Canadian Journal of Gastroenterology and Hepatology

Critical Care Issues in Liver Disease

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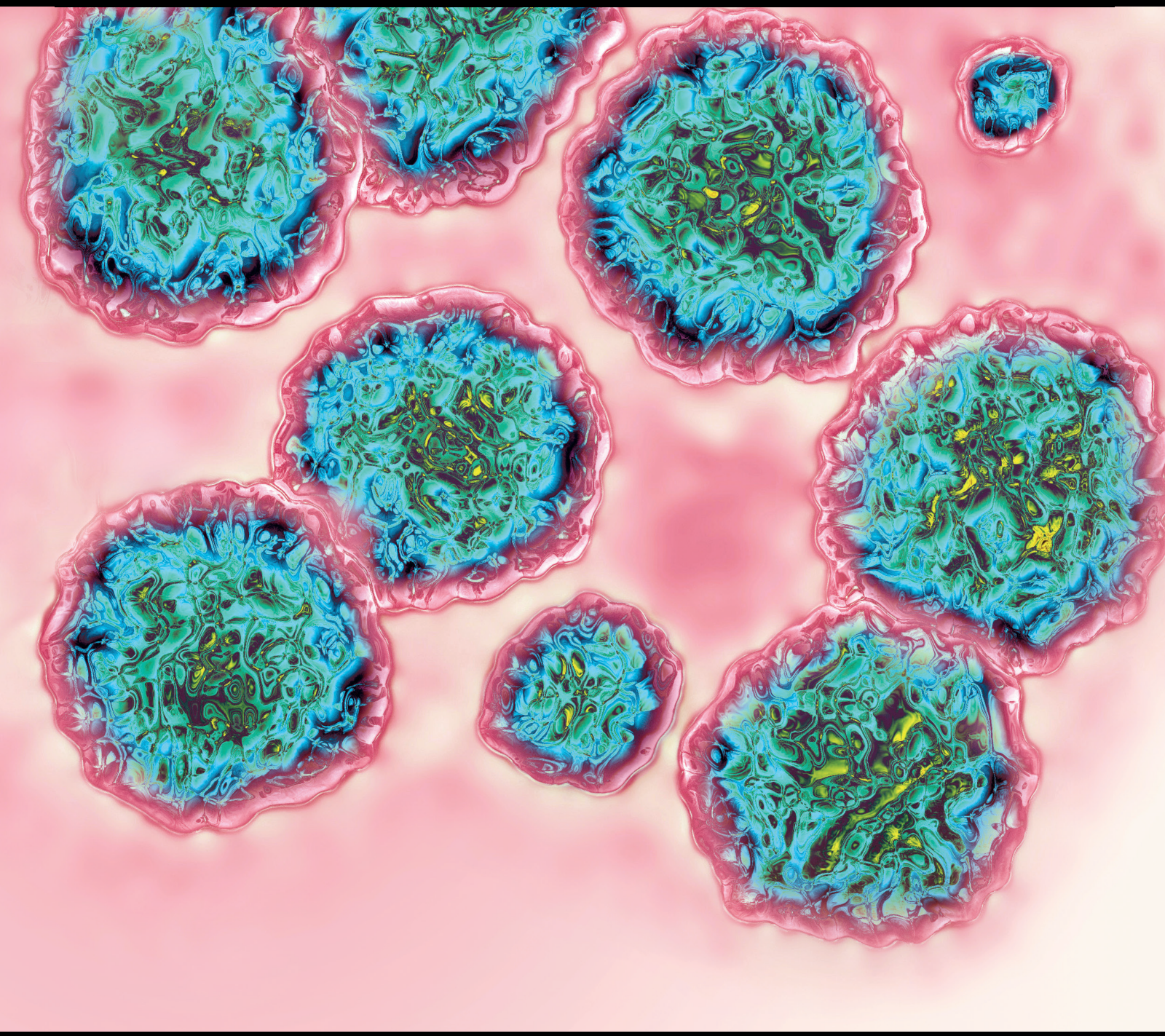

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Research Article

Abnormal Liver Tests during Hospitalization Predict Mortality in Patients with COVID-19: A Multicenter Study from South America

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Background. The role of liver function tests (LFT) as prognostic factors in patients admitted with COVID-19 has not been fully investigated, particularly outside resource-rich countries. We aimed at evaluating the prognostic value of abnormal LFT on admission and during hospitalization of patients with COVID-19. *Methods*. We performed a retrospective study that included 298 adult patients hospitalized for COVID-19, between 05/2020 and 02/2021, in 6 hospitals from 5 countries in South America. We analyzed demographic and comorbid variables and laboratory tests on admission and during hospitalization. LFT over twice the upper limit of normal (ALEx2) were also evaluated in relation to a variety of factors on admission and during hospitalization. De novo-ALEx2 was defined as the presence of ALEx2 at one week of hospitalization in patients without ALEx2 on admission. Patients were followed until hospital discharge or death. Multivariable analysis was used to evaluate the association between ALEx2 on admission and during hospitalization and mortality. *Results*. Of the total of 298 patients, 60% were male, with a mean age of 60 years, and 74% of patients had at least one comorbidity. Of those, 137 (46%) patients were transferred to the intensive care unit and 66 (22.1%) patients died during hospitalization. ALEx2 on admission was present in 87 (29.2%) patients and was found to be independently associated with 1-week mortality (odds ratio (OR) = 3.55; 95% confidence interval (95%CI) 1.05–12.05). Moreover, 84 (39.8%) out of 211 patients without ALEx2 at admission developed de novo-ALEx2, which was independently associated with mortality during second week of hospitalization (OR = 6.09; 95%CI 1.28–29) and overall mortality (OR = 2.93, 95%CI 1.05–8.19). *Conclusions*. A moderate elevation of LFT during admission was associated with a poor short-term prognosis in patients hospitalized with COVID-19. In addition, moderate elevation of LFT at one week of hospitalization was an independent risk factor for overall mortality in these patients.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes coronavirus disease 2019 (COVID-19), which is a rapidly emerging disease that has led to a pandemic of proportions never before seen in modern times. Furthermore, the global mortality associated with the virus has advanced at an unprecedented rate in different regions of the world. Multiple studies have identified several prognosis factors during COVID-19, including age greater than 60 years and comorbidities such as diabetes, cardiovascular disease, or obesity [1, 2]. However, scarce prognostic information is available from populations from South America, a region experiencing a significant impact related to COVID-19 pandemic [3, 4].

SARS-CoV-2 infection presents a significant heterogeneity in its clinical course, ranging from asymptomatic presentations to life-threatening disease such as acute respiratory distress syndrome or multiple organ failure [5]. A great number of infected patients, mainly those critically ill with SARS-CoV-2, present gastrointestinal manifestations, particularly acute alteration of liver function [6, 7]. Several studies have shown that patients with COVID-19 have evidence of liver damage on admission for hospitalization (ranging from 14% to 53%), expressed mainly by abnormal levels of liver transaminases but also by slightly elevated bilirubin levels [8]. In cases of severe COVID-19, the incidence of liver injury can reach 93%, indicating a possible association between COVID-19-related liver disease and mortality [9]. However, there is little information available related to modifications of liver function tests (LFT) during hospitalization and their role as a marker of severity in patients with severe COVID-19 [10].

The aim of the present study was to assess the impact of SARS-CoV-2 infection on LFT on admission and during hospitalization, as well as the prognostic role of abnormal LFT in hospitalized patients with COVID-19 in South America.

2. Methods

A multicenter and retrospective study was performed in order to describe adult patients hospitalized for COVID-19 between 05/2020 and 02/2021 in 6 hospitals from Argentina, Ecuador, Brazil, Peru, and Colombia. Approval was obtained from each institutional review board from all participating centers. A waiver of informed consent was granted for this study, considering its retrospective design.

2.1. Study Population. Patients were included if they were ≥18 years old at the time of hospitalization and were admitted with SARS-CoV-2 infection confirmed by the real-time polymerase chain reaction (RT-PCR) according to the site-specific protocol and if LFT were evaluated on admission. Patients admitted for other causes, but who were then later diagnosed with SARS-CoV-2 infection during hospitalization or had asymptomatic presentations with positive RT-PCR testing, were excluded. Patients who were pregnant at the time of diagnosis and patients with incomplete medical records were also excluded. All patients were followed until discharge or death.

2.2. Variables. Demographics, clinical information, routine and inflammatory laboratory markers, comorbidities, and radiological studies were evaluated at the moment of admission. Etiology of those patients with diagnosis of liver disease was assessed according to history or prior virologic markers. Also, autoimmune liver diseases were excluded according to history or evaluation of autoantibodies during admission [11–13]. Information about medications taken in the 10 days previous to admission was also analyzed.

During hospitalization, data related to admission to intensive care unit (ICU), use of vasopressor drugs (use of vasopressors >12 hours), requirement for mechanical ventilation, length of stay in ICU, length of hospitalization, and mortality were evaluated. LFT, blood count, kidney function tests, and inflammatory markers at 1 week of hospitalization were also evaluated when available.

To assess the impact of abnormal LFT on admission, patients included in the study were categorized into two groups, according to the presence or not of a moderate abnormal value of any LFT >2 times over the upper limit of normal (ULN) on admission (group ALEx2). Thus, we defined ALEx2 as the elevation of at least one of the following: total bilirubin (TBil), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) values to levels greater than twice the ULN value. ULN was taken as the reference value from each participating center.

During hospitalization, de novo-ALEx2 was defined as the occurrence of ALEx2 at 1 week of hospitalization in patients without ALEx2 at admission. Persistent-ALEx2 was defined as the persistence of ALEx2 at 1 week of hospitalization in patients with ALEx2 at admission.

The primary endpoint evaluated was overall mortality. As admission variables may have a different impact during the course of COVID-19 hospitalization, mortality was also evaluated at 1 and 2 weeks after admission.

2.3. Statistical Analysis. Continuous variables were expressed as mean and standard deviation, or as median and interquartile range (IQR), according to their homogeneity. Categorical variables were expressed as number and percentage and were compared using the chi-square test or Fisher's exact test according to the expected frequencies. Continuous variables were compared with the *T* test or the Mann–Whitney test, according to their homogeneity. Values were expressed as odds ratio (OR) and a 95% confidence interval (95% CI). A multivariable logistic regression was used to evaluate the association between ALEx2 and mortality. We first fitted univariate models to evaluate crude effects on mortality related to different variables, including age, sex, comorbidities, clinical and laboratory findings on

admission, and LFT at 1 week of hospitalization. We constructed final multivariable models, including variables with a P value <0.1 in univariate analysis, at 1 and 2 weeks and the overall mortality, respectively. A probability value < 0.05 was used to define statistical significance. The statistical analysis was performed with the statistical software IBM SPSS version 24 (SPSS inc, Armonk, NY.).

3. Results

3.1. Characteristics of the Study Population. During the study period, 337 adult inpatients with confirmed COVID-19 were identified. Of these, 39 had no data relating to LFT at admission and were excluded. Therefore, a total of 298 patients were included in the final analysis. The mean patient age was 60 ± 16 years, and 60% of these individuals were male (Table 1). In all, 74% of patients had at least one comorbidity, with cardiovascular disorders being the most common (24%), followed by obesity (19%) and diabetes (14%). Twenty-one patients (7%) had a history of chronic liver disease, among which 17 of these had nonalcoholic fatty liver disease (NAFLD), 3 had alcoholic liver disease, and 2 had untreated HCV infection (one patient also had alcoholic liver disease). Three patients (1%) had a history of cirrhosis. No patients had history of autoimmune liver disease and 11 patients had history of negative autoantibodies prior to admission. During hospitalization autoantibodies tests were performed in 6 patients and all results were negative. Table 1 describes the medications taken in the 10 days prior to admission. About half of the patients took potentially hepatotoxic medications, including antibiotics (34%), acetaminophen (16%), nonsteroidal anti-inflammatory drugs (NSAIDs, 8%), and statins (7%). The most frequent symptoms of COVID-19 during admission were dyspnea (74%), fever (65%), cough (59%), diarrhea (17%), nausea/vomiting (7%), and abdominal pain (8%). Time from symptoms onset to admission was 7 days (IQR 4–10). The most common radiological findings were bilateral pulmonary infiltrate/consolidation (83%) (Table 1).

3.2. Characteristics of Patients with ALEx2 at Admission. During admission, 87 (29.2%) out of 298 patients presented ALEx2. The main characteristics of patients with or without ALEx2 are described in Table 1. Patients without ALEx2 showed a higher rate of comorbidities (77% vs. 65%; $P = 0.036$). No significant differences were found for any specific comorbidity, although there was a trend for a higher rate of chronic liver disease in patients with ALEx2 (11% vs. 5%; $P = 0.054$). NAFLD also tended to be more frequent in patients with ALEx2 (9% vs. 4%; $P = 0.095$). No association was found between ALEx2 and medications taken in the previous 10 days prior to admission. Patients with ALEx2 presented similar symptoms at admission when compared to those without ALEx2. However, the time from symptoms onset to hospitalization was longer in the group of patients with ALEx2 (7 days (IQR 5–10) vs. 6 days (IQR 3–9), $P = 0.017$). Similarly, patients with ALEx2 had higher levels of D-dimer, lactate dehydrogenase, ferritin, and neutrophils/lymphocytes ratio and a lower platelet count at admission (Table 1). White blood cells (WBC) count, C-reactive protein, hemoglobin, albumin, and procalcitonin on admission were similar in both groups of patients. Concerning thoracic radiological findings at admission, bilateral infiltrate/consolidation was more frequent in patients with ALEx2 (91% vs. 80%, $P = 0.02$). Liver imaging studies were available only in 34 (11.4%) patients during hospitalization (15 in the group of ALEx2 and 19 in those without ALEx2). Changes in liver homogeneity were present in 13 patients with ALEx2 and in 15 patients without ALEx2, and ascites was observed in 2 patients with ALEx2 and in one patient without ALEx2.

3.3. Clinical Course of COVID-19 and Admission to ICU. A total of 230 (77.2%) patients were discharged and 66 (22.1%) patients died during hospitalization, with the median time from admission to death being 17 days (IQR 11–25.8). Fifty (75.8%) out of 66 patients who died did so within 3 weeks of hospitalization, and the remaining 16 (24.2%) patients died between 25 and 59 days after admission. During their hospital stay, 137 (46%) patients were transferred to the ICU, with 65 (21.8%) requiring vasopressors. A total of 99 (33%) patients required mechanical ventilation, with a median length on mechanical ventilation of 14 days (IQR 8–19). The median length of ICU admission was 13 days (IQR 6–20.8) and the median global length of hospitalization was 13 days (IQR 7–22).

3.4. ALEx2 at Admission: Clinical Course during Hospitalization. The proportion of patients transferred to the ICU, requirement for vasopressors, and the need of mechanical ventilation during hospitalization were similar in those with or without ALEx2 (Table 2). Overall mortality was also similar in both groups (24 vs. 22%). However, mortality during the first week of admission was higher in patients with ALEx2 (9% vs. 3%, $P = 0.031$). The median time from admission to death was shorter in patients with ALEx2 (11 days (IQR 5–18) vs. 18 days (IQR 13–30), $P = 0.034$). Finally, the length of ICU hospitalization was similar in both groups, but the overall length of hospitalization tended to be longer in patients without ALEx2 (14 days (IQR 7–23.5) vs. 11 days (IQR 7–20), $P = 0.055$).

3.5. ALEx2 during Hospitalization: Characteristics and Clinical Course. A total of 42 (48.3%) out of 87 patients with ALEx2 upon admission continued with abnormal LFT >2 times UNL (persistent-ALEx2 group). On the other hand, 84 (39.8%) out of 211 patients developed de novo-ALEx2. Patients with or without persistent-ALEx2 presented a similar need of ICU admission (50% vs. 49%, $P = 0.2$), requirement for mechanical ventilation (41% vs. 51%, $P = 0.23$), and use of vasopressors (29% vs. 32%, $P = 0.78$). Similarly, patients with or without de novo-ALEx2 presented a similar need of ICU admission (58% vs. 42%, $P = 0.8$), need for mechanical ventilation (49% vs. 48%, $P = 0.93$), and use of vasopressors (28% vs. 34%, $P = 0.47$).

Table 1: Clinical and laboratory characteristics of patients hospitalized for COVID-19 at the moment of admission.

Variable	Total ($n = 298$)	No ALEx2 ($n = 211$)	ALEx2 ($n = 87$)	P value
Age (years), mean (SD)	59.7 (15.7)	60.3 (16.4)	58.2 (14)	0.26
Gender (male), *n* (%)	178 (59.7)	114 (54)	64 (73.6)	0.002
Comorbidities, *n* (%)	220 (73.8)	163 (77.3)	57 (65.5)	0.036
Cardiovascular, *n* (%)	70 (23.5)	52 (24.6)	18 (20.7)	0.46
Pulmonary, *n* (%)	34 (11.4)	27 (12.8)	7 (8)	0.24
Kidney, *n* (%)	22 (7.4)	16 (7.6)	6 (6.9)	0.84
Obesity (BMI>35), *n* (%)	56 (18.8)	41 (19.4)	15 (17.2)	0.66
Diabetes, *n* (%)	42 (14.1)	30 (14.2)	12 (13.8)	0.92
Immunosuppression, *n* (%)	15 (5)	10 (4.7)	5 (5.7)	0.72
Chronic liver disease, *n* (%)	21 (7)	11 (5.2)	10 (11.5)	0.054
NAFLD, *n* (%)	17 (5.7)	9 (4.3)	8 (9.2)	0.095
Alcoholic, *n* (%)	3 (1)	2 (0.9)	1 (1.1)	0.87
Hepatitis C, *n* (%)	2 (0.7)	2 (0.9)	0 (0)	0.36
Cirrhosis, *n* (%)	3 (1)	1 (0.5)	2 (2.3)	0.43
Medications at admission, *n* (%)	148 (50)	106 (50.7)	42 (48.2)	0.70
NSAID, *n* (%)	25 (8.4)	19 (9)	6 (6.9)	0.55
Statins, *n* (%)	22 (7.4)	18 (8.5)	4 (4.6)	0.24
Antibiotics, *n* (%)	101 (33.9)	69 (32.7)	32 (36.8)	0.5
Acetaminophen, *n* (%)	48 (16.1)	35 (16.6)	13 (14.9)	0.73
Other, *n* (%)	64 (21.5)	46 (21.8)	18 (20.7)	0.83
Active smoker, *n* (%)	39 (14.1)	30 (15.1)	9 (11.5)	0.45
Symptoms				
Fever (38°C), *n* (%)	195 (65.4)	139 (65.9)	56 (64.4)	0.8
Dyspnea, *n* (%)	219 (73.5)	152 (72)	67 (77)	0.38
Cough, *n* (%)	177 (59.4)	119 (56.4)	58 (66.7)	0.1
Diarrhea, *n* (%)	50 (16.8)	34 (16.1)	16 (18.4)	0.63
Nausea/vomiting, *n* (%)	22 (7.4)	17 (8.1)	5 (5.7)	0.49
Abdominal pain, *n* (%)	23 (7.7)	17 (8.1)	6 (6.9)	0.73
Others, *n* (%)	138 (46.3)	103 (48.8)	35 (40.2)	0.18
Time from symptoms to hospitalization (days), median (IQR)	7 (4–10)	6 (3–9)	7 (5–10)	0.017
Hemoglobin (g/L), median (IQR)	13.9 (12.4–15)	13.7 (12.3–15)	14.2 (12.9–15.1)	0.14
WBC ($x10^9$/L), median (IQR)	7.8 (5.6–11.4)	7.8 (5.4–11.2)	7.7 (6.2–12.5)	0.57
Neutrophils/lymphocytes ratio	5.9 (3.4–10.6)	5.6 (3.2–10)	7.4 (4.3–12.1)	0.036
Platelets ($x10^9$/L), median (IQR)	221 (164–280)	226.5 (166–294)	201.5 (145.8–265.3)	0.033
Glucose at admission (mg/dL), median (IQR)	123 (105–160.3)	125 (106–163)	119 (103–152)	0.51
C-reactive protein (mg/L), median (IQR)	16.3 (6.3–82)	15 (5.5–79)	18.4 (6.9–87.5)	0.44
Procalcitonin (mg/L), median (IQR)	0.15 (0.08–0.35)	0.16 (0.09–0.48)	0.15 (0.07–0.3)	0.69
INR, median (IQR)	1.07 (1–1.17)	1.06 (1–1.18)	1.07(1–1.17)	0.85
D-dimer (mg/L), median (IQR)	0.71 (0.33–2.12)	0.64 (0.29–1.8)	0.75 (0.42–4.4)	0.08
Ferritin (mg/L), median (IQR)	842 (509–1644)	800 (446–1262)	1127 (618–2522)	0.004
LDH (U/L), median (IQR)	396 (294–539)	371 (289–514)	454 (321–594)	0.022
AST (U/L), median (IQR)	41 (28–63)	35.5 (24.5–48)	74 (49–99)	<0.001
ALT (U/L), median (IQR)	42 (27–68.5)	35 (23–49)	93 (61–127)	<0.001
GGT (U/L), median (IQR)	50.5 (34–100.5)	43 (28–56)	142 (105–209)	<0.001
ALP (U/L), median (IQR)	86.5 (69–119)	80 (65.3–104.3)	108.5 (78–152.8)	<0.001
Total bilirubin (mg/dL), median (IQR)	0.53 (0.39–0.87)	0.49 (0.31–0.71)	0.63 (0.41–1.2)	<0.001
Direct bilirubin (mg/dL), median (IQR)	0.29 (0.19–0.47)	0.22 (0.17–0.38)	0.39 (0.23–0.7)	<0.001
Albumin (g/dL), median (IQR)	3.7 (3.2–4.1)	3.8 (3.3–4.1)	3.6 (2.9-4-2)	0.29
Serum creatinine (mg/dL), median (IQR)	0.87 (0.69–1.09)	0.85 (0.69–1.08)	0.87 (0.69–1.1)	0.97
Sodium (mEq/L), median (IQR)	137 (134–140)	137 (134–140)	137 (134–140)	0.98
Potassium (MEq/L), median (IQR)	4.03 (3.7–4.43)	4 (3.7–4.4)	4.18 (3.7–4.6)	0.31
Radiological findings at admission				
Unilateral infiltrate, *n* (%)	28 (9.4)	25 (11.8)	3 (3.4)	0.024
Bilateral infiltrate/consolidation, *n* (%)	247 (82.9)	168 (79.6)	79 (90.8)	0.02

ALEx2, abnormal liver enzymes >2 times over the upper limit of normal; BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; NSAID, nonsteroidal anti-inflammatory drug; IQR, interquartile range; WBC, white blood cells; INR, international normalized ratio; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.

Table 2: Clinical course of patients hospitalized for COVID-19.

Variable	No ALEx2 ($n = 211$)	ALEx2 ($n = 87$)	P value
Transfer to ICU, *n* (%)	99 (47.1)	38 (43.7)	0.59
Vasopressors use, *n* (%)	45 (21.8)	20 (23.3)	0.8
Need for mechanical ventilation, *n* (%)	72 (34.1)	27 (31)	0.61
Length of mechanical ventilation (days), median (IQR)	15 (8–24.8)	13 (7.5–16.5)	0.11
Length of ICU admission (days), median (IQR)	13 (6–23.5)	12 (5–16.8)	0.13
Length of hospitalization (days), median (IQR)	14 (7–23.5)	11 (7–20)	0.055
Mortality			
Days 0–7, *n* (%)	6 (2.8)	8 (9.2)	0.031
Days 8–14, *n* (%)	9 (4.4)	4 (5.1)	0.85
Days 15–21, *n* (%)	16 (8.2)	7 (9.4)	0.91
Days 22–28, *n* (%)	2 (1.1)	1 (1.5)	0.63
Days 29–60, *n* (%)	12 (6.7)	1 (1.5)	0.15
Overall, *n* (%)	45 (21.5)	21 (24.1)	0.62

ALEx2, abnormal liver enzymes >2 times over the upper limit of normal; ICU, intensive care unit; IQR, interquartile range.

Age, sex, and comorbidities, including chronic liver disease, were similar in patient with or without de novo-ALEx2. In addition, routine and inflammatory markers such as C-reactive protein, procalcitonin, ferritin, and D-dimer on admission and at one week of hospitalization were similar in patients with or without de novo-ALEx2. The patterns of the abnormal LFT in patients with ALEx2 at admission and de novo-ALEx2 are shown in Table 3. AST and ALT were the most frequently altered LFT at both time points.

3.6. Predictors of COVID-19-Associated Mortality during the First and Second Weeks and Overall Hospitalization. We performed a multivariate logistic regression analysis to evaluate the role of ALEx2 (on admission and during hospitalization) as an independent factor associated with mortality during different periods of hospitalization. After including significant variables in the univariate analysis and adjusting for age, gender, comorbidities, and WBC count at admission, ALEx2 at admission was found to be independently associated with 1-week mortality (OR = 3.55; 95% CI 1.05–12.05; $P = 0.042$) (Table 4). When mortality during the second week of hospitalization was evaluated and after including significant variables in the univariate analysis and adjusting for age, gender, and comorbidities, de novo-ALEx2 was identified as an independent risk factor for mortality (OR = 6.09; 95% CI 1.28–29; $P = 0.022$) (Table 4). In the final model evaluating overall mortality, after including all significant variables in the univariate analysis and adjusting for age, gender, comorbidities, active smocking, and WBC count at one week of hospitalization, de novo-ALEx2 was also found to be an independent risk factor for mortality (OR = 2.93; 95% CI 1.05–8.19; $P = 0.04$) (Table 4).

