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Prevalence and Prognosis of Sepsis-Induced Cardiomyopathy: A Systematic Review and Meta-Analysis

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Abstract

Purpose: The prevalence and its impact on mortality of sepsis-induced cardiomyopathy (SICM) remain controversial. In this systematic review and meta-analysis, we investigated the prevalence and prognosis of SICM.

Materials and Methods: We searched MEDLINE, Cochrane Central Register of Controlled Trials, and Embase. Titles and abstracts were evaluated based on the following criteria: (1) published in English, (2) randomized controlled trials, cohort studies, or cross-sectional studies, (3) ≥ 18 years with sepsis, (4) reporting the prevalence and/or comparison of short-term mortality between those with and without SICM, defined as the new-onset reduction in left ventricular ejection fraction (LVEF) within 72 h on admission or from the diagnosis of sepsis. The random-effect model was used for all analyses. This meta-analysis was registered at PROSPERO (CDR42022332896).

Results: Sixteen studies reported the prevalence of SICM and the pooled prevalence of SICM was 20% (95% confidence interval [CI], 16-25%; $I^2 = 89.9\%$, $P < 0.01$). Eleven studies reported short-term mortality and SICM was associated with significantly higher short-term mortality (The pooled odds ratio: 2.30, 95% CI, 1.43-3.69; $I^2 = 0\%$, $P = 0.001$).

Conclusion: The prevalence of SICM was 20% in patients with sepsis, and the occurrence of SICM was associated with significantly higher short-term mortality.

Keywords

sepsis, septic shock, septic cardiomyopathy, sepsis-induced cardiomyopathy

Introduction

Sepsis, a life-threatening condition related to infection, occurs from dysregulated inflammatory response instigating organ failures.[1] Myocardial depression and impaired contractility are one form of such sepsis-induced organ failure. Parker et al first reported that the reduction in left ventricular ejection fraction (LVEF) and increased end-diastolic volume in patients with septic shock were of acute onset in survivors while they were less common in non-survivors.[2] Although it has been several decades since this seminal study describing new-onset LV systolic dysfunction, it remains controversial whether new-onset LV systolic dysfunction is associated with better outcomes.[3] Prior meta-analyses observed that LV systolic dysfunction defined as reduced LVEF in patients with sepsis was not associated with lower mortality.[4,5] However, studies included in these meta-analyses did not exclude patients with pre-existing myocardial diseases or reduced LVEF. Therefore, these meta-analyses were limited in answering if new-onset LV systolic dysfunction occurring with sepsis is truly associated with better outcomes or not.

This new-onset LV systolic dysfunction in the setting of sepsis is more precisely referred to as sepsis-induced (septic) cardiomyopathy (SICM).[3] SICM can behave differently from chronically reduced LV systolic function.[3] Pre-existing myocardial dysfunction was reported to be better compensated

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than new-onset myocardial dysfunction in the setting of congestive heart failure.[6] This raises the question of whether new-onset myocardial dysfunction in sepsis may also have a higher risk for hemodynamic instability and end-organ damage than pre-existing myocardial dysfunction, translating to worse outcomes. Therefore, to determine the clinical impact of SICM defined as a new-onset LV systolic dysfunction with the onset of sepsis, there has been a necessity to unify existing pieces of evidence. In this systematic review and meta-analysis, we investigated the prevalence and prognosis of SICM.

Methods

Protocol Registration

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[7] The protocol of this study was registered in the PROSPERO on 5/26/2022 (identification number: CDR42022332896).

Search Strategy

We performed a systematic search using the following keywords: sepsis, septic shock, severe sepsis, myocardial dysfunction, left ventricular dysfunction, systolic dysfunction, and cardiomyopathy on MEDLINE, the Cochrane Central Register of Controlled Trials, and Embase on 5/26/2022. The detailed search strategy was shown in Supplemental Table S1.

Study Selection and Inclusion Criteria

Two authors (D.H. and R.S.) screened the abstracts and titles based on the following inclusion criteria. We then retrieved and reviewed the full texts.

The inclusion criteria were as follows:

1. Publication type: articles published in English
2. Study type: randomized controlled trials, cohort studies, cross-sectional studies.
3. Patient population: Patients aged ≥18 years with sepsis based on Sepsis-1,[8] Sepsis-2,[9] Sepsis-3 definitions,[10] or international classification of diseases-9 or −10 coding.
4. Exposure: SICM, defined as a new-onset reduction in LVEF by a transthoracic echocardiogram within 72 h of admission or from the diagnosis of sepsis
5. Control: No SICM, defined as no new-onset reduction in LVEF by transthoracic echocardiogram (TTE) within 72 h on admission or from the diagnosis of sepsis.

We included only studies where authors excluded previous myocardial diseases and/or known reduced LVEF or studies where authors included patients with new reduction of LVEF from the known baselines to ensure the novelty of LV systolic dysfunction in the setting of sepsis. In this systematic review, we did not include studies where authors excluded only valvular diseases since it was not sufficient to conclusively determine the observed reduction in LVEF during sepsis is a new-onset or from a pre-existing condition.

