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Applicability of Sepsis-3 criteria and quick Sequential Organ Failure Assessment in patients with cirrhosis hospitalised for bacterial infections

Fernanda C. Augustinho[1] | Tamara L. Zocche[1] | Ariane Borgonovo[1] | Dariana C. Maggi[1] | Elayne C. M. Rateke[2] | Camila Matiollo[2] | Esther B. Dantas-Correa[1] | Janaína L. Narciso-Schiavon[1] | Leonardo L. Schiavon[1]

[1]Division of Gastroenterology, Federal University of Santa Catarina, Florianópolis, SC, Brazil

[2]Department of Clinical Analysis, Federal University of Santa Catarina, Florianópolis, SC, Brazil

Correspondence
Leonardo L. Schiavon, Division of Gastroenterology, Federal University of Santa Catarina, Florianópolis, SC, Brazil.
Email: leo-jf@uol.com.br

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Abstract

Background & Aims: An algorithm including Sepsis-3 criteria and quick Sequential Organ Failure Assessment (qSOFA) was recently proposed to predict severity of infection in cirrhosis. However, its applicability among patients without a baseline SOFA available for Sepsis-3 definition is unknown. We sought to investigate the applicability and prognostic value of qSOFA and Sepsis-3 criteria in patients with cirrhosis hospitalised for bacterial infections, without pre-hospitalisation SOFA.

Methods: In this cohort study, 164 patients were followed up to 30 days. Data collection, including the prognostic models, was performed at admission and at day-3.

Results: All patients fulfilled Sepsis-3 criteria (admission SOFA ≥ 2) and, therefore, admission Sepsis-3 was not included in further analysis. Admission qSOFA was an independent predictor of survival (HR = 2.271, $P = 0.015$). For patients initially classified as high risk by qSOFA, Chronic Liver Failure - Sequential Organ Failure Assessment (CLIF-SOFA) was the only prognostic predictor. Among patients initially classified as low risk by qSOFA, the following parameters evaluated at day-3 were independent predictors of survival: qSOFA, acute-on-chronic liver failure, and Child-Pugh classification. Although not independently related to survival, Sepsis-3 criteria at day-3 was associated with lower 30-day survival in Kaplan-Meier analysis (66% vs 85%, $P = 0.008$). However, prognosis was better predicted by day-3 qSOFA, with 30-day Kaplan-Meier survival probability of 88% when qSOFA < 2 and 24% among those with qSOFA ≥ 2.

Conclusion: Sepsis-3 criteria evaluated at admission are very limited in infected patients with cirrhosis without baseline SOFA. qSOFA was independently related to survival and appears to be a valuable tool for determining severity of infection and to follow patients initially classified as low risk.

KEYWORDS

acute decompensation, acute-on-chronic liver failure, cirrhosis, organ failure, sepsis

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; AUROC, area under the receiver operating characteristics; CA, community-acquired; CAID, Cirrhosis-associated immune dysfunction; CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment; CRP, C-reactive protein; EASL, European Association for the Study of the Liver; HCA, healthcare-associated; HR, hazard ratio; ICU, intensive care unit; INR, international normalised ratio; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; qSOFA, quick Sequential Organ Failure Assessment; SBP, spontaneous bacterial peritonitis; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

1 | INTRODUCTION

As a consequence of several immunological abnormalities, patients with cirrhosis are susceptible to infections during the course of the disease.[1] Bacterial infections occur in 24%-40% of hospitalised patients with cirrhosis and are associated with an increased risk of progression with organ dysfunction and acute-on-chronic liver failure (ACLF).[2,3] Most importantly, infections are associated with almost four-fold increase in mortality of cirrhotics, with rates of 31.5% at 1 month and 66.2% at 12 months.[4] Therefore, early identification of patients with bacterial infection at high risk of complications and mortality is crucial for an effective management, especially when dealing with cirrhotics at emergency department.

Sepsis, a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection, is a major public health problem and is associated with a poor prognosis in patients with cirrhosis.[4,5] For many years, systemic inflammatory response syndrome (SIRS) criteria were used to define sepsis.[6] However, in patients with cirrhosis, several factors may impair SIRS parameters, including tachypnea induced by encephalopathy, leukopenia related to hypersplenism or bradycardia owing to beta-blockers.[7] Recently, new definitions of sepsis in general population were proposed by the Sepsis Definitions Task Force as an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more (Sepsis-3 criteria).[8] In addition, a new tool named quick SOFA (qSOFA) was proposed as bedside criteria to identify adult patients with suspected infection who are likely to have poor outcomes.[8] These criteria include altered mentation, systolic blood pressure of 100 mm Hg or less, and respiratory rate of 22/min or greater.[8] Recently, qSOFA and Sepsis-3 criteria were validated in patients with cirrhosis and bacterial infections, exhibiting better performance than SIRS criteria in predicting in-hospital mortality.[9] An algorithm for the application of Sepsis-3 criteria and qSOFA was proposed and latter included in the European Association for the Study of the Liver (EASL) clinical practice guidelines for the management of patients with decompensated cirrhosis.[10] In the algorithm, both qSOFA and Sepsis-3 criteria should be applied in subjects without a baseline SOFA. In this case, all patients with a SOFA ≥2 at evaluation will fulfil Sepsis-3 criteria.[8,9] However, several factors in cirrhosis not necessarily related to the severity of infection could increase SOFA score, particularly low platelet count and high bilirubin levels. Consequently, the proposed algorithm might not be the ideal approach for patients admitted in emergency departments where a baseline SOFA is not expected to be available and admission SOFA score will be probably increased in the vast majority of patients.

