

Incidence and Risk Factors for Acute-on-Chronic Liver Failure in Outpatients with Cirrhosis: A Prospective Multicenter Cohort Study

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Research Article

Keywords: cirrhosis, acute-on-chronic liver failure, prognosis, incidence, risk factors, outpatient care, albumin, ascites, anaemia, renal dysfunction

Posted Date: October 7th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11108605/v1>

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Incidence and Risk Factors for Acute-on-Chronic Liver Failure in Outpatients with Cirrhosis: A Prospective Multicenter Cohort Study

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ABSTRACT

Background and Aims: Acute-on-chronic liver failure (ACLF) has been extensively studied in hospitalised patients, but its incidence and risk factors in outpatients remain poorly defined. This study evaluated the incidence and independent risk factors for ACLF in an outpatient cohort of individuals with cirrhosis.

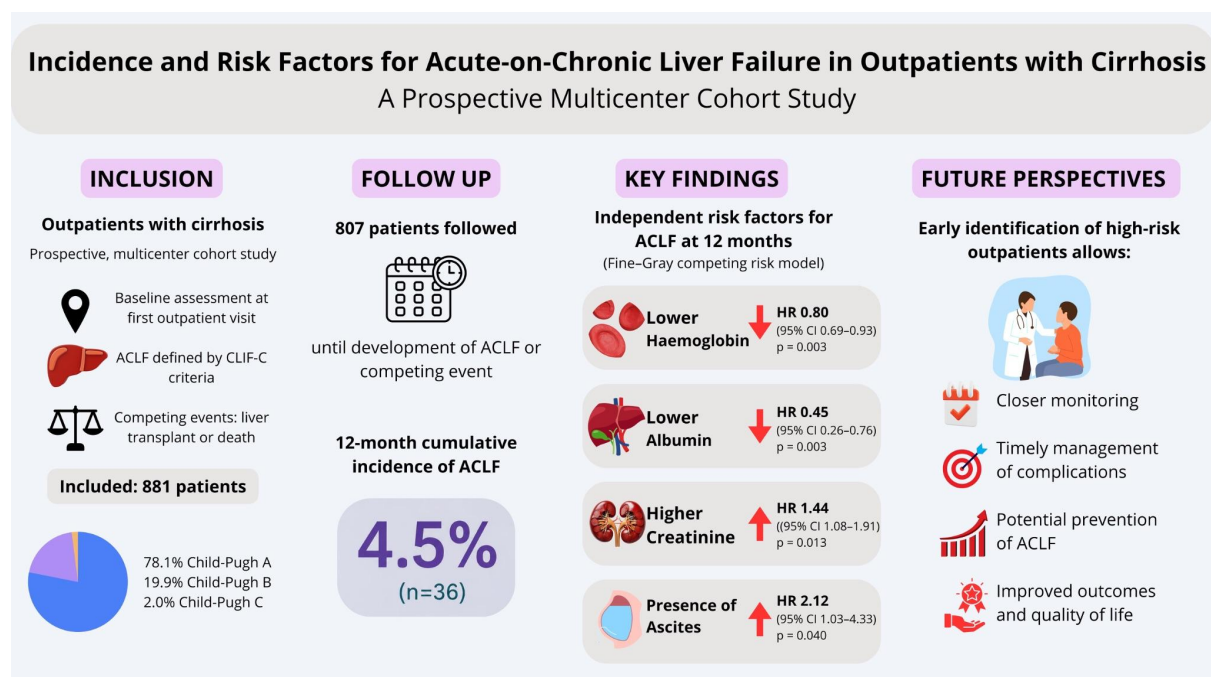
Methods: This is a prospective, multicenter cohort study, in which baseline data were collected at the first outpatient visit of individuals with cirrhosis, who were then followed until the development of ACLF or the competing outcomes (liver transplant or death). ACLF was defined according to the Chronic Liver Failure Consortium (CLIF-C) criteria. Cumulative incidence functions (CIFs) for ACLF were calculated, and multivariate analyses were performed using the Fine–Gray competing risk model to estimate subdistribution hazard ratios (HRs) and their 95% confidence intervals (CIs).

Results: A total of 881 patients were included (78.1% - Child-Pugh A, 19.9% - Child-Pugh B, 2.0% - Child-Pugh C). Eight hundred and seven patients were actually followed, among which the cumulative incidence of ACLF in 12 months was 4.5% (n=36). Independent risk factors for ACLF at 12 months included lower levels of haemoglobin (HR=0.80; 95% CI=0.69–0.93, p=0.003) and albumin (HR=0.45; 95% CI=0.26–0.76, p=0.003), higher levels of creatinine (HR=1.44; 95% CI=1.08–1.91, p=0.013), and the presence of ascites (HR=2.12; 95% CI=1.03–4.33, p=0.040).

Conclusions: The cumulative incidence of ACLF was low, likely reflecting the predominance of compensated cirrhosis at study entry. Baseline markers of anaemia and liver and kidney dysfunction were independently associated with the development of ACLF.

Keywords: cirrhosis; acute-on-chronic liver failure; prognosis; incidence; risk factors; outpatient care; albumin; ascites; anaemia; renal dysfunction.

