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Original Article

Dynamic analysis of acute deterioration in chronic liver disease patients using modified quick sequential organ failure assessment

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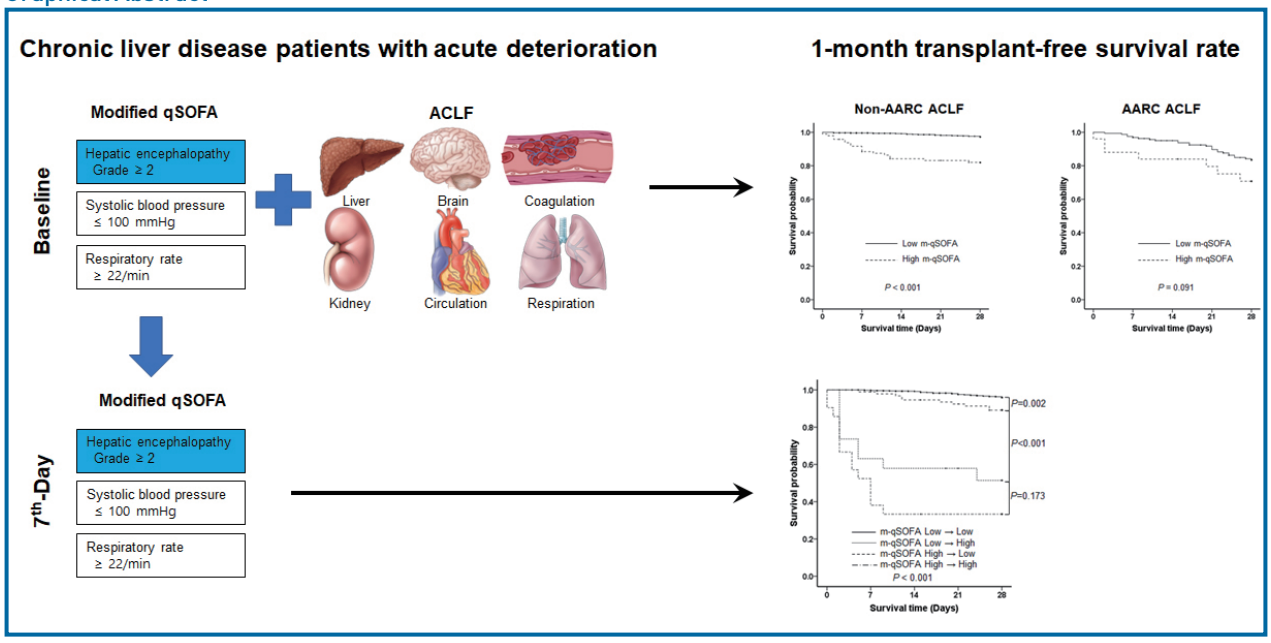
Graphical Abstract



Study Highlights

- The m-qSOFA, which replaces the Glasgow Coma Scale with the West Haven criteria, is a simple scoring system with only three variables.
- Patients with high m-qSOFA had significantly lower 1-month transplant-free survival (TFS) and higher organ failure than those with low m-qSOFA.
- Patients who changed from low m-qSOFA at baseline to high on day 7 had a significantly lower 1-month TFS than those who changed from high to low.
- m-qSOFA is a simple bedside tool for predicting poor outcomes in patients with acutely deteriorated chronic liver disease.

Background/Aims: Quick sequential organ failure assessment (qSOFA) is believed to identify patients at risk of poor outcomes in those with suspected infection. We aimed to evaluate the ability of modified qSOFA (m-qSOFA) to identify high-risk patients among those with acutely deteriorated chronic liver disease (CLD), especially those with acute-on-chronic liver failure (ACLF).

Methods: We used data from both the Korean Acute-on-Chronic Liver Failure (KACLiF) and the Asian Pacific Association for the Study of the Liver ACLF Research Consortium (AARC) cohorts. qSOFA was modified by replacing the Glasgow Coma Scale with hepatic encephalopathy, and an m-qSOFA ≥2 was considered high.

Results: Patients with high m-qSOFA had a significantly lower 1-month transplant-free survival (TFS) in both cohorts and higher organ failure development in KACLiF than those with low m-qSOFA (*P*s<0.05). Subgroup analysis by ACLF showed that patients with high m-qSOFA had lower TFS than those with low m-qSOFA. m-qSOFA was an independent prognostic factor (hazard ratios, HR=2.604, 95% confidence interval, CI 1.353–5.013, *P*=0.004 in KACLiF and HR=1.904, 95% CI 1.484–2.442, *P*<0.001 in AARC). The patients with low m-qSOFA at baseline but high m-qSOFA on day 7 had a significantly lower 1-month TFS than those with high m-qSOFA at baseline but low m-qSOFA on day 7 (52.6% vs. 89.4%, *P*<0.001 in KACLiF and 26.9% vs. 61.5%, *P*<0.001 in AARC).

Conclusions: Baseline and dynamic changes in m-qSOFA may identify patients with a high risk of developing organ failure and short-term mortality among CLD patients with acute deterioration. **(Clin Mol Hepatol 2024;30:388-405)**

Keywords: qSOFA; Acute-on-chronic liver failure; Organ failure; Survival

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Abbreviations:

AARC, Asian Pacific Association for the Study of the Liver Acute-on-chronic liver failure Research Consortium; ACLF, Acute-on-Chronic Liver Failure; ALT, ALanine aminoTransferase; AST; ASpartate aminoTransferase; CI, confidence interval; CLD, chronic liver disease, CLIF-C OF, Chronic LIver Failure Consortium Organ Failure; CLIF-SOFA, Chronic LIver Failure- Sequential Organ Failure Assessment; EASL-CLIF, European Association for the Study of the Liver-Chronic LIver Failure; GCS, Glasgow Coma Scale; HE, Hepatic Encephalopathy; HR, Hazard Ratio; INR, International Normalized Ratio; KACLiF, Korean Acute-on-Chronic Liver Failure; LT, Liver Transplantation; MELD, Model for End-stage Liver Disease; m-qSOFA, modified quick Sequential Organ Failure Assessment; OR, Odds Ratio; qSOFA, Quick Sequential Organ Failure Assessment; SIRS, Systemic Inflammatory Response Syndrome; WBC, White Blood Cell

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a rapid deterioration of liver function in patients with chronic liver disease (CLD).[1,2] Various acute insults, such as alcoholic hepatitis, bacterial infection, viral hepatitis, and hepatotoxic drugs, not only result in hepatic derangement but can also cause extrahepatic organ failures, with high short-term mortality.[3,4] However, ACLF is a disease distinguished from decompensated liver cirrhosis because it is reversible. Therefore, the prediction of poor outcomes in patients with ACLF is crucial given the potential of its reversibility without liver transplantation (LT).

Exaggerated systemic inflammation is one of the main mechanisms driving the occurrence and progression of ACLF, along with portal hypertension. Systemic inflammation causes splanchnic and systemic circulatory dysfunction, immune-mediated tissue damage, and changes in energy metabolism in ACLF patients, and these changes are associated with multiorgan failure.[5] A paradoxical immunoparesis state is associated with severe infection and sepsis.[6] In practice, bacterial and fungal infections develop frequently and are associated with poor clinical courses and high mortality in ACLF patients.[7] The Asian Pacific Association for the Study of the Liver ACLF Research Consortium (AARC) proposes the concept of a golden window of approximately 1 week between ACLF development and sepsis. They suggest that prompt intervention in this window is necessary to reduce the development of sepsis and improve the outcome of ACLF.[2]

Early identification of sepsis is important because of its high mortality. The 3rd International Consensus Definitions for Sepsis and Septic Shock recommend the quick sequential organ failure assessment (qSOFA) score. The qSOFA score includes three components (Glasgow Coma Scale [GCS], systolic blood pressure, and respiratory rate) and serves as a bedside tool to identify adult patients with suspected infection who are at risk of poor outcomes.[8] Considering that infection in patients with cirrhosis is one of the leading causes of death, the usefulness of this simple score was evaluated in those with cirrhosis and infection. However, qSOFA showed conflicting results in predicting adverse outcomes in patients with cirrhosis and infections.[9-12] In addition, studies on the role of the qSOFA score in patients with ACLF are limited.