Therefore, the aim of this study was to investigate the applicability and prognostic value of qSOFA and Sepsis-3 criteria in patients recently hospitalised for acute decompensation of cirrhosis in the emergency department.

Key points

- Sepsis-3 criteria at admission (SOFA score ≥2) are very limited in infected patients with cirrhosis without baseline SOFA.
- High risk qSOFA is strongly related to mortality and appears to be a valuable tool to identify patients requiring intensive care admission.
- Patients initially classified as low risk by qSOFA, should be monitored for development of organ dysfunction, especially during the first days of hospitalisation.

2 | METHODS

2.1 | Patients

This is a retrospective analysis of prospectively collected data from a cohort study that included consecutive subjects admitted to the emergency room of a Brazilian tertiary hospital owing to acute decompensation (AD) of cirrhosis between January 2011 and November 2016. Patients in the following situations were excluded: (a) hospitalisation for elective procedures; (b) admissions not related to complications of cirrhosis; (c) hepatocellular carcinoma outside Milan criteria; (d) extrahepatic malignancy; (e) severe extrahepatic disease; and (f) use of immunosuppressive drugs. All patients were initially admitted in the emergency room. The decision to transfer the patient to the ward or the intensive care unit (ICU) was made at the discretion of the attending physician according to the severity of the AD.

The diagnosis of cirrhosis was established either histologically (when available) or by the combination of clinical, imaging, and laboratory findings in patients with evidence of portal hypertension.

The study protocol complies with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee on Human Research of the Federal University of Santa Catarina. Informed consent was obtained from all participants or their surrogates.

2.2 | Methods

All patients admitted for AD as defined by the acute development of hepatic encephalopathy, large ascites, gastrointestinal bleeding, bacterial infection, or any combination of these were screened. Patients were evaluated at first and third day of admission by one of the researchers involved in the study, and the following clinical variables were collected: age, gender, aetiology of cirrhosis, previous and current complications of cirrhosis, mean arterial pressure (MAP),

heart rate, and SpO_2/FiO_2 ratio. All subjects underwent laboratory evaluation at admission and at day-3.

Active alcoholism was defined as an average overall consumption of 21 or more drinks per week for men and 14 or more drinks per week for women during the 4 weeks before enrolment (one standard drink is equal to 12 g absolute alcohol).[11] Patients were followed during their hospital stay, and 30-day mortality was evaluated by phone call, in case of hospital discharge.

All patients admitted for acute decompensation of cirrhosis in our institution are actively screened for bacterial infections. A diagnostic paracentesis was performed in all patients with ascites at admission. Spontaneous bacterial peritonitis (SBP) was diagnosed when the neutrophil count of the ascitic fluid was ≥250 neutrophils/mm^3 in the absence of intra-abdominal source of infection, regardless of negative culture.[10] Criteria for diagnosing other infections than SBP were adapted from Centers for Disease Control and Prevention and are presented in Appendix S1.[12] Bacterial infections were classified as community-acquired (CA), healthcare-associated (HCA), and nosocomial infections as previously described.[13] Hepatic encephalopathy was graded according to the West-Haven criteria[14] and, if it was present, a precipitant event was actively investigated and lactulose was initiated and the dose adjusted as needed. All subjects with acute variceal bleeding received intravenous octreotide, an antibiotic (either oral norfloxacin or intravenous ceftriaxone) and underwent urgent therapeutic endoscopy after stabilisation. Severity of liver disease was estimated by the Child-Pugh classification system[15] and MELD (Model for End-Stage Liver Disease).[16]

Treatment of infections was initiated at the time of diagnosis or empirically in case of suspected infection without an identified source. The antibiotic choice was determined by the type of infection (CA or HCA), source, severity, and cultures results. During the period of the study, our institution followed a similar approach that the proposed by the EASL Clinical Practice Guidelines in 2014.[17]

2.3 | Definitions

Acute-on-chronic liver failure and CLIF-SOFA were defined as proposed by the EASL-CLIF Consortium.[3] The conventional SOFA score was calculated using the peripheral arterial oxygen saturation (SpO_2) to FIO2 ratio (SpO_2/FiO_2) as previously described.[18] SIRS was defined by the presence of at least two among the following criteria: body temperature <36°C or >38°C, heart rate >90 beats per minute (bpm), respiratory rate >20/min, white blood cells (WBC) <4000/μL or >12 000/μL, or immature neutrophils >10%.[6] The qSOFA score includes the following variables: systolic blood pressure ≤100 mm Hg; respiratory rate ≥22 breaths per minute and altered mental state.[8] For qSOFA calculation, one point is assigned for each of its components if present and a score ≥2 is considered a high risk qSOFA. Altered mental state was defined as a Glasgow Coma Scale of less than 15.[8] Sepsis-3 criteria were defined as an acute change in total SOFA score ≥2 points consequent to the infection.[8] In the present study, Sepsis-3 criteria were applied only at third day of hospitalisation by using day-1 SOFA as the baseline value. All scores were calculated at first and third days of hospitalisation.