The exclusion criteria were as follows:

1. conference proceedings
2. studies not reporting the novelty of reduced LVEF
3. studies that did not report the number of patients required to analyze the prevalence of SICM, or to calculate the pooled odds ratio (OR)
4. studies that performed a transesophageal echocardiogram
5. studies that performed TTE after 72 h or did not specify the timing of echocardiography

When there were different screening results between the two reviewers, we discussed them in detail until a consensus was reached. When there were multiple similar publications from the same investigators' group or institution, both authors carefully evaluated these publications and ensured not to include duplicate data.

Data Extraction

We established a standardized data collection form based on outcomes of interest. Two authors (D.H. and T.M.) independently collected the data from included articles based on this standardized form. The data collected in this standardized form included the followings: first author's name, publication year, country, sample size, study setting, study period, the definition of sepsis, the definition of LV systolic dysfunction, how authors defined new-onset, the timing of TTE, patient characteristics such as age, the proportion of males, and the proportion of septic shock.

The primary outcomes were the prevalence of SICM and short-term mortality defined as mortality within ≤ 30 days, or in-hospital or intensive care unit—mortality, depending on the availability of the data. Articles that divide patients into more than two groups were reviewed by two authors and reorganized to divide into two groups with the cutoff LVEF value of 45 or 50 (%), based on the data availability.

Quality Assessment

Two authors (D.H. and Y.I.) independently assessed the quality of the included studies. When there were different assessments, we discussed them in detail until consensus was achieved. We used a modified version of the Newcastle-Ottawa quality assessment scale.[11]

Statistical Analysis

We performed the meta-analyses using the random-effects models. Regarding the analysis for the prevalence of SICM, a double arcsine transformation was used to stabilize the variance for the pooled prevalence.[12] We used *metaprop*, a program in

STATA software to perform this analysis.[13] The pooled prevalence value was reported with 95% confidence intervals (CI) and *p*-value. We reported the odds ratio (OR) for short-term mortality as point estimates with 95% CIs and *P*-values. This OR was reported as the risk of short-term mortality for the SICM group in comparison with that of the control group. While our main analysis only included articles where TTE was performed within 72 h, we also performed the sensitivity analysis including articles where the timing of TTE was after 72 h or not specified to examine the robustness of the main results.

We examined statistical heterogeneity using the chi-square test and the I^2 statistic as the proportion of total variability explained by heterogeneity.[14] We pre-defined substantial heterogeneity as a *P*-value of <0.10 with the chi-square test or an I^2 value of >50%.

We described funnel plots for the analysis of the short-term mortality in which we plotted the log ORs against their standard errors and tested the symmetry of the funnel plots using both Begg's rank correlation test and Egger's linear regression test. When the publication bias was detected, we performed trim and fill to modify the publication bias and reported the adjusted point estimate with CI.[15,16] We performed all statistical analyses using STATA software, V.14.0 (Stata Corporation, College Station, Texas, United States), and Comprehensive Meta-analysis version 3 software (Biostat Inc, Eaglewood, NJ, USA). *P*-value <0.05 was considered statistically significant.

Result

Literature Search

Our systematic search identified 2602 articles. After duplicates were removed, 2313 articles were screened. After screening the titles and abstracts, 177 articles were reviewed in detail. Of the 177 articles, 161 were excluded (different populations, 13; different intervention, 1; different outcomes, 32; conference proceedings, 44; different study design, 27; different publication type, 1; non-English publication, 4; different definition of SICM, 27; duplication of study subjects, 1; and echocardiography was not performed within 72 h of admission or onset, 11). We excluded Vieillard-Baron et al.[17] because all patients underwent transesophageal echocardiography rather than transthoracic echocardiography. We excluded transesophageal echocardiography because LVEF measurement may be higher when assessed using transesophageal echocardiography as compared to transthoracic echocardiography.[18] Also, we excluded Pulido et al.[19] because Pulido et al.[19] and Vallabhajosyula et al.[20] were published from the same institution, and had the same study period with a similar number of patients. To minimize potential bias and inaccuracy in the estimation of polled prevalence, we decided to include the Vallabhajosyula et al. study,[20] which focused on the impact of new-onset LV systolic dysfunction in sepsis in our meta-analysis after discussion. Sixteen studies were included in the final meta-analysis.[20–35] The PRISMA flowchart of the study selection is shown in Figure 1. The characteristics of the studies are summarized in Table 1. The sample size ranged from 42 to 451. The patients' characteristics are summarized in Table 2.

Quality Assessment

Details of the methodological quality of the included studies are shown in Supplemental Table S2.

