ORIGINAL STUDY

The value of presepsin and procalcitonin as prognostic factors for mortality in patients with alcoholic liver cirrhosis and acute on chronic liver failure

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ABSTRACT

Background: Acute on chronic liver failure (ACLF) is typically characterized by a rapid progression of liver failure in patients with liver cirrhosis and it is triggered by a precipitant factor, usually a bacterial infection (BI). Considering the low accuracy of the inflammation biomarkers in liver cirrhosis, presepsin and procalcitonin have demonstrated a good diagnostic performance for BI. Understanding the key prognostic factors that influence patient outcomes can significantly impact clinical decision-making and improve patient care in ACLF which can lead to lower mortality rates. **Aim:** To evaluate the prognostic factors associated with 30-day mortality in patients with alcohol-related liver cirrhosis and ACLF. **Methods:** This retrospective study on 227 patients diagnosed with ACLF and alcohol-related liver cirrhosis analyzed the prognostic role of presepsin and procalcitonin serum levels. **Results:** The survival analysis according to the grade of ACLF showed that more than 80% of patients with ACLF grade 1 survived after 30 days, with a mean estimated time of death of 29±0.44 days (95 % CI: 28.17-29.92) compared to ACLF grade 2 (24.9±1.064 days; 95 % CI: 22.82-26.99) and ACLF grade 3 (21.05±1.17 days; 95 % CI: 18.75-23.34), with a mean overall survival on entire cohort of 25.69±0.52 days (95 % CI: 24.65-26.73). Presepsin (OR: 4.008, CI 95:3.130-6.456, p=0.001) and procalcitonin (OR: 3.666, CI 95:2.312-5.813, p=0.001) were the most significant factors associated with 30-day mortality. In ACLF grade 2, presepsin provides a better prediction of mortality at the cutoff value of 1050 pg/mL (Sensitivity 72%, Specificity 69%) than procalcitonin (AUC=0.727 95% CI 0.594-0.860, $p<0.002$) whereas in ACLF grade 3, a cutoff of 1450 pg/mL (Sensitivity 89%, Specificity 91%) presepsin had a more significant accuracy of mortality prediction (AUC=0.93 95% CI 0.81-0.99, $p<0.001$) than procalcitonin (AUC=0.731 95% CI 0.655-0.807, $p<0.001$). **Conclusion:** ACLF is associated with a high mortality rate and the risk of death increases with the grade of ACLF. Presepsin and procalcitonin serum levels are good prognostic factors for 30-day mortality and should be used in clinical practice to stratify the risk and provide and early and efficient treatment in patients with ACLF.

KEYWORDS: liver cirrhosis; acute on chronic liver failure; mortality; prognostic factors; presepsin; procalcitonin

1. INTRODUCTION

Liver cirrhosis is a serious medical condition characterized by extensive fibrosis and consequently portal hypertension and liver failure which are associated with high morbidity and mortality rates [1]. It is caused by long-term liver damage due to various etiologic factors such as heavy alcohol consumption, hepatitis B (HBV) or C (HCV) infections, or fatty liver disease. The burden of liver cirrhosis on public health is significant due to its high prevalence worldwide and its associated complications such as liver failure, hepatocellular carcinoma, and increased risk of other health issues [2]. In an effort to decrease the mortality rates in patients with liver cirrhosis, the main liver societies across the globe have been focusing in the last years on the elimination of etiologic factors such as HBV and HCV infections, alcohol consumption and fatty liver disease [3-5]. It is important to raise awareness about cirrhosis, promote healthy liver habits, and improve access to healthcare services for early diagnosis and management of etiologic factors.

Acute on chronic liver failure (ACLF) is a serious condition that occurs in individuals with liver cirrhosis who experience an acute decompensation [6]. ACLF is typically characterized

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by a rapid progression of liver failure and is associated with high short-term mortality rates [7]. ACLF is categorized into three stages based on the severity of the condition: (i) stage 1 ACLF: this stage is considered when there is an acute deterioration of the liver function, but with no organ failures or complications; (ii) stage 2 ACLF is defined by the presence of single or multiple organ failures, such as kidney dysfunction, brain dysfunction (hepatic encephalopathy), or circulatory system issues. (iii) stage 3 ACLF is the most severe stage of ACLF, characterized by multi-organ failure or dysfunction, significantly increasing the risk of mortality [8]. Management of ACLF involves intensive care and treatment to support liver function and stabilize other affected organs [9]. Early recognition and management of ACLF are crucial to improving outcomes for individuals with this condition.

