Original Contribution

Prognostic performance of disease severity scores in patients with septic shock presenting to the emergency department

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ABSTRACT

Background: An accurate disease severity score that can quickly predict the prognosis of patients with sepsis in the emergency department (ED) can aid clinicians in distributing resources appropriately or making decisions for active resuscitation measures. This study aimed to compare the prognostic performance of quick sequential organ failure assessment (qSOFA) with that of other disease severity scores in patients with septic shock presenting to an ED.
Methods: We performed a prospective, observational, registry-based study. The discriminative ability of each disease severity score to predict 28-day mortality was evaluated in the overall cohort (which included patients who fulfilled previously defined criteria for septic shock), the newly defined sepsis subgroup, and the newly defined septic shock subgroup.
Results: A total of 991 patients were included. All disease severity scores had poor discriminative ability for 28-day mortality. The sequential organ failure assessment and acute physiology and chronic health evaluation II scores had the highest area under the receiver-operating characteristic curve (AUC) values, which were significantly higher than the AUC values of other disease severity scores in the overall cohort and the sepsis and septic shock subgroups. The discriminative ability of each disease severity score decreased as the mortality rate of each subgroup increased.
Conclusions: All disease severity scores, including qSOFA, did not display good discrimination for 28-day mortality in patients with serious infection and refractory hypotension or hypoperfusion; additionally, none of the included scoring tools in this study could consistently predict 28-day mortality in the newly defined sepsis and septic shock subgroups.

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1. Introduction

Sepsis and septic shock are the leading causes of mortality in severely ill patients, and result in a large number of deaths worldwide [1]. Despite this, sepsis is difficult to define. In 1991, the first definitions of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock were introduced with detailed physiologic categories of severity. These terminologies and severity scales were recommended for use as a tool for predicting mortality [2]. At the International Sepsis Definitions Conference in 2001, the basic concepts that had been described a decade earlier remained unchanged [3]. However,

in 2016, The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) released a revision, defining sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection." For clinical use, organ dysfunction was represented by an increase in the sequential organ failure assessment (SOFA) score of ≥2 points. Septic shock was defined as "a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone." Septic shock was diagnosed by identifying a vasopressor requirement to maintain a mean arterial pressure (MAP) ≥65 mm Hg and serum lactate concentration > 2 mmol/L despite adequate fluid resuscitation [4].

In addition to the definitions described above, the task force of Sepsis-3 introduced the quick sequential organ failure assessment (qSOFA) as a new bedside screening method to identify patients with infection who are likely to have poor outcomes. Patients with infection can be considered to have poor outcomes if they have 2 or more of the following criteria: respiratory rate ≥ 22 breaths/min, altered mental status, or systolic blood pressure (SBP) ≤100 mm Hg, especially in patients who are out of hospital, in the general ward, and in the emergency department (ED) [5]. However, qSOFA was not validated for patients with sepsis and septic shock as defined by Sepsis-3, and the prognostic performance of qSOFA is controversial. Williams et al. stated that SIRS criteria and qSOFA discriminated organ dysfunction similarly, and that qSOFA was highly specific, but not sensitive for predicting organ dysfunction (96.1% and 29.7%, respectively) [6]. Furthermore, Wang et al. demonstrated that the prognostic performance of qSOFA was inferior to that of other disease severity scores, such as the Mortality in Emergency Department Sepsis (MEDS) score [7]. Therefore, additional research evaluating the predictive value of qSOFA is needed, especially in patients with sepsis and septic shock as defined by Sepsis-3.

Most patients with sepsis are initially assessed in the ED. As these patients present with a wide spectrum of disease courses and mortality risks, an accurately predictive disease severity score is important, not only to predict mortality, but also to distribute resources appropriately or make decisions regarding resuscitation measures. Thus, the objective of this study was to compare the prognostic performance of qSOFA with that of other disease severity scores for patients in the ED with septic shock, as defined by previous criteria and the new definitions of sepsis and septic shock.

