Research Article
Cirrhosis and Liver Failure

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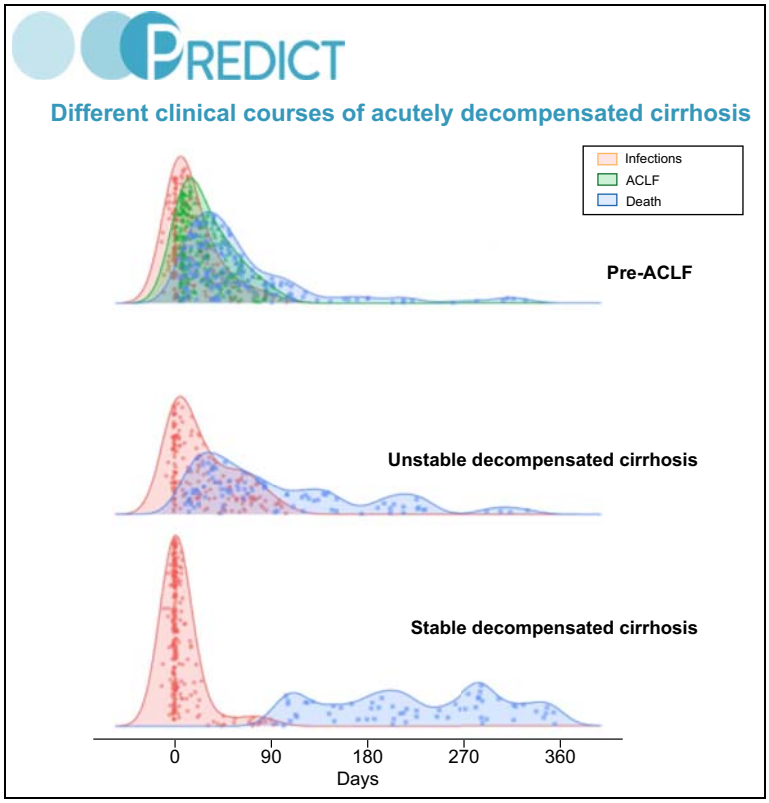
The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology

Graphical abstract



Highlights

- Patients with acutely decompensated cirrhosis without ACLF develop 3 different clinical courses.
- Patients with pre-ACLF develop ACLF within 90 days and have high systemic inflammation and mortality.
- Patients with unstable decompensated cirrhosis suffer from complications of severe portal hypertension.
- Patients with stable decompensated cirrhosis have less frequent complications and lower 1-year mortality risk.

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Lay summary

Herein, we describe, for the first time, 3 different clinical courses of acute decompensation (AD) of cirrhosis after hospital admission. The first clinical course includes patients who develop acute-on-chronic liver failure (ACLF) and have a high short-term risk of death – termed pre-ACLF. The second clinical course (unstable decompensated cirrhosis) includes patients requiring frequent hospitalizations unrelated to ACLF and is associated with a lower mortality risk than pre-ACLF. Finally, the third clinical course (stable decompensated cirrhosis), includes two-thirds of all patients admitted to hospital with AD – patients in this group rarely require hospital admission and have a much lower 1-year mortality risk.

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The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology☆

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See Editorial, pages 755–756

Background & Aims: Acute decompensation (AD) of cirrhosis is defined as the acute development of ascites, gastrointestinal hemorrhage, hepatic encephalopathy, infection or any combination thereof, requiring hospitalization. The presence of organ failure(s) in patients with AD defines acute-on-chronic liver failure (ACLF). The PREDICT study is a European, prospective, observational study, designed to characterize the clinical course of AD and to identify predictors of ACLF.

Methods: A total of 1,071 patients with AD were enrolled. We collected detailed pre-specified information on the 3-month period prior to enrollment, and clinical and laboratory data at enrollment. Patients were then closely followed up for 3 months. Outcomes (liver transplantation and death) at 1 year were also recorded.

Results: Three groups of patients were identified. Pre-ACLF patients (n = 218) developed ACLF and had 3-month and 1-year mortality rates of 53.7% and 67.4%, respectively. Unstable decompensated cirrhosis (UDC) patients (n = 233) required ≥1 readmission but did not develop ACLF and had mortality rates of 21.0% and 35.6%, respectively. Stable decompensated cirrhosis (SDC) patients (n = 620) were not readmitted, did not develop ACLF and had a 1-year mortality rate of only 9.5%. The 3 groups differed significantly regarding the grade and course of systemic inflammation (high-grade at enrollment with aggravation during follow-up in pre-ACLF; low-grade at enrollment with subsequent steady-course in UDC; and low-grade at enrollment with subsequent improvement in SDC) and the prevalence of surrogates of severe portal hypertension throughout the study (high in UDC *vs.* low in pre-ACLF and SDC).