Primary Outcome

All sixteen studies reported the prevalence of SICM. Of the 2132 included patients, the pooled prevalence of SICM was 20% (95% CI, 16-25%; $I^2 = 89.9\%$, $P < 0.01$) (Figure 2).

Eleven studies reported short-term mortality (Figure 3). The pooled OR of short-term mortality associated with SICM was 2.30 (95% CI, 1.43–3.69; $I^2 = 0\%$, $P = 0.001$).

Publication Bias

From the visual assessment of the funnel plots for the studies included in the prevalence and adjusted analyses, there was a concern for a publication bias (Supplemental Figure S1). Publication bias was also assessed using Begg's rank correlation test ($P = 0.16$) and Egger's linear regression test ($P = 0.06$). Given the concern for a publication bias, we performed trim and fill to modify the publication bias, which showed three fills in the funnel plot shown in Supplemental Figure S2 (OR 1.72, 95% CI, 1.06–2.79).

Sensitivity Analysis

There were five articles[36–40] (Supplemental Table S3), which provided the number to calculate the OR for short-term mortality during the second screening but lacked information on the timing of transthoracic echocardiography or the timing not within 72 h to assess the LVEF. The OR of short-term mortality including these articles (sixteen articles in total) was shown in Supplemental Figure S3 (OR 1.39, 95% CI, 1.22–1.59, $P < 0.001$).

Discussion

In this systematic review and meta-analysis, the prevalence of SICM, ie new-onset LV systolic dysfunction with the onset of sepsis, was 20% and was associated with significantly higher short-term mortality. Prior studies have reported a prevalence ranging from 10% to 70%[41] and this wide variation in the prevalence of cardiomyopathy may be explained by sample selection with varying proportions of patients with pre-existing cardiac dysfunction. In addition, previous meta-analyses found no association between reduced LV systolic function and mortality in sepsis.[4,5] Biological plausibility for this observation can be that these studies did not exclusively consist of

