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Systematic Review

Mortality among adult patients with sepsis and septic shock in Korea: a systematic review and meta-analysis

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Objective To evaluate mortality from sepsis and septic shock in Korea during the past 10 years, we conducted a systematic review and meta-analysis.

Methods We searched six databases for studies on mortality from sepsis and septic shock in adult patients. Primary outcomes were 28- or 30-day mortality and in-hospital mortality from sepsis and septic shock. To assess the risk of bias, we used the Newcastle-Ottawa Scale and Risk of Bias 2 tools. The protocol is registered in PROSPERO (No. CRD42022365739).

Results A total of 61 studies were included. The mortality rates from sepsis and septic shock at 28 or 30 days were 22.7% (95% confidence interval [CI], 20.0%–25.6%; $I^2 = 89\%$) and 27.6% (95% CI, 22.3%–33.5%; $I^2 = 98\%$), respectively, according to the Sepsis-3 criteria. Furthermore, in accordance with the Sepsis-3 criteria, the in-hospital mortality rates were 28.1% (95% CI, 25.2%–31.1%; $I^2 = 87\%$) and 34.3% (95% CI, 27.2%–42.2%; $I^2 = 97\%$), respectively.

Conclusion The mortality rates from sepsis and septic shock in Korea are high. In the case of septic shock, the in-hospital mortality rate is approximately 30%.

Keywords Sepsis; Septic shock; Mortality; Republic of Korea; Meta-analysis

Capsule Summary

What is already known

Mortality rates for sepsis and septic shock vary between studies. To appropriately determine the mortality rate from sepsis and septic shock in Korea, it is necessary to conduct a systematic review and meta-analysis.

What is new in the current study

This is the first meta-analysis of published sepsis and septic shock mortality rates in Korea. Sepsis mortality in Korea was similar or higher than in the United States and Europe, whereas septic shock mortality was lower.

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INTRODUCTION

Sepsis is a life-threatening multiorgan dysfunction caused by an inappropriate host response to infection [1]. Despite global efforts to minimize its lethality, sepsis remains the leading cause of death in critically ill patients and a burden on patients and healthcare systems worldwide [1–3]. Through campaigns to reduce the mortality rate of sepsis, experts in various fields have improved the survival rate by defining the Sepsis-3 diagnostic criteria and promoting adherence to recommended treatment protocols [1,4,5]. A total of 48.9 million incident cases and 11.0 million sepsis-related deaths have been reported in 2017, accounting for approximately 20% of global deaths during that time [2]. A recent meta-analysis showed that the pooled mortality rate of sepsis is 19.6% in North America, 23.6% in Europe, 18.7% in Australia, and 29.0% in China [6,7]. The mortality rates differ across countries because of disease severity, study type, period, and region, but different standard care protocols and health care systems also significantly affect the care and prognosis of patients with sepsis [6].

In Korea, previous research analyzing national health insurance data revealed sepsis mortality rates ranging from 17.5% to 30% [8–10]. However, those studies evaluated sepsis or septic shock based on diagnostic International Classification of Diseases, 10th Revision (ICD-10) codes in insurance records, not the sepsis criteria. Thus, their study populations might differ from the population described by the sepsis criteria and inaccurately depict sepsis mortality. Despite the large number of multicenter and single-center studies on sepsis and septic shock, including some multicenter registries, no previous studies in Korea reflect the overall sepsis fatality rate, to the best of our knowledge. To appropriately determine the mortality rate from sepsis and septic shock in Korea, a systematic review and meta-analysis are required. Therefore, we investigated the sepsis and septic shock mortality rates published for Korea during the past 10 years and analyzed those rates based on the Sepsis-3 criteria.

METHODS

Reporting guidelines and protocol registration

This study adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) and the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines for reporting information from observational studies [11,12]. This review protocol is prospectively registered in PROSPERO (No. CRD42022365739).

Search strategy

We systematically searched the PubMed, Embase, Cochrane Library, KMbase (Korean Medical Database), KoreaMed, and KISS (Korean Studies Information Service System) databases for studies about mortality and the frequency of sepsis and septic shock in adult patients that were published between January 2012 and July 2022. As our search strategy, we combined medical subject headings terms and free terms related to "sepsis," "septic shock," and "South Korea" and included Embase subject headings and text words. The detailed search strategy is presented in Supplementary Table 1.

Study selection

We selected studies through title and abstract screening and used the following inclusion criteria: confirmed sepsis, severe sepsis or septic shock in adult patients according to the Sepsis-1, -2, or -3 criteria, and studies conducted in Korea and published between January 1, 2012 and September 23, 2022. We excluded studies with insufficient data and those involving sepsis patients from specific disease groups, reviews, case reports, editorials, letters, conference abstracts, meta-analyses, and animal studies. To prevent duplicate data, we selected studies with the longest study period and largest sample size when we found multiple studies that shared the same registry or institution.

Data extraction

Two reviewers independently extracted the relevant data about the patients in the included studies, and discrepancies between reviewers were discussed and resolved by consensus. We extracted the following variables: publication data; study design and settings; patient information—number of participating centers, patient locations (emergency room, ward, or intensive care unit [ICU]), number of patients, and deaths; sepsis diagnostic criteria; and the time of outcome measurement (28- or 30-day mortality and in-hospital mortality).

Quality assessment of individual studies

The Newcastle-Ottawa Scale, which divides an eight-item score into three domains, was used to evaluate nonrandomized studies [13]. The Risk of Bias 2 tool was used to evaluate randomized controlled trials [14]. Each article was rated based on selection (maximum, four stars), comparability (maximum, two stars), and outcome (maximum, three stars). Both reviewers assessed the 61 included studies independently. Unresolved disagreements between reviewers were resolved by discussion or consultation with a third reviewer.