Conclusions: Acute decompensation without ACLF is a heterogeneous condition with 3 different clinical courses and 2 major pathophysiological mechanisms: systemic inflammation and portal hypertension. Predicting the development of ACLF remains a major future challenge.

ClinicalTrials.gov number: NCT03056612.

Lay summary: Herein, we describe, for the first time, 3 different clinical courses of acute decompensation (AD) of cirrhosis after hospital admission. The first clinical course includes patients who develop acute-on-chronic liver failure (ACLF) and have a high short-term risk of death – termed pre-ACLF. The second clinical course (unstable decompensated cirrhosis) includes patients requiring frequent hospitalizations unrelated to ACLF and is associated with a lower mortality risk than pre-ACLF. Finally, the third clinical course (stable decompensated cirrhosis), includes two-thirds of all patients admitted to hospital with AD – patients in this group rarely require hospital admission and have a much lower 1-year mortality risk.

Introduction

Acute decompensation (AD) of cirrhosis is defined as the acute development of ascites, hepatic encephalopathy, gastrointestinal hemorrhage or bacterial infections or any combination thereof.[1–3] AD is an extremely relevant feature during the clinical course of cirrhosis. The first episode of AD signals the transition from compensated to decompensated cirrhosis.[4] Decompensated cirrhosis is characterized by recurrent episodes of AD. Finally, recent data from the CANONIC study have shown that AD has 2 distinct clinical presentations, depending on the presence or absence of organ failures and the grade of systemic inflammation.[5–8] The presence of both organ failures and high-grade systemic inflammation is the hallmark of acute-on-chronic liver failure (ACLF), a syndrome associated with a very high 28-day mortality rate, while AD is associated with moderate systemic inflammation and a low 28-day mortality rate. Systemic inflammation in AD and ACLF frequently develops in association with exogenous precipitating events (mainly bacterial infections or acute alcoholic liver injury). However, it might also be secondary to translocation of intestinal bacterial immunogenic material to the systemic circulation.[9,10] Systemic inflammation may induce organ dysfunction/failure via a direct immunopathological effect on peripheral organs or via mitochondrial dysfunction, both of which have been identified in decompensated cirrhosis.[8]

The CANONIC study was specifically designed to characterize ACLF but did not provide detailed information on the clinical context prior to and after ACLF and AD development. Yet, the CANONIC study showed that patients with AD had very low mortality rate (~2%) at 28 days but a substantial mortality rate (10%) at 90 days, suggesting a heterogeneity of clinical course in patients with AD. Detailed information on this period is an unmet medical need for the rational management of patients with AD and the prevention of ACLF development.

To answer these questions, we designed the PREDICT study (PREDICTing Acute-on-Chronic Liver Failure), the second prospective large-scale observational investigation performed by the European Association for the Study of the Liver (EASL)-Chronic Liver Failure (CLIF) Consortium. It included 1,071 patients with cirrhosis hospitalized for the treatment of an episode of AD without ACLF. The current article reports the results of the first study derived from this investigation, the aim of which was to characterize the clinical course and pathophysiology of AD, and to predict the development of ACLF.

Patients and methods

Study oversight

The PREDICT study is a European, multicenter, prospective, observational study performed in 48 hospitals. Each hospital had a liver unit, specific ward(s) for liver patients and intensive care facilities, and all of them had access to a liver transplantation program. The study protocol (available with the full text of this article) was approved by the institutional review board (IRB) at each participating center. Patients were screened and enrolled from March 2017 to July 2018. Written informed consent was obtained from patients or their legal surrogates before enrollment. An investigator was responsible for enrolling patients in the study at each center, ensuring adherence to the protocol, and completing the electronic case-report form. Data were continuously monitored on-line by the Data Management Center of the

