Comparison of accuracy in three versions of simplified sequential organ failure assessment scores to predict prognosis of septic patients

Short title: Simplified SOFA score for sepsis

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Funding

This work was supported by the fund of Research Grant for Health Science and Technology of Pudong Municipal Commission Health Committee of Shanghai (Grant NO.PW2019A-25) and funded by the Key Discipline Construction Project of Pudong Health Bureau of Shanghai (Grant NO.PWZxk2017-20)

Abstract

Background: Evidence shows that simplified SOFA scoring system has better clinical practice.

Objective: This study aimed to compare the scores acquired with the simplified sequential organ failure assessment (sSOFA), simplified organ dysfunction criteria optimized for electronic health records (eSOFA), and simplified and accurate sequential organ failure assessment (sa-SOFA) for their accuracies in predicting the prognosis of septic patients.

Methods: This retrospective observational study was conducted at three major academic hospitals. Clinical data from 574 patients diagnosed with sepsis following the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)were retrospectively retrieved and analyzed. Scores from the quick sequential organ failure assessment (qSOFA) and sequential organ failure assessment (SOFA) were used as reference scores. The area under the receiver operating characteristic curve (AUROC) was used to compare the accuracies of eSOFA, sSOFA, and sa-SOFA scores in predicting in-hospital mortality.

Results: AUROC analysis demonstrated the predictability of the five scoring systems for sepsis surveillance, listed in descending order as: sa-SOFA,0.790 (95% confidence interval [CI]: 0.754-0.822); SOFA, 0.774 (95% CI: 0.738-0.808); eSOFA,0.729 (95% CI: 0.691-0.765); sSOFA,0.681 (95% CI: 0.641- 0.719); and qSOFA,0.618(95% CI: 0.577-0.658).

Moreover, sa-SOFA and SOFA scores (Z= 1.950, p = 0.051) did not significantly differ from each other in discriminatory power, but the sa-SOFA score had a higher power than either the sSOFA or eSOFA scores (p values <0.001).

Conclusion: sa-SOFA showed the highest accuracy in predicting in-hospital fatality of septic patients when compared with sSOFA and eSOFA.

Keywords: Sepsis-3; Sequential Organ Failure Assessment Score; sSOFA; qSOFA; eSOFA; sa-SOFA

What is already known about this topic?

·Certain variables and cut-off values of SOFA scores may need to be revised accordingly.

·qSOFA cannot be used to predict in-hospital mortality of patients with sepsis

·The simplified version of the SOFA does not reduce the predictive value, but takes fewer variables into consideration, thus, is more practical in the clinical settings.

What does this article add?

·We compared three versions of simplified SOFA scores reported in the literature, and the results show that the sa-SOFA score achieves better predictive performance.

Introduction

The Third International Consensus Definitions for Sepsis and Septic Shock updated the definition of sepsis, known as Sepsis-3, which is described as life-threatening organ dysfunction caused by a dysregulated host response to infection[1, 2]. The diagnostic criteria to identify patients with sepsis uses a sequential organ failure assessment (SOFA) score above or equal to two in patients with a verified infection.

The SOFA score has been found to have high predictive validity and prognostic accuracy of in-hospital mortality in patients with sepsis [3, 4], but the score was calculated on many variables from complicated clinical settings related to this disease. However, with the advancement of management of sepsis in recent years, including the replacement of dopamine with norepinephrine for managing septic shock [5] and using ventilation in the prone position to improve the prognosis of acute respiratory distress syndrome [6], certain variables and cut-off values used to determine the SOFA score may be outdated and need to be renewed or revised accordingly.

The quick sequential organ failure assessment (qSOFA), a fast and inexpensive bedside assessment score, has been commonly used to screen patients in the early phase of infection[7]. The qSOFA score ranges from 0 to 3based on the summation of three variables,

including respiratory rate (RR) ≥ 22 breaths/min, Glasgow Coma Scale (GCS) < 15 and systolic blood pressure ≤ 100 mmHg[1, 2]. However, recent studies have shown that the qSOFA holds poor sensitivity and only moderate specificity for predicting in-hospital mortality in patients with infections[8, 9]. Therefore, to enhance the prediction of in-hospital septic mortality, qSOFA scoring has been modified to also encompass traditional variables such as plasma lactate[10-12], procalcitonin[13, 14], and heart rate [15].