2.4 | Statistical analysis

The normality of the variable distribution was determined by the Kolmogorov-Smirnov test. Continuous variables were compared using Student's *t* test in the case of normal distribution or Mann-Whitney test in the remaining cases. Categorical variables were evaluated by chi-square test or Fisher's exact test as appropriate. Univariate and multivariate Cox regression analyses (enter method) were used to investigate the association between the variables and survival. The performance of the models in predicting 30-day mortality was analysed by calculating the area under the receiver operating characteristics (AUROC) curves. The cut-offs of SOFA and CLIF-SOFA to predict 30-day survival were chosen based on the ROC curves. Kaplan-Meier curves were used to illustrate survival according to two strata. All tests were performed by the SPSS software, version 17.0 (SPSS, Chicago, IL, USA). A *P* value of less than 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of the sample and factors associated with bacterial infection

A total of 393 individuals were screened for inclusion between January 2011 and November 2016 and 11 were excluded owing to lack of data, thus 382 subjects composed the final sample of the study. Table 1 exhibits the characteristics of the included patients. The mean age was 54.90 ± 11.30 years, 73% were male, and 33% of subjects reported active alcoholism during the past month. The most common aetiology of cirrhosis was alcohol abuse (37%) followed by hepatitis C alone (17%) and with concomitant alcohol abuse (17%).

Upon admission, upper gastrointestinal bleeding was observed in 41% of cases, ascites in 52% and hepatic encephalopathy in 48%. Bacterial infections were present in 43% (164 patients) and were classified in CA in 135 subjects (82%) and HCA in 29 (18%) patients. The most common bacterial infection was spontaneous bacterial peritonitis (28%) followed by urinary tract infection (24%), pneumonia (19%), skin infections (15%), gastroenteritis (5%), and infections without identified focus (13%). Less common types of infection, including bacterascites, otitis media, dental abscess, and primary bacteraemia accounted for 9% of the cases. Table 1 exhibits the characteristics of the patients according to the presence of infection. High risk qSOFA (≥2) was observed in 10% of non-infected patients and in 20% of infected ones ($P = 0.006$). None of the patients exhibited SOFA score of zero, and only three subjected presented with SOFA score of one. All infected individuals had a SOFA ≥2 at admission and a score equal of two was noted in 10 patients (6%), leaving 94% with SOFA ≥3.

TABLE 1 Characteristics of included patients and factors associated with infection at enrolment

	All (n = 382)	Absence of infection (n = 218)	Presence of infection (n = 164)	*P*
Age (y), mean ± SD	54.90 ± 11.30	53.83 ± 11.04	56.31 ± 11.51	0.034
Male Gender, n (%)	278 (73)	154 (71)	124 (76)	0.280
Aetiology of cirrhosis, n (%)				
Alcohol	140 (37)	76 (35)	64 (39)	0.403
Hepatitis C	65 (17)	36 (17)	29 (18)	0.763
Hepatitis C + alcohol	65 (17)	36 (17)	29 (18)	0.400
Hepatitis B	15 (4)	4 (2)	11 (7)	0.015
Other	97 (25)	66 (30)	31 (20)	0.011
Active alcoholism, n (%)	127 (33)	74 (34)	53 (32)	0.738
Complication at admission, n (%)				
Ascites	200 (52)	93 (43)	107 (65)	<0.001
Hepatic encephalopathy	185 (48)	91 (42)	94 (57)	0.003
Gastrointestinal bleeding	155 (41)	118 (54)	37 (23)	<0.001
Laboratory data				
Leucocyte count ($\times 10^9$), median	6.96	6.59	7.30	0.027
Sodium (mEq/L), mean ± SD	135.42 ± 5.14	135.93 ± 4.80	134.73 ± 5.51	0.025
Creatinine (mg/dL), median	1.10	1.00	1.20	<0.001
INR, median	1.45	1.39	1.54	<0.001
Albumin (g/dL), mean ± SD	2.36 ± 0.64	2.50 ± 0.64	2.18 ± 0.61	<0.001
CRP (mg/L),median	14.35	7.18	37.30	<0.001
Total bilirubin (mg/dL), median	2.10	1.70	2.70	<0.001
ACLF, n (%)	96 (25)	37 (17)	59 (36)	<0.001
ACLF grade, n (%)				
Grade 1	74 (19)	29 (13)	45 (27)	
Grade 2	14 (4)	5 (2)	9 (6)	
Grade 3	8 (2)	3 (1)	5 (3)	
Child-Pugh score, mean ± SD	9.16 ± 1.90	8.62 ± 1.85	9.88 ± 1.73	<0.001
MELD score, mean ± SD	17.00 ± 6.66	15.27 ± 5.91	19.21 ± 6.95	<0.001
SOFA, median	5.00	4.00	6.00	<0.001
SIRS criteria, n (%)	104 (27)	54 (25)	50 (31)	0.246
CLIF-SOFA, median	6.00	5.00	7.00	<0.001
qSOFA ≥2, n (%)	55 (14)	22 (10)	33 (20)	0.006

