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ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Julio Coelho, MD, PhD, Professor, Department of Surgery, Federal University of Parana, Curitiba 80240-110, Parana, Brazil. coelhojcu@yahoo.com.br

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The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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MINIREVIEWS

Assessing the prognosis of cirrhotic patients in the intensive care unit: What we know and what we need to know better

Fernando da Silveira, Pedro H R Soares, Luana Q Marchesan, Roberto S A da Fonseca, Wagner L Nedel

ORCID number: Fernando da Silveira 0000-0002-1435-6599; Pedro H R Soares 0000-0003-1504-2396; Luana Q Marchesan 0000-0002-3609-6900; Roberto S A da Fonseca 0000-0001-8116-6878; Wagner L Nedel 0000-0003-2539-4256.

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Fernando da Silveira, Programa de Pós-Graduação em Pneumologia, Universidade Federal do Rio Grande do Sul, Porto Alegre 91430835, Brazil

Fernando da Silveira, Pedro H R Soares, Luana Q Marchesan, Roberto S A da Fonseca, Wagner L Nedel, Intensive Care Unit, Grupo Hospitalar Conceição, Porto Alegre 91430835, Brazil

Pedro H R Soares, Programa de Pós-Graduação em Neurociências, Universidade Federal do Rio Grande do Sul, Porto Alegre 91430835, Brazil

Luana Q Marchesan, Programa de Pós-Graduação em Ciências da Saúde, Universidade Federal de Santa Maria, Santa Maria 97105900, Brazil

Wagner L Nedel, Programa de Pós-Graduação em Bioquímica, Universidade Federal do Rio Grande do Sul, Porto Alegre 91430835, Brazil

Corresponding author: Wagner L Nedel, MD, MHSc, Chief Doctor, Senior Research Fellow, Intensive Care Unit, Grupo Hospitalar Conceição, Av Francisco Trein, 357, Porto Alegre 91430835, Brazil. wagnernedel@uol.com.br

Abstract

Critically ill cirrhotic patients have high in-hospital mortality and utilize significant health care resources as a consequence of the need for multiorgan support. Despite this fact, their mortality has decreased in recent decades due to improved care of critically ill patients. Acute-on-chronic liver failure (ACLF), sepsis and elevated hepatic scores are associated with increased mortality in this population, especially among those not eligible for liver transplantation. No score is superior to another in the prognostic assessment of these patients, and both liver-specific and intensive care unit-specific scores have satisfactory predictive accuracy. The sequential assessment of the scores, especially the Sequential Organ Failure Assessment (SOFA) and Chronic Liver Failure Consortium (CLIF)-SOFA scores, may be useful as an auxiliary tool in the decision-making process regarding the benefits of maintaining supportive therapies in this population. A CLIF-ACLF > 70 at admission or at day 3 was associated with a poor prognosis, as well as SOFA score > 19 at baseline or increasing SOFA score > 72. Additional studies addressing the prognostic assessment of these patients are necessary.

Key Words: Cirrhosis; Extrahepatic organ failure; Organ replacement therapy; Mortality; Prognostic scores; Chronic Liver Failure Consortium-Sequential Organ Failure Assess-

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ment; Sequential Organ Failure Assessment; Model for End-stage Liver Disease

Core Tip: Assessing the potential benefits of maintaining or suspending supportive therapies for cirrhotic patients who are not eligible for liver transplantation is a major challenge at the bedside, especially in those admitted to general intensive care units (ICUs). In this article, we identify the main causes of ICU admission, analyze the main factors associated with prognosis, and provide a tool to assist the decision-making process.