Infections in ACLF significantly contribute to higher mortality rates and pose a considerable challenge in the management of this complex condition [10-12]. Patients with ACLF are particularly susceptible to infections due to immune dysregulation, impaired liver function, and systemic complications [10]. Infection-related complications can further compromise the already altered liver function in ACLF patients, leading to multi-organ dysfunction, sepsis, and increased mortality risk [11,12]. Sepsis is a life-threatening condition caused by an extreme response to infection, leading to tissue damage, organ failure, and potentially death [13]. Despite advancements in medical care, sepsis remains a major cause of morbidity and mortality worldwide. Early diagnosis and prompt treatment are crucial for improving patient outcomes. However, the clinical diagnosis of sepsis is often challenging due to its heterogeneous presentation. The need for reliable biomarkers which can provide an early and accurate diagnosis has led to significant research interest. Among these, presepsin and procalcitonin have emerged as promising biomarkers [14]. Presepsin (soluble CD14 subtype, sCD14-ST) is a fragment of the CD14 molecule, which is released into the bloodstream in response to bacterial infections [15]. It has been shown to rise rapidly during the early stages of sepsis, making it a potential early indicator. Presepsin's ability to differentiate between bacterial and viral infections further enhances its clinical utility. Procalcitonin is another biomarker that has gained attention for its role in diagnosing sepsis. It is a precursor of the hormone calcitonin, and its levels increase significantly in response to bacterial infections [15]. Procalcitonin levels correlate with the severity of infection and sepsis, and they have been used to guide antibiotic therapy, thereby helping to reduce unnecessary antibiotic use and combat antibiotic resistance.

Patients with ACLF are particularly vulnerable to infections and sepsis due to their compromised immune system and underlying chronic liver disease. Prompt recognition, early diagnosis, and appropriate management of infections are critical in improving outcomes for ACLF patients [16]. Timely initiation of antimicrobial therapy, infection control measures, and vigilant monitoring for signs of infection are essential strategies in reducing mortality rates associated with ACLF [8,17].

Despite the potential of these biomarkers, their comparative effectiveness in clinical practice requires further investigation. This study aims to evaluate the value of presepsin and procalcitonin as prognostic factors for mortality in patients with alcoholic liver cirrhosis and ACLF and to assess their utility in guiding therapeutic decisions. By addressing these parameters, this study seeks to provide valuable insights into the early management of ACLF, ultimately contributing to better clinical outcomes for these patients.

2. PATIENTS AND METHODS

2.1. Study design

We retrospectively analyzed consecutive patients diagnosed with alcohol-related liver cirrhosis and ACLF who were admitted in a tertiary hospital from 1st January 2022 to 31st December 2023. The grade of ACLF was assessed using the CLIF-SOFA score [18], and the diagnosis was made using established criteria [19]. The 30-day mortality rate was calculated for all patients and potential thresholds for irreversible ACLF episodes were identified and proposed based on prognostic factors. The exclusion criteria were as follows: advanced malignancies (including hepatocellular carcinoma), decompensated cirrhosis without ACLF, and those with other etiologic factors for liver cirrhosis than alcoholic disease.

2.2. Study population

All cases were identified by reviewing the hospital records during the study period. To ascertain the severity of the chronic liver disease and verify the presence of diagnostic criteria for ACLF, patients who were admitted for liver-related reasons were cross-referenced with their medical records, as previously described.

The Local Ethics Committee granted approval for the study (No. 102/10.10.2019). The study was conducted in accordance with the principles of the Declaration of Helsinki. Before participating in the study, all patients or their legal representatives signed the written informed consent.

2.3. Identifying and categorizing ACLF

ACLF was diagnosed according to the criteria established by the European Association for the Study of the Liver (EASL), which defines it as an acute decompensation of cirrhosis and organ failure [8]. The severity was evaluated using the CLIF-SOFA score, which assesses six organ systems (liver, kidneys, brain, coagulation, circulation, and lungs) on a scale of 0 to 4, with a higher score indicating more severe dysfunction [8]. To establish definitions and parameters for organ failures and ACLF grades, in addition to the indication for Intensive care unit (ICU) admission, the following criteria were used: an urgent need for organ support (vasopressors, mechanical ventilation, or renal replacement therapy); gastrointestinal massive bleeding; cerebral dysfunction caused by hepatic encephalopathy West Haven grade III-IV (airway protection) or septic shock [8]. Acute organ dysfunction caused by confirmed or suspected infection, characterized by hypotension that was not responsive to fluid resuscitation, was the hallmark of septic shock [20].

