ORIGINAL ARTICLE

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The quick sepsis-related organ failure score has limited value for predicting adverse outcomes in sepsis patients with liver cirrhosis

Jeongsuk Son[1], Sunhui Choi[1], Jin Won Huh[2], Chae-Man Lim[2], Younsuck Koh[2], Kang Mo Kim[3], Ju Hyun Shim[3], Young-Suk Lim[3], and Sang-Bum Hong[2]

[1]Medical Emergency Team, Asan Medical Center, Seoul; [2]Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul; [3]Department of Gastroenterology, Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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Correspondence to
Sang-Bum Hong, M.D.
Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-3893
Fax: +82-2-2045-4039
E-mail: sbhong@amc.seoul.kr

Background/Aims: The quick Sepsis-related Organ Failure Assessment (qSOFA) is a newly developed risk stratification tool, which has been presented along with a new sepsis definition, to classify infected patients outside of the intensive care unit (ICU). We evaluated the clinical usefulness of qSOFA for predicting adverse outcomes in sepsis patients with liver cirrhosis.

Methods: We performed a retrospective cohort study to assess the utility of qSOFA in sepsis patients with liver cirrhosis for whom medical emergency teams (METs) were activated in general wards at an academic tertiary care hospital between March 2008 and December 2015. qSOFA, Systemic inflammatory response syndrome (SIRS), modified early warning score (MEWS), and sequential (sepsis-related) organ failure assessment (SOFA) scores were calculated according to data at MET activation.

Results: Of 188 patients, 69 (36.7%) had a qSOFA score of 0 or 1 point and 119 (63.3%) had ≥ 2 points. The areas under the receiver operating characteristic curve (AUROC) for ICU transfer on the SOFA (AUROC, 0.691; 95% confidence interval [CI], 0.615 to 0.767) or MEWS (AUROC, 0.663; 95% CI, 0.586 to 0.739) were significantly higher compared to those for qSOFA (AUROC, 0.589; 95% CI, 0.507 to 0.671) or SIRS (AUROC, 0.533; 95% CI, 0.451 to 0.616).

Conclusions: Our findings suggest that qSOFA score may have limited utility in predicting adverse outcomes in sepsis patients with liver cirrhosis at MET activation. Either MEWS or another screening tool is needed for detecting early sepsis in these patients.

Keywords: Rapid response team; Sepsis; Liver cirrhosis; qSOFA

INTRODUCTION

Patients with cirrhosis are in a state of immune dysfunction and bacterial translocation; hence, bacterial infection is common, causing a poor prognosis, and is a major cause of mortality in such patients [1]. The outcome of patients with cirrhosis and septic shock has improved over time, but in-hospital mortality is still reported to be approximately 70% in 2010 [2].

The hospital mortality rate for sepsis and septic shock is approximately 30%, and this varies significantly among different geographic regions of the world [3]. Early de-

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tection of sepsis is important in order to improve the chances of survival. Sepsis screening is associated with earlier treatment, and lack of timely recognition delays therapy [4]. The Surviving Sepsis Campaign was established in 2002 to assess the public and clinicians' awareness of sepsis and develop evidence-based guidelines for the management of sepsis and septic shock [5].

The European Society of Intensive Care Medicine and the Society of Critical Care Medicine's Third International Consensus task force assembled to re-examine sepsis definitions. Sepsis-3 was defined as life-threatening organ dysfunction provoked by a dysregulated host response to infection [6]. The quick Sepsis-related Organ Failure Assessment (qSOFA) is a recently developed risk stratification tool, which has been presented along with a new sepsis definition, to classify infected patients outside of the intensive care unit (ICU). qSOFA was based on incorporating altered mentation, systolic blood pressure of ≤ 100 mmHg, and respiratory rate of ≥ 22/minutes [7]. Questions have been raised whether qSOFA is appropriate for predicting sepsis outside of the ICU although qSOFA is composed of simple parameters [8,9].

It is difficult to predict sepsis in patients with cirrhosis because cirrhosis itself can lead to clinical presentation of sepsis including low systemic vascular resistance, systemic hypotension, and increased heart rate. Thus, a new tool is needed for early detection of sepsis in patients with cirrhosis [10]. In addition, published data are scant on predicting factors of sepsis in liver cirrhosis. We evaluated the clinical usefulness of qSOFA for predicting adverse outcomes in sepsis patients with liver cirrhosis.

METHODS

Study design and study subjects

We conducted a retrospective cohort study to analyze the usefulness of qSOFA for predicting adverse outcomes in sepsis patients with liver cirrhosis at an academic tertiary care hospital with approximately 2,700 beds (Asan Medical Center, Seoul, Korea). Clinical data were collected and analyzed for sepsis patients with liver cirrhosis who triggered activation of the medical emergency team (MET) in general wards between March 1, 2008, and December 30, 2015. We excluded patients aged < 18 years and those with a confirmed do-not-resuscitate (DNR) order at MET activation.