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INTRODUCTION

Liver cirrhosis (LC) accounts for more than 7000 deaths per year in France and more than 25000 deaths per year in the United States[1]. The World Health Organization recently estimated that cirrhosis is the 12th leading cause of mortality in the world, with alcohol, hepatitis B virus and hepatitis C virus being the main causes of cirrhosis [2,3]. Cirrhotic patients account for 2.3% and 4.5% of all intensive care units (ICUs) admissions[1], and their mortality is traditionally high-approximately 34% to 69% depending on the reason for admission[2]. The increased effectiveness of supportive treatments and the spread of liver transplantation programs have improved the prognosis of these patients[1,4-6]. Nonetheless, the prognosis of cirrhotic patients admitted to the ICU remains poor[7], especially among those admitted to the general ICU who are ineligible for transplantation. The prognosis is determined by the extent of hepatic and extrahepatic organ dysfunction[8]. The occurrence of three or more organ failures in cirrhotic patients has an almost certain fatal outcome[6,9]. For ethical reasons and due to limited resources, physicians need to be able to quickly identify cases that benefit from aggressive treatment and ICU admission, discriminating good candidates for ICUs from those for whom the prognosis is poor despite strong therapeutic interventions.

CIRRHOTIC PATIENTS ADMITTED TO THE ICU – AN OVERVIEW

Hemodynamic changes in patients with cirrhosis, linked to sodium retention, the development of ascites, and alterations in systemic and splanchnic hemodynamics and coagulation, are linked to systemic impairments in organ function, especially cardiomyopathy and renal dysfunction in this population[10]. A systemic inflammatory response has been observed in these patients, with complex immune dysfunction that increases the complexity of treatment and mortality in comparison with the general population[6,11]. High-grade hepatic encephalopathy (HE), septic shock, acute-on-chronic liver failure (ACLF), variceal bleeding, the need for mechanical ventilation and acute kidney injury (AKI) are clinical decompensations that most commonly motivate admission to the ICU[6].

Sepsis and septic shock

Infections are among the main reasons for admission of these patients to the ICU, as 30%–50% of patients with cirrhosis either present with infection during admission or develop infection during hospitalization[2,12]. Sepsis is a consequence of the host response to infection[13] and it is characterized by the release of pro- and anti-inflammatory cytokines and pro- and anti-coagulant substances in response to pathogens [14]. Several studies have highlighted the major influence of cirrhosis on the susceptibility to severe bacterial infections, with higher in-hospital mortality rates as a result

of septic shock in cirrhotic relative to noncirrhotic patients (71% *vs* 49%, respectively) [15,16]. Cirrhotic patients have an altered defense against bacteria associated with reduced bacterial clearance. This immune defect facilitates bacterial translocation induced by the increased intestinal permeability and gut bacterial overgrowth observed in cirrhosis[17]. Sepsis leads to the production of various inflammatory mediators that are increased in cirrhotic patients compared to noncirrhotic septic patients[6]. This state leads to complex organ alterations that often lead to the development of extrahepatic organ dysfunction, including HE and renal, respiratory, and circulatory failure during sepsis, a syndrome referred to as ACLF, which is also associated with a deterioration in hepatic function[18]. Commonly encountered infections in cirrhosis include spontaneous bacterial peritonitis, pneumonia, urinary tract infection, and cellulitis[19]. Sepsis is more common in cirrhotic than in noncirrhotic ICU patients, and it is also associated with a higher mortality rate[15]. Variables associated with mortality in septic cirrhotic patients are the presence of more than one site of infection, Child C status and elevated Model for End-stage Liver Disease (MELD) score[12].

Variceal bleeding

Cirrhotic patients with variceal bleeding are usually transferred to the ICU for hemodynamic stabilization. The fate of variceal bleeding in cirrhotic patients has changed over the last two decades[14]. Overall hospital mortality decreased from 42% in 1980 to 14% in 2000[20]. ICU admissions for variceal bleeding fell significantly in the last decade and were associated with a decrease in mortality over time[21]. Although overall mortality rates have decreased in cirrhotic patients with variceal bleeding, it is still high in the first 6 wk after the initial episode, and could exceed 30% in those with more severe disease and in those with multiorgan failure[5,6,22]. Rebleeding occurs in up to 20% of patients during the first 6 wk, and in this case, the mortality rate can exceed 50%. Patients with Child C or MELD ≥ 18, portal vein thrombosis, bacterial infections, and renal failure have a high likelihood of recurrence or death[6].