2.4 Data Acquisition

The following demographic data was collected: age, sex, BMI, presence of type 2 diabetes mellitus, sarcopenia, other comorbidities, and etiology of liver disease. Sarcopenia was diagnosed by calculating the target body weight for height and age based on anthropometric measurements (hand grasp, mid-arm muscle circumference, triceps skin-fold thickness). If a hand grasp was not feasible, two clinicians conducted a subjective bedside assessment. The laboratory data collected at the time of ICU admission: platelet count,

CRP, WCC, albumin levels, INR, creatinine, bilirubin, serum sodium levels, presepsin, and procalcitonin to determine the risk of infection. The serum presepsin level was assessed upon admission using the chemiluminescent enzyme immunoassay method. A PATHFAST® presepsin analyzer (Mitsubishi Chemical Mediace Corporation, Tokyo, Japan) was used for determination with a detection limit of the method of 20 pg/mL. Procalcitonin was assessed using an immunoassay (Cobas 8000, Roche Diagnostics, Basel, Switzerland), with a limit of detection of 0.02 ng/mL. The duration of ICU and hospital stay, the number and type of organ failures, the primary reason for admission, and the mortality rates at 30 days were all recorded. Additionally, the prognostic score for the liver disease severity Model for End-Stage Liver Disease (MELD and MELD-Na) was documented.

2.5. Statistical Analysis

Data were analyzed using the Student's t-test for parametric data and the Mann–Whitney U Test for non-parametric data. Continuous variables were reported as median (interquartile range) based on their distribution, as assessed by the Shapiro–Wilk test while categorical variables, were described using absolute numbers and percentages. To identify independent predictors of 30-day survival, variables were assessed using binary logistic regression. Survival of the patients according to the grade of ACLF at admission was estimated using Kaplan–Meier plots and log-rank tests. The accuracy of presepsin and procalcitonin in predicting mortality was evaluated using the ROC (Receiver Operating Characteristic) curve. Statistical significance was defined as a p-value of less than 0.05. SPSS version 24 software (IBM Corp, Armonk, NY) was employed to conduct statistical analyses.

3. RESULTS

3.1. Patients Characteristics

During the study period, 320 patients with liver cirrhosis and ACLF were admitted to our department. Among them, 227 patients were eligible and fulfilled the inclusion criteria (Figure 1). The demographic, clinical and blood tests are presented in Table 1. Overall, 60% were males, with a median age of 58 years (IQR 48.66). Regarding the severity of the liver disease, 34 (15%) of the patients were classified as Child-Pugh class B while 193 (85%) were included in class C. We found higher MELD (26, IQR: 20-32) MELD-Na (28, IQR:23-32) scores in patients in which death occurred at 30 days since admission. Fifty-four (23.8%) of the patients had variceal bleeding, 101 (44%) had infections of which 46 (20.3%) were diagnosed with spontaneous bacterial peritonitis (SBP) and 152 (62%) had overt hepatic encephalopathy (EH). The 30-day mortality rate in all patients was 34.8%, a significant proportion being represented by those with ACLF grade 3 (60.8 %), and Child-Pugh class C (95%). Patients in whom death occurred, had an increased level of white blood cells (WBC) $13.7x10^9$ /L (IQR: 8.2-20.1, p=0.008), total bilirubin 10.36 mg/dl (IQR: 2.36-22.19, p=0.047), INR 2.6 (IQR:1.99-3.25, $p<0.001$), creatinine 2.3 mg/dL (IQR:1.18-3.41, p=0.003), serum Na 122 mmol/L (IQR: 117-126, $p<0.001$) and an albumin level <2.8 g/dl (84.8%). Furthermore, deceased patients had more increased levels of C-reactive protein (CRP), (5.6 mg/dL, IQR:2.12-14, $p<0.001$), procalcitonin, (13 ng/mL, IQR: 11-15, $p<0.001$) and presepsin (1630 pg/mL, IQR:1200-2425, $p<0.001$), than those who were alive at 30 days since admission.

3.2. Prognostic factors of mortality

According to binary logistical regression analysis (Table 2), an increased score of Child-Pugh (OR: 1.766, CI 95%: 1.326-2.715, p=0.015), respectively MELD (OR: 1.926, CI 95%: 1.537-2.182, p=0.007) and MELD-Na (OR: 1.974, CI 95%: 1.780-2.992, p=0.001) scores at admission, increased with approximately two folds the risk of 30-day mortality. Moreover, the altered coagulation status (OR: 2.472, CI 95:1.008-6.064, p=0.048) and decreased sodium level (OR: 1.827, CI 95:1.458-2.771, p=0.001) bring an additional risk of mortality. The presence of variceal bleeding (OR: 1.430, CI 95:1.207-1.728, p=0.001) and SPB (OR: 2.052, CI 95:2.009-5.289, p=0.001) at inclusion, stress the increased risk of death. Presepsin (OR: 4.008, CI 95:3.130-6.456, p=0.001) and procalcitonin (OR: 3.666, CI 95:2.312-5.813, p=0.001) were the most significant factors associated with 30-day mortality.