Graphical abstract:



Introduction

Liver disease is a major cause of global morbidity and mortality, accounting for approximately two million deaths annually and nearly 4% of all deaths worldwide¹. Disease progression is closely linked to the development of portal hypertension, the

principal consequence of cirrhosis and the main driver of its clinical complications, including ascites, variceal bleeding and hepatic encephalopathy. These complications define the decompensated stage of the disease². The natural history of cirrhosis comprises a compensated phase, which is generally asymptomatic and associated with survival exceeding 12 years, and a decompensated phase characterised by clinical complications and a marked reduction in survival to approximately 2–4 years³. Acute-on-chronic liver failure (ACLF) is characterised by acute decompensation (AD) of cirrhosis associated with failure of one or more organ systems and a markedly increased risk of short-term mortality. This condition affects approximately 35% of patients with cirrhosis hospitalised for AD and is associated with a 90-day mortality rate of 58%⁴.

Data regarding the incidence of ACLF among outpatients with cirrhosis remain limited. In a prospective single-center Italian cohort, the probability of developing ACLF was 14% at 1 year and 29% at 5 years. Baseline predictors included ascites, lower mean arterial pressure, higher Model for End-stage Liver Disease (MELD) scores and lower haemoglobin levels. In contrast, a retrospective study of a cohort of United States veterans demonstrated an ACLF incidence of 6.3% over 3.35 years, while a retrospective single-center Brazilian cohort study reported an ACLF incidence of 3.9% at 12 months and 12.7% at 60 months⁷.

The aim of this study was to determine the incidence of ACLF and identify independent predictors of its development in a large multicenter prospective cohort of outpatients with cirrhosis.

Materials and Methods

This was a prospective cohort study conducted at six Brazilian hospitals. Consecutive adult patients with cirrhosis attending scheduled outpatient hepatology clinics were enrolled between 2021 and 2024. Cirrhosis was diagnosed histologically when liver biopsy was available or, alternatively, on the basis of a combination of clinical, laboratory, radiological and/or endoscopic findings consistent with advanced chronic liver disease. Exclusion criteria were age younger than 18 years; hepatocellular carcinoma (HCC) beyond Milan criteria at study inclusion; extrahepatic malignancy within the two years preceding study inclusion (except non-melanoma skin cancer); pregnancy; solid organ transplantation prior to study inclusion; New York Heart Association (NYHA) class IV heart failure; Global Initiative for Chronic Obstructive Lung Disease (GOLD) class D chronic obstructive pulmonary disease; and inability to obtain informed consent from the patient or their legal representative.

A predefined REDCap form was used for data collection. The coordinating center (Federal University of Health Sciences of Porto Alegre) was responsible for monitoring the data entered into REDCap and requesting participating centers to review incomplete or potentially inaccurate information. Data were extracted from electronic medical records at the time of the inclusion outpatient visit and whenever the patient was hospitalized. The main variables of interest were age; sex; ethnicity; cause of cirrhosis; alcohol consumption; comorbidities; body mass index (BMI); mean arterial pressure; biochemical variables (complete blood count, serum

creatinine, sodium, and liver function tests); medication use (diuretics, beta-blockers, statins, anticoagulants, vasopressors); hemodialysis; ventilatory support; presence of cirrhosis complications (ascites, hepatic encephalopathy, gastroesophageal varices, portal vein thrombosis, HCC); reasons for hospitalisation (gastrointestinal bleeding, ascites without spontaneous bacterial peritonitis [SBP], SBP or other infections, hepatic encephalopathy, acute kidney injury, alcohol-related hepatitis); and prognostic scores for liver disease (Child-Pugh score, MELD, and MELD-Na). For the analyses, anaemia was defined as haemoglobin <13 g/dL in men and <12 g/dL in women. For creatinine assessment, the cutoff value used was ≤ 1.2 mg/dL versus > 1.2 mg/dL, and for albumin assessment, the cutoff value used was ≥ 3.5 g/dL versus < 3.5 g/dL.

The primary outcome of the study was the development of ACLF. Death and liver transplantation were considered competing outcomes. The Chronic Liver Failure Consortium (CLIF-C) definition of ACLF was adopted because of its superior performance in mortality prediction compared with other definitions and because it has been previously validated in Brazil and Latin America⁸⁻¹⁰.

Statistical Analysis

Sample size was calculated assuming a 14% probability of developing ACLF within 1 year and the following risk factors: ascites (hazard ratio [HR] = 2.53, 95% confidence interval [95% CI] = 1.17–5.49), haemoglobin (HR = 0.07, 95% CI = 0.01–0.55), mean arterial pressure (HR = 0.96, 95% CI = 0.94–0.99), and MELD

score (HR = 1.26, 95% CI = 1.17–1.35), according to Piano et al. (5). With a statistical power of 80% and a significance level of 5%, the estimated sample size was 407 patients. Considering the possibility of loss to follow-up during the study period, the inclusion of at least 814 individuals was planned. Sample size calculation was performed using the online PSS Health tool (https://hcpa-unidade-bioestatistica.shinyapps.io/PSS_Health/).

Follow-up began at the inclusion outpatient visit and ended at the time of ACLF diagnosis or after up to 12 months for patients who did not develop the outcome. Patients lost to follow-up were censored at the time of their last assessment.

