Received: 10 May 2023 | Revised: 31 July 2023 | Accepted: 2 September 2023

DOI: 10.1111/liv.15734

Liver INTERNATIONAL WILEY

ORIGINAL ARTICLE

Predictors of clinical trajectories of patients with acutely decompensated cirrhosis. An external validation of the PREDICT study

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Funding information
Fondazione del Monte di Bologna e Ravenna; Ministero della Salute; Regione Emilia-Romagna

Handling Editor: Alejandro Forner

Abstract

Background and Aims: The PREDICT study recently showed that acutely decompensated (AD) patients with cirrhosis can present three different clinical phenotypes in the 90 days after admission: (1) pre-ACLF, developing acute-on-chronic liver failure (ACLF); (2) unstable decompensated cirrhosis (UDC), being re-admitted for AD without ACLF and (3) stable decompensated cirrhosis (SDC), not presenting readmission or ACLF. This study aimed to externally validate the existence of these three distinct trajectories and to identify predictors for the occurrence of each trajectory.

Methods: Baseline data, 3-month ACLF and readmission incidence and 1-year survival were analysed in a prospective cohort of patients admitted for AD. A multinomial multivariable model was used to evaluate the association between baseline features and clinical trajectories.

Results: Of the 311 patients enrolled, 55% met the criteria for SDC, 18% for UDC and 27% for pre-ACLF, presenting a significantly different 1-year mortality: pre-ACLF 65%, UDC 46%, SDC 21% ($p < .001$). The presence of hepatic encephalopathy (HE) was associated with UDC ($p = .043$), while the absence of ascites to SDC ($p = .017$). Among laboratory parameters, an increase in MELD-Na ($p = .001$) and C-reactive protein ($p = .009$) and a decrease in haemoglobin ($p = .004$) and albumin ($p = .008$) levels were associated with pre-ACLF.

Conclusion: The present study confirms that AD patients have three different clinical trajectories with different mortality rates. Besides the severity of cirrhosis, the association with C-reactive protein supports the predominant role of systemic inflammation

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; CLIF-C AD, chronic liver failure consortium—acute decompensation score; CRP, C-reactive protein; EASL, European Association for the Study of the Liver; GI, gastrointestinal; Hb, haemoglobin; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HR, heart rate; INR, international normalized ratio; IQI, interquartile interval; MAP, mean arterial pressure; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; OLT, orthotopic liver transplantation; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis; WBC, white blood cells.

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in ACLF pathophysiology. Finally, HE is associated with the UDC phenotype highlighting the need for better management of this complication after discharge.

KEYWORDS
acute decompensation, acute-on-chronic liver failure, ascites, decompensated cirrhosis, hepatic encephalopathy, mortality, portal hypertension

1 | INTRODUCTION

Acute decompensation (AD) is a leading cause of hospitalization in patients with cirrhosis and is defined by the development of at least one of the main complications of the disease (hepatic encephalopathy [HE], ascites, gastrointestinal [GI] bleeding or bacterial infections).[1]

In the last decade, two large international cohort studies have deepened our knowledge of AD.[2,3] The CANONIC study developed diagnostic criteria for acute-on-chronic liver failure (ACLF), which is the most severe phenotype of AD and is defined by the presence of at least one organ failure and high 28-day mortality.[2] More recently, the PREDICT study unveiled that patients presenting AD without ACLF at admission have three possible trajectories with different clinical outcomes and mortality rates at 3 and 12 months.[3] The first group, defined as pre-ACLF, includes patients developing ACLF within 3 months from admission; the second group, defined as unstable decompensated cirrhosis (UDC), comprises patients requiring hospitalization within 3 months but not developing ACLF; lastly, the third group, defined as stable decompensated cirrhosis (SDC), consists of patients who are alive and not readmitted to hospital at 3 months. While each clinical phenotype had a distinct 3- and 12-month survival, the identification of predictors of each trajectory remained unsatisfactory.[3]

After the PREDICT study, few investigations have evaluated the predictors of early ACLF (within 28 days from admission due to AD) confirming the importance of disease severity and systemic inflammation.[4–6] Moreover, Balcar and colleagues have reproduced the PREDICT classification in a retrospective cohort with a different percentage of distribution of patients among groups.[7] To the best of our knowledge, a full external validation of the three clinical trajectories revealed by the PREDICT study and a better identification of clinical predictors are still lacking.

Thus, the aims of the present study were as follows: (1) to compare the 3-month and 1-year mortality rate in a cohort of patients admitted for AD of cirrhosis with prospectively collected data and divided into pre-ACLF, UDC or SDC based on the PREDICT definition[3]; and (2) to identify predictors of the occurrence of each clinical phenotype.

Key points

- The PREDICT study has recently identified three different clinical trajectories of patients with acute decompensation (AD) of cirrhosis but not presenting acute-on-chronic liver failure (ACLF): stable decompensated cirrhosis, unstable decompensated cirrhosis, and pre-ACLF.
- This study provides an external validation of the existence of these trajectories, which are associated with different 1-year mortality rates.
- Clinical (ascites and hepatic encephalopathy) and laboratory (MELD-Na, albumin, C-reactive protein and) features are associated to such trajectories.