Table 1. Characteristics of the studies included in the systematic review and meta-analysis

Study	Study design	Study period	No. of centers	Patient location	Cohort screened	Outcome	Diagnostic criteria	Study details
Cha et al. [15] (2022)	Retrospective cohort study	Nov 2013–May 2017	1	ICU	Patients ≥ 18 yr, ICU LOS > 3 day with sepsis and septic shock	30-Day, in-hospital	Sepsis-3	Investigation of the effects of nutritional support on clinical prognosis
Cho et al. [16] (2012)	Prospective cohort study	Sep 2007–Nov 2010	1	General ward, ICU	Patients suspected of sepsis in either the general wards or ICU	28-Day	Other	Assessment of the prognostic power of lysophosphatidylcholine for sepsis
Choi et al. [17] (2020)	Retrospective cohort study	Mar 2015–Jun 2018	1	ICU	Patients > 18 yr, admitted to the medical ICU with sepsis	28-Day, in-hospital	Sepsis-3	Clinical value of full-length tryptophanyl-tRNA synthetase for sepsis detection
Choi et al. [18] (2021)	Retrospective cohort study	Mar 2008–Dec 2017	1	General ward, ICU	Patients with septic shock who received rapid response system treatment in hospital wards	28-Day, in-hospital	Sepsis-3	Investigation of the effects of the rapid response system on outcomes in patients with septic shock
Chung et al. [19] (2019)	Prospective cohort study	Mar 2010–Jun 2016	1	ED	Patients ≥ 18 yr, with severe sepsis or septic shock	28-Day	Other	Evaluation of the association between monocyte counts and mortality
Hong et al. [20] (2016)	Retrospective cohort study	Nov 2012–Sep 2014	1	ED	Patients ≥ 18 yr, with sepsis and without dialysis	28-Day	Other	Assessment of neutrophil gelatinase-associated lipocalin as a prognostic biomarker for hospital mortality in patients with sepsis in EDs
Hong et al. [21] (2020)	Retrospective cohort study	Sep 2015–Feb 2019	1	ICU	Patients ≥ 18 yr, with sepsis or septic shock who underwent echocardiography	28-Day	Sepsis-3	Effects of left ventricular dysfunction and fluid balance on the outcomes of patients with sepsis
Huh et al. [22] (2013)	RCT	Aug 2007–Jan 2009	1	ED	Patients ≥ 18 yr, with severe sepsis or septic shock	In-hospital	Other	Comparison of clinical outcomes between intermittent and continuous monitoring of central venous oxygen saturation
Hwang et al. [23] (2018)	Retrospective cohort study	Aug 2008–Sep 2014	1	ED	Patients ≥ 18 yr, diagnosed with severe sepsis or septic shock	28-Day, in-hospital	Other	Evaluation of the diagnostic value of the qSOFA score for mortality in septic patients
Hwang et al. [24] (2019)	Retrospective cohort study	Aug 2008–Sep 2016	1	ED	Patients ≥ 18 yr, with septic shock	28-Day	Other	Investigation of the effect of antibiotic timing on the outcomes of sepsis
Hwang et al. [25] (2020)	RCT	Dec 2018–Jan 2020	6	ED	Patients (19–89 yr) with septic shock	28-Day, in-hospital	Sepsis-3	Evaluation of the effects of early combination therapy with intravenous vitamin C and thiamine in patients with septic shock
Im et al. [26] (2020)	Prospective cohort study	Apr 2014–Jan 2019	1	ICU	Patients ≥ 19 yr, admitted to the medical ICU with sepsis or septic shock	28-Day, in-hospital	Sepsis-3	Association of plasma exosomes with severity of organ failure and mortality in patients with sepsis
Im et al. [27] (2021)	Prospective cohort study	Apr 2014–Jan 2019	1	ICU	Patients ≥ 19 yr, with sepsis admitted to the medical ICU	28-Day, in-hospital	Sepsis-3	Evaluation of the association between exosomal CD63 level and clinical outcomes in patients with sepsis
Im et al. [28] (2022)	Prospective cohort study	Sep 2019–Dec 2020	19[a]	ED	Patients ≥ 19 yr, diagnosed with sepsis or septic shock	In-hospital	Sepsis-3	Evaluation of the effects of time-to-antibiotics on in-hospital mortality in patients with sepsis
Jang et al. [29] (2016)	Retrospective cohort study	Jan 2013–Jun 2015	1	ED	Patients ≥ 19 yr, suspected to have sepsis and admitted to the ICU	28-Day	Other	Comparison of the usefulness of the PIRO score and MEDS score in predicting the mortality of septic patients
Jang et al. [30] (2020)	Retrospective cohort study	Mar 2010–Apr 2017	1	ED	Patients ≥ 18 yr, with sepsis or septic shock	28-Day	Other	Investigation of the association between initial phosphate concentration and mortality in patients with sepsis
Jang et al. [31] (2021)	Retrospective cohort study	May 2014–Apr 2018	3	ED	Patients ≥ 18 yr, with sepsis or septic shock	28-Day	Other	Investigation of the relationship between the serum total cholesterol concentration and the outcomes of sepsis patients
Jee et al. [32] (2020)	Retrospective cohort study	Nov 2016–Dec 2016	1	ED	Patients ≥ 18 yr, diagnosed with sepsis	In-hospital	Sepsis-3	Comparison of the mortality rates of patients with early-identified sepsis and late-identified sepsis
Jeon et al. [33] (2019)	Retrospective cohort study	Jan 2018	19[a]	ED	Patients ≥ 19 yr, with sepsis	In-hospital	Sepsis-3	Investigation of the characteristics, management, and clinical outcomes of sepsis patients
Jeong et al. [34] (2019)	Prospective cohort study	Jan 2011–Jun 2017	1	ICU	Patients ≥ 18 yr, with sepsis who stayed in the ICU for more than 7 day	28-Day	Other	Relationship between nutrition intake and mortality in patients with sepsis

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Table 1. (Continued)