2. Methods

2.1. Study design and populations

We performed a prospective, observational, registry-based study to validate the performance of several scoring systems for predicting the prognosis of patients with newly defined sepsis and septic shock in EDs. We used the Korean Shock Society (KoSS) septic shock registry and analyzed data registered from October 2015 to February 2017. The KoSS is a collaborative research network comprising 10 EDs with the aim of evaluating the clinical characteristics, therapeutic interventions, and outcomes of patients with septic shock in EDs. The methodology of the KoSS septic shock registry has been previously reported in detail [8-10]. Patients aged 19 years or older who met the following inclusion criteria were enrolled: suspected or confirmed infection and evidence of refractory hypotension or hypoperfusion. SIRS criteria were not obligatory for inclusion. Hypotension was defined as an SBP <90 mm Hg, a MAP <70 mm Hg, or a decrease in SBP of >40 mm Hg. Refractory hypotension was defined as persistent hypotension after intravenous fluid challenge (≥1 L administered over 30 min) or as the need for vasopressors after fluid resuscitation. Hypoperfusion was defined as a serum lactate concentration of ≥4 mmol/L. Patients who signed a "Do not attempt resuscitation" order met the inclusion criteria 6 h after ED arrival, were transferred from other hospitals without meeting the inclusion criteria upon ED arrival, or were directly transferred from EDs to other hospitals were excluded from the KoSS septic shock

registry. In this study, we also excluded patients with missing data. The study was approved by the institutional review boards of the individual participating centers and informed consent was obtained according to local institutional review board policy.

2.2. Data collection

The following data were retrieved from the KoSS septic shock registry: demographics, comorbidities, vital signs, suspected infection sources, serum lactate levels, disease severity scores, and interventions. The severity of enrolled patients was assessed using a disease severity score. The qSOFA, SIRS criteria [11], SOFA score [12], and acute physiology and chronic health evaluation (APACHE) II score [13] were evaluated using the worst parameters within 24 h of ED arrival. Additionally, we calculated the mortality in severe sepsis in the emergency department (MISSED) score [14] using demographic and laboratory variables recorded within the first 24 h after ED arrival.

In patients who were enrolled in the KoSS septic shock registry, those with an increase in the SOFA score of ≥2 points at the time of study enrollment were defined as having newly defined sepsis. Among the subgroup of patients with newly defined sepsis, patients with vasopressor requirement to maintain a MAP ≥65 mm Hg and serum lactate concentration >2 mmol/L despite adequate fluid resuscitation were defined as having newly defined septic shock. The primary outcome was overall mortality at 28 days after presentation.

2.3. Statistical analysis

Statistical analysis was performed using SAS version 9.2 (SAS Inc., Cary, NC, USA). The results are presented as mean $\pm$ standard deviation (SD) or median (interquartile range) for continuous variables and frequencies (%) for categorical variables. For comparisons of continuous variables, we used independent two-sample *t*-tests if the data were normally distributed or the Mann–Whitney *U* test if the data were not normally distributed. The chi-squared test or Fisher's exact test were used for categorical variables. The generalized estimating equation method was used to compare variables among overall, sepsis, and septic shock subgroups, as some patients were included in more than one subgroup. The prognostic performance of each disease severity score was assessed in the overall cohort, sepsis subgroup, and septic shock subgroup. The discriminative ability of each disease severity score to predict 28-day mortality was evaluated using area under the receiver-operating characteristic curve (AUC) values with their 95% confidence intervals (CIs). A standard bootstrap method with resampling 1000 times was used to compare AUCs among the disease severity scores in each subgroup and to compare AUCs of each disease severity score among the three subgroups. P < 0.05 was considered statistically significant.