Continuous variables with normal distribution were described as mean and standard deviation (SD) and compared using Student's t-test. Continuous variables without normal distribution were described as median and interquartile range (IQR) and compared using the Mann–Whitney U test. Categorical variables were described as proportions and compared using the chi-square test with continuity correction and/or Fisher's exact test, when appropriate. Missing data were handled using multiple imputation by chained equations.

For ACLF incidence analyses, liver transplantation and death were considered competing events. Cumulative incidence functions (CIFs) of ACLF were calculated for the overall study population and for patient subgroups. Patients who developed ACLF were compared with those who did not regarding the variables of interest in univariate and multivariate analyses. Collinearity was assessed prior to

model construction. Fine–Gray competing-risk regression was chosen because death and liver transplantation preclude subsequent ACLF occurrence. Variables with p-values <0.10 in the univariate analysis were included in the multivariate Fine–Gray competing-risk models, with subdistribution HRs and their respective 95% CIs. To avoid multicollinearity, three distinct models were constructed for ACLF incidence analyses: (1) a model including individual variables; (2) a model including the Child-Pugh score while excluding its component variables; and (3) a model including the MELD score while excluding its component variables.

Overall survival was estimated using the Kaplan–Meier method. Patients who underwent liver transplantation during follow-up were censored at the time of transplantation.

Competing-risk analyses were conducted using R software (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria) with the `comparison`, `survival`, and `tidycmprsk` packages. All other analyses were performed using SPSS statistical software (version 27.0; IBM Corp., Armonk, NY, USA). All tests were two-sided, and p-values <0.05 were considered statistically significant.

The writing and reporting of this study followed the recommendations of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies.

Ethical Considerations

The study was conducted in accordance with the 1975 Declaration of Helsinki, revised in 2008, and was approved by the Research Ethics Committee of Irmandade Santa Casa de Misericórdia de Porto Alegre and subsequently by the Research Ethics Committees of each participating center. All patients or their legal representatives provided written informed consent before study inclusion.

Results

Baseline Characteristics and ACLF Incidence

A total of 887 consecutive outpatients with cirrhosis were considered potentially eligible for the study. Six records were excluded because they contained substantially incomplete baseline data. And 881 patients were included in the study, with a mean age of 60.1 ± 12.7 years, of whom 51.9% were male.

Regarding the etiology of liver disease, the main causes identified were alcohol-related liver disease (35.5%), hepatitis C virus (HCV) infection (32.5%), and metabolic dysfunction-associated steatotic liver disease (20.3%). Among the 61 patients with hepatitis B virus (HBV)-related cirrhosis, 50 (82.0%) were under antiviral therapy, and treatment information was unavailable for three individuals. Among the 281 patients with HCV infection, 237 (84.3%) had undergone specific antiviral treatment (85.8% in the group that did not develop ACLF and 66.7% in the group that developed ACLF, $p=0.215$), while treatment data were missing for five patients. It should be noted that one of the individuals with missing data had HBV/HCV coinfection; therefore, the total number of cases with missing information

does not correspond to the simple sum of missing data observed in each etiological group. Concerning alcohol exposure, current alcohol consumption was reported by 48 patients (5.7%).

Regarding comorbidities present at study inclusion, systemic arterial hypertension was observed in 48.7% of patients, and the mean arterial pressure was 94.4 ± 13.1 mmHg. Diabetes mellitus was present in 38.8% of individuals. The mean BMI was 27.8 ± 5.3 kg/m², indicating overweight. Anaemia was observed in 297 patients (33.7%).

With respect to liver disease severity at inclusion, the mean MELD score was 10.5 ± 4.3 , the mean MELD-Na score was 11.7 ± 4.8 , and the mean Child-Pugh score was 5.8 ± 1.3 . The distribution of Child-Pugh classes showed that most patients were classified as Child-Pugh A (78.1%), whereas 19.9% were classified as Child-Pugh B and 2.0% as Child-Pugh C, indicating a predominance of compensated cirrhosis. Ascites were present in 20.5% of individuals, and gastroesophageal varices were present in 66.3%. Hepatic encephalopathy was present in only 31 patients at baseline (3.5%). Portal vein thrombosis was identified in 52 patients (5.9%). Forty-four patients had HCC (5.0%). A small proportion of patients were undergoing hemodialysis at the beginning of follow-up (1.0%).

Seventy-four patients (8.4%) had no follow-up after study inclusion and were therefore excluded from the analyses. Among the remaining 807 individuals, 36 (4.5%) developed ACLF, 15 (1.9%) underwent liver transplantation, and 18 (2.2%) died within a 12-month period. The patient inclusion and follow-up flowchart is shown

in Figure 1. The cumulative incidence of ACLF in the study population was 2.0% at 3 months, 3.0% at 6 months, and 4.5% at 12 months (Figure 2). Mortality was significantly higher among patients who developed ACLF during follow-up (55.6% of patients who developed ACLF were dead at 12 months, compared with 3.4% of those who did not develop ACLF, $p<0.001$). Table 1 compares the baseline characteristics of patients who did and did not develop ACLF within 12 months after excluding individuals who died or underwent liver transplantation during the study period (competing outcomes).

