Evaluation of qSOFA score, and conjugated bilirubin and creatinine levels for predicting 28-day mortality in patients with sepsis

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Abstract. Sepsis is a dangerous disease that develops rapidly and has a high mortality rate. A timely and accurate assessment of the patient's condition is beneficial in improving prognosis and reducing mortality. Therefore, the present study was designed to investigate the potential association between quick sequential organ failure assessment (qSOFA) scores and biochemical indicators, such as conjugated bilirubin (CB) and creatinine levels, with the 28-day prognosis of patients with sepsis in a retrospective observational study. All cases were divided into survival and non-survival groups on the 28th day after diagnosis. The qSOFA scores, and CB and creatinine levels were significantly higher in the non-survival group than in the survival group (both P<0.01). Cox regression models identified CB [hazard ratio (HR), 1.006; P=0.002] and creatinine levels (HR, 1.002; P=0.024) as independent factors affecting 28-day mortality. The area under the curve (AUC) for CB and creatinine levels plus qSOFA score was 0.792 (95% confidence interval, 0.745-0.834), which was larger than the values for CB level, creatinine level and qSOFA score alone (all P<0.01) in the prognosis of 28-day mortality. The cut-off value of CB and creatinine levels plus qSOFA score for the 28-day mortality was 0.275 (-2.466 + 0.012 x CB + 0.002 x creatinine + 1.289 x qSOFA). Patients with lower combined predictor values had a better prognosis as demonstrated by Kaplan-Meier survival curves (log-rank test, 10.060; P=0.002). In both the septic shock and sepsis groups, the combined predictor value was higher in the non-survival group than in the survival group (P<0.001). Therefore, an increase in the combined predictor value of CB and creatinine levels plus qSOFA score may be an important predictor of disease progression and prognosis in patients with sepsis and septic shock.

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Abbreviations: qSOFA, quick sequential organ failure assessment; CB, conjugated bilirubin; HR, hazard ratio; AUC, area under the curve; CRP, C-reactive protein; PCT, procalcitonin; ROC, receiver operating characteristic; CI, confidence interval; BMI, body mass index; UTI, urinary tract infection; BP, blood pressure

Key words: qSOFA, CB, creatinine, sepsis, mortality

Introduction

Sepsis is a condition of life-threatening organ dysfunction caused by a dysregulated host response to infection (1). As sepsis progresses, the systemic inflammatory response can lead to multiple organ failures, including that of the lung, kidney and liver. According to research data published in The Lancet in 2020 (2), it is estimated that there were 48.9 million global cases of sepsis in 2017, resulting in ~11 million deaths and accounting for 19.7% of all global deaths. Due to its complex

pathogenesis, high morbidity and high fatality rate, sepsis has caused a notable burden on human health and medical resources, and has therefore become a major clinical research area in the field of critical care medicine.

In recent years, a large number of studies have explored the significance of biochemical indicators in the diagnosis, staging, prognosis and clinical monitoring of patients with sepsis (3-5). Early diagnosis of sepsis allows clinicians to initiate effective interventions at an early stage, such as the use of antibiotics and supportive care, through the implementation of goal-directed treatment to reduce the risk of mortality and improve the prognosis of patients with sepsis. C-reactive protein (CRP) and procalcitonin (PCT) are proteins produced during infection and inflammatory response, and are currently the most widely used biomarkers in sepsis diagnosis and disease monitoring (6,7). CRP is an acute-phase protein, the level of which increases with the inflammatory response; however, it has limited accuracy in reflecting disease progression (6). PCT is a sensitive marker of the early stages of infection (8), but it does not reflect the disease progression in later stages, and therefore its prognostic value is not high. It can be argued that there is a lack of useful indicators for the rapid diagnosis and prognosis of sepsis, and there is an urgent need to develop more prognostic markers.

The third international consensus on sepsis in 2016 (9) emphasized the use of the sequential organ failure assessment (SOFA) score for functional assessment and risk stratification of organs, and proposed the 'infection + quick SOFA score (qSOFA) ≥2' for the rapid diagnosis of patients with suspected sepsis. The qSOFA score contains three indicators: Hypotension [systolic blood pressure (BP) ≤100 mmHg], shortness of breath (respiratory rate ≥22 breaths/min) and altered mental status (Glasgow Coma Scale score ≤13). Each index is assigned 1 point, and the risk of sepsis is significantly increased in patients with qSOFA ≥2 points (10). This criterion will help clinicians identify patients with sepsis as well as infected patients at risk of developing sepsis.