The MET was implemented in 2008 and operates for 24 hours, 7 days a week. The team is activated by a medical doctor or nurse using an electronic medical recording-based monitoring system if a patient's condition deteriorates. The calling criteria for MET intervention include crisis components based on physiological parameters: threatened airway, respiratory rate >30 breaths/min or < 6 breaths/min, oxygen saturation < 90% on venturi mask 40% or O_2 12 L/min, pulse rate < 40 beats/min or > 140 beats/min, systolic blood pressure < 90 mmHg, sudden mental change.

The experimental plan and waiving of informed consent for the present study received approval from Asan Medical Center Institutional Review Board (IRB No: 2017-0430) and was conducted in accordance with the Korea Food and Drug Administration and the International Conference on Harmonization Good Clinical Practice guidelines.

Data collection and definitions

We extracted the following data on patients with sepsis triggering MET activation from the MET registry and electronic medical records and recorded characteristics such as age, sex, and comorbidities.

Several scores were collected to evaluate the clinical usefulness of qSOFA for predicting adverse outcomes in sepsis patients with liver cirrhosis [11-14]. There are scoring system tools that can predict adverse outcomes in patients with sepsis: systemic inflammatory response syndrome (SIRS), which was included in the previous definition of sepsis; qSOFA, which was a new tool in the 2016 definition of sepsis; sequential (sepsis-related) organ failure assessment (SOFA), and modified early warning score (MEWS), which predicts deterioration of the patient (Table 1).

The qSOFA incorporated altered mentation, systolic blood pressure ≤ 100 mmHg, and respiratory rate ≥ 22/minutes [11]. The SIRS comprises four criteria: body temperature > 38°C or < 36°C, heart rate > 90 minutes, hyperventilation indicated by a respiratory rate of > 20 minutes or $PaCO_2$ of < 32 mmHg, and white blood cell count of > 12,000 cells/μL or < 4,000 cells/μL [12]. The MEWS consists of a simple algorithm based on physiological parameters such as heart rate, systolic blood

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Table 1. Components of the known scoring systems in patients with critically ill

Scoring system	Criteria						
MEWS [13]	3 point	2 point	1 point	0 point	1 point	2 point	3 point
Systolic blood pressure, mmHg	≤ 70	71–80	81–100	101–199		≥ 200	
Heart rate, beats/min		≤ 40	41–50	51–100	101–110	111–129	≥ 130
Respiratory rate, breaths/min		< 9		9–14	15–20	21–29	≥ 30
Temperature, °C		< 35.0		35.0–38.4		≥ 38.5	
Conscious level				Alert	Confuse	Drowsy	Unresponsive
SOFA [14]	0 point	1 point	2 point	3 point		4 point	
PaO_2/FiO_2	≥ 400	< 400	< 300	< 200 with respiratory support		< 100 with respiratory support	
Platelet, $\times 10^3/\mu L$	≥ 150	< 150	< 100	< 50		< 20	
Total bilirubin, mg/dL	< 1.2	1.2–1.9	2.0–5.9	6.0–12.0		> 12.0	
Cardiovascular, hypotension	MAP ≥ 70	MAP < 70	Dopamine ≤ 5 or dobutamine	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine≤ 0.1		Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1	
GCS	15	13–14	10–12	6–9		< 6	
Creatinine (mg/dL) or urine output (mL/day)	< 1.2	1.2–1.9	2.0–3.4	3.5–5.0 Urine output < 500		> 5.0 Urine output < 200	
qSOFA [11]	Respiratory rate ≥ 22/min						
	Altered mentation						
	Systolic blood pressure ≤ 100 mmHg						
SIRS [12]	Temperature > 38°C or < 36°C						
	Heart rate > 90/min						
	Respiratory rate > 20/min or $PaCO_2$ < 32 mmHg						
	White blood cell count > 12,000/mm^3 or > 10% immature bands						

MEWS, modified early warning score; SOFA, sequential (sepsis-related) organ failure assessment; MAP, mean arterial pressure; GCS, Glasgow coma scale; qSOFA, quick sepsis-related organ failure assessment; SIRS, systemic inflammatory response syndrome.

pressure, respiratory rate, temperature, and mental state [13]. SOFA is a weighted organ dysfunction score comprised of PaO_2/FiO_2 ratio, Glasgow Coma Scale score, mean arterial pressure, serum creatinine, bilirubin, and platelet count [14]. Each score was calculated according to the data at MET activation.

Illness severity was assessed by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Child-Turcotte-Pugh (CTP) class measured within 6 hours after MET activation. The Model for End-Stage Liver Disease (MELD) score was calculated to examine compensated and decompensated liver cirrhosis [15]. We classified compensated liver cirrhosis as MELD < 15 and decompensated liver cirrhosis as MELD ≥ 15. MELD score was calculated based on the data at MET activation.