Characteristics and Risk Factors for ACLF

ACLF was classified as grade 1 in 18 patients (50.0%), grade 2 in 13 (36.1%), and grade 3 in 5 individuals (13.9%). Regarding the time to ACLF development, 26 patients developed the outcome within the first 6 months of follow-up (72.2%). The most frequent reasons for hospitalisation among patients with ACLF were infections (25.0%), hepatic encephalopathy (25.0%), gastrointestinal bleeding (13.9%), and acute kidney injury (11.1%).

When patients who developed ACLF within 12 months were compared with those who did not develop this condition, the groups exhibited distinct baseline characteristics. In the univariate analysis (Table 1), the proportion of males was higher among patients who developed ACLF (69.4% vs. 49.2%, $p=0.028$). Regarding etiology, a lower incidence of ACLF was observed among patients with hepatitis C (16.7% vs. 34.8%, $p=0.039$). In addition, MELD (10.1 vs. 14.7, $p<0.001$) and MELD-Na (11.2 vs. 15.9, $p<0.001$) scores were significantly higher among patients

who developed ACLF. The distribution of Child-Pugh classes revealed a lower proportion of patients classified as Child-Pugh A (36.1% vs. 82.8%) and a higher proportion of individuals classified as Child-Pugh B (50.0% vs. 16.7%) and Child-Pugh C (13.9% vs. 0.5%) among those who developed ACLF ($p<0.001$).

Among the laboratory variables evaluated, patients who developed ACLF had higher baseline levels of creatinine, bilirubin, and INR, as well as lower baseline levels of albumin and haemoglobin ($p<0.01$). Moreover, at study inclusion, individuals who subsequently developed ACLF more frequently presented with ascites (58.3% vs. 16.1%, $p<0.001$), gastroesophageal varices (83.3% vs. 64.8%, $p=0.035$), portal vein thrombosis (13.9% vs. 5.3%, $p=0.047$), and a requirement for dialysis (5.6% vs. 0.5%, $p=0.028$). They also had lower mean arterial pressure values than patients who did not develop ACLF (89.8 mmHg vs. 94.9 mmHg, $p=0.022$).

For the multivariate analysis of factors associated with the incidence of ACLF within 12 months, three models were developed (Table 2): one including only individual variables (Model 1), one including the Child-Pugh score (Model 2), and another including the MELD score (Model 3). In Model 1, haemoglobin, creatinine, albumin, and ascites were independent predictors of ACLF development. In Model 2, haemoglobin, creatinine, and the Child-Pugh score were independently associated with the development of ACLF. Finally, in Model 3, haemoglobin, albumin, ascites, and the MELD score were independently associated with the outcome. The variables included in Model 1 were also associated with the development of ACLF in Models 2

and 3, either individually or as components of the Child-Pugh and MELD scores, respectively, supporting the robustness of the observed associations.

Figure 3 depicts the cumulative incidence curves of ACLF at 12 months according to the presence of anaemia (assessed by haemoglobin levels in all three models), impaired renal function (assessed by creatinine levels in Models 1 and 2 or by the MELD score, which incorporates creatinine, in Model 3), ascites, and hypoalbuminemia (both assessed as individual variables in Models 1 and 3 or through the Child-Pugh score, which incorporates them, in Model 2). Whereas the cumulative incidence of ACLF among patients without anaemia at baseline was 0.5% at 3 months, 0.8% at 6 months, and 1.3% at 12 months, it reached 5.4%, 7.7%, and 11.4%, respectively, among those with anaemia ($p<0.001$). For the same time points, among individuals without ascites at study inclusion, the cumulative incidence of ACLF was 1.2%, 1.8%, and 2.3%, whereas it was 5.4%, 8.6%, and 13.6%, respectively, among those with baseline ascites ($p<0.001$). When patients were evaluated according to renal function, the cumulative incidence of ACLF was 1.4%, 2.0%, and 3.4% among those with creatinine ≤ 1.2 mg/dL and 7.1%, 10.7%, and 13.1% among those with creatinine >1.2 mg/dL, respectively ($p<0.001$). Regarding albumin levels at study inclusion, patients with albumin levels ≥ 3.5 g/dL had cumulative incidences of ACLF of 1.5%, 2.1%, and 2.6%, whereas those with albumin levels <3.5 g/dL had cumulative incidences of 4.2%, 7.5%, and 12.5% at the same time points, respectively ($p<0.001$).

Discussion

In this large prospective cohort of outpatients with cirrhosis, the cumulative incidence of ACLF was 4.5% over 12 months. Baseline anaemia, ascites, hypoalbuminaemia and impaired renal function were independently associated with the subsequent development of ACLF. To our knowledge, this represents the largest prospective cohort evaluating ACLF incidence and predictors in the outpatient setting.

