Liver INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER

Liver International ISSN 1478-3223

CIRRHOSIS AND LIVER FAILURE

Single-centre validation of the EASL-CLIF Consortium definition of acute-on-chronic liver failure and CLIF-SOFA for prediction of mortality in cirrhosis

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Keywords
acute decompensation – acute-on-chronic liver failure – cirrhosis – organ failure

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Received 27 February 2014
Accepted 13 May 2014

DOI:10.1111/liv.12597

Abstract

Background & Aims: The idea of acute-on-chronic liver failure (ACLF) has emerged to identify those subjects with organ failure and high mortality rates. However, the absence of a precise definition has limited the clinical application and research related to the ACLF concept. We sought to validate the ACLF definition and the CLIF-SOFA Score recently proposed by the EASL-CLIF Consortium in a cohort of patients admitted for acute decompensation (AD) of cirrhosis. *Methods:* In this prospective cohort study, patients were followed during their hospital stay and thirty and 90-day mortality was evaluated by phone call, in case of hospital discharge. All subjects underwent laboratory evaluation at admission. *Results:* Between December 2010 and November 2013, 192 cirrhotic patients were included. At enrolment, 46 patients (24%) met the criteria for ACLF (Grades 1, 2 and 3 in 18%, 4% and 2% respectively). The 30-day mortality was 65% in ACLF group and 12% in the remaining subjects ($P < 0.001$). Logistic regression analysis showed that 30-day mortality was independently associated with ascites and ACLF at admission. The Kaplan–Meier survival probability at 90-day was 92% in patients without ascites or ACLF and only 22% for patients with both ascites and ACLF. The AUROC of CLIF-SOFA in predicting 30-day mortality was 0.847 ± 0.034, with sensitivity of 64%, specificity of 90% and positive likelihood ratio of 6.61 for values ≥9. *Conclusion:* In our single-centre experience the CLIF-SOFA and the EASL-CLIF Consortium definition of ACLF proved to be strong predictors of short-term mortality in cirrhotic patients admitted for AD.

Cirrhosis is usually characterized by a long-standing phase of compensated cirrhosis, followed by the occurrence of specific complications in about 60% of the patients after 10 years of the diagnosis (1). Once the patient has progressed to the decompensated phase, complications tend to accumulate and the survival is markedly reduced (2). Acute decompensation (AD) (i.e. ascites, hepatic encephalopathy, gastrointestinal bleeding) is the most common cause of hospitalization among patients with cirrhosis. However, it is a heterogeneous entity with different clinical presentations and variable prognosis.

Over the last few years, the concept of acute-on-chronic liver failure (ACLF) has emerged to identify those subjects with cirrhosis and an acute deterioration of liver function, either secondary to superimposed liver injury or because of extrahepatic precipitating factors such as infection (3). Although a precipitating event is usually present, it can be occasionally not clearly recognized (3, 4). ACLF is also characterized by a short-term mortality higher than expected for decompensated cirrhosis and by the progression to organ failure (3). While the underlying cirrhosis is not reversible, ACLF is considered a reversible component of acute deterioration with potential to recovery to the state the patient was in, prior to the acute event (3). Even though the general aspects of ACLF are vaguely defined, the absence of a precise definition has limited the clinical application and research related to the ACLF concept.

Recently, the EASL-Chronic Liver Failure (EASL-CLIF) Consortium proposed diagnostic criteria for ACLF based on analyses of 1343 patients with cirrhosis admitted for acute decompensation of the disease (5). The definition of ACLF was based on a modification of

the Sequential Organ Failure Assessment (SOFA), the Chronic Liver Failure-SOFA (CLIF-SOFA), and was divided into three ACLF grades (ACLF 1–3) according to the pattern and number of organ failures. By using this new classification, the authors reported a high prevalence of ACLF (22.6% at enrolment) and a strong association with mortality (51.2% at the third month) (5). Although the CANONIC study represents a landmark in efforts to understand and better define ACLF, there is still a need to validate its results. In addition, the severity and prognosis of AD (and also ACLF) episodes may differ across the countries and institutions depending on several factors including the availability of specialized personal, intensive care facilities and liver transplantation programs. So, we sought to validate the ACLF definition and the CLIF-SOFA score recently proposed by the EASL-CLIF Consortium in a cohort of patients admitted for AD of cirrhosis.

