Original Article

Quick sepsis-related organ failure assessment score as a possible predictor for in-hospital adverse events in infective endocarditis

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Aim: Infective endocarditis (IE) can be life-threatening because of various associated adverse events. The quick Sepsis-related Organ Failure Assessment (qSOFA) score is a straightforward useful method for predicting in-hospital mortality in patients with suspected infections. However, few data exist regarding the clinical impact of the qSOFA score on predicting adverse events in IE during hospitalization. We studied the usefulness of qSOFA score for predicting in-hospital adverse events in patients with IE.

Methods: We retrospectively analyzed 104 consecutive patients diagnosed with IE on the basis of modified Duke criteria. We defined in-hospital adverse events as occurrence of any of the following events during hospitalization: death, embolism, hemorrhage, or abscess formation. The high qSOFA group was defined as those with a qSOFA score ≥2. We used Cox regression analysis to estimate the hazard ratio for high qSOFA score on in-hospital adverse events adjusted for age, sex, and *Staphylococcus aureus* infection.

Results: We analyzed 83 patients (57 men, mean age 61 ± 18 years) from the total cohort of 104 patients enrolled. Among these, 12 (14.5%) had high qSOFA scores. The high qSOFA group had higher in-hospital mortality compared to the low qSOFA group (50.0% vs. 4.2%, $P < 0.01$). In the Cox proportional hazards model, high qSOFA was significantly associated with in-hospital adverse events (adjusted hazard ratio, 2.29; confidence interval, 1.02–5.12; $P = 0.044$).

Conclusion: These results showed that high qSOFA score was significantly associated with in-hospital adverse events in IE patients, although further prospective study is necessary to confirm our results.

Key words: Infective endocarditis, in-hospital, quick SOFA score, risk factor

INTRODUCTION

INFECTIVE ENDOCARDITIS (IE) is an infection of endocardium, usually of heart valves, and can be life-threatening because of persistent bacteremia and various adverse events that occur during hospitalization. In-hospital mortality of patients presenting with IE is currently 18–

26%.[1–3] In addition, in-hospital adverse events such as embolism, abscess formation, intracranial hemorrhage, and cardiac complications account for up to 50% of cases.[4] Embolism is especially common, and occurs in approximately 44% of patients with IE.[5,6] Moreover, embolic complication is a predictor of in-hospital death due to IE.[7] Several studies have reported risk factors for death or complications in IE patients, including age, infection with *Staphylococcus aureus*, large vegetation (≥10 mm), and prosthetic valve IE.[2,3,8–14] In the 2015 European Society of Cardiology Guidelines for the management of infective endocarditis, the predictors of poor outcome in patients with IE are classified by four components: patient characteristics, clinical complications of IE, microorganism, and echocardiographic findings.[15] However, in-hospital mortality and adverse event rates have still been high (20.7% and 29.5%, respectively,

mortality at 30 days after admission and embolic events) in patients with IE despite using these conventional risk factors.[16] Therefore, novel risk factor would be needed to more efficiently predict in-hospital adverse events in IE patients.

Recently, Sepsis-related Organ Failure Assessment (SOFA) score has been reported to be useful for predicting in-hospital mortality and organ dysfunction among patients with suspected infection.[17,18] Moreover, the quick SOFA (qSOFA) score, a simplified version of the SOFA score, can more accurately identify patients at high risk of in-hospital mortality due to suspected infections in non-intensive care unit (ICU) patients.[19–21] The most important advantage of the qSOFA score is its simplicity in predicting in-hospital adverse events. Furthermore, as we can evaluate the qSOFA score using only three vital signs, this can contribute to rapid stratification of in-hospital risks in primary medical settings. However, few data exist regarding the clinical impact of qSOFA score on predicting adverse events in IE patients during hospitalization. Therefore, we evaluated whether the qSOFA score could predict future in-hospital adverse events in patients with IE.