ACFL, Acute-on-chronic liver failure; CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment; CRP, C-reactive protein; INR, international normalised ratio; MELD, Model for End-stage Liver Disease; qSOFA, quick Sepsis Related Organ Failure Assessment; SD, Standard deviation; SIRS, Systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

3.2 | Factors associated with mortality in patients with cirrhosis and bacterial infection

During the first 30 days, among subjects with infection, 45 patients (27%) died and no patient underwent liver transplantation. Table 2 shows the comparison between survivors and non-survivors. Thirty-day mortality among infected patients was associated with lower albumin levels and higher leucocyte count, creatinine, CRP, and total bilirubin. As expected, the prognostic scores Child-Pugh, MELD, SOFA, and CLIF-SOFA were higher in non-survivors. Non-survivors had higher proportion of patients with ACLF (60% vs 27%, HR = 3.384, $P < 0.001$), high risk qSOFA (40% vs 13%, HR = 3.620, $P < 0.001$) and SIRS criteria (44% vs 25%, HR = 2.091, $P = 0.014$) than survivors.

The following variables were included in a multivariate Cox regression analysis: ACLF, Child-Pugh score, SIRS criteria, qSOFA together with SOFA or CLIF-SOFA scores (included separately). MELD score and other variables already included in the prognostic models (leucocyte count, creatinine, albumin, and total bilirubin) were not included in the multivariate analysis to avoid collinearity and to keep an acceptable number of events per variable. In the analysis including SOFA score, qSOFA (HR = 2.007, IC 95% 1.006-4.004, $P = 0.048$)

TABLE 2 Comparison of demographic, clinical, and laboratory data between infected cirrhosis according to 30-day survival

	Survivors (n = 119)	Non-survivors (n = 45)	HR (95% CI)	*P*
Age (y), mean ± SD	56.92 ± 11.39	54.73 ± 11.80	0.987 (0.963-1.011)	0.287
Male Gender, n (%)	91 (77)	33 (73)	0.866 (0.477-1.677)	0.670
Aetiology of cirrhosis, n (%)				
Alcohol	44 (37)	20 (44)	1.319 (0.732-2.374)	0.356
Hepatitis C	20 (17)	9 (20)	1.174 (0.565-2.437)	0.668
Hepatitis C + alcohol	22 (19)	7 (17)	0.855 (0.382-1.915)	0.703
Hepatitis B	9 (8)	2 (4)	0.597 (0.145-2.463)	0.475
Active alcoholism, n (%)	38 (32)	15 (33)	1.119 (0.602-2.080)	0.723
Beta-blockers, n (%)	40 (34)	13 (30)	0.872 (0.455-1.673)	0.681
Healthcare-associated infection, n (%)	18 (15)	11 (24)	1.497 (0.758-2.956)	0.245
Complication at admission, n (%)				
Ascites	72 (61)	35 (78)	1.963 (0.972-3.964)	0.060
Hepatic encephalopathy	65 (55)	29 (64)	1.504 (0.817-2.770)	0.190
Gastrointestinal bleeding	23 (19)	14 (31)	1.839 (0.978-3.458)	0.059
Laboratory data				
Leucocyte count ($\times 10^9$), median	4.80	10.12	1.069 (1.034-1.102)	<0.001
Sodium (mEq/L), mean ± SD	135.05 ± 5.17	133.77 ± 6.28	0.958 (0.908-1.010)	0.111
Creatinine (mg/dL), median	1.10	1.90	1.764 (1.484-2.099)	<0.001
INR, median	1.51	1.65	1.734 (0.930-3.233)	0.083
Albumin (g/dL), mean ± SD	2.31 ± 0.58	1.83 ± 0.53	0.257 (0.142-0.465)	<0.001
CRP (mg/L),median	32.40	47.00	1.004 (1.001-1.008)	0.021
Total bilirubin (mg/dL), median	2.50	3.10	1.043 (1.010-1.078)	0.011
ACLF, n (%)	32 (27)	27 (60)	3.384 (1.861-6.154)	<0.001
Child-Pugh score, mean ± SD	9.62 ± 1.77	10.59 ± 1.39	1.333 (1.118-1.590)	0.001
MELD score, mean ± SD	17.69 ± 6.21	23.21 ± 7.29	1.091 (1.054-1.130)	<0.001
SOFA, median	5.00	7.00	1.350 (1.228-1.484)	<0.001
SIRS criteria, n (%)	30 (25)	20 (44)	2.091 (1.161-3.765)	0.014
CLIF-SOFA, median	7.00	9.00	1.315 (1.203-1.437)	<0.001
qSOFA ≥2, n (%)	15 (13)	18 (40)	3.620 (1.989-6.588)	<0.001

ACFL, Acute-on-chronic liver failure; CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment; CRP, C-reactive protein; HR, Hazard Ratio; INR, international normalised ratio; MELD, Model for End-stage Liver Disease; qSOFA, quick Sepsis Related Organ Failure Assessment; SD, Standard deviation; SIRS, Systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

and SOFA (HR = 1.224, IC 95% 1.065-1.406, *P* = 0.004) were independently related to 30-day survival. In the analysis including CLIF-SOFA, also qSOFA (HR = 2.271, IC 95% 1.171-4.404, *P* = 0.015) and CLIF-SOFA (HR = 1.234, IC 95% 1.064-1.432, *P* = 0.006) were predictors of survival. From a practical point of view, when applying qSOFA at admission, the 30-day Kaplan-Meier survival probability

of patients classified as low risk was 79% and for those classified as high risk was 45% (Figure 1A; $P < 0.001$).