Furthermore, for the purpose of easy and effective practice, SOFA has been simplified into three different versions including simplified SOFA (sSOFA)[16], simplified organ dysfunction criteria optimized for electronic health records (eSOFA) [17], and simplified and accurate SOFA (sa-SOFA)[18]. Researchers have shown that the predictability of sepsis using these three simplified SOFA scores are similar to or better than that of SOFA. The purpose of our study was to compare the accuracy of these three simplified versions of the SOFA score to predict in-hospital mortality related to sepsis.

Methods

Study design and settings

This retrospective, multicenter, observational study was conducted at three academic hospitals with an extensive period from January 2016 through December 2018.The definition

of sepsis in this study followed the Third International Consensus Definitions for Sepsis and Septic Shock[1], and the primary outcome of this study was in-hospital mortality. The study was approved by the institutional review board of each participating hospital, and complied with the Principles of the Declaration of Helsinki and received ethics approval by the respective institutional review boards. Informed consent was waived because this study was retrospective and observational in nature, and patients' data were anonymized

Inclusion and exclusion criteria

Inclusion criteria for the study was as follows: 1) Patient must have been 18 years of age or older, and 2) The length of hospital stay was24 hours or longer. While the patients were excluded from the study based on the following criteria: 1) Malignancy of any kind, 2) Presence of acquired immunodeficiency syndrome, 3) Pregnancy, or 4) Incomplete medical records.

Data collection

The electronic or paper medical records of the patients were thoroughly reviewed and necessary data were extracted in the following categories: age, sex, comorbidities, vital signs, Glasgow Coma Scale (GCS) score, infection source, and laboratory tests performed within the first 24 hours following admission. The patients without PaO2, serum lactate and bilirubin data were excluded from the participation of this study. Additionally, the "band" in sSOFA is not routine in all hospitals, so if it is lost, it score was considered as 0.

Calculation of the scoring systems

The various SOFA scores were calculated, and the patients with the highest SOFA scores within 24 hours after admission were used for the major parameters of this study. Specialized personnel were chosen to perform the scoring, and to avoid any bias all of the scorers were unaware of the patients' prognoses.

Data analysis

Statistical analyses were performed using SPSS Statistics 23.0 software. Data were expressed as mean ± standard deviation (SD; normal distribution) or median (interquartile range; non-normal distribution) for continuous variables and as percentages for categorical variables. Intra-group comparisons of normally distributed data were performed using the Student's *t*-test. Dichotomous variables were compared using the Fisher's exact test. Results are expressed as odds ratios (OR) with95% confidence intervals (CI). The discriminatory power of the scoring systems for in-hospital mortality was determined from the area under the receiver operating characteristic (AUROC) curve with corresponding 95% CIs. The AUROCs of the various scoring systems were compared using Hanley and McNeil's method with MedCalc software Ver. 12.7.0.0. An AUROC < 0.700 represented poor discriminatory power. A p value< 0.05 was considered statistically significant.

Results

Characteristics of study subjects

A total of 643 patients who met the diagnostic criteria of Sepsis-3 were included in the study. Of these patients, 69 were excluded from the study, including 34 without complete medical records, 25 with malignant pathologies, and 10 with the record of readmission. Therefore, the final demographic data for the analyses included 574 patients (374 males and 200 females)(Figure 1), with an average age of 71.34 ± 11.87 years (range: 28-88 years), and 432 patients (75.3%) with the age of 65 or over. Among these 574 patients, 288 (50.2%) developed septic shock and 136 died from sepsis, which gave an in-hospital mortality rate of 23.7% (Table 1).

Comparison of clinical data between surviving and non-surviving groups

Compared to the surviving group, patient age, number of patients older than 65 years, number of patients with renal dysfunction, number of patients with diabetes, and number of patients who developed septic shock were higher in the non-surviving group ($p<0.05$). The incidence of abdominal infections in non-survivors was significantly increased compared to the survivors ($p<0.05$), and laboratory tests including white blood cell count, hemoglobin, urea, creatinine, bilirubin, albumin and lactate were significantly elevated in non-survivors ($p< 0.001$). The SOFA, qSOFA, sSOFA, eSOFA, and sa-SOFA scores in the non-survivors were significantly higher than those in the survivor group ($p<0.001$). Oddly, non-survivors have a significantly lower incidence of urinary tract infections than survivors ($p<0.05$,Table1).