3. Results

A total of 1046 patients were enrolled during the study period. Fifty-five patients with incomplete data were excluded, and 991 patients were included for the analysis. Of these, 819 (82.6%) patients met the Sepsis-3 criteria for sepsis (newly defined sepsis) and 361 (36.4%) patients for septic shock (newly defined septic shock) (Fig. 1). The baseline characteristics of each group are summarized in Table 1. Age and sex were not different among the overall, sepsis, and septic shock subgroups, but initial respiratory and heart rates in the septic shock subgroup were higher than those in the overall cohort and sepsis subgroup. Disease severity scores, with the exception of SIRS, were different among the subgroups. The 28-day mortalities were 22.3%, 24.7%, and 29.6% in the overall cohort, newly defined sepsis subgroup, and newly defined septic shock subgroup, respectively. In the overall patient group, the mortality rate was 1.93 times higher when the qSOFA score was ≥2 than when the score was <2. However, in patients with newly
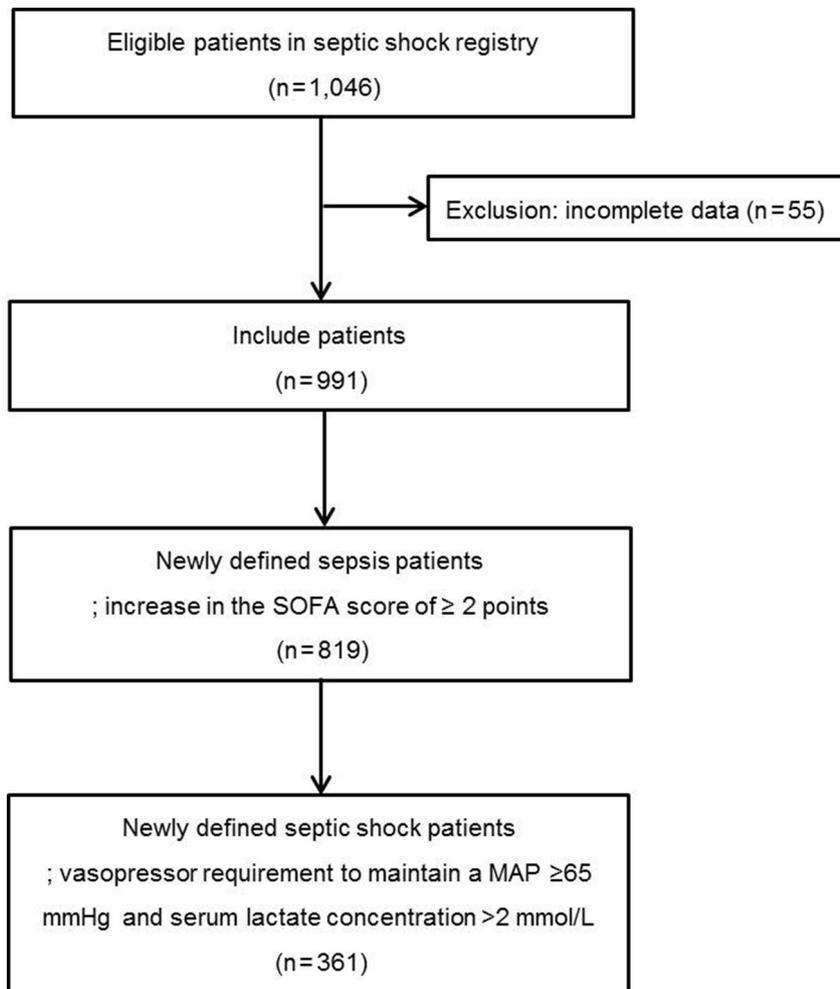
Fig. 1. Flowchart of the study population. SOFA, sequential organ failure assessment; MAP, mean arterial pressure.

defined sepsis and septic shock, mortality rates decreased by 1.86 times and 1.57 times, respectively.

In the overall study cohort, the average of the APACHE II, SOFA, qSOFA, and MISSED scores were considerably higher in non-survivors (P < 0.001), but SIRS scores were not significantly different (P = 0.40). These results were similar in patients with sepsis and in those with septic shock, with the exception of the MISSED score in patients with septic shock (Table 2). A qSOFA score ≥2 had moderate sensitivity for 28-day mortality in the overall cohort (65.6%; 95% CI, 59.3–71.9), newly defined sepsis (66.3%; 95% CI, 59.8–72.9), and septic shock (70.1%; 95% CI, 61.4–78.8) subgroups. A qSOFA score ≥2 also showed moderate specificity in all subgroup analyses (overall: 54.8%; 95% CI, 51.3–58.3; sepsis: 53.5%; 95% CI, 49.5–57.4; and septic shock: 44.5%; 95% CI, 38.4–50.6). However, a SIRS score ≥2 had high sensitivity for 28-day mortality in overall (91.9%; 95% CI, 88.2–95.5), newly defined sepsis (91.1%; 95% CI, 87.2–95.0), and septic shock (91.6%; 95% CI, 86.3–96.8) subgroups, while it showed poor specificity in all subgroup analyses (overall: 11.0%; 95% CI, 8.7–13.2; sepsis: 10.5%; 95% CI, 8.0–12.9; and septic shock: 6.7%; 95% CI, 3.6–9.8).

