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**Acute-on-chronic liver failure is independently associated with higher mortality for cirrhotic patients with acute esophageal variceal hemorrhage: Retrospective cohort study**

Terres AZ *et al.* ACLF and acute esophageal variceal hemorrhage

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## **Abstract**

### **BACKGROUND**

Acute esophageal variceal hemorrhage (AEVH) is a common complication of cirrhosis and might precipitate multi-organ failure, causing acute-on-chronic liver failure (ACLF).

### **AIM**

To analyze if the presence and grading of ACLF as defined by European Society for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) is able to predict mortality in cirrhotic patients presenting AEVH.

### **METHODS**

Retrospective cohort study executed in Hospital Geral de Caxias do Sul. Data from medical records from 2010 to 2016 were obtained by searching the hospital electronic database for patients who received terlipressin. Medical records were reviewed in order to determine the diagnosis of cirrhosis and AEVH, including 97 patients. Kaplan-Meier survival analysis was used for univariate analysis and a stepwise approach to the Cox regression for multivariate analysis.

## RESULTS

All- cause mortality for AEVH patients was 36%, 40.2% and 49.4% for 30-, 90- and 365-day, respectively. The prevalence of ACLF was 41.3%. Of these, 35% grade 1, 50% grade 2 and 15% grade 3. In multivariate analysis, the non-use of non-selective beta-blockers, presence and higher grading of ACLF and higher Model for End-Stage Liver Disease scores were independently associated with higher mortality for 30-day with the addition of higher Child-Pugh scores for 90-day period.

## CONCLUSION

Presence and grading of ACLF according to the EASL-CLIF criteria was independently associated with higher 30- and 90-day mortality in cirrhotic patients admitted due to AEVH.

**Key Words:** Gastrointestinal hemorrhage; Prognosis; Esophageal and gastric varices; Liver cirrhosis; Acute-on-chronic liver failure; Organ dysfunction scores

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**Core Tip:** Acute esophageal variceal hemorrhage (AEVH) is a common complication of cirrhosis and might precipitate multi-organ failure, causing acute-on-chronic liver failure (ACLF). The purpose of this study is to analyze if the presence and grading of ACLF as defined by European Society for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) is able to predict mortality in cirrhotic patients presenting AEVH. This is a retrospective cohort study executed in Hospital Geral de Caxias do Sul, which gathered data from medical records from 2010 to 2016 were obtained by searching the hospital electronic database for patients who received terlipressin. Medical records were reviewed in order to determine the diagnosis of cirrhosis and AEVH, including 97 patients. Kaplan-Meier survival analysis was used for univariate analysis and a stepwise approach to the Cox regression for multivariate analysis. All- cause mortality for AEVH patients was 36%, 40.2% and 49.4% for 30-, 90- and 365-day, respectively. The prevalence of ACLF was 41.3%. Of these, 35% grade 1, 50% grade 2 and 15% grade 3. In multivariate analysis, the non-use of non-selective beta-blockers, presence and higher grading of ACLF and higher Model for End-Stage Liver Disease scores were independently associated with higher mortality for 30-day with the addition of higher Child-Pugh scores for 90-day period. In conclusion, the presence and grading of ACLF according to the EASL-CLIF criteria was independently associated with higher 30- and 90-day mortality in cirrhotic patients admitted due to AEVH.

## **INTRODUCTION**

Portal hypertension occurs in 90% of cirrhotic patients<sup>[1]</sup>, caused by structural abnormalities of the liver and intra-hepatic vasoconstriction due to sinusoidal endothelial dysfunction<sup>[2,3]</sup>. This will in turn cause the recanalization of collateral veins, leading to the development of esophageal varices<sup>[4]</sup>. These varices will increase in size and become more likely to rupture, causing acute esophageal variceal hemorrhage (AEVH). This is secondary to the growing portal hypertension, and not to the thrombocytopenia caused by hypersplenism<sup>[5,6]</sup>. Therefore, esophageal varices are

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expected to be present in 42.7% of Child-Pugh class A patients, 70.7% of Child-Pugh class B patients and 75.5% of Child-Pugh class C patients<sup>[4]</sup>.