Study	Study design	Study period	No. of centers	Patient location	Cohort screened	Outcome	Diagnostic criteria	Study details
Jeong et al. [35] (2020)	Retrospective cohort study	Jun 2018–Apr 2019	1	ED	Patients ≥ 19 yr, with sepsis	30-Day	Sepsis-3	Investigation of the efficacy of the albumin-adjusted ischemia-modified albumin level to predict mortality in patients with sepsis
Jung et al. [36] (2019)	Prospective cohort study	Jun 2012–Dec 2016	1	ED	Patients ≥18 yr, with septic shock	28-Day	Other	Evaluation of relationship between low hemoglobin levels and mortality in patients with septic shock
Kim et al. [37] (2012)	Prospective cohort study	Jul 2009	25	ICU	Patients admitted to an ICU for severe sepsis	28-Day, in-hospital	Other	Investigation of the influence of full-time intensivist and nurse to patient ratio on the implementation of severe sepsis bundles
Kim et al. [38] (2013)	Prospective cohort study	Jul 2010–Jan 2011	22	ICU	Patients ≥ 18 yr, with severe sepsis or septic shock	28-Day	Other	Comparison of clinical outcomes between pneumonia and other infections in patients with sepsis
Kim et al. [39] (2017)	Retrospective cohort study	Dec 2014–Jun 2015	1	ED, ICU	Patients diagnosed with sepsis	30-Day, in-hospital	Sepsis-3	Investigation of the prognostic utilities of multiple biomarkers for mortality in septic patients
Kim et al. [40] (2019)	Retrospective cohort study	Sep 2018–Aug 2019	1	ICU	Patients ≥ 19 yr, with septic shock who were treated with the vitamin C protocol	28-Day, in-hospital	Sepsis-3	To identify septic phenotypes in patients receiving vitamin C, hydrocortisone, and thiamine using temperature and white blood cell count
Kim et al. [41] (2019)	Retrospective cohort study	Jun 2011–Aug 2017	1	ICU	Patients ≥ 18 yr, diagnosed with sepsis who underwent abdominal CT	In-hospital	Sepsis-3	Investigation of association between skeletal muscle mass and clinical outcomes in patients with sepsis
Kim et al. [42] (2020)	Retrospective cohort study	Aug 2016–Aug 2017	1	Not mentioned	Patients diagnosed with sepsis or septic shock	30-Day	Sepsis-3	Investigation of prognostic value of proenkephalin for renal failure and mortality in patients with sepsis
Kim et al. [43] (2020)	Retrospective cohort study	Jan 2016–Sep 2019	1	ED	Patients ≥18 yr, with septic shock	In-hospital	Other	Evaluation of the prognostic value of the inferior vena cava diameter ratio measured on CT in patients with septic shock.
Kim et al. [44] (2020)	Prospective cohort study	Sep 2009–Jun 2015	1	ICU	Patients ≥ 18 yr, ICU LOS > 1 day with sepsis	30-Day, in-hospital	Other	To identify the risk factors of sepsis-associated delirium and its effects on patient outcomes in ICU patients
Kim et al. [45] (2020)	Retrospective cohort study	Jan 2015–Jun 2018	1	ICU	Patients ≥ 18 yr, with septic shock who underwent echocardiography	In-hospital	Sepsis-3	Association between left ventricular systolic dysfunction and mortality in patients with septic shock
Kim et al. [46] (2021)	Retrospective cohort study	Jan 2016–Feb 2019	1	ED	Patients ≥ 18 yr, with sepsis	28-Day	Sepsis-3	Investigation of the prognostic value of a modified simple scoring system based on the red cell distribution width, delta neutrophil index, and mean platelet volume to platelet count ratio in predicting the mortality of patients with sepsis
Kim et al. [47] (2022)	Prospective cohort study	Mar 2019–Jun 2020	1	ICU	ICU patients with sepsis	In-hospital	Sepsis-3	Assessment of the prognostic power of estimated plasma volume status in critically ill patients with sepsis
Kim et al. [48] (2022)	Retrospective cohort study	Oct 2015–Dec 2019	12[b]	ED	Patients ≥ 19 yr, with septic shock	28-Day	Sepsis-3	Evaluation of prognostic factors for late death in septic shock survivors
Kim et al. [49] (2022)	Prospective cohort study	May 2016–May 2020	1	ED	Patients ≥18 yr, with suspected or confirmed septic shock	28-Day	Sepsis-3	Investigation of the effects of myosteatosis percentage on mortality in patients with septic shock
Ko et al. [50] (2018)	Prospective cohort study	Oct 2015–Feb 2017	10[b]	ED	Patients ≥ 19 yr, with septic shock	28-Day, in-hospital	Sepsis-3	Evaluation of the prognosis of septic shock patients based on their lactate levels after initial fluid resuscitation
Ko et al. [51] (2019)	Prospective cohort study	Jun 2015–Dec 2016	1	ED	Patients ≥ 18 yr, with septic shock	30-Day	Other	Investigation of the association between the thrombotic microangiopathy score and 30-day mortality among patients with early-stage septic shock
Ko et al. [52] (2020)	Prospective cohort study	Oct 2015–Dec 2017	10[b]	ED	Patients ≥ 19 yr, with suspected or confirmed infection and evidence of refractory hypotension or hypoperfusion	In-hospital	Sepsis-3	Evaluation of the association between antibiotic administration timing and in-hospital mortality in septic shock patients

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Table 1. (Continued)

Study	Study design	Study period	No. of centers	Patient location	Cohort screened	Outcome	Diagnostic criteria	Study details
Lee et al. [53] (2012)	Retrospective cohort study	Jan 2010–Dec 2010	1	ED	Patients ≥18 yr, with severe sepsis	28-Day	Other	Investigation of the association between nutritional risk and mortality in severe sepsis patients
Lee et al. [54] (2013)	Prospective cohort study	Jul 2008–Jun 2011	1	ED	Patients ≥ 18 yr, with severe sepsis or septic shock	28-Day	Other	Investigation of the association between hypoalbuminemia and mortality in patients with severe sepsis and septic shock
Lee et al. [55] (2017)	Retrospective cohort study	Oct 2015–Apr 2016	1	ED	Patients ≥ 19 yr, with sepsis	30-Day	Sepsis-3	Investigation of the efficacy of red cell distribution width as a prognostic factor for Sepsis-3 patients
Lee et al. [56] (2018)	Retrospective cohort study	Mar 2007–Feb 2016	1	ED	Patients ≥18 yr, sepsis who underwent abdominal CT	28-Day	Sepsis-3	Evaluation of the association between muscle mass depletion and outcomes in sepsis patients
Lee et al. [57] (2021)	Prospective cohort study	Mar 2010 – Nov 2017	1	ED	Patients ≥ 18 yr, diagnosed with sepsis or septic shock	28-Day	Sepsis-3	Investigation of the association among the respiratory rate, oxygenation index, and mortality in patients with sepsis or septic shock
Lee et al. [58] (2021)	Retrospective cohort study	Jan 2016–Dec 2019	1	ED	Patients ≥ 19 yr, with sepsis and septic shock	30-Day	Sepsis-3	Investigation of the prognostic value of lactate levels and lactate clearance in sepsis and septic shock with initial hyperlactatemia
Lee et al. [59] (2022)	Prospective cohort study	Sep 2019–Feb 2020	16[a]	ED	Patients ≥ 19 yr, with sepsis	28-Day, in-hospital	Sepsis-3	Investigation of the association between preexisting clinical frailty and clinical outcomes in patients with sepsis
Oh et al. [60] (2017)	Retrospective cohort study	Jan 2010–Dec 2015	1	ED	Patients ≥18 yr, with severe sepsis or septic shock	28-Day	Sepsis-3	Assessment of the association between the serum chloride level and mortality in patients with severe sepsis or septic shock
Oh et al. [61] (2019)	Retrospective cohort study	Nov 2007–Mar 2016	1	ED	Patients ≥ 18 yr, with septic shock treated with early goal-directed therapy	28-Day	Other	Assessment of the prognostic significance of the lactate level in septic shock patients
Park et al. [62] (2012)	Prospective cohort study	Apr 2005–Feb 2009	12	ED, ICU	Patients ≥ 18 yr, with severe sepsis or septic shock	28-Day, in-hospital	Other	Investigation of clinical outcomes of ICU patients with community-acquired severe sepsis and septic shock
Park et al. [63] (2012)	Retrospective cohort study	Jan 2008–Dec 2010	1	ICU	Patients admitted to the medical ICU for sepsis	30-Day, in-hospital	Other	Investigation of the association between mild hypoglycemia and hospital mortality
Park et al. [64] (2015)	Prospective cohort study	Jan 2005–Jun 2007, Dec 2007–Jun 2008	1	ED	ED patients with severe sepsis and septic shock	In-hospital	Other	Validation assessment of the low oxygen extraction ratio to predict mortality
Park et al. [65] (2020)	Retrospective cohort study	Jan 2017–Jul 2018	1	ED	Patients ≥ 18 yr, with septic shock	28-Day	Other	Evaluation of the effects of early combination therapy with vitamin C and thiamine on ICU delirium-free days in patients with septic shock
Ryoo et al. [66] (2015)	Prospective cohort study	Jan 2010–Dec 2012	1	ED	Adult patients with sepsis who received early goal-directed therapy	28-Day	Other	Validation assessment of the MISSED score to predict mortality in patients with severe sepsis and septic shock
Ryoo et al. [67] (2019)	Prospective cohort study	Oct 2015–Dec 2017	10[b]	ED	Patients ≥18 yr, with septic shock	28-Day	Sepsis-3	Assessment of the prognostic value of lactate normalization
Song et al. [68] (2012)	Retrospective cohort study	Aug 2008–Jul 2010	1	ED	Sepsis patients ≥ 18 yr, without hypotension or hypoperfusion	In-hospital	Other	Investigation of factors for predicting early deterioration in sepsis patients with intermediate levels of serum lactate
Song et al. [69] (2021)	Retrospective cohort study	Jan 2016–31 Mar 2020	1	ED	Patients ≥ 18 yr, with sepsis	30-Day	Sepsis-3	Investigation of the association between the vasoactive-inotropic score and mortality in patients with sepsis
Suh et al. [70] (2013)	Retrospective cohort study	Jan–Dec 2010	1	ED	Patients ≥ 18 yr, with sepsis or septic shock excluding chronic renal replacement	In-hospital	Other	Investigation of the clinical characteristics of acute kidney injury in patients with sepsis and septic shock