Methods

Patients

This is a cohort study that included consecutive subjects admitted to the emergency room of a Brazilian tertiary hospital because of AD of cirrhosis between December 2010 and November 2013. Patients in the following situations were excluded: hospitalization for elective procedures, admissions not related to complications of cirrhosis, hepatocellular carcinoma outside Milan criteria and doubtful diagnosis of cirrhosis. 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.

This 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.

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 within 24 h of admission by one of the researchers involved in this 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 the following tests were performed for this study: total leucocytes, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Gamma-glutamyltransferase (GGT), serum sodium, creatinine, international normalized ratio (INR), albumin, C-reactive protein (CRP), venous lactate and total bilirubin.

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) (6). Patients were followed during their hospital stay and thirty and 90-day mortality was evaluated by phone call, in case of hospital discharge. Ninety-day mortality rates were estimated as transplant-free mortality (patients who received a liver transplant were considered lost to follow-up).

Individuals with suspected infection at hospital admission were submitted to clinical examination to confirm this diagnosis and to establish the primary source of infection. The diagnosis of infection was made according the criteria of the Center for Diseases Control (7). 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 $\geq$250 neutrophils/mm^3 in the absence of intra-abdominal source of infection, regardless of negative culture (8). All patients with SBP received ceftriaxone plus weight-based intravenous albumin in the first and third day after the diagnosis. Hepatic encephalopathy was graded according to the West-Haven criteria (9) 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 stabilization. Suspicion of alcoholic hepatitis was based on clinical and laboratory data. Liver biopsy was not systematically performed in the present study for the diagnosis of alcoholic hepatitis. Severity of liver disease was estimated by the Child-Pugh classification system (10) and MELD (Model for End-Stage Liver Disease) (11) calculated based on laboratory tests performed on admission. The conventional SOFA score was calculated using the peripheral arterial oxygen saturation (SpO_2) to FIO2 ratio (SpO_2/FiO_2) as previously described (12).

CLIF-SOFA score and ACLF definition

The CLIF-SOFA is a modification of the original SOFA score and includes subscores ranging from 0 to 4 for each of six components (liver, kidneys, brain, coagulation, circulation and lungs), with higher scores indicating more severe organ impairment (5). Combined scores range from 0 to 24 and provide information on overall severity. In this study, the respiratory component was evaluated by the SpO_2/FiO_2 ratio.

Acute-on-chronic liver failure was defined according to the EASL-CLIF Consortium definition, as follows (5):

No ACLF: (i) patients with no organ failure; or (ii) patients with a single 'non-kidney' organ failure who had a serum creatinine level <1.5 mg/dl and no hepatic encephalopathy or (iii) patients with single cerebral failure who had a serum creatinine level <1.5 mg/dl.

ACLF grade 1: (i) patients with single kidney failure; or (ii) patients with single failure of the liver, coagulation, circulation or respiration who had a serum creatinine level ranging from 1.5 to 1.9 mg/dl and/or mild to moderate hepatic encephalopathy or (iii) patients with single cerebral failure who had a serum creatinine level ranging from 1.5 to 1.9 mg/dl.

ACLF grade 2: patients with two organ failures.

ACLF grade 3: patients with three organ failures or more.

The definition of organ failure was based on the CLIF-SOFA score and performed according to the original publication (5).

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. Multiple logistic regression analysis (forward stepwise regression) was used to investigate the factors independently associated with 30-day mortality. The survival curve was calculated using the Kaplan–Meier method and survival differences between groups were compared using the log-rank test. The performance of the CLIF-SOFA, SOFA, MELD and Child-Pugh score in predicting 30- and 90-day mortality was analysed by calculating the area under the receiver operating characteristics (AUROC) curves. Based on the ROC curves, the best cut-offs points were chosen. Comparisons of the ROC curves were performed by MedCalc software version 12.4 (MedCalc Software, Mariakerke, Belgium) using the technique described by DeLong *et al.* (13). All the remaining tests were performed by the SPSS software, version 17.0 (SPSS, Chicago, IL, USA). A *P*-value of <0.05 was considered statistically significant.

Results

Characteristics of the sample

Two hundred and seventy-seven admissions because of acute decompensation of cirrhosis were reported between December 2010 and November 2013. When evaluated based only on the most recent hospitalization, a total of 192 individuals composed the final sample of this study.

