ORIGINAL RESEARCH PAPER
Volume-9 | Issue-5 | May-2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

# ACUTE-ON-CHRONIC LIVER FAILURE DATA FROM A TEACHING HOSPITAL IN BRAZIL. A HISTORICAL COHORT.

Gastroenterology

**Rafael Maciel Grochot** MD. Physician, Internal Medicine, Hospital Virvi Ramos. Residency in Oncology, Hospital Geral, Caxias do Sul (RS), Brazil.

**Laís Bender Luz** MD. Physician, Universidade de Caxias do Sul (UCS), Caxias do Sul (RS), Brazil.

**Rafael Garcia** Medical student, Universidade de Caxias do Sul (UCS), Caxias do Sul (RS), Brazil.

**Raul Ângelo Balbinot** MD, PhD. Physician, Titular Professor of Gastroenterology and Hepatology, Universidade de Caxias do Sul (UCS), Caxias do Sul (RS). Doctorate in Gastroenterology, Department of Gastroenterology, Universidade de São Paulo (USP), São Paulo (SP), Brazil.

**Silvana Sartori Balbinot** MD, PhD. Physician, Titular Professor of Gastroenterology and Hepatology, Universidade de Caxias do Sul (UCS), Caxias do Sul (RS). Doctorate in Gastroenterology, Department of Gastroenterology, Universidade de São Paulo (USP), São Paulo (SP), Brazil.

**Jonathan Soldera*** MD. MSc, Associate Professor of Gastroenterology and Hepatology, Universidade de Caxias do Sul (UCS), Caxias do Sul (RS). Master's in Medicine: Hepatology, Department of Hepatology, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre (RS), Brazil. *Corresponding Author

## ABSTRACT

**BACKGROUND:** Patients with organ failures associated with cirrhosis may have a higher risk of death in the short term. It has been suggested that a particular clinical entity, acute-on-chronic liver failure (ACLF), could be responsible for this increase in mortality.
**DESIGN AND SETTING:** Historical cohort study conducted in a mixed public and private tertiary care teaching hospital.
**METHODS:** Data from hospital charts from January 2013 to December 2014 were obtained by searching the hospital electronic database for codes of liver disease. Paper medical charts were hand-analyzed. Liver-specific scores were calculated and Cox regression was used to access the association of the variables with survival, through univariate and multivariate analysis.
**RESULTS:** In the final analysis, 51 patients were included. Of these, 18 had ACLF (7 grade 1, 10 grade 2 and 1 grade 3). In a multivariate analysis, female sex, higher Chronic Liver Failure Sequential Organ Failure Assessment (CLIF-SOFA) score, presence of ACLF, hepatocellular carcinoma and HIV were associated with a higher 30-, 90- and 365-day mortality.
**CONCLUSION:** The presence of ACLF was able to predict adverse outcomes in a cohort of a mixed public and private teaching hospital in Brazil.

## KEYWORDS

Liver cirrhosis, End stage liver disease, Organ dysfunction scores, Prognosis, Cohort studies, Acute-on-chronic Liver Failure.

## INTRODUCTION

Cirrhosis is the final stage of progressive liver injury, which leads to fibrosis and nodular regeneration.[1] There are many etiologies for such injury, where the most common are viral hepatitis, alcoholic liver disease and non-alcoholic fatty liver disease. After cirrhosis is established, the clinical course of the disease is marked by progression to decompensated cirrhosis (DC), which is the most important cause of hospital admission for these patients.[2-6] The World Health Organization stated that cirrhosis was the 9th leading cause of death in the West in 2015.[7]

In the last decade, it has been observed that patients with organ failures associated with cirrhosis have a higher risk of death in the short term.[8-12] It has been suggested that a particular clinical entity, acute-on-chronic liver failure (ACLF), could be responsible for this increase in mortality, which may range from 50 to 90%.[10-13] The differentiation between DC and ACLF has been attempted by creating scoring systems that define and stage ACLF. This is important because while DC translates into the progression of the disease, ACLF is defined as an acute event, potentially reversible, and with a high mortality.[14,15]

The pathogenesis of ACLF is yet to be fully understood. Use of the acronym PIRO (Predisposition, Injury, Response and Organ failure) has been suggested as a means of explaining what is known so far.

Predisposition means basically the presence of an end-stage liver disease, such as cirrhosis, which is commonly evaluated using liver scores such as Model for End-Stage Liver Disease (MELD) and Child-Pugh-Turcotte (CTP). Nevertheless, these models are not reliable for the evaluation of ACLF, since they do not take into account organ failures.[16-18]

Injury derives from the concept that ACLF takes place after an acute event, which leads to DC which is followed by ACLF. This event can be hepatic (such as an alcoholic or viral hepatitis, portal vein thrombosis) or extra-hepatic (such as an infection, variceal bleeding).