3.3 Assessing the risk of mortality using the levels of presepsin and procalcitonin

To proactively assess the 30-day mortality risk, the levels of presepsin and procalcitonin were evaluated upon admission depending on the ACLF level. According to the ROC

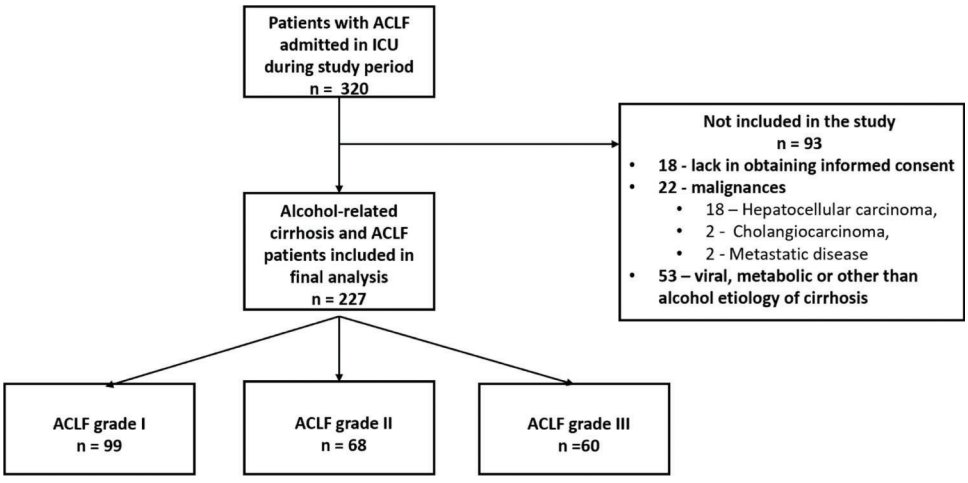

Fig. 1. Flow chart of patients' selection process.

Table 1. Patients' characteristics and descriptive analysis between 30-day mortality groups.

Variable	All patients n = 227	30-day survivors n = 148 (65.2%)	30-day deaths n = 79 (34.8)	*p* - value
Age, median (IQR)	58 (48-66)	58 (47-66)	58 (50-66)	0.633
Male, n (%)	136 (59.9)	86 (58.1)	50 (63.3)	0.174
ACLF grade 1/2/3, n (%)	99 (43.6) / 68 (30) / 60 (26.4)	92 (62.2) / 44 (29.7) / 12 (8.1)	7 (8.9) / 24 (30.4) / 48 (60.8)	< 0.001
Child-Pugh class B/C, n (%)	34 (15) / 193 (85)	30 (20) / 118 (80)	4 (5) / 75 (95)	< 0.001
Child-Pugh score, median (IQR)	12 (10-13)	11 (10-12)	12 (12-14)	< 0.001
MELD score, median (IQR)	26 (20-32)	24 (20-29)	29 (22-33)	< 0.001
MELD-Na score, median (IQR)	28 (23-33)	27 (22-32)	30 (25-36)	< 0.001
WCC (x109/L), median (IQR)	12.7 (6.18-16.9)	8.1 (5.5-11.4)	13.7 (8.2-20.1)	0.008
Total bilirubin (mg/dL), median (IQR)	8.02 (2.23-18.48)	7.26 (2.16-15.77)	10.36 (2.36-22.19)	0.047
INR, median (IQR)	1.9 (1.6-2.6)	1.9 (1.56-2.09)	2.6 (1.99-3.25)	< 0.001
Creatinine (mg/dL), median (IQR)	1.92 (0.95-2.64)	1.73 (0.87-2.4)	2.3 (1.18-3.41)	0.003
Serum Na (mmol/L), median (IQR)	129 (122-135)	132 (128-137)	122 (117-126)	< 0.001
C-reactive protein, (mg/dL), median (IQR)	3.87 (1.77-8.49)	3 (1.35-6.13)	5.6 (2.12-14)	< 0.001
Ammonia (mmol/L), median (IQR)	134.5 (78-198.5)	126 (71-180.5)	144 (93-220)	0.036
Presepsin, (pg/mL), median (IQR)	77 (66-1017)	67 (45-88)	1630 (1200-2425)	< 0.001
Procalcitonin, (ng/mL) median (IQR)	2.01 (1.50-12)	1.7 (1.3-2)	13 (11-15)	< 0.001
Albumin < 2.8 g/dl, n (%)	122 (53.7)	55 (37.2)	67 (84.8)	< 0.001
Variceal bleeding, n (%)	54 (23.8)	9 (6.1)	45 (57)	< 0.001
SBP, n (%)	46 (20.3)	6 (4.1)	40 (50.6)	< 0.001
Overt HE, n (%)	152 (62)	102 (68.9)	50 (63.3)	0.392
T2DM, n (%)	55 (24.2)	26 (17.6)	29 (36.7)	0.001