A subsequent analysis was performed in order to better stratify severity among those patients initially classified as high risk by qSOFA. The same covariates previously evaluated were included in this analysis that was restricted to patients with qSOFA ≥2 at admission. When SOFA was included in the analysis, no variable was independently related to survival. However, in the analysis including CLIF-SOFA, this score was the only prognostic predictor (HR = 1.400, IC 95% 1.078-1.819, $P = 0.012$). In addition, the AUROC for CLIF-SOFA was numerically higher than SOFA to predict 30-day survival (0.765, IC 95% 0.600-0.929 vs 0.657, IC 95% 0.471-0.844; Figure 2). The best cut-off for both SOFA and CLIF-SOFA to predict 30-day survival among patients initially classified as high risk by qSOFA was nine. The 30-day Kaplan-Meier survival probability was 58% in subjects with SOFA <9% and 28% among those with values ≥9 ($P = 0.050$). Survival was better predicted by CLIF-SOFA, with 30-day probability of 82% for subjects with CLIF-SOFA <9% and 27% for those with values ≥9 (Figure 1B; $P = 0.005$).

Similar approach was used to identify potential prognostic markers in those patients classified as low risk by qSOFA at admission. None of patients with initial qSOFA <2 died during the first 2 days of hospitalisation. In multivariate Cox regression analysis including variables at admission, SOFA score (HR = 1.209, IC 95% 1.005-1.453, $P = 0.044$) but not CLIF-SOFA (HR = 1.102, IC 95%