In the general intensive care unit, the SOFA score has been used to assess the severity of organ failure.[13] However, some components, such as GCS and platelet count, do not reflect the specificity of CLD.[14] Therefore, the European Association for the Study of the Liver (EASL)-Chronic LIver Failure (CLIF) consortium developed the CLIF-SOFA score by replacing GCS with the West Haven criteria and platelet count with prothrombin time to modify the SOFA score.[4] The CLIF-SOFA score has been similar or superior to the SOFA score in predicting poor outcomes in patients with ACLF or decompensated cirrhosis.[3,15-17] To apply qSOFA to patients with CLD, a modification replacing the GCS with the West Haven criteria would be necessary. In this study, we aimed to evaluate the usefulness of the modified qSOFA (m-qSOFA) score in identifying high short-term mortality in CLD patients with acute deterioration, particularly those with ACLF.

MATERIALS AND METHODS

Patients

This study was conducted using patients from two different cohorts. The first cohort included patients from the prospective Korean Acute-on-Chronic Liver Failure (KACLiF) study. The KACLiF study screened and enrolled CLD patients who were hospitalized with acute deterioration in 31 university hospitals between October 2015 and May 2019. Acute deterioration of CLD in this study included ascites, hepatic encephalopathy (HE), infection, gastrointestinal bleeding, and bacterial infection, which are decompensations defined by the EASL-CLIF consortium, and liver dysfunction which is defined as serum bilirubin ≥3 mg/dL. The underlying CLD included not only cirrhosis but also noncirrhotic CLD. The etiology of CLD included hepatitis B virus infection, hepatitis C virus infection, alcohol-associated liver disease, nonalcoholic fatty liver disease, and autoimmune liver disease. Cirrhosis was diagnosed histologically or based on clinical parameters, such as radiologic or laboratory findings.[18] The exclusion criteria were as follows: 1) age under 18 years, 2) absence of CLD, 3) presence of radiologically definite hepatocellular carcinoma, 4) hospitalization due to extrahepatic diseases, 5) admission for symptomatic control of CLD, and 6) human immunodefi-

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ciency virus infection. A total of 1,533 patients were screened, and 1,497 patients were enrolled in this study (Supplementary Fig. 1). The study was registered on ClinicalTrials.gov (number: NCT02650011).

The second cohort included patients from the AARC database, which collected multicenter ACLF data from the Asia-Pacific region prospectively beginning in 2009.[19] From 2009 to 2021, 5,345 patients were enrolled in more than 80 hospitals in the Asia-Pacific region. In this study, we analyzed 1,217 patients after excluding 4,128 patients with insufficient data.

This study was approved by the institutional review board at each participating hospital and was in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki.

Data collection

We collected data on patient demographics, history (including past decompensation and etiology of CLD), potential precipitating factors, laboratory measurements, and development of ACLF. Clinical data within 24 hours of admission and 7 days (5–9 days) after admission were collected. Potential precipitating factors of acute deterioration included acute infection or reactivation of underlying viral hepatitis, gastrointestinal bleeding, bacterial infection, active alcohol drinking, toxic liver injury, and others, which included the precipitants of both the AARC and EASL-CLIF definitions. Active alcoholism was defined as more than 21 drinks per week in men and more than 14 drinks per week in women within 3 months of admission.[20] Scores predicting the prognosis of patients with liver disease, such as Child–Pugh, Model for End-stage Liver Disease (MELD), MELD-Na,[21] CLIF-SOFA, CLIF Consortium Organ Failure (CLIF-C OF), and AARC scores, were calculated at admission.

Definitions

The m-qSOFA used the following parameters: 1) HE grades by West Haven criteria ≥2, 2) respiratory rate ≥22/min, and 3) systolic blood pressure ≤100 mmHg. When at least 2 of the 3 criteria were met, the m-qSOFA score was defined as high, and when fewer than 2 criteria were met, the m-qSOFA score was defined as low. Systemic inflammatory response syndrome (SIRS) was defined as 2 or more of the following criteria: 1) body temperature <36°C or >38°C, 2) heart rate >90 beats per minute, 3) respiratory rate >20 breaths per minute, and 4) white blood cell (WBC) count <4,000/mm^3 or >12,000/mm^3. ACLF was defined by the EASL-CLIF[4] and AARC definitions.[2] The day 7 m-qSOFA of patients who died or received LT within 7 days was considered high to prevent these patients from being excluded from analyzing the effect of dynamic changes in m-qSOFA. Organ failures included liver, renal, coagulation, cerebral, circulatory, and respiratory failures, and they were defined by the CLIF-SOFA score.

Statistics

The primary outcomes were 1-month transplant-free survival (TFS) (28 days in the KACLiF cohort and 30 days in the AARC cohort). Continuous variables were expressed as the mean ± standard deviation (SD) for normally distributed variables and median and interquartile range (IQR) for non-normally distributed variables, and categorical variables were expressed as number (%). The normal distribution was tested using the Kolmogorov–Smirnov test. Categorical variables were analyzed by the chi-square test or Fisher's exact test, and continuous variables were analyzed by Student's *t* test. TFS was calculated using the Kaplan–Meier method, and survival differences were compared using the log-rank test. A Cox proportional hazard regression model by the backward stepwise likelihood ratio method was used to identify the independent predictor of 1-month TFS. When m-qSOFA and prognostic scores were included in multivariate analysis, their components were excluded to avoid multicollinearity. For missing data, a complete case analysis was used. Variables with $P<0.05$ in univariate analysis were included in multivariate analysis. The optimal cut-off value of prognostic scores was determined using the Youden index defined as sensitivity + specificity - 1. A *P*-value of <0.05 was considered statistically significant. Statistical tests were performed using SPSS 18.0 (SPSS, Inc.; IBM Company, Armonk, NY, USA).

Table 1. Baseline characteristics

Characteristic	KACLiF cohort				AARC cohort			
	Total (n=1,497)	Low m-qSOFA (n=1,376)	High m-qSOFA (n=121)	*P*-value	Total (n=1,217)	Low m-qSOFA (n=982)	High m-qSOFA (n=235)	*P*-value
Age, years	54.7±11.5	54.6±11.5	55.5±10.9	0.433	46.4±12.2	46.1±11.9	47.5±13.2	0.137
Gender (male, %)	1,114 (74.4)	1,026 (74.6)	88 (72.7)	0.657	1,056 (86.8)	855 (97.1)	201 (85.5)	0.533
Cirrhosis (%)	1,395 (93.2)	1,277 (92.8)	118 (97.5)	0.057				
Etiology (%)				0.041				0.117
HBV	180 (12.0)	172 (12.5)	8 (6.6)		177 (14.5)	155 (15.8)	22 (9.4)	
HCV	26 (1.7)	23 (1.7)	3 (2.5)		29 (2.4)	23 (2.3)	6 (2.6)	
Alcohol	1,017 (67.9)	924 (67.2)	93 (76.9)		769 (63.2)	617 (62.8)	152 (64.7)	
HBV+Alcohol	108 (7.2)	102 (7.4)	6 (5.0)					
HCV+Alcohol	21 (1.4)	17 (1.2)	4 (3.3)					
Autoimmune					46 (3.8)	35 (3.6)	11 (4.7)	
Others	145 (9.7)	138 (10.0)	7 (5.8)		196 (16.1)	152 (15.5)	44 (18.7)	
Decompensation								
Ascites	434 (29.0)	410 (29.8)	24 (19.8)	0.012	1,081 (93.9)	865 (93.1)	216 (97.3)	0.01
Hepatic encephalopathy	220 (14.7)	169 (12.3)	51 (42.1)	<0.001	471 (38.9)	288 (29.3)	186 (79.1)	<0.001
Jaundice	524 (35.0)	498 (36.2)	26 (21.5)	0.001				
GI bleeding	520 (34.7)	468 (34.0)	52 (43.0)	0.031				
Infection	161 (10.8)	137 (10.0)	24 (19.8)	0.001				
Prior decompensation								
AARC definition	438 (29.3)	395 (28.7)	43 (35.5)	0.071				
EASL-CLIF definition	583 (38.9)	530 (38.5)	53 (43.8)	0.148				
AARC ACLF (%)	188 (12.6)	163 (11.8)	25 (20.7)	0.005	971 (79.8)	767 (78.1)	204 (86.8)	0.003
AARC ACLF grade*				0.026				<0.001
Grade 1	23 (18.1)	23 (21.9)	0 (0)		102 (13.3)	91 (15.1)	11 (6.6)	
Grade 2	67 (52.8)	55 (52.4)	12 (54.5)		380 (49.4)	324 (53.8)	56 (33.5)	
Grade 3	37 (29.1)	27 (25.7)	10 (45.5)		287 (37.3)	187 (31.1)	100 (59.9)	
EASL-CLIF ACLF (%)	248 (16.6)	192 (14.0)	56 (46.3)	<0.001				
EASL-CLIF ACLF Grade				<0.001				
Grade 1	127 (51.2)	109 (56.8)	18 (32.1)					