Furthermore, patients with elevated conjugated bilirubin (CB) levels have presented with higher illness severity scores, and higher incidences of sepsis, shock and organ failure (11). In addition, sepsis is often accompanied by acute kidney injury, of which serum creatinine level is a reliable indicator. As an independent risk factor, it has significance for the diagnosis of acute kidney injury secondary to sepsis (12,13). Thus, the qSOFA score, along with CB and creatinine levels, may play a role as indicators in the progression of sepsis. However, the significance of these factors in the prediction of sepsis remains unknown. Hence, the aim of the present study was to evaluate qSOFA scores, and serum CB and creatinine levels during sepsis and septic shock to identify whether they are associated with disease prognosis (28-day mortality).

Patients and methods

Patients. A retrospective, observational study was conducted at The Second Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China). A total of 360 nonsurgical and non-trauma adult patients with sepsis or septic shock, who were admitted to the Department of Emergency Intensive Care consecutively between January 2015 and December 2019, were included in the present study. The inclusion criteria included a diagnosis for sepsis or septic shock according to the Third International Consensus Definitions (9). The exclusion criteria were as follows: i) Age of <18 or >90 years; ii) presence of conditions, such as surgical trauma and/or severe heart, liver, lung, kidney, blood system or metabolic diseases; iii) presence of tumors; iv) pregnancy; v) receipt of antibiotic treatment within 28 days before study enrollment; and vi) patients with rapid death outcomes (within 24 h after admission). The basic and test data of the enrolled patients within 24 h of the first visit to the emergency room were collected. All patients were followed up for 28 days after admission, and those who were discharged within 28 days were followed up by telephone. All eligible patients were divided into two groups: i) The survival group, which included patients who survived 28 days after the initial diagnosis; and ii) the non-survival group, which included patients who died within 28 days after diagnosis. The study was carried out in accordance with The Declaration of Helsinki for research involving humans. The present study received approval from the Ethics Committee of The Second Affiliated Hospital, Zhejiang University School of Medicine (approval no. 2021-0641; Hangzhou, China), while the Ethics Committee waived the need for written informed consent of the patients because of the anonymous nature of the clinical data acquired retrospectively.

Clinical data collection and processing. Basic patient data, such as age, sex, height, weight, comorbidities, infection site, qSOFA score and preliminary diagnosis within 24 h after admission, were collected. The following evaluations were performed within 24 h after the patients first arrived at the emergency room: Routine blood examination, arterial blood gas analysis, biochemical examination, coagulation parameters, myocardial enzyme spectrum, PCT, CRP, and blood, urine or sputum pathogen detection. The routine blood tests were performed using an automatic blood analyzer (XN-9000; Sysmex Corporation). Arterial blood gas analyses were conducted using an automated blood gas analyzer (ABL800; Radiometer Medical ApS). The levels of biochemical markers and CRP were determined using an automated dry chemistry analyzer (v5600; Johnson & Johnson). Coagulation parameters were measured with an automated blood coagulation analyzer (STA R Max systems; Stago). Myocardial enzyme and PCT levels were determined using an automated electrochemical enzyme immunoluminescence analyzer (E601; Roche Diagnostics).

Statistical analysis. All statistical analyses were performed using SPSS software (version 24.0; IBM Corp.), and $P<0.05$ was considered to indicate a statistically significant difference. Data with normal distribution are presented as the mean ± standard deviation, and those not conforming to normal distribution are presented as median (25-75%). All numerical variables were compared using the Mann-Whitney U test. χ^2 or Fisher's exact probability test was used to compare categorical variables. Bonferroni's correction was used to compare differences among three or more groups. Cox regression analysis was used to analyze potential prognostic risk factors. Risk factors were incorporated into the multivariate model based on univariate analyses. Receiver operating characteristic (ROC) curves for mortality risk factors were plotted. The area under

Table I. Baseline characteristics of the study population.

