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Original Article

Prognostic Accuracy of Quick SOFA is different according to the severity of illness in infectious patients☆

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ABSTRACT

Background: Sepsis-3 proposed the quick Sequential Organ Failure Assessment (qSOFA) to identify sepsis patients likely to have poor outcome. The clinical utility of qSOFA still remains controversial because its predictive accuracy for mortality is quite different across the validation studies. We hypothesized that one of the major causes for these controversial findings was the heterogeneity in severity across the studies, and evaluated the association between severity of illness and the prognostic accuracy of qSOFA.
Materials and methods: This was a post hoc analysis of a prospective nationwide cohort of consecutive adult patients with sepsis in 59 intensive care units in Japan. Regression trees analysis for survival was used to classify patients according to severity of illness as determined by SOFA score on registration. We conducted receiver operating characteristic (ROC) analyses and evaluated the differences in the area under the ROC curve (AUROC). As a subgroup analysis, we conducted the above evaluations in emergency department (ED) and non-ED patients separately.
Results: We included 1114 patients fulfilling the criteria and classified them into three subsets according to severity. The AUROC for mortality was significantly different according to the severity of illness ($p = 0.007$), with the highest AUROC being in the low-severity subset (patients with SOFA score ≤ 7). Interestingly, our subgroup analysis revealed that a significant difference in the AUROC of qSOFA was observed only in ED patients.
Conclusion: This study suggested that lower severity of illness was associated with the relatively higher prognostic accuracy of qSOFA, especially in ED patients.

1. Introduction

Sepsis-3 is a new definition of sepsis presented in 2016 at the 45th Critical Care Congress of the Society of Critical Care Medicine (SCCM) [1]. In this new definition, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, which corresponds most closely with the definition of severe sepsis in the conventional definition in Sepsis-1 and Sepsis-2 [2,3]. Sepsis-3 also proposed the quick Sequential Organ Failure Assessment (qSOFA) criteria for use in screening for patients likely to have poor outcome under this new definition, and there has been considerable interest in the clinical utility of this new screening system. To assist the bedside clinician in promptly identifying patients with suspected infection who are likely to have sepsis, the qSOFA criteria consist of three clinical signs that do not require blood tests, i.e., altered mentation, systolic blood pressure (sBP) of 100 mmHg or less, and respiratory rate (RR) of 22/min or greater. The initial retrospective analysis conducted by Seymour et al. reported that qSOFA had great utility in predicting unfavorable outcome, especially for infected patients outside the intensive care unit (ICU) [4]. However, the utility of qSOFA still remains a matter of dispute due to controversial evidence on the actual prognostic accuracy of qSOFA. Although several studies reported the greater accuracy of qSOFA for predicting mortality [5–8], other studies have suggested that the qSOFA might not be more accurate for predicting death than other commonly used early scoring systems [9–11]. Then, what is causing the widely heterogeneous evidence regarding the prognostic accuracy of qSOFA? In a recent systematic review including 23 observational studies, Song et al. reported that overall mortality rate and disease severity were the probable sources of heterogeneity in the prognostic performance of qSOFA [12]. However, the current clinical evidence regarding the relation between patient characteristics and the prognostic performance of qSOFA remains limited. Herein, using data from the Japanese Association for Acute Medicine (JAAM) registry database enrolling patients with infection, we aimed to evaluate whether the severity of illness influenced the predictive accuracy of qSOFA for in-hospital mortality in infectious patients.

2. Materials and methods

2.1. Study population

This was a post hoc analysis of a multicenter prospective cohort of consecutive patients with sepsis in 59 ICUs of tertiary hospitals in Japan between January 2016 to March 2017. The dataset used was a sepsis sub-cohort of the Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma (FORECAST), which included patients with acute respiratory distress syndrome, sepsis, and trauma [13]. Patients were included in the FORECAST sepsis registry if they were older than 16 years and diagnosed as having severe sepsis by the Sepsis-2 criteria [3]. In this study, we excluded patients with missing data on survival or qSOFA evaluation. This study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committees of Osaka University Hospital. Because of the anonymous and retrospective nature of this study, the board of Osaka University Hospital waived the need for informed consent.

