software was used along the apical longitudinal axis of the left ventricle in four-, two-, and three-chamber views. When the system focused on two mitral annular and apical points of the three left ventricle longitudinal sections, the software automatically tracked the speckles of the endocardial border throughout the cardiac cycle. Any part of the myocardium that seemed imprecisely tracked was manually and carefully modified by the investigators. In each myocardial segment, the strain was measured, and GLS was calculated by averaging the peak strain values of the whole 17 segments during systole (Fig. 1A). GLS > -13% was considered as a kind of SICM diagnostic criteria[18].

TMAD

TMAD was measured offline in the apical four-chamber views using the TMAD package of the QLAB software. To assess TMAD, three regions of interest (ROIs) were selected: the septal (TMAD1) and lateral (TMAD2) areas of the mitral annulus, as well as the apex of the LV. The midpoint (TMADMid) between the two annuli ROIs was automatically detected after setting these three ROIs. Then, tracking was automatically performed frame by frame and the average of the base-to-apical displacement of the two mitral annulus ROIs was calculated in millimeters. Midpoint displacement was also calculated in millimeters, and a percentage value of the midpoint displacement in relation to the total length of the left ventricle was calculated (%TMAD) (Fig. 1B). For the TMAD technique, the only manual procedure was setting the ROIs. TMADMid < 10 mm was considered as a kind of SICM diagnostic criteria[28]. All echocardiographic data were recorded over three consecutive cardiac cycles and then averaged.

Intra-observer and inter-observer variability

To ensure the accuracy and repeatability of the speckle tracking echocardiographic data, a random sample of 20 echocardiographic examinations (LVEF, TMAD, and GLS) were reassessed by the same investigator with a minimum interval of 4 weeks from the first evaluation as the intra-observer variability. Then, to calculate inter-observer variability, the same 20 samples were examined by another investigator who was blinded to the results of the first investigator. Intra- and inter-observer agreement was evaluated

using the intraclass correlation coefficient (ICC), which ranged from +1 (100% agreement) to −1 (100% disagreement). ICC scores of 0.75 or higher were considered as indicators of a quality control criterion with acceptable reliability. The duration of the LVEF, GLS, and TMAD offline analyses, respectively, was also recorded for these 20 echocardiographic examinations.

Study endpoints

All recruited patients were followed up retrospectively from admission to discharge or until the 28th day, whichever occurred later. The primary endpoint of the study was the 28d mortality according to different diagnostic criteria. The secondary endpoint of the study was in-hospital mortality according to different diagnostic criteria, the lengths of ICU / hospital stay, and the duration of mechanical ventilation among SICM or non-SICM patients according to TMAD criteria.

Statistics

Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as frequency and percentage. Comparisons between normally distributed continuous variables were performed using the Student's t-test, whereas non-normally distributed variables were analyzed with the Wilcoxon signed-rank test. Chi-squared test or Fisher's exact test was used for categorical variables. The relationships between the selected variables were assessed by Pearson's correlation analysis. Kaplan-Meier curves with log-rank tests were used to compare the 28d and in-hospital mortality according to the presence of SICM. The diagnostic values of TMAD were obtained by calculating the area under the receiver operating characteristic curves (AUROC). AUROC values were interpreted as follows: <0.70 = poor; 0.70 to 0.80 = fair; 0.80 to 0.90 = good; >0.90 = excellent. The optimal cutoff value of TMAD was determined according to the Youden index. All statistical analysis was conducted using SPSS 19.0 (IBM, Armonk, NY, USA). The graphic presentation was created by GraphPad Prism 9.0 (GraphPad Software, La Jolla, CA, USA). A *p*-value < 0.05 was considered statistically significant.

Results

Basic Clinical Characteristics

From March 2019 to July 2021, 4865 critically ill adult patients were consecutively admitted to SICU, and 656 of them were diagnosed with sepsis. Among these patients, 358 completed echocardiography examinations within the first 24h after admission to SICU. Of them, 215 patients were excluded mainly for the following reasons: poor echocardiographic image quality (n=87), incomplete echocardiographic data (n=21), incomplete clinical data (n=36), history of valvular heart disease (n=22), history of congestive heart failure (n=20), holder of implanted devices (n=12), atrial fibrillation (n=10), refusal to participate (n=4), and other reasons (n=3). Among the 87 patients with poor echocardiographic image quality, 35 patients had indistinct imaging of the entire endocardium (LVEF, GLS, and TMAD could not be measured accurately), and the other 52 patients had legible imaging of the apex and mitral annulus but indistinct imaging of the other endocardium parts, especially the lateral wall of the LV (TMAD could be measured,

but LVEF and GLS could not be assessed) (Fig. 2). The acquisition ratio of TMAD was significantly higher than that of LVEF and GLS (84.8% vs. 62.2%, $p < 0.001$). Finally, 143 patients were included. The flow diagram of the study is shown in Fig. 3. Of all participants, 94 patients (65.7%) were male, mean age was 66.3 ± 16.6 years old, BMI was 22.9 ± 3.2, APACHE II score was 17.1 ± 6.2, and SOFA score was 6.8 ± 2.7. Baseline and clinical information of the patients were summarized in Table 1.

Incidence of SICM and survival analysis according to three different diagnostic criteria

The incidence of SICM in this study was 18.2%, 32.9%, and 38.5% according to the LVEF, GLS, and TMADMid criteria, respectively. When considering the speckle tracking technology criteria (GLS or TMAD), the incidence of SICM was significantly higher than that according to LVEF criteria (32.9% vs. 18.2%, $p = 0.006$; 38.5% vs. 18.2%, $p < 0.001$) (Fig. 4). The 28d mortality in the SICM group was 34.6% (LVEF criteria), 27.7% (GLS criteria) and 29.1% (TMADMid criteria), respectively, while the in-hospital mortality in the SICM group was 42.3% (LVEF criteria), 36.2% (GLS criteria) and 36.4% (TMADMid criteria), respectively. Kaplan-Meier curves demonstrated that, compared to non-SICM patients, SICM positives had significantly lower 28d ($p = 0.011$, LVEF criteria; $p = 0.031$, GLS criteria; $p = 0.0064$, TMADMid criteria) and in-hospital survival rates ($p = 0.0097$, LVEF criteria; $p = 0.0157$, GLS criteria; $p = 0.0061$, TMADMid criteria), regardless of the diagnostic criteria (Fig. 5).