AKI

Cirrhosis-associated AKI is usually multifactorial and commonly involves bacterial infections, hypovolemia (secondary to overdiuresis, hemorrhagic shock, large-volume paracentesis or diarrhea), drug-induced nephrotoxicity, parenchymal renal disease and, in the absence of these causes, hepatorenal syndrome (HRS)[5,23]. With a yearly rate of 8%–12%, HRS-AKI is quite common in decompensated cirrhosis with ascites[10,23]. In hospitalized patients, it is approximately 25% and it increases up to 40%–60% in those admitted to the ICU[14,24]. AKI is associated with a poor prognosis and represents an important predictor for short-term mortality in patients with cirrhosis [25].

Encephalopathy

HE is a brain dysfunction caused by liver failure and/or portosystemic shunts and it manifests as a wide spectrum of neurological and/or psychiatric abnormalities[26]. Approximately 30%–40% of patients with cirrhosis present with an episode of HE at some time of their illness, with a poor prognosis and a mortality increase of 50% within 1 year after the episode of HE[6]. Patients with more severe grades (grade III-IV) could require admission to the ICU and orotracheal intubation and eventually prolonged MV, variables that are associated with increased mortality in this scenario [27,28].

Short and long-term mortality in ICU-cirrhotic patients

Short-term mortality in ICU-cirrhotic patients ranges from 42% in the ICU to 54% during hospitalization[29]. There is variability between different studies due to different selection criteria for patient admission between centers, differences between therapeutic strategies (including liver transplantation) and the low number of patients studied in each cohort in this short period of time[30]. During the ICU stay, prolonged MV is an important prognostic marker for ICU mortality[28]. Among the long-term mortality data for cirrhotic patients, there is high in-hospital mortality with reduced survival rates at 6 mo and 1 year. Thus, the one-year survival rate was 32% among patients alive at discharge from the ICU[9]. In another large study of short- and long-term survival, we found a comparable reduction in survival, with 8%–21% patients dying shortly after ICU discharge. In the ICU, 28-d, 3-, 6-mo, and 1-year mortality rates were 47%, 53% (116/218), 66%, 74%, and 77%, respectively[7]. The Glasgow coma scale, mean arterial pressure, bilirubin, and albumin determined on admission to the ICU have independent prognostic significance for assessing 6-month mortality. Severe

sepsis had the strongest association with increased 6-month mortality among the primary ICU admission reasons[29].

PROGNOSTIC SCORES IN CIRRHOTIC PATIENTS ADMITTED TO THE ICU

Liver cirrhosis is characterized by a long phase of compensated disease until the first episode of decompensation occurs. The time elapsed until such an event is variable and unpredictable; however, it marks a change in the progression of the liver disease [30]. Upon acute decompensation, some of these patients develop organ failure and need to be admitted to the ICU for optimal treatment. Historically, the in-hospital mortality rates of these patients are very high, promoting the idea that admitting them to the ICU would be a futile measure[22]. More current series show that the hospital mortality of these patients is quite heterogeneous, reflecting the varying degrees of hepatic involvement that these patients may present on admission to the ICU, as well as their different reasons for admission to the ICU[31].

Even so, the nonnegligible mortality rates of critically ill patients with liver cirrhosis, associated with scarce and expensive intensive care resources, make the indication of ICU admission of this population a matter of debate. Prognostic scores are helpful in this decision-making, aiming at therapeutic proportionality at the individual level and an adequate allocation of resources at the institutional level. The prognostic scores can be specific to each pathology. In the case of liver cirrhosis, we can mention Child–Pugh (CP), the MELD, and the Chronic Liver Failure-Consortium ACLF (CLIF-ACLF) score, for example, or assessments common to all patients admitted to the ICU, such as the Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. These scores can be performed immediately upon admission to the ICU (first 24 h) or during the first days of hospitalization, leading to an evolutionary assessment over this short period of time. We can also evaluate the prognosis of decompensated liver cirrhosis taking into account the number of organic disorders at its presentation. The most relevant studies regarding prognostic scores are summarized in Table 1.