4. Discussion

In the present study, which analyzed data obtained from several hospitals in South America, we found that the moderate alteration of LFT at admission was a factor associated with a worse short-term prognosis in patients with COVID-19. In addition, we showed that the de novo alteration of LFT at one week of hospitalization was an independent risk factor for overall mortality in patients hospitalized for COVID-19.

Moderately (2–5 times the ULN) abnormal LFT at admission have been reported in 4–32% of patients hospitalized for COVID-19, and a more severe course during hospitalization has been observed in these patients [7, 9, 14–16]. In the present study ALEx2 at admission was observed in one-third of patients admitted for COVID-19, with a small proportion of these patients presenting a history of chronic liver disease. We verified that this group of patients presented a higher mortality during the first week of hospitalization than those without this biochemical alteration, an association which was independent of age and associated comorbidities including cardiovascular and chronic liver disease. Moreover, the period of time between admission and death was shorter in patients with ALEx2. However, in contrast to other studies, we detected a similar rate of overall mortality for patients with or without ALEx2 at admission [16–18]. This finding is possibly related to the influence of a higher percentage of comorbidities in the group of patients without ALEx2, which was associated with a severe course of COVID-19 in prior studies [5, 15, 16]. The observation that comorbidities were less common in patients with ALEx2 at admission in the present study reinforces their role as independent initial marker for worse short-term outcome.

A variety of factors present prior to hospitalization may be related to abnormal LFT on admission, with previous studies highlighting age, male sex, and comorbidities, including hypertension, obesity, and chronic liver disease [16, 18–20]. In our study, only male sex was associated with ALEx2 on admission, and a lower percentage of comorbidities was present in this group. Some prior studies have shown that the use of different medications before admission may be related to abnormal LFT at admission [9, 16]. However, we observed that the medication use during the 10 days prior to hospitalization was similar in patients with or without ALEx2 on admission, indicating that drug-induced liver injury may not be the main reason for abnormal LFT at admission in the present cohort [9].

We also observed that the presence of de novo-ALEx2 at one week of hospitalization was related to mortality during

Table 3: Distribution of abnormal liver enzymes at admission and at 1 week of hospitalization.

Liver enzyme	Patients with ALEx2 at admission ($n = 87$)	Patients with de novo-ALEx2 ($n = 84$)
AST > 2UNL, *n* (%)	59 (67.8)	67 (79.8)
ALT >2 UNL, *n* (%)	46 (52.9)	45 (53.6)
TBil >2 UNL, *n* (%)	6 (6.9)	8 (9.5)
ALP >2 UNL, *n* (%)	8 (9.2)	11 (13.1)
GGT >2 UNL, *n* (%)	32 (36.2)	13 (15.5)

ALEx2, abnormal liver enzymes >2 times over the upper limit of normal; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBil, total bilirubin; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.

Table 4: Multivariate logistic regression evaluating risk factors for death associated with COVID-19 during different periods of hospitalization.

Variable	First week (days 0–7)		Second week (days 8–14)		Overall hospitalization	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Age (years)	1.04 (1.002–1.08)	—	1.08 (1.04–1.12)	—	1.05 (1.03–1.07)	—
Gender (male)	2.57 (0.7–9.41)	—	2.1 (0.7–6.7)	—	1.57 (0.86–2.85)	—
Cardiovascular comorbidity	4.77 (1.59–12.28)	8.65 (2.37–31.62)	6.17 (2.16–17.7)	9.53 (2.17–41.9)	3.75 (2.08–6.75)	3.1 (1.14–8.45)
Obesity (BMI>35)	1.06 (1.03–1.1)	—	3.63 (0.47–28.1)	—	2.87 (1.17–7.02)	—
Diabetes	1.02 (0.2–4.71)	—	0.86 (0.19–3.9)	—	1.1 (0.49–2.43)	—
Chronic liver disease	4.3 (1.03–15.75)	7.17 (1.51–34.16)	1.76 (0.48–6.4)	—	4.25 (1.72–10.5)	4.25 (0.95–19)
Time from symptoms to hospitalization (days)	0.99 (0.97–1.02)	—	0.98 (0.96–0.99)	—	0.99 (0.97–1.01)	—
Active smoker	11.35 (0.29–6.62)	—	1.44 (0.39–5.31)	—	2.7 (1.3–5.46)	6.45 (1.98–21)
WBC count (x109/L) on admission	1.15 (1.07–1.24)	1.17 (1.08–1.28)	1 (0.91–1.1)	—	1.07 (1.02–1.12)	—
WBC count (x109/L) at 1 week from admission	—	—	1.1 (0.95–1.17)	—	1.1 (1.04–1.18)	1.13 (1.04–1.23)
ALEx2 at admission	4.75 (1.55–14.62)	3.55 (1.05–12.05)	0.8 (0.25–2.5)	—	1.11 (0.62–2)	—
De novo-ALEx2 at 1 week after admission	—	—	6.3 (1.53–25.9)	6.09 (1.28–29)	2.79 (1.21–6.43)	2.93 (1.05–8.19)
Persistent-ALEx2 at 1 week after admission	—	—	9.57 (1.12–81.9)	4.98 (0.53–46.7)	3.24 (1.18–8.87)	3.73 (0.91–15.37)
Neutrophils/lymphocytes ratio	1.05 (1.01–1.08)	—	1 (0.95–1.05)	—	1.02 (0.99–1.05)	—
C-reactive protein (mg/L)	1 (0.99–1.003)	—	1 (0.99–1.01)	—	1.004 (1.001–1.006)	—
Procalcitonin (mg/L)	1.003 (0.91–1.09)	—	0.99 (0.91–1.09)	—	1.005 (0.97–1.05)	—
Serum creatinine (mg/dL)	1.22 (0.96–1.57)	—	1.37 (1.09–1.71)	—	1.24 (1.01–1.5)	—
Bilateral consolidation at admission	0.75 (0.2–2.77)	—	0.31 (0.04–2.4)	—	2.15 (1.12–4.13)	—

ALEx2, abnormal liver enzymes >2 times over the upper limit of normal; BMI, body mass index; WBC, white blood cells.

the second week of hospitalization and to overall mortality. A previous study that evaluated LFT during hospitalization demonstrated that patients with de novo-liver test abnormalities presented a trend for a higher requirement of ICU admission or death [21]. The evaluation of de novo-ALEx2 can distinguish patients who present normal or subtle elevation of LFT at admission with a progressive increase during hospitalization [9]. In this regard, another study showed that the peak level of ALT in patients with severe COVID-19 infection was progressively reached within 10–15 days after admission [7].

The presence of de novo-ALEx2 could be related to the combination of multiple factors including baseline comorbidities, medications prescribed during early hospitalization, or liver injury related to SARS-CoV-2-induced systemic inflammatory response [7, 21–23]. In our study, age, sex, and

comorbidities were similar in patients with or without de novo-ALEx2. The inflammatory markers at admission and at one week of hospitalization were also similar in patients with or without de novo-ALEx2. The influence of drug toxicity has been evaluated in other studies, which have shown the use of lopinavir and ritonavir to be risk factors for liver test abnormalities [9, 19]. In our study, therapy carried out during hospitalization was not evaluated because of the complexity of interpretation and the lack of a uniform algorithm among participating centers. As the role of de novo-ALEx2 has not been fully evaluated as a marker of the hospitalization course, this deserves further validation in prospective studies.

Although the exact pathogenesis of liver injury in COVID-19 remains unknown [22], our findings suggest, similar to other studies, that liver enzymes abnormalities are related to SARS-CoV-2 infection itself [9]. On the one hand, hepatocytes do not express high levels of angiotensin-converting enzyme 2 receptor (ACE2), which is involved in SARS-CoV-2 cell entry, and therefore these cells are unlikely to be a target of this virus [24]. On the other hand, cholangiocytes express high levels of ACE2 and could be the target of SARS-CoV-2 in the liver. Nevertheless, ALP was not usually as elevated in our or other studies as it might be expected [10, 24]. A proposed mechanism that has gained popularity based on preliminary data includes the cytokine storm associated with systemic inflammatory response syndrome, especially in patients with severe COVID-19 infection [19, 25]. Other explanations put forward include ischemia and reperfusion injury, drug toxicity, and the exacerbation of preexisting chronic liver diseases [24]. However, we did not find a greater requirement for vasoactive drugs or mechanical ventilation in patients with ALEx2 at admission or during hospitalization. Moreover, similar to other studies, no differences were observed between patients with or without abnormal LFT related to medications that were indicated prior to admission [20]. Finally, as was suggested by other authors, it is possible that patients with ALEx2 might present a higher percentage of undiagnosed chronic liver disease [10]. Prior studies showed that patients with underlying liver disease have a higher percentage of liver test abnormalities and decompensated cirrhosis, which were associated with severe COVID-19 [18, 26].

The mortality observed in this series was higher than that reported by others, with about 40% of the fatalities occurring within the first 2 weeks of hospitalization [18]. Compared with another study from Latin America that included more than 1600 patients, the requirement for mechanical ventilation, the need for vasopressors, and the overall mortality were higher in our study, indicating that more severe patients were included [16]. These differences are likely related to the fact that asymptomatic patients with SARS-CoV-2 infection or patients admitted for other causes with COVID-19 diagnosis during hospitalization were excluded in the present study. Another possibility to explain the differences encountered is that we included older patients with a higher rate of comorbidities [16]. Finally, a great proportion of patients were included in our study at the peak of the pandemic in their respective countries, when a higher percentage of less severely ill patients were probably managed on an outpatient basis according to the resources available in each center.

We found cardiovascular comorbidity, active smoking, WBC count at 1 week from admission, and de novo-ALEx2 to be independent risk factors for overall mortality. Cardiovascular comorbidity has been extensively evaluated and has been uniformly identified as one of the main risk factors for mortality associated with COVID-19 [3, 4]. The presence of active smoking at admission has already been indicated as a risk factor as well [27]. Furthermore, active smoking could be a marker of undiagnosed chronic lung disease, a known risk factor associated with severity of infection and death in patients with COVID-19 [3]. WBC count at one week of hospitalization has not been extensively evaluated. A prior study found that elevated WBC count at 1 week of hospitalization was more common in patients with severe COVID-19 compared to nonseverely ill patients [28]. Although this laboratory value may be influenced by several variables as the use of drugs as corticosteroids and the presence of other infections, we found that WBC at one week of hospitalization was an independent predictor of COVID-19-associated death. A multicenter study found that patients of Hispanic ethnicity had a higher risk for severe COVID-19 compared with non-Hispanic whites, even after adjusting for age and comorbidities [26]. The influence of ethnicity was not evaluated in our study, as all the participating centers are from South America, and Hispanic ethnicity was predominant.

The present study has some limitations. Similar to other retrospective studies, there is a possibility of a selection bias leading to the inclusion of more severe cases. Furthermore, the number of patients included in the present study was lower than in other series, which might have limited some of the findings. In addition, autoimmune liver diseases were ruled out mainly by history and a small proportion of patients had autoantibodies assessed prior or during hospitalization, a limitation associated with the retrospective design of the study. Nevertheless, it should be highlighted that the study cohort is representative of 5 countries from South America, one of the regions most severely affected by the pandemic and for which clinical data in COVID-19 are still lacking in medical literature. Another limitation of this study is that medications were not assessed during hospitalization due to the difficulty of evaluating overlapping therapies used for patients with COVID-19. However, considering that the treatment protocols of each center and country were different, it is unlikely that treatments during hospitalization would uniformly affect LFT in all centers.

In summary, in this multicenter study performed in South America, we found that a moderate alteration in LFT at admission was an independent risk factor for short-term mortality in patients with COVID-19. In addition, we showed that de novo-ALEx2 at one week of admission was associated with overall mortality in patients hospitalized for COVID-19. Future prospective studies are necessary to validate the role of LFT alteration during specific periods of hospitalization, in order to identify possible modifications in the assessment of the prognosis of patients admitted with COVID-19.

Data Availability

The database used to support the findings of this study is available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Comparison of General and Liver-Specific Prognostic Scores in Their Ability to Predict Mortality in Cirrhotic Patients Admitted to the Intensive Care Unit

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Introduction. Acute Physiology and Chronic Health Evaluation (APACHE) II and III and Sequential Organ Failure Assessment (SOFA) are prognostic scores commonly used in the intensive care unit (ICU). Their accuracy in predicting mortality has not been adequately evaluated in comparison to prognostic scores commonly used in critically ill cirrhotic patients with acute decompensation (AD) or acute-on-chronic liver failure (ACLF). *Aims*. This study was conducted to evaluate the performance of prognostic scores, including APACHE II, SOFA, Chronic Liver Failure Consortium (CLIF-C) SOFA, Child–Turcotte–Pugh (CPS), Model for End-Stage Liver Disease (MELD), MELD-Na, MELD to serum sodium ratio (MESO) index, CLIF-C organ failure (CLIF-C OF), CLIF-C ACLF, and CLIF-C AD scores, in predicting mortality of cirrhotic patients admitted to the ICU. *Patients and Methods*. A total of 382 patients (280 males, mean age 67.3 ± 10.6 years) with cirrhosis were retrospectively evaluated. All prognostic scores were calculated in the first 24 hours of ICU admission. Their ability to predict mortality was measured using the analysis of the area under the receiver operating characteristic curve (AUC). *Results*. Mortality was observed in 31% of the patients. Analysis of AUC revealed that CLIF-C OF (0.807) and CLIF-SOFA (0.776) had the best ability to predict mortality in all patients, but CLIF-C OF (0.749) had higher prognostic accuracy in patients with ACLF. CLIF-SOFA, SOFA, and CLIF-C AD had the highest AUC values in patients with AD, with no statistical difference ($p = 0.971$). *Conclusions*. When compared to other general or liver-specific prognostic scores, CLIF-C OF, CLIF-SOFA, SOFA, and CLIF-C AD have good accuracy to predict mortality in critically ill patients with cirrhosis and patients with AD. According to the clinical scenario, different scores should be used to provide prognosis to patients with cirrhosis in the ICU.

1. Introduction

End-stage liver disease, particularly due to hepatitis B and C, alcoholic liver disease, and nonalcoholic steatohepatitis, accounts roughly for 1.16 million deaths worldwide [1]. It usually evolves over several years from compensated to decompensated cirrhosis, which is identified by the onset of acute decompensation (AD) with the development of hepatic encephalopathy (HE), ascites, and variceal hemorrhage (VH) [2, 3]. Further decompensation usually is preceded by recurrent ascites, HE, VH, and persistent jaundice, leading frequently to the terminal stage of cirrhosis characterized by occurrence of acute kidney injury (AKI), hepatorenal failure, and acute-on-chronic liver failure (ACLF), usually triggered by bacterial infections [2–5]. Patients with either AD or ACLF usually require admission to the intensive care unit (ICU) for monitoring organ dysfunction or organ support [6]. In those individuals, in-hospital mortality was shown to vary

from 39% to 83%, depending on the reason for ICU admission, presence of organ failure, and sepsis [7].When compared to patients without cirrhosis, critically ill patients with the disease have more infections at ICU admission, increased overall mortality, and increased mortality due to sepsis or septic shock [8].

Several ICU and liver-specific scores have been used to predict outcomes of critically ill patients with cirrhosis [7, 9–14], as well as futility rules to withhold intensive care support [15, 16]. The most often used ICU scores are Acute Physiology and Chronic Health Evaluation (APACHE) II and III and Sequential Organ Failure Assessment (SOFA) scores [17], whereas liver-specific scores routinely applied to patients with cirrhosis are Child–Turcotte–Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores [18, 19]. Both were designed to predict mortality in patients with cirrhosis, respectively, after surgery [18] and transjugular intrahepatic portosystemic shunt (TIPS) placement [19]. While CTP is commonly used in clinical practice to assess disease severity, MELD is also currently used for indication and prioritization for liver transplantation [20].

Recently, MELD has been updated to incorporate serum sodium (sodium MELD (MELD-Na)) and MELD to serum sodium ratio index (MESO index) [21–23], age, and serum sodium (integrated-MELD (iMELD)) [24], attempting to improve prognostication.

Due to its better assessment of organ failure, ICU scores usually have a better accuracy to predict mortality, when compared to CTP and MELD scores [12–14]. Recently, the concept of ACLF was introduced in the literature by the Chronic Liver Failure Consortium (CLIF-C) to describe a syndrome characterized by advanced chronic liver disease associated with organ failure and a 28-day mortality higher than 15% [25, 26]. The authors have employed a prospectively validated modified SOFA score (CLIF-SOFA) to characterize CLIF-C OF and proposed two new prognostic scores: CLIF-C ACLF [27] for patients with ACLF and CLIF-C AD [28] for patients with AD of cirrhosis, without ACLF.

It is important to note that the CLIF-C criteria for ACLF have not been endorsed worldwide, and different definitions have been proposed by the Asian Pacific Association for the Study of the Liver-ACLF Research Consortium and the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) [29].

The purpose of the present study was to evaluate the accuracy of liver-specific prognostic scores, such as CTP, MELD, and its variants MELD-Na, iMELD, and MESO index, as well as ICU scores, such as APACHE II and SOFA, in their ability to predict in-hospital mortality of cirrhotic patients admitted to the ICU with either AD of cirrhosis or ACLF and also to assess the performance of CLIF-C AD and CLIF-C ACLF, respectively, in those patients with either AD or ACLF.

2. Patients and Methods

All patients admitted to the Gastroenterology and Hepatology Unit of Hospital Português, from January 2012 to June 2018, with AD of cirrhosis or ACLF, were retrospectively reviewed. This ICU is a referral unit for critically ill patients with cirrhosis in Salvador, Brazil. The diagnosis of cirrhosis was based on clinical, biochemical, and echographic findings, as well as liver histology, whenever liver biopsy results were available. The etiology of cirrhosis and clinical features responsible for ICU admission were recorded in all patients. All cirrhotic patients admitted in the postoperative period of abdominal surgery, including liver transplantation, intra-arterial chemoembolization for hepatocellular carcinoma, and patients with HIV coinfection or advanced liver cancer were excluded from the study. Data regarding demographics, presence of comorbidities, cause of cirrhosis, clinical features, and baseline laboratory parameters including leucocyte counts, platelets, international normalized ratio (INR), total bilirubin, serum sodium, albumin, and creatinine levels were collected. General ICU and liver-specific prognostic scores were calculated within 24 hours of ICU admission, including updated Charlson Comorbidity Index (CCI), SOFA, APACHE II, CTP, MELD, MELD-Na, MESO-index, and iMELD, as previously described [17–19, 21, 23, 24, 30]. Patients were categorized into two groups, according to the presence of ACLF or AD without ACLF [31]. In addition, CLIF-C ACLF [27] and CLIF-C AD [29] scores were calculated on day one of ICU admission in patients, respectively, with ACLF and AD of cirrhosis. Acute kidney injury was diagnosed according to International Club of Ascites definition [32]. ACLF and AD of cirrhosis were evaluated in the first 24 hours of admission and graded based on CLIF-C criteria [26, 31]. NACSELD definition of ACLF [33] was also used based on parameters obtained within the first 24 hours in the ICU for better characterization of the patients. The presence of organ failures was assessed based on definitions of either CLIF-C or NACSELD [26, 27, 31, 33]. Patients were followed up until death, liver transplantation, and 28-day survival. The primary outcome was in-hospital mortality or transplant-free survival. This study was approved by the Ethics Committee in Research of Hospital Português, Salvador, Bahia.

2.1. Statistical Analysis. Dichotomous variables are presented in text and tables as numbers and percentage and continuous variables were expressed as mean ± standard deviation (SD) or as median and interquartile range, respectively, whether the distribution was normal or skewed. Demographic, clinical, and laboratorial variables were comparing between survivors and nonsurvivors using the chi-square test or Fisher's test for categorical variables or Student's *t*-test or the Mann–Whitney *U* test for continuous variables when appropriate. All scores were compared using nonparametric receiver operator characteristic (ROC) curves with respective 95% confidential interval (95% CI). The areas under the curve (AUC) provided the discriminative ability of the score and were compared as previously described [34]. Additionally, the prognostic score with the highest AUC obtained was considered a gold standard ROC curve. The other scores were compared to the gold standard using the Bonferroni-adjusted significance probability. In this analysis, models with an AUC equal to or greater than 0.7 were considered clinically significant. The Youden index

Table 1: Demographics, clinical features, and outcomes of cirrhotic patients admitted to the ICU.

Characteristics	All patients ($n = 382$)	Patients with ACLF ($n = 178$)	Cirrhosis with AD ($n = 204$)
Age (years)	67.3 ± 10.6	58.2 ± 24.7	62.4 ± 20.8
Male sex	280 (73%)	133 (74.7%)	147 (72.1%)
Ascites	321 (84%)	154 (86.5%)	167 (81%)
Hepatic encephalopathy	211 (55%)	110 (61.7%)	101 (49.5%)
Variceal bleeding	24 (6%)	12 (6.7%)	12 (5.9%)
Bacterial infections/sepsis	233 (61%)	98 (55%)	135 (66%)
Acute kidney injury	123 (32%)	80 (45%)	43 (21%)
ACLF by CLIF-C criteria	178 (47%)		
(i) Grade I	90 (24%)		
(ii) Grade II	36 (9%)		
(iii) Grade III	52 (14%)		
ACLF by NACSELD criteria	33 (9%)		
Serum sodium (mEq/L)[1]	136 (132–140) 109–157	137 (131–140) 109–157	136 (132–140) 109–155
Serum creatinine (g/dl)[1]	1.0 (0.7–1.6) 0.3–8.4	1.4 (0.87–2.5) 0.4–8.4	0.9 (0.6–1.2) 0.3–3.5
Serum albumin (mg/dl)[1]	2.5 (2.2–2.9) 0.4–4.4	2.5 (2.1–2.9) 1.0–4.2	2.6 (2.3–2.9) 0.4–4.4
Serum bilirubin (mg/dl)[1]	2.0 (1.2–4.2) 0.4–36.7	2.3 (1.2–5.3) 0.4–36.7	2.0 (1.1–3.10) 0.4–27
INR[1]	1.7 (1.4–2.1) 0.51–13.44	1.87 (1.4–2.3)0.93–12.7	1.6 (1.4–2.0) 0.5–3.4
Leukocyte count (109/L)[1]	7,330 (5,060–11,030) 1,070–45,090	8,670 (6,460–13,722) 1,070–45,090	6,545 (4,360–6,545) 1,140–24,120
MELD-Na	22 ± 8		
SOFA	4 ± 3		
CLIF-SOFA	5 ± 3		
CLIF-C OF	8 ± 2		
CLIF-C ACLF	48 + 12		
CLIF-C AD	57 + 9		
ICU length of stay[1]	4.0 (2.0–9.0) 0.8–51.0	5 (2–10) 1.0–51.0	3.0 (1–6) 1.0–29.0
Hospital length of stay[1]	11.0 (8.0–18.0) 1.0–103.0	16.5 (9.0–12.5) 1.0–103.0	10 (7–16) 1.0–64.0
Mortality	118 (30.9%)	95 (53.4%)	23 (11.3%)

[1]Expressed by median (25th–75th)/min–max; ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure Consortium; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; MELD, Model for End-Stage Liver Disease; SOFA, Sequential Organ Failure Assessment; OF, organ failure; AD, acute decompensation; ICU, intensive care unit.

was used to identify the optimal cut-off point for each score [35], and the corresponding sensitivity, specificity, positive, and negative predictive value (PPV and NPV) with respective 95% CI and likelihood ratio positive (LR+) and negative (LR−) were calculated. Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 21.0 for Windows, Stata for Mac (Stata Corp LLC., Texas, TX, USA), version 13.0, and OpenEpi, version 3.01 [36]. A p value <0.05 was considered significant. Quintile's cut-off points to Apache II, MELD-Na, SOFA, CLIC-SOFA, CLIC-C OF (for all patients), CLIF-C ACLF (for patients with ACLF), and CLIF-C AD (for patients with cirrhosis with AD), in addition to sensitivity and specificity parameters, were obtained using TG-ROC curves with graphic analysis, using Prism for Mac, version 9.1.2 (GraphPad Software, San Diego, California USA).

3. Results

A total of 382 consecutive patients (280 males, mean age 67.3 ± 10.7 years) were admitted to the ICU due to AD of cirrhosis ($n = 204$) or ACLF ($n = 178$). Table 1 shows demographics and baseline clinical and laboratory features of these patients. Most of them had alcoholic liver disease (29%), cryptogenic cirrhosis (25%), hepatitis C (19%), or nonalcoholic steatohepatitis (11%). The main clinical features of those individuals were bacterial infections with or without sepsis or septic shock ($n = 233$), HE ($n = 211$), AKI ($n = 123$), and VH ($n = 24$). Among the patients, 321 had concurrent ascites (84%). According to CLIF-C criteria [26, 27, 31], 178 patients (47%) had ACLF grade I ($n = 90$), grade II ($n = 36$), or grade III ($n = 52$). The remaining patients (53%) did not fulfill the proposed CLIF-C criteria for ACLF and were categorized as AD of cirrhosis. Using NACSELD definition (33), only 33 patients (9%) had ACLF. Mechanical ventilation and vasopressors were required at ICU admission, respectively, in 7% and 5% of the cases. Most patients had advanced cirrhosis with several comorbidities presenting, respectively, mean CCI, APACHE II, CTP, and MELD scores of 7 ± 3, 15 ± 6, 10 ± 2, and 18 ± 8. Other ICU and liver-specific prognostic scores, calculated on day one, are shown in Table 1. Mortality was observed in 118 patients (31%), mainly due to septic shock ($n = 83$), ACLF ($n = 12$), hypovolemic shock ($n = 4$), respiratory failure ($n = 4$), AKI ($n = 3$), or other causes ($n = 12$). Mean (SD) ICU and length of hospital stay were 6 ± 6 and 15 ± 12 days, respectively. Demographics, clinical features, and outcomes of patients with ACLF and those with AD of cirrhosis are shown separately in Table 1. In this cohort, only 6.5% of patients underwent liver transplantation. A total of 249 (65%) patients had 28-day transplant-free survival.