The study included a cohort of outpatients with cirrhosis in which 78.1% were classified as Child-Pugh A, reflecting a population predominantly composed of patients with compensated cirrhosis. This characteristic is important in explaining the lower incidence of ACLF (4.5% at 1 year) when compared with the 14% incidence at 1 year and 29% incidence at 5 years reported in the Italian prospective cohort study that first proposed this analysis and included a lower proportion of Child-Pugh A patients (54%) (5). On the other hand, the incidence of ACLF observed in the present study was closer to that reported in two retrospective cohorts with comparable proportions of Child-Pugh A patients: a United States cohort with 81.1% Child-Pugh A patients and an ACLF incidence of 6.3% over 3.35 years, and a single-center Brazilian cohort with approximately 70% Child-Pugh A patients and ACLF incidences of 3.9%, 8.8%, and 12.7% at 1, 3, and 5 years, respectively. This finding reinforces the concept that the natural history of cirrhosis, divided into compensated and decompensated phases, is directly related to the risk of clinical events and mortality, with cirrhosis decompensation representing a critical prognostic milestone, including with respect to the risk of ACLF development.

The hypothesis that the incidence of ACLF in populations of outpatients with cirrhosis depends on baseline liver disease severity is supported by several factors identified as independently associated with this condition not only in the present study, but also in previous publications on the topic^{5,7}. In the present study, ascites, albumin levels, Child-Pugh score, and MELD score were associated with ACLF development in different multivariate models. Likewise, ascites and MELD score were independent predictors of ACLF development in the original Italian study⁵, whereas the Child-Pugh score was significantly associated with the development of ACLF in the Brazilian retrospective study⁷. Ascites emerged as one of the strongest predictors of ACLF, increasing the risk of developing this condition more than two-fold, similarly to what was verified in the study by Piano et al.⁵. This finding is biologically plausible, as ascites reflect clinically significant portal hypertension and advanced circulatory dysfunction³.

Hypoalbuminaemia, which also had a substantial impact on ACLF development, is closely related not only to hepatic dysfunction but also to the systemic inflammation involved in the pathogenesis of the syndrome¹¹. The relevance of systemic inflammation in the pathophysiology of cirrhosis decompensation and ACLF was reaffirmed by a recent study that proposed a genetic score for its quantification and prognostic prediction¹². In addition, albumin replacement has been evaluated as a therapeutic alternative in different settings of cirrhosis decompensation^{13,14}. Although there is insufficient evidence of a significant benefit from albumin administration in hypoalbuminemic patients hospitalised for

acute decompensation of cirrhosis¹⁵ or in patients with cirrhosis and extra-peritoneal infections¹⁶, a randomized controlled trial demonstrated that patients with cirrhosis treated with albumin for extra-peritoneal infections had higher rates of ACLF resolution, as well as reductions in leukocytes, C-reactive protein and interleukin-6, markers of the exacerbated systemic inflammatory state¹⁷. Furthermore, although some controversy remains, long-term albumin administration for outpatients with cirrhosis and ascites appears to have a positive impact on several clinical outcomes^{18,19}, representing an intervention that addresses two of the main risk factors associated with ACLF development identified in the present study, namely ascites and hypoalbuminaemia.

As observed in the present study, lower haemoglobin levels have also been identified by different authors as an independent predictor of ACLF development in outpatients with cirrhosis^{5,7,20}. A study evaluating the role of anaemia in patients with advanced chronic liver disease demonstrated that individuals with anaemia had higher Child-Pugh and MELD scores ($p < 0.001$), as well as lower albumin levels ($p < 0.001$). The study also found that moderate-to-severe anaemia (haemoglobin < 10 g/dL) was associated with increased portal pressure and was related to higher risks of hepatic decompensation, hospitalisation, and ACLF²⁰. Anaemia may represent a surrogate marker of exacerbated systemic inflammation, a key driver of ACLF development²¹, since increased oxidative stress and systemic inflammation lead to phosphatidylserine externalization on erythrocytes and to the production of erythrocyte-derived microparticles, causing these cells to be recognized by

macrophages and prematurely removed from the circulation through an apoptotic process known as eryptosis²².

Whereas the study by Piano et al.⁵ identified lower mean arterial pressure as an independent predictor of ACLF development, suggesting a role of circulatory dysfunction in predisposing to organ failure, the present study was only able to demonstrate this association in the univariate analysis and not in the multivariate models. On the other hand, renal dysfunction, reflected by higher creatinine levels at baseline, which is a recognised consequence of advanced circulatory disturbances in cirrhosis²³, was identified in this study as an independent predictor of ACLF development. It is noteworthy that the study by Piano et al. also identified an association between MELD score, which includes creatinine, and ACLF development⁵.

Another point that should be highlighted as a possible additional explanation for the lower incidence of ACLF observed in the present study compared with that reported by Piano et al.⁵ relates to the etiology of the underlying liver disease. Hepatitis C virus infection was the etiological factor of cirrhosis in 32.5% of patients in the present study, and 84.3% of these patients had already received treatment for hepatitis C before study inclusion. The study by Piano et al.⁵ included patients between 2003 and 2015, and direct-acting antiviral agents (DAAs) against hepatitis C virus became available from 2013 onward. Therefore, it is reasonable to assume that most individuals with hepatitis C-related cirrhosis had not been treated at the time of inclusion in that study. Considering that treatment of the underlying liver

disease is a key intervention for reducing the rate of decompensation and, consequently, the incidence of ACLF, this factor may help explain the lower incidence of ACLF observed in the present study, despite the fact that the trend toward an association between hepatitis C treatment and ACLF development did not reach statistical significance.