2.2. Data collection

The FORECAST database was compiled by the investigators in each institution. Patients were followed up until hospital discharge or death during their hospitalization. Patient data including age, sex, body mass index (BMI), pre-existing comorbidities, primary infection site, vital signs, and general laboratory tests were recorded. We evaluated qSOFA based on the initial vital signs recorded in emergency departments (EDs), wards, or ICUs at the time infectious disease was suspected. Therefore, calculations of qSOFA for ED patients were based on the vital signs obtained before medical interventions. We also evaluated the severity of illnesses according to the Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation (APACHE) II, and the severity of sepsis-induced coagulopathy as indicated by the International Society on Thrombosis and Haemostasis (ISTH) overt disseminated intravascular coagulation (DIC) score and the Japanese Association for Acute Medicine (JAAM) DIC score. We evaluated the accuracy of qSOFA criteria (index test) when used to identify patients likely to have a poor prognosis and thus defined

in-hospital mortality as the reference standard. Calculation of the qSOFA score was conducted without knowing the patient outcomes.

2.3. Definitions

The qSOFA score was proposed by Singer et al. in February 2016 as an initial way to identify patients at high risk of death [1]. The qSOFA simplifies the SOFA score by including 3 clinical signs: altered mental status, sBP of 100 mmHg or less, and RR of 22 breaths or more per minute. In this study, we defined altered mental status as a Glasgow Coma Scale (GCS) score of $\leq$14. We also defined patients who were directly admitted to the ICUs via the EDs with the diagnosis of sepsis as "ED patients" and those who were transferred from other hospitals or other departments with the suspicion of sepsis or who developed sepsis after ICU admission for another disease as "non-ED patients".

2.4. Patient categorization

In this study, we aimed to evaluate the difference in the predictive accuracy of qSOFA for in-hospital mortality according to the severity of illness and to identify a subset of patients in whom qSOFA criteria exerted the best performance. For this purpose, classification and regression trees for survival data (survival CART) were used to classify study patients according to severity of illness as determined by SOFA score at the time of study registration. As a subgroup analysis, we also conducted these evaluations in ED and non-ED patients separately.

2.5. Statistical analysis

Baseline characteristics were compared by the Mann-Whitney *U* test or chi-square test. Descriptive statistics are summarized as group medians with the first and third quartiles for continuous variables and frequencies with percentages for categorical variables. We conducted the survival CART analysis using the STATA module "CART" to split the study population according to the risk of death. Survival CART analysis for failure-time data used the martingale residuals of a Cox model to calculate chi-square values for possible thresholds on SOFA and APACHE II scores. We conducted receiver operating characteristic (ROC) analyses to assess the accuracy of qSOFA in predicting mortality and evaluated the differences of the area under the ROC curve (AUROC) due to severity of illness using the method of DeLong et al. [14] All hypotheses were two-sided, and a p value of <0.05 indicated statistical significance. All statistical analyses were conducted using STATA Data Analysis and Statistical Software version 15.0 (StataCorp, College Station, TX).

3. Results

3.1. Study population

The patient flow diagram is shown in Fig. 1. During the study period, 1184 consecutive patients fulfilled the inclusion criteria and were registered in the FORECAST study database. After excluding 70 patients, we analyzed 1114 patients as the final study cohort. Among them, 733 patients had qSOFA scores of 2 points or more (qSOFA-positive), and 381 patients had qSOFA scores of 1 point or less (qSOFA-negative).

3.2. Patient characteristics

Baseline characteristics, severity of illness, and outcomes are shown in Table 1 qSOFA-positive patients had a significantly higher age and lower BMI than the qSOFA-negative patients. The distribution of infection sites was significantly different between the groups ($p = 0.012$), i.e., lung was the most common infection site in the qSOFA-positive group, whereas abdomen was the most common site in the qSOFA-negative group. In contrast, there was little difference in the types of pathogens between the two groups. Although many of the pre-existing comorbidities were similar between the two groups, the qSOFA-positive group had a significantly higher rate of cerebrovascular disease. Illness severity, as indicated by the SOFA, APACHE II, and DIC scores, was significantly higher in the qSOFA-positive versus -negative group, as was in-hospital mortality (26.1% vs 17.4%, $p = 0.001$). However, the sensitivity, specificity, and AUROC for mortality in the overall study population were 74.6%, 36.8%, and 0.563 (95% confidence interval [CI]: 0.527–599) and were much lower than those of previous studies.