Response is meant to exemplify that the injury itself is not solely responsible for ACLF and that there is an inadequate response of the host to the injury, which leads to excessive inflammation and immune dysfunction, increasing susceptibility to infections.[19,20] Systemic inflammatory syndrome has been associated with acute liver failure, leading to hepatic encephalopathy, infections, kidney failure and a poorer prognosis.[21] The levels of many pro- and anti-inflammatory cytokines have been shown to be increased in ACLF.[22-25] Infections are generally associated with higher mortality. About 40 to 50% of admitted cirrhotic patients have an infection on admission and 20 to 40% will develop one during their hospital stay.[26] It is estimated that around 15% of cirrhotic patients admitted because of an infection will die during their hospital stay, twice as much as those without an infection. Also, mortality from septic shock in cirrhotic patients is around 60 to 100%.[5,6,26]

Organ failure-associated scores, used generally in the intensive care setting, have been shown to be better than liver scores at predicting ACLF-related mortality. It was shown that mortality in cirrhotic patients who were admitted in the intensive care unit (ICU) with three or more organ failures was 70% in the first day of admission, increasing to 89% by the third day.[14,27] What changed how we perceive ACLF is the CANONIC study, a prospective cohort study published in 2013, which transformed a commonly used score in the ICU to the ACLF setting, called CLIF-SOFA (Chronic Liver Failure Sequential Organ Failure Assessment), dividing ACLF into three categories with

distinct mortality.[28]

The purpose of this paper is to analyze, in a mixed public and private tertiary care teaching hospital in Brazil, the accuracy of the presence of ACLF to predict mortality.

## METHODS

### Study population

The study was approved by the research ethics committee of the hospital on October 20, 2014, under protocol no. 35359813. 4.0000.5523. A historical cohort study was conducted, analyzing data from hospital charts from January 2013 to December 2014. Patients were found by searching through a mixed public and private teaching hospital electronic database for International Classification of Diseases (ICD-10) codes F10, K70, K70.1, K70.2, K70.3, K71.7, K74, K74.2, K74.3, K74.6, K77. Paper medical charts were hand-analyzed. Patients over 18 years old with laboratory and imaging data supporting the diagnosis of cirrhosis were included. Patients were excluded if they did not have a diagnosis of cirrhosis when the chart was reviewed or had incomplete charts. Data regarding clinical and laboratory variables were gathered and liver-specific scores were calculated.

### Variables

Clinical and laboratorial variables were gathered by analyzing paper medical charts and electronic laboratory data. Laboratory data is expressed in units used in the hospital. Diagnosis of hepatocellular carcinoma (HCC) was made using standardized imaging techniques[29]. Diagnosis of hepatorenal syndrome were made using the previously published criteria in 2007 for diagnosis[30]. Diagnosis of infection was made through a positive culture or neutrophil count in ascites fluid: a count of 250 or higher neutrophil/mm³ defined spontaneous bacterial peritonitis.

### MELD and MELD-Na

MELD (Model for End-Stage Liver Disease)[32] and MELD-Na (MELD-Sodium)[33] are scores used to predict 90-day mortality and are currently used for organ allocation in liver transplantation. They were calculated using an online calculator (MELD: https://www.mdcalc.com/meld-score-model-end-stage-liver-disease-12-older) (MELD-Na: https://www.mdcalc.com/meldna-meld-na-score-liver-cirrhosis).

### CLIF-SOFA

CLIF-SOFA is a score developed by the EASL-CLIF group, adapted from the SOFA score used in intensive care (**Table 1**). It aims to define ACLF and divide it in three grades[28]. Both CLIF-SOFA and ACLF grade were calculated using an online calculator developed by the CLIF Research Group (https://www.clifresearch.com/ToolsCalculators.aspx). CLIF-SOFA score defines failure of each system, and by the number of failures it further stratifies ACLF into grade 1, 2 and 3:

**DC (non-ACLF):** no organ failure; or an isolated non-renal organ failure with creatinine < 1.5 and absence of encephalopathy; or an isolated neurological failure with creatinine < 1.5.

- **ACLF grade 1:** an isolated renal failure; or an isolated non-renal and non-neurological organ failure with creatinine ranging between 1.5 and 1.9 or mild to moderate hepatic encephalopathy; or an isolated neurological failure with creatinine ranging between 1.5 and 1.9
- **ACLF grade 2:** two organ failures.
- **ACLF grade 3:** three organ failures.

### ACLF grade

The CLIF-SOFA score is also used to analyze organ failures and define the presence of ACLF and its grade[28]. It was calculated using an online calculator (https://www.clifresearch.com/ToolsCalculators.aspx).

### CLIF-C AD / ACLF

CLIF Consortium Acute Decompensation (CLIF-C AD) score and CLIF-C ACLF are scores also developed by the CANONIC group that predict expected mortality for 30-day, 90-day, 180-day and 365-day for DC and ACLF patients[34]. They were calculated using an online calculator (https://www.clifresearch.com/ToolsCalculators.aspx). The online calculator, after the result of the presence of ACLF and the value of CLIF-SOFA, automatically analyzes if CLIF-C AD or ACLF applies in each case and calculates accordingly.

### Outcome

Outcome data regarding survival were gathered using hospital charts and searching through national death databases (https://www.falecidosnobrasil.org.br/). If the patient had more than one hospital admission, data regarding only the first were collected.

### STATISTICALANALYSIS

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 15.0. Categorical variables are described using frequency and continuous variables by mean and standard deviation. Cox regression model for survival analysis was used for univariate and multivariate analysis. Kaplan-Meyer curves were used for the graphical description of survival.

## RESULTS

Electronic ICD search retrieved 190 hospital admissions. Of these, 131 admissions were excluded due to the other diagnosis for admission than cirrhosis; and 8 admissions were excluded for being for the same patients. After chart analysis, 51 patients in their first hospital admission in the analyzed period were included in the study. Of these, 18 were diagnosed with ACLF (7 grade 1, 10 grade 2 and 1 grade 3). Demographic, clinical and laboratorial data are described in **Table 2** for the study population and for each ACLF grade.

Univariate analysis was performed using 28, 90 and 365-day survival as outcome. The data with hazard ratios is presented in **Table 3** and Kaplan-Meyer curves for ACLF are shown in **Figure 1**. A lower body mass index (BMI), female sex, higher CLIF-SOFA, higher creatinine, and presence of ACLF, HCC, HIV and hepatitis C were associated with a higher chance of mortality in the univariate analysis.