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Table 1. Continued

Characteristic	KACLiF cohort				AARC cohort			
	Total (n=1,497)	Low m-qSOFA (n=1,376)	High m-qSOFA (n=121)	*P*-value	Total (n=1,217)	Low m-qSOFA (n=982)	High m-qSOFA (n=235)	*P*-value
Grade 2	81 (32.7)	63 (32.8)	18 (32.1)					
Grade 3	40 (16.1)	20 (10.4)	20 (35.7)					
SIRS (%)	355 (23.7)	268 (19.5)	87 (71.9)	<0.001	513 (43.6)	328 (34.5)	185 (82.2)	<0.001
Body temperature (°C)	36.8±0.6	36.8±0.6	36.7±0.9	0.426	36.9±0.7	36.9±0.6	37.0±0.8	0.34
Heart rate (/min)	89.9±19.7	88.8±18.8	102.4±24.8	<0.001	91.2±15.7	89.6±14.6	97.5±18.1	<0.001
Respiratory rate (/min)	19.8±2.5	19.5±2.1	23.3±3.7	<0.001	20.8±4.2	20.1±2.4	23.6±7.5	<0.001
SBP (mmHg)	119.6±22.8	121.7±21.7	96.0±22.2	<0.001	114.1±16.3	115.9±14.3	106.5±21.0	<0.001
DBP (mmHg)	72.2±14.1	73.4±13.5	58.3±13.7	<0.001	68.8±10.6	70.3±9.8	62.6±11.6	<0.001
MBP (mmHg)	88.0±16.1	89.5±15.2	70.9±15.8	<0.001	83.9±11.2	85.5±10.0	77.2±13.3	<0.001
WBC ($\times 10^9/mm^3$)	7.62±5.35	7.38±5.03	10.32±7.66	<0.001	14.11±10.65	13.23±9.97	17.75±12.47	<0.001
ANC ($\times 10^9/mm^3$)	5.42±4.64	5.21±4.33	7.86±6.83	<0.001	10.62±8.99	9.95±8.53	13.59±10.35	<0.001
Hemoglobin (g/dL)	10.5±2.8	10.6±2.7	9.3±2.9	<0.001	10.5±2.4	10.5±2.3	10.6±2.5	0.442
Platelet count ($\times 10^9/mm^3$)	112.6±69.3	113.1±69.8	106.4±63.2	0.305	145.7±94.4	148.2±95.2	135.0±90.4	0.055
Albumin (g/dL)	2.94±0.63	2.96±0.63	2.64±0.57	<0.001	2.33±0.62	2.35±0.62	2.25±0.62	0.039
Bilirubin (mg/dL)	3.54 (1.56–8.18)	3.50 (1.55–8.14)	3.95 (1.55–8.71)	0.456	19.3 (10.7–27.0)	19.0 (10.7–26.7)	20.2 (11.0–27.8)	0.199
ALT (IU/L)	34.0 (20.0–69.0)	33.0 (20.0–69.0)	37.0 (21.5–78.5)	0.305	55.0 (34.0–110.8)	55.0 (34.0–111.3)	52.5 (32.8–106.0)	0.526
AST (IU/L)	84.0 (44.0–188.0)	83.5 (43.0–188.0)	88.0 (51.5–183.5)	0.304	142.0 (97.0–223.8)	142.0 (97.0–219.0)	138.0 (97.0–138.0)	0.755
INR	1.47 (1.27–1.78)	1.45 (1.27–1.75)	1.67 (1.37–2.19)	<0.001	2.10 (1.68–2.69)	2.08 (1.65–2.59)	2.30 (1.82–3.11)	<0.001
CRP (mg/dL)	0.68 (0.25–2.04)	0.66 (0.24–1.99)	1.16 (0.30–3.19)	0.008				
Creatinine (mg/dL)	0.88 (0.70–1.20)	0.85 (0.68–1.15)	1.20 (0.86–1.90)	<0.001	0.92 (0.58–1.76)	0.88 (0.56–1.53)	1.28 (0.72–2.61)	<0.001
Na (mEq/L)	135.1±6.1	135.2±5.9	133.6±7.9	0.027	130.9±7.4	130.7±7.1	131.5±8.6	0.204
Procalcitonin (ng/mL)	0.24 (0.12–0.56)	0.22 (0.11–0.48)	0.55 (0.21–1.41)	<0.001				
Lactate (mmol/L)†	2.00 (1.24–3.70)	1.86 (1.20–3.20)	4.44 (2.59–7.66)	<0.001	1.80 (1.30–2.60)	1.80 (1.30–2.50)	2.00 (1.40–2.80)	0.007
Child-Pugh score	9.0±2.1	8.9±2.0	10.4±2.3	<0.001	11.2±1.6	11.0±1.6	12.1±1.3	<0.001
MELD score	18.1±7.2	17.8±7.0	21.7±9.1	<0.001	28.5±7.9	27.8±7.6	31.4±8.3	<0.001
MELD-Na score	20.6±7.5	20.3±7.3	24.4±8.3	<0.001	30.7±6.9	28.5±8.0	32.3±7.4	<0.001
AARC score†	7.7±1.8	7.5±1.7	9.6±1.9	<0.001	9.4±2.1	9.2±2.0	10.6±2.1	<0.001
CLIF-SOFA	5.6±3.0	5.2±2.6	9.3±4.3	<0.001				

Table 1. Continued

Characteristic	KACLiF cohort				AARC cohort			
	Total (n=1,497)	Low m-qSOFA (n=1,376)	High m-qSOFA (n=121)	*P*-value	Total (n=1,217)	Low m-qSOFA (n=982)	High m-qSOFA (n=235)	*P*-value
CLIF-OF score	7.4±1.7	7.2±1.7	9.4±2.5	<0.001				
Death or LT within 1 month[‡]	80 (5.9)	56 (4.5)	24 (21.1)	<0.001	421 (34.7)	295 (30.1)	126 (53.6)	<0.001

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
[*]127 patients (67.6%) in KACLiF and 769 patients (79.2%) in AARC cohort were available. [†]883 patients (59.0%) in KACLiF and 947 patients (75.9%) in AARC cohort were available. [‡]130 patients (8.7%) in KACLiF and 3 patients (0.2%) in AARC cohort were excluded due to follow-up loss.
KACLiF, Korean acute-on-chronic liver failure; AARC, Asian Pacific Association for the Study of the Liver ACLF Research Consortium; GI, gastrointestinal; EASL-CLIF, European Association of the Study for The Liver-Chronic Liver Failure; m-qSOFA, modified quick sequential organ failure assessment; HBV, hepatitis B virus; HCV, hepatitis C virus; ACLF, acute-on-chronic liver failure; SIRS, systemic inflammatory response syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; WBC, white blood cells; ANC, absolute neutrophil count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; CRP, C-reactive protein; MELD, Model for End-stage Liver Disease; CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment; CLIF-C OF, Chronic Liver Failure Consortium Organ Failure.