2 | PATIENTS AND METHODS

2.1 | Study design

This investigation was performed as a secondary analysis of a prospective observational cohort study to assess the prognostic role of bacterial and fungal infections in patients with cirrhosis.[8] Briefly, consecutive patients with cirrhosis admitted for unplanned reasons to the regular wards of the IRCCS Azienda Ospedaliera-Universitaria di Bologna from January 2014 to March 2016 were eligible for the study. Inclusion criteria were as follows: (1) age ≥18 years; (2) liver cirrhosis diagnosed by a composite of clinical signs, laboratory tests, endoscopy and imaging, or by liver biopsy; (3) hospital admission because of an episode of AD.[2] Exclusion criteria were as follows: (1) scheduled hospital admission; (2) hepatocellular carcinoma (HCC) beyond the Milan criteria[9]; (3) extrahepatic malignancy; (4) previous liver transplantation (LT).

The study was approved by the local Ethical Committee and complied with the Declaration of Helsinki. Written informed consent was obtained from patients or legal representatives. The study protocol is described in detail elsewhere.[8]

2.2 | Data collection

The following data were collected at hospital admission in an electronic case report form: demographic features, aetiology of cirrhosis, laboratory and clinical data, including the presence of HCC and other co-morbidities, as assessed by the Charlson comorbidity score.[10] The model for end-stage liver disease (MELD), MELD-Na, Child-Pugh and Chronic Liver Failure Consortium (CLIF-C) acute decompensation (CLIF-C AD) scores were also calculated.[11–14] For the purposes of this study, readmissions and occurrence of ACLF were recorded up to 3 months, while death and LT were recorded up to 1 year.

2.3 | Definition of AD and ACLF

AD of cirrhosis was defined by at least one of the following: (1) acute onset of grade 2 or 3 ascites, according to the International Club of Ascites[15]; (2) new episode of HE in a patient with previously normal consciousness and lack of acute neurologic disease (HE was graded using the West Haven criteria)[16]; (3) upper or lower GI bleeding related to portal hypertension; (4) bacterial infection.

ACLF was diagnosed and graded according to the criteria proposed by the European Association for the Study of the Liver – Chronic LIver Failure (EASL-CLIF) consortium.[1,2] Nosocomial ACLF (nACLF) was defined as the occurrence of ACLF ≥48 h from hospital admission. Bacterial infections were diagnosed according to international and local guidelines.[17,18]

2.4 | Classification of patients according to the PREDICT study

Based on the criteria derived by the PREDICT study,[3] the patients included in the present analysis were classified into three groups: (1) pre-ACLF, patients developing ACLF within 3 months from enrolment (including those not having ACLF at admission but developing nACLF during the index hospitalization); (2) UDC, patients who had at least one hospital readmission or died without ACLF within 3 months and (3) SDC, patients not developing ACLF or having a hospital readmission within 3 months.

2.5 | Assessment of plasma levels of interleukin-6 and human non-mercaptalbumin-1

Plasma levels of interleukin-6 (IL-6) and human non-mercaptalbumin-1 (HNA-1) were determined in a subset of patients with available plasma samples. Briefly, IL-6 was determined by means of an automated immunoassay system (ELLA; ProteinSimple) using a precast Simple Plex cartridge kit (R&D Systems). The relative amount of HNA-1 was determined by means of liquid chromatography coupled to mass spectrometry according to a previously published method[19] allowing the relative quantification of different albumin isoforms resulting from different structural defects among which the reversible oxidation of the cysteine-34 residue which characterize the HNA-1 fraction of circulating albumin.

2.6 | Statistical analysis

For continuous variables, the Kolmogorov–Smirnov test was used to assess whether they were Gaussian-distributed, and the Levene test was used to evaluate the equality of their between-group variances. Continuous variables were reported as mean (SD) or median (interquartile interval, IQI) as appropriate. Categorical variables were reported as number and proportion of subjects with the characteristic of interest.

Between-group comparisons were performed using Student's *t* test, the Wilcoxon–Mann–Whitney test, the analysis of variance (ANOVA) or the Kruskal–Wallis test when appropriate. Multiple comparisons were taken into account using the Bonferroni method. Between-group comparisons of categorical variables were performed with Pearson's chi-squared or Fisher's exact test.

The 1-year cumulative death rate of pre-ACLF, SDC and UDC patients was assessed starting from admission to the index hospitalization using the Kaplan–Meier method and the log-rank test was used to evaluate between-group differences in death rate.

A multinomial logistic regression model (MNM) was used to evaluate the association between baseline features and the development of the pre-ACLF, UDC or SDC phenotypes at 3 months from admission.[20,21] The multinomial outcome of the MNM was coded as 0 = SDC (largest sample size), 1 = UDC and 2 = pre-ACLF. The predictors of the MNM model were selected between most clinically relevant parameters included in the univariate analyses. The continuous predictors of the MNM were MELD-Na (score), albumin (g/dL), natural log (ln)-transformed CRP (mg/dL) and haemoglobin (mg/dL); the binary predictors (0 = no; 1 = yes) were ascites and grade III or IV HE according to West Haven criteria.[16] The linearity of the logits of the continuous predictors of the MNM was checked using multivariable fractional polynomials.[22] For binary predictors, marginal estimates of the probability of pre-ACLF, SDC or UDC were calculated for presence versus absence and for one IQI increase for continuous predictors.[21] The IQI was chosen as the unit of measurement to compare the effect of continuous predictors with different units of measurement.