Mortality rate was significantly associated with clinical features of bacterial infections, HE, and AKI (Table 2). Patients with ACLF assessed by either CLIF-C or NACSELD criteria had higher mortality when compared to their

Table 2: Comparison of survivors and nonsurvivors with cirrhosis admitted to the ICU.

Parameters	Survivors ($n = 264$)	Nonsurvivors ($n = 118$)	p values
Age (years)	67.6 + 10.4.5	66.7 + 11.3	0.88
Male sex	200 (76%)	80 (68%)	0.11
Clinical features			
Ascites	223 (85%)	98 (83%)	0.73
Bacterial infections/sepsis	130 (49%)	103 (87%)	<0.0001
Hepatic encephalopathy	128 (49%)	83 (70%)	<0.0001
Acute kidney injury	49 (19%)	70 (59%)	<0.0001
Variceal bleeding	13 (5%)	11 (9%)	0.11
AD of cirrhosis	181 (69%)	23 (20%)	<0.001
ACLF by CLIF criteria	83 (31%)	95 (80%)	< 0.001[1]
(i) Grade I	59 (22%)	31 (26%)	
(ii) Grade II	15 (6%)	21 (18%)	
(iii) Grade III	9 (3%)	43 (36%)	
ACLF by NACSELD criteria	3 (1%)	30 (25%)	<0.0001
Laboratory features			
Serum sodium (mEq/L)	135.2 + 7.2	135.2 + 8,1	0.11
Serum creatinine (mg/dl)	1.2 + 1.0	1.8 + 1.4	<0.0001
Serum bilirubin (mg/dl)	3.1 + 4.0	5.7 + 7.0	<0.0001
Serum albumin(g/dl)	2.6 + 0.5	2.5 + 0.5	0.84
INR	1.8 + 0.9	2.2 + 1.5	0.01
Leukocyte count (109/L)	7512 + 4105	11808 + 7321	<0.0001
Organ support admission			
Vasopressor therapy	4 (1, 5%)	13 (11%)	<0.0001
Mechanical ventilation	4 (2%)	24 (20%)	<0.0001
Scores			
CCI	6.5 + 3.4	7.8 + 2.9	0.008
Apache II	13.1 + 3.9	18.3 + 8.6	0.001
CTP	9.6 + 2.2	11.1 + 1.7	0.02
MELD	17.8 + 6.2	24.6 + 8.6	0.001
MELD-Na	20.2 + 6.5	26.5 + 7.9	0.001
iMELD	41.9 + 9.4	47.0 + 12.4	<0.0001
MESO index	1.3 + 0.5	1.8 + 0.7	<0.0001
SOFA	3.7 + 2.0	6.1 + 3.0	<0.0001
CLIF-SOFA	4.1 + 2.1	6.9 + 3.1	<0.0001
CLIF-C OF	7.2 + 1.7	9.7 + 2.3	<0.0001
CLIC-C ACLF	44.6 + 10.0	50.4 + 13.1	0.03
CLIF-C AD	56.6 + 9.2	63.2 + 9.3	0.48

[1]Chi-square for trend; AD, acute decompensation; ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure Consortium; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; CCI, Charlson comorbidities index; APACHE II, Acute Physiology and Chronic Health Evaluation II; MELD, Model for End-Stage Liver Disease; MELD-Na, sodium MELD; MESO index, MELD to serum sodium ratio index; iMELD, integrated-MELD; CTP, Child–Turcotte–Pugh; SOFA, Sequential Organ Failure Assessment; CLIF-SOFA, CLIF Sequential Organ Failure Assessment; CLIF-C OF, CLIF-C organ failure; CLIF-C ACLF, CLIF acute-on-chronic liver failure; CLIF-C AD, CLIF-C acute decompensation; ICU, intensive care unit.

counterparts without ACLF (Table 2). As expected, increased risk of death was associated with the number of organ failures, assessed by either CLIF-C or NACSELD criteria (Figure 1). Other variables associated with in-hospital mortality were creatinine and bilirubin levels, INR, and leukocyte count, as well as the need for vasopressors and mechanical ventilation at admission. All general and liver-specific prognostic scores were significantly higher in nonsurvivors when compared to their counterparts who were discharged alive from the hospital, except for the CLIF-C AD score (Table 2).

ROC curves were used to assess the ability of the scores calculated within 24 hours of admission to predict in-hospital mortality for all patients and those with either ACLF or AD (Figure 2 and Table 3). SOFA (0.753; 95% CI: 0.708–0.796), CLIF-SOFA (0.776, 95% CI: 0.724–0.827), and CLIF-C OF scores (0.807; 95% CI: 0.758–0.855) had the highest AUC values in all critically ill cirrhotic patients, and these scores were not statistically different from each other ($p = 0.083$) (Figure 3). Since the CLIF-C OF score was considered the reference score (gold standard), the AUC values of the MELD ($p = 0.013$), MELD-Na ($p = 0.037$), and APACHE II ($p = 0.042$) scores were significantly lower than CLIF-C OF.

In patients with ACLF, higher AUC values were obtained with CLIF-C OF (0.749; 95% CI: 0.679–0.820), when compared to CLIF-C ACLF (0.665; 95% CI: 0.585–0.745; $p = 0.029$), SOFA ($p = 0.037$), and MELD-Na ($p = 0.002$), but no CLIF-SOFA score ($p = 0.085$). It is of note that CLIF-SOFA, SOFA, and CLIF-C AD had the highest AUC values in those patients with AD of cirrhosis, with no statistical difference ($p = 0.971$) (Figure 2 and Table 3).

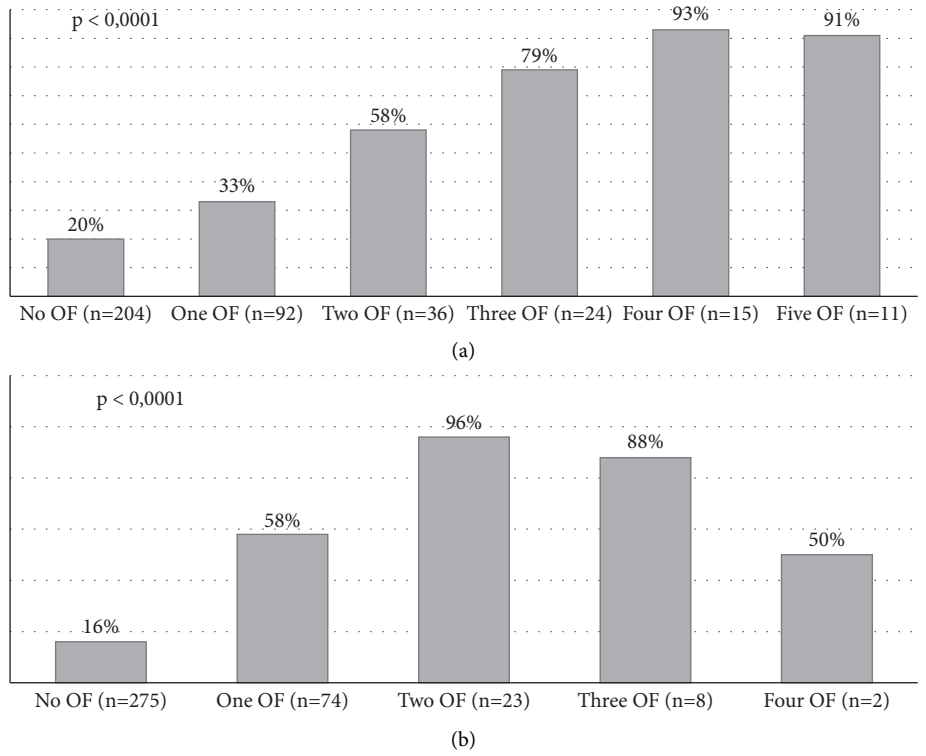


Figure 1: Mortality according to the number of organ failures defined by (a) CLIF-C and (b) NACSELD criteria. OF, organ failure; CLIF-C, Chronic Liver Failure Consortium; NACSELD, North American Consortium for the Study of End-Stage Liver Disease.

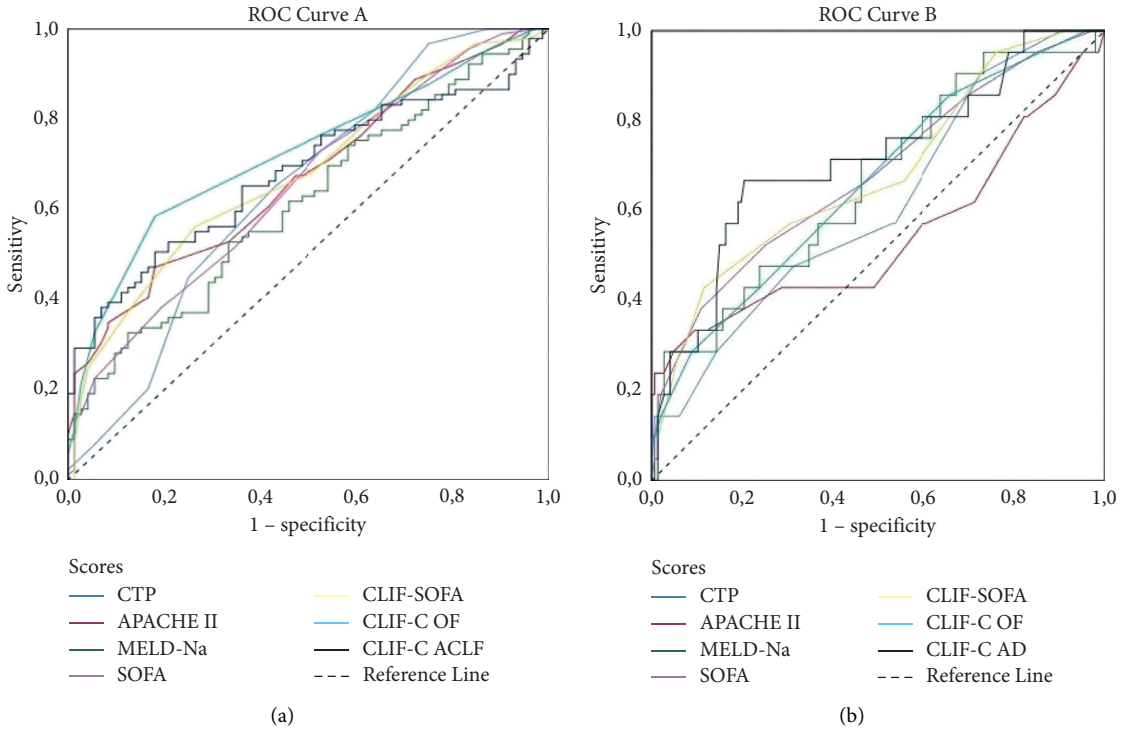


Figure 2: Comparison of the general and liver-specific prognostic scores to predict in-hospital mortality by AUROC in (a) patients with ACLF and (b) AD of cirrhosis. ACLF, acute-on-chronic liver failure; AD, acute decompensation; CLIF-C, Chronic Liver Failure Consortium; APACHE II, Acute Physiology and Chronic Health Evaluation II; MELD, Model for End-Stage Liver Disease; MELD-Na, sodium MELD; CTP, Child–Turcotte–Pugh; SOFA, Sequential Organ Failure Assessment; CLIF-SOFA, CLIF Sequential Organ Failure Assessment; CLIF-C OF, CLIF-C organ failure.

Table 3: Performance of prognostic scores in cirrhotic patients admitted to the ICU.

Score	AUC	Standard error	95% confidence interval[1]	p values
All patients ($n = 382$)				
CTP	0.701	0.027	0.648–0.754	<0.001
APACHE II	0.695	0.032	0.632–0.759	<0.001
MELD	0.727	0.030	0.669–0.785	<0.001
MELD-Na	0.729	0.029	0.670–0.784	<0.001
MESO index	0.723	0.030	0.665–0.781	<0.001
iMELD	0.640	0.033	0.576–0.705	<0.001
SOFA	0.753	0.027	0.708–0.796	<0.001
CLIF-SOFA	0.776	0.0269	0.724–0.827	<0.001
CLIF-C OF	0.807	0.025	0.758–0.855	<0.001
CCI	0.627	0.029	0.571–0.683	<0.001
Patients with ACLF ($n = 178$)				
CTP	0.662	0.041	0.581–0.743	0.002
APACHE II	0.674	0.042	0.592–0.755	<0.001
MELD	0.647	0.041	0.566–0.729	0.01
MELD-Na	0.638	0.041	0.557–0.719	0.01
MESO index	0.633	0.041	0.552–0.714	0.02
iMELD	0.540	0.043	0.455–0.625	0.27
SOFA	0.677	0.039	0.600–0.754	0.001
CLIF-SOFA	0.698	0.039	0.622–0.773	<0.001
CLIF-C OF	0.749	0.036	0.679–0.820	<0.001
CLIF-C ACLF	0.665	0.041	0.585–0.745	<0.001
Patients with AD of cirrhosis ($n = 204$)				
CTP	0.650	0.060	0.532–0.768	0.10
APACHE II	0.543	0.083	0.380–0.707	0.52
MELD	0.650	0.072	0.510–0.790	0.06
MELD-Na	0.676	0.065	0.549–0.803	0.02
MESO index	0.654	0.070	0.519–0.790	0.04
iMELD	0.682	0.077	0.532–0.832	0.02
SOFA	0.715	0.063	0.592–0.837	0.008
CLIF-SOFA	0.716	0.062	0.595–0.837	0.008
CLIF-C AD	0.695	0.065	0.569–0.822	0.001

[1]Asymptotic normal 95% CI; AD, acute decompensation; ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure Consortium; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; CCI, Charlson comorbidities index; APACHE II, Acute Physiology and Chronic Health Evaluation II; MELD, Model for End-Stage Liver Disease; MELD-Na, sodium MELD; MESO index, MELD to serum sodium ratio index; iMELD, integrated-MELD; CTP, Child–Turcotte–Pugh; SOFA, Sequential Organ Failure Assessment; CLIF-SOFA, CLIF Sequential Organ Failure Assessment; CLIF-C OF, CLIF-C organ failure; CLIF-C ACLF, CLIF acute-on-chronic liver failure; CLIF-C AD, CLIF-C acute decompensation.

The most discriminative cut-off point was determined using the highest Youden Index (for each prognostic score), and corresponding sensitivity, specificity, PPV, NPV, LR +, and LR− are shown in Table 4 and Figures 4(a)–4(c). Figure 4(a) shows that the most discriminative cut-off obtained to all patients was similar between patients with ACLF and AD to APACHE II score (cut-off = 17). But higher cut-off points considered optimal were observed for the other analyzed mortality prognostic scores in the group of patients with ACFL compared with patients with AD of cirrhosis (Figures 4(b) and 4(c)). Notably, the optimal cut-off points were associated with higher specificity values, reaching maximum values for MELD-Na (89.2% and 97.8%, respectively in patients with ACLF and AD of cirrhosis).

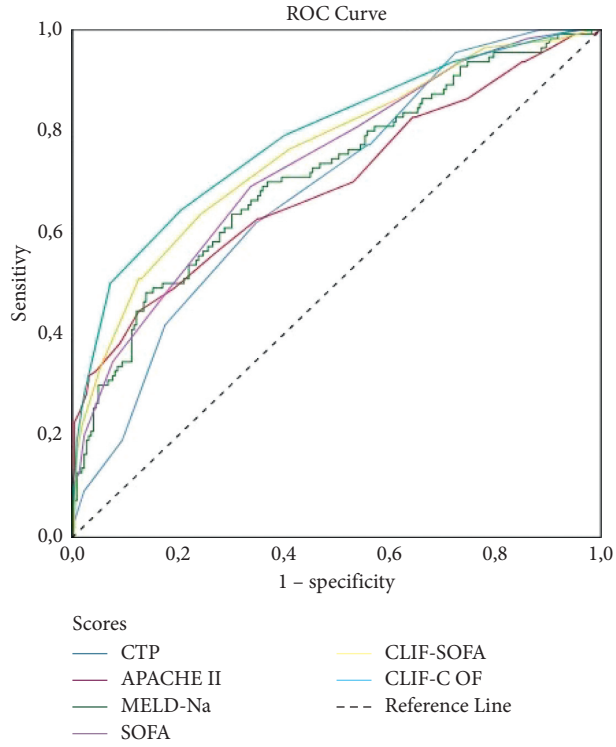


Figure 3: Comparison of general and liver-specific prognostic scores calculated on day 1 to predict in-hospital mortality by receiver operating characteristic curves in all patients either with ACLF or AD of cirrhosis. ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure Consortium; APACHE II, Acute Physiology and Chronic Health Evaluation II; MELD, Model for End-Stage Liver Disease; MELD-Na, sodium MELD; CTP, Child–Turcotte–Pugh; SOFA, Sequential Organ Failure Assessment; CLIF-SOFA, CLIF Sequential Organ Failure Assessment; CLIF-C OF, CLIF-C organ failure.

In Table 5, we observe that the quintiles of the cut-off points for the APACHE II, MELD-Na, SOFA, CLIF-SOFA, and CLIF-C OF scores produce a low prediction for death in patients with cirrhosis with AD, even considering the 80th percentile. More consistent values were observed in the group with ACLF.

4. Discussion

This 6-year retrospective single-center study evaluated 382 critically ill patients with cirrhosis with and without ACLF, which was assessed within 24 hours of ICU admission. In-hospital mortality rate was 31%, in accordance with previous reports, showing an increase in survival of cirrhotic patients admitted to the ICU in recent years [7, 14]. In the present study, mortality was associated with clinical and laboratory parameters, previously associated with prognosis, in several other studies, including bacterial infections or sepsis [8, 35, 37], HE [38], AKI [32, 39], and ACLF [26, 31] at admission; baseline sodium [12, 31, 40], creatinine [12, 31, 40], bilirubin [12, 31, 40], INR [12, 31, 40], and leukocyte counts [12, 31, 40]; and need for mechanical ventilation [12, 31] or vasopressors [12, 31].

Table 4: Performance of different prognostic scores in predicting mortality using the optimal cut-off point in all patients, patients with ACLF (CLIF-C ACLF) and patients with AD of cirrhosis (CLIF-C AD).

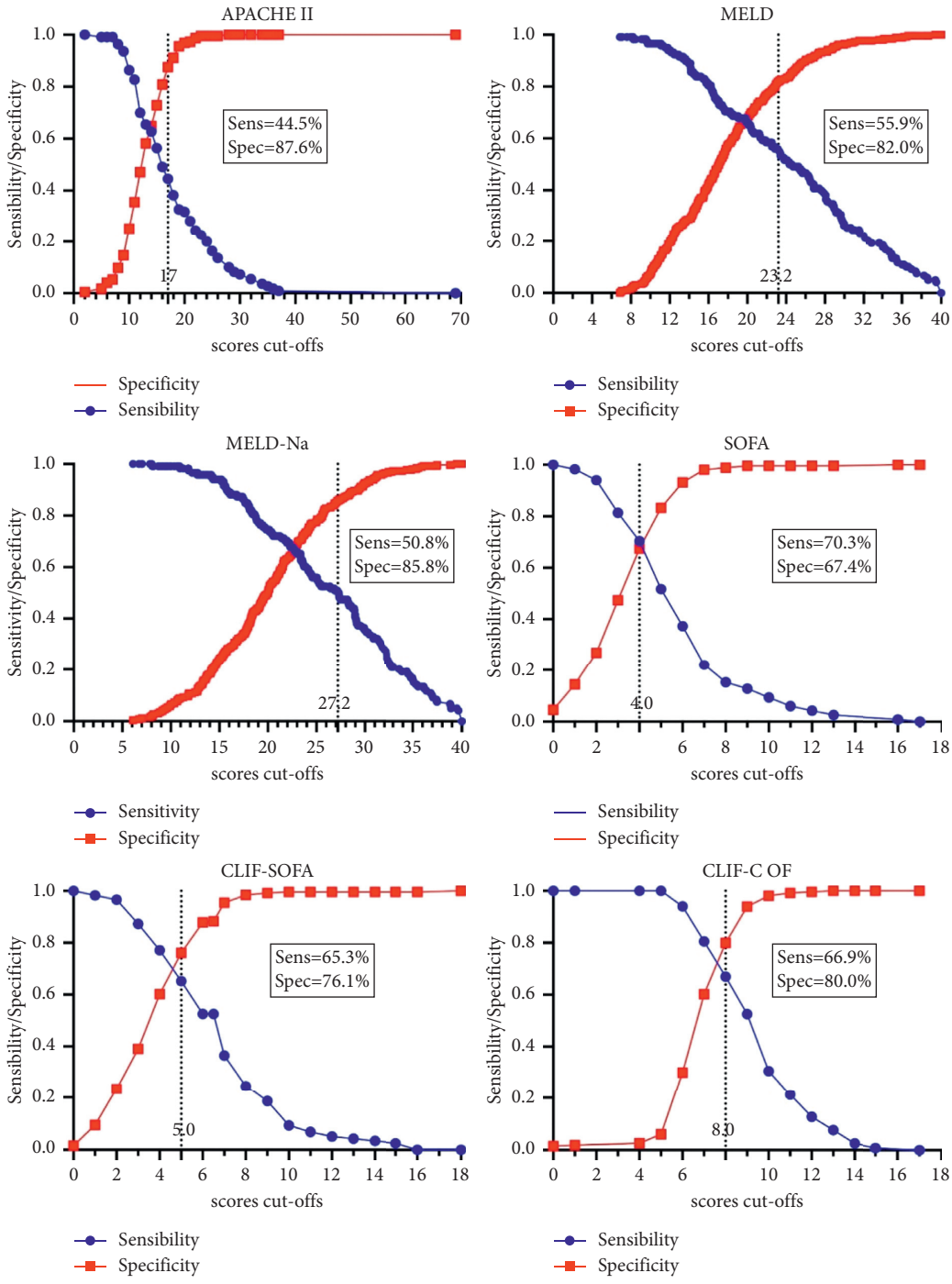
Score	Cut-off point	Youden index	Sens[1] (%)	Spec[1] (%)	PPV[1]	NPV[1]	LR+	LR−
APACHE II	17	0.321	44.6 (35.6–56.9)	87.6 (82.6–91.3)	63.6 (52.5–73.5)	76.4 (70.8–81.1)	3.6	0.63
CTP	10	0.296	64.4 (55.4–72.5)	65.2 (59.2–70.6)	45.2 (37.9–52.8)	80.4 (74.5–85.1)	1.9	0.55
SOFA	4	0.378	70.3 (61.6–72.8)	67.4 (61.6–72.8)	49.1 (41.7–56.7)	83.6 (78.0–87.9)	2.2	0.44
CLIF-SOFA	5	0.414	65.3 (56.3–73.2)	74.1 (70.6–80.9)	55.0 (46.7–63.0)	83.1 (77.8–87.3)	2.7	0.46
CLIF-C OF	8	0.469	67.0 (58.1–74.8)	79.9 (74.7–84.3)	59.9 (51.3–67.8)	84.4 (79.4–88.4)	3.3	0.41
MELD	23.2	0.379	65.3 (56.3–73.2)	76.1 (70.6–80.9)	55.0 (46.-63.0)	83.1 (77.8–87.3)	2.7	0.46
MELD-Na	27.2	0.367	50.9 (41.9–59.7)	85.8 (81.1–89.5)	61.9 (51.9–70.9)	79.4 (74.3–83.7)	3.6	0.57
iMELD	47	0.296	52.5 (43.6–61.3)	77.0 (71.5–81.7)	50.8 (42.1–59.5)	78.2 (72.8–82.8)	2.3	0.62
MESO index	1.8	0.404	54.2 (45.3–63.0)	85.1 (80.2–88.9)	62.1 (52.5–70.9)	80.4 (75,4–84.7)	3.6	0.54
CCI	4	0.259	89.7 (82.9–94.0)	36.1 (30.6–42.1)	38.5 (32.9–44.4)	88.8 (81.4–93.5)	1.4	0.28
CLIF-C ACLF[2]	54.6	0.296	44.2 (34.6–54.2)	84.2 (74.7–90.5)	76.4 (63.7–85.6)	56.6 (47.7–65.0)	2.8	0.66
CLIF-C AD[3]	62.9	0.394	60.9 (40.8–77.8)	78.0 (71.3–81.4)	26.4 (16.4–39.6)	93.9 (88.8–96.8)	2.8	0.50

[1]Data expressed in % and 95% CI; [2]only patients with ACLF ($N = 178$); [3]only patients with AD of cirrhosis ($N = 204$). Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: likelihood ratio positive; LR−: likelihood ratio negative.