Table 1 exhibits the characteristics of the included patients. The mean age was 53.52 ± 11.48 years, 69% were caucasians, and male predominance was observed (73%). Previous history of cirrhosis decompensation was observed in 63.0% of the sample and 36.5% of subjects reported active alcoholism during the past month. The most common aetiology of cirrhosis was hepatitis C (41%) followed by alcohol abuse (36%) and cryptogenic (8%).

Upon admission, upper gastrointestinal bleeding was observed in 53% of cases, ascites in 49%, hepatic encephalopathy in 59% and bacterial infections in 26%. The most common bacterial infection was spontaneous bacterial peritonitis (10%) followed by pneumonia (5%), urinary tract infection (5%) and skin infections (2%). Twenty-eight patients (15%) were later transferred to the intensive care unit. None of the included patients underwent liver transplantation within 30 days and three patients underwent liver transplantation within 90 days of hospitalization.

Prevalence and factors associated with ACLF at enrolment

At admission, 46 patients (24%) fulfilled the criteria for ACLF. ACLF was classified as grade 1 in 34 patients (18%), grade 2 in 8 (4) and grade 3 in 4 individuals (2%). As detailed in Table 1, patients with ACLF admission showed a higher prevalence of ascites (70% vs. 43%, $P = 0.001$), hepatic encephalopathy (85% vs. 51%, $P < 0.001$), bacterial infections (50% vs. 19%, $P < 0.001$) and lower prevalence of upper gastrointestinal bleeding (39% vs. 57%, $P = 0.036$). As expected, ACLF was associated with higher median respiratory rate (20.00 breaths/min vs. 18.00 breaths/min, $P = 0.013$), higher mean heart rate (88.44 ± 18.10 bpm vs. 81.39 ± 18.58 bpm, $P = 0.026$) and lower median SpO_2/FiO_2 ratio (450.00 vs. 461.90, $P = 0.001$). No differences were observed between those who fulfilled the criteria and the remaining subjects regarding the aetiology of liver disease, alcohol abuse (previous or current) and mean arterial pressure.

Concerning laboratory variables, individual with ACLF at admission exhibited higher median leucocyte count (10.28 × 109/L vs. 7.23 × 10^9/L, $P < 0.001$), creatinine levels (2.15 mg/dl vs. 1.00 mg/dl, $P < 0.001$), INR (1.55 vs. 1.39, $P = 0.002$), CRP (39.60 mg/L vs. 7.75 mg/L, $P < 0.001$), venous lactate (2.30 mmol/L vs. 1.60 mmol/L, $P = 0.006$) and total bilirubin (3.40 mg/dl vs. 1.50 mg/dl, $P < 0.001$). Conversely, ACLF subjects showed lower mean sodium (131.39 ± 6.22 mEq/L vs. 136.27 ± 4.92 mEq/L, $P < 0.001$) and albumin levels (2.01 ± 0.54 g/dl vs. 2.47 ± 0.70 g/dl, $P < 0.001$) as compared to the remaining patients.

Table 1. Characteristics of included patients and factors associated with ACLF at enrolment