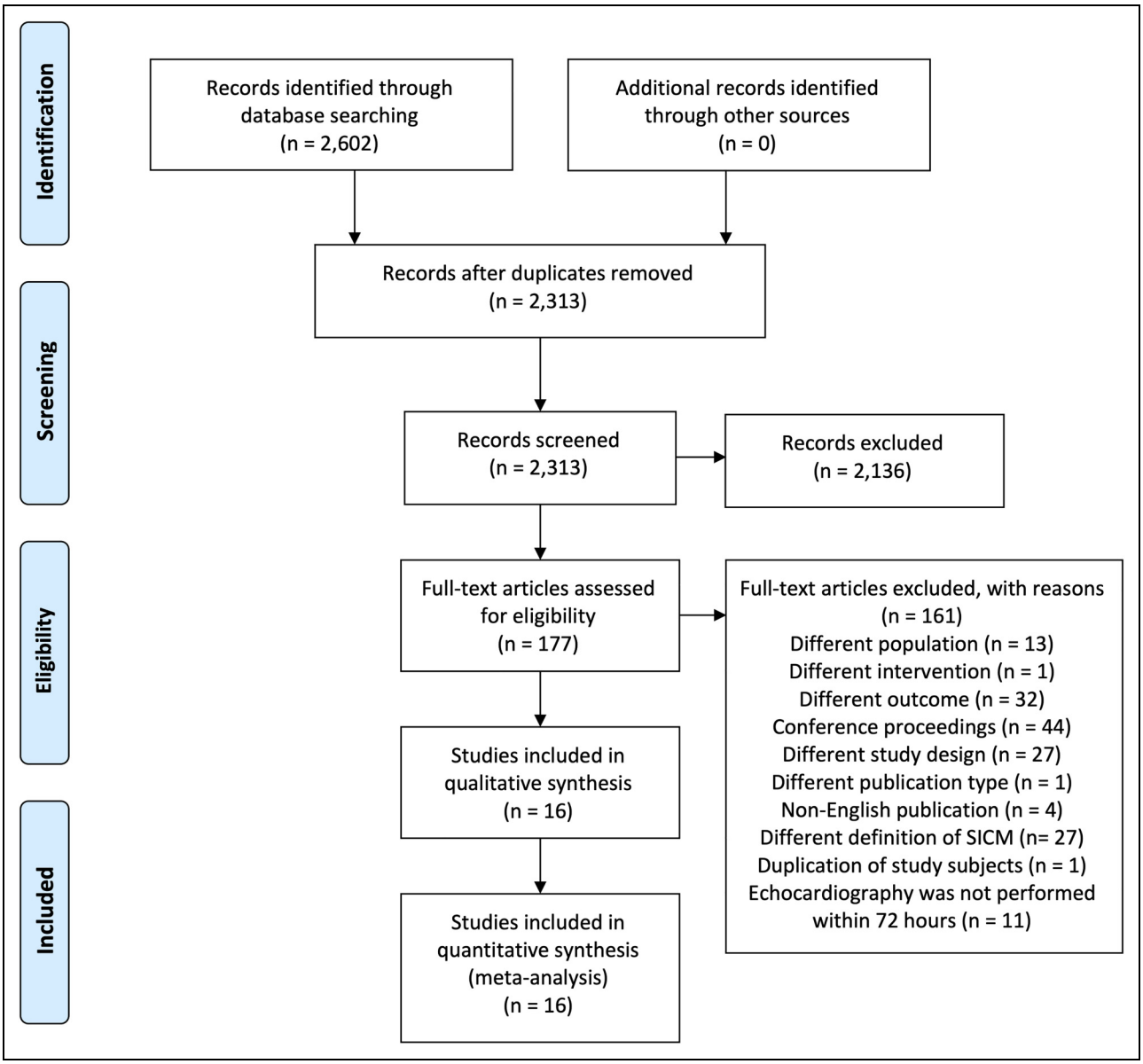

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) chart. Identification and selection of studies for inclusion.

new-onset LV systolic dysfunction. Therefore, the true prevalence of SICM and its association with mortality have been controversial despite its clinical importance. The novelty of our study is that we united existing evidence to generate the prevalence of SICM, strictly defined as new-onset LV systolic dysfunction in the setting of sepsis and its association with mortality.

Our study is clinically important for mainly two reasons. Firstly, the prevalence of 20% is not negligible given sepsis is the most frequent cause of admission to an intensive care unit (ICU) and the leading cause of death in hospitalized patients.[42] Given the high prevalence of new-onset LV systolic dysfunction, our study supports the idea of routine cardiac assessments in patients with sepsis. A prior study has shown that those who underwent TTE were weaned off vasopressors more quickly and had lower in-hospital mortality than those who did not.[43] On the other hand, given that sepsis is the most frequent cause of admission to the ICU, a routine TTE can be a significant cost burden. Therefore, a study investigating the cost-effectiveness of routine echocardiogram in sepsis is still warranted. In addition, as typical findings of SICM include reduced LV systolic function and dilatation,[2] these findings can be easily identified by focused TTE with good accuracy. Therefore, an approach using focused TTE may strike an appropriate balance between cost and benefit.

Secondly, our analysis indicated that the presence of SICM was associated with higher in-hospital mortality. While it has been controversial whether LV systolic dysfunction is associated with worse outcomes in sepsis or not,[4,5] most of the previous studies did not distinguish between pre-existing and

Table 1. Characteristics of Each Study.

Authors	Country	Sample size	Setting	Study period	Definition of sepsis	Definition of SICM	Definition of New-onset	Timing of Echocardiogram
Chen 2022	China	72	Single-center prospective observational study	September 2021-December 2021	Sepsis-3	High sensitivity Troponin-I 0.04 ng/ml and initial admission echocardiogram confirming LVEF <50% and/or ≥10% decrease in comparison to the patient's baseline LVEF	Excluded 1) cardiac inflammation including myocarditis, pericarditis, and endocarditis; 2) active myocardial dysfunction, such as acute myocardial infarction, unstable arrhythmia, and post-cardiopulmonary resuscitation status; 3) significant underlying cardiac conditions, such as congenital heart disease and valvular heart disease; 4) cardiac surgery within 2 months	Within 24 h of admission to the ICU
Chayakul 2021	Thailand	75	Single center prospective observational	October 2013-November 2014	Sepsis-2	LVEF < 50%	Excluded 1) infective endocarditis, cardiac tamponade, pulmonary embolism, or post-cardiac arrest; 2) history of documented myocardial infarction, decompensated heart failure, history of impaired LV systolic function, or had an electrocardiogram showing a Q wave in two or more consecutive leads.	On the first day and Day 3–4
Hanumanth 2021	United States	359	Single-center retrospective cohort	January 2016-December 2017	Sepsis-3	LVEF < 50% in the setting of sepsis and evidence of either reversibility (defined as a return to normal LVEF on follow-up TTE) and/or novelty (defined as a decline of ≥10% in LVEF in comparison to the patient's baseline LVEF)	Based on evidence of either reversibility (defined as a return to normal LVEF on follow-up TTE) and/or novelty (defined as a decline of ≥ 10% in LVEF in comparison to the patient's baseline LVEF).	Within 72 h of admission
Song 2020	Korea	308	Single-center retrospective cohort	June 2016-September 2017	Sepsis-3	LVEF <50% and ≥10% decrease in LVEF in comparison to the patient's baseline LVEF SICM: Among patients with left ventricular function deterioration, those whose EF recovered to the baseline level within 2 weeks	Left ventricular function deterioration was defined as EF <50% and ≥10% decrease in baseline EF. Among patients with left ventricular function deterioration, those whose EF recovered to the baseline level within 2 weeks were defined as having SICM.	Within 48 h of admission to the ICU
Razazi 2019	France	74	Single-center prospective cohort	Not available	Sepsis-2	LVEF < 45%	Excluded 1) chronic heart failure which was defined as a baseline LVEF below 45%; 2) severe valvulopathy.	On the first and second days of septic shock
Jeong 2018	Korea	451	Single-center retrospective cohort	January 2012-February 2015	Sepsis-3	SICM: EF <50% and a ≥ 10% in LVEF in comparison to the patient's baseline LVEF. If the	Excluded 1) Valvular heart diseases; 2) structural heart diseases	Within 24 h after admission