RESULTS

Baseline characteristics

The baseline characteristics of the enrolled patients, including cirrhosis and non-cirrhosis, and ACLF and non-ACLF in the KACLiF and AARC cohorts are reported in Table 1. The mean age was 54.7±11.5 years and 46.4±12.2 years in the KACLiF and AARC cohorts, respectively. The sexes of both cohorts were mostly male (74.4% in the KACLiF cohort and 86.8% in the AARC cohort). Most patients (n=1,395, 93.2%) in the KACLiF cohort had cirrhosis. The most common etiology of CLD was alcohol (67.9% in the KACLiF cohort and 63.2% in the AARC cohort), followed by HBV (12.0% in the KACLiF cohort and 14.5% in the AARC cohort). High m-qSOFA was found in 121 (8.1%) and 235 (19.3%) patients in the KACLiF and AARC cohorts, respectively. The patients with high m-qSOFA had more frequent SIRS and ACLF at baseline than the patients with low m-qSOFA in both cohorts (all *P*s<0.05). The patients with high m-qSOFA had a higher heart rate, respiratory rate, WBC count, absolute neutrophil count, international normalized ratio (INR), creatinine, and lactate level and lower systolic, diastolic and mean blood pressure, and albumin levels than patients with low m-qSOFA. At baseline, those with high m-qSOFA had higher Child–Pugh, MELD, MELD-Na, AARC, CLIF-SOFA, and CLIF-C OF scores (all *P*s<0.001) than those with low m-qSOFA.

Survival difference according to m-qSOFA

In the KACLiF cohort, those with high m-qSOFA had a significantly lower 1-month TFS than those with low m-qSOFA (80.2% vs. 95.9%, *P*<0.001) (Supplementary Fig. 2A). In the AARC cohort, the patients with high m-qSOFA also had a significantly lower 1-month TFS than the patients with low m-qSOFA (46.4% vs. 69.9%, *P*<0.001) (Supplementary Fig. 2B).

Survival difference according to ACLF and m-qSOFA

In the KACLiF cohort, the patients with high m-qSOFA had a significantly lower TFS than those with low m-qSOFA in the patients without AARC ACLF (82.3% vs. 97.4%,

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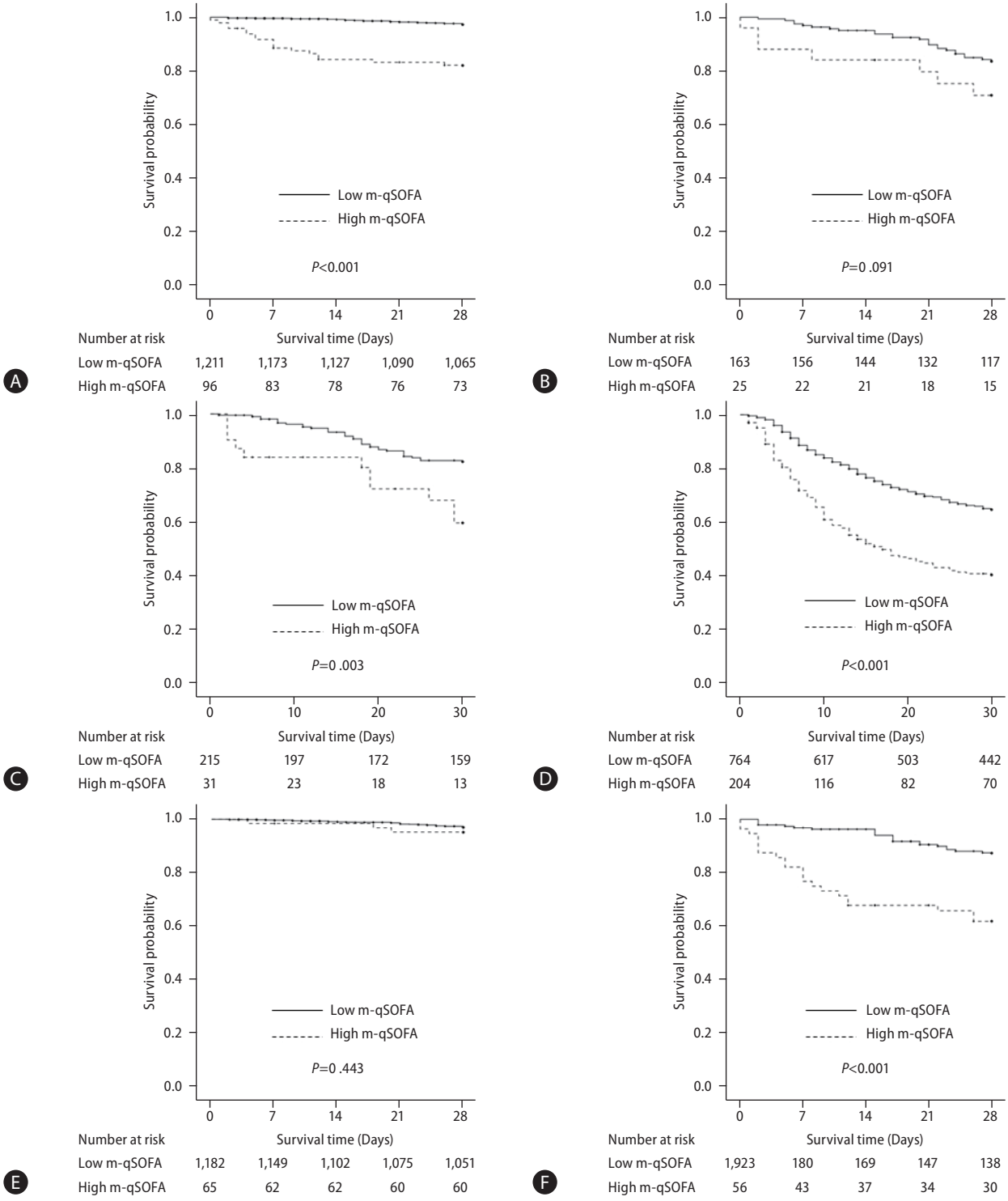

Figure 1. One-month transplant-free survival rate according to m-qSOFA and ACLF. (A) Non-AARC ACLF and (B) AARC ACLF patients in the KACLiF cohort. (C) Non-AARC ACLF and (D) AARC ACLF patients in the AARC cohort. (E) Non-EASL-CLIF ACLF and (F) EASL-CLIF ACLF patients in the KACLiF cohort. m-qSOFA, modified quick sequential organ failure assessment; ACLF, acute-on-chronic liver failure; AARC, Asian Pacific Association for the Study of the Liver ACLF Research Consortium; EASL-CLIF, European Association for the Study of the Liver-Chronic liver failure; KACLiF, Korean acute-on-chronic liver failure; AARC, Asian Pacific Association for the Study of the Liver ACLF Research Consortium.

P<0.001) (Fig. 1A), whereas the difference was not significant in the patients with AARC ACLF (72.0% vs. 84.7%, *P*=0.091) (Fig. 1B).

In the AARC cohort, the patients with high m-qSOFA had a significantly lower 1-month TFS than those with low m-qSOFA in the patients without (64.5% vs. 83.3%, *P*=0.003) or with (43.6% vs. 66.1%, *P*<0.001) AARC ACLF (Fig. 1C and D).

In the KACLiF cohort, the patients with high m-qSOFA had a similar 1-month TFS to those with low m-qSOFA in the patients without EASL-CLIF ACLF (95.4% vs. 97.1%, *P*=0.443) (Fig. 1E), but had significantly lower 1-month TFS in the patients with EASL-CLIF ACLF (62.5% vs. 88.5%, *P*<0.001) (Fig. 1F).

m-qSOFA as a predictor of mortality

We performed Cox hazard proportional regression analysis to identify the significant predictor of 1-month TFS in both cohorts. In the KACLiF cohort, HE (≥grade 2), gastrointestinal bleeding, bacterial infection, SIRS, WBC count, platelet count, serum albumin, bilirubin, AST, INR, C-reactive protein, creatinine, sodium, and lactate levels, and high m-qSOFA were significant factors in the univariate analysis, and SIRS, platelet count, serum albumin, bilirubin, AST, INR, and m-qSOFA were significant factors in the multivariate analysis (Table 2). In the AARC cohort, age, ascites, HE (≥grade 2), SIRS, WBC count, serum bilirubin, INR, creatinine, sodium, lactate levels, and high m-qSOFA were significant factors in the univariate analysis. Age, ascites, WBC count, serum bilirubin, INR, creatinine, lactate levels, and m-qSOFA were significant factors in the multivariate analysis (Table 2). When the m-qSOFA was adjusted by CLD-specific prognostic scores and significant variables by multivariate analysis (excluding the variables included in the prognostic scores), m-qSOFA was an independent factor in both the KACLiF and AARC cohorts (all *P*s<0.05) (Table 3).