We included several prognostic scores to predict mortality in cirrhotic patients since liver and ICU scores have been proposed. However, the discriminatory power of these scores in critically ill cirrhotic patients is not well defined. Few studies have analyzed the predictive value of MELD score, including its modified versions to predict in-hospital mortality [12].

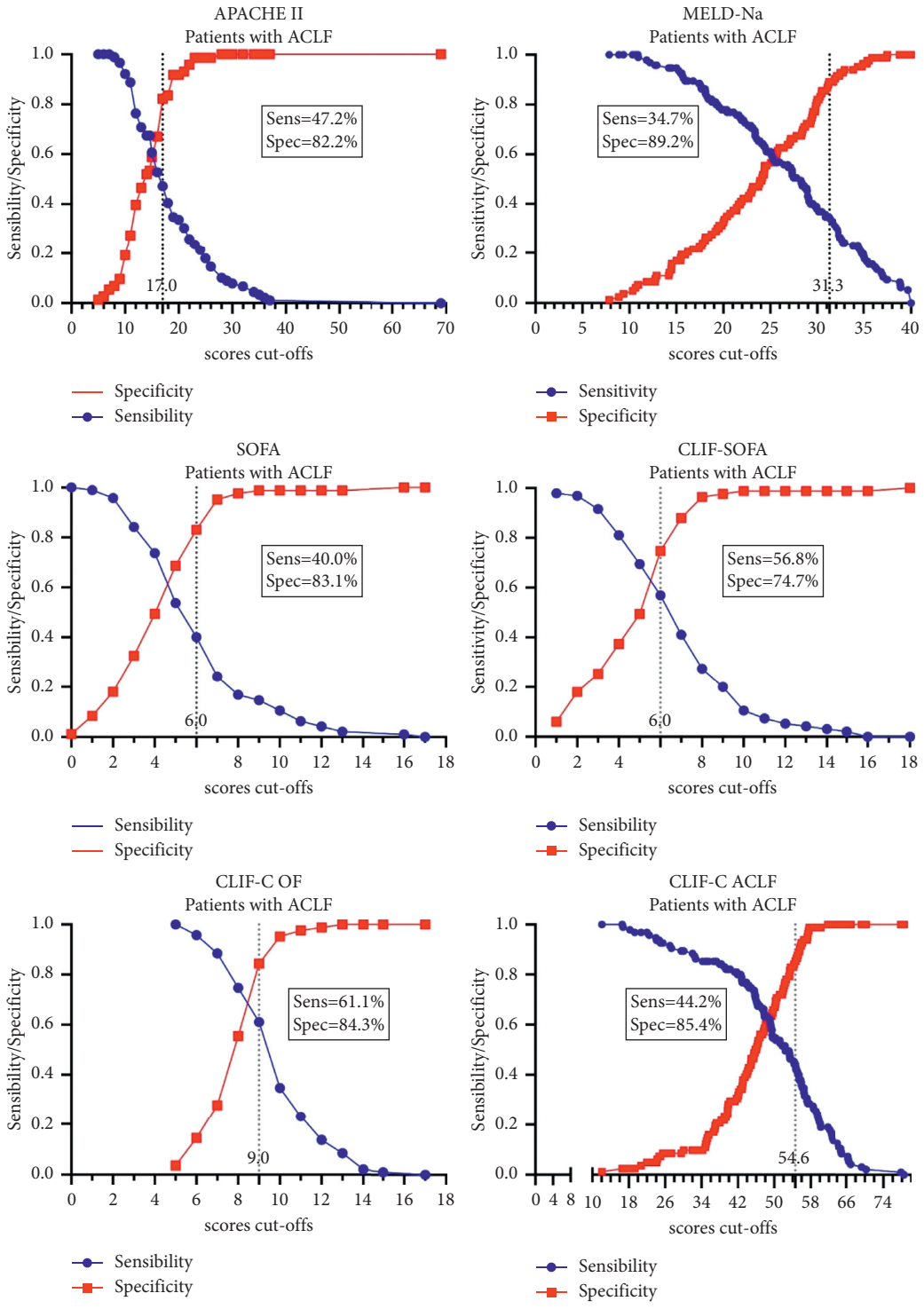
As previously described [31, 33], occurrence and severity of ACLF, defined by either CLIF-C or NACSELD criteria, were robust predictors of hospital mortality. In the present cohort, 91% and 53% of the patients who had ACLF at admission, respectively, by NACSELD and CLIF-C definition, died at the hospital. Using AUC analysis, the authors have compared the performance of general and liver-specific scores in their ability to predict in-hospital mortality in all cirrhotic patients admitted to the ICU as well as in those patients with or without ACLF. We have found that SOFA, CLIF-SOFA, and CLIF-COF scores had a better performance when compared to other general ICU and liver-specific scores, such as APACHE II, CCI, MELD, and its variants and CTP scores in the entire group of patients. SOFA score was previously associated with better prognostication, particularly when compared to MELD and CTP scores, for every patient with cirrhosis in several [9, 12, 41–44] but not all publications [45]. Due to these findings, CLIF-C investigators adapted SOFA score to incorporate INR, instead of platelet count (CLIF-SOFA), to better evaluate liver dysfunction and organ failure (CLIF-C OF) in critically ill cirrhotic patients [26, 27, 31]. It is worth mentioning that both scores outperformed SOFA in their ability to predict mortality in the present study. Other authors have found similar performance of SOFA and CLIF-SOFA [14, 40, 46, 47] or better performance of CLIF-SOFA over SOFA [48] when calculated within 24 hours of ICU admission and even better prognostication when recalculated after 72 hours in some [14, 46] but not all studies [47]. Those differences may be due to comparison of heterogeneous cohorts comprised of patients from different genetic backgrounds and more importantly with differing percentages of organ failures. Another key point to better understand these discrepancies is to recognize that most of those studies, evaluating the accuracy of the prognostic scores, used distinct time intervals to assess outcomes, including in-ICU [25], in-hospital [40, 42, 45, 46], 28-day [49, 50], 6-week [9], and 90-day mortality [50]. Few studies have assessed accuracy of general ICU and liver-specific prognostic scores in critically ill patients with cirrhosis according to the presence of ACLF [16, 41, 51, 52], and none of them have compared the accuracy of those scores to predict in-hospital mortality. In the present study, CLIF-C OF outperformed other scores including CLIF-C ACLF and CLIF-SOFA in patients with ACLF and CLIF-C AD had a good accuracy to predict mortality in those patients with AD. Our findings were different from those reported by other North American and European authors [51, 52], who have reported better prognostication in patients with ACLF using CLIF-C ACLF score. It is important to mention that this score was prospectively developed using the CANONIC cohort of hospitalized Caucasian patients with cirrhosis, not particularly in the ICU, with external validation using an independent French cohort [27]. The CLIF-C ACLF score is calculated combining the CLIF-C OF score with age and leukocyte count and outperformed, up to now, all other prognostic scores in the evaluation of cirrhotic patients with ACLF. One possible reason for the discrepancies observed in the present study, in face of all others, is not just the short time interval to assess mortality (in-hospital mortality), but also some clinical features presented by our patients, such as older age, with mean age at least 10 years higher when compared to other studies, and a high index of comorbidities. Different genetic backgrounds could also be responsible since CLIF-C ACLF was validated almost exclusively in European and North American Caucasian patients [27, 51]. On the other hand, CLIF-C AD had better accuracy to predict mortality in comparison to CTP, MELD, and MELD-Na in our patients with AD of cirrhosis. CLIF-C AD was also developed by the CANONIC group of investigators [28], using the following parameters: age, INR, serum creatinine, and leukocyte count. Other [53–55], but not all [50], studies have disclosed similar findings. Our results report a good ability of CLIF-C AD to predict in-hospital mortality in cirrhotic patients admitted to the ICU with AD of cirrhosis, per definition without ACLF.

To increase the prognostic accuracy of the mentioned scores, several authors have suggested that incorporation of



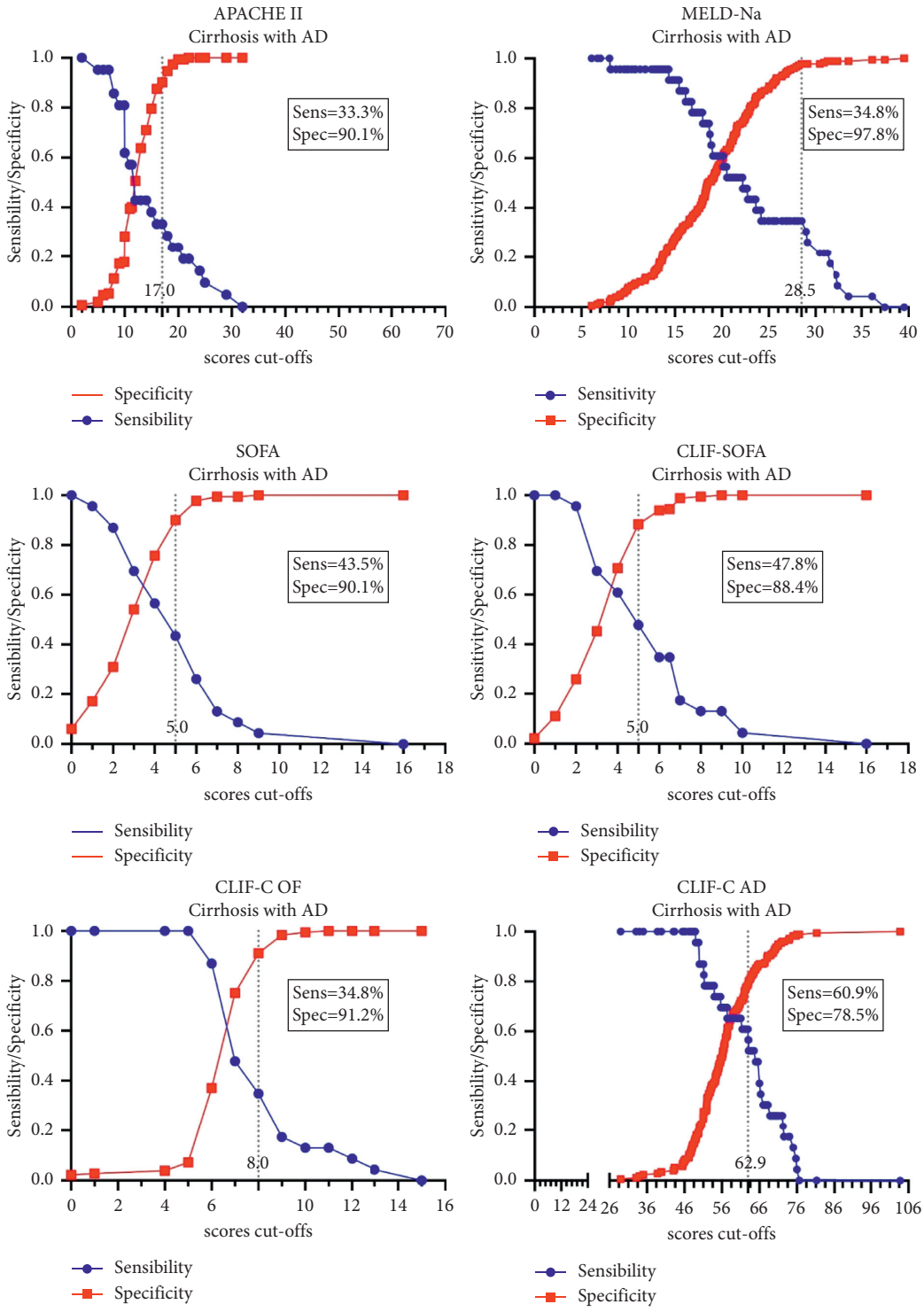
(a)

Figure 4: Continued.



(b)

Figure 4: Continued.



(c)

Figure 4: (a) Curves of sensibility and specificity relative to different cut-off values (TG-ROC curves) of the mortality prognostic scores and sensibility and specificity of the optimal cut-off point in 382 patients either with ACLF or AD of cirrhosis. (b) Curves of sensibility and specificity relative to different cut-off values (TG-ROC curves) of the mortality prognostic scores and sensibility and specificity of the optimal cut-off point in 178 patients with ACLF of cirrhosis. (c) Curves of sensibility and specificity relative to different cut-off values (TG-ROC curves) of the mortality prognostic scores and sensibility and specificity of the optimal cut-off point in 204 patients with AD of cirrhosis.

Table 5: Cut-off points, sensibility, specificity, area under curve, and positive predictive value (to predict mortality) of the quintiles of APACHE II, MELD-Na, SOFA, CLIF-SOFA, CLIF-C ACLF, and CLIF-C AD scores.

Score	20^{th}					40^{th}					60^{th}					80^{th}				
	Co	Se	Sp	AUC	PPV	Co	Se	Sp	AUC	PPV	Co	Se	Sp	AUC	PPV	Co	Se	Sp	AUC	PPV
All patients ($N = 382$)																				
APACHE II	10	86.4	25.3	0.558	36.1	12	70.0	47.1	0.586	39.3	15	56.4	72.9	0.646	50.4	18	38.2	91.1	.646	67.7
MELD-Na	15.4	93.2	25.7	0.594	36.2	19.5	76.3	47.5	0.619	39.6	23.4	63.6	70.5	0.670	49.3	29.0	40.7	89.7	0.652	64.0
SOFA	2	94.1	26,9	0.605	36.5	4	70.3	67.4	0.689	49.1	5	51,7	83,8	0.675	58.1	6	37.3	93.2	0.652	71.0
CLIF-SOFA	3	87.3	39.0	0.632	39.0	4	77.1	60.2	0.687	46.4	5	65.3	76.1	0.707	55.0	7	36.4	95.5	0.659	78.2
CLIF-C OF	6	94.1	29.9	0.620	37.5	7	80.5	60.2	0.704	47.5	8	66.9	79.9	0.734	59.8	10	30.5	98.1	0.643	87.8
Patients with ACFL ($N = 178$)																				
APACHE II	12	76.4	39.7	0.581	60.7	14	67.4	52.1	0.597	63.2	17	47.2	82.2	0.647	76.4	21.4	30.3	93.2	0.617	84.4
MELD-Na	18.1	85.3	25.3	0.553	56.6	23.7	66.3	47.0	0.567	58.9	28.4	47.4	68.7	0.580	63.4	32.3	29.5	91.6	0.605	80.0
SOFA	3	84.2	32.5	0.584	58.5	5	53.7	68.7	0.612	66.2	6	40.0	83.1	0.616	73.1	7	24.2	95.2	0.597	85.2
CLIF-SOFA	4	81.1	37.3	0.592	59.7	6	56.8	74.7	0.658	72.0	7	41.1	88.0	0.645	79.6	8	27.4	96.4	0.619	89.7
CLIF-C OF	8	74.7	55.4	0.651	65.7	9	61.1	84.3	0.727	81.7	9.4	61.1	84.3	0.727	81.7	11	23.2	97.6	0.604	91.7
CLIF-CACLF	39.2	83.2	23.2	0.532	55.6	46.2	68.4	51.2	0.598	61.9	52.0	51.6	73.2	0.624	69.0	56.9	31.6	93.9	0.627	85.7
Patients with AD of cirrhosis ($N = 204$)																				
APACHE II	10	61.9	28.3	0.451	10.7	11.2	57.1	39.5	0.483	11.5	13	42.9	63.8	0.533	14.1	16	33.3	87.5	0.604	26.9
MELD-Na	14.1	95.7	21.9	0.588	13.7	17.9	78.3	42.1	0.602	14.9	20.3	56.5	62.4	0.594	16.3	23.6	43.5	83.1	0.633	25.0
SOFA	2	87.0	30.9	0.589	13.8	3	69.6	54.1	0.619	16.2	4	56.5	75.7	0.661	22.8	5	43.5	90.1	0.668	35.7
CLIF-SOFA	2	95.7	26.0	0.608	14.1	3	69.6	45.3	0.574	13.9	4	60.9	70.7	0.658	20.9	5	47.8	88.4	0.681	34.4
CLIF-C OF	6	87.0	37.0	0.620	14.9	7	47.8	75.1	0.615	19.6	7	47.8	75.1	0.615	19.6	8	34.8	91.2	0.630	33.3
CLIF-CAD	50	87.0	21.5	0.542	12.6	54.4	73.9	41.8	0.579	14.2	58	65.2	63.8	0.645	19.0	64.9	52.2	84.2	0.682	30.0

Co = cut-off; Se=sensibility; Sp = specificity; AUC = area under curve; PPV = positive predictive value.

lactate in MELD [56] and CTP [25], as well as CLIF-C ACLF [52] scores, could increase their capacity of predicting mortality. One limitation of our study was the unavailability of data concerning lactate to confirm the findings.

It is noteworthy that in this study, we did not aim to assess the clinical course of patients with ACLF. Therefore, the scores were not recalculated throughout the hospital stay. These data can be evaluated in further studies. Additionally, the low rate of transplantation in this cohort helps to avoid a competing-risk analysis, since higher rates of transplantation during hospitalization could modify prognostic scores accuracy.

In conclusion, lower mortality rates are nowadays observed in cirrhotic patients admitted to the ICU, particularly in the absence of ACLF. In their ability to predict survival, for patients admitted in the ICU, the following scores outperformed other prognostic scores: CLIF-C OF and CLIF-SOFA, for all cirrhotic patients, CLIF-C OF, for patients with ACLF, and SOFA, CLIF-SOFA, and CLIF-C AD, for patients with AD. Stratification of patients with or without ACLF at admission, as well as during hospital stay, is important to improve prognostication. According to the clinical scenario, different scores should be used to provide prognosis to patients with cirrhosis in the ICU.

Abbreviations

AD: Acute decompensation
ACLF: Acute-on-chronic liver failure
CLIF-C: Chronic Liver Failure Consortium
NACSELD: North American Consortium for the Study of End-Stage Liver Disease
CCI: Charlson comorbidities index
APACHE II: Acute Physiology and Chronic Health Evaluation II
MELD: Model for End-Stage Liver Disease
MELD-Na: Sodium MELD
MESO index: MELD to serum sodium ratio index
iMELD: Integrated-MELD
CTP: Child–Turcotte–Pugh
SOFA: Sequential Organ Failure Assessment
CLIF-SOFA: CLIF Sequential Organ Failure Assessment
CLIF-C, OFCLIF-C: Organ failure
CLIF-C ACLF: CLIF acute-on-chronic liver failure
CLIF-C AD, CLIF-C: Acute decompensation.

Ethical Approval

The study was approved by the Ethics Committee in Research of Hospital Português, Salvador, Bahia, Brazil. The project has been registered at http://plataformabrasil.saude.gov.br (CAAE no. 26209119.4.0000.5029).

Conflicts of Interest

The authors declare no conflicts of interest.

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Research Article

Bone Marrow Mesenchymal Stem Cells in Acute-on-Chronic Liver Failure Grades 2 and 3: A Phase I-II Randomized Clinical Trial

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Introduction. Acute-on-chronic liver failure (ACLF) is an acute liver decompensation in cirrhotic patients, which leads to organ failures and high short-term mortality. The treatment is based on the management of complications and, in severe cases, liver transplantation. Since specific treatment is unavailable, we aimed to evaluate the safety and initial efficacy of bone marrow mesenchymal stem cells (BM-MSC) in patients with ACLF Grades 2 and 3, a population excluded from previous clinical trials. *Methods*. This is a randomized placebo-controlled phase I-II single center study, which enrolled 9 cirrhotic patients from 2018 to 2020, regardless of the etiology. The control group ($n = 5$) was treated with standard medical therapy (SMT) and placebo infusion of saline. The intervention group ($n = 4$) received SMT plus 5 infusions of 1×10^6 cells/kg of BM-MSC for 3 weeks. Both groups were monitored for 90 days. A Chi-square test was used for qualitative variables, and the *t*-test and Mann–Whitney *U* test for quantitative variables. The Kaplan–Meier estimator was used to build survival curves. In this study, we followed the intention-to-treat analysis, with a significance of 5%. *Results*. Nine patients with a mean Child–Pugh (CP) of 12.3, MELD of 38.4, and CLIF-C score of 50.7 were recruited. Hepatitis C and alcohol were the main etiologies. The average infusion per patient was 2.9 and only 3 patients (2 in control and 1 in the BM-MSC group) received all the protocol infusions. There were no infusion-related side effects, although one patient in the intervention group presented hypernatremia and a gastric ulcer, after the third and fifth infusions, respectively. The survival rate after 90 days was 20% (1/5) for placebo versus 25% (1/4) for the BM-MSC. The patient who completed the entire MSC protocol showed a significant improvement in CP (C-14 to B-9), MELD (32 to 22), and ACLF (grade 3 to 0). *Conclusion*. BM-MSC infusion is safe and feasible in patients with ACLF Grades 2 and 3.

1. Introduction

Acute-on-chronic liver failure (ACLF) is a syndrome in patients with chronic liver disease, which is characterized by acute decompensation, organ failure, and high short-term mortality [1]. Since the first definition of ACLF in 2002 [2], there have been several attempts to put forward a better definition and diagnostic criteria by some Hepatology societies worldwide [3–6]. However, the methodology used was inappropriate, which has led to a lack of consensus.

In 2013, after the publication of a prospective multicenter observational study, the CANONIC trial, it was possible to define this syndrome in a more detailed and accurate way. Diagnostic criteria used in these cohorts applied a new scoring system, the Chronic Liver Failure Sequential Organ Failure Assessment score (CLIF-SOFA), improving the standardization of diagnostic criteria [7].

Despite the progress in the characterization and the diagnosis of ACLF, its management is still limited, which explains the high short-term mortality. Currently,

therapeutic alternatives include treating the underlying etiology when feasible, controlling the precipitating factors, and supportive measures for organ failures. In cases of clinical deterioration, a liver transplantation (LT) is an option [8, 9]. However, due to the scarcity of donors, the severity of the organ failures, and the risk of being futile, LT is restricted to a few cases.

In this context, other strategies have been studied, including extracorporeal liver support systems [10, 11], immunomodulatory treatments such as granulocyte colony-stimulating factor [12, 13], and faecal microbiota transplantation [14]. One of the most promising treatments is the use of mesenchymal stem cells (MSC), which has been shown to have anti-inflammatory effects, reducing both hepatocyte damage [15] and hepatic stellate cell activation [16]. Although few trials have shown benefits from its use [17–20], and given that its role in ACLF is still uncertain, the lack of effective treatment has led to an increased interest in exploring MSC therapy further for this condition.

The aim of this study was to evaluate the security and eventual efficacy of bone-marrow mesenchymal stem cell (BM-MSC) transfusions in patients with ACLF.

2. Methods

2.1. Study Design, Criteria, and Ethical Issue. This was a double blind, placebo-controlled, Phases I and II, randomized clinical trial carried out in one center in Brasil (Hospital de Clínicas de Porto Alegre) from September 2018 to January 2020. The purpose was to evaluate the safety and efficacy of allogeneic bone-marrow mesenchymal stem cells (BM-MSC) infusion in patients with ACLF Grades 2 and 3.

We used the ACLF definitions based on the CANONIC trial [7] in patients with a previously known history of cirrhosis, who were hospitalized due to acute decompensation of the liver, brought about by conditions such as voluminous ascites, hepatic encephalopathy, gastrointestinal hemorrhage, bacterial infection, or any combination of these. Inclusion criteria also required (a) fulfilling ACLF diagnostic criteria and ACLF Grade 2 or 3 and (b) being aged between 18 and 70 years. Exclusion criteria were (a) patient's or family member's refusal; (b) hepatocellular carcinoma (HCC); (c) formal contraindication for liver transplantation (e.g., advanced heart or pulmonary disease); (d) pregnancy and lactation; (e) previous liver transplantation; (f) HIV coinfection; (g) ACLF grade 1; (h) patients admitted for elective procedures; and (i) renal chronic disease requiring dialysis.

The study protocol was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre (register number: 92330718.0.0000.5327) and by the Brazilian Registry of Clinical Trials (register number: RBR-8n8csf).

2.2. Randomization and Masking. Before the start of the trial, manual randomization was performed, prespecifying which patient would receive BM-MSC or placebo. Both the medical team that assisted the patient and the patient were unaware of the assignment group.

2.3. Patients and Procedures. Nine patients were eligible and either the patients or a family member gave a signed informed consent when the patient was not able to sign it. A physician trained and certified for the interview and collection of the informed consent was also responsible for the collection of clinical and biochemical data from electronic medical records. After this, patients were assigned standard medical treatment (SMT) with allogeneic bone-marrow mesenchymal stem cells or SMT plus placebo.

In the intervention group, MSC was given in the form of 5 IV infusions of 1.0×10^6 cells/kg, twice a week for 2 weeks and one dose in the third week; the placebo group received, in a similar recipient, the same amount of saline.

Vital signs and clinical status were documented immediately before and up to one hour after the end of the infusion. All possible adverse reactions (e.g., rash, fever, and changes in blood pressure) were recorded every 30 minutes. One day after infusion, clinical status and possible adverse reactions (e.g., diarrhea) were reassessed. Laboratory tests along with evaluation of the Child–Pugh (CP), Model for End-Stage Liver Disease (MELD), MELD-Na, and CLIF-SOFA scores were performed before the first infusion and at 28 and 90 days following treatment.