General ICU scores have been frequently used in the evaluation of cirrhotic patients. However, these scores do not include the complexity of chronic liver disease, including the heterogeneity of its clinical stages and possible etiologies, thus imposing caution in the use of these tools. On the other hand, CP and MELD incorporate limited information about extrahepatic organic dysfunction. Next, the main scores will be discussed, as well as comparisons of their performances.

HEPATIC-SPECIFIC SCORES

CP and MELD

The chronic liver disease severity score described by Child in 1964 and modified by Pugh in 1973 was used to describe the prognosis of patients undergoing surgical ligation of esophageal varices, demonstrating that patients with less perioperative liver dysfunction had lower mortality in six months[32]. It is currently used to assess the severity of chronic liver disease. The MELD score was described to predict mortality at 3 mo in patients electively submitted to the placement of portosystemic shunts[33] and later used to prioritize patients listed for liver transplantation because it proved to be a reliable mortality risk index[34].

Specific scores for cirrhosis, such as CP and MELD, seem ideal for prognosis in cirrhotic patients with slow decompensation but do not perform well in those with acute decompensation accompanied by multiple organ and system dysfunction (DMOS). DMOS is a clinical condition where there are multiple acute systemic failures (renal, circulatory, neurologic, hematological, pulmonary, hepatic) associated with an initial injury, most commonly sepsis, trauma or shock[35,36]. They show moderate results[37], with the MELD score showing slightly better results than the CP[3]. The MELD score has reasonable discriminatory power (AUROC = 0.81) in predicting mortality in cirrhotic patients admitted to the ICU, approaching the SOFA score (AUROC = 0.83)[31].

Variations of MELD: MELD-sodium

Dilutional hyponatremia is common in patients with advanced cirrhosis, and the inclusion of natremia in the MELD score has been suggested to increase its prognostic

Table 1 Accuracy of prognostic scores in intensive care units cirrhotic patients

Ref.	Year	*n*	ICU/hospital mortality	APACHE II	SAPS II	SOFA	CP	MELD	MELD-Na	RFH	CLIF-SOFA
Cholongitas *et al*[31], 2006	2006	312	65%	0.78		0.83	0.72	0.81		0.83	
Das *et al*[41], 2010	2010	138	54%		0.78	0.84	0.76	0.77	0.75		
Levesque *et al*[42], 2012	2012	377	43%		0.89	0.92	0.79	0.82	0.79		
Cholongitas *et al*[44], 2008	2012	412	61%	0.74		0.85	0.67	0.80	0.75		
Emerson *et al*[45], 2014	2014	59	48%	0.72		0.76	0.70	0.74			0.75
Campbell *et al*[46], 2015	2015	115	46%	0.71		0.71	0.68	0.70		0.77	0.74
McPhail *et al*[51], 2015	2015	971	52%	0.76	0.78	0.79		0.78			0.81

ICU: Intensive care units.

capacity for mortality, with greater importance when the MELD scores are lower[38, 39]. The MELD-Na score was better than the MELD score for predicting mortality in some studies[40] but less accurate than the SOFA score[41-43].