Multivariate analysis was performed using 28, 90 and 365-day survival as outcome. The data with hazard ratios is presented in **Table 4**. Female sex, higher CLIF-SOFA, presence of HIV, HCC and ACLF were independently associated with a higher chance of mortality. The presence of ACLF increased mortality 3 to 4-fold, whereas each point in the CLIF-SOFA score increased mortality around 1.3-fold.

## DISCUSSION

In the past couple of decades, several studies have been published regarding the clinical nature of ACLF, but they have been undermined because of the lack of a consensual definition of ACLF. In this study, we analyzed the role of the definitions and scores proposed by the EASL-CLIF (European Associaton fos the Study of the Liver - Chronic Liver Failure) consortium, exploring their relationship with survival.[28]

Understanding ACLF has become paramount in expanding our knowledge regarding cirrhosis, to complete the gap between DC and death. Hepatology has come a long way since the first supplement dedicated to this subject,[8,35-40] which integrated intensive care and Hepatology, and the publication of CANONIC, responsible for the current definition of this entity.[28] Although, it is important to mention that a different set of criteria developed by the Asia-Pacific Association for the Study of the Liver has been described, but it appears to be inferior to the one developed by the EASL-CLIF[41,42].

In this study, the prevalence of ACLF was 35.3% (grade 1 in 13.7%, grade 2 in 19.6% and grade 3 in 2%). These results are not very close to those obtained in the CANONIC study, with an ACLF prevalence of 22.6%,[28] or in a similar Brazilian study, with a prevalence of 24%,[43] or in a similar North American study, with a prevalence of 26.4%[44], where grade 1 was 11.0%, 17.7% and 12.8%, respectively. This population also had a predominance of grade 2, which was different from other studies.

Besides the presence of ACLF, other variables were associated with survival. A higher BMI was associated with improved survival, which has been demonstrated in a previous study, and it makes sense, hence malnutrition has been widely associated to poorer prognosis in cirrhotic patients.[45] Although there were fewer female patients in this population, there was a higher rate of death among females, which differs from previous studies.[46,47]

Higher serum creatinine levels, HIV and HCV infection and the presence of HCC were associated with poorer survival, which was

described in the CANONIC study and in a recent North American Study[28,44]. In this study, infection was not associated with higher mortality, possibly due to the small sample size. The activation of cytokines and vasoactive hormones and the alteration in circulatory function in advanced cirrhosis and ascites without overt sepsis are similar to that seen in sepsis and septic shock without cirrhosis, which results in a higher mortality associated with bacterial infections in most studies.[48]

The ACLF group showed a 28-day mortality of 39% (29, 40 and 100% in ACLF grades 1, 2 and 3, respectively), compared to 22% in non-ACLF patients. In the CANONIC study, 28-day mortality was 33.9%, significantly lower than that reported here,[28] whereas the Brazilian study showed very similar mortality rates, i.e., 39%.[43]

As expected, mortality was independently associated with a higher CLIF-SOFA but not with a higher MELD or CLIF-C AD/ACLF. This is compatible with other studies, which have shown CLIF-SOFA to be superior to other liver-specific scores in predicting mortality[49-52].

Although the sample was of a mixed private and public teaching hospital, there was no significant difference between private and public patients regarding survival.

A major drawback of our study was the small sample size, which was probably due to the fact that the hospital is not a referral center for liver diseases. Nonetheless, the complete data gathered allowed for an in-depth study of the population and provided more data regarding the prognosis and treatment of cirrhosis in Brazil. Many patients were excluded because of the ICD search – this hospital has a psychiatric wing and most excluded patients were with a diagnosis of ICD F10.

## CONCLUSION

In conclusion, the presence of ACLF was able to independently predict adverse outcomes in a cohort of a mixed public and private teaching hospital in Brazil. An increase in the use of these evidence-based scores may help define optimal diagnostic and therapeutic strategies for ACLF.

**Table 1. Chronic liver failure- sequential organ failure assessment (CLIF-SOFA) score**

| CLIF-SOFA score | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| **Respiration** | | | | | |
| PaO2/FiO2<br>or SpO2/FiO2 | >400<br>>512 | >300 to ≤400<br>>357 to ≤512 | >200 to ≤300<br>>214 to ≤357 | >100 to ≤200<br>89 to ≤214 | ≤100<br>≤89 |
| INR | <1.1 | ≥1.1 to <1.25 | ≥1.25 to <1.5 | ≥1.5 to <2.5 | ≥2.5 or<br>platelet ≤20 |
| **Liver** | | | | | |
| Bilirubin, mg/dL<br>(lmol/L) | <1.2 (<20) | ≥1.2 to <2.0<br>(20–32) | ≥2.0 to <6.0<br>(33–101) | ≥6.0 to <12.0<br>(102–204) | ≥12.0 (>204) |
| **Cardiovascular** | | | | | |
| Hypotension | MAP ≥70 mmHg | MAP <70 mmHg | Dopamine ≤5 or<br>dobutamine<br>(any dose)* or<br>terlipressin | Dopamine >5 or<br>epi ≤0.1 or<br>norepi ≤0.1* | Dopamine >15 or<br>epi >0.1 or<br>norepi >0.1* |
| **CNS** | | | | | |
| HE grade | No HE | I | II | III | IV |
| **Renal** | | | | | |
| Creatinine<br>(mg/dL) | <1.2 | ≥1.2 to <2.0 | ≥2.0 to <3.5 | ≥3.5 to <5.0 or<br>use of RRT | ≥5.0 |

CNS = central nervous system; epi = epinephrine; FiO2 = fractional inspired oxygen; HE = hepatic encephalopathy; INR = international normalized ratio; MAP = mean arterial pressure; norepi = norepinephrine, PaO2 = arterial oxygen tension; RRT = renal replacement therapy; SpO2 = pulse oximetric saturation. **Gray shading in the table cells defines insufficiency of that organ**
* Adrenergic agents administered for at least 1 h (doses are given in lg/kg/min).