Characteristics	Overall (n=360)	Survivors (n=257)	Non-survivors (n=103)	χ^2 or U value	P-value
Age, years [median (IQR)]	64.50 (54.00-74.00)	64.00 (52.00-72.50)	66.00 (58.00-75.00)	-1.994[a]	0.046
Male sex, n (%)	212 (58.89)	142 (55.25)	70 (67.96)	4.905[b]	0.033
BMI, kg/m^2 (mean ± SD)	21.80±3.79	22.18±3.86	20.47±3.23	-3.776[a]	<0.001
BP, mmHg (mean ± SD)					
Systolic	119.74±22.88	121.99±21.59	113.26±25.28	-3.048[a]	0.002
Diastolic	69.16±14.95	71.23±13.37	63.19±17.54	-4.015[a]	<0.001
Heart rate, beats/min [median (IQR)]	87.00 (76.00-102.00)	83.00 (74.00-97.75)	98.00 (86.00-119.00)	-6.136[a]	<0.001
Respiratory rate, breaths/min [median (IQR)]	19.00 (18.00-20.00)	18.00 (18.00-20.00)	20.00 (18.00-25.00)	-3.710[a]	<0.001
Body temperature, ˚C [median (IQR)]	37.10 (36.80-37.70)	37.10 (36.80-37.60)	37.20 (36.60-37.90)	-0.467[a]	0.641
Comorbidities, n (%)				2.617[b]	0.454
No	326 (90.56)	229 (89.11)	97 (94.17)	1.833[b,c]	0.176
Hypertension	10 (2.78)	9 (3.50)	1 (0.97)	0.561[b,d]	0.454
Diabetes	19 (5.28)	15 (5.84)	4 (3.89)	0.003[b,e]	0.959
Combination of hypertension and diabetes	5 (1.39)	4 (1.56)	1 (0.97)	71.956[b,f]	0.005
qSOFA score, n (%)				75.857[b]	<0.001
≥2	60 (16.67)	15 (5.84)	45 (43.69)		
<2	300 (83.33)	242 (94.16)	58 (56.31)		
Septic shock, n (%)	144 (40.00)	94 (36.58)	50 (48.54)	4.388[b]	0.043
Infection site, n (%)				15.148[b]	0.001
Lung	134 (37.22)	81 (31.52)	53 (51.46)	11.063[b,g]	0.001
Urinary tract	42 (11.67)	37 (14.40)	5 (4.85)	3.127[b,h]	0.099
Others	184 (51.11)	139 (54.09)	45 (43.69)	8.287[b,i]	0.005
WBC, x10^9/l [median (IQR)]	12.85 (7.43-19.68)	12.70 (7.90-18.80)	13.10 (6.40-21.00)	-0.447[a]	0.655
RBC, x10^{12}/l [median (IQR)]	3.73 (3.09-4.27)	3.81 (3.21-4.32)	3.57 (2.60-4.15)	-3.147[a]	0.002
RDW, % [median (IQR)]	13.75 (12.80-15.28)	13.50 (12.70-14.70)	14.70 (13.30-16.50)	-4.706[a]	<0.001
PLT, x10^9/l [median (IQR)]	126.00 (64.00-201.50)	138.00 (81.50-202.50)	89.00 (40.00-190.00)	-3.044[a]	0.002
PCT, ng/ml [median (IQR)]	10.85 (1.22-54.01)	10.53 (1.14-54.03)	11.15 (1.53-52.79)	-0.492[a]	0.623
NT-proBNP, pg/ml [median (IQR)]	3,057.00 (915.59-9,072.38)	2,180.00 (775.00-6,309.00)	4,204.50 (1,465.25-1,6156.75)	-3.245[a]	0.001
CB, μmol/l [median (IQR)]	1.10 (0.10-7.73)	0.80 (0.10-6.18)	3.10 (0.65-17.20)	-3.303[a]	0.001
AST, U/l [median (IQR)]	45.00 (25.00-106.50)	40.00 (23.00-81.00)	69.00 (35.00-278.50)	-4.400[a]	<0.001
LDH, U/l [median (IQR)]	254.00 (191.00-415.50)	233.00 (182.00-340.75)	350.00 (231.00-720.50)	-5.314[a]	<0.001

Table I. Continued.