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Table 1. (Continued)

Study	Study design	Study period	No. of centers	Patient location	Cohort screened	Outcome	Diagnostic criteria	Study details
Um et al. [71] (2018)	Prospective cohort study	Mar 2010–Sep 2016	1	ED	Patients ≥18 yr, with sepsis or septic shock	28-Day	Other	Evaluation of the relationship between the time to positivity blood culture and mortality in patients with sepsis and septic shock
Wang et al. [72] (2021)	Retrospective cohort study	Mar 2016–Dec 2018	3	ED	Patients ≥18 yr, with sepsis	28-Day, in-hospital	Sepsis-3	Association between health insurance status and outcomes of sepsis in adult patients
Yeo et al. [73] (2022)	Prospective cohort study	Sep 2019–Feb 2020	16[a]	Not mentioned	Patients with septic shock	28-Day, in-hospital	Sepsis-3	Evaluation of the effect of administering a vasopressor within 1 hr of first fluid loading on clinical outcomes in septic shock patients
Yoo et al. [74] (2020)	Prospective cohort study	Mar–Dec 2018	1	ICU	Patients with sepsis who were admitted to the medical ICU	30-Day	Other	Evaluation of the association between 25(OH) D and vitamin D binding protein levels and sepsis mortality
You et al. [75] (2022)	Prospective cohort study	Nov 2015–Dec 2017	11[b]	ED	Patients >18 yr, with septic shock	28-Day, in-hospital	Sepsis-3	Investigation of the rate of compliance with the surviving sepsis campaign 3-hr bundle for nighttime and daytime ED admissions and the clinical effects of compliance on mortality in patients with septic shock

ICU, Intensive care unit; LOS, length of stay; tRNA, transfer RNA; ED, emergency department; RCT, randomized controlled trial; qSOFA, quick Sequential Organ Failure Assessment; PIRO, predisposition, infection, response, and organ dysfunction; MEDS, Mortality in Emergency Department Sepsis; CT, computed tomography; MISSED, Mortality in Severe Sepsis in the Emergency Department.
[a]Korean Sepsis Alliance (KSA) registry. [b]Korean Shock Society (KoSS) registry.

Table 2. Subgroup analyses for sepsis and septic shock

Characteristic	Mortality			
	No. of studies	Proportion (95% CI)	P-value[a]	I^2 (%)
Sepsis				
28- or 30-day mortality				
Sepsis criteria				
Sepsis-3	17	22.7 (20.0–25.6)	<0.01	89
Other	10	29.1 (23.3–35.6)	<0.01	97
Study design				
Retrospective	17	22.6 (19.5–25.9)	<0.01	94
Prospective	10	29.1 (23.4–35.5)	<0.01	96
Included hospital				
Single center	22	23.3 (20.5–26.5)	<0.01	93
Multicenter	5	31.3 (22.1–27.7)	<0.01	98
In-hospital mortality				
Sepsis criteria				
Sepsis-3	13	28.1 (25.2–31.1)	<0.01	87
Other	4	21.6 (9.2–30.5)	<0.01	98
Study design				
Retrospective	10	23.8 (18.2–30.4)	<0.01	97
Prospective	7	30.5 (26.1–35.2)	<0.01	85
Included hospital				
Single center	11	24.8 (17.3–34.3)	<0.01	96
Multicenter	6	28.1 (25.7–30.7)	<0.01	80
Septic shock				
28- or 30-day mortality				
Sepsis criteria				
Sepsis-3	16	27.6 (22.3–33.5)	<0.01	98
Other	15	22.6 (18.8–26.8)	<0.01	95
Study design				
Retrospective	13	28.0 (21.1–36.0)	<0.01	98
Prospective	17	23.4 (20.1–27.0)	<0.01	95
Randomized controlled trial	1	18.0 (11.9–26.3)	-	-
Included hospital				
Single center	22	24.8 (19.8–30.7)	<0.01	98
Multicenter	9	26.0 (22.7–29.6)	<0.01	93
In-hospital mortality				
Sepsis criteria				
Sepsis-3	12	34.3 (27.2–42.2)	<0.01	97
Other	6	26.0 (19.4–33.9)	<0.01	95
Study design				
Retrospective	6	34.1 (21.1–50.2)	<0.01	99
Prospective	10	29.8 (25.4–34.7)	<0.01	93
Randomized controlled trial	2	29.6 (15.8–48.6)	<0.01	86
Included hospital				
Single center	11	33.3 (24.2–44.0)	<0.01	97
Multicenter	7	28.6 (23.8–34.1)	<0.01	94

CI, confidence interval.
[a]For heterogeneity.