Clinical information of SICM and non-SICM patients

Conventional and speckle tracking echocardiographic data of all patients were collected. According to the TMADMid criteria, all enrolled patients were divided into SICM or non-SICM groups. No significant differences were found in the APACHE II score, comorbidity, medication history, and sepsis source between the SICM and non-SICM. However, the SOFA score of the SICM group was significantly higher than that of the non-SICM group (7.8 ± 3.1 vs 6.1 ± 2.2, $p < 0.001$), and the mortality was significantly higher in those with SICM than in non-SICM patients (36.4% vs. 17.0%, $p = 0.016$). According to the laboratory results, patients in the SICM group had significantly higher cTnT, NT-proBNP, and CK-MB within the first 24 hours after admission, when compared to the non-SICM group (all $p < 0.05$). There was no significant difference in the length of ICU or hospital stay, nor in the duration of mechanical ventilation between the two groups (Table 1).

Echocardiographic data among patients with abnormal TMAD

All the echocardiogram data of SICM and non-SICM patients (TMADMid criteria) are shown in Table 1. LVEF, MAPSE, TAPSE, a', MA Smax, LVOT VTI, SV, CO, TMAD 1, TMAD 2, TMADMid, and %TMAD were significantly lower in the SICM group than in the non-SICM group (all $p < 0.05$). Meanwhile, LVESV and GLS in those with SICM were significantly higher than in non-SICM patients (all $p < 0.05$).

On the other hand, correlations between TMAD and other LV systolic function echocardiographic parameters were analyzed. Positive correlations were detected between TMAD and LVEF, MAPSE, and MA

Smax, respectively, while a negative correlation between TMAD and GLS was confirmed (all $p < 0.001$) (Fig. 6).

Furthermore, the diagnostic value of TMAD for SICM was evaluated using LVEF and GLS, consecutively, as diagnostic “golden standards”. According to the “LVEF standard”, the AUROC values of TMAD1, TMAD2, TMADMid, and %TMAD were 0.893, 0.887, 0.902, and 0.887 respectively. Based on the “GLS standard”, the AUROC values of TMAD1, TMAD2, TMADMid, and %TMAD were 0.885, 0.884, 0.911, and 0.908 respectively (Fig. 7). The cutoff value, sensitivity and specificity of each TMAD parameter were stated in Table 2.

Intra- and inter-observer variability

Adequateintra- and inter-observer reliabilities for LVEF, GLS, and TMAD were detected (all ICC > 0.75). Particularly, TMAD had the highest ICC value when compared to LVEF or GLS (Table 3). Regarding the required time for the LVEF, GLS, and TMAD offline analyses, respectively, the mean single measurement time for TMAD was significantly shorter than that for LVEF or GLS (40.5s ± 9.3s vs. 82.6s ± 15.2s, $p < 0.001$; 40.5s ± 9.3s vs. 70.2s ± 11.3s, $p = 0.006$, respectively).

Discussion

In this study, the incidence of SICM after assessment with the speckle tracking technology criteria (GLS or TMAD) was found to be higher than that according to the LVEF criteria. Regardless of the diagnostic principles, mortality among SICM patients was significantly superior versus the non-SICM cases. TMAD not only had significant correlations with conventional LV systolic function echocardiographic parameters, but also showed high diagnostic value for SICM. Compared with GLS and LVEF, TMAD examination took less time and demonstrated excellent intra- and inter-observer reliability.

Nowadays, SICM diagnosis does not count with a golden standard, which results in the use of different diagnostic criteria among researchers and a wide variation in the SICM incidence reports. In our study, this incidence, for all three diagnostic criteria, was about 20-40%, and thus similar to most literature reports[11,19,28]. The incidence of SICM, based on the LVEF criteria, was significantly lower than that based on GLS or TMAD, which might be related to the superiority of STE in detecting subclinical cardiac insufficiency[29]. Unequivocally, the mortality of patients with SICM was significantly higher than that of non-SICM patients, which was reported as high as 70-90% in some literature[7,8]. Consistent with previous investigations, SICM mortality in our study was significantly higher (about two-fold) than that of non-SICM patients.

As an indispensable hemodynamic diagnostic tool in the field of critical care medicine, echocardiography plays an important role in the evaluation of LV systolic and/or diastolic function, as well as in volume management. In recent years, there has been an increased interest in applying STE to characterize the LV function in sepsis[18,19,30-32]. The strain imaging technique is based on regional myocardial deformation,

and GLS, the mean longitudinal strain value from each segment of the LV [33], is the most frequently used strain parameter. In this regard, Chang WT et al found that the LVEF outcome was similar between survivors and deceased, while GLS values were significantly better in those survivors, with an even greater difference in ICU mortality[18]. Nevertheless, in clinical practice, we have indeed found that it is difficult to obtain clear echocardiographic images from critically ill patients; for instance, those with primary diseases like COPD, recent thoracic surgery, limited body position, mechanical ventilation, and many other conditions. Poor continuity in endocardial imaging causes inaccuracy in the LVEF and GLS measurements, which is, in turn, manifested in poor intra- and inter-observer repeatability. As mentioned above, a large proportion of patients in our study were excluded for the poor quality of their echocardiographic images, and especially for the poor endocardium continuity.

The STE-based TMAD is a novel method for assessing LV longitudinal systolic function[34] and a technology with several advantages. First and foremost, TMAD is less dependent on echocardiographic image quality. Compared with LVEF and GLS, the TMAD feasibility is higher, because its measurement process only requires locating the mitral annulus and the cardiac apex, instead of tracing the whole distinct endocardium border[22]. Therefore, less perfect echocardiographic image quality is acceptable. In this study, a considerable number of patients were excluded because they counted with echocardiographic images of poor quality; in most cases, with discontinuous endocardium, which entailed the inability to complete LVEF or GLS measurement. This deficiency can be effectively circumvented by the TMAD technology. Second, TMAD assessment is easy, quick, and angle independent. According to the semi-automatically detection principle, TMAD measurement omits the whole endocardium tracing step, which allows a quick completion and has a good correlation with LVEF[21,34,35]. In our study, we confirmed that the required time for TMAD offline analyses was significantly shorter than that for LVEF or GLS. Third, TMAD presents significant correlations with many conventional LV systolic function parameters. In both animal and human researches, TMAD has been significantly correlated with LVEF and GLS[36-38]. Consistent with previous literature, we detected significant correlations between TMAD and LVEF, GLS, MAPSE, and MA Smax, respectively. According to the AUROC value, TMADMid had an excellent diagnostic value for SICM, regardless of the “golden standard” employed (LVEF or GLS). Fourth, the TMAD examination is highly repeatable. Buss et al reported that TMAD has a relatively low inter- and intra-observer variability[21], an aspect confirmed in the present study. Here, both intra- and inter-observer ICCs of TMAD were considerably high, and superior to that of LVEF and GLS. These advantages support the feasibility and reliability of TMAD for the accurate assessment of the LV longitudinal systolic function in septic patients for daily clinical practice. Furthermore, Zaky A et al found that TMAD was significantly correlated with the LV diastolic function, a result that was not confirmed in our study[28].