METHODS

Study participants

THIS RETROSPECTIVE COHORT study was approved by the Institutional Review Board of Kanazawa University Hospital (Kanazawa, Japan). We retrospectively enrolled IE patients hospitalized in Kanazawa University Hospital from January 2006 to February 2017. Infective endocarditis was diagnosed based on modified Duke criteria.[22] We collected basic characteristics of patients from medical records, including age, gender, predisposing cardiac disease, coexisting disease, echocardiographic findings, causative microorganism, and complications during hospitalization. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or receiving antihypertensive medication. Diabetes mellitus was defined as glycosylated hemoglobin ≥6.5% or receiving antidiabetic medication. Dyslipidemia was defined as total cholesterol >220 mg/dL or receiving medication for dyslipidemia. Chronic kidney disease was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2.

We defined steroids, cyclosporine, and chemotherapeutic agents as immunosuppressive agents. We checked for the presence of dental infection by treatment history or dental examination. Left ventricular ejection fraction was measured by the Teichholz method. Blood cultures were deemed positive when microorganisms were detected from two or more separate blood cultures.

Quick SOFA score calculation

Quick SOFA scores were rated on a scale of 0, 1, 2, 3 (1 point each added for systolic hypotension [≤100 mmHg], tachypnea [≥22/min], or altered mentation [Glasgow Coma Scale <15]).[23] We evaluated each qSOFA score by their vital signs at admission. The high qSOFA group consisted of patients with qSOFA score ≥2.

Study end-points

Primary outcome was a composite of in-hospital adverse events, defined as occurrence of any of the following events during hospitalization: all-cause death, embolism, intracranial hemorrhage, or abscess formation. These complications would be fatal or could often cause serious physical disability over a long period in IE patients. Complications were diagnosed by imaging studies (computed tomography or magnetic resonance imaging) regardless of symptoms.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range) for continuous variables according to their distribution, and as numbers (percentages) for categorical variables. We compared two variables by *t*-test or Mann–Whitney *U*-test for continuous variables according to their distributions, and Fisher's exact test for categorical variables. We used the Kaplan–Meier method and log–rank test for estimation of cumulative incidence and differences between groups, respectively. We used the Cox proportional hazard model to estimate hazard ratios for in-hospital adverse events adjusted for age, sex, and variables significantly associated with the composite events by univariate analysis. We used R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) for statistical analyses. All *P*-values of tests were two-tailed and *P*-values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

AMONG 104 IE patients enrolled, 21 were excluded due to incomplete availability of data for qSOFA score calculation. Eighty-three patients (57 men, mean age 61 ± 18 years) were finally enrolled for further analyses. Baseline characteristics of IE patients are summarized in Table 1. There were 12 patients (14.5%) with high qSOFA scores. There were fewer men (41.7% vs. 73.2%, *P* < 0.05)

Table 1. Baseline characteristics in high and low quick Sepsis-related Organ Failure Assessment (qSOFA) groups of hospitalized patients with infective endocarditis