Abbreviations: WCC, white blood cell count; SBP, spontaneous bacterial peritonitis; T2DM, type 2 diabetes mellitus.

Table 2. Prognostic factors of mortality in ACLF patients.

Parameter	OR	CI 95%	*p* - Value
Age, median (IQR)	1.024	0.981-1.069	0.287
Male, n (%)	0.985	0.363-2.673	0.976
Child-Pugh score, median (IQR)	1.766	1.326-2.715	0.015
MELD score, median (IQR)	1.926	1.537-2.182	0.007
MELD-Na score, median (IQR)	1.974	1.780-2.992	0.001
WCC (x109/L), median (IQR)	1.335	1.186-1.834	0.012
Total bilirubin (mg/dL), median (IQR)	1.529	1.144-1.978	0.005
INR, median (IQR)	2.472	1.008-6.064	0.048
Creatinine (mg/dL), median (IQR)	1.105	1.002-1.668	0.035
Serum Na (mmol/L), median (IQR)	1.827	1.458-2.771	0.001
C-reactive protein, (mg/dL), median (IQR)	1.202	1.071-1.349	0.002
Ammonia (mmol/L), median (IQR)	0.996	0.911-1.001	0.318
Presepsin, (pg/mL), median (IQR)	4.008	3.130-6.456	0.002
Procalcitonin, (ng/mL) median (IQR)	3.666	2.312-5.813	0.001
Albumin < 2.8 g/dl, n (%)	1.857	1.314-2.342	0.044
Variceal bleeding, n (%)	1.430	1.207-1.728	0.001
SBP, n (%)	2.052	2.009-5.289	0.001
Overt HE, n (%)	0.568	0.105-3.085	0.513
T2DM, n (%)	1.012	0.813-1.268	0.296

Abbreviations: WCC, white blood cell count; SBP, spontaneous bacterial peritonitis; T2DM, type 2 diabetes mellitus.

curve analysis, both biomarkers do not provide significant mortality prediction in patients with ACLF grade 1 regarding 30-day mortality risk (presepsin-AUC=0.679, 95% CI 0.433-0.881, p=0.168, respectively procalcitonin- AUC=0.679, 95% CI 0.506-0.853, p=0.155). Notably, in what concerns ACLF grade 2, presepsin (AUC=0.901, 95% CI 0.816-0.986, $p<0.001$) provides better prognosis of mortality at a cutoff of 1050 pg/mL (Sensitivity 72 %, Specificity 69 %) than procalcitonin (AUC=0.727, 95% CI 0.594-0.860, $p<0.002$). Similar results were noticed in patients with ACLF grade 3, presepsin having a more significant prognostic value (AUC=0.93, 95% CI 0.81-0.99, $p<0.001$) at cutoff value of 1450 pg/mL (Sensitivity 89 %, Specificity 91 %) than procalcitonin (AUC=0.731, 95% CI 0.655-0.807, $p<0.001$) (Figures 2-4).

The survival analysis according to the grade of ACLF at admission stresses that more than 80 % of patients with ACLF grade 1 survived after 30 days of admission with a mean estimated time of death of 29 $\pm$0.44 days (95 % CI: 28.17-29.92) compared to ACLF grade 2 (24.9 $\pm$ 1.064 days; 95 % CI: 22.82-26.99) and ACLF grade 3 (21.05 $\pm$ 1.17 days; 95 % CI: 18.75-23.34) with a mean overall survival on entire cohort of 25.69 $\pm$ 0.52 days; 95 % CI: 24.65-26.73) (Figure 5).