In this work, four TMAD parameters were collected. Among them, TMADMid represented the midpoint displacement between TMAD1 and TMAD2, which better reflected the global systolic function of LV. Additionally, %TMAD represented the percentage value of TMADMid in relation to the total length of the LV and was supposed to reduce the bias caused by the different LV sizes in different individuals.

According to the results, TMADMid exhibited the highest diagnostic value for SICM among the four TMAD parameters. However, the other three TMAD parameters also evidenced good to excellent diagnostic value according to the AUROC values. Therefore, we believe that the overall TMAD parameters had promising prospects for the diagnosis of SICM. In particular, TMADMid was the optimal choice.

Several limitations in this study should be considered. First, it was a retrospective single-center study with a relatively limited sample size. Several patients were excluded due to poor echocardiographic image quality or incomplete echocardiographic data, which might affect the results. Second, the possible effect of the annulus calcification on TMAD measurement was not assessed. Gökdeniz T et al found that GLS is correlated with the presence and severity of mitral annulus calcification[39]. In our study, the degree of mitral annulus calcification was also not assessed systematically, which might influence TMAD values in some patients. On the other hand, according to the excluding criteria, no patients with valvular heart disease were included. Third, right ventricular STE was not performed while SICM might present as right ventricular insufficiency. We reported here that TAPSE in the SICM group was significantly lower than in the non-SICM group; however, the right ventricular longitudinal strain and the TMAD values of the tricuspid annulus were not collected. Therefore, additional well-designed prospective studies with a larger sample size and a comprehensive STE that includes both ventricles are expected to validate the present results in the future.

Conclusion

SICM is a common disease among septic patients and reports significantly high mortality. In addition to LVEF and GLS, STE-based TMAD is a feasible, reliable, and less time-consuming option for assessing the LV systolic function. Finally, STE-based TMAD evidences a high diagnostic value for SICM in septic patients.

Abbreviations

SICM, sepsis-induced cardiomyopathy; GLS, global longitudinal strain; LVEF, left ventricle ejection fraction; STE, speckle tracking echocardiography; TMAD1, septal tissue motion annular displacement; TMAD2, lateral tissue motion annular displacement; TMADMid, midpoint tissue motion annular displacement; %TMAD, percentage value of the midpoint displacement in relation to the total length of the left ventricle; BMI, body mass index; APACHE II, acute physiology and chronic health evaluation II ; SOFA, sequential organ failure assessment; COPD, chronic obstructive pulmonary disease; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; ICU, intensive care unit; MV, mechanical ventilation; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; Hb, hemoglobin; TBil, total bilirubin; Ccr, creatinine clearance rate; Bun, blood urea nitrogen; cTnT, cardiac troponin T; NT-proBNP, N-terminal pro-B type natriuretic peptide; CK-MB, creatine kinase-MB; BE, base excess; LA, left atrium; LVEDV, left ventricle end diastolic volume; LVESV, left ventricle end systolic volume; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic

excursion; PASP, pulmonary arterial systolic pressure; E, early diastolic trans-mitral inflow velocity; A, late diastolic trans-mitral inflow velocity; e', early lateral diastolic mitral annular tissue velocity; a', late lateral diastolic mitral annular tissue velocity; E/A, ratio of E and A; E/e', ratio of E and e'; MA Smax, maximal lateral systolic mitral annular tissue velocity; IVC, inferior Vena Cava; LVOT VTI, left ventricular outflow tract velocity time integral; SV, stroke volume; CO, cardiac output; ICC, intraclass correlation coefficient.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Zhongshan Hospital Fudan University (Approval No: B2021-501R). All participants have signed informed consent.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this manuscript. The corresponding author may provide specified analyses or fully de-identified parts of the dataset upon reasonable request.

Competing interests

All authors declare that they have no financial, ethical, or other conflicts of interest.

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Authors' contributions

Jieqiong Song contributed to acquisition and interpretation of data, and drafting of the manuscript; Yao Yao contributed to acquisition of data, writing—review, editing and revision of the manuscript; Ming Zhong contributed to the design and implementation of the study; Shilong Lin and Yizhou He participated in the acquisition and interpretation of data and statistical analysis. Duming Zhu coordinated the study, supervised its implementation, and revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics, clinical information and echocardiogram data of the patients

	All patients (n=143)		SICM (n=55)		non-SICM (n=88)		*p*-value
	Mean	SD	Mean	SD	Mean	SD	
Basic characteristic information							
Age (yrs)	66.3	16.6	66.7	18	66	15.7	0.823
Gender (male, %)	94 (65.7%)		36 (65.5%)		58 (65.9%)		0.956
BMI (kg/m2)	22.9	3.2	23	2.9	22.9	3.5	0.86
APACHE II score	17.1	6.2	18.2	6.1	16.3	6.1	0.08
SOFA score	6.8	2.7	7.8	3.1	6.1	2.2	<0.001
Comorbidity (n, %)							
Hypertension	52 (36.4%)		18 (32.7%)		34 (38.6%)		0.475
Diabetes mellitus	35 (24.5%)		14 (25.5%)		21 (23.9%)		0.83
COPD	18 (12.6%)		8 (14.5%)		10 (11.4%)		0.577
Peripheral vascular disease	8 (5.6%)		3 (5.5%)		5 (5.7%)		1
Cancer	22 (15.4%)		10 (18.2%)		12 (13.6%)		0.464
others	10 (7.0%)		6 (10.9%)		4 (4.5%)		0.184
Medication history (n, %)							
β-blocker	18 (12.6%)		8 (14.5%)		10 (11.4%)		0.577
CCB	40 (28.0%)		16 (29.1%)		24 (27.3%)		0.814
ACEI / ARB	28 (19.6%)		12 (21.8%)		16 (18.2%)		0.594
Statin	12 (8.4%)		5 (9.1%)		7 (8.0%)		0.812
Septic Source (n, %)							
Abdominal	66 (46.2%)		29 (52.7%)		37 (42.0%)		0.213
Pneumonia	36 (25.2%)		15 (27.3%)		21 (23.9%)		0.648
Urinary tract	16 (11.2%)		7 (12.7%)		9 (10.2%)		0.645
Bloodstream	15 (10.5%)		6 (10.9%)		9 (10.2%)		0.897
Catheter	5 (3.5%)		2 (3.6%)		3 (3.4%)		1
Soft tissue	3 (2.1%)		1 (1.8%)		2 (2.3%)		1
Central nervous system	2 (1.4%)		1 (1.8%)		1 (1.1%)		1