**Table 2. Demographic, clinical and laboratory findings of the study population and for each acute-on-chronic liver failure (ACLF) grade**

| Variable | Study population (n = 51) | Acute-on-chronic liver failure | | | | |
|---|---|---|---|---|---|---|
| | | Absent(n = 33) | Present (n = 18) | Grade 1 (n = 7) | Grade 2 (n = 10) | Grade 3 (n = 1) |
| Age (years)* | 53 (11) | 54 (11) | 51 (12) | 53 (10) | 51 (13) | 37 |
| Leukocytes ($10^3$/mm$^3$)* | 8,8 (4,8) | 8.1 (4.1) | 10.3 (5.9) | 12.2 (8) | 8.3 (3.4) | 15.9 |
| Platelets ($10^3$/mm$^3$)* | 134 (93) | 155 (98) | 97(71) | 109(73) | 87(76) | 108 |
| BMI (kg/m$^2$)* | 25 (3.6) | 25 (3.9) | 25 (2.9) | 25 (1.9) | 24 (3.3) | 29 |
| MBP (mmHg)* | 75 (14) | 75 (15) | 75 (14) | 73 (14) | 74 (14) | 92 |
| Creatinine (mg/dL)* | 1.59 (1.1) | 0.97 (0.17) | 2.7 (1.3) | 2.2 (0.7) | 3 (1.6) | 3 |
| Urea (mg/dL)* | 48 (37) | 35 (24) | 72 (45) | 77 (48) | 73 (46) | 24 |
| Sodium (mmol/L)* | 137 (5.2) | 137 (5.2) | 135 (5.2) | 134 (4.6) | 136 (5.9) | 132 |
| PaO2 (mmHg)* | 85 (26) | 84 (30) | 85 (17.2) | 81 (16.9) | 88 (18.8) | 87 |
| AST (U/L)* | 125 (157) | 104 (103) | 163 (223) | 222 (336) | 117 (114) | 210 |
| ALT (U/L)* | 137 (303) | 77 (110) | 248 (477) | 272 (560) | 247 (466) | 98 |
| GGT (U/L)* | 541 (729) | 498 (582) | 620 (956) | 631 (892) | 580 (1083) | 1052 |
| Alkaline phosphatase (U/L)* | 220 (137) | 243 (148) | 177 (104) | 224 (131) | 153 (76) | 89 |
| Albumin (g/dL)* | 2.0 (1.0) | 1.9 (1.7) | 2.1 (0.5) | 2.1 (0.3) | 2.1 (0.7) | 2 |
| INR* | 1.5 (0.6) | 1.3 (0.4) | 1.8 (0.7) | 1.7 (0.4) | 1.7 (0.6) | 4 |
| Bilirubin (mg/dL)* | | | | | | |
| Liver scores* | | | | | | |
| MELD | 15.2 (9.7) | 10.4 (5.6) | 23.9 (9.6) | 21.8 (6.4) | 24.1 (11) | 37.9 |
| MELD-Na | 16.6 (10.4) | 11.9 (6.7) | 25.3 (10.4) | 24.6 (5) | 24.5 (13) | 38.3 |
| CLIF-SOFA | 10.9 (2.4) | 10.3 (2.1) | 11.9 (2.6) | 10.8 (2.4) | 12.6 (2.6) | 13 |
| CLIF-C AD/ACLF | 54 (11.5) | 49.7 (8.5) | 63.1 (11.2) | 53.8 (9.7) | 61.2 (12.1) | 78 |
| Sex** | | | | | | |
| Male | 42 (82) | 25 (76) | 17 (94) | 7 (100) | 9 (90) | 1 |
| Female | 9 (18) | 8 (24) | 1 (6) | 0 | 1 (10) | 0 |
| Health Service** | | | | | | |
| Public | 46 (90) | 30 (90) | 16 (89) | 6 (75) | 9 (100) | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Private | 5 (10) | 3 (10) | 2 (11) | 2 (25) | 0 | 0 |
| Etiology** | | | | | | |
| Alcohol | 46 (90) | 29 (88) | 17 (94) | 6 (85) | 10 (100) | 1 |
| Other | 5 (10) | 4 (12) | 1 (6) | 1 (15) | 0 | 0 |
| Virus** | | | | | | |
| Hepatitis B | 1 (2) | 1 (3) | 0 | 0 | 0 | 0 |
| Hepatitis C | 9 (18) | 6 (18) | 3 (17) | 1 (15) | 2 (20) | 0 |
| HIV | 1 (2) | 0 | 1 (6) | 1 (15) | 0 | 0 |
| Hepatocellular carcinoma** | | | | | | |
| Yes | 5 (10) | 4 (12) | 1 (6) | 1 (15) | 0 | 0 |
| No | 46 (90) | 29 (88) | 17 (94) | 6 (85) | 10 (100) | 1 |
| Hepatorenal syndrome** | | | | | | |
| Yes | 6 (12) | 1 (3) | 5 (28) | 1 (15) | 3 (30) | 1 |
| No | 45 (88) | 32 (97) | 13 (72) | 6 (85) | 7 (70) | 0 |
| Infection** | | | | | | |
| SBP | 6 (12) | 2 (6) | 4 (22) | 2 (29) | 2 (20) | 0 |
| UTI | 30 (59) | 20 (61) | 10 (56) | 3 (41) | 7 (70) | 0 |
| RTI | 6 (12) | 3 (9) | 3 (16) | 1 (15) | 1 (10) | 1 |
| Other | 3 (5) | 2 (7) | 1 (6) | 1 (15) | 0 | 0 |
| None | 6 (12) | 6 (17) | 0 | 0 | 0 | 0 |
| Hepatic encephalopathy** | | | | | | |
| Absent | 26 (51) | 19 (58) | 7 (40) | 3 (41) | 4 (40) | 0 |
| Present | 25 (49) | 14 (42) | 11 (60) | 4 (59) | 6 (60) | 1 |
| Grade I | 12 (23) | 8 (24) | 4 (22) | 1 (15) | 3 (30) | 0 |
| Grade II | 4 (8) | 2 (6) | 2 (11) | 2 (29) | 0 | 0 |
| Grade III | 1 (2) | 0 | 1 (5) | 1 (15) | 0 | 0 |
| Grade IV | 8 (16) | 4 (12) | 4 (22) | 0 | 3 (30) | 1 |
| Survival** | | | | | | |
| 28-day | 37 (72) | 26 (78) | 11 (61) | 5 (71) | 6 (60) | 0 |
| 90-day | 29 (57) | 23 (69) | 6 (33) | 3 (43) | 3 (30) | 0 |
| 365-day | 16 (31) | 13 (39) | 3 (17) | 2 (29) | 1 (10) | 0 |