The primary outcome of the study was to evaluate the prediction ability of qSOFA, SIRS, MEWS, and SOFA for ICU transfer, 28-day mortality, and in-hospital mortality in sepsis patients with liver cirrhosis. A secondary outcome was to compare ICU transfer and hospital mortality rates according to qSOFA scores.

Statistical analysis

Statistical analysis of the collected data was performed using IBM SPSS Statistics software, version 21 (IBM Co., Armonk, NY, USA).

Data are presented as median and interquartile range (IQR) for continuous variables, including age, APACHE II score, and laboratory data, and as number (%) for categorical variables, including sex, type of sepsis, and source of infection. Statistical analysis was performed using the Mann-Whitney *U* test for continuous variables and the chi-square or Fisher exact test for categorical variables as appropriate. The areas under the curve (AUC) for the ICU transfer and hospital mortality prediction models of qSOFA, SIRS, MEWS, and SOFA were calculated on the receiver operating characteristic curve.

All tests of significance were 2-tailed, and p values < 0.05 were considered significant.

RESULTS

Fig. 1 shows the flow diagram for the study. During the study period, the MET was activated for 2,145 sepsis patients. Overall, 46 of 234 liver cirrhosis patients with a DNR order at MET activation were excluded from analysis. Among the 188 included patients, qSOFA score was 0 or 1 point in 69 (36.7%, group 1) and ≥ 2 points in 119 (63.3%, group 2).

CTP class C was higher (6.3% vs. 69.2%, p < 0.001) in decompensated liver cirrhosis but etiology of liver disease and reason for admission were not significantly different between compensated and decompensated liver cirrhosis. SOFA score was higher in decompensated liver cirrhosis (5.0 [IQR, 4.0 to 6.8] vs. 8.0 [IQR, 6.0 to 10.0], p < 0.001), but qSOFA, SIRS, and MEWS were not different between compensated and decompensated liver cirrhosis (2.0 [IQR, 1.0 to 2.0] vs. 2.0 [IQR, 1.0 to 2.0], p = 0.494; 3.0 [IQR, 1.3 to 4.0] vs. 2.0 [IQR, 1.3 to 3.0], p = 0.066; and 5.5 [IQR, 4.0 to 7.0] vs. 5.0 [IQR, 3.0 to 6.0], p = 0.103, respectively) (Table 2).

Initial management of shock within 6 hours was not different between compensated and decompensated liver cirrhosis. A total of 87 patients (46.3%) were transferred to the ICU, but the rate of ICU transfer was not different between compensated and decompensated liver cirrhosis (34.4% vs. 48.7%, p = 0.138). Overall 28-day mortality rate (28.7%) was significantly higher in decompensated compared to compensated liver cirrhosis (12.5% vs. 32.1%, p = 0.026) as was in-hospital mortality rate (18.8% vs. 41.7%, p = 0.0.15) (Table 3).

Median age of our patients was 59 years (IQR, 52 to

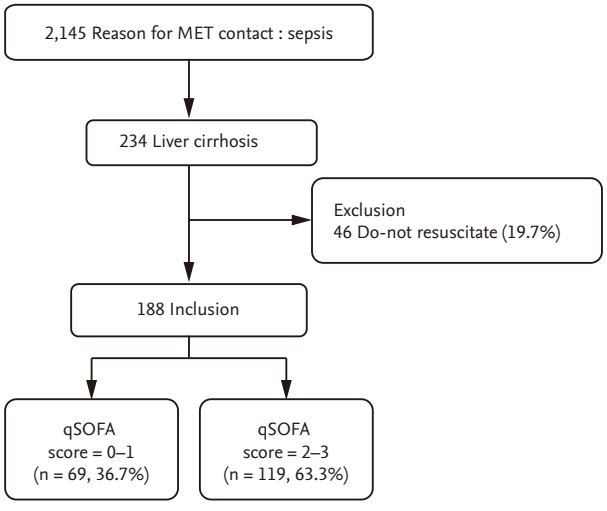

Figure 1. Flow diagram of study patients. MET, medical emergency teams; qSOFA, quick sepsis-related organ failure assessment.

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Table 2. Clinical characteristics of the 188 sepsis patients with liver cirrhosis classified by compensated LC (MELD < 15)