Receiver-operating characteristic curve analysis showed that all scoring systems had poor discriminative ability for 28-day mortality. The SOFA and APACHE II scores had the highest AUC values, which were significantly higher than the AUC values of qSOFA, SIRS, and MISSED scores in the overall cohort and significantly higher than the AUC values of the SIRS criteria and MISSED score in the sepsis and septic shock subgroups (Fig. 2). In comparison among the subgroups, the AUC of SOFA scores for the overall cohort was higher than that for the sepsis subgroup (P = 0.004); otherwise, there

were no statistical differences between AUC values of each scoring system for each subgroup.

4. Discussion

Disease severity scores are considered useful for stratifying patients with sepsis according to risk [15]. Appropriate recognition of high-risk patients leads to timely treatment, and is therefore expected to improve prognosis [16-19]. Thus, various disease severity scoring systems have been developed and validated to date. In this prospective, multi-center, observational study, all disease severity scores, including qSOFA, did not display good discrimination for 28-day mortality in patients with serious infection and refractory hypotension or hypoperfusion; furthermore, all scores could not consistently predict the 28-day mortality of patients in the newly defined sepsis and septic shock subgroups. Although the mortality of patients with qSOFA scores ≥2 was 1.9 times higher than that of patients with qSOFA scores <2, the predictive performance of qSOFA for 28-day mortality was unsatisfactory.

The SIRS, APACHE II, and SOFA scores remain the most frequently cited measures of disease severity [11-13]. However, each of these systems has inherent shortcomings. SIRS scores appear to be less predictive in patients with severe infection and high mortality. Henriksen et al. found that among 1169 patients who presented to the ED and were admitted for infection, in which SIRS was observed in 75.8%, SIRS was not associated with an increased mortality risk (adjusted hazard ratio, 1.17; 95% CI, 0.84–1.64) [20]. In addition, Williams et al. reported that SIRS was present in 89% of patients with shock (mortality, 23.8%); however, SIRS did not reflect mortality risk in patients with shock, although it was

Table 1
Comparison of baseline characteristics in overall, sepsis, and septic shock group.