(continued)

Table 1. (continued)

Authors	Country	Sample size	Setting	Study period	Definition of sepsis	Definition of SICM	Definition of New-onset	Timing of Echocardiogram
						baseline EF was unknown, EF <50% and a ≥ 10% decrease in the patient's initial EF assessed on admission.	Definition of SICM includes EF <50% and a ≥ 10% decrease in the patient's baseline EF. If the baseline EF was unknown, EF <50% and a ≥ 10% decrease in the patient's initial EF assessed on admission.	
Vallabhajosyula 2018	United States	58	Single-center prospective cohort	August 2007-January 2009	Sepsis-2	LVEF < 50%	Excluded 1) Patients with prior heart failure; 2) Documentation of abnormal echocardiographic function within the past 1 year	Within 24 h of meeting sepsis criteria
Boissier 2017	France	132	Single-center prospective cohort	November 2010-March 2013	Sepsis-2	LVEF < 45% or inotrope infusion was needed to achieve a value ≥45% at 1–24 h	Excluded 1) chronic heart failure, defined as a baseline (before ICU admission) LVEF below 45%; 2) a severe valve heart disease	Echo was performed each day during the first 72 h of septic shock
Narváez 2017	Spain	57	Single-center prospective cohort	May 2014-October 2015	Sepsis-2	LV systolic dysfunction (LVEF <50%), attributable to sepsis (excluding patients with previous heart disease).	Excluded 1) Hypertensive heart disease; 2) valve disorders; 3) prior ischemia and/or acute coronary syndrome; 4) absence of sinus rhythm (atrial fibrillation or flutter or tachyarrhythmia, any type of atrioventricular block, or the presence of some cardiac electrostimulation device); 5) structural cardiomyopathy (dilated, hypertrophic); 6) combinations of the above.	Within 24 h of the admission
Wang 2017	China	53	Single-center prospective cohort	October 2012-September 2013	Sepsis-2	LVEF of <50	Excluded 1) myocardial infarction; 2) angina pectoris; 3) coronary angioplasty; 4) coronary bypass surgery; 5) cardiovascular dysfunction.	Within 72 h of admission
Sato 2016	Japan	210	Single-center retrospective	January 2013-December 2015	Sepsis-3	LVEF <50% and a ≥ 10% decrease compared to the baseline EF which recovered within 2 weeks, in sepsis or septic shock.	LVEF <50% and a ≥ 10% decrease compared to the baseline EF which recovered within 2 weeks. If the baseline was unknown, we defined the baseline as increase of >10% compared to the initial LVEF assessed on admission. The definition of recovery is LVEF improving to baseline within 2 weeks.	Within 24 h of admission to the ICU

(continued)

Table 1. (continued)

Authors	Country	Sample size	Setting	Study period	Definition of sepsis	Definition of SICM	Definition of New-onset	Timing of Echocardiogram
Dalla 2015	Sweden	48	Single-center retrospective	January 2011-December 2014	Sepsis-1	LVEF < 50%	Excluded 1) ischemic cardiac disease; 2) presence of congestive heart failure; 3) moderate to severe valvular heart disease; 4) arrhythmias.	within 48 h after arrival to the intensive care unit
Rolando 2015	Argentina	53	Single-center prospective observational	July 2009-January 2012	Sepsis-2	LVEF with ≤50%	Excluded 1) moderate-to-severe mitral and/or aortic valve disease and pre-existing severe impairment of the left or right ventricular ejection fraction (LVEF or RVEF, respectively); 2) myocardial revascularization surgery, received prosthetic valves, or had severe pulmonary hypertension.	Within the first 48 h of ICU admission
Klouche 2014	France	47	Single-center prospective observational	March 2008-May 2010	Sepsis-1	LVEF <45%	Excluded 1) previous congestive heart failure (class III New York Heart Association and higher); 2) right ventricular failure; 3) echocardiographic abnormal ventricular wall motions.	Repeated daily from Day1–5
Papanikolaou 2014	Greece	42	Single-center prospective observational	February 2009-January 2012	Sepsis-2	LVEF was defined as normal or slightly reduced (LVEF ≥50%), moderately reduced (LVEF between <50% and ≥35%) and severely reduced (LVEF <35%).	Excluded chronic heart disease (coronary artery disease, cardiac failure, severe valvulopathy and/or cardiomyopathy)	Within 24 h after the induction of critical sepsis
Zhang 2012	China	93	Single-center observational	April 2008-December 2010	Sepsis-1	LVEF less than 45%	Excluded 1) preexisting reduction of left ventricular function; 2) dilated cardiomyopathy; 3) acute or chronic valvular disease; 4) acute coronary ischemia; 5) cardiogenic or hemorrhagic shock	Within 24 h after enrollment

Abbreviations: SICM, sepsis induced cardiomyopathy; LVEF, left ventricular ejection fraction; ICU, intensive care unit; TTE, transthoracic echocardiogram; RVEF, right ventricular ejection fraction.