Characteristic	All (n = 188)	Compensated LC (n = 32)	Decompensated LC (n = 156)	*p* value
Etiology of liver disease				
ALD	34 (18.1)	10 (31.3)	24 (15.4)	0.232
HBV	107 (56.9)	17 (53.1)	90 (57.7)	
HCV	21 (11.2)	1 (3.1)	20 (12.8)	
ALD + HBV	4 (2.1)	0	4 (2.6)	
ALD + HCV	1 (0.5)	0	1 (0.6)	
NASH	2 (1.1)	0	2 (1.3)	
Autoimmune hepatitis	2 (1.1)	0	2 (1.3)	
Other	17 (9.0)	4 (12.5)	13 (8.3)	
Reason for admission				
Infection	74 (39.4)	11 (34.4)	63 (40.4)	0.069
Gastrointestinal bleed	2 (1.1)	0	2 (1.3)	
Hepatic encephalopathy	11 (5.9)	0	11 (7.1)	
Renal/metabolic	1 (0.5)	0	1 (0.6)	
Ascites control	10 (5.3)	3 (9.4)	7 (4.50)	
Respiratory failure	2 (1.1)	2 (6.3)	0	
Liver failure	20 (10.6)	0	20 (12.8)	
Circulatory failure	16 (8.5)	0	16 (10.3)	
Neurologic event	3 (1.6)	1 (3.1)	2 (1.3)	
Surgery	14 (7.4)	4 (12.5)	10 (6.4)	
Other	35 (18.6)	11 (34.4)	24 (15.4)	
CTP class				
Class A	2 (1.1)	2 (6.3)	0	< 0.001
Class B	76 (40.4)	28 (87.5)	48 (30.8)	
Class C	110 (58.5)	2 (6.3)	108 (69.2)	
Scores				
qSOFA	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.494
SIRS	2.0 (1.3–3.0)	3.0 (1.3–4.0)	2.0 (1.3–3.0)	0.066
MEWS	5.0 (3.0–6.0)	5.5 (4.0–7.0)	5.0 (3.0–6.0)	0.103
SOFA	8.0 (6.0–10.0)	5.0 (4.0–6.8)[a]	8.0 (6.0–10.0)[a]	< 0.001

Values are presented as number (%) or median (interquartile range).
LC, liver cirrhosis; MELD, Model for End-Stage Liver Disease; ALD, alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; CTP, Child-Turcotte-Pugh; qSOFA, quick sepsis-related organ failure assessment; SIRS, systemic inflammatory response syndrome; MEWS, modified early warning score; SOFA, sequential (sepsis-related) organ failure assessment.
[a]$p < 0.05$.

66). APACHE II score was higher (15 [IQR, 10 to 20] vs. 18 [IQR, 12 to 25], $p = 0.010$) and septic shock was more frequent (39.1% vs. 61.3%, $p = 0.003$) in group 2. Type of activation, source of new infection, and laboratory findings were not significantly different between the two groups. SIRS criteria and MEWS were higher in group 2 (2.0 [IQR, 1.0 to 3.0] vs. 3.0 [IQR, 2.0 to 3.0], $p < 0.001$; and 4.0 [IQR, 3.0 to 5.0] vs. 5.0 [IQR, 4.0 to 7.0], $p < 0.001$, respectively), but SOFA score was not different between the two groups (7.0 [IQR, 5.0 to 9.0] vs. 8.0 [IQR, 6.0 to

Table 3. Management of shock over the initial 6 hours and clinical outcomes in sepsis patients with liver cirrhosis classified by compensated LC (MELD < 15)

Variable	All (n = 188)	Compensated LC (n = 32)	Decompensated LC (n = 156)	*p* value
Vasopressor	123 (65.4)	18 (56.3)	105 (67.3)	0.231
Dopamine	6 (3.2)	1 (3.1)	5 (3.2)	0.981
Norepinephrine	120 (63.8)	16 (50.0)	104 (66.7)	0.074
Vasopressin	23 (12.2)	4 (12.5)	19 (12.2)	NS
Epinephrine	7 (3.7)	1 (3.1)	6 (3.8)	NS
Arterial catheter	94 (50.0)	13 (40.6)	81 (51.9)	0.244
Ventilator support	33 (17.6)	6 (18.8)	27 (17.3)	0.845
Use of corticosteroid therapy	22 (11.7)	4 (12.5)	18 (11.5)	0.772
ICU transfer	87 (46.3)	11 (34.4)	76 (48.7)	0.138
28-Day mortality	54 (28.7)	4 (12.5)[a]	50 (32.1)[a]	0.026
Hospital mortality	71 (37.8)	6 (18.8)[a]	65 (41.7)[a]	0.015
Hospital stay, day	30 (16–52)	26 (13–50)	30 (17–53)	0.323

Values are presented as number (%) or median (interquartile range).
LC, liver cirrhosis; MELD, Model for End-Stage Liver Disease; NS, not significant; ICU, intensive care unit.
[a]$p < 0.05$.

10.0], $p = 0.091$) (Table 4).

Initial management of shock within 6 h differed in the two study groups. Group 2 patients more frequently required vasopressors (49.3% vs. 74.8%, $p < 0.001$) and mechanical ventilation (10.1% vs. 21.8%, $p = 0.042$). A total of 87 patients (46.3%) were transferred to the ICU, but the rate of ICU transfer was not different between the two groups (37.7% vs. 51.3%, $p = 0.072$). Overall 28-day mortality rate (28.7%) was significantly higher in group 2 than in group 1 (15.9% vs. 36.1%, $p = 0.003$) as was in-hospital mortality rate (26.1% vs. 44.5%, $p = 0.012$) (Table 5).