3.3. Predictive accuracy for mortality according to severity

Results of the survival CART analysis based on SOFA score are shown in Fig. 2. The analysis revealed that the first split points at which to partition risk of death for study patients were a SOFA score of 13 or more (high-risk subset) and 12 or less, and the second split points were SOFA scores of 8 or more (middle-risk subset) and 7 or less (low-risk subset). Therefore, the predictive value of qSOFA for mortality was evaluated across these 3 subsets.

The ROC curves of qSOFA for in-hospital mortality are shown in Fig. 3. The AUROC for mortality was significantly different among the three subsets ($p = 0.007$) and was highest in the low-risk subset (AUROC: 0.574, 95% CI: 0.494–0.653). We also conducted ROC

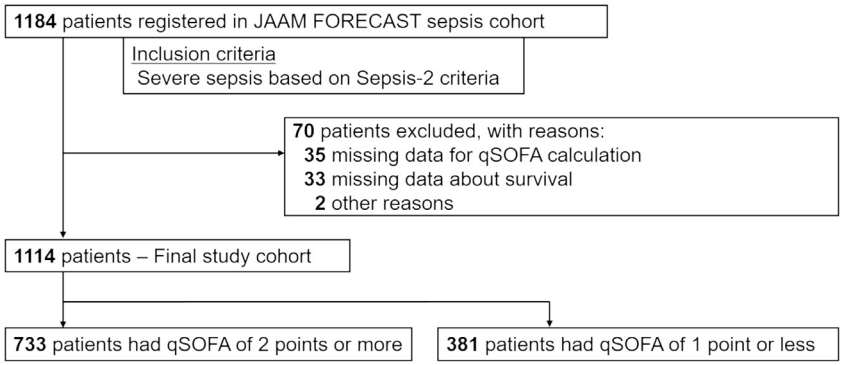


Fig. 1. Patient flow diagram. *JAAM*: Japanese Association for Acute Medicine; *qSOFA* quick Sequential Organ Failure Assessment.

Table 1
Baseline characteristics, severity, and outcomes of the study patients.

	qSOFA positive	qSOFA negative	*P* Value
	n = 733	n = 381	
Age (years)	74 (65–74)	72 (60–72)	<0.001
Sex, Male	440 (60%)	231 (61%)	0.845
BMI (kg/m^2)	21.2 (18.8–21.2)	22.3 (19.3–22.3)	0.002
Settings			0.002
EDs	435 (59%)	192 (51%)	
Wards	265 (36%)	178 (47%)	
ICUs	33 (5%)	10 (3%)	
Site of infection			0.012
Lung	238 (32%)	109 (29%)	
Urinary tract	153 (21%)	60 (16%)	
Abdomen	174 (24%)	113 (30%)	
Soft tissue	83 (11%)	64 (17%)	
Cardiovascular	28 (4%)	8 (2%)	
Central nervous system	14 (2%)	6 (2%)	
Others	43 (6%)	21 (6%)	
Types of pathogens			
GPC	124 (33%)	227 (31%)	0.592
GPR	14 (4%)	19 (3%)	0.312
GNC	8 (2%)	12 (2%)	0.581
GNR	137 (36%)	324 (44%)	0.008
Fungi	9 (2%)	18 (2%)	0.923
Comorbidities			
Cancer	98 (13%)	57 (15%)	0.467
Diabetes mellitus	164 (22%)	95 (25%)	0.337
Chronic kidney disease	50 (7%)	28 (7%)	0.743
Chronic respiratory failure	58 (8%)	21 (6%)	0.139
Cerebrovascular disease	114 (16%)	35 (9%)	0.003
GCS	12 (8–12)	15 (14–15)	<0.001
Respiratory rate (/min)	28 (24–28)	21 (18–21)	<0.001
Heart rate (bpm)	113 (98–113)	106 (92–106)	<0.001
sBP (mmHg)	88 (76–88)	121 (105–121)	<0.001
Body temperature (°C)	37.6 (36.6–37.6)	37.5 (36.7–37.5)	0.41
SOFA score	9 (7–9)	7 (4–7)	<0.001
APACHE II score	24 (18–24)	19 (14–19)	<0.001
JAAM DIC score	4 (2–4)	3 (2–3)	<0.001
ISTH overt-DIC score	3 (2–3)	2 (1–2)	<0.001
In-hospital mortality	191 (26.1%)	65 (17.4%)	<0.001