	All (n = 192)	No ACLF (n = 146)	ACLF (n = 46)	P
Age (years), mean ± SD	53.52 ± 11.48	53.66 ± 11.51	53.07 ± 11.50	0.761
Male Gender, *n* (%)	140 (73)	104 (71)	36 (78)	0.350
Aetiology of cirrhosis, *n* (%)				
Alcohol	70 (36)	49 (34)	21 (46)	0.137
Hepatitis C	78 (41)	61 (42)	17 (37)	0.561
Hepatitis B	8 (4)	5 (3)	3 (7)	0.400
Cryptogenic	15 (8)	13 (9)	2 (4)	0.529
Other	21 (11)	18 (12)	3 (7)	0.271
Previous decompensation, *n* (%)	121 (63)	90 (62)	31 (67)	0.481
Active alcoholism, *n* (%)	70 (37)	51 (35)	19 (41)	0.434
Complication at admission, *n* (%)				
Ascites	94 (49)	62 (43)	32 (70)	0.001
Hepatic encephalopathy	113 (59)	74 (51)	39 (85)	<0.001
Gastrointestinal bleeding	101 (53)	83 (57)	18 (39)	0.036
Bacterial infection	50 (26)	27 (19)	23 (50)	<0.001
Suspected alcoholic hepatitis, *n* (%)	17 (9)	11 (8)	6 (13)	0.247
Organ failures, *n* (%)				
Liver	14 (7)	5 (3)	9 (20)	0.001
Kidney	20 (10)	0 (0)	26 (57)	<0.001
Cerebral	17 (9)	7 (5)	10 (22)	0.001
Coagulation	3 (2)	0 (0)	3 (7)	0.013
Circulation	5 (3)	0 (0)	5 (11)	0.001
Lungs	4 (2)	0 (0)	4 (9)	0.003
Laboratory data				
Leucocyte count ($\times 10^9$), median	7.23	6.47	10.28	<0.001
Platelet count ($\times 10^9$), median	89.50	86.50	94.00	0.420
AST (U/L), median	70.00	68.00	76.50	0.177
ALT (U/L), median	52.00	54.00	47.50	0.493
GGT (U/L), median	138.50	138.00	178.00	0.325
Sodium (mEq/L), mean ± SD	135.09 ± 5.65	136.27 ± 4.92	131.39 ± 6.22	<0.001
Creatinine (mg/dl), median	1.10	1.00	2.15	<0.001
INR, median	1.41	1.39	1.55	0.002
Albumin (g/dl), mean ± SD	2.36 ± 0.69	2.47 ± 0.70	2.01 ± 0.54	<0.001
CRP (mg/L),median	10.00	7.75	39.60	<0.001
Lactate (mmol/L), median	1.70	1.60	2.30	0.006
Total bilirubin (mg/dl), median	2.00	1.50	3.40	<0.001
Child-Pugh score, mean ± SD	9.06 ± 2.02	8.58 ± 1.86	10.60 ± 1.74	<0.001
MELD score, mean ± SD	16.31 ± 6.50	13.79 ± 4.19	24.32 ± 6.03	<0.001

ACFL, acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, Gamma-glutamyltransferase; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; SD, standard deviation.

ACLF as a predictor of mortality

Overall 30-day and 90-day mortality was 25% and 30% respectively. The 30-day mortality was 65% in ACLF group and 12% in the remaining subjects ($P < 0.001$). When evaluated according to ACLF severity, the 30-day mortality was 53%, 100% and 100% in grades 1, 2 and 3 respectively ($P = 0.001$ for comparison of mortality between ACLF 1 vs. ACLF 2/3). Among the 17 subjects without ACLF who died, one presented with isolated liver failure (bilirubin ≥ 12.0 mg/dl) and three with cerebral failure (hepatic encephalopathy ≥ III). The remaining patients did not meet criteria for any other organ failures at admission.

Bivariate analysis (Table 2) showed that 30-day mortality was directly associated with active alcoholism (49% vs. 32%, $P = 0.041$), ascites (77% vs. 40%, $P < 0.001$), hepatic encephalopathy grades III or IV (23% vs. 4%, $P < 0.001$), bacterial infection (47% vs. 19%, $P < 0.001$), suspected alcoholic hepatitis (17% vs 6%, $P = 0.036$) and the presence of ACLF at admission (64% vs. 11%, $P < 0.001$). Thirty-day mortality was also related to higher median leucocyte count (8.06×10^9/L vs. 6.65×10^9/L, $P < 0.001$), creatinine (1.80 mg/dl vs. 1.00 mg/dl, $P < 0.001$), INR (1.57 vs. 1.38, $P < 0.001$), CRP (27.20 mg/L vs. 8.40 mg/L, $P < 0.001$), venous lactate (2.10 mmol/L vs. 1.55 mmol/L, $P = 0.007$), total bilirubin (3.10 mg/dl vs. 1.49 mg/dl, $P < 0.001$) and lower median SpO_2/FiO_2 ratio (442.86 vs. 461.90, $P < 0.001$), lower mean sodium (133.20 ± 6.75 mEq/L vs. 135.68 ± 5.15 mEq/L, $P = 0.027$) and albumin levels (2.00 ± 0.53 g/dl vs. 2.47 ± 0.70 g/dl, $P < 0.001$).