Fig. 2 presents the distribution of qSOFA, SIRS, MEWS, and SOFA score. Increased scores were associated with increased ICU transfer and mortality rates in the MEWS and SOFA scores. The 28-day mortality rate was 33.5% (SIRS), 32.0% (SOFA), and 36.1% (qSOFA) for each group.

The areas under the receiver operating characteristic curve (AUROC) for ICU transfer of SOFA (AUROC, 0.691; 95% confidence interval [CI], 0.615 to 0.767), 28-day mortality (0.757; 95% CI, 0.678 to 0.835), and in-hospital mortality (AUROC, 0.722; 95% CI, 0.644 to 0.799) or MEWS (AUROC, 0.663; 95% CI, 0.586 to 0.739; AUROC, 0.699; 95% CI, 0.617 to 0.782; and AUROC, 0.674; 95% CI, 0.595 to 0.753, respectively) were significantly higher compared to those for qSOFA (AUROC, 0.589; 95% CI, 0.507 to 0.671; AUROC, 0.671; 95% CI, 0.582 to 0.759; and AUROC, 0.626; 95% CI, 0.542 to 0.710, respectively) or SIRS (AUROC, 0.533; 95% CI, 0.451 to 0.616; AUROC, 0.638; 95% CI, 0.556 to 0.721; and AUROC, 0.649; 95% CI, 0.571 to 0.727, respectively) (Fig. 3).

DISCUSSION

Our study attempted to determine the clinical usefulness of the qSOFA score for predicting adverse outcomes in sepsis patients with liver cirrhosis. The results revealed that qSOFA score had limited value in such patients. In total, 36.7% of patients with sepsis and liver cirrhosis could not be detected with ≥ 2 points of qSOFA score. In our study, qSOFA score had more prognostic accuracy for ICU transfer and hospital mortality compared to SIRS but a lower prognostic accuracy compared to MEWS or SOFA scores. A new screening tool is needed for use in these patients. Importantly, our study confirms the clinical usefulness of qSOFA as a risk classification tool for predicting adverse outcomes in sepsis patients with liver cirrhosis.

Choosing an appropriate screening tool is important because early recognition of sepsis is associated with earlier treatment. Potentially preventable secondary infections are associated with a significantly high mortal-

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Table 4. Clinical characteristics of the 188 sepsis patients with liver cirrhosis classified by qSOFA score

Characteristic	All (n = 188)	qSOFA 0–1 (n = 69)	qSOFA 2–3, (n = 119)	*p* value
Age, yr	59 (52–66)	55 (51–63)[a]	61 (53–67)[a]	0.028
Male sex	145 (77.1)	57 (82.6)	88 (73.9)	0.173
APACHE II score	17 (12–22)	15 (10–20)[a]	18 (12–25)[a]	0.010
Type of activation				
Screening	100 (53.2)	43 (62.3)	57 (47.9)	0.156
Doctor call	73 (38.8)	22 (31.9)	51 (42.9)	
Nurse call	15 (8.0)	4 (5.8)	11 (9.2)	
Sepsis definitions				
Sepsis	88 (46.8)	42 (60.9)[a]	46 (38.7)[a]	0.003
Septic shock	100 (53.2)	27 (39.1)[a]	73 (61.3)[a]	
Source of infection				
Intra-abdominal	110 (58.5)	39 (56.5)	71 (59.7)	0.107
Pneumonia	35 (18.6)	11 (15.9)	24 (20.2)	
Bacteremia	14 (7.4)	4 (5.8)	10 (8.4)	
Urinary tract infection	9 (4.8)	7 (10.1)	2 (1.7)	
Other	18 (9.6)	8 (11.6)	10 (8.4)	
Unknown	2 (1.1)	0	2 (1.7)	
Positive culture				
Gram-positive	38 (20.2)	11 (15.9)	27 (22.7)	0.267
Gram-negative	91 (48.4)	33 (47.8)	58 (48.7)	0.904
Other	20 (10.6)	3 (4.3)[a]	17 (14.3)[a]	0.033
Culture not obtained	50 (26.6)	22 (31.9)	28 (23.5)	0.211
Laboratory findings				
White blood cell, $\times 10^9$/L	8.9 (4.3–13.5)	8.5 (4.4–11.7)	9.4 (4.1–14.2)	0.275
Hemoglobin, g/dL	9.9 (8.6–11.3)	9.8 (8.6–11.6)	10.0 (8.6–11.3)	0.959
Platelets, $\times 10^9$/L	68.0 (41.0–106.8)	69.0 (41.0–117.0)	67.0 (41.0–106.0)	0.709
C-reactive protein, mg/L	6.2 (2.7–11.4)	6.7 (2.8–11.9)	5.9 (2.7–10.9)	0.729
BNP, pg/mL	176.0 (92.0–405.0)	167.0 (86.8–420.3)	206.0 (95.0–396.5)	0.570
Procalcitonin, ng/mL	6.7 (2.0–17.8)	6.1 (2.2–25.5)	6.9 (2.0–17.7)	0.872
Creatinine, mg/dL	1.4 (0.9–2.0)	1.3 (0.9–1.9)	1.5 (1.0–2.0)	0.159
Bilirubin, mg/dL	4.1 (2.1–9.7)	5.6 (2.0–9.7)	3.8 (2.2–8.8)	0.439
Albumin, g/dL	2.5 (2.2–2.9)	2.5 (2.2–3.0)	2.5 (2.2–2.8)	0.504
Lactic acid, mmol/L	4.2 (2.7–6.1)	4.1 (2.8–5.5)	4.4 (2.6–7.6)	0.234
Scores				
SIRS	2.0 (1.3–3.0)	2.0 (1.0–3.0)[a]	3.0 (2.0–3.0)[a]	< 0.001
MEWS	5.0 (3.0–6.0)	4.0 (3.0–5.0)[a]	5.0 (4.0–7.0)[a]	< 0.001
SOFA score	8.0 (6.0–10.0)	7.0 (5.0–9.0)	8.0 (6.0–10.0)	0.091