We also used binary logistic regression models to compare the baseline features of the pre-ACLF group with those of the remaining patients (SDC + UDC) and for the SDC versus UDC groups. Results are reported as odd ratio and 95% confidence interval.

The relationship between markers of systemic inflammation and the clinical trajectories was evaluated by binary logistic regressions in a subgroup of patients with available IL-6 (1 pg/mL increase) and HNA-1 (1% increase). Results are reported as odd ratio and 95% confidence interval.

Statistical analysis was performed using SPSS 27 (IBM Corp.), R 4.2.1 (R Foundation for Statistical Computing) and Stata 17.0 (Stata Corporation) using the SPost 13 package.[20]

3 | RESULTS

3.1 | Baseline characteristics

Five hundred and sixteen patients with cirrhosis admitted to the hospital because of AD were consecutively enrolled in the core study. Of these patients, 106 had ACLF at study inclusion and were therefore excluded from the analysis. Following discharge after the index hospitalization, clinical data and information about readmissions were not available for 99 patients who were not included in the analysis. Therefore, the final cohort consists of 311 (76%; 311/410) patients (Figure 1).

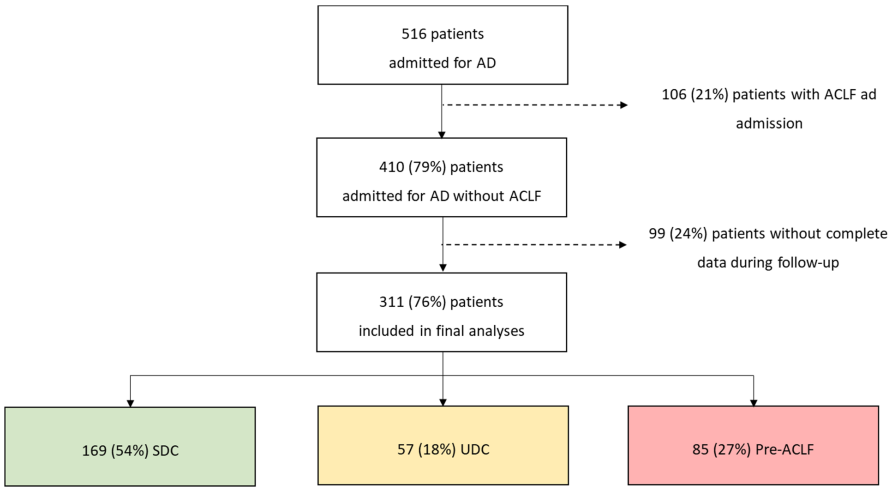

FIGURE 1 Patient disposition. ACLF, acute-on-chronic liver failure; AD, acute decompensation; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.

The baseline clinical features are presented in Table 1. The median (IQI) age was 62 (51–73) years, and most patients were male (184, 59%). The most common complications were ascites (56%), bacterial infections (22%) and grade III or IV HE (12%). The median (IQI) MELD score was 14,[10–18] the median (IQI) MELD-Na score 16[12–20] and the mean (SD) CLIF-AD score was 50.3 ± 8.5.

Baseline characteristics of the 311 patients included in the analysis were similar to those of the 99 patients excluded because of incomplete follow-up data, except for a lower prevalence of HCC (Table S1).

3.2 | Clinical trajectories

Among the 311 patients, 169 meet the criteria for SDC (55%), 57 (18%) for UDC and 85 (27%) for pre-ACLF within 3 months after admission (Figure 1). The UDC group included two patients who died during the index hospitalization without developing ACLF, while the pre-ACLF group included 59 (19%) patients with nosocomial ACLF, whereas 26 patients (8%) experienced ACLF after discharge from the index hospitalization.

During the 1-year follow-up, 110 (35%) patients died, 28 underwent LT (9%) and 9 (3%) underwent TIPS placement. Overall, 1-year mortality rate from admission to the index hospitalization was significantly different between the three groups (Figure 2, log-rank $p < .001$): in pre-ACLF patients, it was 38% (95% CI 29–49%) at 3 months and 65% (95% CI 54–76%) at 1 year; while, in the UDC patients, 30% (95% CI 20–44%) at 3 months and 46% (95% CI 34–60%) at 1 year. SDC patients had no mortality at 3 months and 21% (95% CI 15–28%) at 1 year. A similar result was obtained starting the observation from 90 days after admission. Indeed, the 1-year mortality rate was 44% (95% CI 31–60%) in the pre-ACLF, 24% (95% CI 23–41%) in the UDC and 21% (95% CI 15–28%) in the SDC group (log-rank $p = .005$).

No significant differences were seen in the proportion of patients who underwent LT at 1 year, although the number was higher in the UDC (12%) and pre-ACLF (13%) groups than in the SDC (6%) group.

Figure 3 shows the clinical trajectories of the three pre-defined groups for the first 3 months and between 3 and 12 months after the admission of the index hospitalization.