Logistic regression analysis to investigate factors independently associated with 30-day mortality was

Table 2. Factors associated with 30-day mortality among patients hospitalized for acute decompensation of cirrhosis

	Survivors (n = 145)	Deaths (n = 47)	P
Age (years), mean ± SD	53.56 ± 11.47	53.41 ± 11.63	0.940
Male Gender, *n* (%)	103 (71)	37 (78)	0.303
Aetiology of cirrhosis, *n* (%)			
Alcohol	49 (34)	21 (45)	0.178
Hepatitis C	61 (42)	17 (36)	0.474
Hepatitis B	6 (4)	2 (4)	1.000
Cryptogenic	14 (10)	1 (2)	0.122
Previous decompensation, *n* (%)	88 (61)	33 (70)	0.240
Active alcoholism, *n* (%)	47 (32)	23 (49)	0.041
Complication at admission, *n* (%)			
Ascites	58 (40)	36 (77)	<0.001
Hepatic encephalopathy	74 (51)	39 (83)	<0.001
Hepatic encephalopathy grade ≥ III	6 (4)	11 (23)	<0.001
Gastrointestinal bleeding	83 (57)	18 (38)	0.024
Bacterial infection	28 (19)	22 (47)	<0.001
Suspected alcoholic hepatitis, *n* (%)	9 (6)	8 (17)	0.036
Vital signs			
MAP (mmHg), mean ± SD	85.50 ± 15.00	80.54 ± 15.17	0.055
Heart rate (bpm), mean ± SD	81.37 ± 19.09	88.53 ± 16.23	0.024
SpO_2/FiO_2 ratio, median	461.90	442.86	<0.001
Laboratory data			
Leucocyte count ($\times 10^9$), median	6.65	8.06	0.008
Platelet count ($\times 10^9$), median	85.00	94.00	0.587
Sodium (mEq/L), mean ± SD	135.68 ± 5.15	133.20 ± 6.75	0.027
Creatinine (mg/dl), median	1.00	1.80	<0.001
INR, median	1.38	1.57	<0.001
Albumin (g/dl), mean ± SD	2.47 ± 0.70	2.00 ± 0.53	<0.001
CRP (mg/L),median	8.40	27.20	0.001
Lactate (mmol/L), median	1.55	2.10	0.007
Total bilirubin (mg/dl), median	1.49	3.10	<0.001
ACLF, *n* (%)	16 (11)	30 (64)	<0.001

ACFL, acute-on-chronic liver failure; bpm, beats per minute; CRP, C-reactive protein; INR, international normalized ratio; MAP, mean arterial pressure; SD, standard deviation.

performed including variables with P-value <0.02 in the bivariate analysis (leucocyte count, CRP, creatinine, INR, albumin, total bilirubin, SpO_2/FiO_2 ratio, ascites, infection and hepatic encephalopathy grades III or IV). As the definition of ACLF is based on several of those variables, the variable ACLF was not included in the regression analysis initially. The parameters that were independently associated with 30-day mortality were creatinine (OR 5.625, 95% CI 2.732–11.585, $P < 0.001$), INR (OR 7.705, 95% CI 1.922–30.898, $P = 0.004$) and SpO_2/FiO_2 ratio (OR 0.984, 95% CI 0.973–0.995, $P = 0.004$). As all these three variables are included in the definition of ACLF, we performed a new regression analysis including ACLF and the other parameters with P-value <0.02 in the bivariate analysis but excluding those variables that composed the ACLF definition (SpO_2/FiO_2 ratio, creatinine, INR, total bilirubin, hepatic encephalopathy grades III or IV). Therefore, this final analysis comprises the following parameters: ACLF, albumin, ascites, infection, leucocyte count and CRP. In this regression analysis, 30-day mortality was independently associated with the presence of ascites (OR 3.588, 95% CI 1.486–8.662, $P = 0.004$) and ACLF at admission (OR 11.001, 95% CI 4.701–25.745, $P < 0.001$).

Figure 1 exhibited the Kaplan–Meier curves for mortality during the follow-up period, according to the presence of ascites and ACLF. The Kaplan–Meier survival probability at 90-day was 92% in patients without ascites or ACLF, 69% for those with ascites only, 50% for those with ACLF only and 22% for patients with both ascites and ACLF. As compared to those without these complications, survival was significantly lower in patients with ascites ($P = 0.001$, long-rank test), ACLF ($P < 0.001$) or both ($P < 0.001$). Similarly, lower survival was observed for those with ACLF only (0.055) or with ACLF plus ascites (<0.001), as compared to patients with ascites only. No differences in survival was noted when those with ACLF only were compared to subjects with both ascites and ACLF ($P = 0.211$).