Values are presented as number (%) or median (interquartile range).
qSOFA, quick sepsis-related organ failure assessment; APACHE II, acute physiology and chronic health evaluation II; BNP, brain natriuretic peptide; SIRS, systemic inflammatory response syndrome; MEWS, modified early warning score; SOFA, sequential (sepsis-related) organ failure assessment.
[a]$p < 0.05$.

Table 5. Management of shock over the initial 6 hours and clinical outcomes in sepsis patients with liver cirrhosis classified by qSOFA score (n = 188)

Variable	All (n = 188)	qSOFA 0–1 (n = 69)	qSOFA 2–3 (n = 119)	*p* value
Vasopressor	123 (65.4)	34 (49.3)[a]	89 (74.8)[a]	< 0.001
Dopamine	6 (3.2)	3 (4.3)	3 (2.5)	0.671
Norepinephrine	120 (63.8)	31 (44.9)[a]	89 (74.8)[a]	< 0.001
Vasopressin	23 (12.2)	6 (8.7)	17 (14.3)	0.260
Epinephrine	7 (3.7)	1 (1.4)	6 (5.0)	0.426
Arterial catheter	94 (50.0)	30 (43.5)	64 (53.8)	0.173
Ventilator support	33 (17.6)	7 (10.1)[a]	26 (21.8)[a]	0.042
Use of corticosteroid therapy	22 (11.7)	4 (5.8)	18 (15.1)	0.055
ICU transfer	87 (46.3)	26 (37.7)	61 (51.3)	0.072
28-Day mortality	54 (28.7)	11 (15.9)[a]	43 (36.1)[a]	0.003
Hospital mortality	71 (37.8)	18 (26.1)[a]	53 (44.5)[a]	0.012
Hospital stay, day	30 (16–52)	32 (18–57)	29 (15–52)	0.722

Values are presented as number (%) or median (interquartile range).
qSOFA, quick sepsis-related organ failure assessment; ICU, intensive care unit.
[a]$p < 0.05$.

ity rate independent of liver disease severity and were predictors of mortality in a multicenter cirrhosis cohort [16]. The model for mortality included secondary infection (odds ratio, 4.42) as a significant variable. Therefore, selecting the most appropriate tools for sepsis screening in patients with liver cirrhosis is necessary. The most important index for diagnosing sepsis was SIRS criteria and infection [17]. Hyperdynamic circulation, hepatic encephalopathy (HEP), tense ascites, and hypersplenism in cirrhotic patients may change heart and respiratory rate, temperature, and white blood cell count despite the absence of bacterial infection [10]. SIRS has been described in 10% to 30% of patients with cirrhosis without bacterial infection [18]. Thus, the lack of sensitivity and specificity of conventional parameters for the definition of SIRS makes a sepsis diagnosis difficult in these patients. In this study, SIRS demonstrated the lowest predictive power for ICU transfer and hospital mortality in sepsis patients with liver cirrhosis, which supports previous research that SIRS is not a useful screening criterion for sepsis in patients with liver cirrhosis and does not help predict clinical deterioration.

Unlike previous results, our main finding indicated that qSOFA score was a poor screening tool. The diagnosis of sepsis recently was revised for the third time, and diagnostic criteria based on qSOFA and SOFA have been suggested. Seymour et al. [7] reported that qSOFA score results are much simpler and faster compared to other screening tools for infected patients outside of the ICU and reported the predictive validity of qSOFA as a good predictor of in-hospital mortality (AUROC, 0.81). Studies to determine the usefulness of qSOFA since the introduction of the new definition (Sepsis-3) are currently in progress. A previous study showed that mortality analyses performed during the hospital stay and at 1 year after discharge supported the use of SOFA and qSOFA as screening tools and demonstrated that these criteria can identify infected patients at high risk for poor outcomes [19]. The most interesting findings of the present study were that 36.7% of patients had a qSOFA score of 0 to 1, of whom 37.7% were high-risk patients requiring ICU care, and the hospital mortality rate in these patients was 26.1%. Furthermore, qSOFA had lower discrimination for hospital mortality; however, this result has not been described previously to our knowledge. In patients with liver cirrhosis, the clinical exacerbation course may cause mental changes, such as HEP, and breathing and consciousness are likely to change accompanied by decreased lung capacity due to increased ascites [20]. Indeed, bacterial infection is a common cause of acute decompensated cirrhosis, and patients with liver cirrhosis and acute organ failure are at high risk for early death.