2.4. Allogeneic BM-MSCs. The mesenchymal cells were obtained from a bag and filter from bone marrow donors at the Hospital de Clínicas de Porto Alegre, used in hematopoietic stem cell transplantation, after the consent had been signed. Such procedures have no influence on this type of transplantation and studies have previously shown that it is possible to obtain these cells for cell therapy, with the advantage that this material aggregates the marrow donor serology data [21].

2.4.1. MSC Cultivation. The bags and filters used in the hematopoietic stem cell transplantation that served as a source of MSC for cultivation were sent to the Advanced Cell Processing Center at the Hospital de Clínicas de Porto Alegre shortly after transplant. The cells were removed by eluting the filter and bag with saline. After isolation by centrifugation, the cells were counted in the Neubauer chamber, and the viability was verified by the exclusion method with Tripan Blue dye. The cells were then plated in culture flasks at a density of 300,000 live nucleated cells/cm^2 in DMEM medium (Eagle medium modified by Dulbecco, Gibco) supplemented with 10% human platelet lysate and with 1% penicillin/streptomycin antibiotic added (Gibco). The culture flasks were then transferred to incubators humidified with 5% CO_2, at 37°C. Cell growth was monitored through microscopy, and when a confluence of approximately 80% was reached, the cells were detached from the flask using 0.05% trypsin/EDTA (Invitrogen) and plated in new culture bottles at a concentration of 5,000 cells/cm^2. The cells were expanded until the second passage (P2), at which time they were cryopreserved and stored at −80°C while awaiting quality control tests.

2.4.2. Platelet Lysate. Antibodies against Bovine Fetal Serum (BFS) proteins were detected in patients who received MSC expanded with this supplement [22]. As a substitute for BFS, human serum has been used successfully through platelet lysate (LP). In vitro studies have shown LP to be as effective as BFS for the expansion of MSC [22, 23], and another study showed an expansion of mesenchymal stem cells cultured with LP 3.75 times greater than BFS [21]. Therefore, LP is safer from a biological point of view and is at least as efficient as BFS for cell expansion.

2.4.3. Cryopreservation. The cells were cryopreserved in a transfer bag with cell counts equivalent to 1×10^6 live cells per kg, in a volume of 25 ml composed of 17.5 ml of albumin +5 ml of 6% hydroxyethyl starch (HES) + 2.5 ml of dimethylsulfoxide (DMSO). They were stored at −80°C and quarantined until quality control tests were ready for clinical use.

2.4.4. Quality Control

(1) Immunophenotyping. The cells were analyzed for their membrane markers by flow cytometry on a FACSCantoII cytometer (BD Biosciences) at the time of cryopreservation and immediately before being administered to the patient. CTMs must express the markers DC73, DC90, and DC105 and must be negative for DC14, DC34, DC19, HLADR, and DC45 [24]. Harvested cells were adjusted for cell concentration of 1×10^6/ml in PBS, and at 100 μl the suspension per tube was incubated with the respective monoclonal antibodies for 30 minutes at room temperature and protected from light. After being washed, the cells were then fixed with 4% paraformaldehyde and analyzed on the flow cytometer.

The data acquisition and analysis of the sample was performed using Diva software on a FACSCantoII flow cytometer (BD Biosciences). The results were evaluated using a dot-plot graph and histogram, and the fluorescence intensity was measured using the MFI (mean of fluorescence intensity) [24, 25].

(2) Differentiation Tests. MSCs must have the ability to differentiate in osteocyte, adipocyte, and chondrocyte strains. At the P2 passage, three small aliquots were differentiated in each of the three cell lines using specific commercial reagents as per the manufacturer's instructions (StemPro®, Gibco) and were recorded by microscopy.

(3) Test to Check for the Presence of Mycoplasma. The presence of mycoplasma was tested with a commercial kit (VenorGeM Mycoplasma Detection Kit, Sigma-Aldrich). This kit uses the polymerase chain reaction (PCR), established as the gold standard, due to its greater sensitivity in detecting *Mycoplasma* contamination in cell cultures. This kit is able to detect 1–5 fg of contaminating DNA in 2–5 units of *Mycoplasma* per sample volume. The primer set is specific to a highly conserved region, or more precisely, the 16S rRNA coding region in the Mycoplasma genome. This allows for the detection of all *Mycoplasma* species tested so far, which are normally found as contaminants in cell cultures.

(4) Test to Check for the Presence of Endotoxin. To detect endotoxins in the sample, an Endosafe®-PTS test (Charles River, USA) was used with cartridges with sensitivity of 0.05–0.1 EU/ml. The cartridge has 4 channels, two positive controls and two for reading the sample. The presence of endotoxins in the sample triggers an enzymatic reaction, generating a yellow color, through the cleavage of a chromogenic substrate. These kinetics are read by the optical cells of the PTS-Endosafe equipment.

(5) Sterility. To check for the presence of microorganisms in the cell product, the supernatant (final product) from a 3 ml aliquot culture was subjected to aerobic and anaerobic blood culture tests carried out (by means of the automated BactAlert® system) at the Microbiology Laboratory of the Hospital de Clínicas de Porto Alegre.

2.5. Thawing and Preparing Cells for Infusion. For infusion in a patient, the transfer bag was thawed in a water bath at 37°C for 2 minutes and in a closed system: 15 mL of albumin (20%), 3.75 mL of anticoagulant solution for apheresis (ACD), and 56.25 mL of saline solution (0.9%) were added for dilution of DMSO. An aliquot was then removed for counting and cell viability. Preferably 1×10^6 live cells/kg were infused and only bags with viability above 70% were used. MSCs were administered intravenously to patients who met the criteria for inclusion in this study.

2.6. MSC Infusions. We aimed to perform five infusions of MSC in a peripheral vein in a dose of 1×10^6 cells/kg over three weeks: two in the first week, two in the second week, and one in the third week. The MSCs were infused in a transfer bag using equipment with a macroaggregated retention filter with a minimum duration of 10 to 20 minutes. Throughout the procedure and 60 minutes after the end of the infusion, vital signs were recorded every 30 minutes. The presence of transfusion reactions and the patient's clinical evolution were also recorded.

2.7. Outcomes. The primary outcomes were incidence of adverse events and survival after infusions. Secondary outcomes were liver transplantation rates and changes in CP, MELD, MELD-Na, and CLIF-SOFA scores.

We also evaluated liver function through bilirubin, prothrombin time and albumin levels as well as inflammatory stage via leukocytes and C-reactive protein after the first infusion of MSC.

2.8. Sample Size and Statistical Analysis. As there are few studies analyzing the use of BM-MSC, we defined a convenience sample of 9 patients, four in the intervention group and five in the placebo group.

For quantitative variables, both the mean and the standard deviation were presented, while for the qualitative variables, the absolute frequency was followed by the percentage that this represents of the total (n (%)).

For the comparison of groups, a Chi-square test was used for qualitative variables, and the t-test for quantitative variables, and, when abnormal, the Mann–Whitney U test. The Kaplan–Meier estimator was used to estimate survival curves and the curves were compared using the log-rank test. We followed the intention-to-treat analysis, which was performed using a software R, version 3.6.0. Tests were performed at 5% significance level.

3. Results

3.1. Population and General Characteristics at Baseline. Of the 9 study participants, four received BM-MSC. There were no significant differences in baseline clinical and biochemical profiles between the two groups (Tables 1 and 2). The mean age was 54.4 years and 66.7% were male. Two-thirds of patients had alcohol and hepatitis C as the etiology of cirrhosis and the main reason for development of ACLF was infection (44.4%). The mean scores were CP 12.3 (SD ± 1.2), MELD 38.4 (SD ± 7.3), ACLF grade 2.3 (SD ± 0.5), and CLIF-C 50.7 (SD ± 10.9). Six patients died before the end of the study protocol (3 in the placebo group and 3 in the intervention group).

3.2. Safety. There were no adverse events observed up to 1-hour after infusion. The most important adverse events were hypernatremia (162 mEq/L) and gastrointestinal bleeding due to a gastric ulcer, which was observed after the third and fifth doses, respectively. Both adverse reactions were found in the same patient from the MSC group and were not related to MSC infusions.

3.3. Efficacy. The average number of infusions in all patients was 2.9, with a median of 2, with at least 1 and a maximum of 5 infusions. Only three patients received all the five doses according to the study protocol, two in the placebo group and one in the intervention group.

The median survival time was 32 days with a standard deviation of 47.4 days. The survival rate after 90 days was 20% for the placebo group (1/5) and 25% for the MSC group (1/4) (Figure 1). On day 28 of the follow-up, six patients had died, and of the three who remained alive, two were from the placebo group. At 90 days after the infusions, two patients remained alive (one in the placebo and one in the MSC groups). None of the patients received a liver transplant over the period of the study.

Additionally, we analyzed the liver and inflammatory laboratory tests from three days before the first dose of MSC through to the seventh day after the first infusion. In the intervention group, there was a slight decrease in prothrombin time and total bilirubin and a small increase in albumin levels, features which were not observed in the placebo group. As for inflammatory features, C-reactive protein, and leukocytes, there were no differences between the groups (Figure 2).

Regarding those patients who survived until the end of the protocol, the patient in the MSC had a clear improvement in the liver function (Figure 3), which was not observed in the placebo group.

Table 1: Clinical characteristics of patients at baseline.

Characteristics	Stem cell group ($n = 4$) n (%)	Placebo group ($n = 5$) n (%)
Age (years)	55.8 ± 12.8	53.4 ± 14.4
Gender		
Female	2 (50.0)	1 (20.0)
Male	2 (50.0)	4 (80.0)
Race		
White	4 (100.0)	4 (80.0)
Brown	0 (0.0)	1 (20.0)
Hypertension		
No	2 (50.0)	2 (40.0)
Yes	2 (50.0)	3 (60.0)
Insulin resistance		
No	4 (100.0)	3 (60.0)
Yes	0 (0.0)	2 (40.0)
Smoker		
No	3 (75.0)	5 (100.0)
Yes	1 (25.0)	0 (0.0)
Alcohol abuse		
No	4 (100.0)	4 (80.0)
Yes	0 (0.0)	1 (20.0)
Renal injury		
No	4 (100.0)	4 (80.0)
Yes	0 (0.0)	1 (20.0)
ACLF trigger		
Unknown	3 (75.0)	0 (0.0)
Non-SBP infection	0 (0.0)	2 (40.0)
SBP	1 (25.0)	1 (20.0)
Variceal bleeding	0 (0.0)	1 (20.0)
Surgery	0 (0.0)	1 (20.0)
Etiology		
Alcohol	1 (25.0)	2 (40.0)
Hepatitis C	1 (25.0)	3 (60.0)
NASH	1 (25.0)	0 (0.0)
Hepatitis B	1 (25.0)	0 (0.0)

*Mean ± standard deviation. **p value from Chi-square test. ***ACLF, acute-on-chronic liver failure; SBP, spontaneous bacterial peritonitis; NASH, nonalcoholic steatohepatitis.

4. Discussion

Given that there is no approved specific therapy for ACLF, our study aimed to evaluate the safety and efficacy of BM-MSC infusions in patients with Grades 2 and 3 ACLF. Although we have demonstrated the safety of MSC in this population, 90-day survival rates were similar between the MSC and placebo groups. As far as we have been able to determine, this is the first MSC trial under such severe forms of ACLF as well as the first to enroll patients with liver disease of a different etiology.

Unlike the other trials which have evaluated MSC in ACLF using the Asian Pacific Association for the Study of

Table 2: Biochemical and clinical scores of patients at baseline.

Characteristics	All ($n = 9$)	MSC group ($n = 4$)	Placebo group ($n = 5$)
Hb (g/dL)	9.5 ± 1.8	10.0 ± 1.3	9.0 ± 2.1
WBC (mm^3)	9655.6 ± 599.3	7792.5 ± 5297.1	11146.0 ± 6668.9
PLT ($\times 10^9/mm^3$)	72.2 ± 58.1	53.5 ± 12.2	87.2 ± 77.5
TBili (mg/dL)	11.5 ± 10.3	12.4 ± 11.5	10.9 ± 10.6
INR	3.5 ± 1.5	3.9 ± 2.1	3.1 ± 0.8
sALB (g/dL)	2.7 ± 0.7	3.0 ± 1.0	2.4 ± 0.3
Cr (mg/dL)	2.8 ± 1.0	2.9 ± 0.8	2.7 ± 1.2
Na (mEq/L)	138.1 ± 4.9	140.5 ± 5.2	136.2 ± 4.1
AST (U/L)	102.1 ± 69.4	103 ± 54.7	101.4 ± 85.9
ALT (U/L)	95.9 ± 137.5	75.2 ± 42.9	112.4 ± 188.9
ALP (U/L)	114.9 ± 67.2	92.0 ± 54	133.2 ± 76.9
GGT (U/L)	106.0 ± 109.2	62.0 ± 4.2	123.6 ± 128.6
CRP (mg/dL)	54.0 ± 25.7	45.5 ± 23.6	60.8 ± 27.8
Child–Pugh	12.7 ± 1.2	12.2 ± 1.7	13.0 ± 0.7
MELD	38.4 ± 7.3	38.0 ± 11.3	38.8 ± 2.9
MELD-Na	37.8 ± 6.7	39.0 ± 10.2	36.8 ± 2.9
ACLF grade	2.3 ± 0.5	2.5 ± 0.6	2.2 ± 0.4
CLIF-C	50.7 ± 10.9	51.2 ± 6.2	50.2 ± 14.4

*p value from Mann–Whitney U test. **MSC, mesenchymal stem cells; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; TBili, total bilirubin; INR, international normalized ratio; sALB, serum albumin; Cr, creatinine; Na, sodium; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; CRP, C-reactive protein; MELD, model for end-stage liver disease; ACLF, acute-on-chronic liver failure; CLIF-C, chronic liver failure consortium (https://www.clifresearch.com/ToolsCalculators.aspx).

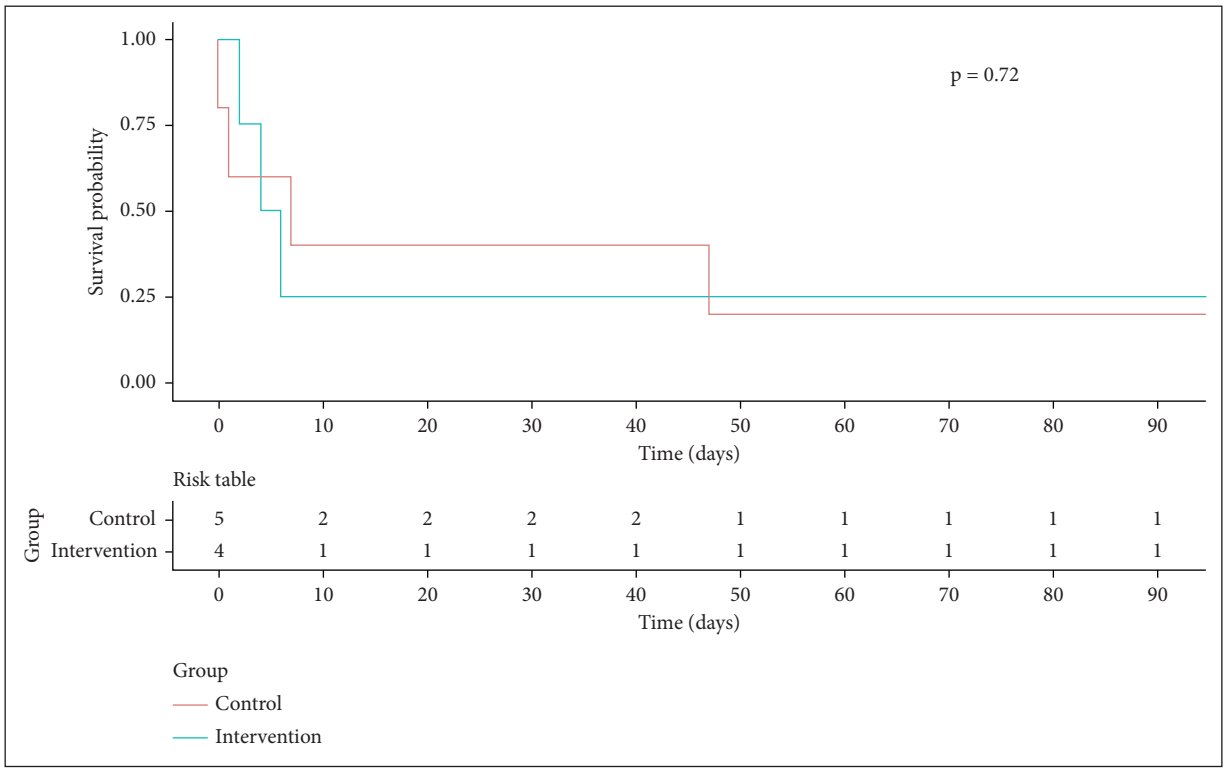


Figure 1: Kaplan–Meier survival curves ($n = 9$).

the Liver (APASL) criteria for defining ACLF [17–20], we decided to employ a different criterion, the EASL-CLIF, because there is growing evidence which shows that it performs better in defining ACLF [26–28]. This makes comparing our data with those of previous studies somewhat complicated. In addition to the criteria used for enrollment, there are many other differences between the previous protocols of infusion of multipotent cells in ACLF and ours. First of all, they include only patients infected with hepatitis B (HBV). Moreover, not all were cirrhotic. Indeed, these studies probably included chronic hepatitis patients with HBV flares, as they had high alanine transaminase levels and

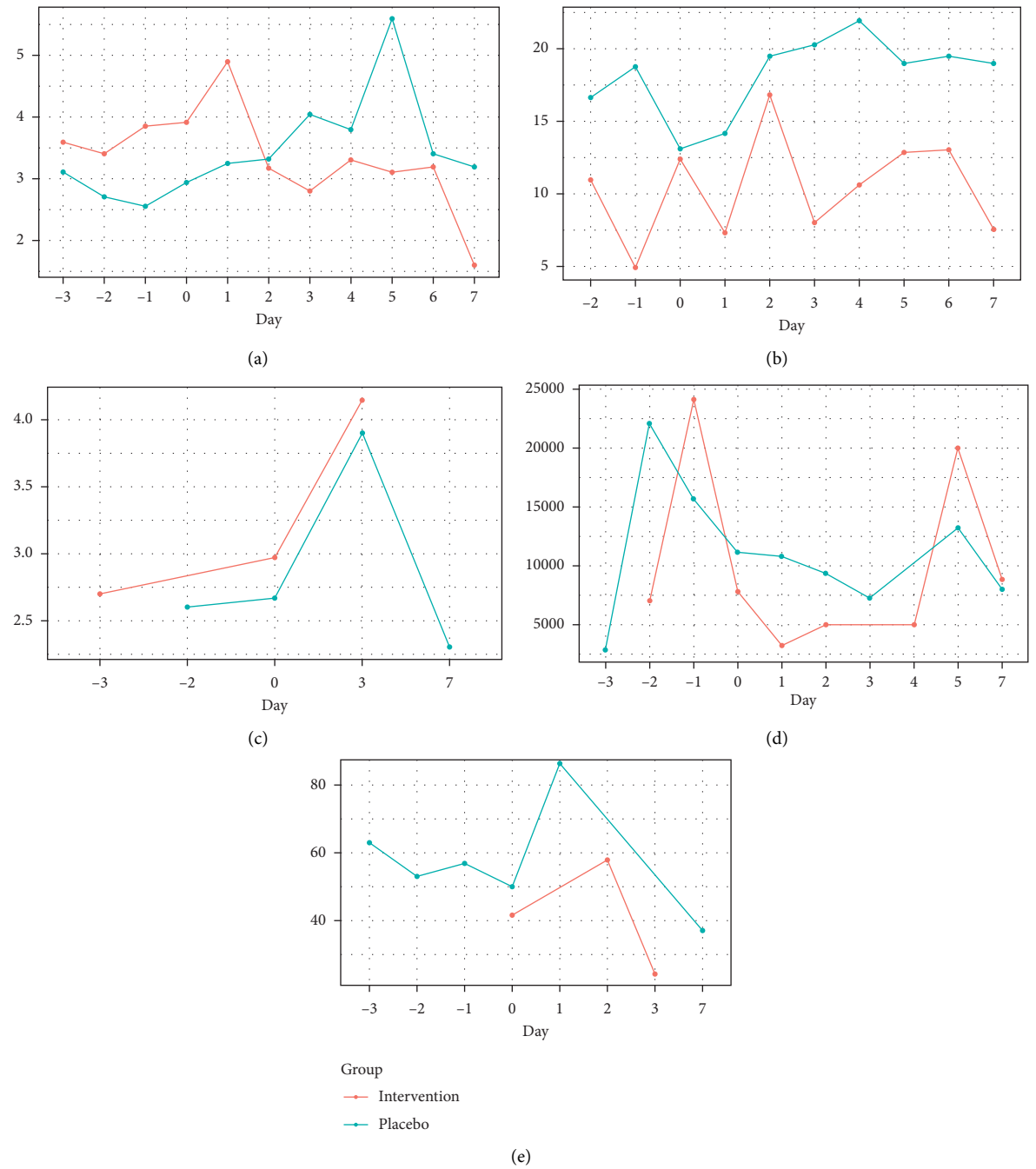
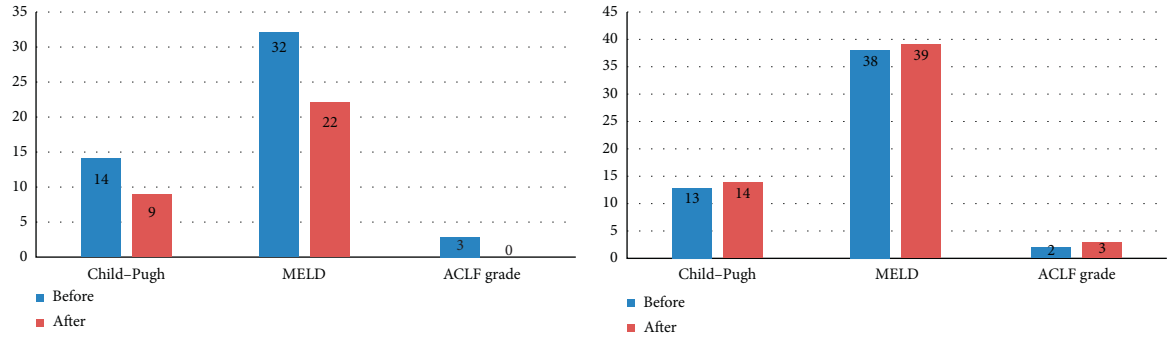


Figure 2: Changes in liver and inflammatory laboratory tests from three days before the first dose of MSC through the seventh day after the first infusion. PT, prothrombin time; TB, total bilirubin; Alb, albumin; CRP, C-reactive protein. (a) PT evolution. (b) TB evolution. (c) Alb evolution. (d) Leukocytes evolution. (e) CRP evolution.

high viral loads as well. Therefore, the overall results obtained were not only from the use of MSC but from the association of MSC and antivirals as well. Additionally, MSC origin and infusion protocols were not the same utilized in the present study. Most studies administrated MSC from umbilical cord [17, 19, 20]. Lin et al. [18] also treated patients with BM-MSC in a different protocol (1 infusion per week for 4 weeks). Our research group has been working on MSC in other scenarios [29–32], especially in acute graft-versus-host disease [33, 34] with good results. Based on these previous studies, we hypothesize that a similar protocol might be able to change the course of ACLF. Another remarkable difference between the present study and the previous studies is the severity of liver disease in patients. As well as including noncirrhotic patients, some exclusion criteria, like history of variceal bleeding, recent infection, and severe renal failure [17], suggest patients were in better condition than those included in this study. All of our patients were cirrhotic and when randomized were in the intensive care unit for ACLF management. Six of the patients



(a) (b)

Figure 3: Variations regarding Child–Pugh, MELD and ACLF scores before and after the infusion of 5 doses of the intervention group ((a); $n = 1$) and in the placebo group after 90 days ((b); $n = 2$). MELD, Model for end-stage liver disease; ACLF, acute-on-chronic liver failure.

had ACLF Grade 2, and three had ACLF Grade 3, with high CP, MELD, and CLIF-C scores, evidencing a much more severely affected population than previously evaluated.

BM-MSC infusion was safe, without significant side effects, similar to previous studies [17–20]. In the follow-up, five patients died up to 4 days after the randomization process (one on the same day of the enrollment and another patient one day after randomization, both from the placebo group). Three patients in the intervention group died (all three having received only two doses of BM-MSC), without showing improvement in their clinical status or laboratory tests.

In terms of laboratory data, we examined patients closely from three days before the first infusion up to the seventh day in order to examine the acute effects of MSC on liver function and systemic inflammatory response. In general, there was a slight improvement seen in liver function in the MSC group compared to the placebo group. On the other hand, we were not able to show any improvement in inflammation. This is important, as the CANONIC trial [7] has demonstrated a worse inflammatory profile in patients with ACLF.

In terms of safety evaluation, this study has demonstrated that the MSC infusion is safe, when compared with previous reported trials [17–20], regardless of their source (bone marrow or umbilical cord), doses, or infusion sites. There were only two side effects observed (hypernatremia and gastric ulcer), which were presumed not to be associated with the treatment, as the low quantity of sodium in each infusion was not able to cause hypernatremia, and there is a lack of plausibility in the development of a gastric ulcer with MSC.