Table 2. the Characteristics of Included Patients.

Authors		Age	Male (%)	Septic shock
Chen/2022	SICM	65 (48.8-74.8)	55.6% (10/18)	61.1% (11/18)
	Non SICM	65 (49.3-77.0)	55.6% (10/18)	16.7% (3/18)
Chayakul/2021	SICM	73.1 ± 17.4	45.8% (11/24)	100% (24/24)
	Non SICM	65.8 ± 16.5	39.2% (20/51)	100% (51/51)
Hanumanthu/2021	SICM	64 ± 18	36.8% (7/19)	84.2% (16/19)
	Non SICM	67 ± 16	45.6% (155/340)	37.6% (128/340)
Song/2020	SICM	65.1 ± 11.2	65.3% (32/49)	100% (49/49)
	Non SICM	64.6 ± 15.0	62.9% (163/259)	95% (246/259)
Razazi/2019	Hypokinesia	68 (57-80)	71% (17/24)	100% (24/24)
	No hypokinesia	65 (48-78)	60% (30/50)	100% (50/50)
Jeong/2018	SICM	70.4 ± 15.3	60.9% (14/23)	N/A
	Stress-induced cardiomyopathy	73.7 ± 9.0	47.8% (11/23)	N/A
Vallabhajosyula/2018	LVSD	68.0 (51-73)	35.3% (6/17)	N/A
	No LVSD	N/A	N/A	N/A
	LVDD	76.0 (67-82)	54.6% (6/11)	N/A
	No LVDD	N/A	N/A	N/A
Boissier/2017	Hyperkinesia	63 (50-75)	73% (35/48)	100% (48/48)
	Normokinesia	65 (54-75)	56% (31/55)	100% (55/55)
	Hypokinesia	64 (50-71)	79% (23/29)	100% (29/29)
Narvaez/2017	SICM	54.5 ± 12.9	61.5% (8/13)	76.9% (10/13)
	Non SICM	64.4 ± 16.6	56.8% (25/44)	68.2% (30/44)
Wang/2017	High NGAL	63 (55.5-71)	61% (8/13)	N/A
	Low NGAL	57 (52-62)	57% (23/40)	N/A
Sato/2016	SICM	69 (57-79)	75.9% (22/29)	N/A
	Non SICM	77 (65-85)	51.9% (94/181)	N/A
Dalla/2015	All	54 ± 14	62% (30/48)	N/A
	Non SICM	53 ± 14	65% (22/34)	N/A
Ronaldo/2015	SICM	74 ± 10	All: 55% (29/53)	N/A
	Non SICM	74 ± 15		N/A
Klouche/2014	SICM	53 ± 8	50%	All: 85% (40/47)
	Non SICM	66 ± 12	64.3%	
Papanikolaou/2014	Septic Shock	60.9 ± 1.8	60% (18/30)	100% (30/30)
	Severe Sepsis	58.8 ± 3	66.7% (8/12)	0% (0/12)
Zhang/2012	N/A	N/A	N/A	N/A

Abbreviations: SICM, sepsis-induced cardiomyopathy; LVSD, Left ventricular systolic dysfunction; LVDD, Left ventricular diastolic dysfunction; NGAL, Neutrophil gelatinase-associated lipocalin.

new-onset LV dysfunction, which may have influenced the results of those studies. While the original study describing SICM even suggested the potential association between SICM and better survival, our study suggests that SICM is one of the major organ failures that is associated with worse outcomes. In patients with heart failure, it was suggested that pre-existing impaired LV contractility may be able to better compensate for higher filling pressure than new-onset LV dysfunction.[6] Therefore, one potential cause of higher mortality in SICM may be due to impaired contractility, reduced cardiac output, and impaired distal organ perfusion. This leads to a cascade of subsequent multi-system organ dysfunction, which is associated with increased mortality and poor outcomes in sepsis. Another potential cause of higher mortality is that the optimal vasoactive agents might differ in this population. While norepinephrine is the first-choice vasoactive agent, the hemodynamic response to vasopressin, which is an adjunct vasopressor to reduce norepinephrine dosage, varies depending on pre-drug LVEF.[44] While inotropes have been often used in patients with myocardial depression as suggested by the Surviving Sepsis Campaign Guidelines,[1] some studies have suggested that the use of inotropes may be associated with worse outcomes.[45,46] Even in patients with cardiogenic shock, the use of inotropes failed to show mortality benefits, and the use of epinephrine was associated with worse outcomes.[47,48] Recent observational studies suggested that invasive hemodynamic monitoring with the pulmonary artery catheter may be associated with better outcomes in patients with cardiogenic shock though this hypothesis still lacks clinical trials.[49,50] Given the lack of evidence,[51] the higher mortality with SICM presented in this study highlights the urgent necessity for further studies regarding optimal approaches including fluid management, vasoactive agent selections, and monitoring methods.