Clinical information							
HR (bmp)	98.9	21.3	99.6	22.2	98.5	20.9	0.926
MAP (mmHg)	70.4	11.4	66.2	10.5	73.6	12.1	0.228
CVP (mmHg)	9.8	2.8	10.9	3.2	8.6	2.3	0.376
Fluid balance of the first 24h (mL)	1878	467	1526	436	2038	486	0.124
28d mortality (n, %)	25 (17.5%)		16 (29.1%)		9 (10.2%)		0.004
In-hospital mortality (n, %)	35 (24.5%)		20 (36.4%)		15 (17.1%)		0.016
Length of ICU stay (days)	12.6	18.4	13.1	14.9	12.3	20.3	0.811
Length of hospital stay (days)	25.4	23.4	25.4	24.9	25.3	22.5	0.98
Duration of MV (days)	148	294	165	275	137	307	0.593
Laboratory date							
Hb (g/L)	118	19	110	17	122	21	0.204
TBil (μmol/L)	8.3	2.7	7.2	2.5	9.2	2.8	0.612
Albumin (g/L)	32.5	4.2	28.4	3.8	35.6	4.5	0.158
Ccr (ml/min/1.73m2)	88.6	15.6	80.4	16.2	94.5	15.1	0.245
Bun (mmol/L)	6.5	2.5	7.9	2.3	5.3	2.6	0.462
cTnT (ng/mL)	0.09	0.19	0.16	0.29	0.05	0.08	0.002
NT-proBNP (pg/mL)	5120	7687	8244	9901	3195	5112	<0.001
CK-MB (ng/mL)	15.5	43.2	29.1	65.9	6.6	9.2	0.006
Lactate (mmol/L)	2.1	1.7	2.9	1.8	1.5	1.7	0.377
pH	7.38	0.18	7.33	0.16	7.41	0.20	0.446
PaO2 (mmHg)	125	22	117	20	130	23	0.354
PaCO2 (mmHg)	39.2	6.4	36.5	5.8	41.8	6.9	0.549
P/F ratio (mmHg)	312	54	292	50	326	58	0.218
$HCO3^-$ (mmol/L)	23.6	3.2	22.8	2.9	24.3	3.4	0.687
BE (mmol/L)	-1.8	2.8	-2.8	2.6	-1.1	3.0	0.508
Echocardiogram data							
LA (mm)	38.5	3.4	39.2	3.6	37.5	3.2	0.645
LVEDV (mL)	82.9	27.0	86.3	26.2	80.9	27.4	0.255

LVESV (mL)	35.6	14.0	42.6	15.6	31.2	10.9	<0.001
LVEF (%)	57.1	9.3	51.1	10.7	60.9	5.7	<0.001
MAPSE (mm)	12.6	3.9	10.9	3.7	13.8	3.5	<0.001
TAPSE (mm)	19.1	4.9	16.6	4.8	20.8	4.2	<0.001
PASP (mmHg)	32.3	11.7	32.8	11.0	32.0	12.1	0.692
E (cm/s)	80.4	25	76.7	25.6	82.7	24.5	0.164
A (cm/s)	88.8	21.9	86.4	22.7	90.1	21.6	0.395
e' (cm/s)	11.9	3.5	11.3	3.5	12.3	3.4	0.096
a' (cm/s)	12.9	3.2	11.7	3.2	13.6	3.1	0.003
E/A ratio	0.9	0.3	0.9	0.4	0.9	0.3	0.837
E/e' ratio	7.1	2.5	7.2	2.66	7.1	2.4	0.816
MA Smax (cm/s)	11.8	3.1	10.1	2.5	12.8	3.0	<0.001
IVC (mm)	17.2	3.8	17.9	4.4	16.7	3.3	0.114
IVC variation□%□	27.9	17.6	23.2	14.8	30.9	18.7	0.029
LVOT VTI (cm)	19.7	5.5	17.2	4.8	21.5	5.2	<0.001
SV (mL)	52.4	16.9	46.1	17.8	56.6	15.2	<0.001
CO (L/min)	5.1	1.7	4.5	1.7	5.5	1.6	0.002
GLS (%)	-13.9	3.6	-11.2	3.2	-15.8	2.6	<0.001
TMAD 1 (mm)	10.9	4.1	7.3	2.6	13.1	3.2	<0.001
TMAD 2 (mm)	13.1	5.3	8.3	2.9	16.1	4.2	<0.001
TMADMid (mm)	11.5	4.6	7.1	2.2	14.3	3.3	<0.001
%TMAD	16.1	6.3	10.2	3.1	19.8	4.9	<0.001

BMI, body mass index; APACHE II, acute physiology and chronic health evaluation II ; SOFA, sequential organ failure assessment; COPD, chronic obstructive pulmonary disease; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; ICU, intensive care unit; MV, mechanical ventilation; Hb, hemoglobin; TBil, total bilirubin; Ccr, creatinine clearance rate; Bun, blood urea nitrogen; cTnT, cardiac troponin T; NT-proBNP, N-terminal pro-B type natriuretic peptide; CK-MB, creatine kinase-MB; BE, base excess; LA, left atrium; LVEDV, left ventricle end diastolic volume; LVESV, left ventricle end systolic volume; LVEF, left ventricle ejection fraction; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary arterial systolic pressure; E, early diastolic trans-mitral

inflow velocity; A, late diastolic trans-mitral inflow velocity; e', early lateral diastolic mitral annular tissue velocity; a', late lateral diastolic mitral annular tissue velocity; E/A, ratio of E and A; E/e', ratio of E and e'; MA Smax, maximal lateral systolic mitral annular tissue velocity; IVC, inferior Vena Cava; LVOT VTI, left ventricular outflow tract velocity time integral; SV, stroke volume; CO, cardiac output; GLS, global longitudinal strain; TMAD1, septal tissue motion annular displacement; TMAD2, lateral tissue motion annular displacement; TMADMid, midpoint tissue motion annular displacement; %TMAD, percentage value of the midpoint displacement in relation to the total length of the left ventricle.