Dynamic change in m-qSOFA in subgroups according to ACLF

In the KACLiF cohort, those with high m-qSOFA scores at both baseline and on day 7 had the worst 1-month TFS. Interestingly, patients who changed from low baseline m-qSOFA to high on the 7th day had a significantly lower 1-month TFS than those who shifted from high to low (52.6% vs. 89.4%, *P*<0.001). In KACLiF cohort, no statistically significant difference was observed between the patients who changed from low baseline m-qSOFA to high on the 7th day and those who had a consitently high m-qSOFA in the KACLiF cohort (52.6% vs. 33.3%, *P*=0.173) (Fig. 2A). In both subgroups of the KACLiF cohort based on the presence of AARC ACLF at the baseline, those who changed from low baseline m-qSOFA to high on the 7th day had significantly lower 1-month TFS than those who shifted from high to low (25.0% vs. 75.0%, *P*=0.023 in the ACLF group and 60.0% vs. 92.3%, *P*<0.001 in the non-ACLF group) (Fig. 2B and C).

In the AARC cohort, similar results were shown. The patients with high m-qSOFA on both baseline and the 7th day had the worst 1-month TFS, and those who changed from low baseline m-qSOFA to high on the 7th day had a significantly lower 1-month TFS than those who shifted from high to low (26.9% vs. 61.5%, *P*<0.001) (Fig. 2D). In the ACLF group of the AARC cohort, those who changed from low to high m-qSOFA had a significantly lower 1-month TFS than those who changed from high to low (25.0% vs. 58.9%, *P*<0.001) (Fig. 2E). Similar results were shown in the non-ACLF group of the AARC cohort, but they were not significant (43.8% vs. 72.2%, *P*=0.053) (Fig. 2F).

The effect of dynamic changes in m-qSOFA according to the presence of EASL-CLIF ACLF was analyzed in the KACLiF cohort alone. In both subgroups, those who had changed from m-qSOFA low to high had significantly lower 1-month TFS than those who had changed from high to low (45.5% vs. 77.8%, *P*=0.006 in the ACLF group and 62.5% vs. 96.6%, *P*<0.001 in the non-ACLF group) and had similar TFS compared to those who had high m-qSOFA on both the baseline and 7th day (45.5% vs. 27.8%, *P*=0.321 in the ACLF group and 62.5% vs. 66.7%, *P*=0.959 in the non-ACLF group) (Fig. 3A and B).

Even after excluding patients who died or received LT within 7 days, the KACLiF and AARC cohorts showed similar results (Supplementary Figs. 3 and 4).

m-qSOFA according to CLD-specific prognostic scores

Given that the MELD score and m-qSOFA were shown to

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Table 2. Predictors for 28-day LT-free survival in the KACLiF cohort and 30-day survival in the AARC cohort

Variable	KACLiF						Variable	AARC					
	Univariate			Multivariate*				Univariate			Multivariate*		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value		HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.002	0.983–1.021	0.853				Age	1.016	1.008–1.023	<0.001	1.024	1.014–1.034	<0.001
Sex (male)	0.98	0.595–1.612	0.936				Sex (male)	0.973	0.733–1.292	0.849			
Ascites	0.97	0.598–1.574	0.902				Ascites‡	2.319	1.306–4.119	0.004	2.661	1.164–6.086	0.02
Hepatic encephalopathy (≥G2)	3.166	1.951–5.138	<0.001				Hepatic encephalopathy (≥G2)	4.732	3.728–6.006	<0.001			
GI bleeding	0.582	0.348–0.974	0.039										
Infection	2.105	1.217–3.640	0.008										
Cirrhosis	0.178	0.025–1.278	0.086										
Diabetes mellitus	1.07	0.650–1.761	0.79										
Hypertension	0.637	0.345–1.177	0.15										
Prior decompensation (AARC definition)													
None	Ref	Ref	Ref										
Within 1 year	1.002	0.574–1.749	0.994										
More than 1 year	1.211	0.598–2.450	0.595										
Prior decompensation (EASL-CLIF definition)													
None	Ref	Ref	Ref										
Within 1 year	0.901	0.530–1.533	0.702										
More than 1 year	1.245	0.674–2.297	0.484										
SIRS	2.586	1.663–4.023	<0.001	1.931	1.026–3.635	0.041	SIRS‡	1.55	1.276–1.884	<0.001			
WBC ($\times 10^3$ mm^3)	1.075	1.045–1.105	<0.001				WBC ($\times 10^3$ mm^3)	1.012	1.008–1.017	<0.001	1.015	1.005–1.025	0.004
Hb (g/dL)	0.955	0.883–1.033	0.249				Hb (g/dL)	1.015	0.972–1.060	0.49			
PLT ($\times 10^9$/mm^3)	0.995	0.991–0.999	0.014	0.994	0.989–0.999	0.015	PLT ($\times 10^9$/mm^3)	0.999	0.998–1.000	0.181			
Albumin (g/dL)	0.264	0.176–0.396	<0.001	0.364	0.210–0.633	<0.001	Albumin (g/dL)	0.865	0.740–1.013	0.071			
Bilirubin (mg/dL)	1.075	1.058–1.095	<0.001	1.075	1.049–1.101	<0.001	Bilirubin (mg/dL)	1.019	1.013–1.025	<0.001	1.031	1.019–1.043	<0.001
AST (IU/L)	1	1.000–1.000	0.004	1	1.000–1.000	<0.001	AST (IU/L)	1	1.000–1.000	0.108			
ALT (IU/L)	1	1.000–1.000	0.343				ALT (IU/L)	1	1.000–1.000	0.977			
GGT (IU/L)	1	0.999–1.000	0.256				GGT (IU/L)	1	0.999–1.000	0.307			

Table 2. Continued

Variable	KACLiF						Variable	AARC					
	Univariate			Multivariate*				Univariate			Multivariate*		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value		HR	95% CI	*P*-value	HR	95% CI	*P*-value
INR†	1.328	1.244–1.417	<0.001	1.333	1.141–1.558	<0.001	INR‡	1.2	1.154–1.248	<0.001	1.19	1.132–1.250	<0.001
CRP (mg/dL)†	1.054	1.016–1.094	0.005										
Creatinine (mg/dL)	1.168	1.087–1.254	<0.001				Creatinine (mg/dL)‡	1.22	1.168–1.275	<0.001	1.17	1.108–1.235	<0.001
Na (mEq/L)†	0.942	0.916–0.970	<0.001				Na (mEq/L)‡	0.986	0.973–0.999	0.041			
Procalcitonin (ng/mL)	1.029	0.995–1.064	0.094										
Lactate (mmol/L)†	1.06	1.034–1.085	<0.001				Lactate (mmol/L)‡	1.143	1.114–1.173	<0.001	1.159	1.127–1.192	<0.001
High m-qSOFA	5.404	3.350–8.719	<0.001	2.604	1.353–5.013	0.004	High m-qSOFA	2.399	1.947–2.957	<0.001	1.904	1.484–2.442	<0.001

*Hepatic encephalopathy was excluded to avoid multicollinearity with m-qSOFA. †Missing data in KACLiF cohort: INR 0.13%, CRP 2.7%, Na 0.2%, and lactate 40.9%. ‡Missing data in AARC cohort: ascites 5.4%, SIRS 3.3%, INR 0.2%, creatinine 0.25%, Na 0.5%, and lactate 22.1%.
HR, hazard ratio; CI, confidence interval; KACLiF, Korean acute-on-chronic liver failure; GI, gastrointestinal; EASL-CLIF, European Association of the Study for The Liver-Chronic Liver Failure; SIRS, systemic inflammatory response syndrome; WBC, white blood cells; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; CRP, C-reactive protein; m-qSOFA, modified quick sequential organ failure assessment.