It is important to emphasize that the only patient in the intervention group who received the whole pre-established protocol five BM-MSC infusions has shown an improvement after the fourth dose, with a significant recovery in liver function; ACFL was resolved as well, enabling his discharge one week after the end of the study protocol, as shown in Figure 3. Although this study is underpowered to draw conclusions regarding mortality, aspects that may have reduced the benefits of the BM-MSC infusion in this study were related to the following flaws: (a) the low number of patients enrolled; (b) patients presenting an extremely severe disease (ACLF Grades 2 and 3), mean MELD of 38; and (c) the infusion protocol was not completed due to the high early mortality. We probably started the MSC therapy too late (when a systemic inflammatory response had already established), thus blocking the effects of the progenitor cells, as has been suggested by some other authors [35–37].

In conclusion, we evaluated a new protocol of infusion of BM-MSC and demonstrated the safety of this treatment in high grades of ACLF in cirrhotic patients. There was a definite improvement in liver function in one case, suggesting MSC therapy could be explored further, perhaps in less severe forms of ACLF, such as ACLF 1, and in a larger group of patients.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

FCS and MRAS were responsible for the conception and design of the study. All authors were responsible for acquisition and analysis of data; furthermore, FCS and MRAS were in charge of statistical analysis. FCS and MRAS drafted the manuscript. All authors revised and commented on the draft and approved the final version of the manuscript.

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Research Article

Admission Serum Bicarbonate Predicts Adverse Clinical Outcomes in Hospitalized Cirrhotic Patients

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A low serum bicarbonate (SB) level is predictive of adverse outcomes in kidney injury, infection, and aging. Because the liver plays an important role in acid-base homeostasis and lactic acid metabolism, we speculated that such a relationship would exist for patients with cirrhosis. To assess the prognostic value of admission SB on adverse hospital outcomes, clinical characteristics were extracted and analyzed from a large electronic health record system. Patients were categorized based on admission SB (mEq/L) into 7 groups based on the reference range (22–25) into mildly (18–21), moderately (14–17), and severely (<14) decreased groups and mildly (26–29), moderately (30–33), and severely (>30) increased groups, and the relationship of SB category with the frequency of complications (acute kidney injury/hepatorenal syndrome, portosystemic encephalopathy, gastrointestinal bleeding, ascites, and spontaneous bacterial peritonitis) and hospital metrics (length of stay [LOS], admission to an intensive care unit [ICU], and mortality) was assessed. A total of 2,693 patients were analyzed. Mean SB was 22.9 ± 4.5 mEq/L. SB was within the normal range (22–25 mEq/L) in 1,072 (39.8%) patients, and 955 patients (36%) had a low SB. As the SB category decreased, the incidence of complications progressively increased ($p < 0.001$). Increased MELD-Na score and low serum albumin also correlated with frequency of complications ($p < 0.001$). As the SB category decreased, LOS, ICU admission, and mortality progressively increased ($p < 0.001$). On multivariate analysis, the association of decreased SB with higher odds of complications, LOS, ICU admission, and mortality persisted. *Conclusion.* Low admission SB in patients with cirrhosis is associated with cirrhotic complications, longer LOS, increased ICU admissions, and increased hospital mortality.

1. Introduction

Acid-base disturbances are common in patients with cirrhosis. In early stages of cirrhosis, acidosis results from dilutional hypervolemia and hyperchloremia, whereas alkalosis occurs due to hypoalbuminemia and respiratory alkalosis [1]. As a result, many cirrhotic patients demonstrate a complex combination of acidosis and alkalosis [1, 2]. As the severity of cirrhosis progresses, patients often develop a net metabolic acidosis, especially in those with acute and chronic liver failure with sepsis in which increased levels of lactic acid and unmeasured anions accumulate [1, 3, 4]. The resulting acidosis is frequently accompanied by a decreased serum bicarbonate (SB) level [3].

Acid-base imbalances with decreased SB levels are also common in patients with chronic kidney disease (CKD), acute kidney injury (AKI), and infection, and the elderly. In AKI and CKD low SB is associated with increased severity of illness and is predictive of adverse hospital outcomes and mortality [5, 6]. Additionally, low SB correlates with

increased hospital length of stay (LOS) in patients with cellulitis and with increased mortality in the elderly and in trauma intensive care unit (ICU) admissions [7–9].

The significance of SB in cirrhosis has only received limited attention. Most studies have assessed the impact of increased serum lactate levels and unmeasured anion acidosis on ICU mortality [3, 4, 10–12], whereas only three studies have evaluated SB as a prognostic marker [4, 13, 14]. Based on the significance of acidosis in cirrhosis and low SB in other chronic disease states, we speculated that SB would be predictive of adverse hospital outcomes for the hospitalized cirrhotic patient.

2. Materials and Methods

2.1. Subjects. A retrospective cohort study was conducted on data extracted from an electronic health record system (EPIC®) using Clinical Looking Glass© (Emerging Health Information Technology, Yonkers, NY). EPIC is a computerized patient database that contains comprehensive data, including patient demographics, hospitalizations, discharge diagnoses (International Classification of Diseases [ICD] codes), laboratory and imaging results, histopathology, endoscopic and surgical procedures, and medications. Clinical Looking Glass© is a proprietary software that permits exploration of the database contained within EPIC®. Using Clinical Looking Glass©, it is possible to obtain desired clinical data on consecutive patients meeting predefined criteria. The study was approved by the Institutional Review Board at the Albert Einstein College of Medicine.

Diagnoses were based on ICD, 9th revision or 10th revision, clinical modification codes recorded at hospital discharge. Patients analyzed included those aged ≥18 years with a diagnosis of cirrhosis (ICD-9 : 571.2, 571.5, 571.6, 571.42, 571.49, 571.5, 571.6, 571.8; ICD-10 : K70.30, K70.31, K74.60, K74.69, K74.3, K74.4, K74.5, K75.4) between November 2015 and March 2019. Patients were excluded if a SB within 24 hours of admission was not available or if there was a discharge diagnosis of diabetic ketoacidosis (ICD-9 : 250.1; ICD-10 : E10.10), acute coronary syndrome (ICD-9 : 410, 411; ICD-10 : I21, I22, I23, I24), or fulminant liver failure (ICD-9 : 570; ICD-10 : K72.00). Patients were also excluded if there was a preexisting diagnosis of end-stage renal disease (ICD-9 : 585.6; ICD-10 : N18.6), chronic obstructive pulmonary disease (ICD-9 : 491, 492, 494, 496; ICD-10 : J40, J41, J42, J43, J44, J47), systolic heart failure (ICD-9 : 428.2; ICD-10 : I50.2), or organ (liver, kidney, heart) transplantation (ICD-9 : V42.0, V42.1, V42.6, V42.7, V42.83, V42.84; ICD-10 : Z94.0, Z94.1, Z94.2, Z94.4, Z94.82, Z94.83) as well as a prescription for bicarbonate therapy prior to hospitalization. For patients with more than one hospitalization during the time period, only the index admission was analyzed.

2.2. Admission SB Stratification and Clinical Characteristics. Patients were categorized by admission SB milliequivalents per liter (mEq/L) into 7 groups based on the reference range (22–25) that spanned 4 mEq/L into those with mildly (18–21), moderately (14–17), and severely (<14) decreased levels and mildly (26–29), moderately (30–33), and severely (>34) increased levels as previously described in studies examining prognosis of SB on mortality and cardiovascular events in kidney transplant recipients [15]. Admission clinical characteristics for the entire cohort and for each SB category were recorded.

2.3. Relationship of Admission SB Category and Adverse Hospital Metrics. Patient discharge diagnoses were queried for complications of renal failure (AKI/hepatorenal syndrome [HRS], ICD-9 : 584, 572.4; ICD-10 : N17, K76.7), portosystemic encephalopathy (PSE, ICD-9 : 572.2; ICD-10 : 1K70.41, K72.11, K72.91), gastrointestinal or variceal bleeding (GIB, ICD-9: 456.0, 456.2, 569.3, 578, 578.0, 578.9; ICD-10 : I85.01, I85.11, K92.0, K92.1), ascites (ICD-9 : 789.5; ICD-10 : K70.31, R18.8), and spontaneous bacterial peritonitis (SBP, ICD-9: 567.23; ICD-10 : K65.2). The percentage of patients with each complication in the various SB categories was recorded.

2.4. Relationship of Admission SB Category and Hospital Metrics. Patient discharge records were queried for LOS, requirement for ICU care, and mortality.

Average LOS and the percentages of patients who required ICU admission and died during the hospitalization were determined for each SB category.

2.5. Statistical Analysis. Summary statistics were described as means and standard deviations or counts and percentages. Categorical variables between SB groups were compared using Pearson's chi-squared test or Fisher's exact test, and continuous variables were compared using the analysis of variance (ANOVA). General linear model was used to examine the difference in LOS between the SB groups adjusting for covariates. Multivariable logistic regression models were used to calculate adjusted odds ratios (aOR) of cirrhosis-related complications, ICU admission, and mortality. All models were adjusted for clinically significant covariates (i.e., age, gender, Model of End-Stage Liver Disease-Sodium [MELD-Na], and serum albumin [SA]). Amongst the 7 SB groups, SB 22–25 was considered as the reference group against which other SB groups were compared. Statistical significance was set at p-value <0.05. All analyses were performed using IBM SPSS, Version 25.0 (IBM Corp., Armonk, NY).

3. Results

3.1. Subjects. Between November 2015 and March 2019, 3,663 patients with cirrhosis aged ≥18 years were hospitalized, of which 3,540 had a SB level measured within the first 24 hours of admission.

A total of 2,693 admissions were available for analysis after excluding patients with diabetic ketoacidosis ($n = 134$), acute coronary syndrome ($n = 21$), fulminant liver failure ($n = 54$), end-stage renal disease ($n = 296$), chronic obstructive pulmonary disease ($n = 129$), systolic heart failure

Table 1: Baseline characteristics of study cohort ($N = 2693$).

Baseline characteristic	Mean ± SD	SB < 14 ($N = 66$, 2.5%)	SB 14–17 ($N = 227$, 8.4%)	SB 18–21 ($N = 662$, 24.6%)	SB 22–25 ($N = 1072$, 39.8%)	SB 26–29 ($N = 531$, 19.7%)	SB 30–33 ($N = 100$, 3.7%)	SB >33 ($N = 35$, 1.3%)
Age[§]	61.1 ± 12.3	60.5 ± 13.4	60 ± 13	60.7 ± 12.5	61.3 ± 12.4	61.8 ± 11.5	62 ± 13	61.1 ± 11.3
Male/female	1642/1051	46/20	138/89	406/256	636/436	335/196	59/41	22/13
Initial SB[§†]	22.9 ± 4.5	10.4 ± 2.7	16.0 ± 1.0	19.9 ± 1.1	23.5 ± 1.1	27.1 ± 1.1	31.1 ± 1.1	36.5 ± 3.4
Initial pH[†]	7.38 ± 0.08	7.21 ± 0.17	7.33 ± 0.09	7.38 ± 0.07	7.39 ± 0.05	7.38 ± 0.05	7.39 ± 0.07	7.38 ± 0.09
Initial BUN[§†]	91.3 ± 239.2	162.7 ± 319.2	105.5 ± 108.7	105.4 ± 424.6	82.0 ± 95.3	77.6 ± 142.7	92.3 ± 180.3	68.0 ± 67.7
Initial Cr[§†]	1.19 ± 1.04	2.76 ± 2.95	2.04 ± 1.95	1.29 ± 0.95	0.99 ± 0.52	0.96 ± 0.50	1.02 ± 0.68	0.95 ± 0.53
Initial Cl[§†]	100.2 ± 6.1	101.0 ± 9.4	101.3 ± 7.8	101.1 ± 6.2	100.5 ± 5.5	99.0 ± 5.2	96.6 ± 6.0	92.8 ± 6.4
Initial CO_2[§†]	42.7 ± 9.8	31.3 ± 13.0	34.9 ± 7.1	38.5 ± 6.3	42.6 ± 6.5	48.8 ± 8.1	54.2 ± 10.4	66.3 ± 20.1
Initial Na[§†]	137.8 ± 5.2	137.8 ± 6.9	136.2 ± 6.2	137.1 ± 5.4	138.0 ± 4.8	138.5 ± 4.5	138.5 ± 5.1	138.7 ± 5.3
AST[§]	91.7 ± 239.4	163.2 ± 319.2	105.5 ± 108.6	105.5 ± 423.9	82.9 ± 98.4	77.9 ± 142.3	92.2 ± 180.2	67.0 ± 67.7
ALT[§†]	49.8 ± 101.9	98.5 ± 355.9	54.0 ± 66.4	51.6 ± 106.6	46.2 ± 60.5	44.0 ± 80.3	67.2 ± 173.8	31.8 ± 24.1
Alk phos[§†]	155.6 ± 128.8	160.4 ± 122.5	176.4 ± 164.5	161.4 ± 132.8	152.8 ± 127.2	149.9 ± 117.0	139.2 ± 95.8	118.8 ± 58.5
Albumin[§†]	3.3 ± 0.7	3.0 ± 0.9	2.9 ± 0.8	3.2 ± 0.7	3.3 ± 0.7	3.4 ± 0.7	3.4 ± 0.7	3.2 ± 0.8
TB[§†]	3.0 ± 5.4	5.7 ± 10.2	5.3 ± 8.3	3.6 ± 6.0	2.6 ± 4.5	2.1 ± 3.3	1.8 ± 2.5	2.2 ± 3.8
INR[§†]	1.4 ± 0.8	1.9 ± 1.6	1.5 ± 0.7	1.4 ± 0.9	1.3 ± 0.5	1.3 ± 0.6	1.3 ± 0.5	2.0 ± 3.3
MELD[†]	13.8 ± 6.9	22.5 ± 9.8	18.6 ± 8.4	14.9 ± 6.9	12.6 ± 5.7	11.8 ± 5.7	11.8 ± 6.2	13 ± 5.9
MELD-Na[§†]	15.9 ± 8.3	23.8 ± 9.5	20.8 ± 8.5	17.1 ± 7.3	14.6 ± 7.3	13.5 ± 6.1	13.4 ± 7	14.6 ± 6.6

[§]Age (years at index date), SB units (mEq/L), BUN (mg/dL), Cr (mg/dL), Cl (mEq/L), CO2 (mEq/L), Na (mEq/L), AST (U/L), ALT (U/L), Alk Phos (U/L), albumin (g/dL), TB (mg/dL), INR ratio, and MELD-Na score. [†]Significant difference in frequency between SB groups ($p < 0.05$).SD, standard deviation; N, sample size; SB, serum bicarbonate; BUN, blood urea nitrogen; Cr, creatinine; Cl, chloride; CO_2, carbon dioxide; Na, sodium; AST, aspartate transaminase; ALT, alanine aminotransferase; Alk Phos, alkaline phosphatase; TB, total bilirubin; INR, international normalized ratio; MELD-Na, Model of End-Stage Liver Disease-Sodium.

Table 2: Frequency of outcomes among the study cohort*.

Outcome	Total ($N = 2693$)	SB < 14 ($N = 66$)	SB 14–17 ($N = 227$)	SB 18–21 ($N = 662$)	SB 22–25 ($N = 1072$)	SB 26–29 ($N = 531$)	SB 30–33 ($N = 100$)	SB >33 ($N = 35$)
Renal failure (AKI/HRS)[†]	624 (23.2)	46 (69.7)	120 (52.9)	197 (29.8)	164 (15.3)	67 (12.6)	14 (14)	8 (22.9)
PSE[†]	193 (7.2)	12 (18.2)	32 (14.1)	47 (7.1)	60 (5.6)	27 (5.1)	9 (9)	4 (11.4)
GIB[†]	255 (9.5)	13 (19.7)	36 (15.9)	67 (10.1)	109 (10.2)	24 (4.5)	6 (6)	0 (0)
Ascites[†]	518 (19.2)	19 (28.8)	66 (29.1)	152 (23)	176 (16.4)	77 (14.5)	12 (12)	8 (22.9)
SBP[†]	173 (6.4)	10 (15.2)	27 (11.9)	51 (7.7)	55 (5.1)	21 (4.0)	6 (6)	3 (8.6)
ICU care[†]	233 (8.7)	22 (33.3)	36 (15.9)	69 (10.4)	69 (6.4)	26 (4.9)	8 (8)	3 (8.6)
Death[†]	172 (6.4)	11 (16.7)	37 (16.3)	49 (7.4)	50 (4.7)	17 (3.2)	7 (7)	1 (2.9)
Hospital LOS (days)[†]	8.8 ± 10.9	14.2 ± 15.8	12.8 ± 13.7	10 ± 12.4	7.6 ± 9.2	7 ± 8.4	8.9 ± 13.9	9.9 ± 11

*Values represented as count (column %) or mean (±SD). [†]Significant difference in frequency between SB groups ($p < 0.001$).SB, serum bicarbonate; AKI/HRS, acute kidney injury or hepatorenal syndrome; PSE, portosystemic encephalopathy; GIB, gastrointestinal bleed; SBP, spontaneous bacterial peritonitis; ICU, intensive care unit; LOS, length of stay.

($n = 421$), previous transplantation ($n = 206$), and preadmission supplemental bicarbonate therapy ($n = 128$).

3.2. Admission SB Stratification and Clinical Characteristics. Baseline characteristics of the study cohort and the various SB groups are presented in Table 1. Mean SB was 22.9 ± 4.5 mEq/L. SB was within the normal range (22–25 mEq/L) in 1,072 (39.8%) patients, and 955 patients (36%) had a SB below the reference range. Sixty-six patients had severely decreased SB (<14 mEq/L), 227 moderately decreased SB (14–17 mEq/L), 662 mildly decreased SB (18–21 mEq/L), 531 mildly increased SB (26–29 mEq/L), 100 moderately increased SB (30–33 mEq/L), and 35 severely increased SB (>30 mEq/L). Mean age was 61 ± 12 years, and 61% were male. Recorded causes of cirrhosis were alcohol (37.2%), hepatitis C virus (33.3%), nonalcoholic steatohepatitis/cryptogenic (21.7%), hepatitis B virus (3.6%), and other (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis; 4.1%).

Age and gender distributions were similar across the SB groups. Patients with lower SB had more advanced liver disease. Serum creatinine, alanine aminotransferase, alkaline phosphatase, total bilirubin, international normalized ratio, and MELD-Na were higher in the lower SB groups, while SA was lower ($p < 0.05$).

3.3. Relationship of Admission SB Category and Cirrhosis Complications. The frequency of cirrhosis complications and adverse hospital metrics among SB categories are presented in Table 2. Univariate associations of SB categories with cirrhosis complications are presented in Table 3. As the

Table 3: Univariable association of admission SB with cirrhosis complications during hospitalization.

Variable	AKI/HRS[†]	PSE[†]	GIB[†]	Ascites[†]	SBP[†]
SB 22–25[*]	1	1	1	1	1
SB < 14	**13.22 (7.59–23.08)**	**3.75 (1.9–7.38)**	**2.17 (1.15–4.1)**	**2.06 (1.18–3.59)**	**4.96 (2.17–11.33)**
SB 14–17	**6.32 (4.64–8.60)**	**2.77 (1.76–4.37)**	**1.67 (1.11–2.5)**	**2.09 (1.5–2.9)**	**5.69 (3.35–9.65)**
SB 18–21	**2.36 (1.87–2.98)**	1.29 (0.87–1.91)	1 (0.72–1.37)	**1.52 (1.19–1.93)**	**2.44 (1.5–3.95)**
SB 26–29	0.77 (0.57–1.05)	0.9 (0.57–1.44)	**0.42 (0.27–0.66)**	0.86 (0.65–1.16)	0.41 (0.17–1.0)
SB 30–33	0.87 (0.48–1.57)	1.67 (0.8–3.47)	0.56 (0.24–1.32)	0.69 (0.37–1.3)	0.73 (0.17–3.12)
SB >33	1.58 (0.71–3.54)	2.18 (0.74–6.37)	—	1.51 (0.67–3.38)	**4.96 (2.17–11.33)**
Age[§]	**1.01 (1.004–1.02)**	1.01 (0.99–1.02)	**0.99 (0.98–0.999)**	**0.97 (0.96–0.98)**	0.99 (0.98–1.001)
Male vs female	1.16 (0.97–1.40)	1.10 (0.79–1.44)	0.92 (0.71–1.20)	**1.75 (1.42–2.16)**	1.02 (0.75–1.40)
MELD-Na[§]	**1.15 (1.13–1.16)**	**1.04 (1.03–1.06)**	1.01 (0.99–1.02)	**1.10 (1.08–1.11)**	**1.14 (1.12–1.17)**
Albumin[§]	**0.48 (0.43–0.55)**	**0.49 (0.4–0.6)**	**0.69 (0.58–0.83)**	**0.37 (0.32–0.42)**	**0.45 (0.35–0.59)**

Statistically significant ORs are in bold. [*]Reference SB group against which other SB categories were compared. [†]Unadjusted ORs (95% CI) calculated using univariable logistic regression analysis. [§]Continuous variables: age (years), MELD-Na score, and albumin (g/dL). SB, serum bicarbonate; AKI/HRS, acute kidney injury or hepatorenal syndrome; PSE, portosystemic encephalopathy; GIB, gastrointestinal bleed; SBP, spontaneous bacterial peritonitis; MELD-Na, Model of End-Stage Liver Disease-Sodium; OR, odds ratio; CI, confidence interval.

Table 4: Association of admission SB with cirrhosis complications during hospitalization.

Variable	AKI/HRS[†]	PSE[†]	GIB[†]	Ascites[†]	SBP[†]
SB 22–25[*]	1	1	1	1	1
SB < 14	**8.49 (4.31–16.72)**	**2.22 (1.08–4.56)**	**2.19 (1.12–4.27)**	0.75 (0.39–1.43)	**2.13 (1.01–4.52)**
SB 14–17	**3.64 (2.53–5.24)**	**1.69 (1.03–2.76)**	**1.56 (1.02–2.40)**	0.97 (0.66–1.41)	1.10 (0.56–2.15)
SB 18–21	**1.99 (1.52–2.62)**	1.11 (0.73–1.68)	1.00 (0.72–1.39)	1.19 (0.90–1.56)	1.44 (0.93–2.22)
SB 26–29	0.91 (0.64–1.30)	0.97 (0.59–1.59)	**0.40 (0.25–0.65)**	1.04 (0.75–1.43)	0.70 (0.42–1.16)
SB 30–33	0.98 (0.50–1.93)	1.20 (0.50–2.90)	0.56 (0.24–1.31)	0.76 (0.39–1.50)	1.29 (0.44–3.78)
SB >33	1.52 (0.59–3.95)	2.12 (0.70–6.37)	–	1.46 (0.60–3.55)	1.92 (0.56–6.55)
Age[§]	**1.03 (1.02–1.04)**	1.01 (0.99–1.02)	0.99 (0.98–1.01)	**0.97 (0.97–0.98)**	0.99 (0.97–1.00)
Male vs female	0.94 (0.74–1.18)	1.01 (0.72–1.39)	0.90 (0.69–1.19)	**1.52 (1.21–1.92)**	1.02 (0.72–1.45)
MELD-Na[§]	**1.15 (1.13–1.17)**	**1.04 (1.02–1.06)**	0.98 (0.96–1.01)	**1.08 (1.06–1.10)**	**1.15 (1.12–1.18)**
Albumin[§]	**0.84 (0.71–0.98)**	**0.61 (0.48–0.76)**	**0.73 (0.59–0.89)**	**0.52 (0.44–0.61)**	**0.65 (0.52–0.77)**

Statistically significant ORs are in bold. [*]Reference SB group against which other SB categories were compared. [†]Adjusted ORs (95% CI) calculated using multivariable logistic regression analysis adjusting for age, gender, MELD-Na, and serum albumin. [§]Continuous variables: age (years), MELD-Na score, and albumin (g/dL). SB, serum bicarbonate; AKI/HRS, acute kidney injury or hepatorenal syndrome; PSE, portosystemic encephalopathy; GIB, gastrointestinal bleed; SBP, spontaneous bacterial peritonitis; MELD-Na, Model of End-Stage Liver Disease-Sodium; OR, odds ratio; CI, confidence interval.

SB category decreased compared to the reference range, the incidence of renal failure, PSE, GIB, ascites, and SBP progressively increased ($p < 0.001$). Even a mild decrease in SB (18–21) from reference range resulted in a marked increase in frequency of SBP and renal failure [OR: 2.44 (95% CI: 1.5–3.95) and 2.36 (1.87–2.98), resp.]. Additional factors predictive of complications on univariate analysis included age, gender, MELD-Na, and SA ($p < 0.05$). Older age was associated with renal failure, and younger age and a male gender were associated with ascites ($p < 0.05$). MELD-Na score correlated with renal failure, PSE, and ascites. Lower SA was associated with renal failure, PSE, GIB, ascites, and SBP ($p < 0.05$).