Characteristics	Overall (n=360)	Survivors (n=257)	Non-survivors (n=103)	χ^2 or U value	P-value
cTn-T, ng/ml [median (IQR)]	0.04 (0.02-0.12)	0.03 (0.01-0.09)	0.07 (0.03-0.22)	-4.841[a]	<0.001
BUN, mmol/l [median (IQR)]	8.44 (5.77-13.35)	7.78 (5.37-11.31)	11.80 (7.51-21.72)	-5.318[a]	<0.001
Creatinine, μmol/l [median (IQR)]	102.00 (68.00-183.75)	92.00 (65.00-157.00)	142.00 (82.50-244.00)	-3.762[a]	<0.001
Coagulation parameter					
PT, sec [median (IQR)]	15.70 (14.50-17.60)	15.15 (14.30-16.90)	16.95 (15.30-19.35)	-5.870[a]	<0.001
PT, % (mean ± SD)	69.33±18.76	73.09±17.40	59.94±18.83	-5.853[a]	<0.001
INR [median (IQR)]	1.25 (1.14-1.46)	1.21 (1.12-1.39)	1.40 (1.22-1.64)	-5.880[a]	<0.001
APTT, sec [median (IQR)]	42.45 (37.53-49.00)	41.90 (37.40-47.60)	45.75 (38.18-52.48)	-2.947[a]	0.003
TT, sec [median (IQR)]	16.00 (15.10-17.50)	15.80 (15.00-17.23)	16.45 (15.28-18.38)	-2.709[a]	0.007
Fbg, g/l (mean ± SD)	5.02±2.15	5.22±2.04	4.52±2.33	-2.949[a]	0.003
DD, μg/l [median (IQR)]	3,770.00 (2,210.00-9,080.00)	3,425.00 (2,030.00-7,927.50)	4,390.00 (2,715.00-10,585.00)	-2.234[a]	0.025

Data are presented as mean ± SD, median (IQR) or n (%). [a]Mann-Whitney U test; [b]χ^2 test. Compared with [c]hypertension; [d]diabetes; [e]combination of hypertension and diabetes; [f]no comorbidities; [g]urinary tract; [h]others; and [i]lung. IQR, interquartile range; SD, standard deviation; BMI, body mass index; BP, blood pressure; WBC, white blood cell; RBC, red blood cell; RDW, red blood cell distribution width; PLT, platelet; PCT, procalcitonin; NT-proBNT, N terminal pro B type natriuretic peptide; CB, conjugated bilirubin; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; cTn-T, cardiac troponin T; BUN, blood urea nitrogen; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time; Fbg, fibrinogen; DD, D-dimer; qSOFA, quick sequential organ failure assessment.

the curve (AUC) was calculated using MedCalc software (version 18.2.1; MedCalc software bvba).

A multivariable Cox proportional hazard regression analysis was performed to evaluate the independent association of qSOFA score, CB level or creatinine level with 28-day mortality, and the results are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). The survival curves for the two groups according to the qSOFA score, CB level or creatinine level were plotted using the Kaplan-Meier method, and the log-rank test was applied. Age, sex, body mass index (BMI) and variables considered to be associated with infection, such as whether the lung and urogenital organs were primary sites of infection, serum creatinine concentration and coagulation parameters, were included in the analysis.