Table 2. AUROC curve analysis of TMAD

	AUROC	Cutoff value	95% CI	Sensitivity	Specificity	*p*-value
LVEF Standard						
TMAD1	0.893	7.6	0.829-0.958	91.5	76.9	p<0.001
TMAD2	0.887	10.9	0.819-0.956	77.8	88.5	p<0.001
TMADMid	0.902	9.95	0.844-0.961	73.5	92.3	p<0.001
%TMAD	0.887	11.55	0.819-0.954	86.3	76.9	p<0.001
GLS Standard						
TMAD1	0.885	10.3	0.930-0.940	72.9	87.2	p<0.001
TMAD2	0.884	11.95	0.827-0.940	77.1	82.9	p<0.001
TMADMid	0.911	9.75	0.865-0.958	86.2	83.0	p<0.001
%TMAD	0.908	12.05	0.858-0.958	93.8	72.3	p<0.001

TMAD1, septal tissue motion annular displacement;

TMAD2, lateral tissue motion annular displacement;

TMADMid, midpoint tissue motion annular displacement;

%TMAD, percentage value of the midpoint displacement in relation to the total length of the left ventricle.

Table 3. Intra- and inter-observer reliabilities for LVEF, GLS and TMAD

Intra-observer variability	ICC	95% CI	*p*-value
LVEF	0.943	0.862-0.977	<0.001
GLS	0.871	0.703-0.947	<0.001
TMAD	0.962	0.907-0.985	<0.001
Inter-observer variability	ICC	95% CI	*p*-value
LVEF	0.912	0.791-0.964	<0.001
GLS	0.896	0.758-0.958	<0.001
TMAD	0.965	0.914-0.986	<0.001

ICC, intraclass correlation coefficient;

LVEF, left ventricle ejection fraction;

GLS, global longitudinal strain;

TMAD, tissue motion annular displacement.

Figures

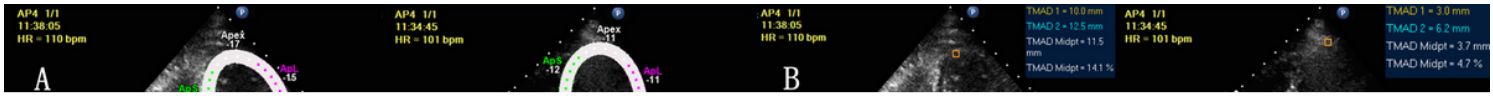

Figure 1

STE of septic patients. A: four-chamber view of the GLS measurement (left: one non-SICM patient with GLS -15%; right: one SICM patient with GLS -8%). B: four-chamber view of the TMAD measurement (left: one non-SICM patient with TMADMid 11.5mm; right: one SICM patient with TMADMid 3.7mm).

BIS: basal inferior septum; MIS: mid-inferior septum; ApS: apical septum; BAL: basal anterolateral; MAL: mid-anterolateral; ApL: apical lateral; TMAD1: septal tissue motion annular displacement; TMAD2: lateral tissue motion annular displacement; TMADMid: midpoint tissue motion annular displacement; %TMAD: the percentage value of the midpoint displacement in relation to the total length of the left ventricle.

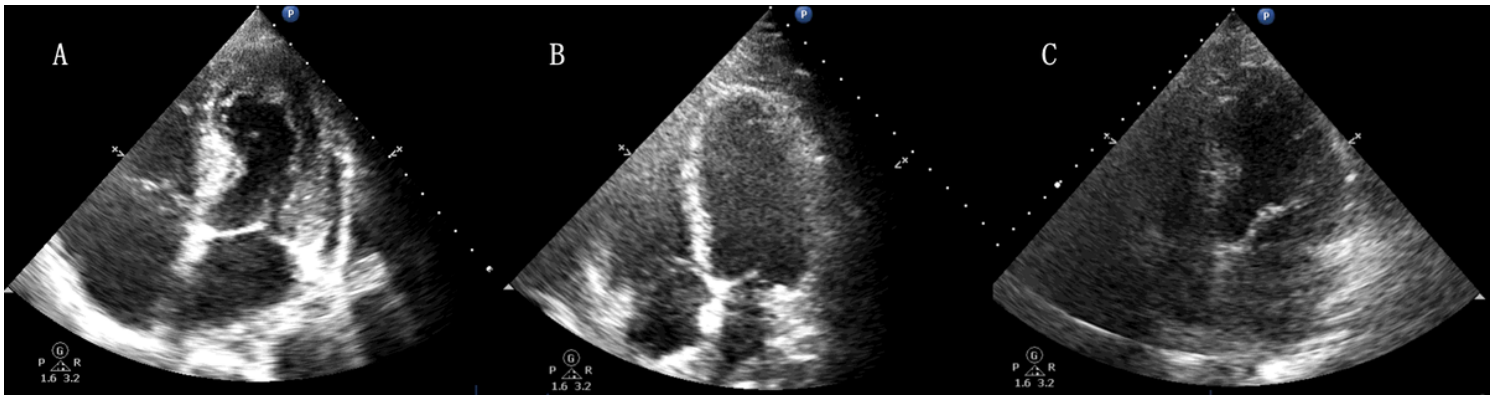

Figure 2

Transthoracic echocardiography of different imaging qualities performed in septic patients. A: one patient with a legible image of the entire endocardium (LVEF, GLS, and TMAD could be measured accurately); B: one patient with an image that was legible for the apex and mitral annulus but indistinct for the LV lateral wall (TMAD could be measured, but LVEF and GLS could not be achieved accurately); C: one patient with an indistinct image of the entire endocardium (none of LVEF, GLS, or TMAD could be measured accurately).

LVEF: left ventricle ejection fraction; GLS: global longitudinal strain; TMAD: tissue motion annular displacement.