Around one third of cirrhotic patients will present AEVH, which is one of the most common life-threatening complications of cirrhosis and is responsible for 80% to 90% of gastrointestinal bleedings in these patients<sup>[7-9]</sup>. The first episode of AEVH is associated with a mortality of 15% to 20%<sup>[10]</sup> and a high rate of recurrence<sup>[9]</sup>.

When AEVH occurs, it is defined as decompensated cirrhosis. Nevertheless, an additional step called acute-on-chronic liver failure (ACLF) has been postulated to take place in-between decompensated cirrhosis and death, characterized by multi-organ failure<sup>[11]</sup>. Although the discussion between Hepatology and Intensive Care has began over a decade ago<sup>[12-18]</sup>, 1 a definitive definition of ACLF has only been introduced by the multi-centric prospective study CANONIC, developed in Europe and published in 2013<sup>[19]</sup>. 2 This was done when the European Society for the Study of the Liver – Chronic Liver Failure (EASL-CLIF) group adapted the Sequential Organ Failure Assessment (SOFA) score into the CLIF-SOFA score. This dichotomizes systems as sufficient or insufficient and is able to stratify patients as having an acute decompensation (AD) or ALCF, which was stratified into three grades<sup>[19]</sup>. In the general population of decompensated cirrhotic patients, the grade of ACLF was associated with higher mortality. CANONIC study was designed with a prospective approach to determine the levels of organ dysfunction that are associated with a 28-day mortality rate exceeding 15%.

In the presence of AEVH, liver-specific scores have been shown to be superior to predict mortality than those used for acute esophageal non-variceal hemorrhage, as they indirectly evaluate liver function and portal hypertension, 11 such as Child-Turcotte-Pugh (CTP), Model for End-Stage Liver Disease (MELD) and CLIF-SOFA<sup>[20-22]</sup>. CLIF-SOFA, in turn, score has been shown to be superior to CTP and MELD for prognosticating AEVH<sup>[23,24]</sup>.

Prior to the first episode of AEVH, an upper digestive endoscopy is performed to assess the presence of esophageal varices and undertake primary prophylaxis with non-

selective beta-blockers (NSBB), such as propranolol, nadolol or carvedilol<sup>[25]</sup>. Once AEVH occurs, it is generally treated with the association of terlipressin with endoscopic variceal banding (EVB)<sup>[26,27]</sup>. This demands afterwards a lifelong secondary prophylaxis with NSBB and EVB<sup>[28,29]</sup>.

The purpose of this study is to analyze if the presence and grading of ACLF as defined by EASL-CLIF is able to predict mortality in cirrhotic patients presenting AEVH.

## **MATERIALS AND METHODS**

### ***Study population***

This study was approved by the Research ethics committee of Universidade de Caxias do Sul on June 20, 2017, under protocol no. 66646617.3.0000.5341. This was done in conformity to the ethical guidelines of the 1975 Declaration of Helsinki. As this study analyzed solely medical records, the need for an informed consent was waived by this human research ethics committee.

A search for every patient which received terlipressin from 2010 to 2016 was conducted in the hospital electronic database, as the hospital protocol for suspected AEVH mandates that patients receive terlipressin for 48 h. Data from electronic and physical medical records were retrieved.

Patients were included if they were over 18 years old, had a definitive diagnosis of cirrhosis using laboratory and imaging data and had a diagnosis of AEVH confirmed by endoscopy, defined as a bleeding esophageal varices, signs of recent AEVH or the presence of blood in the stomach with no other cause of hemorrhage other than esophageal varices. Patients who did not have cirrhosis, had incomplete medical records that could not safely confirm the diagnosis of AEVH, had no varices in the index endoscopy, had hemorrhage caused by gastric varices or had used terlipressin solely for the treatment of hepatorenal syndrome (HRS) were excluded. Then, data was collected in specific forms for each patient, with extensive data on clinical and laboratory variables.