Results

Patient characteristics. The current study investigated patients with sepsis admitted between January 2015 and December 2019. Patients with rapid death outcomes (within 24 h after admission) were excluded from the analysis, and 360 patients with sepsis were eventually included in the study. Among them, 216 (60.0%) and 144 (40.0%) cases were diagnosed with sepsis and septic shock, respectively. These patients included 212 men (58.9%) and 148 women (41.1%), aged between 18 and 89 years (median age, 64.5 years). The 28-day mortality rate was 28.6% (103/360). The 28-day mortality of the septic shock group was significantly higher than that of the sepsis group (34.7% vs. 24.5%; χ^2=4.388; P=0.043). In comparison with survivors, non-survivors were older (P<0.05), more frequently male (P<0.05) and had a lower BMI and BP (both P<0.01), as well as higher heart rate, respiratory rate and qSOFA scores (all P<0.01). The 28-day mortality rates associated with pulmonary infection, urinary tract infection (UTI) and other infections were significantly different between the two groups (χ^2 =15.148; P=0.001). The 28-day mortality rate of pulmonary infection was the highest (39.6%; 53/134), followed by other infections (24.5%; 45/184), while the 28-day mortality rate of UTIs was the lowest (11.9%; 5/42). The 28-day mortality rate of pulmonary infection was significantly different from those of other infections and UTIs (Bonferroni correction, P<0.0167), while there was no significant difference in 28-day mortality rates between UTIs and other infections (Bonferroni correction, P≥0.0167) (data not shown). Prothrombin time, international normalized ratio, activated partial thromboplastin time, thrombin time and D-dimer values in non-survivors were higher than those in the survival group, and fibrinogen values in non-survivors were significantly lower than those in the survival group (all P<0.05). The levels of red blood cell distribution width, pro B-type natriuretic peptide, CB, aspartate aminotransferase, lactate dehydrogenase, cardiac troponin T, blood urea nitrogen and creatinine in the non-survival group were significantly higher than those in the survival group, whereas red blood cell and platelet counts were significantly lower in the non-survival group (all P<0.01). The white blood cell count and PCT level in the non-survival group were higher than those in the survival group, but the difference was not significant. Table I presents the baseline clinical characteristics of the 360 patients included in the current study.

Analysis of relevant variables using Cox regression. qSOFA scores ≥2 and the CB and creatinine levels were closely

Table II. Cox regression analysis of the risk factors for 28-day mortality.

A, Univariable Cox regression

Variables	β	HR	95% CI	P-value
qSOFA (≥2)	0.541	1.718	1.155-2.555	0.008
Septic shock	0.320	1.377	0.932-2.035	0.108
Heart rate	0.009	1.009	0.999-1.019	0.081
CB	0.004	1.004	1.001-1.008	0.014
Creatinine	0.001	1.001	1.000-1.003	0.041
APTT	0.008	1.008	0.998-1.018	0.102
TT	0.008	1.008	0.998-1.018	0.107

B, Multivariable Cox regression

Variables	β	HR	95% CI	P-value
CB	0.006	1.006	1.003-1.011	0.002
Creatinine	0.002	1.002	1.000-1.005	0.024

HR, hazard ratio; CI, confidence interval; qSOFA, quick sequential organ failure assessment; CB, conjugated bilirubin; APTT, activated partial thromboplastin time; TT, thrombin time.

associated with 28-day mortality. Cox regression models identified CB (HR, 1.006; P=0.002) and creatinine levels (HR, 1.002; P=0.024) as independent factors of 28-day mortality (Table II).

Combined evaluation of CB and creatinine levels, and qSOFA scores in the prognosis of 28-day mortality. A logistic regression model was established based on the CB and creatinine levels and qSOFA values, and a ROC curve analysis was used to generate the combined diagnostic curve to evaluate the prognostic value of CB and creatinine levels plus qSOFA scores in 28-day mortality (Fig. 1). The larger the AUC, the better the prognostic performance. AUC <0.5 was considered to have no prognostic significance and AUC >0.9 was considered to have high prognostic accuracy (14). The AUC of CB level alone was 0.613 (95% CI, 0.558-0.665). The AUC of creatinine level alone was 0.628 (95% CI, 0.575-0.678), and that of the qSOFA score alone was 0.749 (95% CI, 0.701-0.793). However, the AUC of CB and creatinine levels plus the qSOFA score was 0.792 (95% CI, 0.745-0.834), which was larger than the AUCs of the individual factors alone (all P<0.01) (Table III).

The cut-off was defined as the value of the point on the curve when the Youden index (sensitivity + specificity-1) was the greatest. A value greater than the cut-off value may be considered to indicate the possibility of dying within 28 days.

The sensitivity and specificity of combined detection were 74.75 and 74.36%, respectively. The specificity of combined detection was notably higher than that of the single tests, while the sensitivity of combined detection was almost the same as those of CB alone and qSOFA alone, and was higher than that of creatinine alone (Table III).