The factors predictive of cirrhosis complications on multivariate analysis are presented in Table 4. SB <14 was independently associated with a higher odds of a diagnosis of AKI/HRS [aOR 8.49 (4.31–16.72)], SBP [aOR 2.1 (1.01–4.52)], PSE [aOR 2.22 (1.08–4.56)], and GIB [aOR 2.19 (1.12–4.27)]. SB 14–17 predicted higher odds of AKI/HRS [aOR 3.64 (2.53–5.24)], PSE [aOR 1.69 (1.03–2.76)], and GIB [aOR 1.56 (1.02–2.40)]. In contrast, SB higher than the reference range (SB 26–29) was associated with a lower odds of GIB [aOR 0.40 (0.25–0.65)]. Additional factors on multivariable analysis predictive of cirrhosis complications included lower SA (all complications) and higher MELD-Na (AKI/HRS, PSE, ascites, and SBP).

3.4. Relationship of Admission SB Category and Adverse Hospital Metrics

3.4.1. Hospital LOS. Mean LOS was 9 ± 11 days. As the SB category decreased compared to the reference range, LOS progressively increased (Table 5; $p < 0.001$). Even a mild decrease in SB (18–21) from reference range resulted in a substantial increase in LOS. Additional factors associated with increased LOS on univariate analysis included increased MELD-Na and lower SA. Older age, in contrast, was associated with shorter hospital LOS ($p < 0.001$).

Results of multivariate analysis of the factors associated with adverse hospital metrics are presented in Table 6. Patients in SB categories <14, 14–17, and 18–21 had significantly longer hospital LOS compared to those with SB within the reference range after adjusting for covariates [mean difference 4.07 (1.21–6.93), 3.14 (1.48–4.81), and 1.46 (0.31–2.6) days, resp.]. Higher MELD-Na and lower SA also predicted a longer LOS (0.2 days per unit increase and 1.5 days per unit decrease, resp.), and older

Table 5: Univariable association of admission SB with adverse hospital metrics.

Variable	Hospital LOS[†] Mean difference (95% CI) days	p-value	ICU care[‡] OR (95% CI)	Mortality[‡] OR (95% CI)
SB 22–25*	0	–	1	1
SB < 14	**6.60 (3.91–9.27)**	**<0.001**	**7.27 (4.12–12.81)**	**4.09 (2.02–8.29)**
SB 14–17	**5.12 (3.58–6.66)**	**<0.001**	**2.74 (1.78–4.22)**	**3.98 (2.53–6.26)**
SB 18–21	**2.32 (1.27–3.36)**	**<0.001**	**1.69 (1.19–2.4)**	**1.63 (1.09–2.45)**
SB 26–29	−0.62 (−1.74–0.50)	0.276	0.75 (0.47–1.19)	0.68 (0.39–1.18)
SB 30–33	1.29 (−0.92–3.50)	0.253	1.26 (0.59–2.71)	1.54 (0.68–3.49)
SB >33	2.28 (−1.35-5.91)	0.217	1.36 (0.41–4.56)	0.6 (0.08–4.48)
Age[§]	**−0.06 (−0.09–0.03)**	**<0.001**	**1.01 (1.001–1.02)**	**1.02 (1.01–1.03)**
Male vs female	**−0.99 (−1.82–0.15)**	**0.020**	**0.94 (0.72–1.24)**	**0.98 (0.72–1.34)**
MELD-Na[§]	**0.30 (0.25–0.36)**	**<0.001**	**1.03 (1.01–1.04)**	**1.10 (1.08–1.12)**
Albumin[§]	**−2.91 (−3.47–2.35)**	**<0.001**	**0.59 (0.49–0.71)**	**0.34 (0.27–0.43)**

Statistically significant ORs and p- values are in bold. [†]Mean difference (95% CI) in LOS calculated using general linear modeling. [‡]ORs (95% CI) calculated using univariable logistic regression analysis. *Reference SB group against which other SB categories were compared. [§]Continuous variables: age (years), MELD-Na score, and albumin (g/dL). SB, serum bicarbonate; LOS, length of stay; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; MELD-Na, Model of End-Stage Liver Disease-Sodium.

Table 6: Association of admission SB with adverse hospital metrics.

Variable	Hospital LOS[†] Mean difference (95% CI) days	p-value	ICU care[‡] adjusted OR (95% CI)	Mortality[‡] adjusted OR (95% CI)
SB 22–25*	0	—	1	1
SB < 14	**4.07 (1.21–6.93)**	**<0.01**	**6.45 (3.50–11.89)**	1.23 (0.55–2.75)
SB 14–17	**3.14 (1.48–4.81)**	**<0.001**	**2.39 (1.52–3.77)**	**1.73 (1.04–2.87)**
SB 18–21	**1.46 (0.31–2.6)**	**0.01**	**1.72 (1.20–2.46)**	1.14 (0.73–1.77)
SB 26–29	−0.19 (−1.44–1.06)	0.77	0.80 (0.49–1.30)	0.70 (0.38–1.28)
SB 30–33	0.62 (−1.77–3.01)	0.61	0.98 (0.41–2.34)	1.52 (0.61–3.80)
SB >33	2.04 (−1.8–5.89)	0.30	1.34 (0.39–4.54)	0.49 (0.61–3.90)
Age[§]	**−0.04 (−0.08–-0.01)**	**0.02**	**1.02 (1.00–1.03)**	**1.04 (1.02–1.05)**
Male vs female	0.38 (−0.54–1.3)	0.42	0.87 (0.65–1.16)	0.84 (0.59–1.20)
MELD-Na[§]	**0.23 (0.17–0.3)**	**<0.001**	1.00 (0.98–1.02)	**1.11 (1.08–1.13)**
Albumin[§]	**−1.55 (−2.21–0.89)**	**<0.001**	**0.67 (0.55–0.83)**	**0.50 (0.38–0.65)**

Statistically significant ORs and p -values are in bold. [†]Adjusted mean difference (95% CI) in LOS calculated using general linear modeling adjusting for age, gender, MELD-Na, and serum albumin. [‡]Adjusted ORs (95% CI) calculated using multivariable logistic regression analysis adjusting for age, gender, MELD-Na, and serum albumin. *Reference SB group against which other SB categories were compared. [§]Continuous variables: age (years), MELD-Na score, and albumin (g/dL). SB, serum bicarbonate; LOS, length of stay; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; MELD-Na, Model of End-Stage Liver Disease-Sodium.

age predicted a shorter LOS (−0.04 days per increase, $p = 0.02$).

3.4.2. ICU Admission. A total of 233 (8.7%) patients required ICU care. The odds of ICU admission among the SB groups on univariate analysis are presented in Table 5. Low SB was associated with ICU admission. Additional risk factors for ICU admission included older age, higher MELD-Na, and lower SA ($p < 0.05$). On multivariate analysis (Table 6) SB <14, 14–17, and 18–21 remained independent predictors of ICU admission [aOR: 6.5 (3.5–11.9), 2.4 (1.5–3.8), and 1.7 (1.20–2.46), resp.]. Other significant risk factors for ICU admission included older age [aOR 1.7 (1.04–2.87)] and lower SA [aOR 0.67 (0.6–0.80)].

3.4.3. Hospital Mortality. 172 (6.4%) patients died during the hospitalization. The odds of hospital mortality among the SB groups on univariate analysis are presented in Table 4. Declining SB, older age, higher MELD-Na, and lower SA were all associated with mortality. On multivariate analysis (Table 6) SB 14–17 predicted hospital mortality [aOR 1.7 (1.04–2.87)]. Other significant risk factors for mortality included older age [aOR 1.04 (1.02–1.05)], higher MELD-Na [aOR 1.11 (1.08–1.13)], and lower SA [aOR 0.50 (0.38–0.65)].

4. Discussion

In this study we report that admission SB was an important prognostic marker for adverse hospital outcomes for the cirrhotic patient. Low admission SB was significantly associated with an increased risk of a discharge diagnosis of renal failure, PSE, GIB, and SBP. In addition, low SB was significantly associated with longer hospital LOS, ICU admission, and inpatient mortality. Although higher MELD-Na had a similar correlation [16, 17] and higher admission albumin had a protective effect [18] as has been previously reported, the impact of admission SB persisted after adjusting for these variables. The finding of lower LOS among older patients was unexpected but might be explained by a higher mortality rate.

The liver performs a variety of metabolic processes involved in acid-base homeostasis. These include acidifying processes such as urea production and synthesis of albumin and ketoacids and alkalizing ones such as metabolism of lactate and amino acids. [1] Importantly, the healthy liver is responsible for the metabolism of up to 70% of all serum lactate with its conversion to serum bicarbonate via the Cori Cycle [19].

Patients with cirrhosis of increasing severity have progressively impaired acid-base regulation [1]. Compensated hypocapnic respiratory alkalosis is common in stable early cirrhosis [1]. In advanced cirrhosis, portal hypertension-induced vasodilation leads to low effective circulatory volume and subsequent upregulation of compensatory mechanisms that, in turn, lead to increased resorption of free water and resultant dilutional acidemia [20, 21]. Additional factors that affect acid-base status include activation of the renin-angiotensin-aldosterone system, diarrhea, and diuretic use. There is also accumulation of unmeasured anions attributed to uremic acidosis and ketoacidosis from dysregulated ketogenesis [1, 21] and reduced hepatic amino acid uptake [1, 22].

Net acidosis is frequently encountered in the cirrhotic patient with acute on chronic liver failure and sepsis that is closely associated with hyperlactacidemia [1]. Lactate is a marker of tissue hypoxia due to impaired mitochondrial oxidation [23]. Patients with decompensated cirrhosis have increased lactate production due to tissue malperfusion, impaired cellular oxygen metabolism, and a hypermetabolic state as well as reduced lactate clearance by the cirrhotic liver [19, 24, 25]. All of these acidifying factors are only moderately balanced by the alkalizing effect of hypoalbuminemia and tachypnea [26, 27].

The importance of acidosis in cirrhosis has been most extensively studied in relation to elevated lactate levels in the ICU setting. In a retrospective study comparing the acid-base profile of 178 patients with acute on chronic liver disease to that of 178 patients without liver disease, the lactate level on admission to the ICU predicted mortality only in patients with liver disease [4]. The prognostic value of lactate levels during ICU admission in liver disease was validated in a separate cohort in which it was directly associated with vasopressor use, bilirubin and INR levels, Acute-on-Chronic Liver Failure (ACLF) grade, and 28-day mortality and 1-year mortality [11].

There are multiple potential pathophysiologic processes that lead to a low SB level in the cirrhotic patient. In early cirrhosis compensatory renal acidification via decreased excretion of tubular hydrogen ions and ammonium and increased bicarbonate excretion balance the alkalizing effects of hypoalbuminemia and chronic respiratory alkalosis. A new steady state develops in which the kidney chronically suppresses bicarbonate reabsorption in return for increased chloride reabsorption, leading to low SB [28–30]. Diarrhea, which frequently occurs with lactulose therapy, is associated with the gastrointestinal loss of bicarbonate [31]. Patients with fatty liver disease often have concurrent insulin resistance which has been associated with acidosis and low SB due to excess ketone bodies [32]. Elevated intrarenal ammonia levels activate chemotactic and cytolytic complement components leading to tubule-interstitial inflammation and acidosis [33]. The effect of metabolic acidosis on renal tissue and decreased SB is further exacerbated by greater in situ activation of angiotensin II, aldosterone, and endothelin [34–36]. Spironolactone therapy is associated with serum potassium inhibition of ammonia production and subsequent metabolic acidosis [37]. In the hospitalized cirrhotic patient, administration of large volume saline can lead to hyperchloremic acidosis [1]. Finally, there is impaired retransformation of lactate to glucose and an equimolar release of bicarbonate in the liver by the Cori Cycle in critically ill patients [38].

SB level decreases in a linear fashion with increasing acid load [39], and a low SB predicts the presence of significant metabolic acidosis more reliably than pH, the anion gap, and the lactate level [8]. However, the clinical significance of SB levels in cirrhosis has received relatively little attention. In a study of 178 ICU patients with cirrhosis, those with ACLF had significantly lower SB levels than the cirrhotic patients without ACLF (18.9 mEq/L versus 22.7 mEq/L), and a low SB level was associated with 28-day mortality. [4] In a follow-up study of 185 cirrhotic patients admitted to the ICU, the SB had prognostic significance for 7-day mortality [14]. Finally, the SB level on admission was an independent predictor of ICU mortality in 177 critically ill patients with cirrhosis, and replacement of the bilirubin level with the SB level to create a "MELD-bicarbonate" score actually outperformed the original MELD score in predicting mortality [13].

Our study is the first to examine the prognostic significance of admission SB among all hospitalized cirrhotic patients with respect to adverse hospital outcomes. The attractiveness of the use of SB as a potential prognostic marker is that it is readily available as a standard test for all patients in all hospitals without the requirement for special preparation or testing, and it provides an indirect estimate of total acid accumulation. A strength of the study was the use of a large sample size and a diverse patient population. Limitations included the retrospective nature of the analysis and the use of discharge ICD coding which cannot distinguish diagnoses present on admission from those that develop during the hospitalization and the use of a one-time SB assessment. Future studies are necessary to validate our findings and to determine a possible relationship between changes in SB levels and outcomes.

Abbreviations

AKI: Acute kidney injury
ACLF: Acute-on-Chronic Liver Failure
aOR: Adjusted odds ratio
ANOVA: Analysis of variance
CKD: Chronic kidney disease
GIB: Gastrointestinal bleed
HRS: Hepatorenal syndrome
ICU: Intensive care unit
ICD: International classification of diseases
LOS: Length of stay
mEq/L: Milliequivalents per liter

MELD-Na: Model of End-Stage Liver Disease-Sodium
PSE: Portosystemic encephalopathy
SA: Serum albumin
SB: Serum bicarbonate
SBP: Spontaneous bacterial peritonitis.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon request.

Ethical Approval

This study was approved by Montefiores institutional review board and adheres to the most rigorous of ethical standards.

Disclosure

M. Schopis and A. Kumar are co-first authors.

Conflicts of Interest

The authors of this study have no conflicts of interest to disclose.

Authors' Contributions

M. Schopis and A. Kumar contributed equally to this work.

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Research Article

Systemic Inflammatory Response Syndrome in Patients Hospitalized for Acute Decompensation of Cirrhosis

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Background. Although recently challenged, systemic inflammatory response syndrome (SIRS) criteria are still commonly used in daily practice to define sepsis. However, several factors in liver cirrhosis may negatively impact its prognostic ability. *Goals*. To investigate the factors associated with the presence of SIRS, the characteristics of SIRS related to infection, and its prognostic value among patients hospitalized for acute decompensation of cirrhosis. *Study*. In this cohort study from two tertiary hospitals, 543 patients were followed up, up to 90 days. Data collection, including the prognostic models, was within 48 hours of admission. *Results*. SIRS was present in 42.7% of the sample and was independently associated with upper gastrointestinal bleeding (UGB), ACLF, infection, and negatively related to beta-blockers. SIRS was associated with mortality in univariate analysis, but not in multiple Cox regression analysis. The Kaplan–Meier survival probability of patients without SIRS was 73.0% and for those with SIRS was 64.7%. The presence of SIRS was not significantly associated with mortality when considering patients with or without infection, separately. Infection in SIRS patients was independently associated with Child-Pugh C and inversely related to UGB. Among subjects with SIRS, mortality was independently related to the presence of infection, ACLF, and Child-Pugh C. *Conclusions*. SIRS was common in hospitalized patients with cirrhosis and was of no prognostic value, even in the presence of infection.

1. Introduction

Cirrhosis is the final stage of liver diseases from different etiologies, characterized by nodular regeneration and liver fibrosis [1]. Forty percent of patients with cirrhosis may be asymptomatic and may remain that way for more than a decade, but progressive deterioration is usually observed when complications such as ascites, variceal hemorrhage, encephalopathy, hepatorenal syndrome, and infections arise. In the decompensated stage of cirrhosis, 5-year mortality is around 50%, with 70% of these deaths directly attributable to liver disease [2].

Liver cirrhosis is characterized by several systemic abnormalities, including cirrhosis-associated immune dysfunction, a condition associated with both systemic inflammation and immunosuppression [3]. As a result, infections are among the most relevant clinical problems in patients with cirrhosis. Bacterial infections are present at

admission in about one-third of the patients [4, 5] and are related to significant morbidity, mortality, and progression with acute-on-chronic liver failure (ACLF) [4, 6, 7]. Consequently, early identification of patients with cirrhosis at high risk of complications and mortality related to infections is decisive for an effective management.

For many years, systemic inflammatory response syndrome (SIRS) was used to define sepsis. Nevertheless, SIRS criterion was recognized to be limited as a prognostic tool in general population [8] and, particularly, among patients with cirrhosis [5, 9]. Several factors commonly observed among cirrhotics may impair SIRS parameters, including tachypnea due to encephalopathy, hypersplenism-related leukopenia, or bradycardia induced by beta-blockers. Recently, the Sepsis-3 criterion was proposed as new definitions of sepsis in general population and subsequently validated in patients with cirrhosis [5, 10, 11]. One of the most important limitations of these new criteria is that, in the context of a patient with cirrhosis recently admitted and without a baseline SOFA score available, Sepsis-3 criterion is of little value [5]. In addition, even outside the context of cirrhosis, these new definitions are not unanimously accepted [12]. For that reason, SIRS criterion is still commonly used in daily practice and its clinical significance in patients with cirrhosis is not completely known. Therefore, the aim of this study was to investigate the factors associated with the presence of SIRS, the characteristics of SIRS related to infection, and its prognostic value among patients recently hospitalized for acute decompensation of cirrhosis.

2. Materials and Methods

2.1. Patients. This was a prospective cohort study that evaluated patients admitted in two Brazilian tertiary hospitals (University Hospital of Polydoro Ernani São Thiago of Florianópolis, SC and Federal Hospital Bonsucesso, Rio de Janeiro, RJ) due to acute decompensation cirrhosis (AD), between January 2011 and October 2015. Subjects in the following situations were excluded: (1) hospitalization for elective procedures; (2) hospitalization for less than 48 hours; (3) admissions not related to complications of liver cirrhosis; (4) hepatocellular carcinoma outside Milan criteria; (5) extrahepatic malignancy; (6) severe extrahepatic disease; (7) use of immunosuppressive drugs; and (8) human immunodeficiency viruses (HIV) infection.

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 from the two institutions involved in the study. Informed consent was obtained from all participants or their surrogates.

3. Methods

AD was defined as the acute development of hepatic encephalopathy, large ascites, gastrointestinal bleeding, bacterial infection, or any combination of these [4].

Patients were evaluated in the first 48 hours of hospitalization by one of the researchers involved in the study, and the following clinical variables were collected: age, gender, etiology of cirrhosis, previous and current complications of cirrhosis, use of beta-blockers, and mean arterial pressure (MAP). 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 admitted for acute decompensation of cirrhosis in the hospitals involved in the study are actively screened for bacterial infections. Diagnostic paracentesis was performed in all patients with ascites. 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 [13]. Criteria for diagnosing other infections than SBP were adapted from the Centers for Disease Control and Prevention [14]. Hepatic encephalopathy was graded according to the West-Haven criteria [15] 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 vasoactive drugs (terlipressin or octreotide) and an antibiotic (either oral norfloxacin or intravenous ceftriaxone) and underwent urgent therapeutic endoscopy after stabilization [16]. The severity of liver disease was estimated by the Child-Pugh classification system [17] and MELD (Model for End-Stage Liver Disease) [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) < 4.000/μL or >12.000/μL, or immature neutrophils >10% [19]. ACLF was defined as proposed by the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium [4].

3.1. 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 the chi-square test or Fisher's exact test as appropriate. Multiple logistic regression analysis (enter method) was used to investigate the factors independently associated with the presence of SIRS and with infection among patients with SIRS. Univariate and multivariate Cox regression analyses (enter method) were used to investigate the association between the variables and survival. The Kaplan–Meier curves were used to illustrate survival according to two strata. All tests were performed by the MedCalc software, version 19.1 (MedCalc Software, Mariakerke, Belgium). A P value of less than 0.05 was considered statistically significant.

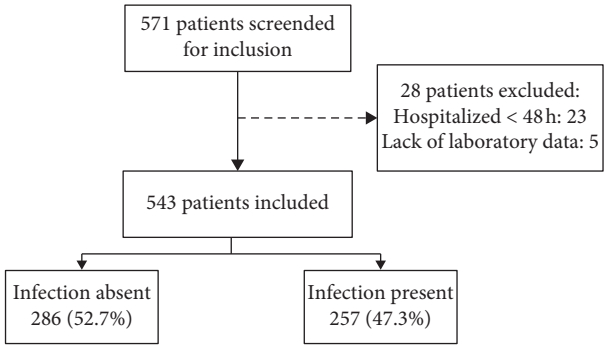

Figure 1: Flow-chart of the patients evaluated for inclusion, reasons for exclusion, and the final sample according to the presence of infection at initial evaluation.

Catarina and 256 from the state of Rio de Janeiro. Table 1 exhibits the characteristics of the included patients. The mean age was 55.4 ± 12.7 years, 64.5% were male, and the most common etiologic factor of cirrhosis was alcohol abuse (47.1%) followed by hepatitis C (40.1%). Upon admission, upper gastrointestinal bleeding was observed in 28.5% of cases, ascites in 60.2%, and hepatic encephalopathy in 45%. Bacterial infections were present in 47.3% of the sample. The most common bacterial infection was spontaneous bacterial peritonitis (10.5%) followed by skin infections (9.4%), urinary tract infection (9.2%), and pneumonia (8.7%). Infections without identified focus and less common types of infection, including bacterascites, and primary bacteraemia, accounted for 8.1% and 3.5% of the cases, respectively.

Table 1: Characteristics of included patients and comparison according to the presence of SIRS.

	All ($n = 543$)	SIRS absent ($n = 311$)	SIRS present ($n = 232$)	P
Age (years), mean ± SD	55.4 ± 12.7	56.1 ± 12.3	54.4 ± 13.0	0.133
Male gender, (%)	64.5	64.0	65.1	0.791
Diabetes, (%)	40.9	44.1	37.4	0.196
Beta-blockers, (%)	44.7	50.2	37.3	0.003
Etiology of cirrhosis (%)				
Hepatitis C	40.1	38.6	42.2	0.390
Hepatitis B Alc	5.4	6.1	4.3	0.362
Alcohol	47.1	43.4	52.2	0.043
Autoimmune hepatitis	3.7	4.2	3.0	0.477
Others	21.4	20.9	22.0	0.761
Complication at admission (%)				
Ascites	60.2	58.8	62.1	0.257
Hepatic encephalopathy	45.0	39.7	52.2	0.004
Gastrointestinal bleeding	28.5	24.8	33.6	0.024
Bacterial infection (%)	47.3	36.0	62.5	<0.001
Laboratory data				
Sodium (mEq/L), mean ± SD	134.6 ± 5.8	135.1 ± 5.4	134.0 ± 6.28	0.032
Albumin (g/dL), mean ± SD	2.4 ± 0.6	2.5 ± 0.6	2.3 ± 0.6	0.029
INR, median	1.5	1.4	1.5	0.029
Total bilirubin (mg/dL), median	2.1	1.9	2.5	0.038
Creatinine (mg/dL), median	1.1	1.0	1.2	0.004
Leukocyte count ($x10^9$), median	6.40	6.27	6.90	0.191
CRP (mg/L), median	7.3	6.3	39.1	<0.001
MELD score, mean ± SD	17.2 ± 7.0	16.3 ± 6.0	18.5 ± 7.9	<0.001
ACLF (%)	26.3	20.7	33.9	0.001
Child-Pugh classification				
A	7.0	7.3	6.6	0.757
B	50.0	55.7	42.5	0.003
C	43.0	37.0	50.9	0.001
MAP (mmHg), mean ± SD	86.4 ± 15.4	86.8 ± 15.7	86.0 ± 15.0	0.552

SIRS = systemic inflammatory response syndrome; SD = standard deviation; INR = international normalised ratio; CRP = C-reactive protein; MELD = Model for End-Stage Liver Disease; ACFL = acute-on-chronic liver failure; MAP = mean arterial pressure.

4. Results

4.1. Characteristics of the Sample. Between January 2011 and October 2015, 571 patients were screened for inclusion. Twenty-three patients were excluded because they were hospitalized for less than 48 hours and five due to lack of laboratory data (Figure 1). Therefore, the final sample was composed of 543 patients, 287 from the state of Santa

4.2. Factors Associated with the Presence of SIRS. Table 1 exhibits the comparison between patients with and without SIRS. SIRS was present in 232 patients (42.7%) and was associated with alcoholic etiology of cirrhosis (52.2% vs. 43.4%, $P = 0.043$), upper gastrointestinal bleeding (UGB) (33.6% vs. 24.8%; $P = 0.024$), hepatic encephalopathy (52.2% vs. 39.7%, $P = 0.004$), bacterial infection (62.5% vs. 36.0%, $P < 0.001$), and a lower proportion of individuals taking

Table 2: Comparison of demographic, clinical, and laboratory data according to 90-day survival.