Data are presented as the median (the first and third quartiles) for continuous variables and number (%) for categorical variables. Differences between groups were assessed using the Mann-Whitney *U* or chi-square test.
qSOFA quick Sequential Organ Failure Assessment, *BMI* body mass index, *EDs* emergency departments, *ICUs* intensive care units, *GPC* Gram-positive cocci, *GPR* Gram-positive rods, *GNC* Gram-negative cocci, *GNR* Gram-negative rods, *GCS* Glasgow Coma Scale, *sBP* systolic blood pressure, *SOFA* Sequential Organ Failure Assessment, *APACHE* Acute Physiology and Chronic Health Evaluation, *JAAM* Japanese Association for Acute Medicine, *DIC* disseminated intravascular coagulation, *ISTH* International Society of Thrombosis and Hemostasis.

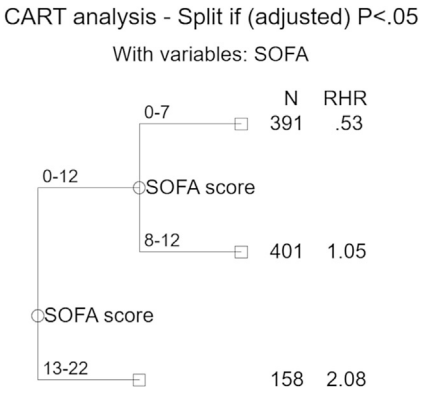
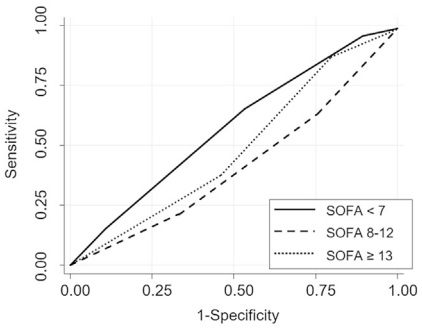


Fig. 2. Patient stratification according to Sequential Organ Failure Assessment (SOFA) score using the classification and regression tree (CART) for survival. *RHR* relative hazard ratio.



Population	N	AUROC	95% CI	p value
SOFA ≤ 7	391	0.574	0.494-0.653	
SOFA 8-12	401	0.416	0.356-0.475	0.007
SOFA ≥ 13	158	0.484	0.400-0.568	

Fig. 3. Receiver operating characteristic curve of qSOFA for predicting death in three subsets according to baseline SOFA score. *qSOFA* quick Sequential Organ Failure Assessment, *SOFA* Sequential Organ Failure Assessment, *AUROC* area under the receiver operating characteristic curve, *CI* confidence interval.

analysis in the ED and non-ED patients separately and found that a significant difference in the AUROC of qSOFA was observed only in the ED patients (Fig. 4). Besides, to enhance the robustness of our findings, we also divided the study population into two subsets based on the APACHE II score (using survival CART analysis) and evaluated the difference in AUROCs between the subsets. As a result, the AUROC for mortality was significantly higher in the low-risk subset ($p = 0.013$) in ED patients, but there were no significant differences according to severity in the non-ED patients (Fig. 5).