Variables	Overall (1) (N = 991)	Sepsis (2) (N = 819)	Septic shock (3) (N = 361)	Global P-value	Post hoc P-value		
					(1) vs. (2)	(1) vs. (3)	(2) vs. (3)
Age (years, mean ± SD)	68.3 ± 13.5	68.6 ± 13.4	67.7 ± 13.3	0.13	0.23	0.27	0.10
Sex (male, %)	563 (56.8)	461 (56.3)	212 (58.7)	0.35	0.47	0.36	0.21
Initial vital signs (mean ± SD)							
Systolic blood pressure (mm Hg)	99.2 ± 29.2	99.5 ± 29.7	100.2 ± 30.6	0.55	0.35	0.40	0.57
Respiratory rate (per minute)	22.0 ± 5.5	22.1 ± 5.7	22.8 ± 5.8	0.003	0.28	0.001	0.001
Heart rate (per minute)	108.6 ± 25.7	109.1 ± 25.8	111.8 ± 25.6	0.01	0.16	0.003	0.009
Body temperature (°C)	37.6 ± 1.8	37.6 ± 1.9	37.5 ± 2.4	0.35	0.31	0.16	0.19
Lactate, initial	4.2 ± 3.3	5.4 ± 3.3	5.4 ± 3.3	<0.001	0.54	<0.001	<0.001
Comorbidities (%)							
Diabetes	289 (29.2)	244 (29.8)	129 (35.7)	0.003	0.33	0.001	0.001
Chronic lung disease	74 (7.5)	66 (8.1)	20 (5.5)	0.02	0.07	0.07	0.02
Chronic liver disease	120 (12.1)	101 (12.3)	62 (17.2)	0.001	0.63	0.001	0.000
Suspected infection focus (%)							
Respiratory infection	312 (31.5)	264 (32.2)	108 (29.9)	0.24	0.26	0.42	0.21
GI tract infection	171 (17.3)	131 (16.0)	60 (16.6)	0.11	0.04	0.69	0.67
Hepatobiliary tract infection	213 (21.5)	185 (22.6)	93 (25.8)	0.03	0.05	0.02	0.06
Urinary tract infection	238 (24.0)	201 (24.5)	93 (25.8)	0.32	0.38	0.37	0.21
Intervention (%)							
Vasopressor	719 (72.6)	748 (91.3)	361 (100)	<0.001	<0.001	<0.001	<0.001
ICU admission	627 (36.7)	548 (66.9)	291 (80.6)	<0.001	<0.001	<0.001	<0.001
Mechanical ventilation	288 (29.1)	253 (30.9)	150 (41.6)	<0.001	<0.001	<0.001	<0.001
Renal replacement therapy	162 (16.4)	146 (17.8)	99 (27.4)	<0.001	0.001	<0.001	<0.001
Disease severity scores							
qSOFA (median, IQR)	1 (1–2)	2 (1–2)	2 (1–2)	<0.001	<0.001	<0.001	0.001
SIRS (median, IQR)	3 (2–3)	3 (2–3)	3 (2–3)	0.22	0.29	0.11	0.19
SOFA, max (median, IQR)	8 (5–11)	8 (6–11)	10 (7–12)	<0.001	<0.001	<0.001	<0.001
APACHE II score (median, IQR)	18 (13–24)	19 (14–25)	22 (17–28)	<0.001	<0.001	<0.001	<0.001
MISSED score (median, IQR)	2 (2–3)	2 (2–3)	2 (2–3)	0.004	0.02	0.003	0.02
Mortality, overall (%)	221 (22.3)	202 (24.7)	107 (29.6)	<0.001	<0.001	<0.001	0.004

SD, standard deviation; ICU, intensive care unit; qSOFA, quick sequential organ failure assessment; IQR, interquartile range; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; APACHE II, acute physiology and chronic health evaluation II; MISSED, mortality in severe sepsis in the emergency department.

associated with an increased risk of organ dysfunction and increased odds of mortality in patients without organ dysfunction [6]. Similarly, 89.7% of patients in our study met 2 or more of the SIRS criteria, and SIRS displayed the poorest discrimination. SOFA scores can be calculated using physiological and laboratory values, but they do not take into account host factors, such as age and comorbidities, which are known to be independent risk factors associated with mortality in patients with sepsis [12]. Moreover, a wide variation in mortality risk has been previously shown to be associated with a SOFA score of 2 in each organ [6].

qSOFA is designed to be easier and more convenient to implement at the bedside and does not require laboratory values. The APACHE II score ranges from 0 to 71 and includes 14 variables. The SOFA score ranges from 0 to 24 and includes 6 components. The MEDS score includes 9 variables that can yield a total score of 27. By contrast, qSOFA contains only 3 variables with a score ranging from just 0 to 4 when all variables are combined. For this reason, qSOFA was introduced by the task force of Sepsis-3 to be used in the initial assessment of a patient in a crowded ED [21]. However, qSOFA also has some limitations in screening severe sepsis. In the KoSS septic shock registry, qSOFA was calculated 3 times for each patient during the patient's ED stay, with a wide variability in scores across all three calculations. Although qSOFA scores ≥2 have been reported as more specific for mortality than SIRS ≥2, they were also shown to be less sensitive [6]. Additionally, the prognostic ability of qSOFA has been found to be lower for patients in the intensive care unit (ICU) [22] and patients with serious infection in the ED [7].

Table 2
Comparison of disease severity scores between survivors and non-survivors in study population.