BMI = body mass index; MBP = mean blood pressure; AST = aspartate transaminase; ALT = alanine transaminase; GGT = gamma-glutamyl transferase; INR = international normalized ratio; MELD = Model for End-Stage Liver Disease; MELD-Na = Modified Model Including Sodium; CLIF-SOFA = Chronic Liver Failure Sequential Organ Failure Assessment; CLIF-C AD/ACLF = CLIF Consortium Acute Decompensation/acute-on-chronic liver failure; SBP = spontaneous bacterial peritonitis; UTI = urinary tract infection; RTI = respiratory tract infection.
*Mean (standard deviation); **Frequency (%).

**Table 3. Univariate analysis**

| Variable | Survival(hazardratio -95%CI) | | |
|---|---|---|---|
| | 28-day | 90-day | 365-day |
| Age | 0.98(0.03-1.03) | 0.92(0.94-1.02) | 1.0(0.96-1.03) |
| Leukocytes | 1.1(0.14-8.8) | 2;03(0.26-15.3) | 1.8(0.4-7.8) |
| Platelets | 0.16(0.01-1.4) | 0.4(0.18-1.2) | 0.7(0.27-2.2) |
| BMI-higher values | 0.8(0.69-0.97)* | 0.8(0.7-0.98)* | 0.9(0.82-1.0)* |
| Creatinine(≥1.5mg/dL) | 2(0.7-5.8) | 2.5(1.08-5.81)* | 2.2(1.1=4.5)* |
| Sodium | 0.8(0.25-2.5) | 1.4(0.6-3.4) | 1.3(0.6-2.8) |
| AST | 1.02(0.28-3.6) | 0.92(0.34-2.5) | 0.9(0.4-2;06) |
| ALT | 1.2(0.6-3.8) | 0.86(0.37-1.9) | 1.2(0.6-2.4) |
| GGT | 0.54(0.12-2.41) | 0.44(0.12-1.5) | 0.6(0.19=-2.14) |
| Albumin | 1.2(0.1-9.5) | 0.22(0.03-1.6) | 0.4(0.08-2.4) |
| INR | 0.94(0.3-2.7) | 0;89(0.38-2.1) | 0.8(0.44-1.7) |
| Total bilirubin | 0.6(0.2-2.0) | 0.4(0.18-1.2) | 0.5(0.26-1.1) |
| Liver scores*** | | | |
| MELD | 1.02(0.96-1.07) | 1.01(0.96-1.05) | 1.0(0.97-1.05) |
| MELD-Na | 1.02(0.97-1.07) | 1.01(0.97-1.05) | 1.01(0.97-1.04) |
| CLIF-SOFA | 1.32(1.07-1.61)** | 1.3(1.1-1.6)** | 1.2(1.08-1.45)** |
| CLIF-C AD/ACLF | 1.0(0.9-1.05) | 1.0(0.96-1.04) | 1.0(0.9-1.03) |
| Sex(Female) | 3.1(1.05-9.4)* | 3.2(1.3-7.9)* | 2.5(1.1-5.7)* |
| Etiology | 2.1(0.47-9.4) | 1.35(0.31-5.7) | 1.1(0.15-8.3) |
| Hepatitis C | 3.5(1.1-10.6)* | 1.9(0.72-5.37) | 1.6(0.7-3.8) |
| HIV | 12(1.3-108)* | 12(1.3-108)* | 12(1.3-108)* |
| Hepatocellular carcinoma | 3.8(1.06-14)* | 2.3(0.68-7.87) | 2.8(1.07-7.82)* |
| Hepatorenal syndrome | 1.3(0.3-6.1) | 1.2(0.3-4.3) | 2.0(0.82-4.85) |
| Infection | 0.9(0.2-3.3) | 1.2(0.4-3.5) | 2.5(0.9-7.3) |
| Hepatic Encephalopathy | 0.38(0.04-3.2) | 0.6(0.13-3.01) | 0.4(0.09-1.9) |
| ACLF | | | |
| Absent x Present | 2(0.7-5.8) | 2.8(1.2-6.5)* | 2.1(1.1-4.3)* |

BMI = body mass index; AST = aspartate transaminase; ALT = alanine transaminase; GGT = gamma-glutamyl transferase; INR = international normalized ratio; MELD = Model for End-Stage Liver Disease; MELD-Na = Modified Model Including Sodium; CLIF-SOFA = Chronic Liver Failure Sequential Organ Failure Assessment; CLIF-C AD/ACLF = CLIF Consortium Acute Decompensation/acute-on-chronic liver failure.
*P≤0.05; **P<0.01; ***HR per point in the score.