Kaplan-Meier survival curve analysis. Using the cut-off value determined by the ROC curve, Kaplan-Meier survival curves

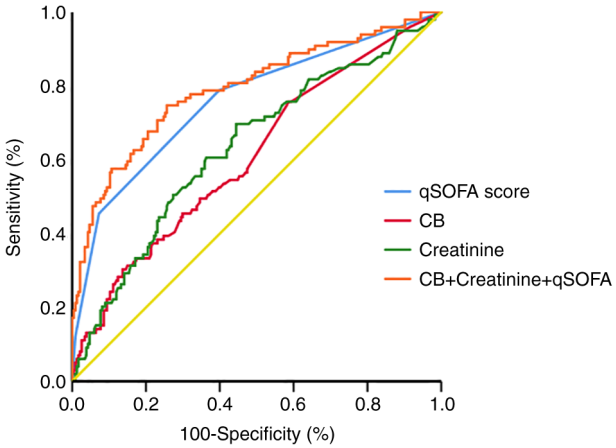

Figure 1. Receiver operating characteristic curves of CB and creatinine levels, and qSOFA scores for 28-day mortality. CB, conjugated bilirubin; qSOFA, quick sequential organ failure assessment.

of CB, creatinine, qSOFA and combined detection were established. The Kaplan-Meier analysis indicated that patients with a qSOFA score of 0 had a better chance of 28-day survival than those with qSOFA ≥1 (log-rank, 4.069; P=0.044). In addition, patients with a combined predictor (-2.466 + 0.012 x CB + 0.002 x creatinine + 1.289 x qSOFA) value ≤0.275 had a better chance of 28-day survival than those with a combined predictor value >0.275 (log-rank, 10.060; P=0.002) (Table IV; Fig. 2).

Subgroup analysis. Of the 360 patients, 144 patients were diagnosed with septic shock. The combined predictor value of CB and creatinine levels, and qSOFA scores in the septic shock group was higher than that in the sepsis group (median, 0.2750 vs. 0.1496; P<0.001). Among patients with septic shock,

Table III. Receiver operating characteristic curve data for CB and creatinine levels, and qSOFA scores in the prediction of 28-day mortality.

Variables	AUC (95% CI)	Cut-off value	P-value	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Vs. CB + Creatinine + qSOFA	
								Z-value	P-value
CB	0.613 (0.558-0.665)	>0.5	0.0008	76.00	41.45	29.94	70.06	4.869	<0.0001
Creatinine	0.628 (0.575-0.678)	117	0.0001	59.41	63.53	28.37	71.63	4.413	<0.0001
qSOFA	0.749 (0.701-0.793)	1	<0.0001	75.73	62.26	28.61	71.39	2.637	0.0084
CB + Creatinine + qSOFA	0.792 (0.745-0.834)	>0.275[a]	<0.0001	74.75	74.36	29.73	70.27	-	-

[a]Combined predictors obtained using the logistic regression equation as follows: -2.466 + 0.012 x CB + 0.002 x creatinine + 1.289 x qSOFA. AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; CB, conjugated bilirubin; qSOFA, quick sequential organ failure assessment.

survivors tended to have lower combined predictor values than non-survivors (median, 0.2545 vs. 0.5780; P<0.001). For patients with sepsis, survivors had significantly lower combined predictor values than non-survivors (median, 0.1103 vs. 0.4500; P<0.001) as shown in Table V.

As presented in Table VI, Cox regression models were applied in subgroup analyses, which indicated that the combination of CB and creatinine levels and qSOFA scores could serve as an independent risk factor of 28-day mortality for patients with septic shock (HR, 4.240; 95% CI, 1.408-12.767; P=0.010), as well as for those with sepsis (HR, 4.068; 95% CI, 1.287-12.858; P=0.017).

Discussion

Sepsis is a rapidly progressive condition and a major cause of death. Therefore, timely and accurate assessment of the patient's condition is beneficial in improving prognosis and reducing mortality (1,2). In the present study, serum CB and creatinine levels, and qSOFA scores at admission in patients with sepsis were higher in the non-surviving group than in the surviving group. In multivariate analysis, serum CB and creatinine levels were indicated to be independent predictors of poor sepsis outcomes. When the combined predictor value of CB and creatinine levels and qSOFA scores reached 0.275, 28-day mortality increased.