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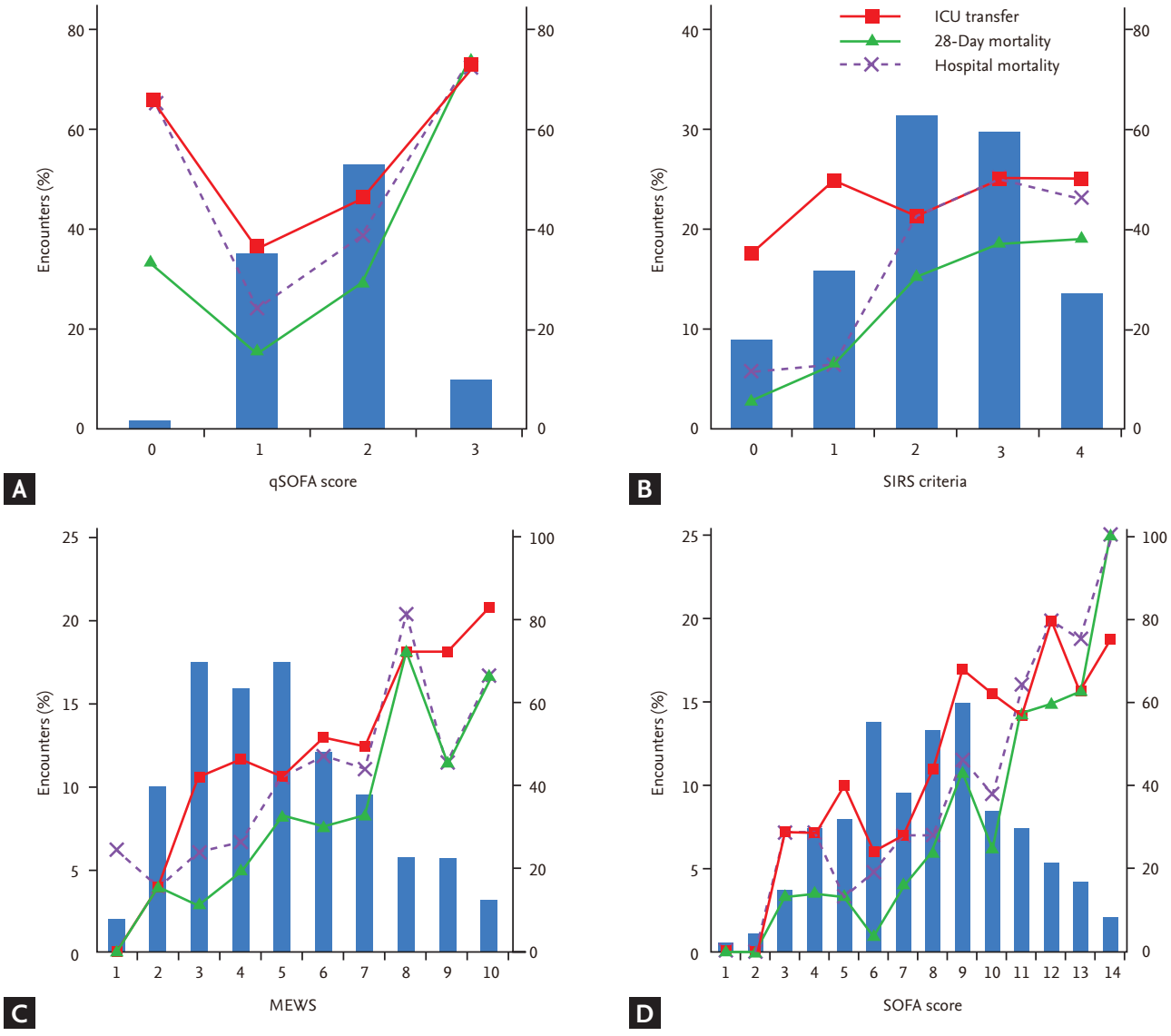

Figure 2. Distribution of patients by scores. Data are presented as percentages. (A) Quick sepsis-related organ failure assessment (qSOFA) score, (B) systemic inflammatory response syndrome (SIRS) criteria, (C) modified early warning score (MEWS), and (D) sequential (sepsis-related) organ failure assessment (SOFA) score. ICU, intensive care unit.