Variables	Overall (N = 991)			Sepsis (N = 819)			Septic shock (N = 361)		
	Survivors (N = 770)	Non-survivors (N = 221)	P-value	Survivors (N = 617)	Non-survivors (N = 202)	P-value	Survivors (N = 254)	Non-survivors (N = 107)	P-value
Age (years, mean ± SD)	67.8 ± 13.4	70.2 ± 13.4	0.02	67.8 ± 13.4	70.8 ± 13.2	0.006	67.4 ± 13.3	68.5 ± 13.5	0.48
Sex (male, %)	424 (55.1)	139 (62.9)	0.05	333 (54.0)	128 (63.4)	0.02	147 (57.9)	65 (60.7)	0.61
Initial vital signs (mean ± SD)									
Systolic blood pressure (mm Hg)	99.1 ± 28.6	99.3 ± 31.3	0.96	99.2 ± 29.0	100.5 ± 31.7	0.61	99.9 ± 30.4	100.9 ± 31.0	0.79
Respiratory rate (per minute)	21.6 ± 5.2	23.3 ± 6.5	<0.001	21.7 ± 5.2	23.4 ± 6.7	0.001	22.2 ± 5.1	24.1 ± 7.1	0.01
Heart rate (per minute)	107.4 ± 25.8	112.7 ± 24.9	0.006	108.1 ± 26.0	112.3 ± 25.0	0.04	110.8 ± 24.8	114.0 ± 27.2	0.28
Body temperature (°C)	37.7 ± 1.9	37.1 ± 1.2	<0.01	37.7 ± 2.0	37.1 ± 1.2	<0.001	37.6 ± 2.7	37.2 ± 1.2	0.17
Lactate, initial (mean ± SD)	3.8 ± 2.9	5.2 ± 4.2	<0.001	3.8 ± 2.9	5.8 ± 4.1	<0.001	4.7 ± 2.5	6.9 ± 4.2	<0.001
Disease severity scores									
qSOFA (median, IQR)	1 (1–2)	2 (1–2)	<0.001	1 (1–2)	2 (1–2)	<0.001	2 (1–2)	2 (1–2)	0.001
SIRS (median, IQR)	3 (2–4)	3 (2–3)	0.40	3 (2–4)	3 (2–3)	0.29	3 (2–4)	3 (2–3)	0.36
SOFA (median, IQR)	7 (5–10)	10 (7–13)	<0.001	8 (5–10)	10 (7–13)	<0.001	10 (7–12)	11 (9–15)	<0.001
APACHE II score (median, IQR)	17 (12–23)	22 (17–30)	<0.001	18 (13–24)	23 (18–31)	<0.001	21 (16–26)	26 (20–34)	<0.001
MISSED score (median, IQR)	2 (2–3)	3 (2–3)	<0.001	2 (2–3)	3 (2–3)	<0.001	2 (2–3)	3 (2–3)	0.14

SD, standard deviation; qSOFA, quick sequential organ failure assessment; IQR, interquartile range; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; APACHE II, acute physiology and chronic health evaluation II; MISSED, mortality in severe sepsis in the emergency department.
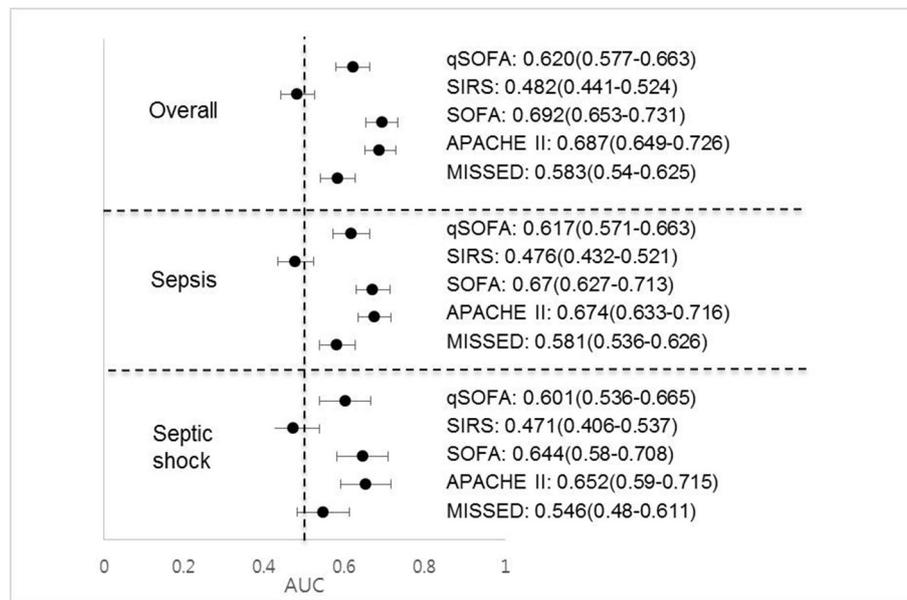
Fig. 2. Comparison of AUC values for disease severity scores in the overall cohort and the sepsis and septic shock subgroups. AUC, area under the receiver-operating characteristic curve; qSOFA, quick sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; APACHE II, acute physiology and chronic health evaluation II; MISSED, mortality in severe sepsis in the emergency department.