Performance of the five versions of the SOFA scoring systems

As shown in Table 2, the AUROC analysis demonstrated that the predictability of these five scoring systems, in descending order, were: sa-SOFA,0.790 (95% CI: 0.754-0.822); SOFA, 0.774 (95% CI: 0.738-0.808); eSOFA,0.729 (95% CI: 0.691-0.765); sSOFA,0.681 (95% CI: 0.641- 0.719); and qSOFA,0.618(95% CI: 0.577-0.658).(Table 2)

Pairwise comparison between any two of the SOFA scoring systems in predicting the prognosis of septic patients

In this study, comparison of the different scoring systems suggested that qSOFA was the least effective in predicting the prognosis of patients with sepsis($p < 0.05$), and further showed that sa-SOFA upheld higher discriminatory power than either sSOFA or eSOFA scores (p values <0.001). Between eSOFA and sSOFA, eSOFA gave higher discriminatory power (p values <0.001). Interestingly, we did not find that sa-SOFA significantly differed in the discriminatory power compared to SOFA scores ($Z = 1.950$, $p = 0.051$, Table 3; Figure 2).

Comparison of the characteristics of three simplified versions of the SOFA scoring system

sa-SOFA showed the highest specificity, followed by eSOFA and sSOFA. For sensitivity, sSOFA was ranked the highest, followed by sa-SOFA and eSOFA. The optimal cut-off values

for in-hospital mortality were sa-SOFA≥ 3, eSOFA ≥ 4 and sSOFA ≥ 4. In these three simplified versions of the SOFA score, sa-SOFA was the most effective at predicting the prognosis of septic patients, and its predictive value was similar to SOFA($p = 0.051$; Table 3; Figure 2).

Discussion

The SOFA score is currently used as a key criterion for identifying septic patients and predicting their prognosis[1, 2].SOFA is a six-parameter scoring system that evaluates the respiratory system, cardiovascular system, liver, coagulation, kidney and nervous system by assigning scores in each category from 0 to 4. After calculations, SOFA score of 1 or 2 can suggest organ dysfunction, while 3 or 4 points indicate organ failure. In clinical practice, a higher SOFA score reflects more serious organ dysfunction[19]. However, the SOFA score possesses many pitfalls when put into practice. For example, the algorithm used for SOFA scoring is inclusive of multiple factors, which contains various laboratory tests, such as platelets, bilirubin, creatinine and blood gas analysis, subsequently potentiating the risk of data loss. In any words, the accuracy of neurological scoring relies upon the experiences of the scorers [19].

Several modifications have been proposed to improve the SOFA scoring system. One of the modifications involves simplifying or removing certain parameters to improve clinical practicability under the premise of withstanding no significant change on its predictive

capacity. Some specific examples include: the cardiovascular component was replaced by reading the systolic blood pressure or inotropes[20]; the respiratory component was replaced by partial pressure of arterial oxygen (PaO_2) with arterial oxygen saturation measured by a pulse oximeter (SpO_2)[21-25]; the liver component was replaced by serum bilirubin with clinical assessment of scleral icterus or jaundice[21, 22]; the coagulation component was replaced by platelet count with clinical assessment of petechia, purpura, ecchymosis, and spontaneous bleeding[21],or eliminating the platelet count[22];the central nervous system component was excluded from the neurological assessment[25]; and the renal SOFA component was replaced by either urine volume[22] or creatinine levels [20].

The modified SOFA scoring systems had achieved better practicability and plausibility, thus providing confidence for further use of SOFA scores. There were three versions of simplified SOFA scoring systems [16-18], which contained slightly more parameters than qSOFA to avoid the disadvantages that qSOFA presented. Evidence has shown that the predictive values of these three new simplified SOFA scoring systems are comparable or even higher than that of standard SOFA[16-18], and more significantly, the three versions of the simplified SOFA scoring systems showed better prospects for clinical application. The purpose of this study was to compare and verify the ability of these three simplified SOFA scoring systems to predict the clinical outcomes of septic patients.