	High qSOFA (*n* = 12)	Low qSOFA (*n* = 71)	*P*-value
Age, years; median (IQR)	69.5 (57.8–78)	64 (52.5–73)	0.330
Male, *n* (%)	5 (41.7)	52 (73.2)	0.043
Hypertension, *n* (%)	7 (58.3)	26 (36.6)	0.210
Diabetes mellitus, *n* (%)	2 (16.7)	11 (15.5)	1.000
Dyslipidemia, *n* (%)	3 (25.0)	13 (18.3)	0.690
Chronic kidney disease, *n* (%)	4 (33.3)	11 (15.5)	0.220
Previous coronary artery disease, *n* (%)	1 (8.3)	5 (7.0)	1.000
Liver cirrhosis, *n* (%)	2 (16.7)	1 (1.4)	0.053
Atrial fibrillation, *n* (%)	3 (25.0)	12 (16.9)	0.450
Immunosuppressive agent, *n* (%)	1 (8.3)	9 (12.7)	1.000
Chronic heart failure, *n* (%)	3 (25.0)	8 (11.3)	0.190
Dental infection, *n* (%)	4 (33.3)	24 (33.8)	1.000
Causative microorganisms			
Staphylococcus aureus, *n* (%)	6 (50.0)	10 (14.1)	9.5×10^{-3}
MRSA, *n* (%)	2 (16.7)	4 (5.6)	0.210
Viridans streptococci, *n* (%)	2 (16.7)	19 (26.8)	0.720
Fungi, *n* (%)	0 (0)	1 (1.4)	1.000
Enterococcus spp., *n* (%)	1 (8.3)	4 (5.6)	0.210
Negative blood culture, *n* (%)	2 (16.7)	14 (19.7)	1.000
Echocardiographic findings			
LVEF %, mean ± SD	61.6 ± 11.2	62.4 ± 10.9	0.820
Size of vegetation mm, median (IQR)	10 (5.75–14)	11 (8–17)	0.590
Vegetation profile			
Native valve			
Aortic valve, *n* (%)	6 (50.0)	21 (33.8)	0.190
Mitral valve, *n* (%)	4 (33.3)	35 (49.3)	0.360
Tricuspid valve, *n* (%)	0 (0)	4 (5.6)	1.000
Pulmonary valve, *n* (%)	0 (0)	2 (2.8)	1.000
Prosthetic valve, *n* (%)	2 (16.7)	6 (8.5)	0.330
Previous complication			
Heart failure, *n* (%)	3 (25.0)	18 (25.4)	1.000
Cerebral infarction, *n* (%)	3 (25.0)	16 (31.4)	1.000
Peripheral embolism, *n* (%)	0 (0)	4 (5.6)	1.000
Splenic infarction, *n* (%)	2 (16.7)	6 (8.5)	1.000
Renal infarction, *n* (%)	3 (25.0)	5 (7.0)	0.086
Pulmonary embolism, *n* (%)	0 (0)	3 (4.2)	1.000
Cerebral abscess, *n* (%)	0 (0)	1 (1.4)	1.000
Spleen-liver abscess, *n* (%)	0 (0)	1 (1.4)	1.000
Lung abscess, *n* (%)	0 (0)	1 (1.4)	1.000
Intracranial hemorrhage, *n* (%)	1 (8.3)	6 (8.5)	1.000

IQR, interquartile range; LVEF, left ventricular ejection fraction; MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation.

and a higher incidence of *S. aureus* infection ($P < 0.01$) in the high qSOFA group. Importantly, left ventricular ejection fraction was preserved and the size of vegetation was relatively large. Of note, four patients (33.3%) with a high qSOFA score were not diagnosed with sepsis at initial hospitalization. Of those, two patients had no adverse events, two patients had cerebral infarction, and one patient died during hospitalization.

Adverse events in high and low qSOFA groups

We then compared the differences of adverse events between high and low qSOFA groups (Table 1). On admission, the numbers of patients with embolism, abscess formation, and intracranial hemorrhage were 22, 2, and 7, respectively. The overall rate of in-hospital adverse events in the high qSOFA group was greater than that in the low qSOFA group (83.3% vs. 38.0%, $P = 4.6 \times 10^{-3}$) and as follows for individual events: embolism (66.7% vs. 32.4%, $P = 0.049$), cerebral infarction (66.7% vs. 25.4%, $P = 7.4 \times 10^{-3}$), intracranial hemorrhage (33.3% vs. 7.0%, $P = 0.022$), and in-hospital death (50.0% vs. 4.2%, $P = 1.7 \times 10^{-4}$) (Table 2).

Predictor of in-hospital adverse events in IE patients

During hospitalization, nine patients died (10.8%) and 37 experienced at least one adverse event (44.6%) (Table 2). The causes of death were uncontrolled infection ($n = 5$), cerebral bleeding ($n = 2$), cerebral infarction ($n = 1$), and heart failure ($n = 1$). High qSOFA score and *S. aureus* infection were associated with in-hospital adverse events by univariate analysis (Table 3). In the Cox proportional hazard model, presence of high qSOFA score was significantly associated with higher rate of in-hospital adverse events (adjusted hazard ratio, 2.29; confidence interval, 1.02–5.12; $P = 0.044$) (Table 3). In the Kaplan–Meier curve, there was a significant difference between the high and low qSOFA groups in terms of in-hospital adverse events (log–rank, $P = 3.7 \times 10^{-3}$) (Fig. 1). Regarding the diagnostic accuracy of a high qSOFA score, the sensitivity was 27.0% and the specificity was 95.7% for in-hospital adverse events.