The findings of the present study also contradict the results of the original study that claimed that qSOFA could predict in-hospital mortality accurately in patients with suspected infection presenting to an ED [21]. The difference between the results of the original study and the present results could be due to considerable variation in case definitions and mortality rates between the previous study and the present study. In the present study, the overall mortality rate of the patients was 22.3%, whereas the mortality rate in the previous study was 8.4%. Reported mortality rates are influenced by the inclusion criteria used. The higher mortality found in the present study could be due to our inclusion criteria being based on previously defined criteria of hypoperfusion or hypotension; additionally, the mean age of our cohort was higher than that in the previous study, which implies greater comorbidities and severities of illness among the patient group.

Similarly, the SOFA and APACHE II scores in the present study were higher than the scores reported in previous studies [5,21]. The function of a predictive model is affected by changes in patient mix and cohort mortality [23,24]. In the present study, the AUC values of the qSOFA score in the overall cohort, newly defined sepsis subgroup, and septic shock subgroup were 0.620 (95% CI, 0.577–0.663), 0.617 (95% CI, 0.571–0.663), and 0.601 (95% CI, 0.536–0.665), respectively. These values were lower than the reported AUC of qSOFA (0.80; 95% CI, 0.74–0.85) in ED patients and similar to the reported AUC of qSOFA (0.607; 99% CI, 0.603–0.611) in ICU patients in the original qSOFA study [21,22]. Our results were also similar to those of a previous study of patients with infection in the ED, which revealed a 28-day mortality of 27.5% [7]. Additionally, our results showed that the SOFA and APACHE II scores had the highest AUC values irrespective of subgroups, which are consistent with those of a previous study demonstrating that scoring systems that use a greater number of variables showed better discriminative performance compared to simpler scoring systems with fewer variables [25]. Moreover, our results support the findings of the study by Williams et al., which demonstrated that the discriminative ability of each disease severity score decreased as the mortality rate of the subgroup increased [26]. Taken together, the findings of the present study suggest that there are notable limitations in qSOFA, despite the tool's ease of use. Thus, additional research is needed before qSOFA can be unequivocally recommended as a screening tool for predicting prognosis of high-risk patients in the ED.

There are some limitations of the present study. First, our study cohort consisted of patients with relatively serious infections accompanied by hypotension or hypoperfusion, who had similar clinical status as patients in the ICU. All ED-based sepsis studies have challenges in patient selection to some extent. Thus, the generalizability of our results to patients with sepsis of all severity spectrums in the ED is limited. Second, the MEDS score could not be validated, as band form neutrophils are not included in the KoSS septic shock registry. Although the limitation of the MEDS score is its subjective nature for assessing short-term mortality, it was specifically developed for use with patients with suspected infection presenting to the ED, and it is widely used in many EDs. Third, calibration analysis was not undertaken to compare the predicted mortality rates with actual observed mortality rates. Finally, as this was a multi-center study, the length of hospitalization and size of case volumes varied between hospitals.

5. Conclusions

In this study, all included disease severity scores, including qSOFA, did not display good discrimination for 28-day mortality in patients with serious infection and refractory hypotension or hypoperfusion. Additionally, none of the included severity scores in this study could consistently predict 28-day mortality in the subgroups of patients with newly defined sepsis and newly defined septic shock. These findings suggest that further studies are needed to support the development of a screening tool that is simple and easy to use at the bedside for high-risk patients presenting to the ED.

Declarations of interest

None.

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