Statistical analysis

Individual and pooled statistics were calculated as frequencies of sepsis and septic shock diagnosed at admission or during an ICU

stay to estimate mortality in the ICU or hospital and to estimate mortality at 28 or 30 days. A random effects model was used to assess mortality for each outcome. Separate analyses were performed in the following subgroups: diagnosed according to Sepsis-3 and non-Sepsis-3 criteria; retrospective and prospective studies; single-center and multicenter studies; and patient location (emergency room, ward, or ICU). Statistical heterogeneity was visually assessed using forest plots and formally assessed using I^2. Publication bias was evaluated using a Begg funnel plot. All analyses were performed using the R ver. 4.0.0 (The R Foundation for Statistical Computing) software packages "meta" (ver. 6.1-0) and "metafor" (ver. 3.8-1). A P-value of <0.05 was considered statistically significant.

RESULTS

Study selection

Our database search yielded 4,012 records. From them, 1,271 duplicates were removed, and 2,349 records were excluded in the review of titles and abstracts. Of the remaining 392 records, 331 were also excluded based on the full article review because they had an irrelevant population (n = 188), irrelevant outcome (n = 46), duplicated data (n = 80), animal study (n = 10), or experimental study (n = 7); details are provided in Supplementary Tables 2 and 3 [15–75]. Therefore, 61 studies of sepsis and septic shock mortality are included in this review [15–75]. Fig. 1 shows the study flow for the selection process.

Study characteristics

Of the 61 included studies, 26 were prospective cohort studies, 33 were retrospective cohort studies, and two were randomized clinical trials; 46 were single-center studies, and 15 were multicenter studies, nine of which investigated the same two prospective sepsis registries (five used the Korean Shock Society [KoSS] registry [48,50,52,67,75] and four used the Korean Sepsis Alliance [KSA] registry [28,33,59,73]). The KoSS registry was established in 2013 to study patients who went into septic shock in emergency departments (EDs); it has been prospectively collecting data since October 2015 [76]. At the beginning of enrollment, 10 EDs participated, but in the most recent study, which used data up to

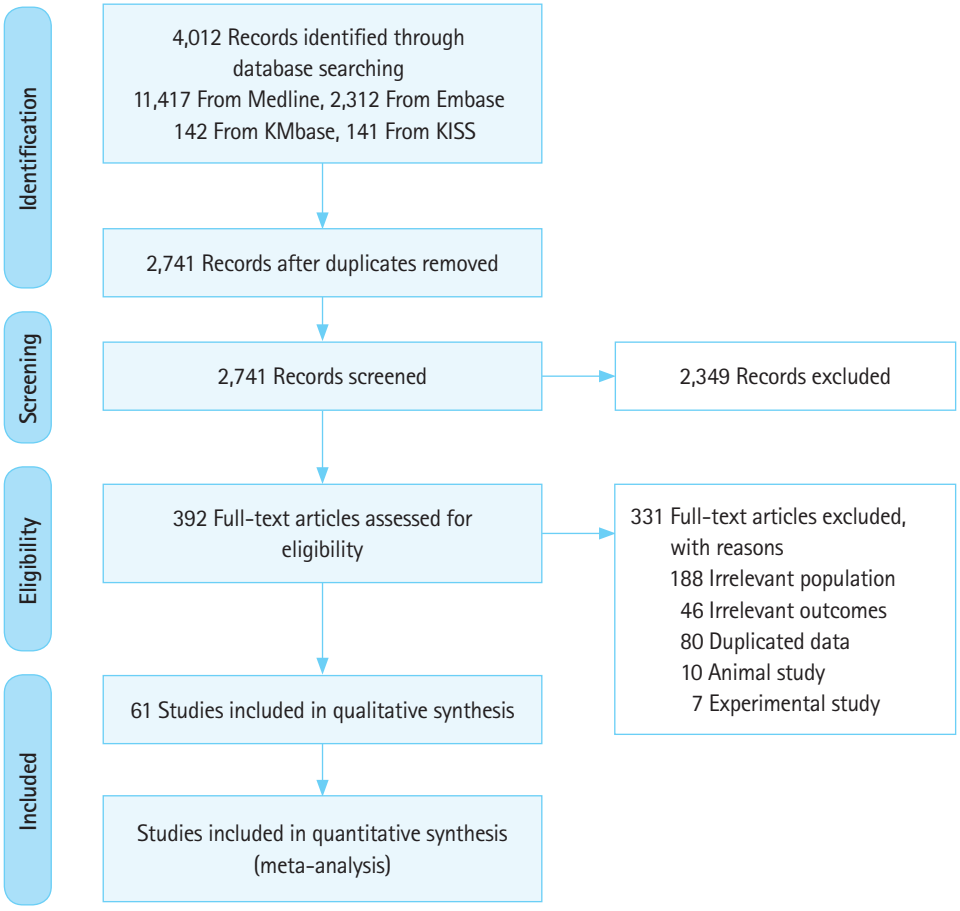

Fig. 1. Flowchart for included studies. KMbase, Korean Medical Database; KISS, Korean Studies Information Service System.

December 2019, 12 EDs participated [48]. The KSA registry was organized mainly by pulmonologists and critical care medicine physicians from 16 secondary and tertiary hospitals nationwide; this database covers 19 hospitals and includes patients who were diagnosed with sepsis in EDs or hospitals [28].

Data on 28- or 30-day mortality and in-hospital mortality among sepsis patients were extracted from 27 and 17 studies, respectively, and those data for septic shock patients were extracted from 32 and 18 studies, respectively. Table 1 summarizes the characteristics of the included studies [15–75].

Sepsis mortality

The studies that examined 28- or 30-day mortality from sepsis analyzed 22,050 patients. The 28- or 30-day mortality from sepsis diagnosed using the Sepsis-3 criteria was 22.7% (95% confidence interval [CI], 20.0%–25.6%; $I^2 = 89\%$) (Table 2 and Fig. 2) [15,17,21,26,27,35,39,42,46,50,55–59,69,72]. The range of mortality in the included studies was 14.4% to 40.8%. In addition, the 28- or 30-day mortality rate by including all sepsis criteria was 24.8% (95% CI, 22.1%–27.7%; $I^2 = 95\%$) (Supplementary Fig. 1) [15–17,20,21,26,27,29–31,34,35,39,42,44,46,50,55–59,63,69,71,72,74]. In the subgroup analyses, 28- or 30-day mortality from sepsis was 22.6% (95% CI, 19.5%–25.9%; $I^2 = 94\%$) in retrospective cohort studies, 29.1% (95% CI, 23.4%–35.5%; $I^2 = 96\%$) in prospective studies, 23.3% (95% CI, 20.5%–26.5%; $I^2 = 93\%$) in single-center studies, and 31.3% (95% CI, 23.4%–40.4%; $I^2 = 98\%$) in multicenter studies (Table 2).