**Table 4. Multivariate analysis**

| Variable | Survival (hazard ratio - 95% CI) | | |
|---|---|---|---|
| | 28-day | 90-day | 365-day |
| Sex (Female) | 4.4 (1.2-16) p = 0.02 | 6.6 (1.6-13) p = 0.003 | 2.9 (1.2-7.3) p = 0.01 |
| HIV | 12.7 (0.9-177) p = 0.05 | 13.3 (1.1-156) p = 0.03 | 11.7 (1.1-124) p = 0.04 |
| Hepatocellular carcinoma | 6.8 (1.4-32) p = 0.015 | 3.5 (0.8-14) p = 0.07 | 3.3 (1.1-9.9) p = 0.03 |
| CLIF-SOFA* | 1.3 (1.03-1.7) p = 0.02 | 1.3 (1.08-1.6) p = 0.006 | 1.2 (1.05-1.48) p = 0.01 |
| ACLF Absent x Present | 3.1 (0.8-12) p = 0.08 | 4.4 (1.4-10.9) p = 0.008 | 2.8 (1.3-6.1) p = 0.006 |

CLIF-SOFA = Chronic Liver Failure Sequential Organ Failure Assessment (HR per point in the score); ACLF =Acute-on-chronic liver failure. *HR per point in the score.

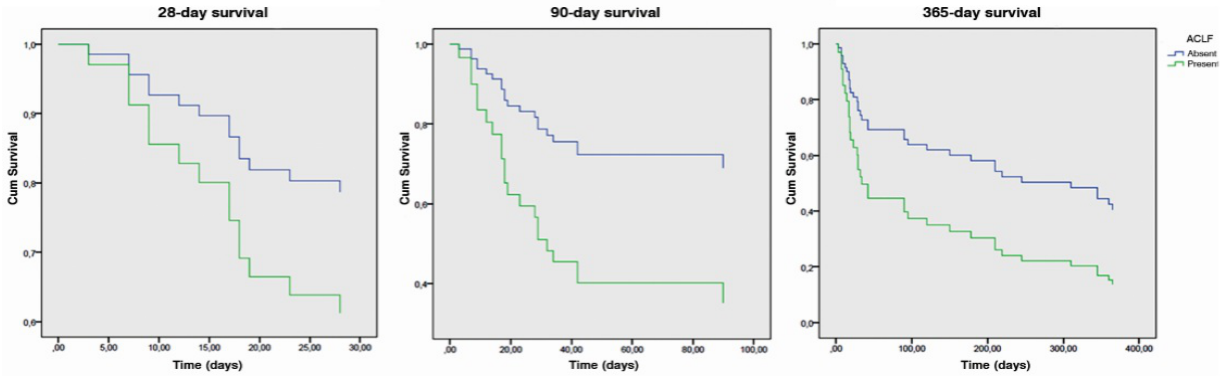


**Figure 1. Kaplan-Meyer curves for 28-, 90- and 365-day survival for acute-on-chronic liver failure (ACLF) present or absent.**