Several studies (15-17) have attempted to predict the prognosis of sepsis by indirectly estimating liver and renal function. Serum bilirubin concentration has been used as one of the indicators for the assessment of liver function in critically ill patients. For example, Pierrakos *et al* (15) reported that hyperbilirubinemia was an independent factor for patient morbidity and mortality in the Intensive Care Unit (ICU), and mortality was linearly associated with bilirubin concentrations between 1.1 and 6 mg/dl. Patel *et al* (16) also found that elevated serum bilirubin levels within 72 h of admission were associated with an increased risk of death in patients with severe sepsis and septic shock. However, in addition to being an indicator of liver dysfunction, bilirubin itself may also influence patient outcomes. Bilirubin can impair the bactericidal properties of neutrophils (17) through its antioxidant action (18), and may be nephrotoxic (19) and neurotoxic (20). It also inhibits inducible nitric oxide synthase (21) and exerts an anti-platelet aggregation effect by inhibiting collagen-induced platelet activation (22). However, certain reports have suggested that bilirubin may play a role in suppressing inflammatory responses (23) and that hyperbilirubinemia may be an adaptive response to critical illness (24). The present data emphasized that altered liver function has an important role in septic multi-organ failure and that elevated serum CB levels are common in patients with sepsis and are associated with 28-day mortality. Multivariable analysis showed that the serum CB level was an independent risk factor for increased mortality. It was demonstrated that an increased bilirubin level was accompanied by increased inflammation (increased white blood cell count), and we hypothesize that high CB levels may reduce blood flow velocity and induce microcirculation disturbances, while stimulating the production of inflammatory factors to promote liver

Table IV. Kaplan-Meier survival curve analysis.

Variables	Cut-off value	Median, days	95% CI	Log-rank	P-value
CB	≤0.5	5	1.399-8.601	1.890	0.169
	>0.5	4	1.677-6.323		
Creatinine	<117	6	3.212-8.788	1.724	0.189
	≥117	3	0.471-5.529		
qSOFA	0	9	7.378-10.622	4.069	0.044
	≥1	3	1.428-4.572		
CB + Creatinine + qSOFA	≤0.275	9	6.456-11.544	10.060	0.002
	>0.275	3	2.216-3.784		

CI, confidence intervals; CB, conjugated bilirubin, qSOFA, quick sequential organ failure assessment.