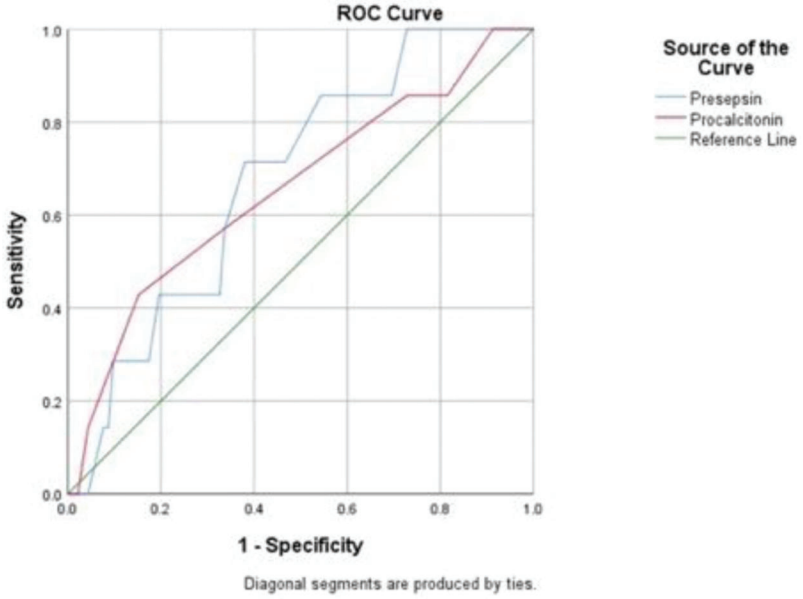

Fig. 2. Comparison of presepsin and procalcitonin in predicting 30-day mortality in ACLF grade 1.

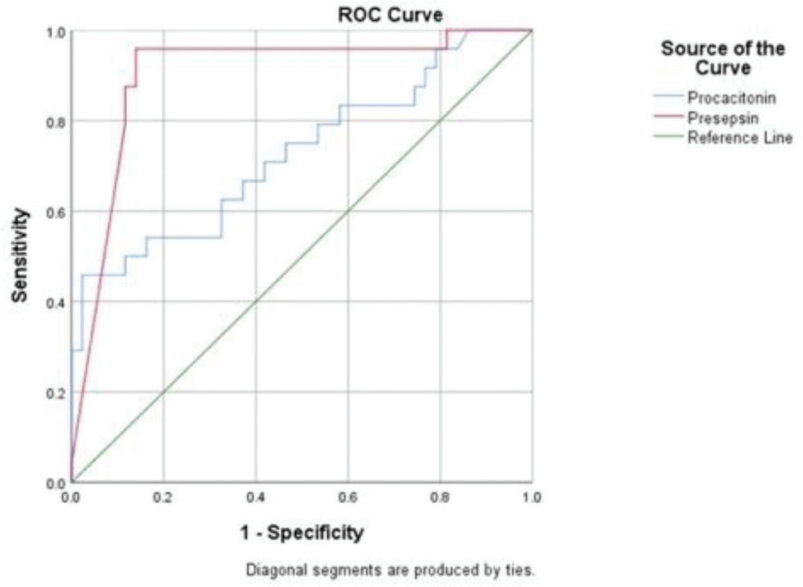

Fig. 3. Comparison of presepsin and procalcitonin in predicting 30-day mortality in ACLF grade 2.

4. DISCUSSION

Due to persistent immune dysfunction associated with liver cirrhosis, these patients are highly susceptible to acquiring bacterial, fungal, or viral infections, increasing the risk of sepsis, severe sepsis, and septic shock [21]. Bacterial infections, particularly with multidrug-resistant organisms (MDRO), are the primary cause of ACLF in patients with cirrhosis, contributing to mortality in up to 50% of cases [22-25]. The most common bacterial infection leading to ACLF in decompensated cirrhosis is spontaneous bacterial peritonitis (SBP), typically caused by Gram-negative bacteria migrating from the gut into ascitic fluid [18]. In patients with alcohol-related cirrhosis who continue heavy alcohol consumption, increased intestinal permeability raises the risk of bacterial translocation and the development of SBP [26]. Therefore, SBP is the predominant precipitating factor for ACLF in alcoholic cirrhosis, with some studies reporting its occurrence in up to 44% of severe alcoholic hepatitis cases upon admission [27]. In our study, SBP accounted for 20.3% of all sepsis-induced ACLF cases.