CP variation: CP + L

More recent data suggest that lactate, a component of the prognostic model of fulminant hepatitis, is an independent marker of mortality in patients with cirrhosis admitted to the ICU[44] and it seems to significantly improve the CP score's ability to predict ICU mortality[45]. Serum lactate and ascites are independent predictors of ICU mortality, as proposed by the CTP + L score. This score incorporates serum lactate levels into CP, increasing its discriminatory ability as a prognostic stratification tool. Subsequently, a retrospective cohort study with a total of 199 cirrhotic patients admitted to a general ICU at two different centers validated the CP + L score as a predictor of mortality, showing results superior to the original CP: AUC CP + L 0.75 and AUC CP 0.68. In this work, the MELD and SOFA scores had AUCs of 0.7 and 0.71, respectively[2].

Royal free hospital score

Studies have suggested that an alternative approach to predict mortality in patients with decompensated cirrhosis could be the number of organ dysfunctions at its presentation, ranging from 4% in patients without DMOS to 90% in those with three or more organ dysfunctions and thus in a DMOS scenario[31]. In this context, a specific score for cirrhosis was developed and subsequently modified[43], taking into account possible organic failures involved during acute decompensation, the Royal Free Hospital Score (RFH). This score was shown to have a performance similar to the SOFA score and superior to APACHE II, MELD, and CP.

A retrospective cohort study by Campbell *et al*[46], with a total of 199 cirrhotic patients admitted to the ICU, validated the RFH score as a predictor of mortality in the ICU with an accuracy of 0.77, which was higher than the other scores evaluated: CP, CP-L, MELD, SOFA and CLIF-SOFA. The RFH score is the first liver-specific score to be matched, in terms of mortality predictive ability, to the general ICU scores used in these patients. In addition to the fact that it includes hepatic and extrahepatic parameters of organ dysfunction associated with higher mortality in this subset of patients, the inclusion of lactate levels in this score should be highlighted. Despite the well-known relationship between serum lactate levels and worse outcomes[2], no other hepatic-specific score proposed thus far has included this parameter.

ICU mortality and morbidity scores (dysfunction)

ICU-specific mortality scores were created to assist the intensive care physician in predicting the outcome of patients admitted to the ICU. Among these scores, the most important are the APACHE II and SOFA scores. APACHE II uses the worst physiological variables of the patient in the first 24 h of ICU stay for its elaboration, in addition to previous comorbidities and age[47]. The SOFA score assesses the severity of patients admitted to the ICU according to the number of organ dysfunctions. The score is graded in five levels (from 0 to 4 points) for six organ systems: neurological, hemodynamic, respiratory, renal, hematological and hepatic, with a score greater than or equal to 3 in any organ system constituting organ failure[48]. Unlike the APACHE II

score, which is performed at a specific time in the ICU (24 h of admission), the morbidity scores allow for an evolutionary assessment throughout the days of ICU admission[48].

These scores have already been evaluated in specific populations of cirrhosis[15]. When compared to each other and with specific scores for cirrhosis, the SOFA score shows moderate to high accuracy, higher than the other scores, even for long-term mortality[3,45,49]. Lindvig *et al*[3], in their systematic review, found that the SOFA score has better accuracy for death prediction, with an AUROC between 0.81% and 0.95%, a value higher than the APACHE II score (AUROC 0.66-083), MELD (AUROC 0.77–0.93) and CP (AUROC 0.71–0.87).

ACLF

ACLF is a clinical syndrome characterized by acute liver cirrhosis decompensation associated with one or more organic disorders and a high short-term mortality rate. The European Association for Study of Liver/CLIF (EASL-CLIF Consortium) has established diagnostic criteria for ACLF with a view, above all, to identify patients at greater risk of death in the short term. For the establishment of the ACLF diagnostic criteria, the presence of organic dysfunction and a high mortality rate at 28 d (> 15%) in cirrhotic patients with acute decompensation were considered. The assessment of organ dysfunction, in turn, was based on the SOFA score, but with modifications taking into account the pathophysiological and clinical characteristics of cirrhosis, giving rise to the CLIF-SOFA score[50].