For each in-hospital event, the high qSOFA group had lower rates of overall survival, embolism-free survival, cerebral infarction-free survival, and intracranial hemorrhage-free survival compared to the low qSOFA group (Fig. S1). The occurrence rate of embolic events was the highest among these events. In the Cox proportional hazard model, the presence of a high qSOFA score was linked to embolic events in IE patients (adjusted hazard ratio, 2.44; confidence interval, 1.00–5.95; $P = 0.049$).

DISCUSSION

IN THIS STUDY, we tested the hypothesis that a high qSOFA score could predict in-hospital adverse events in IE patients. Univariate analysis showed that *S. aureus* infection and qSOFA score were associated with in-hospital adverse events, and qSOFA score was the only predictor of such events in multivariate analysis. These results indicated that IE patients with high qSOFA scores had a higher

Table 2. List of in-hospital adverse events among hospitalized patients with infective endocarditis

	High qSOFA n = 12	Low qSOFA n = 71	Total events
At least one in-hospital adverse event	10 (83.3)	27 (38.0)	37 (44.6)
Death	6 (50.0)	3 (4.2)	9 (10.8)
Embolic complications	8 (66.7)	23 (32.4)	31 (36.9)
Cerebral infarction	8 (66.7)	18 (25.4)	26 (31.3)
Peripheral embolism	1 (8.3)	3 (4.2)	4 (4.8)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)
Renal infarction	1 (8.3)	3 (4.2)	4 (4.8)
Splenic infarction	1 (8.3)	2 (2.8)	3 (3.6)
Hepatic infarction	0 (0.0)	1 (1.4)	1 (1.2)
Abscess formations	0 (0.0)	2 (2.8)	2 (2.4)
Cerebral abscess	0 (0.0)	0 (0.0)	0 (0.0)
Spleen-liver abscess	0 (0.0)	2 (2.8)	2 (2.4)
Renal abscess	0 (0.0)	1 (1.4)	1 (1.2)
Lung abscess	0 (0.0)	0 (0.0)	0 (0.0)
Intracranial hemorrhage	4 (33.3)	5 (70.4)	9 (10.8)

Data presented as *n* (%).
qSOFA, quick Sepsis-related Organ Failure Assessment.

Table 3. Univariate and multivariate analyses of in-hospital adverse events among hospitalized patients with infective endocarditis

	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.005	0.99–1.03	0.580	1.002	0.98–1.02	0.860
Male sex	0.610	0.31–1.21	0.160	0.900	0.43–1.90	0.780
Hypertension	1.140	0.59–2.19	0.700	–	–	–
Diabetes mellitus	0.840	0.33–2.17	0.720	–	–	–
Dyslipidemia	1.360	0.62–3.00	0.440	–	–	–
CKD	0.950	0.39–2.29	0.910	–	–	–
Liver cirrhosis	1.080	0.25–4.57	0.920	–	–	–
Atrial fibrillation	0.950	0.41–2.18	0.900	–	–	–
Immunosuppressive agent	1.070	0.41–2.80	0.890	–	–	–
Chronic heart failure	0.830	0.29–2.34	0.720	–	–	–
Dental infection	1.060	0.53–2.13	0.870	–	–	–
Staphylococcus aureus	2.390	1.19–4.81	0.015	1.990	0.95–4.16	0.069
Viridans streptococci	1.610	0.80–3.21	0.180	–	–	–
Enterococcus spp.	0.410	0.06–2.99	0.380	–	–	–
Negative blood culture	1.440	0.68–3.06	0.350	–	–	–
LVEF	1.010	0.98–1.05	0.360	–	–	–
Size of vegetation	1.020	0.98–1.08	0.340	–	–	–
Prosthetic valve infection	1.150	0.40–3.26	0.800	–	–	–
High qSOFA score	2.790	1.34–10.33	6.3×10^{-3}	2.290	1.02–5.12	0.044