### *Variables*

Electronic and physical medical records were gathered for each case and individually assessed. Standardized imaging criteria findings were considered as sufficient for the diagnosis of hepatocellular carcinoma<sup>[30]</sup>. For the diagnosis of HRS type 1, an evidence-based protocol based on clinical criteria published in 2007 was used<sup>[31,32]</sup>; Hepatic encephalopathy was graded and diagnosed as per West-Haven criteria<sup>[33]</sup>. Laboratory data was noted using the units from the hospital laboratory.

### *Liver-specific scores and ACLF*

Commonly used liver-specific scores were calculated and assessed, using online calculators for standardization. CTP is a classic score, mostly used for prognosticating 1-year mortality for compensated and decompensated cirrhosis<sup>[34,35]</sup>.

MELD<sup>[36]</sup> and MELD-Na<sup>[37]</sup>, initially developed to prognosticate 90-day survival for cirrhotic patients, are currently used to assess the need and urgency for liver transplantation.

CLIF-SOFA was developed by the EASL-CLIF group and adapted from the SOFA score, in order to define and classify ACLF<sup>[19]</sup>. This score defines failure of each organic system, stratifying ACLF into grade 1, 2 and 3:

**AD - non-ACLF:** No organ failure; or an isolated non-renal organ failure with creatinine < 1.5 mg/dL and absence of encephalopathy; or an isolated neurological failure with creatinine < 1.5 mg/dL.

**ACLF grade 1:** an isolated kidney failure; or an isolated non-renal and non-neurological organ failure with creatinine ranging between 1.5 and 1.9 mg/dL or mild to moderate hepatic encephalopathy; or an isolated neurological failure with creatinine ranging between 1.5 to 1.9 mg/dL.

**ACLF grade 2:** two organ failures.

**ACLF grade 3:** three organ failures.

CLIF Consortium (CLIF-C) AD score and CLIF-C ACLF, are a couple of other scores developed by the EASL-CLIF group, intended to predict mortality for 28-day, 90-day, 180-day and 365-day for AD and ACLF patients<sup>[38]</sup>. These scores were calculated using an online calculator developed by the CLIF Research Group (<https://www.clifresearch.com/ToolsCalculators.aspx>), which after defining the presence and grade ACLF and calculating CLIF-SOFA, automatically analyzes if CLIF-C AD or ACLF applies and calculates its value for each case.

### ***Therapy for AEVH***

Our hospital follows an evidence-based institutional protocol to manage suspected cases of AEVH (Figure 1). When suspected, the patient starts to use terlipressin 2 mg q4h for 48 h and the on-call endoscopy team is called in action to perform an upper digestive endoscopy with EVB or sclerotherapy within 24 h of the hospital admission.

The choice whether to treat the varices and between EVB or sclerotherapy was done by the on-call endoscopist. Besides, every patient receives prophylactic antibiotics and lactulose. Prophylactic NSBB are started after three to five days of the AEVH resolution.

### ***Outcomes***

Death from all causes was primary outcome, gathered *via* medical records or the search on national death databases (<https://www.falecidosnobrasil.org.br/>). If the patient was admitted to the hospital with more than one episode of AEVH, data regarding the first episode was collected. Treatment failure was defined as either persistent bleeding or rebleeding in a time frame of 5 days.

### ***Statistical analysis***



Statistical analysis was performed using Statistical Package for the Social Sciences 15.0 (International Business Machines Corporation, Chicago, United States). Frequency was used to describe categorical variables and mean and standard deviation for continuous variables. Univariate analysis was performed by a Cox regression and a multivariate analysis by a stepwise progression to the Cox regression. Every statistical test performed for the analysis excluded missing data. The graphical description of survival was done *via* Kaplan-Meier curves.

## RESULTS

The search in the electronic database of the hospital<sup>8</sup> retrieved 177 hospital admissions of patients who received terlipressin. Of these, 46 were diagnosed with HRS, whereas 16 were admitted because of a suspicion of AEVH not confirmed by index endoscopy, 4 had incomplete records and other 14 cases were re-admissions. Therefore, only 97 hospital admissions were diagnosed as AEVH and<sup>1</sup> included in the study (Figure 2). Demographic, clinical, and laboratory data are described in Table 1 for the study population and stratified by AD or ACLF and its grade.<sup>2</sup> Mean age was 56 years-old and 77.3% of the patients were male. The most common cause of cirrhosis was alcohol abuse (61.8%).