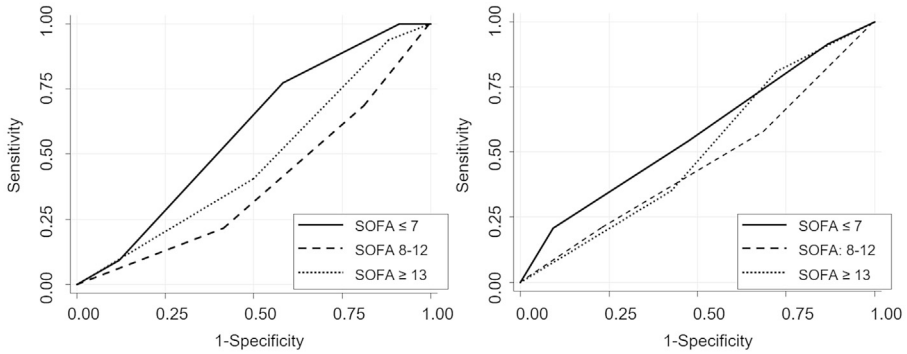
4. Discussion

Despite decades of clinical research, sepsis remains a major cause of death among critically ill patients. One of the most important facets of sepsis management is the factor of time, namely, the rapid diagnosis and initiation of treatments have been reported to influence outcomes and are essential to maximize survival rates [15,16]. Sepsis-3 thus proposed qSOFA criteria to support the clinician in promptly identifying infectious patients likely to have poor outcomes. Following the original research of Seymour et al., numerous validation studies have been carried out, but there is still much controversy regarding the utility of qSOFA to predict mortality across the studies [5–11].

The present nationwide retrospective study represented an attempt to evaluate the association between severity of illness and the prognostic accuracy of qSOFA. It provided clear evidence that severity of illness was associated with a significant difference in the prognostic accuracy of qSOFA. Furthermore, this association was observed only in ED patients and not in non-ED patients. These findings suggested that the predictive value of qSOFA might be reliable only in specific populations and situations.

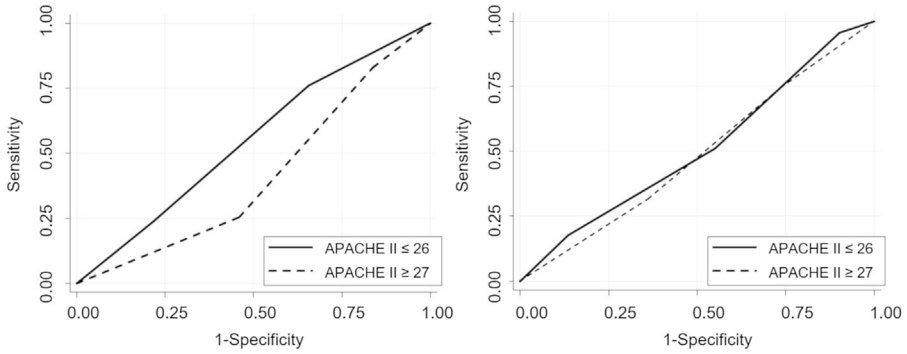
4.1. Prognostic performance of qSOFA

In this study population, elevation of the qSOFA score was associated with significantly higher illness severity scores and higher mortality. However, the overall prognostic performance of qSOFA as indicated by the sensitivity, specificity, and AUROC for in-hospital morality turned out to be much lower than many of those values reported in the previous validation studies [5–8], and quite different from the results of the original study of Seymour et al. One



Population	ED-patients				Non ED-patients			
	N	AUROC	95% CI	p value	N	AUROC	95% CI	p value
SOFA ≤ 7	214	0.585	0.490-0.680		176	0.566	0.443-0.689	
SOFA 8-12	215	0.383	0.302-0.464	0.006	186	0.456	0.367-0.544	0.358
SOFA ≥ 13	74	0.471	0.350-0.591		84	0.498	0.381-0.615	

Fig. 4. Differences in AUROC of qSOFA between three subsets according to baseline SOFA score in the ED and non-ED population. *AUROC* area under the receiver operating characteristic curve, *qSOFA* quick Sequential Organ Failure Assessment, *SOFA* Sequential Organ Failure Assessment, *ED* emergency department, *CI* confidence interval.



Population	ED-patients				Non ED-patients			
	N	AUROC	95% CI	p value	N	AUROC	95% CI	p value
APACHE II ≤ 26	354	0.551	0.469-0.632	0.013	303	0.508	0.421-0.595	0.709
APACHE II ≥ 27	182	0.392	0.334-0.487		161	0.485	0.400-0.570	

Fig. 5. Differences in AUROC of qSOFA between two subsets according to baseline APACHE II score in the ED and non-ED population. *AUROC* area under the receiver operating characteristic curve, *qSOFA* quick Sequential Organ Failure assessment, *APACHE* Acute Physiology and Chronic Health Evaluation, *ED* emergency department, *CI* confidence interval.