Performance of CLIF-SOFA in predicting short-term mortality

Thirty-day mortality was associated with higher CLIF-SOFA (9.49 ± 3.36 vs. 5.60 ± 2.26, $P < 0.001$), SOFA

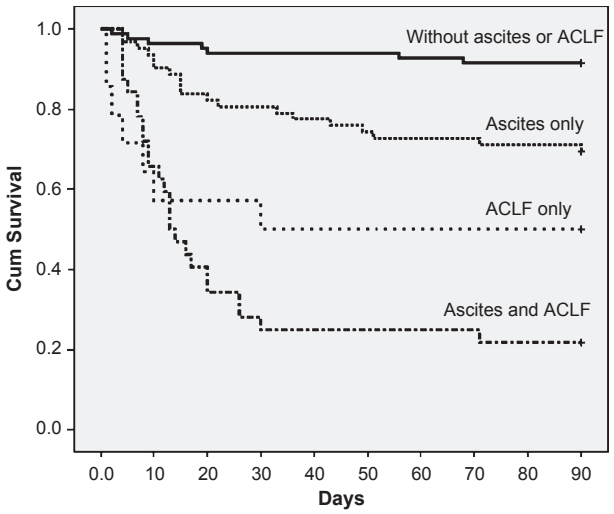

Fig. 1. Cumulative 90-day survival of patients with cirrhosis according to the presence of ascites and acute-on-chronic liver failure (ACLF) at admission. As compared to those without these complications, survival was significantly lower in patients with ascites ($P = 0.001$, long-rank test), ACLF ($P < 0.001$) or both ($P < 0.001$). Lower survival was also observed for those with ACLF only (0.055) or with ACLF plus ascites (<0.001), as compared to patients with ascites only.

(7.62 ± 3.40 vs. 4.70 ± 1.84, $P < 0.001$), MELD score (22.41 ± 6.88 vs. 14.33 ± 4.98, $P < 0.001$) and Child-Pugh score (10.72 ± 3.07 vs. 8.57 ± 1.83, $P < 0.001$). The performance of the models in predicting 30-day mortality was evaluated by ROC curves (Fig. 2). The

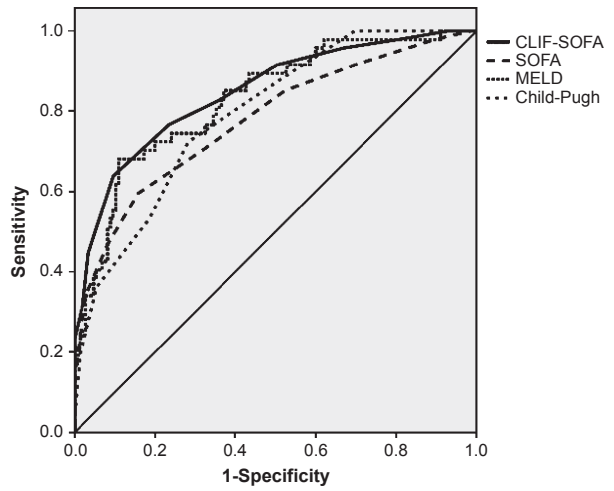

Fig. 2. ROC plot of Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA), SOFA, Model for End-stage Liver Disease (MELD) and Child-Pugh scores in predicting 30-day mortality among patients with cirrhosis. The area under the receiver operating characteristics (AUROCs) for CLIF-SOFA, SOFA, MELD and Child-Pugh were 0.847 ± 0.034, 0.782 ± 0.041, 0.829 ± 0.035 and 0.793 ± 0.035 respectively.

AUROCs for CLIF-SOFA, SOFA, MELD and Child-Pugh score in predicting 30-day mortality were 0.847 ± 0.034, 0.777 ± 0.042, 0.829 ± 0.035 and 0.793 ± 0.035 respectively. There were no statistical differences in comparison of the AUROCs of MELD vs. Child-Pugh score ($P = 0.289$), MELD vs. SOFA ($P = 0.210$) and MELD vs. CLIF-SOFA ($P = 0.627$), but significantly higher AUROC was observed for CLIF-SOFA as compared to SOFA ($P = 0.007$) and Child-Pugh score ($P = 0.044$).