be independent prognostic factors for 1-month TFS, we investigated the usefulness of m-qSOFA according to the MELD score. KACLiF and AARC cohorts were divided into three groups with the cut-off values corresponding to the highest Youden index (MELD 23 in KACLiF cohort and MELD 29 in AARC cohort). In the KACLiF cohort, those with high baseline m-qSOFA showed significantly lower 1-month TFS (all *P*s<0.05) than those with low baseline m-qSOFA except in the subgroup with MELD 23-29 (*P*=0.184) (Supplementary Fig. 5A–C). The 1-month TFS of the patients who changed from low m-qSOFA at baseline to high on the 7th day was lower than those who shifted from high to low or the patients who remained at low over the 7 days, but similar to that of patients who remained at high (Supplementary Fig. 5D–F). In the AARC cohort, those with high baseline m-qSOFA showed significantly lower 1-month TFS than those with low baseline m-qSOFA in all subgroups (all *P*s<0.01) (Supplementary Fig. 6A–C). The 1-month TFS of the subgroups according to the change in m-qSOFA was similar to that of KACLiF (Supplementary Fig. 6D–F). These results were similar in subgroups based on MELD-Na 24 and 34, the cut-off values with the highest Youden index in the KACLiF and AARC cohort (data not shown).

Alcohol-associated liver disease is the most common etiology of underlying CLD accounting for two-thirds in both cohorts. Patients with alcohol-induced CLD and acute insult were divided into two groups based on a Lille score of 0.45. In both the responder group (Lille<0.45) and the non-responder group (Lille≥0.45), those with high m-qSOFA at day 7 showed significantly lower 1-month TFS compared to those with low m-qSOFA (*P*=0.006 and *P*<0.001, respectively, in KACLiF cohort, *P*<0.001 and *P*<0.001, respectively, in AARC cohort) (Supplementary Fig. 7).

Development of new organ failure

In the KACLiF cohort, the new organ failure development rate was significantly higher in those with a high baseline m-qSOFA score than in those with a low score (23.1% vs. 14.4%, *P*=0.009) (Fig. 4A). The new organ failure development rate was highest in the patients with high m-qSOFA scores at both baseline and on day 7 (33.3%), followed by those with low baseline and high day 7 scores (26.3%), high baseline and low day 7 scores (20.2%), and low base-

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Table 3. Multivariate analysis of 28-day LT-free survival in the KACLiF cohort and 30-day survival in the AARC cohort including CLD-specific prognostic scores

Prognostic score		KACLiF cohort			Prognostic score		AARC cohort		
		HR	95% CI	*P*-value			HR	95% CI	*P*-value
Child-Pugh score*	High m-qSOFA	2.673	1.606–4.451	<0.001	Child-Pugh score†	High m-qSOFA	1.394	1.085–1.791	0.009
	Child-Pugh score	1.717	1.529–1.929	<0.001		Child-Pugh score	1.604	1.460–1.764	<0.001
	AST	1	1.000–1.000	0.002		Age	1.026	1.017–1.036	<0.001
						WBC	1.023	1.013–1.032	<0.001
						Creatinine	1.146	1.084–1.211	<0.001
						Lactate†	1.131	1.100–1.163	<0.001
MELD score*	High m-qSOFA	3.029	1.839–4.989	<0.001	MELD score†	High m-qSOFA	1.659	1.298–2.121	<0.001
	MELD score	1.114	1.087–1.141	<0.001		MELD score	1.089	1.072–1.105	<0.001
	Albumin	0.46	0.298–0.709	<0.001		Age	1.028	1.018–1.038	<0.001
	AST	1	1.000–1.000	0.051		Ascites†	1.965	0.919–4.024	0.082
						WBC	1.015	1.006–1.025	0.002
						Lactate†	1.141	1.111–1.172	<0.001
MELD-Na score*	High m-qSOFA	3.101	1.897–5.067	<0.001	MELD-Na score†	High m-qSOFA	1.676	1.312–2.142	<0.001
	MELD-Na score	1.141	1.109–1.175	<0.001		MELD-Na score	1.105	1.084–1.127	<0.001
	Platelet count	0.997	0.993–1.001	0.116		Age	1.028	1.018–1.038	<0.001
	Albumin	0.561	0.366–0.861	0.008		WBC	1.015	1.006–1.025	0.002
						Ascites†	1.868	0.873–3.998	0.107
						Lactate†	1.142	1.112–1.173	<0.001
AARC score*	High m-qSOFA	2.22	1.200–4.108	0.011	AARC score†	High m-qSOFA	1.346	1.047–1.729	0.02
	AARC score	1.524	1.311–1.772	<0.001		AARC score	1.489	1.404–1.579	<0.001
	AST	1	1.000–1.000	<0.001		Age	1.025	1.015–1.035	<0.001
	Albumin	0.443	0.264–0.745	0.002		Ascites†	2.169	1.020–4.613	0.044
						WBC	1.015	1.005–1.026	0.004

*Missing data in KACLiF cohort: Child-Pugh score 0.1%, MELD score 0.1%, MELD-Na score 0.27%, and AARC score 41%. †Missing data in AARC cohort: lactate 22.1%, creatinine 0.25%, ascites 5.4%, Child-Pugh score 4.5%, MELD score 0.2%, MELD-Na score 0.6%, and AARC score 22.2%.

HR, hazard ratio; CI, confidence interval; KACLiF, Korean acute-on-chronic liver failure; m-qSOFA, modified quick sequential organ failure assessment; MELD, Model for End-stage Liver Disease; AARC, Asian Pacific Association for the Study of the Liver ACLF Research Consortium.