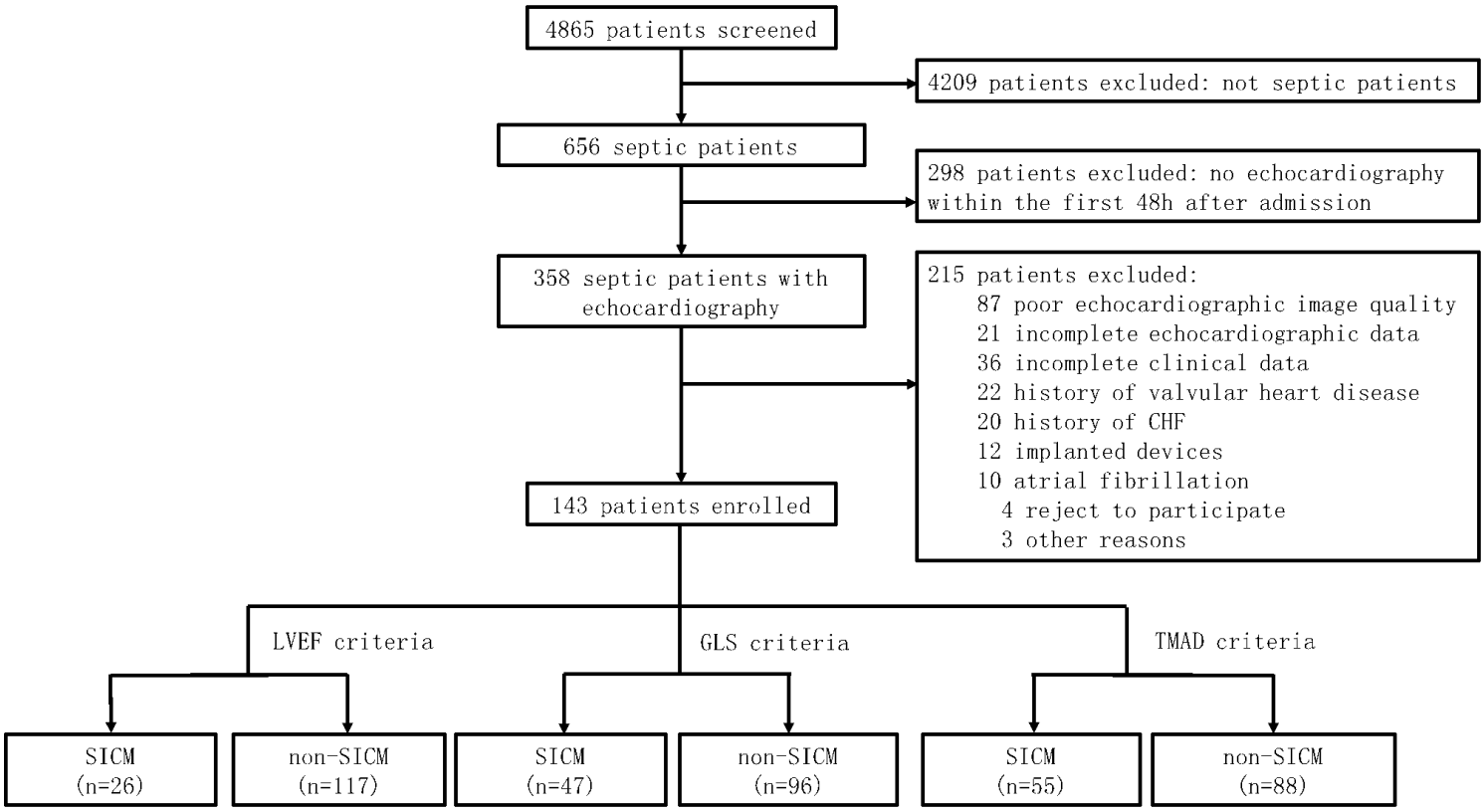

Figure 3

The flow diagram of patient enrollment.