This study showed that the qSOFA score had high specificity but poor sensitivity, and possessed weak predictive ability for the prognosis of patients with sepsis (AUC = 0.618),

which limits its clinical application. The results of this study were similar to those reported in other studies [8, 9], showing that the predictive values of qSOFA were significantly poorer than those of either sa-SOFA, or eSOFA, or sSOFA. In this study, the SOFA predicts the AUC of in-hospital sepsis mortality as 0.774, which is similar to the predictable potentials of eSOFA and sSOFA in the literature [17,31,32]. However , the studies on sa-SOFA [18] showed the SOFA score predicted AUC of the 28-day mortality only as 0.687 due to 22.1% of the included participants (316/1436) being SIRS patients.

As the first simplified SOFA, sSOFA was aimed to supplement the drawback of the poor sensitivity inherent to qSOFA. As such, sSOFA was designed to contain the parameters that were undoubtedly applicable and convenient to measure in the emergency department [16]. Our research revealed that sSOFA scoring could yield high sensitivity in the prediction of the prognosis of septic patients. It is reasonable to remove bilirubin from the measured liver parameters, since elevated bilirubin has been considered a relatively late indicative factor for more advanced liver pathologies[26].Additionally, the neurological component of the score based on GCS was eliminated due to the low inter-examiner reliability[27]. However, testing for increased "bands" is not routine for all hospitals, and certain studies have found that it cannot predict hospital mortality[28].

eSOFA was developed for retrospective monitoring using objective data directly from the electronic health record (EHR)[17]. This scoring system removed the GCS but added a

criterion for lactate ≥ 2.0mmol/L, since lactic acid levels have potential value for evaluating sepsis. The addition of lactic acid to eSOFA can increase its predictive value. In fact, lactic acid has a greater predictive value in the later stages of sepsis. Studies have shown that lactate clearance could better predict mortality than initial lactate levels[29, 30].Subsequent studies confirmed that eSOFA had good overlap with SOFA and might better distinguish hospital mortality[31]. Previous studies have shown that eSOFA tends to identify patients with more severe illness[31, 32], and our research revealed its ability to predict the prognosis of septic patients has low sensitivity and high specificity.

The dimensions and variables of sa-SOFA are undoubtedly appropriate and most like SOFA. Another important advantage of sa-SOFA is that each variable has two cut-off values, which enhances the accuracy of this scoring system [18]. Our research has provided evidence that sa-SOFA was better than sSOFA and eSOFA in predicting hospital mortality of patients with sepsis.

To our knowledge, this study was the first to compare the sa-SOFA, eSOFA and sSOFA scoring systems in patients suffering from sepsis. Additionally, we highlighted the advantages and disadvantages of these three simplified SOFA scoring systems and confirmed that sa-SOFA is the most effective scoring system to use among sa-SOFA, eSOFA and sSOFA.

However, this study has several limitations. First, this is a retrospective study with a small sample size, which excluded patients with malignant tumors, a high proportion of elderly

patients, and a high proportion of septic shock patients. Therefore, a larger sample size is required for confirmation of these findings. Second, it is difficult to determine the details of each patient's treatment. The guidelines for sepsis are continuously updated and along with advances in medical technology, this leads to a heterogeneity of treatment that may affect the patient's prognosis. Third, the bilirubin level from the liver score used in this study was measured within 24 hours following admission, but bilirubin may not increase until a few days after liver injury. Fourth, the criteria for bands> 5% in the sSOFA score was not included in this analysis since bands are not routinely measured by many institutions.

Conclusion

The sa-SOFA scoring system retains the same six dimensions of original SOFA score, but allows for a simple calculation of the score. In predicting hospital mortality of patients with sepsis, sa-SOFA is more effective than either sSOFA or eSOFA. However, before confidently promoting the use of sa-SOFA, additional studies with more patients and more specific conditions are required for verification of these results.

Availability of data

The data that support the findings of this study are always available from the corresponding author upon request.

Conflict of interest

None of the authors have a conflict of interest to declare

Acknowledgments

We acknowledge all the people who helped us.