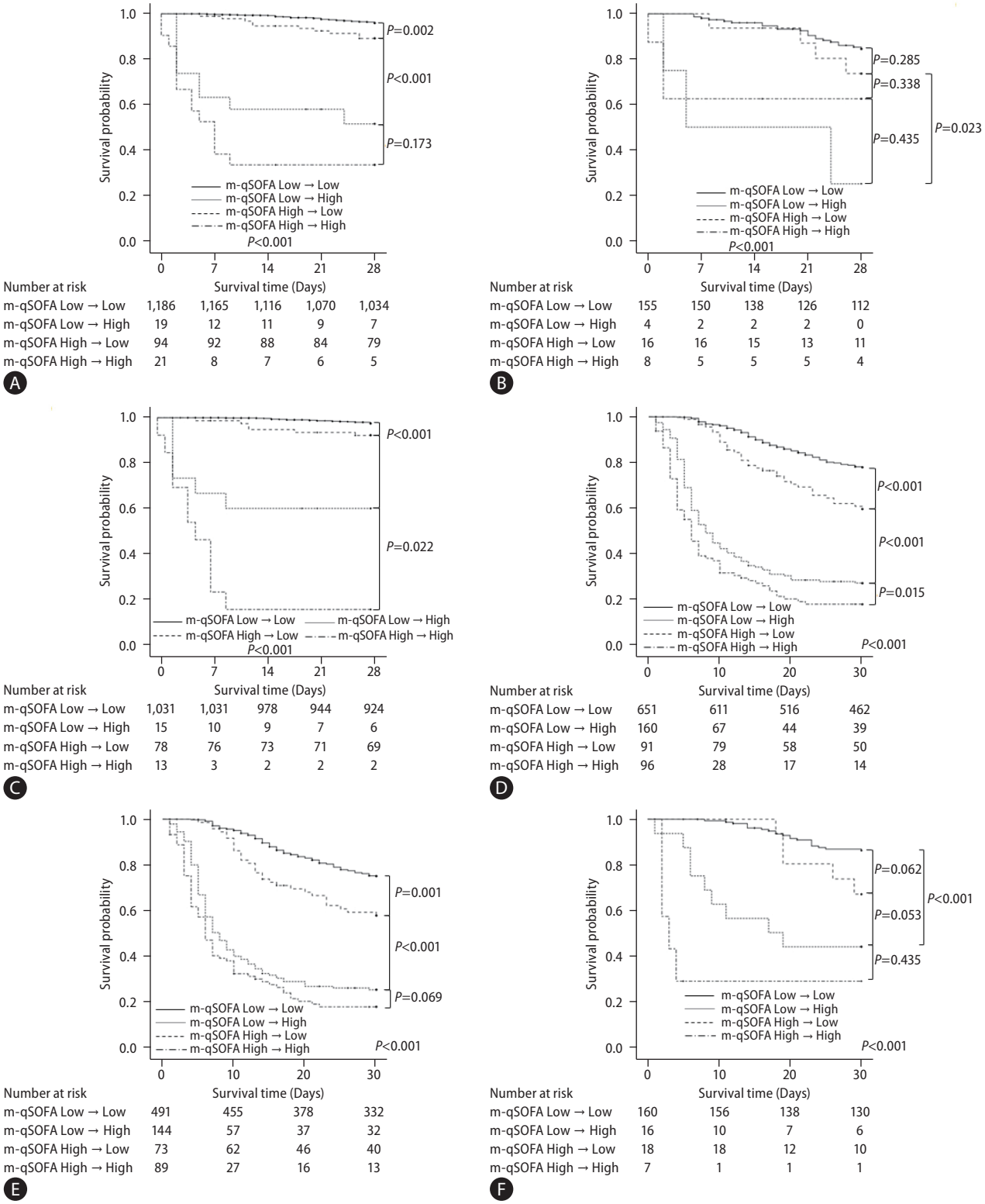

Figure 2. One-month transplant-free survival rate according to the presence of AARC ACLF and dynamic changes in m-qSOFA. (A) Total patients, (B) AARC ACLF patients, and (C) non-AARC ACLF patients in the KACLiF cohort. (D) Total patients, (E) AARC ACLF patients, and (F) non-AARC ACLF patients in the AARC cohort. m-qSOFA, modified quick sequential organ failure assessment; KACLiF, Korean acute-on-chronic liver failure; ACLF, acute-on-chronic liver failure; AARC, Asian Pacific Association for the Study of the Liver ACLF Research Consortium.

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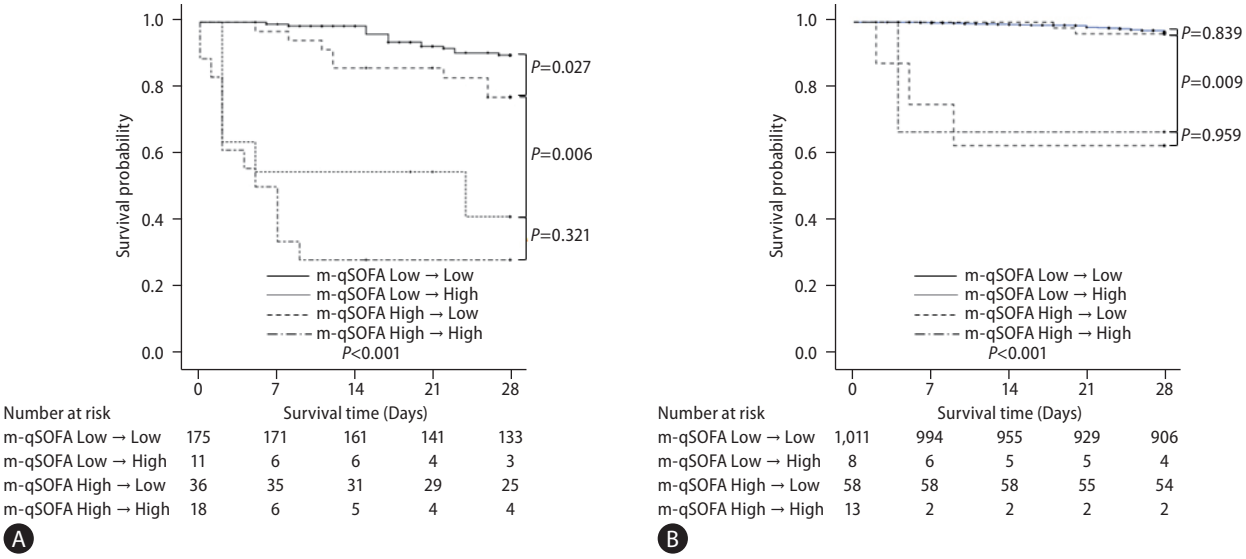

Figure 3. One-month transplant-free survival rate according to the presence of EASL-CLIF ACLF and dynamic changes in m-qSOFA in the KACLiF cohort. (A) EASL-CLIF ACLF patients and (B) non-EASL-CLIF ACLF patients. m-qSOFA, modified quick sequential organ failure assessment; EASL-CLIF, European Association for the Study of the Liver-Chronic liver failure; ACLF, acute-on-chronic liver failure; KACLiF, Korean acute-on-chronic liver failure.

line and day 7 scores (14.2%) (*P*=0.009) (Fig. 4B).

DISCUSSION

The results of our study indicate that patients with high m-qSOFA had a poor 1-month TFS in the KACLiF and AARC cohorts. The m-qSOFA was an independent predictor of short-term mortality in CLD patients with acute deterioration even after considering the CLD-specific prognostic scores. In addition, a change in the m-qSOFA score can also help to identify patients with poor prognosis.

Similar to sepsis, patients with decompensated cirrhosis or ACLF have typical hemodynamic changes called hyperdynamic circulation[22,23] and a systemic inflammatory response as the main pathophysiology.[19,24] Bacterial infection is common in ACLF patients, as infection is present in approximately one-third of ACLF patients at presentation,[25] and infections are important determinants of disease progression and survival. In contrast, bacterial infection could not be detected in a substantial portion of ACLF patients fulfilling the SIRS criteria.[25] Therefore, qSOFA, a score for screening sepsis, can be considered to predict adverse outcomes in patients with acutely deteriorated CLD with similar pathophysiology to sepsis regardless of infection. Previous studies by Piano et al.[11] and Augustinho et al.[9] reported that qSOFA was effective in predicting high-risk cirrhotic patients in those with infection. However, other studies that included cirrhotic patients without infection showed doubtful results on the predictive ability of qSOFA. Müller et al.[26] reported that qSOFA does not predict in-hospital mortality, and Choi et al.[27] showed that qSOFA was a significant predictive factor for in-hospital mortality in critically ill patients with cirrhosis but had limited value.

We investigated the usefulness of the m-qSOFA by replacing the GCS with the HE in the qSOFA, which is used in the general population. The West Haven criteria for HE are used more commonly than the GCS to assess cerebral dysfunction in CLD patients. The CLIF-SOFA score for assessing the severity of ACLF was also developed by replacing the GCS with HE grades in the generally used SOFA score, and it provided an improved prediction of prognosis compared to the original SOFA score in critically ill CLD patients[3,16] and in cirrhotic patients with infection.[9] Likewise, we needed to modify the qSOFA to improve the prediction of prognosis in patients with acutely deteriorated CLD, and it helped to identify those with higher mortality. However, unlike the CLIF-SOFA classifying HE grade 3–4 as organ failure, we used HE grade ≥2 as the m-qSOFA criteria. HE grade 1 is classified as covert HE, which is dif-