3.3 | Baseline features of the pre-ACLF, UDC and SDC patients

At baseline, SDC, UDC and pre-ACLF patients were comparable in terms of anthropometric data, aetiology of cirrhosis, comorbidity (Charlson index) and presence of HCC (Table 2). However, pre-ACLF patients had lower haemoglobin and serum albumin levels and higher C-reactive protein (CRP), bilirubin and creatinine when compared with SDC and UDC patients, while serum sodium and leucocyte count were significantly different only from SDC patients. As a result, pre-ACLF patients had the highest MELD, MELD-Na, Child-Pugh and CLIF-C-AD scores, while no significant differences were found between SDC and UDC in terms of severity of cirrhosis.

3.4 | Factors related to the probability of developing each clinical trajectory

Using a multinominal logistic regression model, we evaluated whether the clinical and laboratory features at admission for AD were associated with the probability of developing pre-ACLF, UDC or SDC phenotypes. The results of such model are reported in Table 3 and plotted in Figure 4 as a marginal effect on the probability.

Among binary predictors, the presence of ascites was significantly associated with a 13.6% reduction in the probability of remaining in the SDC phenotype, while the presence of grade III/IV HE was significantly associated with a 16.6% increase in the probability of belonging to the UDC phenotype.

TABLE 1 Demographic data, biochemical and clinical characteristics of the 311 patients included in the final analysis at baseline.

Demographic data	
Age (years)	62 (51–73)
Male sex (*n*, %)	184 (59)
Aetiology of cirrhosis (*n*, %)	
Viral	132 (42)
Alcohol	58 (19)
NASH	20 (6)
Mixed	55 (18)
Other	46 (15)
Clinical data (*n*, %)	
Ascites	173 (56)
Encephalopathy III/IV grade	36 (12)
Renal dysfunction	31 (10)
Gastrointestinal bleeding	21 (7)
Bacterial infection at admission	69 (22)
Biochemical and haemodynamic data	
Hb (g/dL)	10.7 (9.4–12.1)
WBC (10^9/L)	5.24 (3.59–8.17)
CRP (mg/dL)	1.22 (0.38–3.69)
Platelets (10^9/L)	92 (59–147)
Sodium (mmol/L)	137 (134–139)
Bilirubin (mg/dL)	2.12 (1.11–3.76)
Creatinine (mg/dL)	0.90 (0.72–1.18)
Albumin (mg/dL)	3.20 (2.80–3.60)
INR	1.36 (1.22–1.57)
MAP (mm Hg)	87 (78–93)
HR (bpm)	76 (67–86)
Prognostic scores	
Child-Pugh score	8 (7–10)
MELD	14 (10–18)
MELD-Na	16 (12–20)
CLIF-C AD	50.28 ± 8.47
Comorbidities	
Charlson comorbidity index	6.0 (4.7–7.3)
HCC (*n*, %)	71 (23)
Diabetes (*n*, %)	103 (33)

Note: Values are means and standard deviations (SD) for normally distributed data and medians and interquartile ranges (IQR) for non-normally distributed data.

Abbreviations: ACLF, acute-on-chronic liver failure; CLIF-C-AD, CLIF Consortium Acute Decompensation score; CRP, C-reactive protein; HR, heart rate; Hb, haemoglobin; HCC, hepatocellular carcinoma; INR, international normalized ratio; MAP, mean arterial pressure; NASH, nonalcoholic steatohepatitis; MELD, model for end stage liver disease; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis; WBC, white blood cells.

Among continuous predictors, higher MELD-NA score and CRP were predictors of belonging to the pre-ACLF group. Specifically,

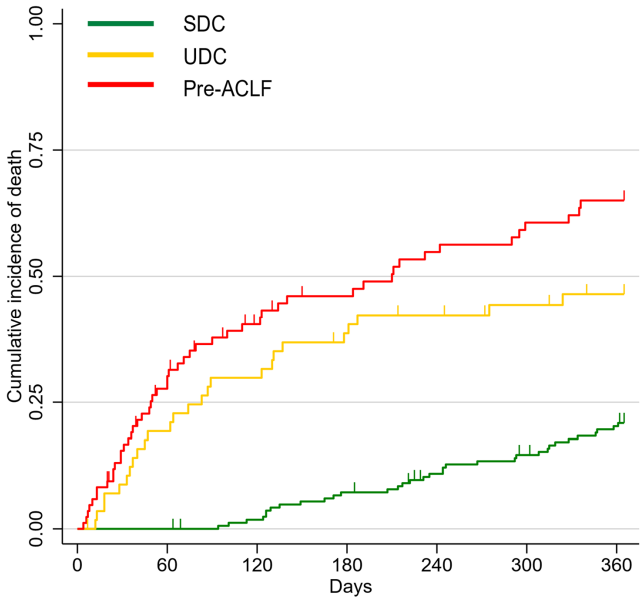

FIGURE 2 Cumulative incidence of 1-year mortality from admission for AD in SDC, UDC and pre-ACLF groups. ACLF, acute-on-chronic liver failure; AD, acute decompensation; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis. Overall log rank test $p < .001$, SDC versus UDC $p < .001$, SDC versus pre-ACLF $p < .001$, UDC versus pre-ACLF $p = .05$.

an IQI increase in the MELD-Na score (corresponding to 8 points) and in the ln-CRP level (corresponding to 3.31 mg/dL) were significantly associated with a 18.2% and 11.4% increase in the probability of belonging to the pre-ACLF group respectively. On the other side, higher serum albumin and haemoglobin concentrations were predictors of belonging to the two less severe phenotypes. Indeed, an IQI increase of serum albumin (corresponding to 0.8 g/dL) or haemoglobin level (corresponding to 2.7 g/dL) were significantly associated with a 8.2% and 7.8% reduction in the probability of belonging to the pre-ACLF group respectively. Finally, similar results were also obtained when the analysis was performed by excluding nine patients who received LT within 90 days from study inclusion (Table S2).