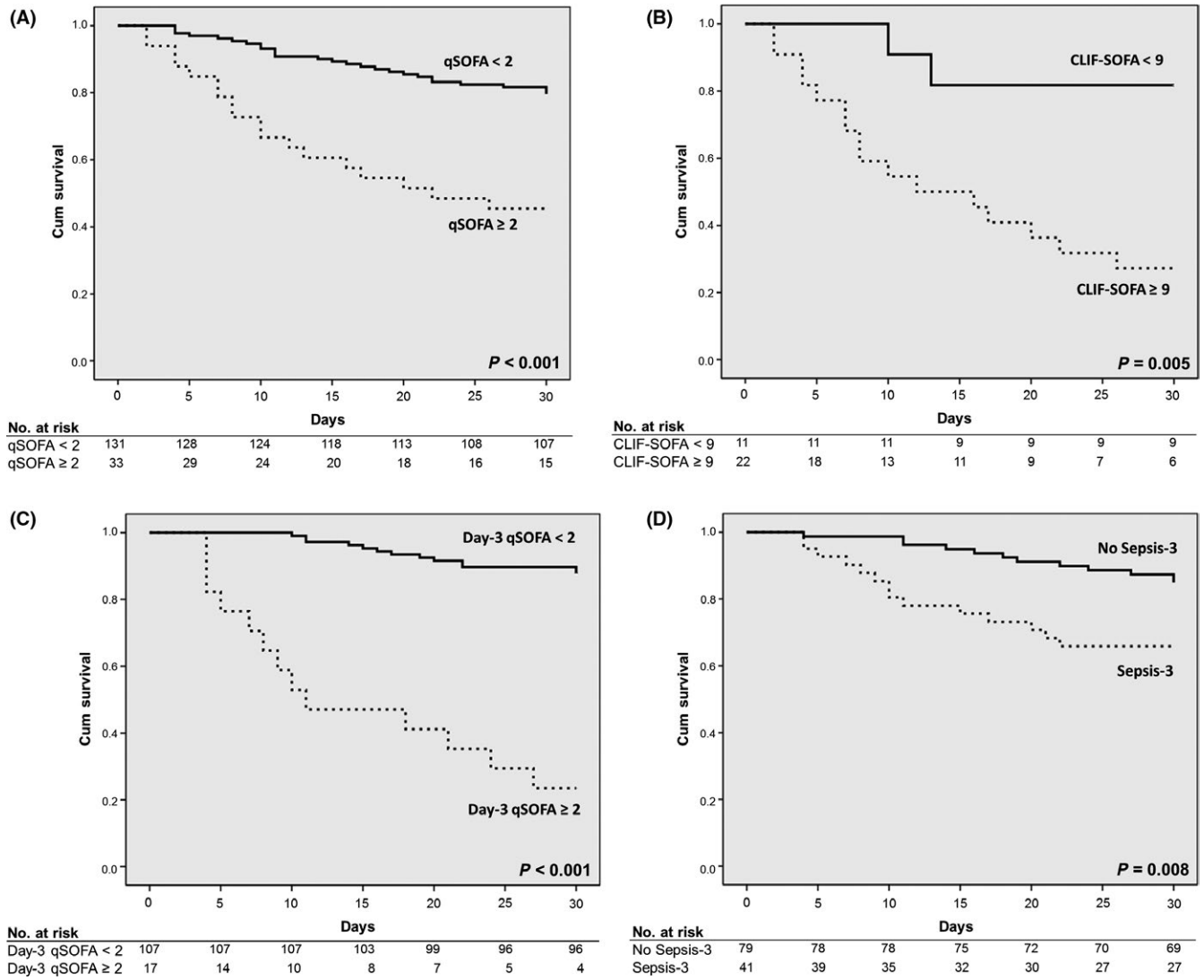

FIGURE 1 Cumulative 30-d survival of patients with cirrhosis according to quick Sequential Organ Failure Assessment (qSOFA), Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA), and Sepsis-3 criteria. When considering the entire cohort, the 30-d survival probability was 79% for patients with low risk qSOFA at day-1% and 45% for those classified as high risk (A). Among patients initially classified as high risk by qSOFA, the 30-d Kaplan-Meier survival probability was 82% in subjects with CLIF-SOFA <9% and 27% among those with values ≥9 (B). Among those initially classified as low risk by day-1 qSOFA, 30-d survival probability was 88% in subjects with day-3 qSOFA <2% and 24% for patients with day-3 qSOFA ≥2 (C). Sepsis-3 criteria were also applied at day-3 in patients initially classified as low-risk by qSOFA and the survival probability was 85% in subjects not fulfilling Sepsis-3 criteria and 66% among those who fulfil it (D)

0.897-1.353, $P = 0.356$) was an independent predictor of mortality. However, both SOFA and CLIF-SOFA exhibited low prognostic accuracy, with AUROCs of 0.679 (IC 95% 0.563-0.796) and 0.641 (IC 95% 0.523-0.758) for predicting 30-day mortality respectively. Therefore, a new multivariate Cox regression analysis was performed for patients classified at admission as low risk by qSOFA. In this analysis, the following parameters evaluated after 48 hours (at day 3) were included: ACLF, Child-Pugh score, SIRS criteria, qSOFA together with Sepsis-3 criteria, SOFA, or CLIF-SOFA scores (included separately). As sepsis-3 criteria are directly based on SOFA score, it was not included in the same analysis with SOFA and CLIF-SOFA (that is also based on SOFA score). SOFA score and qSOFA were not available at third day for 11 and 7 patients respectively. When SOFA was included in the multivariate analysis, only qSOFA (HR = 9.548, IC 95% 3.563-25.584, $P < 0.001$) and Child-Pugh classification (HR = 1.739, IC 95% 1.237-2.446, $P = 0.001$) were predictors of survival. The same variables along with ACLF were associated with 30-day survival when CLIF-SOFA was included in the analysis (qSOFA – HR = 10.715, IC 95% 3.969-28.925, $P < 0.001$; Child-Pugh classification – HR = 1.931, IC 95% 1.291-2.886, $P = 0.001$, and ACLF - HR = 3.648, IC 95% 1.217-10.930, $P = 0.021$). When Sepsis-3 criteria were included in the multivariate analysis, qSOFA (HR = 8.571, IC 95% 3.283-22.378, $P < 0.001$), ACLF (HR = 2.761, IC 95% 1.058-7.206, $P = 0.038$) and Child-Pugh score (HR = 1.715, IC 95% 1.260-2.335, $P = 0.001$), but not Sepsis-3 (HR = 1.908, IC 95% 0.782-4.459, $P = 0.156$), were predictors of survival.

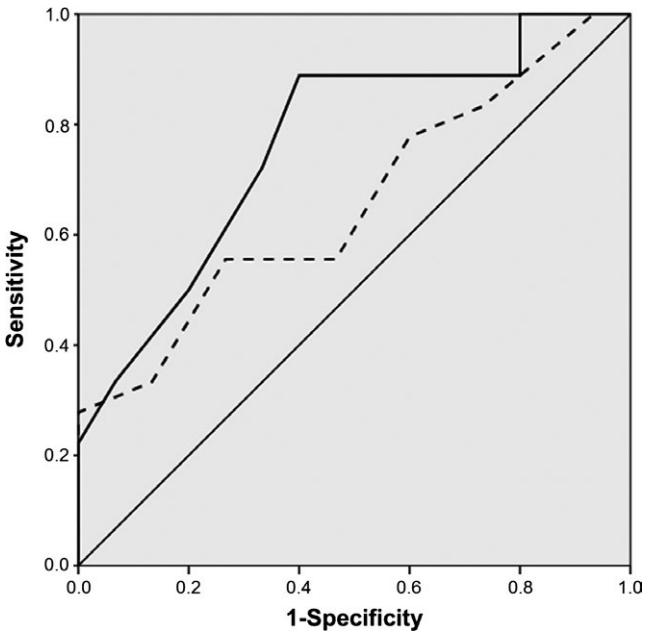

FIGURE 2 Receiver Operating Characteristic (ROC) curve for Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) (continuous line) and SOFA (discontinuous line) for the prediction of 30-d mortality among cirrhotic patients with infection initially classified as high risk by qSOFA. The area under the receiver operating characteristics was 0.765 (IC 95% 0.600-0.929) for CLIF-SOFA and 0.657 (IC 95% 0.471-0.844) for SOFA score