The major strengths of this meta-analysis are that we omitted studies that did not exclude patients with pre-existing LV systolic dysfunction and that we only included studies where the diagnosis of SICM was timely established with TTE within 72 h. Since the typical clinical course of SICM is to occur

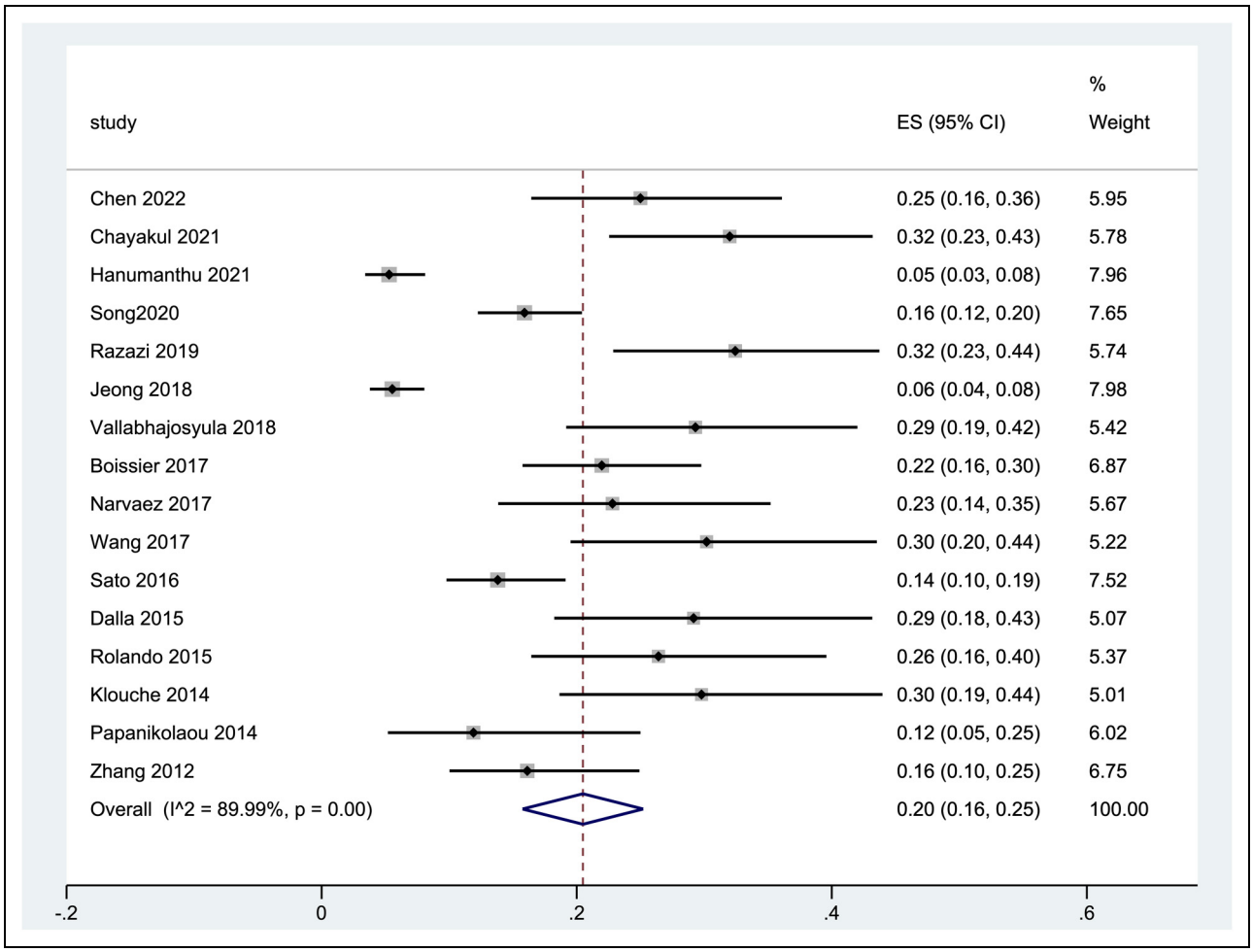

Figure 2. Forest plot of prevalence of SICM: prevalence of SICM in patients with sepsis is shown. SICM: sepsis-induced cardiomyopathy.