Therefore, qSOFA score may be under- or overestimated depending on the clinical changes in patients with liver cirrhosis [10]. A large number of patients have a qSOFA score of ≤ 1 but there is a risk of ICU care or death. Screening for sepsis based on a qSOFA score of ≥ 2 may delay diagnosis in deteriorating patients. Raith et al. [11] demonstrated that, among adults with suspected infection admitted to the ICU, an increase in SOFA score of ≥ 2 points had greater prognostic accuracy for hospital mortality (AUROC, 0.753) compared to SIRS criteria or qSOFA. They showed that SIRS and qSOFA may have limited use in predicting mortality.

In our study, SOFA score was the most accurate of the evaluated scores for predicting ICU transfer and hospital mortality, followed by MEWS. In a large population of nonintubated sepsis patients, Innocenti et al. [21] demonstrated that SOFA score was significantly higher in patients with an adverse outcome in terms of 28-day mortality and ICU transfer compared to those with a good outcome. Since the SOFA score should be reported in the laboratory results for calculation, which is complicated, it may be difficult to confirm immediately after

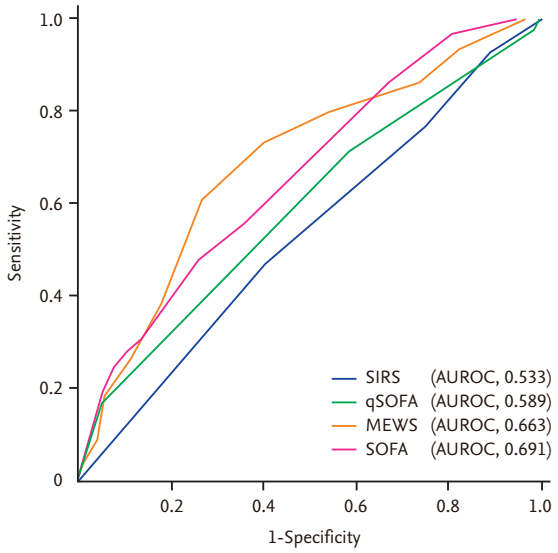

Figure 3. The areas under the receiver operating characteristic (AUROC) curves for discriminatory power for intensive care unit transfer by score. AUC followed by 95% confidence intervals are shown. SIRS, systemic inflammatory response syndrome; qSOFA, quick sepsis-related organ failure assessment; MEWS, modified early warning score; SOFA, sequential (sepsis-related) organ failure assessment.

admission or when the patient's condition changes. In addition, in the Sepsis-3 definition, SOFA was reported to be useful in diagnosing sepsis in the ICU setting. Conversely, MEWS is measured easily but is based only on clinical conditions such as vital signs and consciousness and might be more useful for risk stratification of sepsis patients in general wards.

Our study was performed in acutely deteriorated patients who were referred to MET despite being in general wards (APACHE II score, 17 [IQR, 12 to 22]). The difference in severity was evident when comparing with previous studies. SOFA score was 1 (0 to 2) and 6 (3 to 9) points outside and inside of the ICU, respectively, and the existing study. The qSOFA score had statistically worse predictive validity in the ICU [7]. In our study subjects, the SOFA score was 8 (6 to 10) points, suggesting that acutely deteriorated patients referred to MET require the same level of stratification as that of ICU patients. Therefore, measuring MEWS or SOFA rather than qSOFA would be useful for assessing and predicting patient prognosis, since those referred to MET are typically high-risk patients in general wards.

We analyzed our study patients using the MELD score. There were no differences in qSOFA, SIRS, and MEWS score between compensated and decompensated liver cirrhosis by MELD score. In addition, mortality was different but detecting and managing sepsis was not.

Our study has several limitations. First, it was a retrospective single-center study, thus the findings may not be generalizable to other settings. However, we assembled a large sample size of sepsis patients with liver cirrhosis and used several different screening tools to compare their prediction ability for ICU transfer, 28-day mortality, and in-hospital mortality. Second, the severity was higher in our study objectives because the patients were referred to MET, and patients with liver cirrhosis also had higher severity. Further study is needed to clarify the clinical usefulness of qSOFA in mild sepsis patients with liver cirrhosis in general wards.

In conclusion, among sepsis patients with liver cirrhosis, 36.7% could not be detected with ≥ 2 points of qSOFA score, suggesting that qSOFA score may have limited utility in predicting adverse outcomes in sepsis patients with liver cirrhosis at MET activation. Either MEWS or another screening tool is required for detecting early sepsis in these patients.

KEY MESSAGE

1. This study evaluated the clinical usefulness of quick Sepsis-related Organ Failure Assessment (qSOFA), Systemic Inflammatory Response Syndrome (SIRS), Modified Early Warning Score (MEWS), SOFA scores on predicting factors of sepsis in liver cirrhosis. In our study, qSOFA score and SIRS had a lower prognostic accuracy than MEWS or SOFA scores.
2. Rather than qSOFA, a new screening tool is needed to predict adverse outcomes in sepsis patients with liver cirrhosis.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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