Based on the ROC curve, cut-offs were chosen to predict 30-day mortality (Table 3). The best overall performance for the CLIF-SOFA was observed at a cut-off of 9. This value exhibited sensitivity and specificity of 64% and 90% respectively. Similarly, the best results for the MELD were observed at a cut-off point of 20. This value exhibited sensitivity and specificity of 66% and 89% respectively. Although the numbers are quite similar between the two models, CLIF-SOFA exhibited a higher positive likelihood ratio as compared to MELD (6.61 vs. 5.89). The conventional SOFA score at a cut-off of 6 showed sensitivity of 70% and specificity of 68%, with a positive likelihood ratio of 2.21. A poor performance was also observed for Child-Pugh score, with values ≥10 (Child-Pugh class C) showing sensitivity and specificity of 72%, and a positive likelihood ratio of 2.56.

Similar results were observed for 90-day mortality. The AUROCs for CLIF-SOFA, SOFA, MELD and Child-Pugh score were 0.847 ± 0.031, 0.789 ± 0.036, 0.855 ± 0.030 and 0.824 ± 0.031 respectively. Significantly higher AUROC was observed for CLIF-SOFA vs. SOFA ($P = 0.015$) and there was a trend towards higher AUROC for MELD vs. SOFA ($P = 0.068$). In general, the diagnostic performance for the four models in predicting 90-day mortality was similar to that observed for 30-day mortality (Table 3).

Discussion

Over the last decade, several studies were performed exploring clinical, evolutive and even therapeutics aspects of ACLF. However, these studies have been hampered by the absence of a scientifically oriented definition of ACLF. In this study, we validated the ACLF definition proposed by the EASL-CLIF consortium, investigating factors related to its presence at hospitalization and exploring its relationship with survival.

The prevalence of ACLF was 24.0% (grade 1 in 17.7%, grade 2 in 4.2% and grade 3 in 2.1%). These results are similar to those reported in the CANONIC study, where the prevalence of ACLF was 22.6% with a predominance of grade 1 ACLF (11.0%) (5). ACLF at admission was associated with several clinical and laboratory variables usually associated to more advanced liver disease and poor prognosis. These results are also similar to those reported in the original study and were expected, as the EASL-CLIF Consortium definition of ACLF was based on several of those variables.

Table 3. Performance of different prognostic models in predicting 30- and 90-day mortality using the optimal cut-off point

Prognostic model	Cut-off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR−
30-day mortality							
Clif-SOFA	≥9	64	90	68	89	6.61	0.40
SOFA	≥6	70	68	42	88	2.21	0.43
MELD score	≥20	66	89	66	89	5.98	0.38
Child-Pugh score	≥10	72	72	45	89	2.56	0.39
90-day mortality							
Clif-SOFA	≥9	59	93	77	84	7.80	0.45
SOFA	≥6	69	71	51	84	2.41	0.43
MELD score	≥20	64	93	79	85	8.48	0.39
Child-Pugh score	≥10	88	53	45	91	1.86	0.23

Clif-SOFA, Chronic Liver Failure- Sequential Organ Failure Assessment; LR+, likelihood ratio positive; LR−, likelihood ratio negative; MELD, Model for End-Stage Liver Disease; NPV, negative predictive value; PPV, positive predictive value.

Interestingly, in the present study gastrointestinal bleeding was inversely related to ACLF at admission. This was also the case in the CANONIC study, where ACLF was less common in patients admitted for gastrointestinal haemorrhage, although the difference did not reach statistical significance (5). Variceal bleeding has been associated with improved survival and lower organ failure scores in patients admitted in intensive care units (ICU) (14, 15). One possible explanation is that variceal bleeding in usually a very acute condition that leads patients to seek prompt medical care, avoiding delays in treatment. In addition, the prognosis of variceal bleeding has been markedly improved over the past decades, probably as a result of changes in management including aggressive resuscitation, use of vasoactive drugs and early endoscopic therapy (16).

The 30-day mortality was 65.2% in ACLF group (52.9%, 100% and 100% in ACLF grades 1, 2 and 3 respectively) and 11.6% in the remaining subjects. In the CANONIC study, the 28-day mortality among patients with ACLF was 33.9%, which is significantly lower than that reported here. One possible explanation for this is that we opted to evaluate the most recent hospitalization, which probably maximized 30-day mortality. This is supported by the fact that 90-day mortality among patients with ACLF was 69.9%, which is only slightly higher than the results observed for the 30-day. Another possible explanation would be delay in getting medical care in our country, which could result in late diagnosis and treatment of complications.