The AUROC for day-3 qSOFA in predicting 30-day mortality among patients initially classified as low risk was 0.820 (IC 95% 0.717-0.923). Among patients initially classified as low risk by day-1 qSOFA, the 30-day Kaplan-Meier survival probability was 87% in subjects without ACLF at day-3% and 48% among those with ACLF at day-3 ($P < 0.001$). Prognosis was better predicted by qSOFA at day 3, with 30-day Kaplan-Meier survival probability of 88% in subjects with qSOFA <2 and only 24% among those with qSOFA ≥2 (Figure 1C; $P < 0.001$). Although Sepsis-3 was not related to survival in the multivariate analysis, patients who fulfil Sepsis-3 criteria exhibited lower 30-day survival as compared to those who don't fulfil it (66% vs 85%, $P = 0.008$; Figure 1D). A subanalysis performed excluding cases of infections from sites with lower potential for poor outcomes (eight patients with gastroenteritis, one with otitis, and other with dental abscess) showed similar results (see Appendix S2).

3.3 | Suggested approach for patients with cirrhosis and bacterial infection without a baseline SOFA

Based on the data above, an adjustment on EASL algorithm, specifically for patients without a baseline SOFA, was proposed (Figure 3). The first step is to calculate qSOFA at admission. Patients classified as high risk (scores ≥2) exhibited low survival probability (~45%) and are better managed at ICU. A subset of patients initially classified as high risk by qSOFA, who present a CLIF-SOFA score <9 at admission may have relatively good 30-day survival (~82%) and could be initially observed outside ICU. However, this observation was based on a limited number of patients and requires further validation. On the other hand, patients with CLIF-SOFA or a SOFA score ≥9 are expected to have a poor outcome (survival <30%). In the case of qSOFA at admission <2, prognosis is highly related to progression to organ dysfunction. Patients should be carefully evaluated during the first 48 hours and promptly considered for ICU admission if qSOFA ≥2 (expected survival ~24%), development of ACLF (survival ~48%), or fulfilment of Sepsis-3 criteria (survival ~66%).

4 | DISCUSSION

Giving the recognised limitations of SIRS criteria, sepsis has been recently redefined, taking into account the relevance of organ dysfunction caused by dysregulated host response to infection.[8] The Sepsis Definitions Task Force recommended that organ dysfunction could be recognised as an increase ≥2 points in SOFA score and that the baseline SOFA score should be assumed to be zero unless the patient is known to have pre-existing (acute or chronic) organ dysfunction before the onset of infection.[8] This approach was sustained by EASL guidelines, even though the vast majority of patients with cirrhosis are expected to have baseline SOFA scores greater than 0 and SOFA scores at hospitalisation greater than 2. In fact, in the present study, none of infected patients

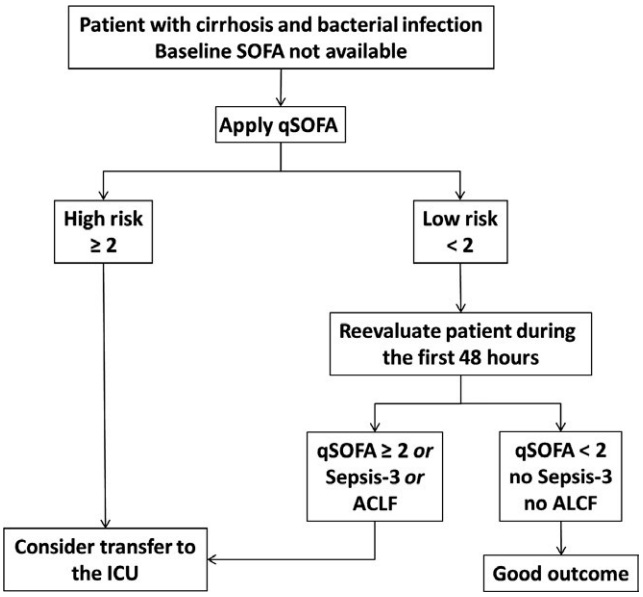

FIGURE 3 Suggested algorithm for defining severity of infection in patients recently hospitalised for acute decompensation of cirrhosis and without a baseline Sequential Organ Failure Assessment score

with cirrhosis exhibited SOFA score lower than 2 and, therefore, none of our patients would be classified as "good outcome" by the EASL algorithm. Also, in the original manuscript that proposed the algorithm, 94% of the patients without a baseline SOFA fulfilled Sepsis-3 criteria.[9] This indicates that, in the vast majority of cases, the EASL algorithm will rely on qSOFA score alone to define severity of infection in those patients without a baseline SOFA. With this approach, 80% of our patients would fall in the "grey zone," where the severity of infection could not be determined. Therefore, it seems that incorporation of Sepsis-3 criteria in the algorithm for initial evaluation of patients without baseline SOFA is of little use in real-world setting, as it will add complexity without increase the prognostic ability. Also, further refinement of the "low risk" category is necessary for clinical application of qSOFA as the majority of patients will fall into this group.