CLIF-SOFA improves the hematological, neurological, cardiovascular, and renal domains by considering commemoratives usually present in chronic liver disease patients, as well as the peculiarities of the clinical manifestations and therapy used during acute decompensation. Objectively, the hematological parameter is no longer the platelet count giving rise to the measurement of INR. The neurological parameter now includes the presence of HE stratified under West Haven criteria, and in the cardiovascular and renal domains, it takes into account the use of terlipressin and renal replacement therapy, respectively. There is also a change in the hepatic domain with elevation of the total bilirubin threshold to characterize this organ dysfunction.

McPhail *et al*[51] demonstrated the validity of the CLIF-SOFA score in terms of its ability to predict mortality with a slight improvement over the SOFA score and other prognostic scores. Aiming at a better performance than CLIF-SOFA, the CLIF-C ACLF score was developed based on CLIF organ failure score scores, the latter also a derivation of SOFA and CLIF-SOFA[52]. However, the CLIF-C ACLF showed a slightly higher prognostic accuracy for 28-d mortality than the CLIF-SOFA scores and it was moderately higher than MELD, MELD-Na and Child–Pugh: agreement index of 0.76; 0.72; 0.68; 0.68; 0.66, respectively[52].

Evolutionary assessment of scores-what we need to know better?

Most prognostic scores in critically ill populations are constructed with data collected over the first 24 h of ICU admission. However, multiorgan failure seems to be related to a worse prognosis among patients with acute cirrhosis decompensation[1,4,22]. Seeking to increase the accuracy of prognostic scores in cirrhotic patients admitted to the ICU, a baseline assessment of the score followed by its reanalysis in a short period of time seems to be more accurate in predicting hospital mortality. The SOFA score seems to be the score with the best discrimination power when compared to the CTP, MELD, APACHE II scores, both at the initial time and when reassessed at 48 h: AUC for mortality, after 48 h of 0.88; 0.78; 0.86 and 0.78, respectively[44]. The modified SOFA score (removing the hepatic component from the score) was also shown to be highly accurate and with better discriminative power when compared to CP, MELD, and APACHE II scores both on the first day of ICU admission (AUC 0.84) and on the third day (AUC 0.83)[41]. It is interesting to note that the presence of 3 to 4 organ dysfunctions after 72 h of admission to the ICU is related to an important increase in mortality during hospitalization[41].

A limitation of the prognostic scores evaluated on admission to the ICU is to neglect the continuum of physiological changes in critical patients with decompensated cirrhosis[53]. The serial assessment of the SOFA score throughout the ICU stay contemplates the dynamics of the occurrence of organic dysfunctions, including the effects of the offered therapy[44,54]. Both the analysis of the variation in the SOFA score (Δ-SOFA) and access to the mean and maximum SOFA values during ICU admission are good prognostic indicators, regardless of the value of the score accessed