Logistic regression analysis showed that 30-day mortality was independently associated with higher creatinine and INR, and lower SpO_2/FiO_2 ratio. As all these three variables are included in the definition of ACLF, we subsequently performed a regression analysis including ACLF and the other parameters with *P*-value lower than 0.02. In this analysis, only the variables ACLF and ascites at admission remained independently related to 30-day mortality. These results were expected as the EASL-CLIF Consortium definition of ACLF was based on variables classically related to prognosis in cirrhotics and non-cirrhotics patients, and was developed with very restrictive thresholds for diagnosis of organ failure (5). Ascites is also an important prognostic marker in cirrhosis and in the context of acute decompensation is probably an indicator of more advanced liver disease (17, 18). Supporting our findings, the CANONIC study showed that ascites at enrolment was a risk factor for post-enrolment development of ACLF (5), probably reflecting the close relationship between the presence of ascites and the risk of renal failure in cirrhosis (19, 20). In the present study, the Kaplan–Meier survival probability at 90-day was 91.6% for those without ascites and ACLF at admission and only 21.9% for patients with both complications. Although no statistical difference was noted for the survival of those with ACLF alone in comparison with those with ACLF plus ascites, the presence of both complications was associated with very poor outcome. We believe that this data is of clinical significance and indicates a possible variable that deserves better exploration in future studies investigating prognostic factors in patients with AD of cirrhosis and ACLF. In addition, our results are in agreement with the data from the CANONIC study, indicating that ACLF is prevalent and strongly related to short-term mortality.

As expected, 30-day mortality was associated with higher CLIF-SOFA, MELD and Child-Pugh scores. The AUROC for CLIF-SOFA in predicting 30-day mortality was similar to that observed for the MELD score, but significantly higher than the AUROC of SOFA and Child-Pugh. Although detailed data regarding the performance of CLIF-SOFA in predicting short-term mortality was not provided in the CANONIC study, in the methods section the authors stated that the CLIF-SOFA was as accurate as MELD score and more accurate than the Child-Pugh score, with an AUROC of 0.831 which is very similar to our results (5). A recent article aimed to identify predictors of mortality in cirrhotic patients admitted in the intensive care unit analysed the performance of several prognostic scores, including CLIF-SOFA, in a subgroup of 306 patients admitted between 2005 and 2012 (21). The AUROC of CLIF-SOFA was

0.745 and was not significantly higher than the other models studied, including the MELD, SOFA and Child-Pugh scores (21). The discrepancy between the results from the British study and those reported here is probably related to methodological differences and by the fact that the former included only patients admitted in the ICU.

Based on ROC, values of CLIF-SOFA ≥ 9 exhibited the best overall performance in predicting 30-day mortality, with a sensitivity of 64% and specificity of 90%. Similar results were observed for MELD scores ≥20 (sensitivity and specificity of 66% and 89% respectively). Although these results are not superior to those observed for the commonly used and widely available MELD score, a higher positive likelihood ratio was observed for the CLIF-SOFA (6.61 vs. 5.89). On the other hand, the SOFA and Child-Pugh scores exhibited poor performances, with sensitivity and specificity of 72% for Child-Pugh class C, and sensitivity of 77% and specificity of 66% for SOFA score at a cut-off of 6. In addition, the SOFA and Child-Pugh scores showed positive likelihood ratios of only 2.27 and 2.56 respectively. Similar results were observed for 90-day mortality. It is important to point that the positive likelihood ratio tells us how much to increase the probability of event if the test is positive. Our results indicate that both CLIF-SOFA and MELD have good performance and are superior to the SOFA and Child-Pugh scores in the prediction of short-term mortality in the setting of AD of cirrhosis.

In conclusion, in our single-centre experience the EASL-CLIF Consortium definition of ACLF and the CLIF-SOFA proved to be strong predictors of short-term mortality in cirrhotic patients admitted for AD. The implementation of these new evidence-based definitions may improve the clinical care and facilitate new studies aimed at identifying innovative diagnostic and therapeutic strategies in ACLF.

Acknowledgements

Financial support: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

Conflict of interest: The authors do not have any disclosures to report.

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