All-cause mortality for AEVH was 36%, 40.2% and 49.4% for 30-, 90- and 365-day,<sup>1</sup> respectively. The prevalence of ACLF was 41.3%. Of these, 35% grade 1, 50% grade 2 and 15% grade 3. All cause-mortality was, respectively, 14%, 21.1% and 29.8% for 30-, 90- and 365-day for AD, 57.1%, 57.1% and 85% for 30-, 90- and 365-day for ACLF grade 1,<sup>5</sup> 70% for 30-, 90- and 365-day for ACLF grade 2 and 83%, 83% and 100% for 30-, 90- and 365-day for ACLF grade 3.<sup>1</sup>

Cox regression univariate analysis was performed. Etiology of cirrhosis, non-use of PPI (proton-pump inhibitor) and NSBB, hepatic encephalopathy, red marks or active bleeding in the index endoscopy, presence of infection, leukocytes > 10000/mm<sup>3</sup>, total bilirubin > 2 mg/dL, International normalized ratio > 1.3, creatinine > 2 mg/dL,<sup>13</sup> albumin < 3.5 mg/dL, higher use of fresh frozen plasma, CTP, MELD, MELD-Na, CLIF-

SOFA, CLIF-C and ACLF scores and ACLF presence and grade<sup>1</sup> were associated with higher 30-day and 90-day mortality (Table 2), using as statistically significant a *P* value below 0.2 for inclusion in the multivariate analysis. Figure 3 presents a Kaplan-Meier curve for 30- and 90-day survival for AEVH patients according to either AD or ACLF grade.

Each one of these variables was used<sup>1</sup> for the multivariate analysis using Cox regression. Using the stepwise approach, the model was reduced until every variable had a level of independent significance of  $P \leq 0.1$ . Previous use of NSBB was protective for 30- and 90-day mortality. MELD score and ACLF grade were associated with higher 30- and 90-day mortality. CTP score was only predictive of 90-day mortality (Table 3).

## **DISCUSSION**

AEVH is one of the most common causes for decompensation of cirrhotic patients. Treatment has advanced greatly in the past few decades, but AEVH still carries a<sup>2</sup> mortality of 10% to 20% in six weeks<sup>[39]</sup>. This study has sought to determine whether the presence of ACLF according to EASL-CLIF criteria might be useful for prognostication of AEVH.

The concept that there is an additional step between AD and death has been in the making for a long time. The initial concept was that ACLF would take place after a triggering event, precipitating multi-organ failure and eventually death. Possible events were infection, AEVH, drug or herb-induced liver injury, alcoholic hepatitis or acute viral hepatitis<sup>[12-18]</sup>. The introduction of well-researched clinical criteria would come only in 2013 by the CANONIC study. In this study, the EASL-CLIF group developed and validated the CLIF-SOFA score and definitions of ACLF, analyzing their role in prognosticating end-stage liver disease (ESLD)<sup>[19]</sup>.

For patients with ACLF and AEVH, 30-day mortality<sup>3</sup> was 67.5%, considerably higher than the 33.9% described in the CANONIC study<sup>[19]</sup> and the 39% described in other studies<sup>[40-42]</sup>. For patients with ACLF diagnosed with Spontaneous Bacterial

peritonitis, a 28-day-mortality of 65% has been described<sup>[43,44]</sup>, while a 30-day mortality of 67.3% has been described for HRS patients<sup>[32,45]</sup>.

Prognosticating AEVH is challenging. There are many scores developed to stratify patients with non-variceal acute upper digestive hemorrhage such as the Rockall score, Glasgow Blatchford Score, AIMS65 score, Almela score, score, Baylor Bleeding score and Cedars-Sinai Medical Center predictive index<sup>[46-50]</sup>. Nevertheless, it is paramount to remember that these scores were not developed to prognosticate AEVH. Therefore, it has been demonstrated that such scores are more accurate to prognosticate non-variceal acute upper digestive hemorrhage than cirrhotic patients with AEVH<sup>[20,21,51,52]</sup>.