In the present study, "high risk" admission qSOFA was an independent predictor of 30-day mortality. Given that all infected patients with cirrhosis presented with SOFA score ≥2, Sepsis-3 criteria were not applicable at admission. In the Italian study that originally proposed the algorithm included in EASL guidelines, qSOFA was also independently related to mortality, along with Sepsis-3 criteria, CLIF-C AD score, and CRP.[9] However, Sepsis-3 criteria exhibited only slightly better discrimination ability than qSOFA for both in-hospital and 28-day mortality.[9] These results suggest that, in the setting of a patient admitted in emergency room where baseline SOFA will be probably unavailable, calculation of qSOFA is a good alternative with the advantage of been simple, fast, and independent of any laboratory test. Although related to prognosis in univariate analysis, SIRS criteria were not independent predictors of mortality in the present study. Similar results were observed in the Italian cohort, reinforcing the limitations of SIRS criteria and highlighting the relevance of organ dysfunction when defining severity of infection in cirrhosis.[9]

When evaluating factors related with mortality among patients classified as "high risk" by admission qSOFA, CLIF-SOFA was the only independent predictor. By using the best cut-off of CLIF-SOFA, 30-day survival probability was 82% in subjects with values <9 and only 27% among those with results ≥9. In the EASL algorithm, for those without baseline SOFA, a positive qSOFA is considered enough to define patients at high risk of poor outcome.[10] Based on our data, this is a reasonable approach as patients classified as "high-risk" qSOFA had 55% 30-day mortality. Nevertheless, prognosis was better defined by adding an additional step in the algorithm, and this could be very helpful in the emergency room setting, where questions about transferring patients to specialised centres or ICU are of great relevance. It should be pointed out, however, that this observation was made based on a limited number of subjects and further validation is required before any recommendation can be offered on CLIF-SOFA use among high risk qSOFA patients.

The majority of our patients were initially classified as "low risk" by qSOFA, even though their 30-day mortality was not negligible. A multivariate analysis to investigate predictors of mortality among patients initially classified as "low risk" including prognostic scores calculated at day-1 showed that only SOFA was independently associated with mortality. However, prognostic ability of SOFA calculate at day-1 was very limited (AUROC 0.679). In the EASL algorithm, the situation of patients without a baseline SOFA who presented with a SOFA score ≥2 (Sepsis-3 criteria) and a "low risk" qSOFA at admission is considered indeterminate and monitoring SOFA and qSOFA is empirically advised.[9,10] For that reason, we decided to investigate parameters evaluated at day-3, including Sepsis-3 criteria considering day-1 SOFA as baseline. This analysis showed that ACLF and qSOFA were independently related with mortality. Prognosis was better predicted by qSOFA at day 3, with 30-day Kaplan-Meier survival probability of 88% in subjects with qSOFA <2 and only 24% among those with qSOFA ≥2. Although Sepsis-3 was not related to survival in the multivariate analysis, patients who fulfil these criteria exhibited lower 30-day survival as compared to those who do not fulfil it (66% vs 85%). These results are in agreement with the current knowledge that severity of infection is closely related to organ dysfunction. For patients without high risk qSOFA at admission, monitoring parameters of organ dysfunction is of major relevance during the first days of hospitalisation.

Based on our data, we proposed adjustments in the EASL algorithm specifically for the case of absent baseline SOFA score (Figure 3). In these patients, assuming baseline SOFA score of 0 for applying Sepsis-3 criteria is of little help and will only increase complexity. Therefore, qSOFA can be used initially as the only criteria and, if indicates "high risk", high mortality is expected and the patient can be better managed in ICU setting. CLIF-SOFA can be used for further refinement of prognosis in subjects initially classified as high risk by qSOFA. However, this approach requires further validation. In case of "low risk" qSOFA, similarly to the original algorithm, we suggest follow-up of those patients. Although our protocol was predefined for day-3

evaluation, it is reasonable to advise a closer follow-up, especially for the first 3 days of hospitalisation. Based on our data, qSOFA is the recommended score to follow those subjects. However, any patient who fulfil Sepsis-3 criteria or develops ACLF during follow-up should also be considered at high risk of mortality and managed accordingly.

In conclusion, in this cohort of patients with cirrhosis hospitalised for bacterial infections, qSOFA was independently related to survival and appears to be a valuable tool for determining severity of infection. In the absence of a baseline SOFA, Sepsis-3 criteria are fulfilled by the vast majority of patients at first evaluation and, therefore, appear to have little potential as a prognostic marker. Patients initially classified as "low risk" are a heterogeneous group and monitoring of organ dysfunction is advised, especially during the first days of hospitalisation.

CONFLICT OF INTEREST

The authors do not have any disclosures to report.

ORCID

Janaína L. Narciso-Schiavon http://orcid.org/0000-0002-6228-4120

Leonardo L. Schiavon http://orcid.org/0000-0003-4340-6820

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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