–, not applicable; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; LVEF, left ventricular ejection fraction; qSOFA, quick Sepsis-related Organ Failure Assessment.

incidence of in-hospital adverse events compared to those with low qSOFA scores. However, a high qSOFA score still had lower sensitivity for predicting in-hospital adverse events. This result could suggest that it might be important to find a better scoring system to identify poor outcomes in IE patients. Indeed, Maitra *et al.*[24] reported similar results in the meta-analysis of predicting in-hospital mortality by qSOFA score in patients with suspected infection.

In the present study, high qSOFA score was an independent predictor of in-hospital adverse events in patients with IE. The revised definition of sepsis (Sepsis-3 definition)[23] already suggested that the qSOFA score identified patients with suspected infection who were likely to have poor outcomes. Actually, in comparison to patients with qSOFA scores <2, patients with scores ≥2 showed a 3- to 14-fold increase of in-hospital mortality due to sepsis.[19] Also, the presence of a high qSOFA score predicted in-hospital mortality in a number of suspected infections more accurately than the systemic inflammatory response syndrome or SOFA score in non-ICU patients.[19–21] As for single disease, in patients with pneumonia, qSOFA score identified those at high risk of mortality and requirement of ICU admission.[25]
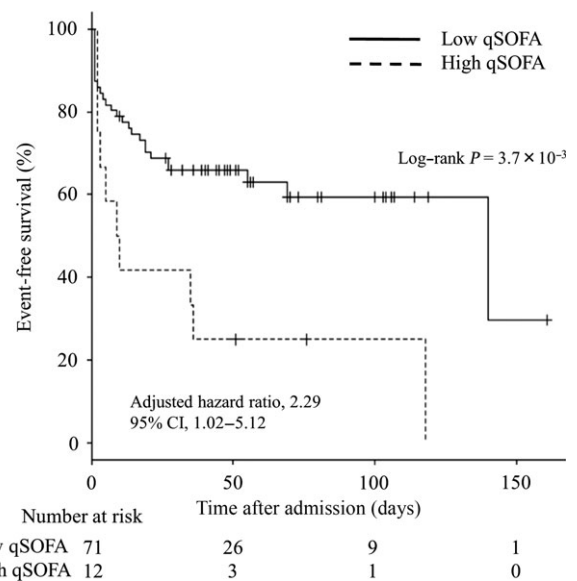

Fig. 1. Kaplan–Meier estimates of in-hospital adverse event-free survival in hospitalized patients with infective endocarditis by high and low quick Sepsis-related Organ Failure Assessment (qSOFA) groups. The high qSOFA group had a lower event-free survival rate compared to the low qSOFA group.

Therefore, a high qSOFA score could also be useful for IE patients, in addition to those uses reported above.

Our study had several limitations. First, we could have underestimated complications because imaging tests were undertaken at the discretion of the attending physician. However, the appropriate period for follow-up imaging tests is not clearly established in IE patients. Second, we did not compare conventional risk scores, such as SOFA and qSOFA scores, in terms of adverse event prediction in patients with IE, because we focused on the rapid evaluation method for IE patients in primary medical settings in this study. Finally, the primary outcome included not only in-hospital mortality but also thromboembolic events, because the number of IE patients enrolled in the study was relatively small. A further large-scale prospective study is required to strengthen the validity of the present results.

CONCLUSIONS

HIGH QSOFA SCORE was significantly associated with in-hospital adverse events in patients with IE. The qSOFA score might have the potential to be a useful tool for risk stratification in IE patients during hospitalization.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Kaplan–Meier estimates of event-free survival in hospitalized patients with infective endocarditis by high and low quick Sepsis-related Organ Failure Assessment (qSOFA) groups: overall survival (a), embolism-free survival (b), cerebral infarction-free survival (c), and intracranial hemorrhage-free survival (d).