It comes to no surprise, therefore, that scores that predict mortality using liver function tests in cirrhotic patients are superior to prognosticate AEVH. This has been demonstrated in a study that found that CLIF-SOFA and MELD scores have better predict hospital mortality and post-EVB 6-week mortality for AEVH patients than other generally used scores<sup>[22,23,24,53]</sup>. In such a complex scenario, artificial intelligence might just outperform every commonly used score<sup>[54,55]</sup>.

Once used to allocate organs for liver transplantation (LT), CTP is a score known by heart by every hepatologist, and helps allocate resources and adjust follow-up for both inpatients and outpatients. It is by large the most researched score, and is extremely important to prognosticate outpatients<sup>[34,35]</sup>, intensive care patients<sup>[56]</sup> and hepatorenal syndrome patients<sup>[45,57]</sup>. In the present study, higher CTP has been independently associated with higher 90-day mortality.

Currently used for LT organ allocation<sup>[58]</sup>, MELD and MELD-Na scores are useful for predicting 90-day mortality for ESLD patients<sup>[36,37]</sup>. This has been true even for AEVH patients<sup>[22]</sup>, where they have been shown to be similar to CTP score for prognosticating AEVH<sup>[59,60]</sup>. In the present study, higher MELD has been independently associated with higher 30- and 90-day mortality.

EASL-CLIF consortium developed the CLIF-SOFA for the CANONIC study<sup>[19]</sup>, a recent score superior to other liver-specific scores in prognosticating ACLF patients<sup>[61-65]</sup>, for both acute decompensations and chronic liver injuries<sup>[19,65-69]</sup>. Although, in the

present study, CLIF-SOFA score was not independently associated with higher mortality.

The use of NSBB (either carvedilol or propranolol) is a mainstay of AEVH primary and secondary prophylaxis<sup>[28,29]</sup>. In this study, the previous use of NSBB was independently associated with lower 30- and 90-day mortality for all patients. This corroborates the findings of a previous randomized controlled trial, where the use of carvedilol reduced mortality for ACLF patients<sup>[70]</sup>. Since a cohort has shown propranolol and carvedilol to be equivalent in clinical outcomes, it is expected that both NSBB are effective in reducing mortality<sup>[71]</sup>.

Transjugular intrahepatic portosystemic shunt (TIPS) has been more recently recommended for refractory and severe AEVH<sup>[72,73]</sup>. In our setting, this is unavailable and might have impacted our results regarding mortality. Although in the studied hospital, protocol mandates the use of prophylactic antibiotics, there was still a high rate of infection. Nevertheless, in a recent study, almost one-fifth of patients with AEVH developed bacterial infections despite antibiotic prophylaxis<sup>[74]</sup>. This rate was not so different from the presented population (24.6% for AD and 40% for ACLF patients). Another factor that might contribute for decompensation and AEVH is portal vein thrombosis<sup>[75]</sup>. This condition did not impact our results, as it was rather uncommon in the presented population.

ACLF has been associated with systemic inflammation, which might cause impairment of the functions of the major organ systems and might act synergistically with the traditional mechanisms involved in the development of AD and ACLF, impairing organ system functions<sup>[76]</sup>. In the present study, the presence and grade of ACLF in AEVH patients were associated with higher 30- and 90-day mortality. This has been demonstrated in a few previous retrospective cohorts<sup>[73,77-81]</sup>. A recent systematic review investigated the ability of the CLIF-SOFA, CLIF-C ACLF, and CLIF-C AD scores for prognosticating acute-on-chronic liver failure and acute decompensation of cirrhosis and found that these scores were accurate short-term and long-term mortality



prognosticating scores, with CLIF-SOFA being the most effective in predicting mortality in ACLF patients, especially in the short-term<sup>[82]</sup>.