## REFERENCES


1. Desmet VJ, Roskams T. Cirrhosis reversal: a duel between dogma and myth. J Hepatol. 2004;40(5):860-7. PMID: 15094237; doi: 10.1016/j.jhep.2004.03.007.
2. Blei AT, Cordoba J. Practice Parameters Committee of the American College of Gastroenterology. Hepatic Encephalopathy. Am J Gastroenterol. 2001;96(7):1968-76. PMID: 11467622; doi: 10.1111/j.1572-0241.2001.03964.x.
3. Moore KP, Wong F, Gines P, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology. 2003;38(1):258-66. PMID: 12830009; doi: 10.1053/jhep.2003.50315.
4. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med. 2010;362(9):823-32. PMID: 20200386; doi: 10.1056/NEJMra0901512.
5. Gustot T, Durand F, Lebrec D, Vincent JL, Moreau R. Severe sepsis in cirrhosis. Hepatology. 2009;50(6):2022-33. PMID: 19885876; doi: 10.1002/hep.23264.
6. Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology. 2010;139(4):1246-56, 1256 e1-5. PMID: 20558165; doi: 10.1053/j.gastro.2010.06.019.
7. World Health Organization (WHO). Projections of mortality and burden of disease to 2030, Available from: http://www.who.int/healthinfo/statistics/bodprojectionspaper.pdf. Accessed in 2018 (Jul 3).
8. Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. Curr Opin Crit Care. 2011;17(2):165-9. PMID: 21326095; doi: 10.1097/MCC.0b013e328344b42d.
9. Martin JA, Smith BL, Mathews TJ, Ventura SJ. Births and deaths: preliminary data for 1998. Natl Vital Stat Rep. 1999;47(25):1-45. PMID: 10641521.
10. Jalan R, Gines P, Olson JC, et al. Acute-on chronic liver failure. J Hepatol. 2012;57(6):1336-48. PMID: 22750750; doi: 10.1016/j.jhep.2012.06.026.
11. Jalan R, Williams R. Acute-on-chronic liver failure: pathophysiological basis of therapeutic options. Blood Purif. 2002;20(3):252-61. PMID: 11867872; doi: 10.1159/000047017.
12. Laleman W, Wilmer A, Evenepoel P, et al. Review article: non-biological liver support in liver failure. Aliment Pharmacol Ther. 2006;23(3):351-63. PMID: 16422994; doi: 10.1111/j.1365-2036.2006.02765.x.
13. Roberts SE, Goldacre MJ, Yeates D. Trends in mortality after hospital admission for liver cirrhosis in an English population from 1968 to 1999. Gut. 2005;54(11):1615-21. PMID: 15980061; doi: 10.1136/gut.2004.058636.
14. Warrillow SJ. Predictions and outcomes for the critically ill patient with cirrhosis: is it time to settle on the SOFA and let jaundiced views on outcome MELD away? Crit Care Med. 2010;38(11):2259-60. PMID: 20959755; doi: 10.1097/CCM.0b013e3181f84a23.
15. Das V, Boelle PY, Galbois A, et al. Cirrhotic patients in the medical intensive care unit: early prognosis and long-term survival. Crit Care Med. 2010;38(11):2108-16. PMID: 20802324; doi: 10.1097/CCM.0b013e3181f3dea9.
16. Aggarwal A, Ong JP, Younossi ZM, et al. Predictors of mortality and resource utilization in cirrhotic patients admitted to the medical ICU. Chest. 2001;119(5):1489-97. PMID: 11348958.
17. Zimmerman JE, Wagner DP, Seneff MG, et al. Intensive care unit admissions with cirrhosis: risk-stratifying patient groups and predicting individual survival. Hepatology. 1996;23(6):1393-401. PMID: 8675156; doi: 10.1002/hep.510230615.
18. Wehler M, Kokoska J, Reulbach U, Hahn EG, Strauss R. Short-term prognosis in critically ill patients with cirrhosis assessed by prognostic scoring systems. Hepatology. 2001;34(2):255-61. PMID: 11481609; doi: 10.1053/jhep.2001.26522.
19. Jalan R, Sen S, Williams R. Prospects for extracorporeal liver support. Gut. 2004;53(6):890-8. PMID: 15138219.
20. Malik R, Mookerjee RP, Jalan R. Infection and inflammation in liver failure: two sides of the same coin. J Hepatol. 2009;51(3):426-9. PMID: 19615779; doi: 10.1016/j.jhep.2009.06.013.
21. du Cheyron D, Bouchet B, Parienti JJ, Ramakers M, Charbonneau P. The attributable mortality of acute renal failure in critically ill patients with liver cirrhosis. Intensive Care Med. 2005;31(12):1693-9. PMID: 16244877; doi: 10.1007/s00134-005-2842-7.
22. Gustot T. Multiple organ failure in sepsis: prognosis and role of systemic inflammatory response. Curr Opin Crit Care. 2011;17(2):153-9. PMID: 21346564; doi: 10.1097/MCC.0b013e328344b446.
23. Sen S, Davies NA, Mookerjee RP, et al. Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: a randomized controlled study. Liver Transpl. 2004;10(9):1109-19. PMID: 15350001; doi: 10.1002/lt.20236.
24. Cazzaniga M, Dionigi E, Gobbo G, et al. The systemic inflammatory response syndrome in cirrhotic patients: relationship with their in-hospital outcome. J Hepatol. 2009;51(3):475-82. PMID: 19560225; doi: 10.1016/j.jhep.2009.04.017.
25. Thabut D, Massard J, Gangloff A, et al. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. Hepatology. 2007;46(6):1872-82. PMID: 17972337; doi: 10.1002/hep.21920.
26. Linderoth G, Jepsen P, Schonheyder HC, Johnsen SP, Sorensen HT. Short-term prognosis of community-acquired bacteremia in patients with liver cirrhosis or alcoholism: A population-based cohort study. Alcohol Clin Exp Res. 2006;30(4):636-41. PMID: 16573581; doi: 10.1111/j.1530-0277.2006.00074.x.
27. Cholongitas E, Senzolo M, Patch D, et al. Risk factors, sequential organ failure assessment and model for end-stage liver disease scores for predicting short term mortality in cirrhotic patients admitted to intensive care unit. Aliment Pharmacol Ther. 2006;23(7):883-93. PMID: 16573791; doi: 10.1111/j.1365-2036.2006.02842.x.
28. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144(7):1426-37, 1437 e1-9. PMID: 23474284; doi: 10.1053/j.gastro.2013.02.042.
29. Soldera J, Balbinot SS, Balbinot RA, et al. Diagnostic and Therapeutic Approaches to Hepatocellular Carcinoma: Understanding the Barcelona Clínic Liver Cancer Protocol. Clin Med Insights Gastroenterol. 2016;9:67-71. PMID: 27812296; doi: 10.4137/CGast.S30190.
30. Salerno F, Gerbes A, Ginès P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007;56(9):1310-8. PMID: 17389705; doi: 10.1136/gut.2006.107789.
31. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Semin Liver Dis. 2008;28(1):26-42. PMID: 18293275; doi: 10.1055/s-2008-1040319.
32. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464-70. PMID: 11172350; doi: 10.1053/jhep.2001.22172.
33. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008;359(10):1018-26. PMID: 18768945; doi: 10.1056/NEJMoa0801209.
34. Hernaez R, Solà E, Moreau R, et al. Acute-on-chronic liver failure: an update. Gut. 2017;66(3):541-53. PMID: 28053053; doi: 10.1136/gutjnl-2016-312670.
35. Jalan R. Acute-on-chronic liver failure: from concept to a new syndrome. Curr Opin Crit Care. 2011;17(2):152. PMID: 21358404; doi: 10.1097/MCC.0b013e3283455c57.
36. Mookerjee RP. Acute-on-chronic liver failure: the liver and portal haemodynamics. Curr Opin Crit Care. 2011;17(2):170-6. PMID: 21346568; doi: 10.1097/MCC.0b013e328344a076.
37. Liu H, Lee SS. Acute-on-chronic liver failure: the heart and systemic hemodynamics. Curr Opin Crit Care. 2011;17(2):190-4. PMID: 21326096; doi: 10.1097/MCC.0b013e328344b397.
38. Cárdenas A, Ginès P. Acute-on-chronic liver failure: the kidneys. Curr Opin Crit Care.