The studies of in-hospital mortality from sepsis analyzed 11,595 patients. In-hospital mortality from sepsis diagnosed using the Sepsis-3 criteria was 28.1% (95% CI, 25.2%–31.1%; $I^2 = 87\%$) (Table 2 and Fig. 3) [15,17,26–28,32,33,39,41,47,50,59,72]. The range of mortality was 15.7% to 47.0%. In addition, in-hospital mortality by including all sepsis criteria was 26.3% (95% CI, 22.6%–30.5%; $I^2 = 95\%$) (Supplementary Fig. 2) [15,17,26–28,32,33,39,41,44,47,50,59,63,68,70,72]. In the subgroup analyses, the in-hospital mortality from sepsis was 23.8% (95% CI, 18.2%–30.4%; $I^2 = 97\%$) in retrospective cohort studies, 30.5% (95% CI, 26.1%–35.2%; $I^2 = 85\%$) in prospective studies, 24.8% (95% CI, 17.3%–34.3%; $I^2 = 96\%$) in single-center studies, and 28.1% (95% CI, 25.7%–30.7%; $I^2 = 80\%$) in multicenter studies (Table 2).

Septic shock mortality

The studies for 28- or 30-day mortality from septic shock analyzed 25,101 patients. The 28- or 30-day mortality from septic shock diagnosed using the Sepsis-3 criteria was 27.6% (95% CI, 22.3%–33.5%; $I^2 = 98\%$) (Table 2 and Fig. 4) [15,17,25–27,42,46,48–50,58,60,67,69,73,75]. The range of mortality was 12.6% to 52.9%. In addition, the 28- or 30-day mortality rate by including all sepsis criteria from septic shock was 25.1% (95% CI, 21.8%–28.8%; $I^2 = 97\%$) (Supplementary Fig. 3) [15–17,19,24–27,29,36–38,42,46,48–51,53,54,58,60-62,65–67,69,73–75]. In the subgroup analyses, the 28- or 30-day mortality from septic shock was 28.0% (95% CI, 21.1%–36.0%; $I^2 = 98\%$) in retrospective cohort studies, 23.4% (95% CI, 20.1%–27.0%; $I^2 = 95\%$) in prospective studies, 18.0% in the one randomized controlled trial, 24.8% in single-center studies (95% CI, 19.8%–30.7%; $I^2 = 98\%$), and 26.0% in

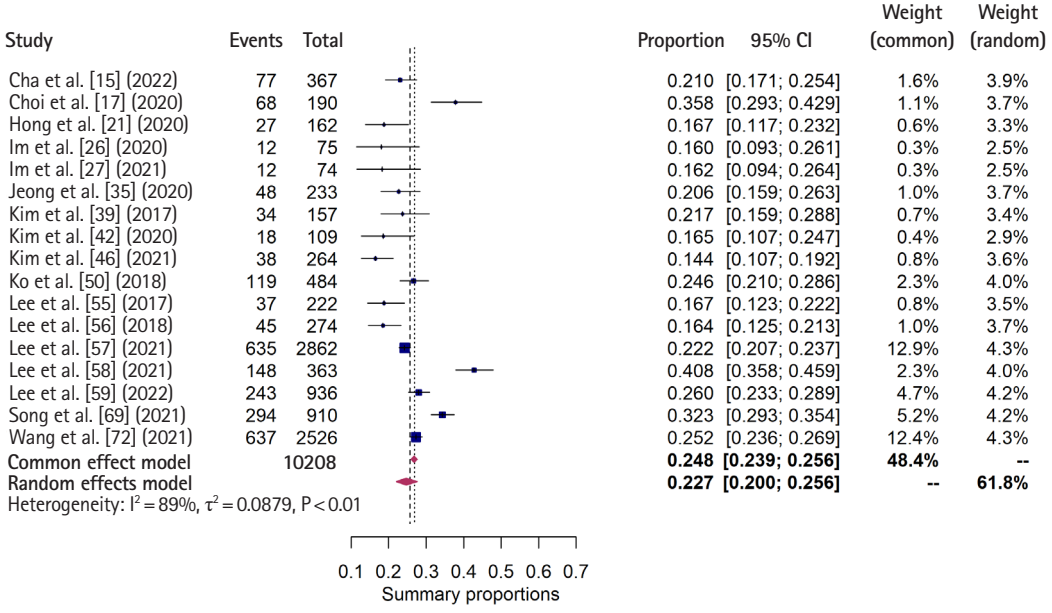

Fig. 2. Forest plot for 28- or 30-day mortality from sepsis using the Sepsis-3 criteria. CI, confidence interval.

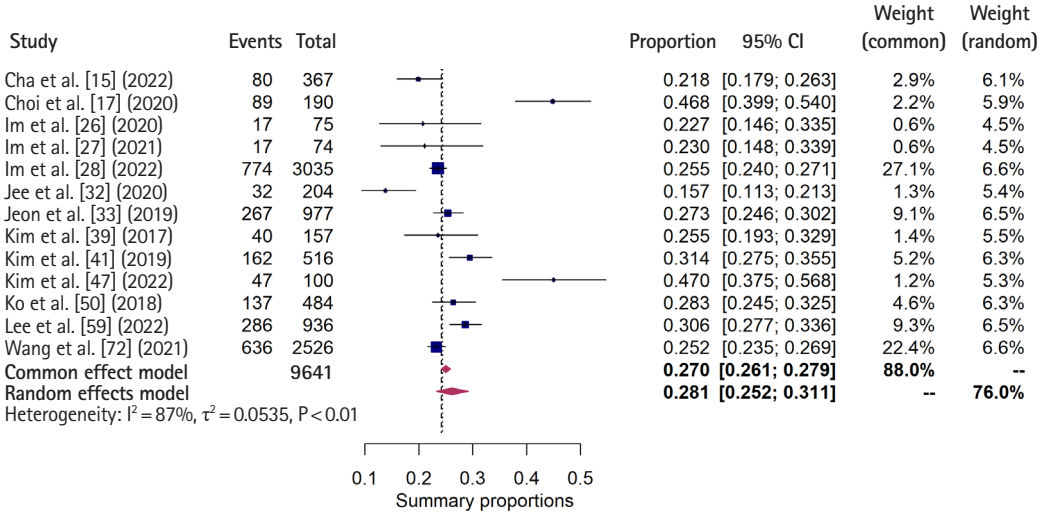

Fig. 3. Forest plot for in-hospital mortality from sepsis using the Sepsis-3 criteria. CI, confidence interval.