	Survivors ($n = 377$)	Nonsurvivors ($n = 166$)	HR (95% CI)	P
Age (years), mean ± SD	54.7 ± 12.8	57.0 ± 12.2	1.012 (0.999–1.025)	0.065
Male gender (%)	63.4	66.9	1.139 (0.825–1.574)	0.429
Diabetes (%)	39.9	43.2	1.124 (0.772–1.636)	0.543
Beta-blockers (%)	45.9	41.9	0.876 (0.640–1.199)	0.409
Complication at admission (%)				
Ascites	50.9	81.3	3.450 (2.334–5.100)	<0.001
Hepatic encephalopathy	33.9	22.9	2.021 (1.483–2.775)	<0.001
Gastrointestinal bleeding	38.8	59.0	0.577 (0.394–0.844)	0.005
SIRS (%)	39.8	49.4	1.428 (1.053–1.936)	0.022
Bacterial infection (%)	20.7	40.4	2.995 (2.156–4.159)	<0.001
Laboratory data				
Sodium (mEq/L), mean ± SD	135.6 ± 5.1	132.4 ± 6.6	0.927 (0.905–0.949)	<0.001
Albumin (g/dL), mean ± SD	2.5 ± 0.6	2.2 ± 0.6	0.455 (0.353–0.586)	<0.001
INR, median	1.4	1.7	1.880 (1.614–2.189)	<0.001
Total bilirubin (mg/dL), median	1.7	3.2	1.071 (1.054–1.089)	<0.001
Creatinine (mg/dL), median	1.0	1.5	1.343 (1.257–1.436)	<0.001
Leukocyte count (x10^9), median	6.11	7.47	1.055 (1.033–1.077)	<0.001
CRP (mg/L), median	6.0	10.5	1.006 (1.004–1.008)	<0.001
MELD score, mean ± SD	14.9 ± 5.2	22.4 ± 7.5	1.119 (1.100–1.138)	<0.001
ACLF (%)	14.7	52.4	4.321 (3.181–5.870)	<0.001
Child-Pugh C (%)	31.1	69.3	3.817 (2.734–5.330)	<0.001
MAP (mmHg), mean ± SD	87.2 ± 14.9	84.6 ± 16.3	0.996 (0.984–1.008)	0.518

HR = hazard ratio; SD = standard deviation; SIRS = systemic inflammatory response syndrome; INR = international normalised ratio; CRP = C-reactive protein; MELD = Model for End-Stage Liver Disease; ACFL = acute-on-chronic liver failure; MAP = mean arterial pressure.

beta-blockers (50.2% vs. 37.3%, $P = 0.003$). Patients with SIRS also presented lower mean sodium (134.0 ± 6.3 vs. 135.1 ± 5.4 mEq/L, $P = 0.032$) and albumin (2.3 ± 0, 6 vs. 2.5 ± 0.6 mg/dL, $P = 0.029$), and higher median INR (1.5 vs. 1.4, $P = 0.029$), total bilirubin (2.5 vs. 1.9 mg/dL, $P = 0.038$), creatinine (1.2 vs. 1.0 mg/dL, $P = 0.004$), and CRP (39.1 vs. 6.3 mg/dL, $P < 0.001$). Patients with SIRS also had a higher proportion of Child-Pugh C (50.9% vs. 37.0%, $P = 0.001$) and a higher MELD score (18.5 ± 7.9 vs. 16.3 ± 6.0, $P < 0.001$).

A logistic regression analysis investigating factors independently associated with SIRS was performed including the following variables with $P < 0.05$ in the bivariate analysis: beta-blockers use, alcoholic etiology, UGB, infection, sodium, Child-Pugh C, and ACLF. Other variables with statistical significance in the bivariate analysis, such as hepatic encephalopathy, creatinine, albumin, total bilirubin, INR, and MELD, were not included in the regression analysis because they are already included or closely related to the Child-Pugh score and ACLF definition. In this analysis, SIRS was associated with UGB (OR 2.811, 95% CI 1.765–4.478; $P < 0.001$), ACLF (OR 1.688, 95% CI 1.064–2.676; $P = 0.026$), beta-blockers (OR 0.598, 95% CI 0.405–0.881; $P = 0.009$), and infection (OR 3.721, 95% CI 2.433–5.698; $P < 0.001$).

4.3. Prognostic Value of SIRS among Patients Hospitalized for Acute Decompensation of Cirrhosis. Among all the individuals included in the study, 108 (19.9%) died within 30 days and 166 (30.6%) died within 90 days of hospitalization. Table 2 shows the comparison between survivors and nonsurvivors. Ninety-day mortality was associated with ascites, hepatic encephalopathy, infection, ACLF, Child-Pugh C, SIRS, and inversely related to UGB. Mortality was also related to lower sodium and albumin levels, and higher INR, total bilirubin, creatinine, leukocyte count, CRP, and MELD. The following variables were included in a multivariate Cox regression analysis: UGB, infection, Child-Pugh C, ACLF, and SIRS criteria. In this analysis, infection (HR = 1.968, IC 95% 1.371–2.826, $P < 0.001$), Child-Pugh C (HR = 2.401, IC 95% 1.671–3.448, $P < 0.001$), and ACLF (HR = 2.824, IC 95% 2.024–3.939, $P < 0.001$) were independently related to 90-day survival. SIRS was not associated with mortality in the multivariate analysis (HR = 1.016, IC 95% 0.736–1.403, $P = 0.923$). The Kaplan–Meier survival probability of patients without SIRS was 73.0% and for those with SIRS was 64.7% (Figure 2(a)) ($P = 0.021$). Survival was evaluated according to the presence or absence of SIRS in patients infected or not. In this analysis, the Kaplan–Meier survival probability of patients without infection was similar, irrespectively of the presence of SIRS (81.4% vs. 82.8%, $P = 0.742$) (Figure 2(b)). Interestingly, even among patients with infection, similar 90-day survival was observed for patients with and without SIRS (58.0% vs. 53.8%, $P = 0.313$) (Figure 2(c)).

4.4. Factors Associated with the Presence of Infection among Patients with SIRS. In this analysis including only patients with SIRS, when compared to patients without infection, infected subjects exhibited a higher proportion of patients with ascites (73.1% vs. 43.7%, $P < 0.001$), hepatic encephalopathy (57.2% vs. 43.7%, $P = 0.045$), ACLF (42.0% vs. 20.7%, $P = 0.001$), Child-Pugh C (61.3% vs. 33.3%, $P < 0.001$), and a lower proportion of UGB (19.3% vs. 57.5%

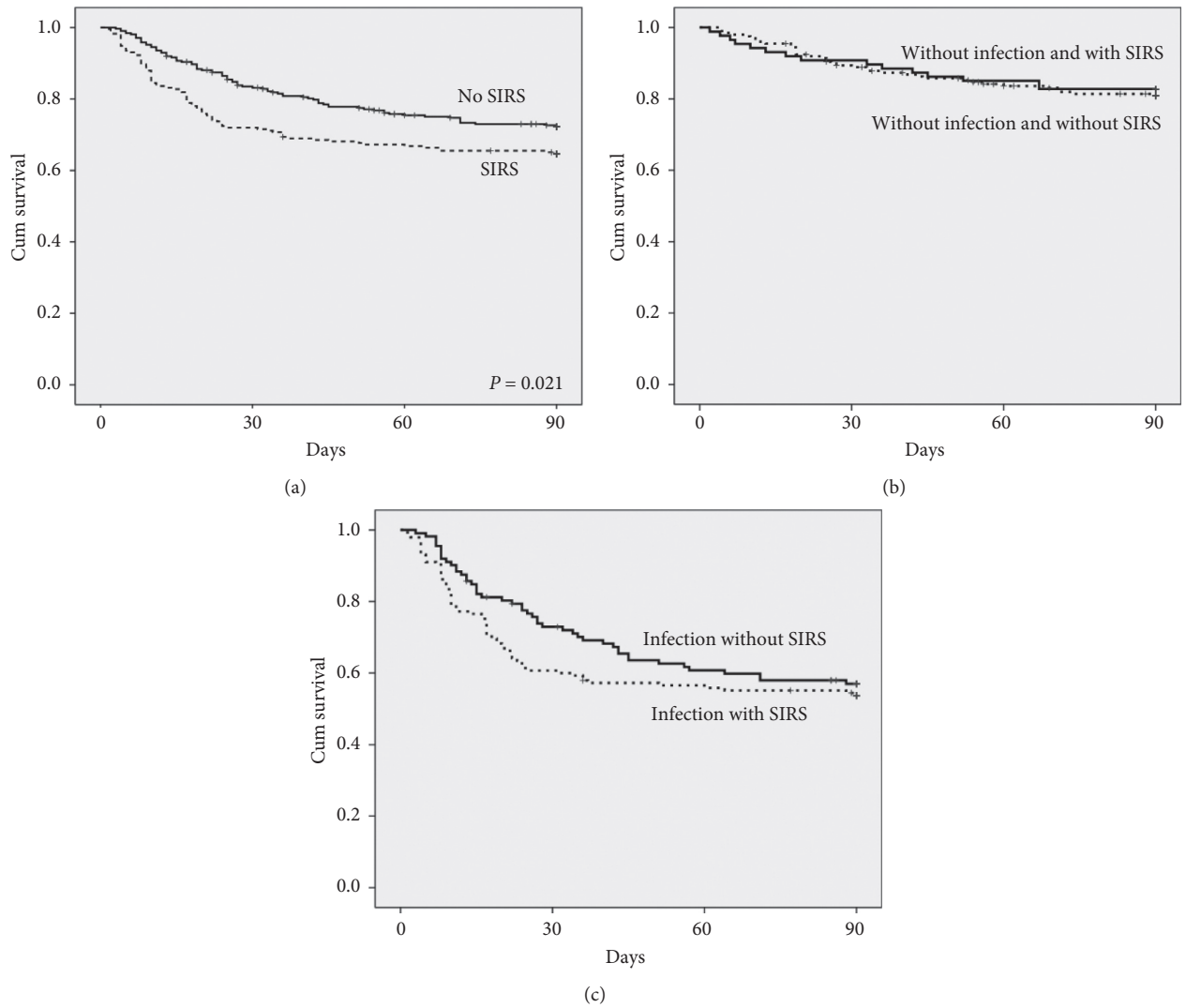

Figure 2: Cumulative 90-day survival of patients with cirrhosis according to the presence of SIRS. When considering the entire cohort, the 90-day survival probability was 73.0% for patients with SIRS and 64.7% for those without it (a). Among patients without infection, the 90-day Kaplan–Meier survival probability was 82.8% in subjects without SIRS and 81.4% in those with SIRS (b). SIRS criterion was also applied in patients with infection and the survival probability was 58.0% in subjects not fulfilling SIRS criterion and 53.8% among those who fulfill it (c).

$P < 0.001$). Patients with infection also had higher mean MELD (20.2 ± 8.2 vs. 15.6 ± 6.4, $P < 0.001$), higher median INR (1.5 vs. 1.4, $P < 0.001$), total bilirubin (3.0 mg/dL vs. 1.6 mg/dL, $P = 0.001$), creatinine (1.3 mg/dL vs. 1.0 mg/dL, $P = 0.003$), CRP (14.1 mg/L vs. 5.6 mg/L, $P = 0.005$), and lower mean serum sodium (132.9 ± 6.5 vs. 135.9 ± 29.2 mEq/L, $P = 0.007$). No relationship was observed between infection and other studied variables, including beta-blockers use (Table 3).

A logistic regression analysis was performed including only SIRS patients and with infection as a dependent variable. This analysis included the following covariates: UGB, serum sodium, ACLF, and Child-Pugh C. Again, variables already included or closely related to the Child-Pugh score and ACLF definition were not included in the regression analysis. CRP was not included in this analysis given the high number of missing values (57 cases). Infection among patients with SIRS was independently associated with Child-Pugh C (OR 2.227, 95% CI 1.147–4.325; $P = 0.018$) and inversely related to UGB (OR 0.210, 95% CI 0.111–0.397; $P < 0.001$).

4.5. Factors Associated with Prognosis among Cirrhotic Patients with SIRS. When only patients with SIRS were analyzed, univariate Cox regression showed that survival was related to the presence of ascites, HE, bacterial infection, sodium, albumin, INR, total bilirubin, creatinine, leukocyte

Table 3: Factors associated with the presence of infection among patients with SIRS.

	SIRS without infection ($n = 87$)	SIRS with infection ($n = 145$)	P
Age (years), mean ± SD	53.5 ± 11.9	55.0 ± 13.7	0.803
Male gender (%)	66.7	64.1	0.696
Diabetes (%)	35.1	39.4	0.563
Beta-blockers (%)	38.4	36.6	0.791
Complication at admission (%)			
Ascites	43.7	73.1	<0.001
Hepatic encephalopathy	43.7	57.2	0.045
Gastrointestinal bleeding	57.5	19.3	<0.001
Laboratory data			
Sodium (mEq/L), mean ± SD	135.9 ± 29.2	132.9 ± 6.5	0.007
Albumin (g/dL), mean ± SD	2.5 ± 0.6	2.2 ± 0.6	<0.001
INR, median	1.4	1.5	<0.001
Total bilirubin (mg/dL), median	1.6	3.0	0.001
Creatinine (mg/dL), median	1.0	1.3	0.003
Leukocyte count (x10^9), median	6.07	8.10	0.008
CRP (mg/L), median	5.6	14.1	0.005
MELD score, mean ± SD	15.6 ± 6.4	20.2 ± 8.2	<0.001
ACLF (%)	20.7	42.0	0.001
Child-Pugh classification			<0.001
A	11.9	3.5	0.014
B	54.8	35.2	0.004
C	33.3	61.3	<0.001
MAP (mmHg), mean ± SD	87.3 ± 13.9	85.2 ± 15.7	0.304

SIRS = systemic inflammatory response syndrome; SD = standard deviation; INR = international normalised ratio; CRP = C-reactive protein; MELD = Model for End-Stage Liver Disease; ACFL = acute-on-chronic liver failure; MAP = mean arterial pressure.

Table 4: Comparison of demographic, clinical, and laboratory data according to 90-day survival among patients with SIRS ($n = 232$).

	Survivors ($n = 150$)	Nonsurvivors ($n = 82$)	HR (95% CI)	P
Age (years), mean ± SD	54.0 ± 13.9	55.2 ± 11.4	1.004 (0.988–1.021)	0.608
Male gender (%)	64.7	65.9	1.048 (0.664–1.654)	0.842
Diabetes (%)	36.9	38.3	1.061 (0.630–1.785)	0.825
Beta-blockers (%)	38.0	35.9	0.914 (0.576–1.452)	0.704
Complication at admission (%)				
Ascites	52.0	80.5	2.935 (1.699–5.073)	<0.001
Hepatic encephalopathy	36.7	28.0	1.576 (1.013–2.451)	0.043
Gastrointestinal bleeding	48.0	59.8	0.742 (0.458–1.202)	0.225
Bacterial infection, (%)	52.0	81.7	3.328 (1.900–5.831)	<0.001
Laboratory data				
Sodium (mEq/L), mean ± SD	135.1 ± 5.8	132.2 ± 6.5	0.945 (0.916–0.976)	0.001
Albumin (g/dL), mean ± SD	2.5 ± 0.7	2.1 ± 0.5	0.454 (0.322–0.639)	<0.001
INR, median	1.4	1.6	1.583 (1.294–1.937)	<0.001
Total bilirubin (mg/dL), median	2.0	3.6	1.069 (1.046–1.092)	<0.001
Creatinine (mg/dL), median	1.0	1.7	1.265 (1.161–1.379)	<0.001
Leukocyte count (x10^9), median	6.07	9.03	1.049 (1.024–1.075)	<0.001
CRP (mg/L), median	8.5	14.9	1.005 (1.002–1.008)	0.002
MELD score, mean ± SD	15.8 ± 6.0	23.3 ± 8.4	1.094 (1.070–1.120)	<0.001
ACLF (%)	19.6	59.8	4.176 (2.679–6.512)	<0.001
Child-pugh C (%)	37.5	74.4	3.604 (2.192–5.924)	<0.001
MAP (mmHg), mean ± SD	85.7 ± 14.5	84.6 ± 16.8	0.995 (0.981–1.010)	0.526

SIRS = systemic inflammatory response syndrome; HR = hazard ratio; SD = standard deviation; INR = international normalised ratio; CRP = C-reactive protein; MELD = Model for End-Stage Liver Disease; ACFL = acute-on-chronic liver failure; MAP = mean arterial pressure.

count, CRP, MELD score, ACLF, and Child-Pugh C (Table 4). A multivariate Cox regression analysis was performed including the following variables: infection, ACLF, Child-Pugh C, and serum sodium. In this analysis, survival was independently related to infection (HR = 2.135, IC 95% 1.200–3.800, $P = 0.010$), ACLF (HR = 2.837, IC 95% 1.782–4.516, $P < 0.001$), and Child-Pugh C (HR = 2.243, IC 95% 1.324–3.803, $P = 0.003$). Among patients with SIRS, the Kaplan–Meier survival probability of patients without ACLF was 78.3% and for those with ACLF was 37.2%

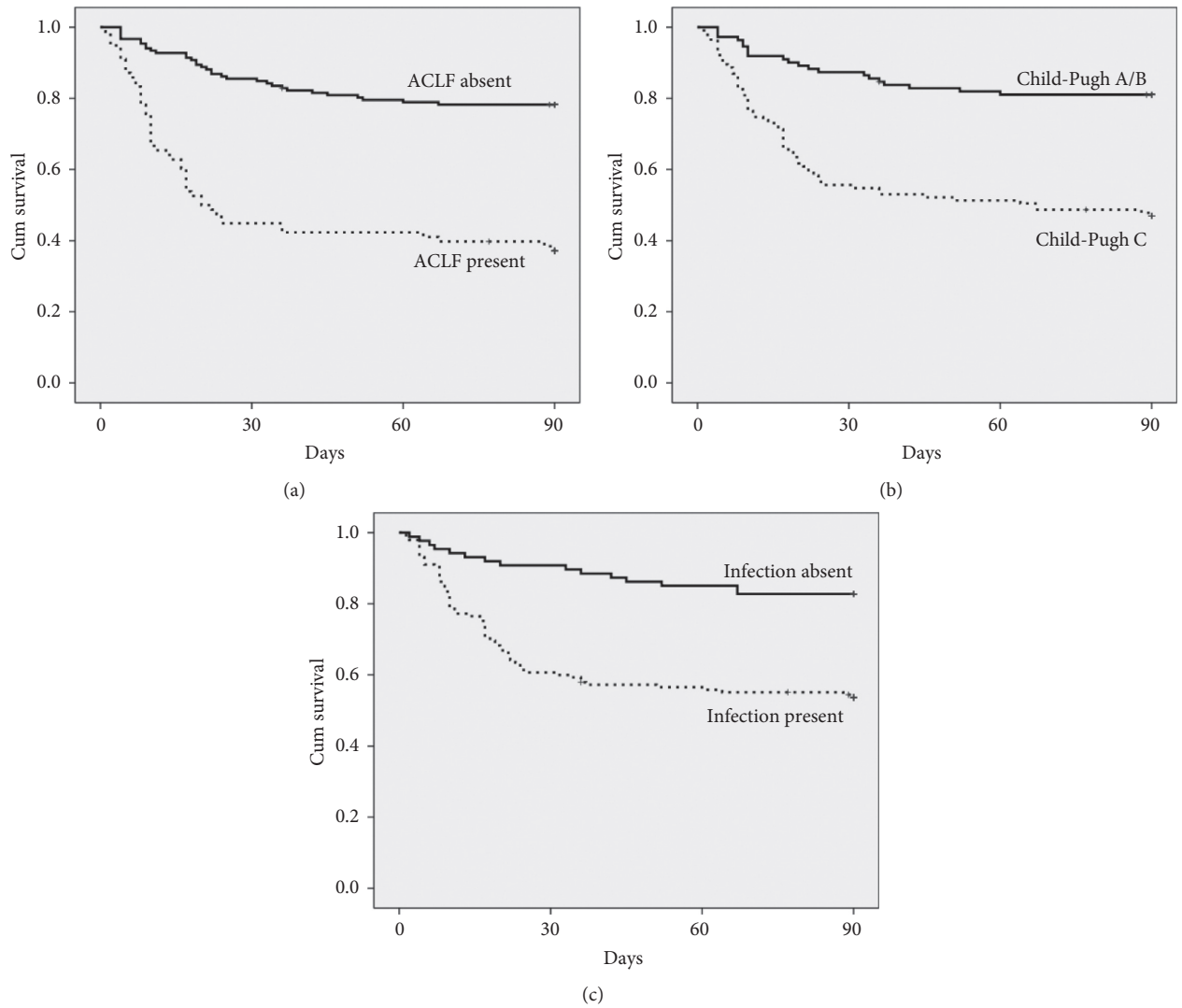

Figure 3: Factors associated with 90-day survival among patients with SIRS. The 90-day survival probability was 78.3% for patients without ACLF and 37.2% for with ACLF (a). Survival was 81.1% among Child-Pugh A/B patients and 47.0% among Child-Pugh C (b). Infection was also strongly related to lower survival among SIRS patients (53.8% vs. 82.8%, $P < 0.001$) (c).

(Figure 3(a)) ($P < 0.001$). Similarly, 90-day survival was 81.1% among Child-Pugh A/B subjects and 47.0% among Child-Pugh C (Figure 3(b)) ($P < 0.001$). Infection was also strongly related to lower survival among SIRS patients (53.8% vs. 82.8%, $P < 0.001$) (Figure 3(c)).

5. Discussion

Cirrhosis is characterized by a persistent inflammatory state that can be highly exacerbated during acute insults, especially bacterial infections [20]. However, even in the absence of clinically apparent bacterial infections, cirrhosis complications are related to an increase in bacterial translocation, contributing to an increase in the proinflammatory phenotype, possibly with systemic consequences [20, 21]. Therefore, SIRS is a common event in patients with cirrhosis admitted for acute decompensation.

In the present study, SIRS was present in 42.7% of the patients and was independently associated with ACLF, infection, and UGB and inversely related to beta-blockers. The connection between SIRS, infection, and ACLF is expected, as bacterial infections are the most common precipitant factors of both SIRS and ACLF, and the two conditions are associated with systemic inflammation and organ dysfunction [4, 22, 23]. UGB can be associated with findings of SIRS by promoting clinical and laboratory abnormalities that can mimic systemic inflammation. However, infection is a common complication of patients with cirrhosis hospitalized for UGB and also a precipitant factor for variceal bleeding [24, 25]. Nevertheless, this is unlikely in our cohort of patients recently hospitalized in whom the frequency of bacterial infection was lower in those with UGB. In the present study, beta-blockers were inversely related to SIRS. It was previously shown that chronic beta-blockers' use is associated with improvement in intestinal permeability, reduced bacterial translocation, and lower risk of infections in cirrhotic patients [26, 27]. In addition, beta-

blockers were also associated with decreased rates of sepsis [27] and improved survival of patients with acute-on-chronic liver failure [28]. However, no association between beta-blockers and survival was observed in the present study, suggesting that this supposed protective effect on SIRS development was not reflected in better prognosis. One possible explanation is that beta-blockers can lower heart rate, decreasing the proportion of patients that fulfill SIRS criteria, without exerting any other significant benefit in this context.

The presence of SIRS was associated with higher mortality in univariate Cox regression analysis. However, when evaluating according to the presence or absence of infection, no prognostic impact of SIRS was observed. In previous studies evaluating the prognostic significance of SIRS among patients with cirrhosis, SIRS was a frequent complication, ranging from 14% to 41% of the cases, and universally associated with worse prognosis [29–35]. However, in the vast majority of cases, SIRS was strongly related to infection and no comparison between patients with SIRS according to the presence of infection was performed. In two recent studies aimed at validating Sepsis-3 criteria and qSOFA in patients with cirrhosis, SIRS was associated with worse survival in univariate analysis, but not multivariate Cox regression [5, 36]. These data suggest that infection appears to be the real prognostic factor in patients hospitalized for acute decompensation of cirrhosis. SIRS criteria are of little value, if any, in determining prognosis and defining sepsis among these individuals.

As bacterial infections are commonly seen in patients with SIRS, an analysis was performed comparing patients with SIRS with and without infection. In this analysis, Child-Pugh C was independently related to the presence of infection, while admission for UGB was related to the absence of infection. There are no previous studies evaluating factors related to the presence of infection specifically among cirrhotic patients with SIRS. However, the severity of cirrhosis is associated with the risk and prognosis of bacterial infections, and also infections can further deteriorate liver function [37]. Regarding the inverse relationship between infections and UGB, these results could be partially explained by the routine use of prophylactic antibiotics that decreases significantly the infection rate [25]. However, the most obvious explanation is that infections are naturally more frequent, at least early during hospitalization, among other presentations of acute decompensation, such as hepatic encephalopathy and rapid worsening of ascites.

Among patients with SIRS, mortality was independently associated with infection, ACLF, and Child-Pugh C. Although the presence of SIRS was associated with some peculiar characteristics, prognostic factors among SIRS patients mirror those of subjects with cirrhosis without SIRS. Infections are more frequent among patients with SIRS and are importantly related to prognosis in cirrhosis [38, 39]. Similarly, ACLF is a frequent complication of advanced cirrhosis, commonly triggered by infection, and strongly related to mortality [40]. Therefore, as observed for cirrhotics in general, among patients hospitalized for acute decompensation of cirrhosis who developed SIRS, the prognosis is related to the severity of the acute insult and presence of organ failure.

In conclusion, SIRS is commonly observed among patients recently hospitalized for acute decompensation of cirrhosis, even in the absence of infections. SIRS without infection was frequently related to UGB and was of no prognostic value. Even in patients with infection, the presence of SIRS was not associated with higher mortality. These data indicate that SIRS criterion is of no value in determining prognosis or in defining sepsis among patients with cirrhosis and its use should be discouraged in clinical practice.

Data Availability

Data are available on request from the authors

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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