The 30-day mortality rate in our cohort was 34.8%, with a significant proportion occurring in patients with ACLF grade 3. Gustot et al., in a study involving 388 patients from the European Chronic Liver Failure (CLIF) ACLF in Cirrhosis study, reported a 28-day mortality rate ranging from low-to-

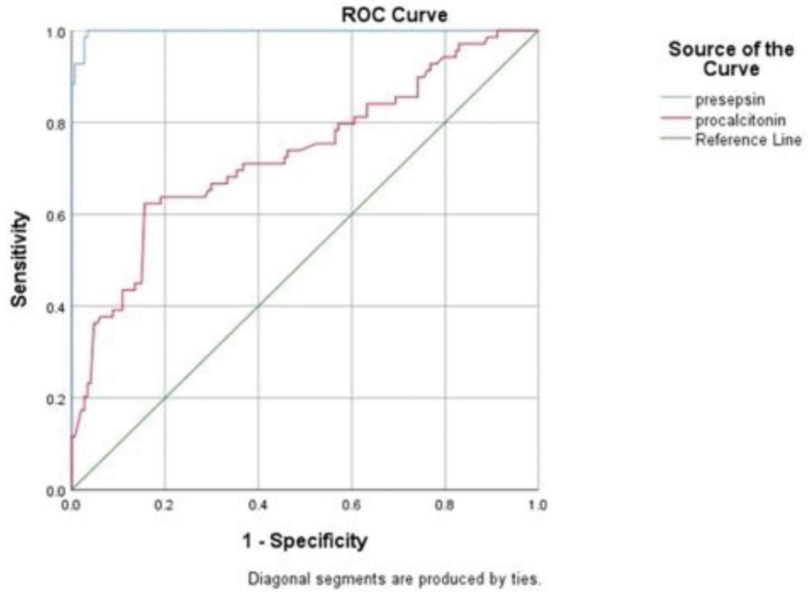

Fig. 4. Comparison of presepsin and procalcitonin in predicting 30-day mortality in ACLF grade 3.

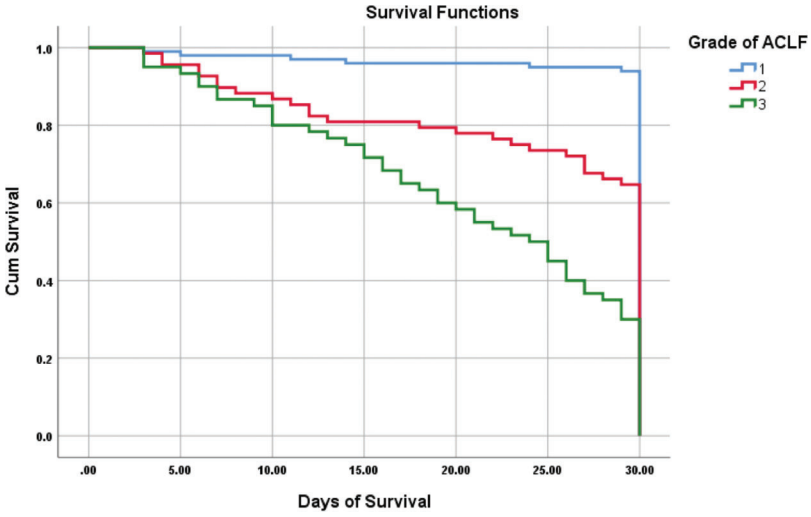

Fig. 5. Kaplan-Meier analysis curve of mortality according to ACLF grade.

moderate (up to 18%) in ACLF grade 1 patients to high-to-very high (between 42% and 92%) in ACLF grade 2 or 3 patients [28]. Similarly, we observed higher mortality rates in ACLF grade 3 compared to grades 2 and 1 (61% vs. 30% and 9%, respectively; $p < 0.001$).

We found that an elevated Child-Pugh score, Model for End-Stage Liver Disease (MELD), and MELD-Na scores upon admission approximately doubled the risk of 30-day mortality. These findings align with previous literature. For example, in a cohort study of 249 ACLF patients, liver-specific (Child-Pugh and MELD) and ACLF prognostic scores (CLIF-C OF, CLIF-SOFA, CLIF-C AD, CLIF-C ACLF) significantly and independently predicted in-hospital mortality [29].

The presence of variceal bleeding and SBP at admission also increased the risk of one-month mortality. Da Silva et al. identified variceal bleeding as a primary factor predicting 28-day mortality in ACLF patients admitted to intensive care units, with half of their cohort presenting with variceal bleeding as the primary reason for ACLF development [30]. Digestive hemorrhage is widely recognized as a leading cause of ACLF in all forms of liver cirrhosis [8,24,25]. Predictive factors for treatment failure and poor prognosis in patients with variceal bleeding include MELD score, renal failure, bacterial infection, and active bleeding during endoscopy [31-33]. ACLF exacerbates the prognosis in variceal bleeding, nearly doubling the risk of rebleeding [34].