2011;17(2):184-9. PMID: 21311322; doi: 10.1097/MCC.0b013e328344b3da.
39. García-Martínez R, Cordoba J. Acute-on-chronic liver failure: the brain. Curr Opin Crit Care. 2011;17(2):177-83. PMID: 21346567; doi: 10.1097/MCC.0b013e328344b37e.
40. Hassanein TI, Schade RR, Hepburn IS. Acute-on-chronic liver failure: extracorporeal liver assist devices. Curr Opin Crit Care. 2011;17(2):195-203. PMID: 21346566; doi: 10.1097/MCC.0b013e328344b3aa.
41. Dhiman RK, Agrawal S, Gupta T, et al. Chronic Liver Failure-Sequential Organ Failure Assessment is better than the Asia-Pacific Association for the Study of Liver criteria for defining acute-on-chronic liver failure and predicting outcome. World J Gastroenterol. 2014;20(40):14934-41. PMID: 25356054; doi: 10.3748/wjg.v20.i40.14934
42. Selva Rajoo A, Lim SG, Phyo WW, et al. Acute-on-chronic liver failure in a multi-ethnic Asian city: A comparison of patients identified by Asia-Pacific Association for the Study of the Liver and European Association for the Study of the Liver definitions. World J Hepatol. 2017;9(28):1133-40. PMID: 29075369; doi: 10.4254/wjh.v9.i28.1133
43. Silva PE, Fayad L, Lazzarotto C, et al. Single-centre validation of the EASL-CLIF consortium definition of acute-on-chronic liver failure and CLIF-SOFA for prediction of mortality in cirrhosis. Liver Int. 2015;35(5):1516-23. PMID: 24840673; doi: 10.1111/liv.12597.
44. Hernaez R, Kramer JR, Liu Y, et al. Prevalence and Short-term Mortality of Acute-on-Chronic Liver Failure: a national cohort study from the USA. J Hepatol. 2018; pii: S0168-8278(18)32637-0. PMID: 30590100; doi: 10.1016/j.jhep.2018.12.018
45. Li Q, Xing H, Liu D, Li H. Negative impact of low body mass index on liver cirrhosis patients with hepatocellular carcinoma. World J Surg Oncol. 2015;13:294. PMID: 26444667; doi: 10.1186/s12957-015-0713-4.
46. Samada M, Hernández JC. Prognostic factors for survival in patients with liver cirrhosis. In: Abdeldayem H. Liver Transplantation. Basic Issues. InTech; 2012. p. 125-144. Available from: https://www.intechopen.com/books/liver-transplantation-basic-issues/prognostic-factors-for-survival-in-patients-with-liver-cirrhosis. Accessed in 2018 (Jul 3).
47. Mokdad AA, Lopez AD, Shahraz S, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med. 2014;12:145. https://doi.org/10.1186/s12916-014-0145-y. PMID: 25242656; doi: 10.1186/s12916-014-0145-y.
48. Krag A, Bendtsen F, Burroughs AK, Moller S. The cardiorenal link in advanced cirrhosis. Med Hypotheses. 2012;79(1):53-5. PMID: 22537409; doi: 10.1016/j.mehy.2012.03.032.
49. Sy E, Ronco JJ, Searle R, et al. Prognostication of critically ill patients with acute-on-chronic liver failure using the Chronic Liver Failure-Sequential Organ Failure Assessment: A Canadian retrospective study. J Crit Care. 2016 Dec;36:234-239. PMID: 27569253; doi: 10.1016/j.jcrc.2016.08.003.
50. Kim HY, Kim CW, Kim TY, et al; Korean Acute-on-Chronic Liver Failure Study Group. Assessment of scoring systems for acute-on-chronic liver failure at predicting short-term mortality in patients with alcoholic hepatitis. World J Gastroenterol. 2016 Nov 7;22(41):9205-9213. PMID: 27895407; doi: 10.3748/wjg.v22.i41.9205.
51. Kulkarni S, Sharma M, Rao PN, et al. Acute on Chronic Liver Failure-In-Hospital Predictors of Mortality in ICU. J Clin Exp Hepatol. 2018 Jun;8(2):144-155. PMID: 29892177; doi: 10.1016/j.jceh.2017.11.008.
52. Grochot RM, Luz LB, Garcia R, Balbinot RA, Balbinot SS, Soldera J. Clif-Sofa is Superior to Other Liver-Specific Scores for Predicting Mortality in Acute-on-Chronic Liver Failure and Decompensated Cirrhosis. Austin J Gastroenterol. 2019; 6(2): 1105. [https://austinpublishinggroup.com/gastroenterology/fulltext/ajg-v6-id1105.php]