Abbreviations:

ARDS: acute respiratory distress syndrome;

AUROC: area under the receiver operating characteristic;

CRP : C-reactive protein;

EHR: electronic health record;

eSOFA: electronic sequential organ failure assessment;

FiO2: Fraction of inspiration oxygen;

GCS: Glasgow Coma Scale;

INR : international normalized ratio;

MAP: mean arterial pressure;

OR: odds ratios;

PaO2: partial pressure of oxygen;

PCT: procalcitonin;

qSOFA: quick sequential organ failure assessment;

RR: respiratory rate;

sa-SOFA: simplified and accurate sequential organ failure assessment;

SBP: systolic blood pressure;

SD: standard deviation;CI:confidence intervals;

SOFA: sequential organ failure assessment;

sSOFA: simple sequential organ failure assessment;

Spo2: oxygen as measured by pulse oximetry;

WBC: white blood cell;

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Table 1. Clinical characteristics and physiological variables of the study population.

	Total (n=574)	Survivors (n=438)	Non-survivors (n=136)	χ^2(t)	p
Age (years)	71.34 ± 11.87	70.37 ± 12.19	74.43 ± 10.20	3.158	<0.001
Age≥65yr, n(%)	432 (75.3)	320 (73.1)	112 (82.4)	4.814	0.028
Sex (male/female)	374/200	288/150	86/50	0.290	0.590
Septic shock, n(%)	288 (50.2)	200 (45.7)	88 (64.7)	15.055	<0.001
Comorbidity					
Congestive heart failure, n(%)	104(18.1)	74(16.9)	30(22.1)	1.865	0.172
Cerebrovascular disease, n(%)	89(15.5)	62(14.2)	27(19.9)	2.572	0.109
Hypertension, n(%)	157(27.3)	125(28.5)	32(23.5)	1.311	0.252
Diabetes, n(%)	142(24.7)	99(22.6)	43(31.6)	4.530	0.033
Chronic kidney disease, n(%)	94(16.3)	60(13.7)	34(25.0)	9.679	0.002
Chronic pulmonary disease, n(%)	132(23.0)	95(21.7)	37(27.2)	1.783	0.182
Primary sites of infection					
Lungs	197 (34.3)	152 (34.7)	45 (33.1)	0.120	0.729
Abdomen	227 (39.5)	155 (35.3)	72(52.9)	13.374	<0.001
Urinary tract	117 (20.4)	104 (23.7)	13 (9.6)	12.868	<0.001

Other	33(5.7)	27 (6.2)	6 (4.4)	0.588	0.443
Laboratory variables after admission					
WBC(x 10^9/L)	14.03 ± 8.02	13.65 ±7.05	15.25 ± 10.49	2.041	0.042
Hemoglobin (g/L)	120.09 ± 23.41	122.29 ± 22.61	113.03 ± 24.60	4.083	<0.001
Platelets(x 10^9/L)	182.60 ± 97.39	184.59 ±91.12	176.18 ± 115.45	0.880	0.379
C-reactive protein (mg/L)	79.92 ± 69.22	79.19 ± 68.38	82.30 ± 72.09	0.457	0.648
PCT (ng/mL)	12.72 ±28.38	12.35 ± 29.00	13.90 ± 26.34	0.554	0.580
Urea (mmol/L)	12.73 ± 7.84	11.51 ± 7.25	16.67 ± 8.37	6.984	<0.001
Creatine (mmol/L)	139.89 ± 101.30	130.58 ± 95.03	169.86 ± 114.64	4.002	<0.001
D-Dimer(ng/mL)	6.72 ± 5.57	6.70 ± 5.90	6.80 ± 4.32	0.188	0.851
INR	1.52 ± 1.62	1.43 ± 1.72	1.81 ± 1.22	2.372	0.018
Bilirubin(μmol/L)	26.11 ± 28.06	22.77 ± 21.02	36.84 ± 41.95	5.221	<0.001
Albumin (g/L)	30.81 ± 6.40	31.49 ± 6.32	28.60 ± 6.17	4.647	<0.001
Lactate (mmol/L)	3.80 ± 3.14	3.18 ± 2.19	5.79 ± 4.61	9.022	<0.001
Scoring systems					
SOFA (score)	7.54 ± 3.58	6.70 ± 3.24	10.26 ± 3.25	11.203	<0.001
qSOFA (score)	1.99 ± 0.79	1.91 ± 0.79	2.26 ± 0.71	4.605	<0.001
sSOFA (score)	4.31 ± 1.67	4.05 ± 1.72	5.15 ± 1.14	7.046	<0.001

eSOFA (score)	3.07 ± 1.72	2.75 ± 1.61	4.13 ± 1.66	8.672	<0.001
sa-SOFA (score)	2.37 ± 1.96	1.84 ± 1.56	4.07 ± 2.15	13.207	<0.001