Despite the robustness of the results of this study, based on the largest prospective cohort conducted to date evaluating the incidence and risk factors for ACLF in outpatients with cirrhosis, some limitations should be acknowledged. Data regarding certain variables were unavailable for some patients, even though a predefined data collection form had been developed before study initiation. However, the impact of this limitation was minimized by the use of a data imputation method to address missing values and because there was no missing data regarding the most relevant outcomes and covariates of the study. In addition, the 12-month follow-up period represents a limitation for direct comparisons with previous publications ⁵⁻⁷. On the other hand, a time horizon longer than 12 months might reduce the applicability of identifying risk factors for ACLF development in clinical practice, which may also explain why Piano et al.⁵ used this time frame in their risk factor analyses.

In conclusion, this study demonstrated a relatively low cumulative incidence of ACLF among outpatients with cirrhosis over a 12-month period, which can be largely explained by the predominance of compensated cirrhosis at baseline in the evaluated cohort. The presence of anaemia, ascites, hypoalbuminaemia and renal

dysfunction at baseline were independently associated with subsequent ACLF development and may help identify outpatients at increased risk for this severe complication.

Declarations

Funding statement: there is no financial support to report.

Competing interests: the authors have no relevant financial or non-financial interests to disclose.

Author contribution:

IZB: Data curation, Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Validation

AAM: Methodology, Conceptualization, Writing - review & editing, Validation

LLG: Data curation, Validation, Writing - review & editing

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DM: Data curation, Validation, Writing - review & editing

CB: Formal analysis, Writing - review & editing, Validation

AZM: Conceptualization, Validation, Writing - review & editing, Writing - original draft, Formal analysis

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TABLES

Table 1. Baseline characteristics of patients according to the development of acute-on-chronic liver failure within 12 months.

Variable	Development of ACLF		p-value
	No (738)	Yes (36)	
Age (years) – mean (SD)	60.1 ± 13.0	56.4 ± 12.1	0.103
Sex (Male) – n (%)	363 (49.2)	25 (69.4)	0.028
Etiology – n (%)			
HBV	54 (7.3)	2 (5.6)	0.999
HCV	257 (34.8)	6 (16.7)	0.039
Alcohol	237 (32.1)	17 (47.2)	0.088
MASLD	144 (19.5)	9 (25.0)	0.553
Others	132 (17.9)	8 (22.2)	0.661
Comorbidities – n (%)			

Diabetes	289 (39.2)	14 (38.9)	0.999
Hypertension	364 (49.3)	19 (52.8)	0.815
Medication– n (%)			
Propranolol	269 (37.8)	21 (46.7)	0.303
Carvedilol	148 (20.8)	11 (24.4)	0.692
Statins	153 (21.5)	7 (15.6)	0.449
Anticoagulants	37 (5.2)	0 (0)	0.159
BMI – mean (SD)	27.9 ± 5.3	27.6 ± 5.1	0.795
Mean arterial pressure (mmHg) – mean (SD)	94.9 ± 13.0	89.8 ± 10.9	0.022
Serum creatinine (mg/dL) – median (IQR)	0.8 [0.7–1.0]	1.0 [0.8–1.3]	0.002
Serum sodium (mmol/L) – mean (SD)	139.6 ± 3.6	138.8 ± 3.4	0.184
Bilirubin (mg/dL) – median (IQR)	0.9 [0.6–1.6]	1.6 [0.9–3.6]	0.001
INR – median (IQR)	1.1 [1.1–1.3]	1.3 [1.2–1.5]	<0.001

Albumin (g/dL) – mean (SD)	4.0 ± 0.6	3.4 ± 0.6	<0.001
Haemoglobin(g/dL) – mean (SD)	13.1 ± 1.9	11.3 ± 2.0	<0.001
Leukocytes (×10³/μL) – median (IQR)	5.1 [3.8–6.5]	5.1 [4.0–6.8]	0.726
Platelets (×10³/μL) – median (IQR)	118 [81.0–170.0]	99 [57.5–146.5]	0.077
MELD – mean (SD)	10.1 ± 4.0	14.7 ± 4.8	<0.001
MELD-Na – mean (SD)	11.2 ± 4.5	15.9 ± 5.0	<0.001
Child-Pugh score – mean (SD)	5.6 ± 1.1	7.3 ± 1.6	<0.001
Child-Pugh class – n (%)			<0.001
A	611 (82.8)	13 (36.1)	
B	123 (16.7)	18 (50.0)	
C	4 (0.5)	5 (13.9)	
Hemodialysis – n (%)	4 (0.5)	2 (5.6)	0.028

Hepatic encephalopathy – n			0.291
(%)			
Absent	717 (97.2)	34 (94.4)	
Grade I/II	21 (2.8)	2 (5.6)	
Grade III/IV	0 (0)	0 (0)	
Ascites – n (%)	119 (16.1)	21 (58.3)	<0.001
Esophagogastric varices – n	478 (64.8)	30 (83.3)	0.035
(%)			
Hepatocellular carcinoma – n	26 (3.5)	3 (8.3)	0.147
(%)			
Portal vein thrombosis – n	39 (5.3)	5 (13.9)	0.047
(%)			

ACLF: Acute-on-chronic liver failure; SD: standard deviation; IQR: interquartile range; BMI: body mass index; INR: international normalized ratio; MELD: Model for End-stage Liver Disease; MELD-Na: MELD-sodium; HBV: hepatitis B virus; HCV: hepatitis C virus; MASLD: metabolic dysfunction-associated steatotic liver disease.