The predictors included in the multinomial model were also evaluated in two different multivariable binary logistic regression models aimed at estimating the odds of belonging to the pre-ALCF versus UDC + SDC phenotypes (Table S3) and to UDC versus SDC phenotype (Table S4). The analysis confirmed that MELD-Na (OR 1.140, 95% CI [1.080–1.204], $p < .001$), CRP (ln-CRP OR 1.350, 95% CI [1.083–1.683], $p = .008$), serum albumin (OR 0.556, 95% CI [0.342–0.906], $p = .019$), haemoglobin (OR 0.815, 95% CI [0.697–0.953], $p = .010$) were all independently associated with pre-ACLF phenotype. In contrast, no association was found between pre-ACLF and the presence of ascites (OR 1.656, 95% CI 0.892–3.075, $p = .110$) or grade III or IV HE (OR 0.920, 95% CI [0.370–2.284], $p = .857$; Table S3).

By using the same approach, we also estimated the odds of belonging to the UDC versus the SDC phenotype. The analysis

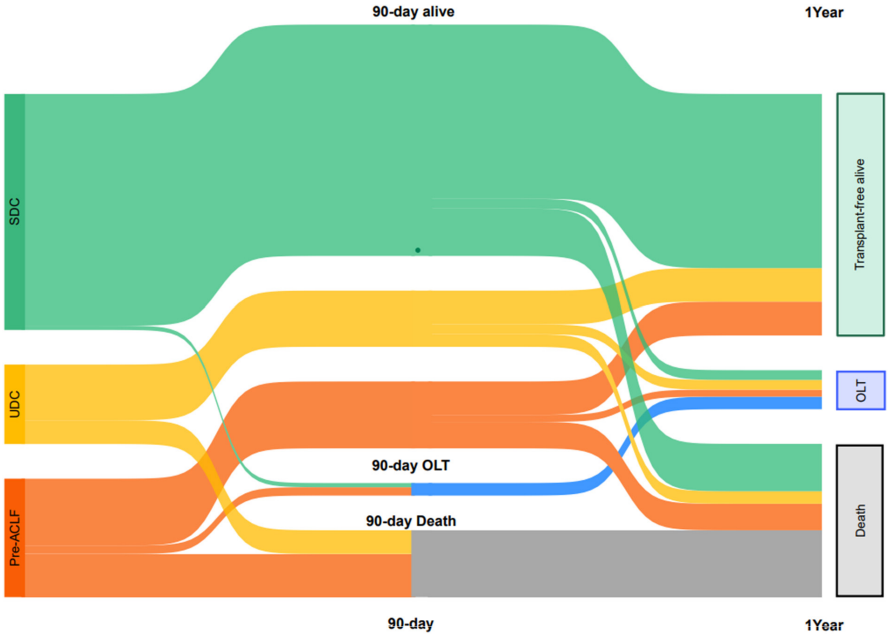

FIGURE 3 Sankey plot of the clinical trajectories of the three pre-defined groups during the first 3 months and between 3 and 12 months after the admission of the index hospitalization.

confirmed what already emerged from the multinomial model: the presence of grade III or IV HE was the only clinical feature significantly associated with the UDC phenotype (OR 2.785, 95% CI [1.149–6.747], $p = .023$; Table S4).

3.5 | Pre-ACLF phenotype and systemic inflammation and oxidative stress

As systemic inflammation and oxidative stress play a predominant role in the pathophysiology of ACLF, we evaluated two well-established biomarkers, namely IL-6 and HNA-1, were predictors of the odds of belonging to the pre-ACLF group.

IL-6 and HNA-1 were available in 206 out of the 311 patients (66%) included in the analysis. Both parameters were significantly higher in pre-ACLF patients in UDC and SDC patients (Table 2). Binary logistic regression analysis confirmed that both IL-6 (OR 1.0022, 95% CI [1.0001–1.0044], $p = .043$) and HNA-1 (OR 1.0505, 95% CI [1.0169–1.0853], $p = .003$) were significantly associated with the pre-ACLF phenotype (Table S5).

3.6 | UDC phenotype and main causes of hospitalization during the first 90 days

During the first 90 days after enrolment, there were 81 hospitalizations among the 57 patients in the UDC group. The causes of re-admission were liver-related in 73% of cases. The most common causes of liver-related hospitalizations were HE (25%) and bacterial infections (23%), followed by ascites (11%), GI bleeding (9%), renal dysfunction (2%) and jaundice (2%; Table S6).