Abbreviations: WBC, white blood cell; PCT, procalcitonin; INR, international normalized ratio; SOFA, sequential organ failure assessment; qSOFA, quick sequential organ failure assessment; sSOFA, simple sequential organ failure assessment; eSOFA, electronic sequential organ failure assessment; sa-SOFA, simplified and accurate sequential organ failure assessment

Table 2. The area under the receiver operator characteristic (AUROC) curve for the different scoring systems.

Scoring systems	AUC	95%CI	Cut-off	Sensitivity (%)	Specificity (%)	+LR	-LR	Youden's index
SOFA	0.774	0.738-0.808	8	70.59	71.00	2.43	0.41	0.416
qSOFA	0.618	0.577-0.658	2	41.18	75.80	1.70	0.78	0.170
sSOFA	0.681	0.641-0.719	4	82.35	51.83	1.71	0.34	0.342
eSOFA	0.729	0.691-0.765	4	55.15	82.42	3.14	0.54	0.376
sa-SOFA	0.790	0.754-0.822	3	67.65	84.93	4.49	0.38	0.526

Abbreviations: AUC, area under the receiver operator characteristic; CI, confidence interval; +LR, positive likelihood ratio; -LR, negative likelihood ratio; SOFA, sequential organ failure assessment; qSOFA, quick sequential organ failure assessment; sSOFA, simple sequential organ failure assessment; eSOFA, electronic sequential organ failure assessment; sa-SOFA, simplified and accurate sequential organ failure assessment.

Table 3. Pairwise comparison between the variousscoring systems[#].

Pairwise Scoring System Comparison	Difference between AUC	S.E.	95%CI	Z	p value
SOFA vs. qSOFA	0.156	0.012	0.133 to 0.178	13.570	<0.001*
SOFA vs. sSOFA	0.093	0.009	0.076 to 0.110	10.711	<0.001*
SOFA vs. eSOFA	0.045	0.007	0.031 to 0.060	6.146	<0.001*
SOFA vs. sa-SOFA	0.015	0.008	-0.000 to 0.031	1.950	0.051
qSOFA vs. sSOFA	0.062	0.013	0.038 to 0.087	4.951	<0.001*
qSOFA vs. eSOFA	0.111	0.013	0.084 to 0.137	8.239	<0.001*
qSOFA vs. sa-SOFA	0.171	0.014	0.144 to 0.198	12.375	<0.001*
sSOFA vs. eSOFA	0.048	0.011	0.027 to 0.070	4.406	<0.001*
sSOFA vs. sa-SOFA	0.109	0.013	0.084 to 0.133	8.709	<0.001*