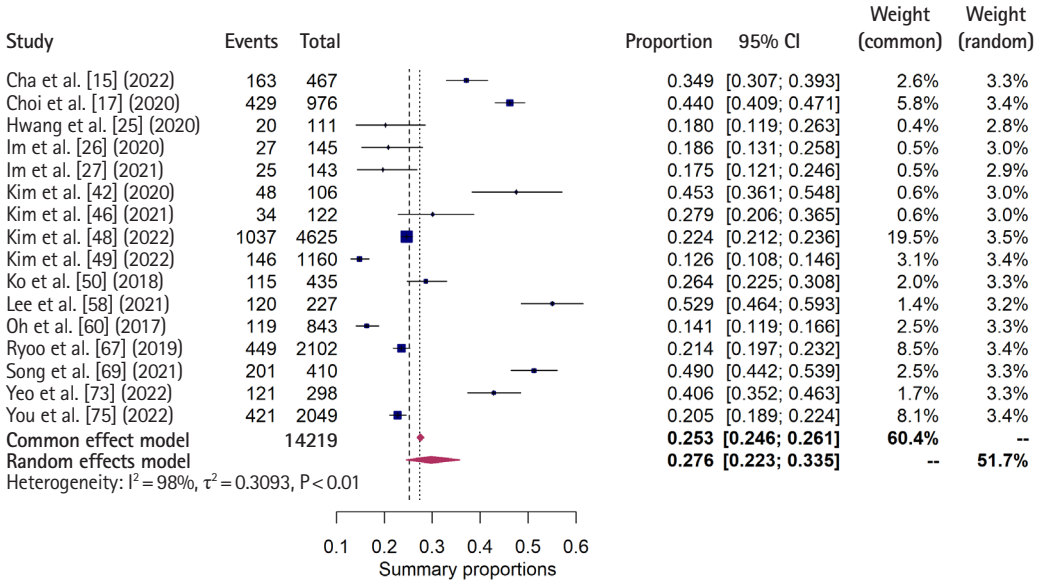

Fig. 4. Forest plot for 28- or 30-day mortality from septic shock using the Sepsis-3 criteria. CI, confidence interval.

multicenter studies (95% CI, 22.7%–29.6%; $I^2 = 93\%$) (Table 2).

The studies of in-hospital mortality from septic shock analyzed 10,769 patients. In-hospital mortality from septic shock diagnosed using the Sepsis-3 criteria was 34.3% (95% CI, 27.2%–42.2%; $I^2 = 97\%$) (Table 2 and Fig. 5) [15,18,25–27,40,45,47,50,52,73,75]. The range of mortality was 21.6% to 50.0%. In addition, in-hospital mortality by including all sepsis criteria from septic shock was 31.4% (95% CI, 26.1%–37.3%; $I^2 = 97\%$) (Supplementary Fig. 4) [15,18,22,23,25–27,37,40,43,45,47,50,52,62,64,73,75]. In the subgroup analyses, the in-hospital mortality from septic shock was 34.1% (95% CI, 21.1%–50.2%; $I^2 = 99\%$) in retrospective cohort studies, 29.8% (95% CI, 25.4%–34.7%; $I^2 = 93\%$) in prospective studies, 29.6% (95% CI, 15.8%–48.6%; $I^2 = 86\%$) in randomized controlled trials, 33.3% (95% CI, 24.2%–44.0%; $I^2 = 97\%$) in single-center studies, and 28.6% (95% CI, 23.8%–34.1%; $I^2 = 94\%$) in multicenter studies (Table 2).

Quality assessment

When we used the Newcastle-Ottawa Scale to evaluate the quality of the included articles, we found that 19 studies were of poor quality. The following assessments were derived from the other studies, which were rated as good quality: 24 studies received 9 points, and the others received 7 or 8 points. Using the Risk of Bias 2 for the two randomized controlled trials, one study had low bias, and the other study had high bias (Supplementary Tables 2, 3).

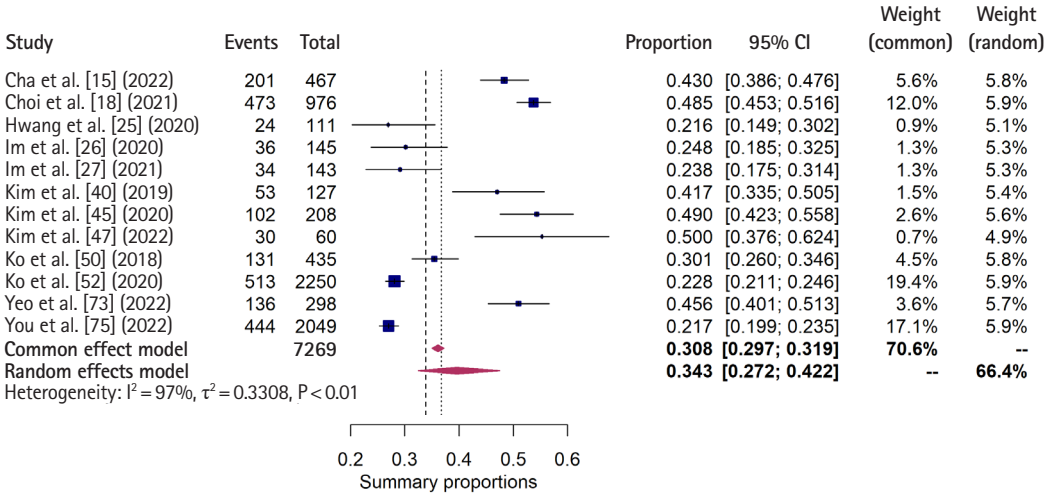

Fig. 5. Forest plot for in-hospital mortality from septic shock using the Sepsis-3 criteria. CI, confidence interval.

Publication bias

All the funnel plots made to assess the publication bias for each outcome showed symmetry. The funnel plots for sepsis (28- or 30-day and in-hospital mortality) and septic shock (28- or 30-day and in-hospital mortality) are shown in Supplementary Fig. 5.

DISCUSSION

To the best of our knowledge, this is the first meta-analysis to investigate mortality among sepsis and septic shock patients in Korea. We found that the pooled mean of the 28- or 30-day mortality rate and in-hospital mortality rate are 24.8% and 26.3%, respectively, in sepsis patients, and 25.1% and 31.4%, respectively, in septic shock patients. Those data reflect the actual clinical prognosis of sepsis patients classified according to the sepsis criteria used in hospitals. The 28- or 30-day sepsis mortality rate in a national cohort study by Oh et al. [77] is higher than our result at approximately 30%. However, that study used National Health Insurance Service of Korea data and ICD-10 codes to classify sepsis patients; therefore, the diagnosis of sepsis might have been overestimated by including septic shock. Moreover, deaths unrelated to sepsis might have been included in the overall mortality data of that study.