Table 2. Multivariate analysis of predictors of acute-on-chronic liver failure within 12 months.

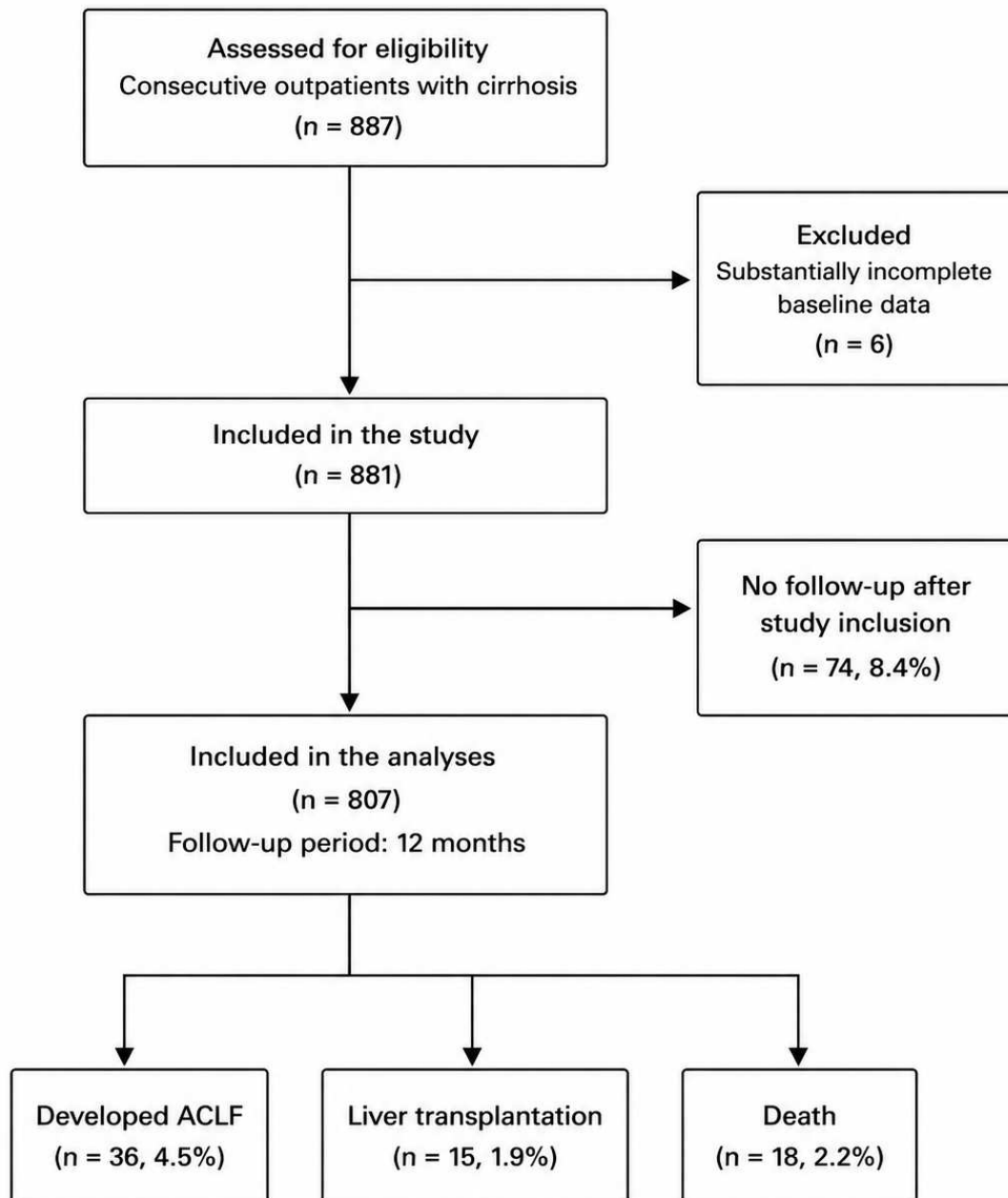
Variables	p-value	HR	95% CI
Model 1			
Haemoglobin	0.003	0.80	0.69–0.93
Albumin	0.003	0.45	0.26–0.76
Ascites	0.040	2.12	1.03–4.33
Creatinine	0.013	1.44	1.08–1.91
Model 2			
Haemoglobin	<0.001	0.77	0.66–0.88
Creatinine	0.020	1.42	1.06–1.91
Child-Pugh score	<0.001	1.50	1.23–1.83
Model 3			
Haemoglobin	0.002	0.80	0.69–0.92
Albumin	0.008	0.50	0.30–0.84

Ascites	0.047	2.12	1.01–4.42
MELD	0.017	1.05	1.01–1.10

HR: Hazard Ratio; 95% CI: 95% Confidence Interval; MELD: Model for End-stage Liver Disease.