4 | DISCUSSION

The first main finding of the present investigation is represented by the validation of the PREDICT study in a relatively large cohort of patients with prospectively collected follow-up data, confirming the existence of three different clinical trajectories of AD patients. However, while the distribution of patients in our cohort is similar to that of the PREDICT study (SDC: 54% vs. 58%, UDC: 18% vs. 22% and pre-ACLF: 27% vs. 20%),[3] the mortality rates of the three clinical phenotypes were in part different.[3] Our pre-ACLF patients had an almost identical 1-year mortality rate as compared to those of PREDICT, but the UDC and SDC groups had higher mortality rates.[3] The high proportion of non-liver-related hospitalizations in the UDC group (27%) may suggest a role for co-morbidities in determining the risk of mortality for patients with decompensated cirrhosis.[3] Alternatively, the higher proportion of HCC patients within Milan criteria in our population than in the PREDICT study (23% vs. 5%) may have influenced the 1-year mortality, particularly in the last part of the follow-up. Unfortunately, since the cause of death was not available in many patients, we cannot back up these hypotheses with strong empirical data.

The second main objective of the present study was the identification of predictors of each clinical trajectory. As expected, the pre-ACLF group at admission had a higher level of liver disease and systemic inflammation. Moreover, high CRP, high MELD, low albumin and low haemoglobin levels were found independent predictors of the pre-ACLF phenotype. The pathogenetic role of systemic inflammation and oxidative stress has been further confirmed by the higher levels at baseline of serum IL-6 and HNA-1, respectively, in the large subgroup of patients for whom plasma samples were available. Finally, as indirect evidence, low MELD, low CRP level

TABLE 2 Demographic data, biochemical and clinical characteristics of stable decompensated cirrhosis (SDC), unstable decompensated cirrhosis (UDC) and pre-ACLF patients.

	SDC	UDC	Pre-ACLF	*p*
n	169	57	85	
Anthropometric data				
Age (years)	63 (51–73)	63 (51–77)	60 (52–69)	.639
Male sex (*n*, %)	94 (56)	39 (68)	51 (60)	.232
Aetiology of cirrhosis (*n*, %)				
Viral	74 (44)	24 (42)	34 (40)	.846
Alcohol	32 (19)	11 (19)	15 (18)	.960
NASH	14 (8)	2 (4)	4 (5)	.334
Mixed	26 (15)	10 (18)	19 (22)	.389
Other	23 (14)	10 (18)	13 (15)	.761
Clinical data (*n*, %)				
Ascites	77 (46)	35 (61)[a]	61 (72)[a]	.000
Encephalopathy III/IV grade	15 (9)	12 (21)[a]	9 (11)	.043
Renal dysfunction	11 (7)	3 (5)	17 (20)[b]	.001
Gastrointestinal bleeding	15 (9)	4 (7)	2 (2)	.147
Bacterial infection at admission	33 (20)	12 (21)	24 (28)	.281
Biochemical and haemodynamic data				
Hb (g/dL)	10.9 (9.5–12.3)	11.1 (10.0–12.2)	10.2 (9.0–11.5)[b]	.011
WBC (10^9/L)	4.51 (3.36–7.46)	5.26 (3.93–8.06)	6.44 (4.97–9.42)[a]	.001
CRP (mg/dL)	0.85 (0.31–2.65)	1.05 (0.25–3.30)	2.13 (0.82–4.89)[b]	.000
Platelets (10^9/L)	94 (61–144)	95 (60–164)	88 (54–139)	.484
Sodium (mmol/L)	138 (135–140)	136 (133–139)[a]	135 (133–139)[a]	.003
Bilirubin (mg/dL)	1.74 (1.01–2.97)	1.82 (0.83–3.42)	3.76 (1.63–6.62)[b]	.000
Creatinine (mg/dL)	0.86 (0.67–1.12)	0.92 (0.74–1.11)	1.08 (0.80–1.45)[b]	.000
Albumin (mg/dL)	3.30 (2.90–3.70)	3.30 (2.90–3.75)	2.90 (2.50–3.30)[b]	.000
INR	1.29 (1.20–1.46)	1.34 (1.22–1.54)	1.52 (1.35–1.80)[b]	.000
MAP (mm Hg)	87 (80–84)	87 (78–92)	83 (76–93)	.205
HR (bpm)	75 (67–87)	73 (60–83)	78 (70–88)	.138
IL-6 (pg/mL)[c]	15.5 (9.2–33.4)	27.8 (9.1–54.0)	41.1 (17.8–95.9)[a]	.000
HNA-1 (%)[c]	36.2 (30.1–43.6)	32.4 (28.1–39.4)	39.1 (32.6–45.8)[b]	.012
Prognostic scores				
Child-Pugh score	7 (6–9)	8 (6–9)	9 (8–11)[b]	.000
MELD score	13 (9–16)	13 (10–16)	17 (14–22)[b]	.000
MELD-Na score	14 (12–18)	17 (12–20)[a]	21 (16–24)[b]	.000
CLIF-C AD score	48.01 ± 8.23	50.08 ± 8.19	54.92 ± 7.25[b]	.000
Comorbidities				
Charlson comorbidity index	6.0 (4.6–7.2)	6.3 (4.5–7.8)	6.0 (5.0–7.5)	.669
HCC (*n*, %)	39 (23)	16 (28)	16 (19)	.434
Diabetes (*n*, %)	55 (33)	20 (35)	28 (33)	.939
Data after enrolment (*n*, %)				
90-day mortality rate	—	17 (30)	31 (38)	
1-year mortality rate	34 (21)	26 (46)	50 (65)	

TABLE 2 (Continued)

	SDC	UDC	Pre-ACLF	*p*
1-year liver transplantation	10 (6)	7 (12)	11 (13)	.115

Note: Values are means and standard deviations (SD) for normally distributed data and medians and interquartile ranges (IQR) for non-normally distributed data.