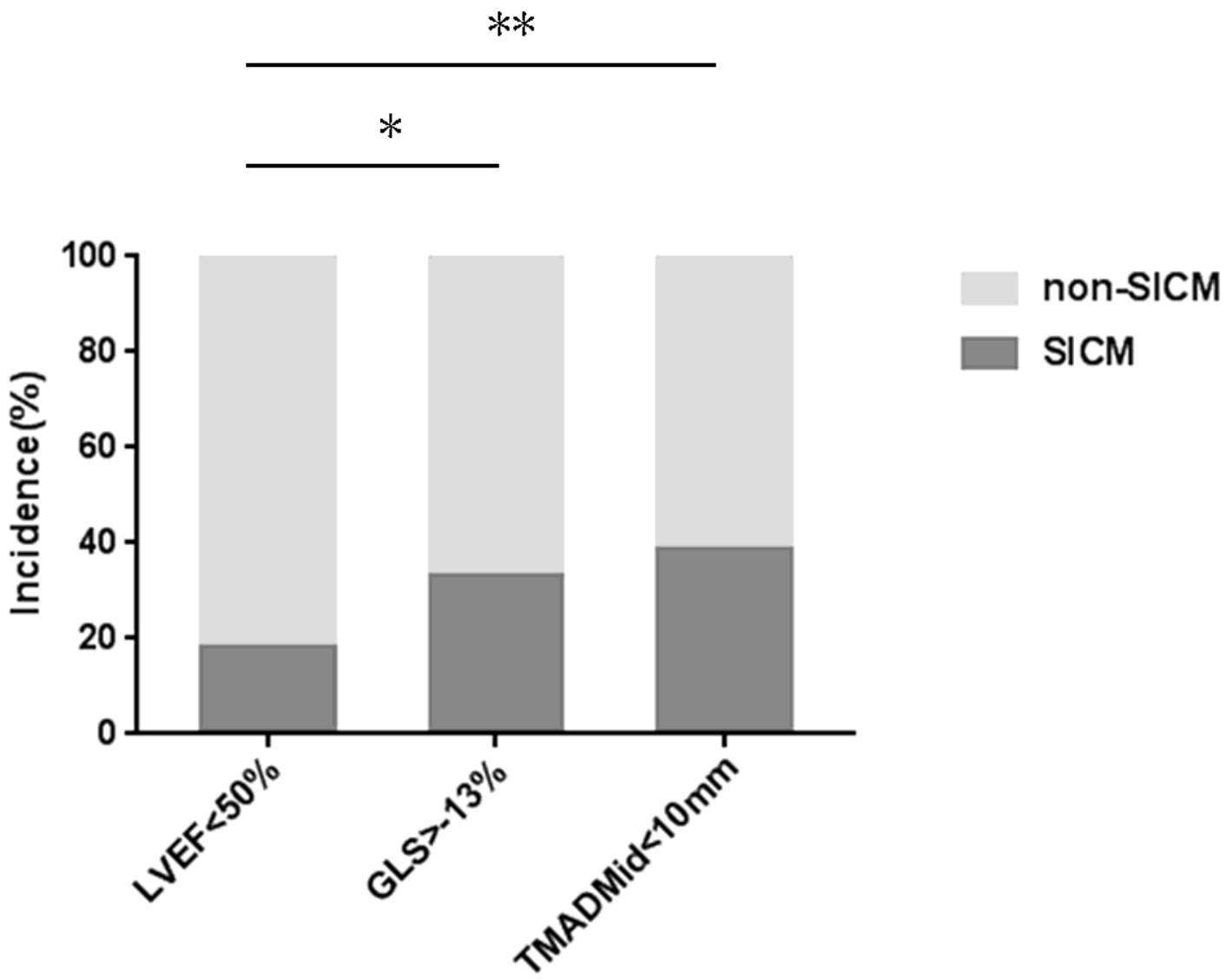

Figure 4

The incidence of SICM according to different diagnostic criteria. According to the LVEF criteria, GLS criteria and TMADMid criteria, the incidence of SICM was 18.2%, 32.9% and 38.5%, respectively.

SICM: sepsis-induced cardiomyopathy; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; TMADMid: midpoint tissue motion annular displacement.

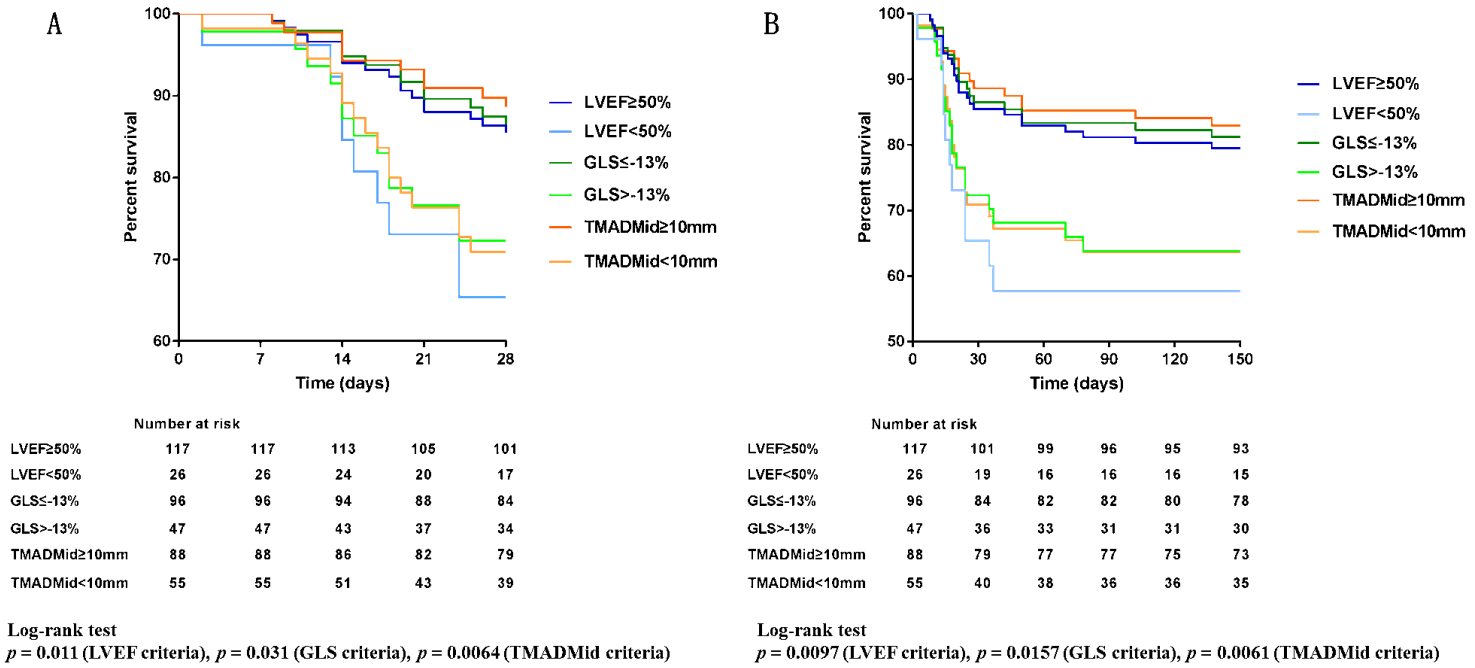

Figure 5

Kaplan-Meier survival curves for SICM or non-SICM patients according to different diagnostic criteria. A: The 28d survival rates of SICM patients were significantly lower than that of non-SICM patients. B: The in-hospital survival rates of SICM patients were significantly lower than that of non-SICM patients.

SICM: sepsis-induced cardiomyopathy; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; TMADMid: midpoint tissue motion annular displacement.