possible reason for the poor prognostic value was the high illness severity of the patients (overall mortality was 23.0%) in the present study. Several previous studies similarly reported very low performance of the qSOFA in predicting survival [9–11]. These studies were also similar to the present study with respect to the severity of the study population; in other words, patients with high severity were also included. For example, Hwang et al. evaluated the clinical utility of qSOFA in ED patients with relatively high illness severity (28-day mortality in their overall study population was 16.3%) and reported that the diagnostic performance of qSOFA for predicting mortality was low [10]. Contrastingly, the previous studies that reported greater prognostic performance of qSOFA tended to include low-severity populations (overall mortality was 4.2% and 4.6% in the Quinten et al. and Huson et al. studies, respectively) [5,8]. This tendency was also reported in a previous systematic review [12] and strongly supported our hypothesis that the severity of patients was associated with the prognostic performance of qSOFA.

4.2. Differences according to severity

In the present study, we stratified infectious patients into three subsets according to severity of illness and demonstrated our hypothesis that the prognostic performance of qSOFA was influenced by the severity of patients, especially in the ED. Thus, why did the qSOFA achieve greater performance in identifying poor prognosis only in low-risk subsets? One of the potential reasons was that the significance of these vital signs might change according to the progression of organ dysfunction. In patients with no or mild organ dysfunction, worsening GCS, sBP, and RR reflect the higher severity of the host response against infection, and qSOFA could be a good predictor for whether the infectious disease could potentially progress to organ dysfunction and subsequent death. However, in patients with overt and severe organ dysfunction, the host response against infection often fails to function in a regular manner, and vital signs might not necessarily reflect further progression of organ dysfunction or a poor outcome. Interestingly, in

the present study, the significant association between severity and the prognostic value of qSOFA was observed only in ED patients. qSOFA is a very simple screening tool consisting of three clinical signs to assist the bedside clinician in promptly identifying patients with suspected infection who are likely to have poor outcomes. However, the three components of qSOFA are easily affected by pre-conducted medical interventions such as fluid resuscitation, sedation, intubation, and ventilation. Therefore, our findings suggested that initial qSOFA assessments in EDs could predict poor outcomes more precisely compared to those performed in wards and ICUs. Finally, according to the current findings, we concluded that qSOFA had reliable predictive value when used to identify septic patients with poor prognosis among the population with "relatively lower severity" in the ED situation.

4.3. Limitations

We acknowledge several limitations of this study. First, it included septic patients admitted to ICUs who thus had much higher severity of illness compared to the overall population of infectious patients generally encountered in EDs. Second, to avoid an exploratory research design, this study focused only on the severity of illness among the many possible factors that might influence the prognostic value of qSOFA. Therefore, there might still be another key pathology in which qSOFA could achieve maximum prognostic performance.

5. Conclusion

The present study suggested that a lower severity of illness was associated with higher prognostic accuracy of qSOFA, especially in ED patients.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the ethics committee of all participant institutes in the Japanese Association for Acute Medicine (JAAM) study group, Japan. (IRB No.014-0306 on Hokkaido University, the representative for FORECAST).

Conflicts of interest

The authors declare that they have no competing interests.

Funding

The authors declare that they have no sources of funding to report.

Authors' contributions

Y. Umemura conceived and designed this study; contributed to acquisition, analysis, and interpretation of the data; and was responsible for drafting, editing, and submission of the manuscript. H. Ogura contributed to the study design; acquisition, analysis, and interpretation of the data; and drafting of the manuscript. S. Gando, K. Yamakawa, A. Shiraishi, D. Saitoh, S. Fujishima, T. Mayumi, S. Kushimoto, and T. Abe had a significant influence on the study design and interpretation of the data. All of the authors contributed to the acquisition of data, reviewed, discussed, and approved the final manuscript.

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List of abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
AUROC	area under the receiver operating characteristic curve
BMI	body mass index
CART	classification and regression trees
DIC	disseminated intravascular coagulation
ED	emergency department
GCS	Glasgow Coma Scale
ICU	intensive care unit
ISTH	International Society on Thrombosis and Haemostasis
JAAM	Japanese Association for Acute Medicine
qSOFA	quick Sequential Organ Failure Assessment
ROC	receiver operating characteristic
RR	respiratory rate
sBP	systolic blood pressure
SCCM	Society of Critical Care Medicine
SOFA	Sequential Organ Failure Assessment

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