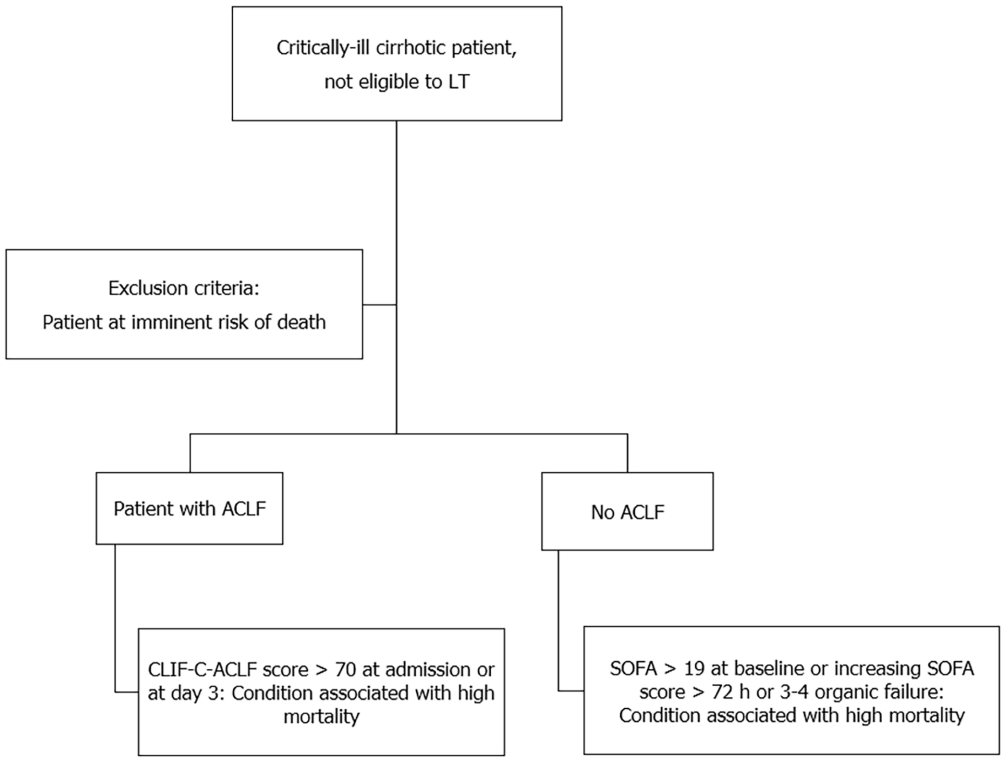

Figure 1 Proposed algorithm for prognostic scores in critically-ill cirrhotic patients. ACLF: Acute-on-chronic liver failure; CLIF: Chronic Liver Failure Consortium; SOFA: Sequential Organ Failure Assessment.

at the time of admission[54]. In a retrospective cohort study comprised of 971 patients, the CLIF-SOFA score seemed to have a slightly higher accuracy than the SOFA score for mortality (AUC 0.81 *vs* 0.79) when evaluated during the first day of hospitalization and an improvement in death prediction at 48 h after ICU admission. However, the results seem overlapping when evaluated on the seventh day of ICU stay, with both showing good discriminatory power[51]. Dynamic prognostication seems to be the most promising strategy when establishing the prognosis of this population, especially in those with ACLF, septic shock and multiorgan failure[55]. A proposed algorithm is summarized in Figure 1. A trial of unrestricted intensive care for a few days could be proposed as a reasonable strategy in this population[41]. There are also opportunities for novel biomarkers of ACLF to improve existing models and potentially reflect information not currently captured in the conventional clinical and biochemical data [56].

An important limitation of prognostic studies in this field is that the interpretation of ROC curves is necessary because the criteria for therapeutic limitations or even the removal of supports are not reported in these studies, which leads to falsely high areas under the curves. Another limitation of prognostic scores is that they were not designed to predict outcomes beyond mortality, such as cost-effective treatment, recovery of physical activity or the quality of life after the ICU stay. In addition, some organ dysfunction scores may give similar weights for organ dysfunction with very different prognoses[57]. Alteration of the level of consciousness due to HE after bleeding from esophageal varices and even chronic thrombocytopenia, common in advanced cirrhosis, has a better prognosis than that of vasopressor or acute loss of renal function. Figure 1 outlines a structured assessment model based on prognostic scores in this population. A condition associated with high mortality, based on these scores, does not necessarily mean that therapeutic efforts should be stopped but that patients, family members and staff can have a better understanding of the prognosis, in light of current knowledge. Knowledge of the patients' wishes, beliefs and desires is fundamental to establish future therapeutic strategies.

CONCLUSION

In critically ill cirrhotic patients who are not awaiting liver transplantation, there is no

"gold standard" for predicting their short- and long-term prognosis. Several variables are associated with a worse prognosis, such as the presence of sepsis, the number and intensity of associated organ failures, and the duration of MV. Baseline severity scores, as well as the sequential assessment of organ failure scores, provide more certainty regarding the impact of critical illness on the prognosis of this population.

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