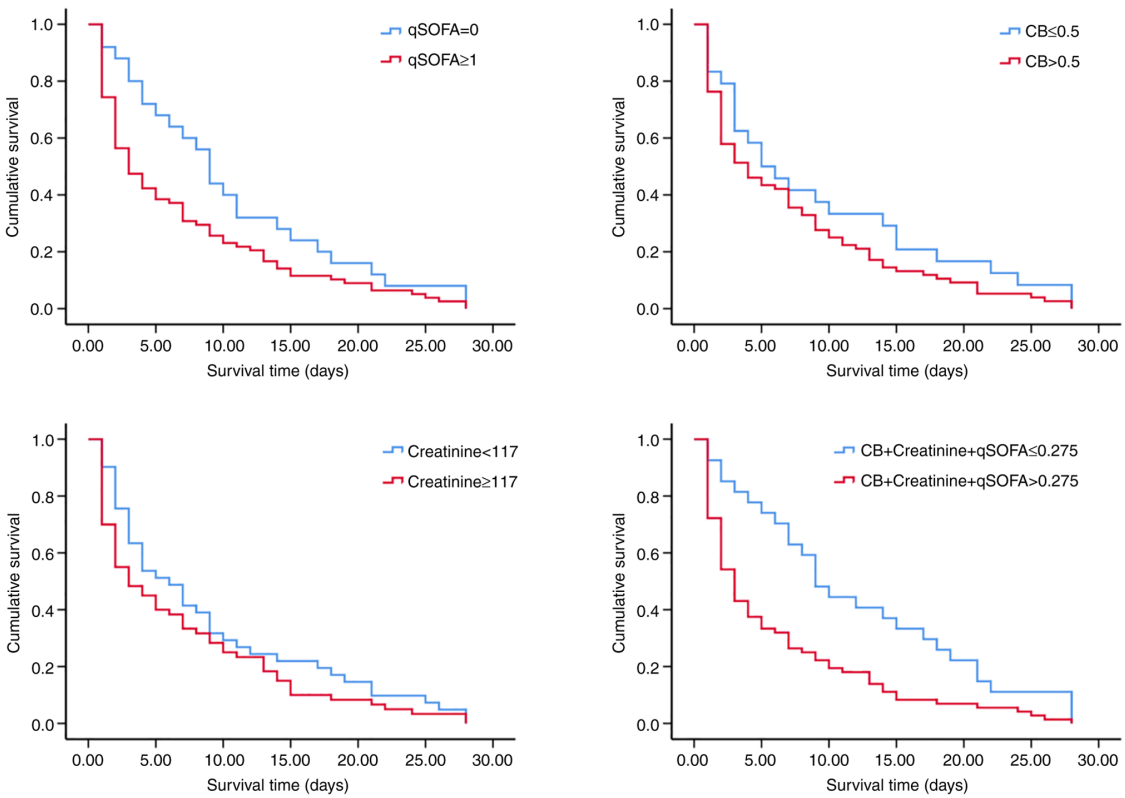

Figure 2. Survival curves of CB and creatinine levels and qSOFA scores. CB, conjugated bilirubin; qSOFA, quick sequential organ failure assessment.

Table V. Combined predictor values in subgroup analyses.

Variables	Combined predictor values (median)	P-value
Sepsis	0.1496	<0.001[a]
Survivors	0.1103	<0.001[b]
Non-survivors	0.4500	
Septic shock	0.2750	
Survivors	0.2545	<0.001[b]
Non-survivors	0.5780	

[a]Compared with septic shock group; [b]compared with non-survivors of the same group.

Table VI. Cox regression models in subgroup analyses.

Variables	β	HR	95% CI	P-value
Septic shock	1.444	4.240	1.408-12.767	0.010
Sepsis	1.403	4.068	1.287-12.858	0.017
All	1.479	4.388	2.007-9.591	<0.001

HR, hazard ratio; CI, confidence interval.

damage and cholestasis, thereby affecting the poor prognosis of sepsis. The specific mechanism remains to be further studied in the future.

One of the most commonly affected organs in sepsis is the kidney, and sepsis-induced acute kidney injury is the most common form of acute kidney injury in the ICU (25). Sepsis-induced acute kidney injury is associated with an increased risk of subsequent chronic kidney disease (26), as well as being associated with increased morbidity and mortality rates in sepsis (27). During sepsis, endothelial cell activation, increased microvascular permeability, changes in regional blood flow distribution, and the resulting hypoperfusion and hypoxemia can lead to acute kidney injury (28). Elevated serum creatinine is one of the indicators of acute renal impairment (29) and is directly related to the prognosis of sepsis. The current study findings suggested that altered renal function may also play an important role in the progression of multi-organ failure in sepsis. It was also indicated that increased serum creatinine levels are common in patients with sepsis, are associated with 28-day mortality, and moreover are an independent risk factor for increased mortality.

In the present study, CB and creatinine levels, and qSOFA scores increased with sepsis progression and were higher in non-survivors compared with survivors of sepsis. All three indicators were better predictors in combination than they would have been individually. Therefore, these three indicators may be useful as commonly used laboratory and clinical tests to assess 28-day mortality and the prognosis of sepsis, with the combined prediction showing greater prognostic ability.

The current study had several limitations. Firstly, studying the qSOFA score, CB and creatinine levels alone does not meet the needs and expectations of all patients with sepsis for diagnosis and treatment management. Studying kinetic changes in CB and creatinine levels may be more clinically meaningful than studying unadjusted CB and creatinine levels, suggesting that further research is required. Secondly, since the current study is a single-center retrospective study, whether the findings can be applied to clinical practice requires further investigation by large-sample, multi-center prospective studies.

In conclusion, the prognostic value of combined CB and creatinine levels plus qSOFA score was greater than the predictive value of CB levels, creatinine levels and qSOFA score alone in the prognosis of 28-day mortality in patients with sepsis. Therefore, the combined predictor based on CB and creatinine levels plus qSOFA scores could be used as a prognostic factor in sepsis or septic shock, which could help to rapidly detect critically ill patients and guide clinical treatment.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

YX and XY worked on data analysis and interpretation. LS and QW collected the patients' data. FL and DY interpreted the data. YQ and WW designed the study. YQ drafted the manuscript. YQ and YX confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Clinical Research Ethics Committee of The Second Affiliated Hospital, Zhejiang University School of Medicine (approval no. 2021-0641; Hangzhou, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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