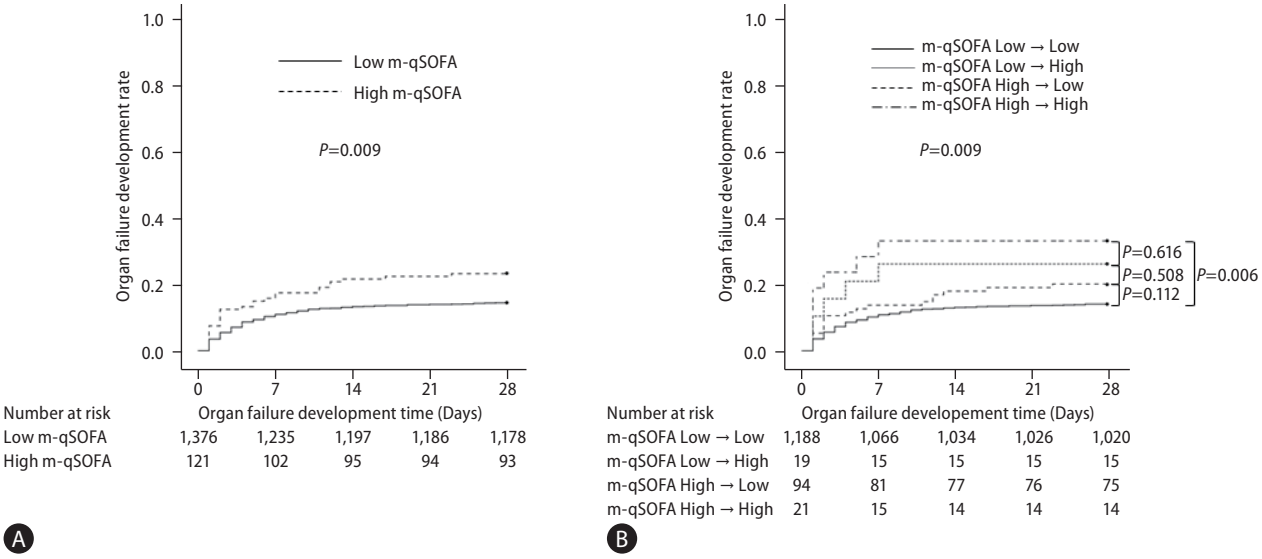

Figure 4. New organ failure development in the KACLiF cohort. (A) New organ failure development according to baseline m-qSOFA, (B) new organ failure development according to dynamic changes in m-qSOFA. m-qSOFA, modified quick sequential organ failure assessment; KACLiF, Korean acute-on-chronic liver failure.

ficult to diagnose because there is no definite clinical manifestation, such as disorientation or asterixis.[28] Therefore, it is more reasonable to adopt HE grade 2, which is the criterion for overt HE, as a simple way to evaluate altered mentation at the bedside.

The qSOFA was originally developed as a bedside method of identifying adult patients who are likely to have poor outcomes among those with suspected infection instead of SIRS.[8] However, the usefulness of qSOFA to make an early diagnosis of sepsis has been questioned because of its lower sensitivity compared to SIRS.[29-31] On the other hand, qSOFA was better than SIRS for the prediction of hospital mortality.[32] Since qSOFA reflects organ failure, such as respiratory and circulatory failure, it may be natural to assume that qSOFA is more effective in predicting poor outcomes. Therefore, it is appropriate to use qSOFA to predict poor outcomes rather than for diagnosing sepsis. In our study, m-qSOFA was an independent factor for 1-month TFS in both cohorts, although not SIRS in the AARC cohort (Tables 2 and 3). The m-qSOFA was able to identify patients with high mortality when combined with ACLF, and the changes in m-qSOFA for 7 days were also useful in predicting poor outcomes, including mortality and the development of new organ failure (Figs. 2–4). The prognostic predictability of m-qSOFA is likely attributed to its variables, which are associated with organ failure in ACLF and reflect disease severity. In addition, m-qSOFA at baseline and day 7 can distinguish patients with high short-term mortality regardless of the liver-specific prognostic score such as MELD, MELD-Na, and the Lille model (Supplementary Figs. 5–7). The advantage of m-qSOFA is that it does not require calculations as with MELD, MELD-Na, or the Lille model and can be obtained with fewer variables than Child-Pugh, AARC, CLIF-SOFA, and CLIF-C OF scores. According to our results, we propose a new algorithm that can distinguish the risk to patients using the presence of baseline ACLF and m-qSOFA and the change in m-qSOFA on day 7 (Fig. 5). According to this algorithm, CLD patients who are hospitalized with acute decompensation can be divided into 3 risk groups at baseline: low, moderate, and high. These patients can be reclassified using the changes in m-qSOFA at 7 days, while the moderate group at baseline cannot be reclassified into the low-risk group even if m-qSOFA is less than 2 at 7 days. If we identify patients with poor outcomes early by using m-qSOFA and perform early interventions in this golden window, we might be able to improve the prognosis of patients with acutely deteriorating CLD.

This study has some limitations. First, the baseline characteristics of the two cohorts are different. The disease severity of the AARC cohort was higher than that of the KACLiF cohort because the AARC cohort included more ACLF

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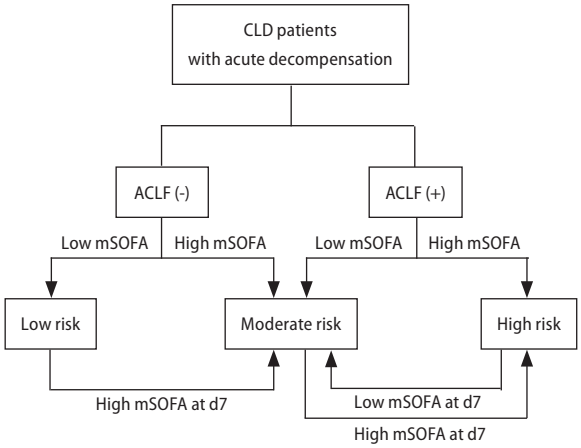

Figure 5. Proposed algorithm for m-qSOFA in patients with ACLF. CLD, chronic liver disease; ACLF, acute-on-chronic liver failure; m-qSOFA, modified quick sequential organ failure assessment.

patients. Different disease severity leads to different cut-off values of the MELD and MELD-Na scores between the two cohorts. However, since the two cohorts showed similar results on the utility of m-qSOFA, disease severity does not seem to have a significant impact on the usefulness of m-qSOFA. In the future, the validation of m-qSOFA is necessary in patients with various characteristics. Second, this study analyzed the utility of m-qSOFA in the EASL-CLIF ACLF patients in the KACLiF cohort only. There are limitations in analyzing EASL-CLIF ACLF in the AARC cohort because the data collected focuses on AARC ACLF. Therefore, it will be necessary to study the usefulness of m-qSOFA in patients with EASL-CLIF ACLF in other cohorts. Third, the etiology of CLD was predominantly alcohol-associated liver disease in both cohorts, accounting for two-thirds of all cases. Therefore, future analyses need to consider the impact according to different CLD etiologies. Fourth, it is necessary to study whether m-qSOFA, which replaces GCS with HE grades, is better than the original qSOFA in CLD patients with acute decompensation. Fifth, despite its utility, m-qSOFA has a low ability to predict 1-month mortality when used alone compared to other prognostic scores showing a significantly lower area under the receiver operating characteristic curve (Supplementary Table 1). Therefore, m-qSOFA should be used in conjunction with ACLF or another scoring system to increase its predictive ability. However, m-qSOFA has the advantage of easily screening high-risk patients at the bedside because it can be obtained simply with only three variables.

In conclusion, m-qSOFA is an independent factor for predicting short-term mortality in patients with acutely deteriorated CLD, and combining m-qSOFA with the presence of ACLF could identify high-risk patients more accurately regardless of the definition of the ACLF. In addition, using dynamic changes in m-qSOFA scores at 7 days is also useful in identifying high-risk patients at the bedside.

Authors' contribution

Study concept and design: D.S.S. and D.J.K.; acquisition of data: D.S.S., H.Y.K., Y.K.J, T.H.K., E.L.Y., K.T.S, J.Y., S. G.K, M.Y.K., Y.C., S.W.J, J.Y.J., S.E.K., J.H.K., J.G.P., W.K., and J.M.Y; analysis and interpretation of data: D.S.S., D.J.K., T.H.K., E.L.Y., J.Y., Y.C., J.Y.J., S.E.K., and J.G.P.; drafting of the manuscript: D.S.S; critical revision of the manuscript for important intellectual content: D.J.K., H.J.Y., J.Y.J., S.G.K., M.Y.K., and W.K.; statistical analysis: D.S.S.; study supervision: D.J.K. and J.M.Y.

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Conflicts of Interest

The authors have no conflicts to disclose.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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