Comparison of continuous variables between groups was made using the Analysis of Variance (ANOVA) or the Kruskal–Wallis test, when appropriate. Post-hoc analysis was performed according to the Bonferroni method. Comparison between groups of categorical variables was performed with Pearson's chi-squared test.

Abbreviations: ACLF, acute-on-chronic liver failure; CLIF-C-AD, CLIF Consortium Acute Decompensation score; CRP, C-reactive protein; Hb, haemoglobin; HCC, hepatocellular carcinoma; HNA-1, human non-mercaptalbumin 1; HR, heart rate; IL-6, interleukin-6; INR, international normalized ratio; MAP, mean arterial pressure; MELD, model for end stage liver disease; NASH, nonalcoholic steatohepatitis; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis; WBC, white blood cells.

[a]$p < .05$ versus SDC.

[b]$p < .05$ versus SDC and UDC.

[c]Available in 206 subjects (114 SDC; 42 UDC; 50 pre-ACLF).

TABLE 3 Marginal change in the probability of stable decompensated cirrhosis (SDC), unstable decompensated cirrhosis (UDC) and pre-ACLF attributable to the increase of one IQI (interquartile interval) of continuous variables and the presence versus absence of binary variables. Values are probabilities and 95% confidence intervals.

	SDC	UDC	preACLF
MELDNa			
IQI	−0.160 (−0.228 to −0.092)	−0.022 (−0.079 to −0.035)	0.182 (0.114–0.250)
p-value	.000	.446	.000
Albumin			
IQI	0.030 (−0.058 to 0.117)	0.053 (−0.029 to 0.134)	−0.082 (−0.142 to −0.022)
p-value	.509	.204	.008
Ascites			
Yes versus No	−0.136 (−0.247 to −0.024)	0.057 (−0.032 to 0.147)	0.078 (−0.016 to 0.173)
p-value	.017	.210	.105
HE III/IV grade			
Yes versus No	−0.154 (−0.318 to 0.011)	0.166 (0.005–0.326)	−0.012 (−0.152 to 0.127)
p-value	.068	.043	.863
ln (CRP)			
IQI	−0.092 (−0.171 to −0.014)	−0.022 (−0.079 to 0.036)	0.114 (0.029–0.199)
p-value	.022	.458	.009
Haemoglobin			
IQI	0.036 (−0.037 to 0.109)	0.042 (−0.025 to 0.109)	−0.078 (−0.131 to −0.025)
p-value	.330	.217	.004

Abbreviations: ACLF, acute on chronic liver-failure; HE, hepatic encephalopathy; IQI, interquartile interval; ln(CRP), natural logarithm transformed C-reactive protein; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.

and absence of ascites were significantly associated with the SDC phenotype. All together, these findings are consistent with previous several studies showing that ACLF is more common in patients with more advanced liver disease and a higher degree of systemic inflammation.[4,5] Furthermore, low haemoglobin levels, which have been already correlated to the development of ACLF both patients with AD and in those with SDC, may be expression of both severity of cirrhosis and chronic inflammation.[6,23–25] Thus, it could be expected that, in the near future, novel biomarkers related to inflammation or oxidative stress, either alone or integrated into the current prognostic scores, might be able to predict the development of ACLF and reach the daily clinical levels.

An open issue of the PREDICT classification remains how to discriminate between patients belonging to the UDC or SDC clinical phenotypes. Indeed, these patients have different 3-month and 1-year mortality rates, but they all present quite similar clinical and