Regarding the prediction of 30-day mortality, presepsin (OR: 4.008, 95% CI: 3.130-6.456, p=0.001) and procalcitonin (OR: 3.666, 95% CI: 2.312-5.813, p=0.001) were identified as significant factors. However, both biomarkers did not significantly predict mortality in ACLF grade 1 patients regarding one-month mortality. Notably, in ACLF grade 2, presepsin demonstrated better prognostic ability for

mortality at a cutoff of 1050 pg/mL (Sensitivity 72%, Specificity 69%) compared to procalcitonin (AUC=0.727, 95% CI 0.594-0.860, $p<0.002$). Similar results were observed in ACLF grade 3 patients, where presepsin showed higher accuracy in predicting mortality (AUC=0.93, 95% CI 0.81-0.99, $p<0.001$) at a cutoff of 1450 pg/mL (Sensitivity 89%, Specificity 91%) compared to procalcitonin (AUC=0.731, 95% CI 0.655-0.807, $p<0.001$). Presepsin, a protein derived from the co-receptor for bacterial ligands CD14, serves as an effective biomarker of innate immune activation and is useful for early infection diagnosis in cirrhotic patients [35,36]. In a previous study, we demonstrated that presepsin levels $\geqslant$2300 pg/mL were associated with infections in ACLF patients [12]. Furthermore, we found a direct correlation between presepsin levels, disease severity assessed by MELD score, and Child-Pugh class. A 2018 study including compensated and decompensated cirrhosis patients showed that presepsin levels >600 pg/mL were associated with increased one-year liver-related mortality [37]. In contrast, we identified higher cutoff values (1050 pg/mL for ACLF grade 2 and 1450 pg/mL for ACLF grade 3). It is important to note that our cohort consisted of alcoholic patients with acute decompensated cirrhosis and ACLF, all meeting ICU admission criteria, whereas the previous study included both compensated and decompensated cirrhosis patients, with mortality assessed at one year after inclusion.

Our study underscores the superior prognostic value of presepsin over procalcitonin in assessing 30-day mortality risk in ACLF grades 2 and 3. This finding is supported by various pathophysiological mechanisms and existing literature. Presepsin, a soluble CD14 subtype, is released during bacterial infections and inflammation [15]. It serves as a marker for innate immune response activation, particularly in sepsis and systemic inflammatory response syndrome (SIRS) [38]. Elevated presepsin levels in advanced ACLF patients likely reflect the severity of inflammatory response and immune dysregulation associated with the disease. This is consistent with ACLF pathophysiology, where systemic inflammation plays a crucial role in disease progression and mortality. In contrast, procalcitonin is a precursor of calcitonin and is produced in response to bacterial infections and endotoxemia. While procalcitonin is also a reliable sepsis biomarker, its levels may not rise significantly in early-stage or localized infections, potentially limiting its sensitivity in predicting mortality in ACLF patients compared to presepsin [39]. Our findings are in line with other studies that have evaluated the prognostic utility of presepsin and procalcitonin. For example, Behnes et al. found significantly higher presepsin levels in non-survivors compared to survivors among sepsis patients, suggesting its potential as a mortality predictor [40]. Similarly, Liu et al. reported higher diagnostic accuracy for presepsin than procalcitonin in predicting septic shock and mortality [41]. In contrast, Bianchini et al. reported excellent prognostic value for procalcitonin in 28- and 90-day mortality in patients with decompensated cirrhosis with or without ACLF at admission [42].

The superior performance of presepsin in predicting 30-day mortality in ACLF grades 2 and 3, with higher sensitivity and specificity at identified cutoff values, highlights its potential clinical utility. The identified thresholds (1050 pg/mL for grade 2 and 1450 pg/mL for grade 3) could serve as important risk stratification and management tools.

Our study has some strengths and limitations. The main strength is the large number of patients included in our cohort. Considering the wide range of clinical presentation and sometimes unpredictable behavior of ACLF, it is important to obtain as much data as possible to depict a clear landscape of this condition. The limitations of our study are represented by the short follow-up period, the retrospective nature of the study and the alcoholic etiology as the only cause of liver cirrhosis.

5. CONCLUSION

ACLF is associated with a high mortality rate and the risk of death increases with the grade of ACLF. Presepsin and procalcitonin serum levels are good prognostic factors for 30-day mortality and should be used in clinical practice to stratify the risk and provide and early and efficient treatment in patients with ACLF. Our study supports the use of presepsin as a more reliable biomarker than procalcitonin for predicting 30-day mortality in patients with advanced ACLF. Future research should focus on validating these findings in larger cohorts and exploring the integration of presepsin measurement into routine clinical protocols for managing ACLF.

Conflict of Interest

None.

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