FIGURES

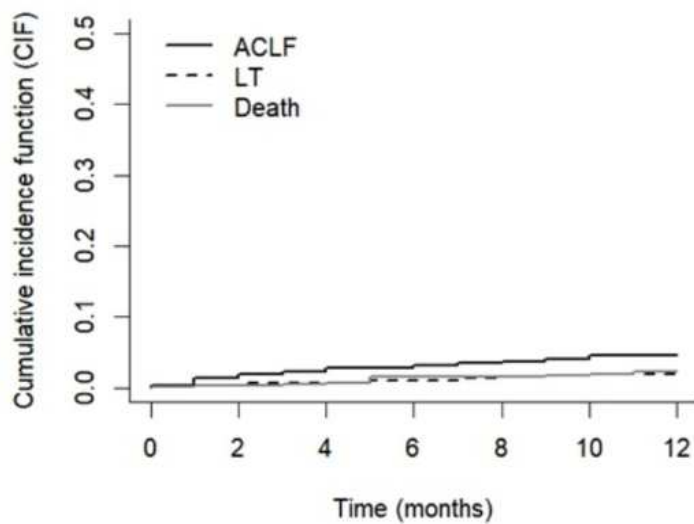
Figure 1. Flowchart of patient selection and follow-up.



ACLF, acute-on-chronic liver failure.

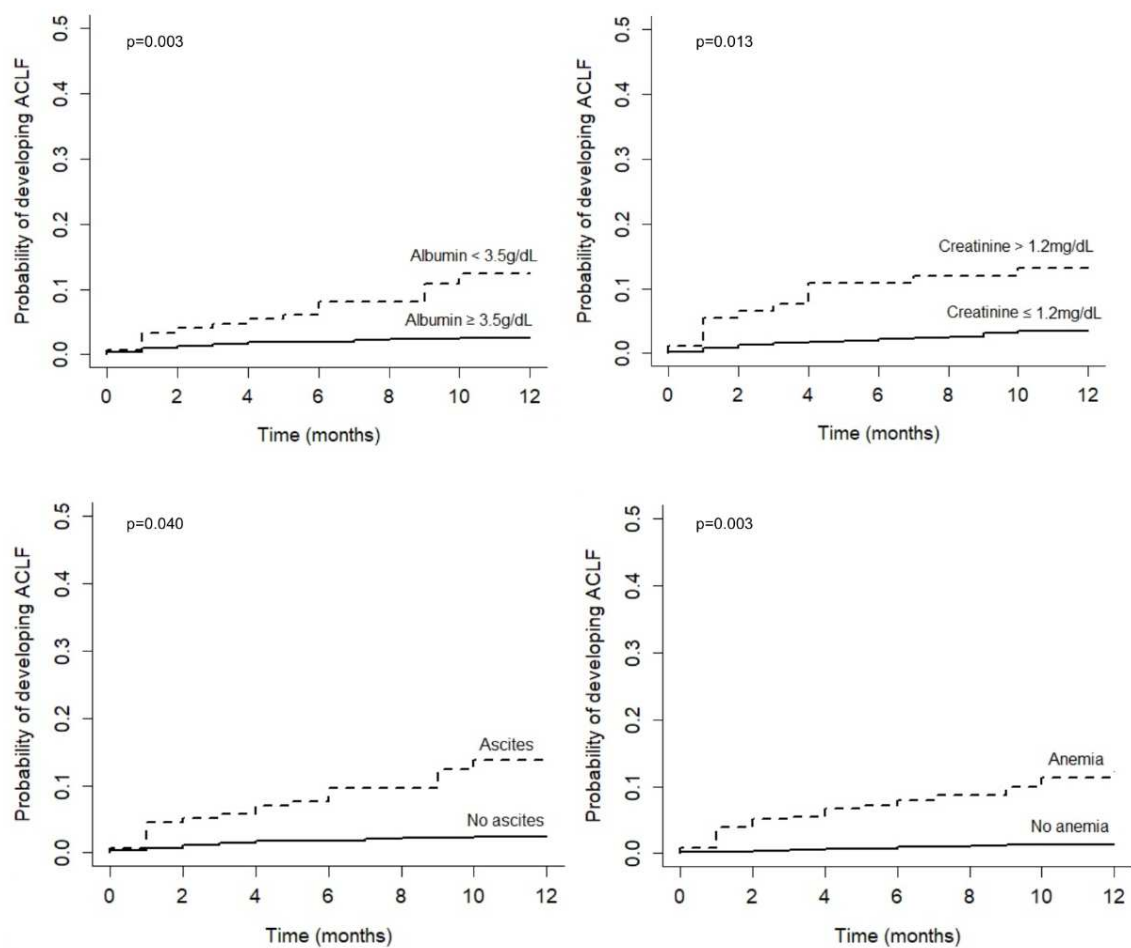
Note: Percentages are expressed as a proportion of the 881 patients included in the study. ACLF, acute-on-chronic liver failure.

Figure 2. Cumulative incidence of acute-on-chronic liver failure, liver transplantation, and death within 12 months.



ACLF: *Acute-on-Chronic Liver Failure*; LT: Liver transplantation.

Figure 3. Probability of developing acute-on-chronic liver failure within 12 months in patients with ascites, anaemia, impaired renal function, and hypoalbuminaemia.



ACLF: *Acute-on-Chronic Liver Failure*;