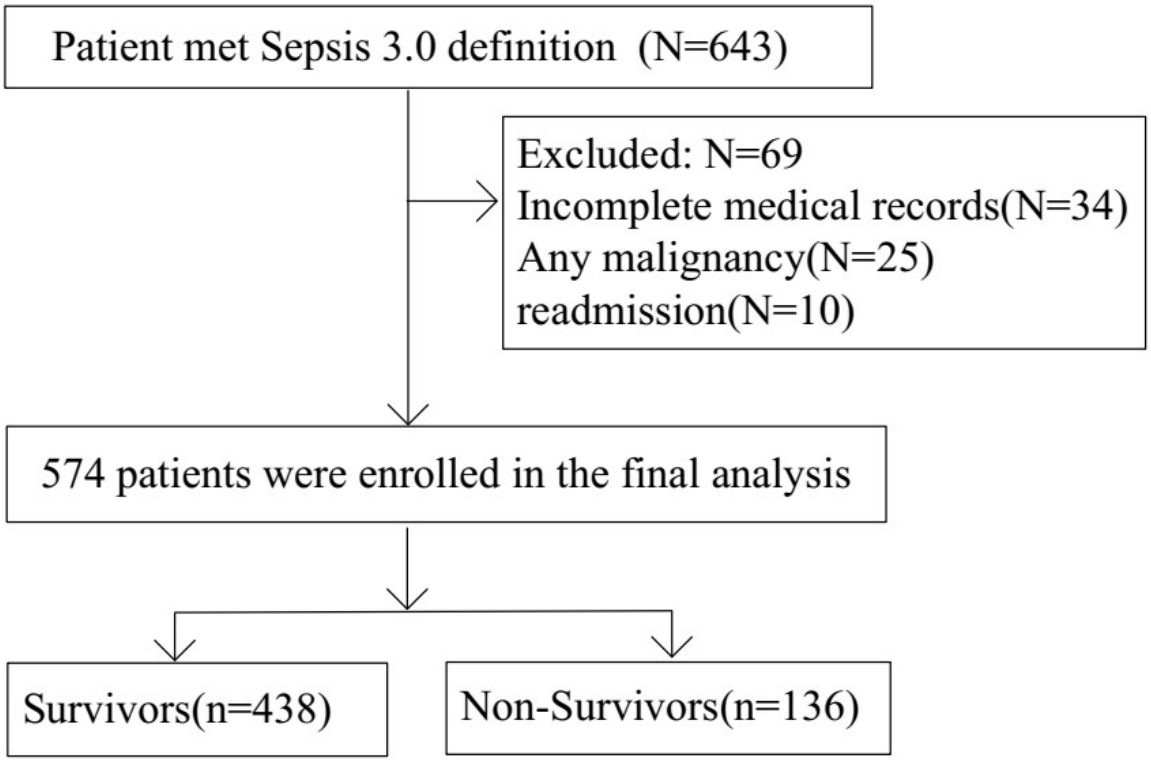
eSOFA vs. sa-SOFA	0.061	0.010	0.041 to 0.080	6.147	<0.001*

Abbrevitions: AUC, area under the receiver operator characteristic; S.E., standard error; CI, confidence interval; SOFA, sequential organ failure assessment; qSOFA, quick sequential organ failure assessment; sSOFA, simple sequential organ failure assessment; eSOFA, electronic sequential organ failure assessment; sa-SOFA, simplified and accurate sequential organ failure assessment.

[#]Hanley & McNeil's method

Figure legends

Figure 1. Flow diagram illustrating outcomes of patients included in the analysis



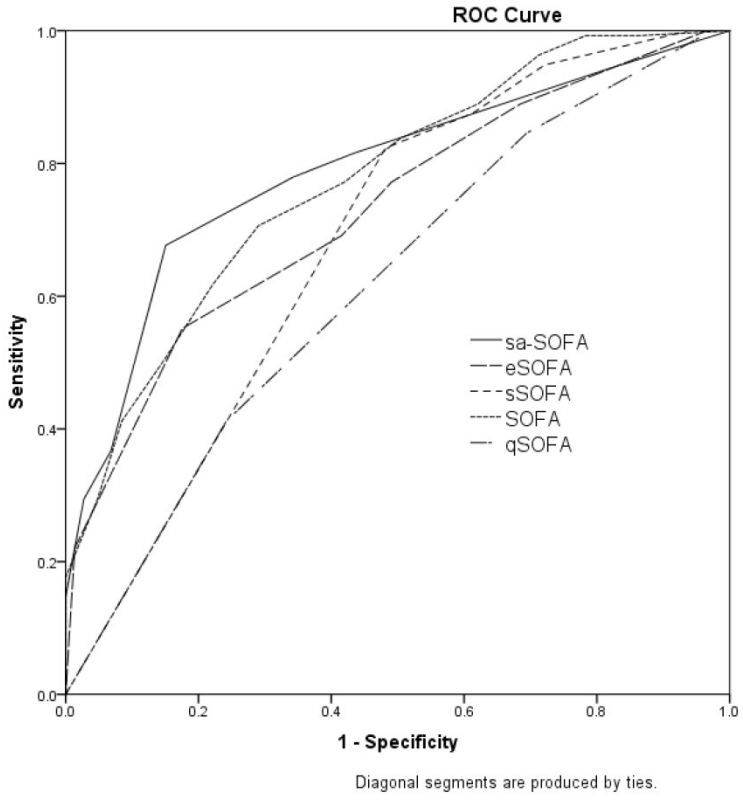


Figure 2. The receiver operating characteristic (ROC) curves of five scoring systems for predicting the prognosis of septic patients.