The major limitation of our study is the small sample size. Nevertheless, most of the studies that analyzed ACLF were multi-centric, gathering large data banks. Our institution does not have TIPS or liver transplantation facilities, and patients with AEVH require transfer to another city, which is challenging. Moreover, this study is a historical cohort, without sufficient numbers of patients to stratify them accurately, and hence adequate results may not be obtained. The present study provides a thorough analysis of the data, shedding light on the role of ACLF definitions in predicting AEVH prognosis. What sets our paper apart is its novel finding of a significant association between ACLF grade and mortality in AEVH patients.

## **CONCLUSION**

In conclusion, the use of NSBB was protective for mortality associated with AEVH, while MELD and CTP scores and the presence and grading of ACLF according to the EASL-CLIF criteria was independently associated with higher 30- and 90-day mortality in cirrhotic patients admitted due to AEVH. A large prospective cohort study on AEVH and ACLF would be beneficial to better understand the association between the two. It is becoming paramount in this era to develop more accurate tools for predicting outcomes and optimizing medical therapy in these patients.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Acute-on-chronic liver failure (ACLF) is a severe syndrome affecting patients with liver disease, characterized by decompensation, organ failure, and high mortality rates. ACLF diagnosis is based on clinical criteria, while treatment options remain limited, underscoring the need for predictive tools and targeted therapies to improve outcomes. This study aimed to identify prognostic factors and therapeutic targets associated with ACLF and acute variceal hemorrhage (AEVH) to improve patient management. The

mechanisms of ACLF remain unclear, highlighting the importance of further research in this area.

### ***Research motivation***

The study on ACLF and AEVH aims to identify predictors of poor outcomes in AEVH and the development of ACLF, which has gained significant attention due to poor prognosis and limited treatment options. Understanding the pathophysiology and clinical implications of ACLF remains crucial, and identifying risk factors for its development could enhance our knowledge of this condition and inform future therapies. The study thus has important clinical implications for managing patients with liver disease.

### ***Research objectives***

The main objective of the study on ACLF and AEVH was to identify risk factors for mortality and to evaluate the role of non-selective beta-blockers (NSBB) in improving patient outcomes.

### ***Research methods***

The study analyzed data of cirrhosis patients who received terlipressin for AEVH from 2010 to 2016. Patients with incomplete medical records or without cirrhosis were excluded. Extensive clinical and laboratory data was collected for each patient, and liver-specific scores were calculated. AEVH therapy involved terlipressin, prophylactic antibiotics, and lactulose. Outcomes were recorded as all-cause deaths, collected from medical records or national death databases.

### ***Research results***

This study provides insights into the prognosis of AEVH and ACLF. The study found that the all-cause mortality rate for AEVH ranged from 36% to 49.4% depending on the time point, while the prevalence of ACLF was 41.3%, with a higher mortality rate

ranging from 57.1% to 100%. Various factors were associated with higher mortality rates, including etiology of cirrhosis, laboratory abnormalities, and scoring systems. The study emphasizes the importance of early identification and treatment of AEVH and ACLF, with previous use of NSBB being protective and MELD score and ACLF grade associated with higher mortality rates.

### ***Research conclusions***

The study aimed to assess the utility of ACLF criteria for predicting AEVH prognosis. Patients with ACLF and AEVH had a high 30-day mortality rate of 67.5%. CLIF-SOFA and MELD scores were better predictors of hospital mortality and 6-week post-EVB mortality than other scores. Higher CTP and MELD scores were associated with higher 90-day and 30- and 90-day mortality rates, respectively. The previous use of NSBB was associated with lower 30- and 90-day mortality.

### ***Research perspectives***

Future research on AEVH and ACLF should investigate long-term outcomes, including factors associated with better outcomes and novel therapeutic approaches. Developing new biomarkers for early detection and diagnosis is necessary, as current methods are limited in accuracy and specificity. Further research is needed to understand the underlying mechanisms of these conditions, particularly inflammation and immune dysregulation. Randomized controlled trials evaluating the efficacy and safety of various treatments, including pharmacological and non-pharmacological approaches, are necessary to manage AEVH and ACLF and improve patient outcomes.

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