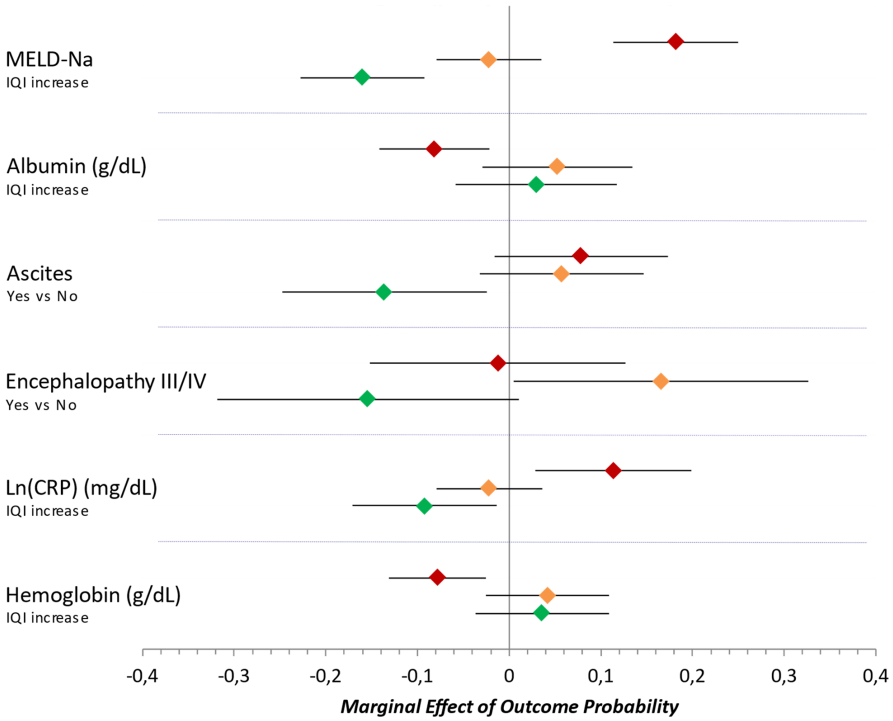

FIGURE 4 Marginal effect on the probability of pre-ACLF (red), UDC (yellow) and SDC (green) attributable to the increase in one IQI interval of continuous predictors and presence versus absence for binary predictors. IQI, interquartile interval; ln, natural logarithm. See the underlying probabilities with 95% confidence intervals in Table 3.

laboratory features when admitted to hospital.[3] In our study, the only difference was that HE was more likely associated with UDC than SDC. Interestingly, in the PREDICT study, UDC was significantly associated with GI bleeding or TIPS placement.[3] It would appear that the UDC trajectory is linked to the presence of complications more strictly linked to portal hypertension, which represents frequent causes of hospitalizations independent of ACLF. We have therefore looked up the causes of hospitalizations in the UDC group and found that HE was the main reason of readmission among the liver-related causes.

These findings support the implementation of care management programmes after discharge aiming to prevent readmission because of HE, GI bleeding or ascites,[26–28] leading to the shift of patients from the UDC to the SCD trajectory. Whether this change of trajectory will automatically produce an improvement in survival remains unclear, as the need of hospitalization varies according to multiple factors not strictly related to the severity of disease, such as family support, socio-economic status, healthcare organization and available outpatient services. Nevertheless, it is already known that early readmission increases the risk of mortality.[25,29]

Finally, these results prompt the execution of prospective studies aiming to identify predictors useful to discriminate between the UDC and SDC phenotypes at the time of discharge rather than at admission of the index hospital admission, in the pragmatic perspective of defining more accurately the type and intensity of the outpatient follow-up.

The present study has several limitations. First, it is a secondary analysis of a cohort of patients with prospectively collected data. This prevented us from including data of interest, such as the exact causes of death during the 1-year follow-up, which were available only in a relatively low number of patients. Second, being a single centre study, the incidence of hospitalization may be affected by the local healthcare organization not reflecting what happens in all centres around the world. Third, almost one-fourth of patients was excluded from the original dataset due to missing data in the follow-up. Although this may have introduced a bias, it is important to note that included and excluded patients presented similar baseline characteristics, except for the higher prevalence of HCC in the latter group. Finally, our cohort was recruited some years ago when the most frequent aetiology of cirrhosis was viral hepatitis. So, it does not show the actual epidemiology of the disease, with alcoholic and metabolic cirrhosis being the most common causes.

In conclusion, the present study is the first external validation done in a large cohort of patients with prospectively collected data, showing that AD patients can evolve in the three different clinical trajectories already identified by the PREDICT study. Systemic inflammation and oxidative stress are not only distinctive features of patients with ongoing ACLF but also of those who will soon develop the syndrome. Finally, these data further highlight that improving the outpatient management of complications more strictly related to portal hypertension remains a major objective in patients with AD cirrhosis, with the objective of preventing readmissions after discharge and possibly improving survival. Unfortunately, biomarkers able to predict the three clinical trajectories are still lacking and represent an unmet need to be addressed by future research.

AUTHOR CONTRIBUTIONS

Enrico Pompili, Maurizio Baldassarre, Giacomo Zaccherini, Giorgio Bedogni, Marco Domenicali and Paolo Caraceni carried out study

concept and design, interpretation of data and drafting of the manuscript. Enrico Pompili, Giacomo Zaccherini, Maurizio Baldassarre, Giulia Iannone, Dario Pratelli, Clara De Venuto and Francesco Palmese carried out collection of data. Enrico Pompili, Maurizio Baldassarre and Giorgio Bedogni were involved in analysis of data. Enrico Pompili, Maurizio Baldassarre, Giacomo Zaccherini, Giorgio Bedogni, Marco Domenicali and Paolo Caraceni were involved in critical revision for important intellectual content.

FUNDING INFORMATION

The present study was supported by grants from the Italian Ministry of Health (rf-2010-2 310 623), from the Emilia-Romagna Region (PRUa1GR-2012-002), and from Fondazione del Monte di Bologna e Ravenna. The Funders had no role in the design and conduct of the study, in the collection, analysis and interpretation of the data, or in the preparation and review of the manuscript.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest that are relevant to the content of this article. The following authors disclose conflicts of interests outside the submitted work: GZ: Grifols SA (speaking bureau); PC: Grifols SA and Octapharma SA (speaking bureau and research grant), CSL Behring and Takeda (speaking bureau and advisory boards), Kedrion Biopharma (educational consultancy).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL STATEMENT

The study protocol was approved by the local institutional review boards.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from patients or legal representatives.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pompili E, Baldassarre M, Bedogni G, et al. Predictors of clinical trajectories of patients with acutely decompensated cirrhosis. An external validation of the PREDICT study. *Liver Int*. 2024;44:72-82. doi:10.1111/liv.15734