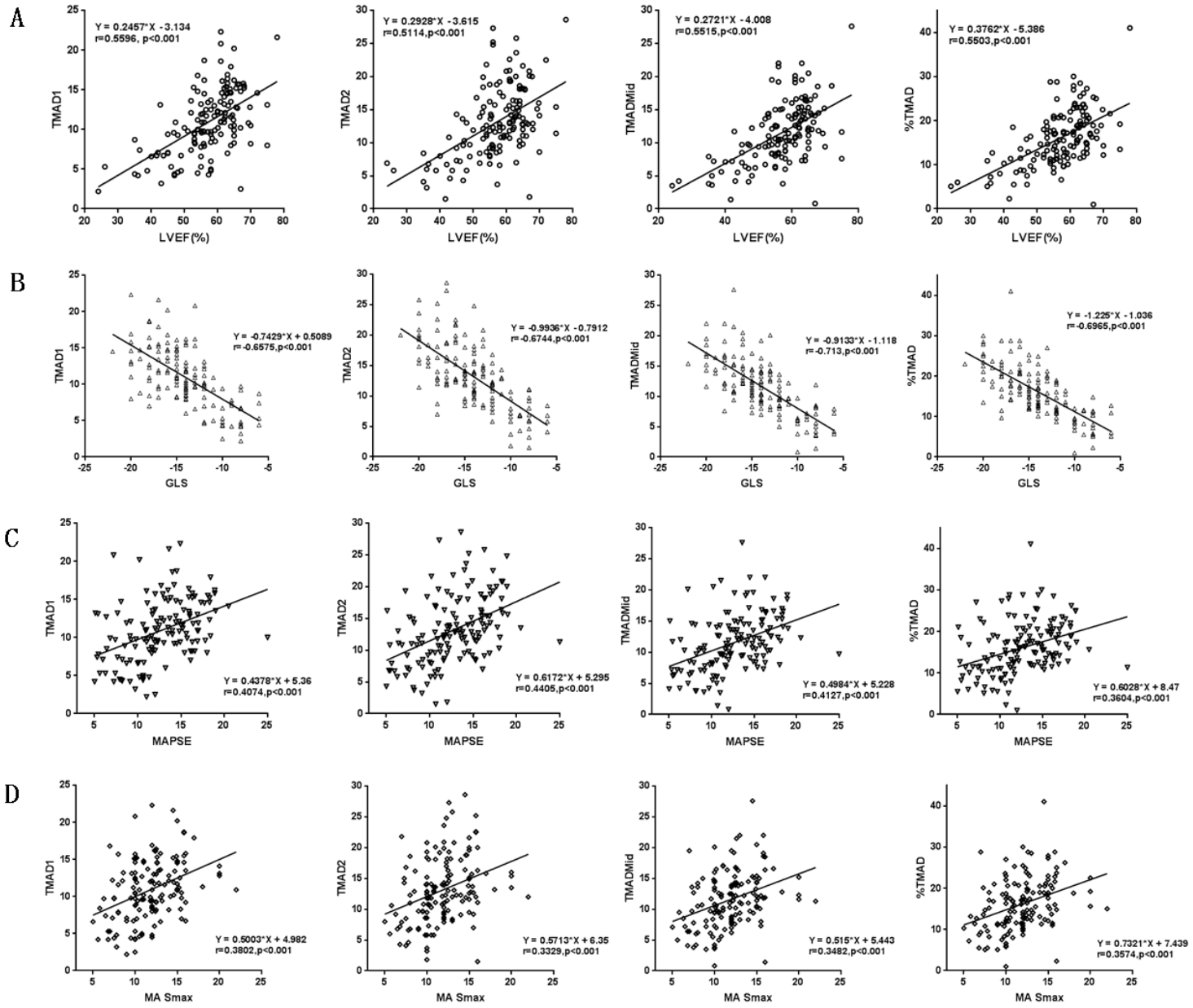

Figure 6

Relationship between TMAD and other LV systolic function echocardiographic parameters. A: Positive correlations between TMAD and LVEF. B: Negative correlations between TMAD and GLS. C: Positive correlations between TMAD and MAPSE. D: Positive correlations between TMAD and MA Smax.

TMAD: tissue motion annular displacement; TMAD1: septal tissue motion annular displacement; TMAD2: lateral tissue motion annular displacement; TMADMid: midpoint tissue motion annular displacement; %TMAD: the percentage value of the midpoint displacement in relation to the total length of the left ventricle; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; MAPSE: mitral annular plane systolic excursion; MA Smax: maximal lateral systolic mitral annular tissue velocity.

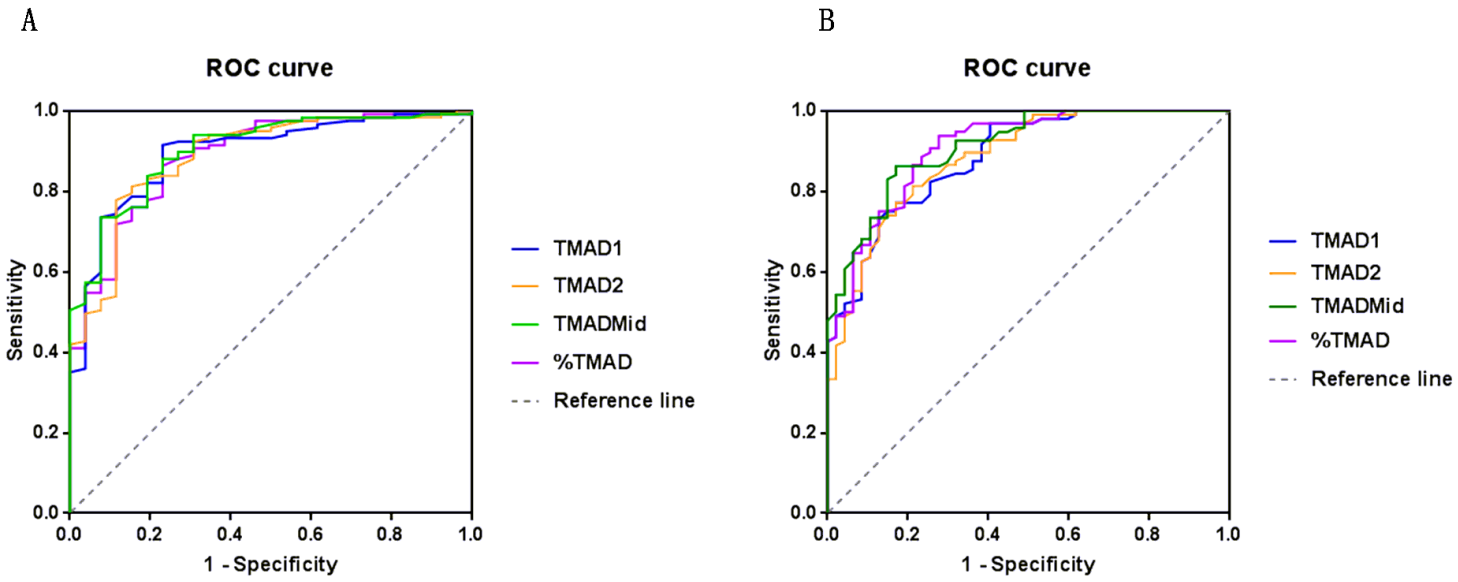

Figure 7

ROC curves to estimate the diagnostic value of TMAD for SICM. A: ROC curves of TMAD for the diagnosis of SICM according to the “LVEF standard”. B: ROC curves of TMAD for the diagnosis of SICM according to the “GLS standard”.

TMAD: tissue motion annular displacement; TMAD1: septal tissue motion annular displacement; TMAD2: lateral tissue motion annular displacement; TMADMid: midpoint tissue motion annular displacement; %TMAD: the percentage value of the midpoint displacement in relation to the total length of the left ventricle.