The sepsis mortality rates in the present study are higher than those reported in a recent meta-analysis for the United States (19.6%) and Australia (18.7%), but similar to that in Europe (23.6%) and lower than that in China (29.1%) [6,7]. In contrast, the mortality rate among septic shock patients appears to be similar or lower than that in other countries (North America, 33.7%; Australia, 26.4%; Europe, 32.5%; China, 35.9%) [6,7]. Most of the sepsis studies evaluated in our meta-analysis included sepsis with shock, introducing the possibility of heterogeneity among studies and inaccurately high death rates. In addition, because our study includes research from the past 10 years, our data are based on several sets of sepsis criteria (Sepsis-1, -2, and -3), and that inconsistency could increase heterogeneity. On the other hand, we found clinically relevant results when the Sepsis-3 criteria were used.

Another finding of this study is that in-hospital mortality was higher than 28- or 30-day mortality in sepsis and septic shock patients. This result is consistent with that of previous meta-analyses conducted by Vincent et al. [78] and Liu et al. [7] in Europe, North America, and China. The studies included in this meta-analysis presented their outcomes as either 28- or 30-day mortality or in-hospital mortality, and the study populations differed in their inclusion of sepsis or septic shock patients. In other words, 28- or 30-day mortality and in-hospital mortality were not measured consecutively in the same studies but represent the sum of values extracted from different studies. Therefore, because of the statistical constraints of a meta-analysis, caution is needed in interpreting the result that in-hospital mortality was higher than 28- or 30-day mortality in sepsis and septic shock patients.

We analyzed the mortality rates from sepsis and septic shock after dividing the patients into those diagnosed with the Sepsis-3 criteria and those diagnosed with other criteria. The 28- or 30-day mortality rate and in-hospital mortality rates for septic shock diagnosed according to the Sepsis-3 criteria were 27.6% and 34.3%, respectively, which are higher than those based on the non-Sepsis-3 criteria (28- or 30-day mortality, 22.6%; in-hospital mortality, 26.0%) (Figs. 4, 5) [15,17,18,25–27,40,42,45–50,52,58,60,67,69,73,75] That finding is consistent with a previous meta-

analysis in Europe and North America, which reported that in-hospital septic shock mortality increased significantly, from 39.0% to 52.1%, when the Sepsis-3 criteria were used for diagnosis [78]. The criteria prior to Sepsis-3 defined sepsis as a state with at least two of the four systemic inflammatory response syndrome (SIRS) criteria, which focus solely on the inflammatory response [79,80]. Because the SIRS criteria do not exactly reflect organ dysfunction and life-threatening conditions, the new Sepsis-3 criteria, which were published in 2016, include the Sequential Organ Failure Assessment (SOFA) score and lactate level [1]. Therefore, the increase in septic shock mortality when using the Sepsis-3 criteria could be explained by the advanced disease severity reflected by the change in diagnostic criteria.

Variations in mortality rates among the included studies are likely attributable to differences in the disease severity of the patients. For example, to identify the risk factors of sepsis-associated delirium and their effects on the outcomes of ICU patients, Kim et al. [44] excluded patients with < 24 hours of ICU stay or deep or full sedation from their assessment of 28- or 30-day sepsis mortality. Those factors could exacerbate the severity of the patients included, resulting in a higher mortality rate. In addition, Hong et al. [20] excluded patients admitted for hemodialysis or peritoneal dialysis, transferred from other hospitals, or admitted for palliative care. In that case, the mortality rate might have been underreported due to the exclusion of critically ill patients.
It is challenging to generalize the findings of this study to all sepsis patients in Korea. The majority of the research included in this meta-analysis was conducted at tertiary medical institutions or large hospitals, and the sepsis registries include only hospitals with the ability to provide quality care. Thus, data from institutions that are treating sepsis but not reporting their results were not included here. If the outcomes from ineffective-performance medical settings are not considered, the overall results of sepsis treatment might appear to be better than they actually are. Additionally, a recent Korean report indicated that the surviving sepsis campaign had low compliance [81]. Therefore, the mortality rate might increase further when the sepsis outcomes of all medical institutions are considered. Further investigation is needed to examine sepsis outcomes according to the performance level of the medical institution.

This review has several limitations. First, heterogeneity among the studies included in the meta-analysis is very high, all over 95%. One reason for this high heterogeneity is the diversity of study designs included in the analysis. In addition, the definition of sepsis in the included studies was heterogeneous because the new Sepsis-3 criteria were only published in 2016, and that diversity of definitions might have resulted in a wide range of mortality rates. Therefore, we analyzed the mortality rates according to the use of the Sepsis-3 and non-Sepsis-3 criteria. Second, the sepsis criteria were met when patients were included in these studies, but it is possible that critically ill patients might have been only selectively included based on particular domains, such as the lactate level. Third, when several studies were conducted in a single institution or used the same registry during the same study period, we selected only the study with the longest study period and largest sample size because we suspected that the study population might be duplicated. Thus, despite our efforts to include as many studies as possible, we cannot completely rule out the possibility of selection bias. Fourth, despite that attempt to prevent duplicated data, the possibility of duplication between registry studies and single-center studies whose data are included in that registry remains. Fifth, the medical history and care conditions of individual patients, which influence the mortality rate, were not considered. Personal factors were not considered in this study, and our meta-analysis simply confirmed the mortality rate.

In conclusion, our study shows that the mortality rates from sepsis and septic shock in Korea are high. In the case of septic shock, the in-hospital mortality rate is approximately 30%, and that rate was higher when septic shock was diagnosed according to the Sepsis-3 criteria than when it was diagnosed using other criteria.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Search strategy
Supplementary Table 2. Quality assessment using Newcastle-Ottawa Scale for cohort studies
Supplementary Table 3. Quality assessments using Risk of Bias 2 for randomized controlled trials
Supplementary Fig. 1. Forest plot for 28- or 30-day sepsis mortality by including all sepsis criteria.
Supplementary Fig. 2. Forest plot for in-hospital sepsis mortality by including all sepsis criteria.
Supplementary Fig. 3. Forest plot for 28- or 30-day septic shock mortality by including all sepsis criteria.
Supplementary Fig. 4. Forest plot for in-hospital septic shock mortality by including all sepsis criteria.
Supplementary Fig. 5. Funnel plots for each outcome.
Supplementary materials are available from https://doi.org/10.15441/ceem.23.005.

ETHICS STATEMENTS

Not applicable.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: MN, CA; Data curation: MN, YP, MW; Formal analysis: IYK, JL; Visualization: CA; Writing–original draft: MN, CA; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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