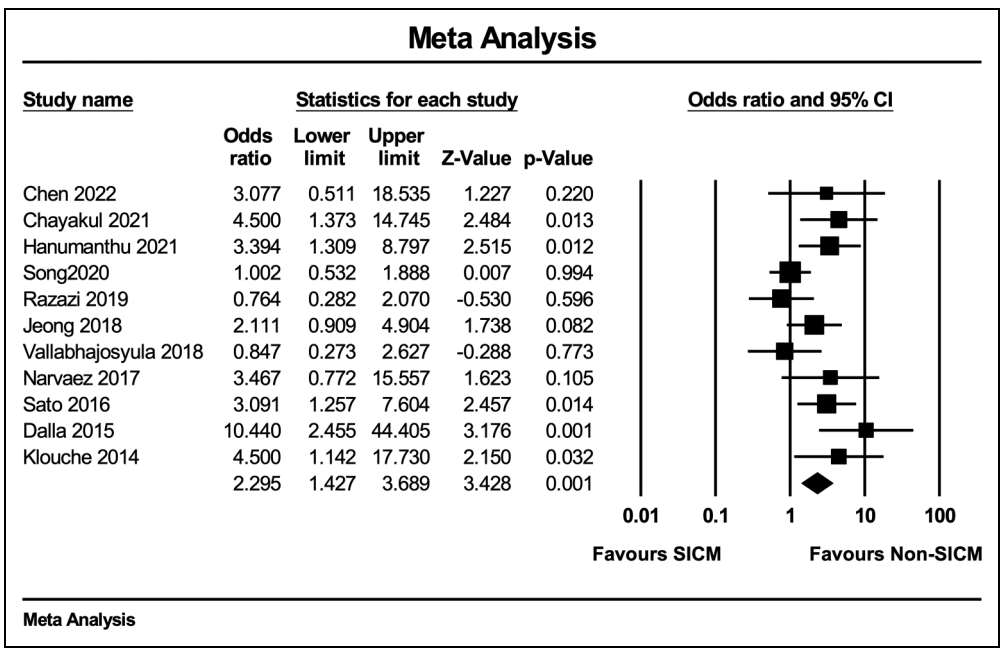

Figure 3. Forest plot of short-term mortality in patients with SICM compared with that with non-SICM: short-term mortality of patients with SICM compared with patients with no-SICM are shown. SICM: sepsis-induced cardiomyopathy.

within the first few days of sepsis and lasts for 7–10 days,[2,3] it may be suboptimal and can potentially cause immortal time bias to include studies that did not report the timing of TTE or underwent TTE after 72 h. While our study has several strengths, there are several limitations in this study. Firstly, because all included studies were single-center observational studies, there can be inevitable selection biases and questions regarding generalizability. On the other hand, we ensured that all included studies enrolled consecutive patients to calculate the pooled prevalence of SICM. In addition, the hospitals where included studies were conducted appeared to be diverse as shown in Table 1. Therefore, such risks were minimized. Secondly, we dichotomized LV systolic function based on LVEF of typically < 45% or 50%. However, in clinical practice, LVEF of 20% can behave differently from 40%. Therefore, future studies should focus on a more detailed relationship between new-onset LVEF and outcomes. Third, although we used only LVEF as a parameter to evaluate LV systolic function based on the data availability, there is a growing interest in LV outflow tract velocity time integral, stroke volume, and cardiac output as tools to assess LV systolic function for prognostication. However, studies assessing these parameters and their association remain limited. Fourth, there was substantial heterogeneity in the prevalence of SICM with an I^2 of 89.9%. However, the meta-analysis of the prevalence is known to have a higher heterogeneity and the recent article reported that the majority of systematic reviews of the prevalence of diseases had an I^2 estimate of 90% or greater.[52] Thus, the result of the prevalence that we obtained can be considered valid despite a substantial heterogeneity among included studies based on the characteristic of the analysis.

In conclusion, this systematic review and meta-analysis reported that the prevalence of SICM was 20% and the development of SICM was associated with significantly higher short-term mortality. Although there is a lack of evidence regarding hemodynamic management and proper monitoring in patients with SICM, these patients may benefit from personalized hemodynamic management.

Abbreviation List

SICM	sepsis-induced cardiomyopathy
LV	left ventricle / left ventricular
EF	ejection fraction
TTE	transthoracic echocardiography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
OR	odds ratio
CIs	confidence intervals
ICU	intensive care unit

Author's Contributions

DH was responsible for conceptualization, data curation, investigation, methodology, validation, writing-review & editing.

YI contributed to data curation, validation writing-review & editing.

TM contributed to data curation, validation, and writing-review & editing.

NP contributed to data curation, validation, and writing-review & editing.

KN contributed to formal analysis, methodology, and writing-review & editing.

SD contributed to conceptualization, methodology, investigation, supervision, and writing-review & editing.

RS was responsible for conceptualization, data curation, formal analysis, investigation, supervision, methodology, writing-original draft, and writing-review & editing.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Consent for Publication

N/A as this is a systematic review and meta-analysis.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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