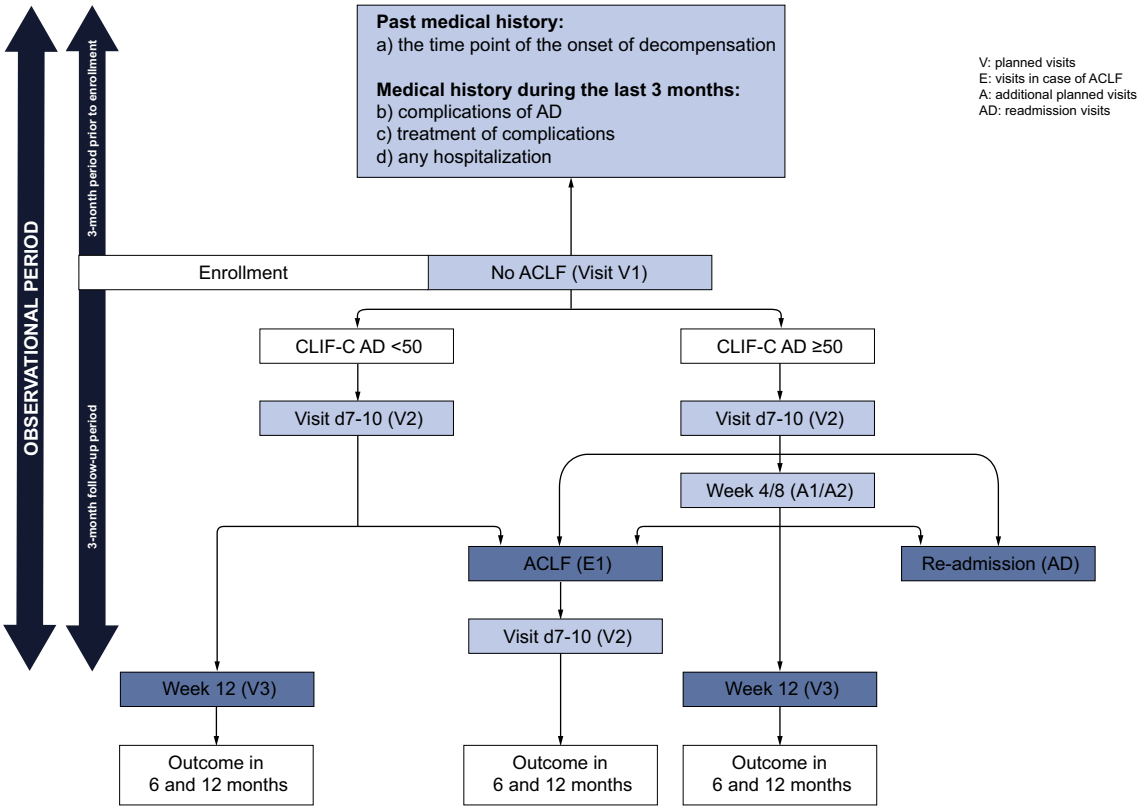

Fig. 1. Scheme of visits and collection of data and samples during the 6-month observational period. The 6-month period which included the 3-month period prior to enrollment, the enrollment visit, and the 3-month follow-up period after enrollment. At enrollment patients were initially stratified into 2 groups based on the risk of ACLF development: high-risk group (CLIF-C AD-score ≥50) and low-risk group (CLIF-C AD-score <50).[12] In the high-risk group, the scheduled visits were performed at enrollment (visit 1) and 1, 4, 8 and 12 weeks after enrollment (visits 2–5). In the low-risk group, scheduled visits were performed only at enrollment (visit 1) and week 1 (visit 2) and 12 (visit 5) after enrollment. Any patient of both groups developing ACLF within the follow-up period received unplanned ACLF visits at the time of diagnosis of ACLF and 7 days later. Additional study visits were performed whenever a patient had to be readmitted for any reason except ACLF (readmission visits) in the high-risk group only, but the number of readmissions was recorded in both groups. Finally, data on liver transplantation or death and causes of death were prospectively collected 3, 6 and 12 months after enrollment in all patients. ACLF, acute-on-chronic liver failure; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation.

EF-Clif. All authors had access to the study data and reviewed and approved the final manuscript.

Patients

A total of 1,421 patients non-electively admitted for the treatment of an episode of AD were eligible, of whom 148 patients met exclusion criteria (Table S1), 202 patients presented with ACLF and 1,071 patients were analyzed. Among these, 218 developed AD for the first time, and the remaining 853 had a prior history of AD. The diagnosis of cirrhosis was based on previous liver biopsy findings or a composite of clinical signs and findings provided by laboratory test results, endoscopy and ultrasonography. Diagnostic criteria for AD upon hospitalization were based on the development of ascites, hepatic encephalopathy, gastrointestinal hemorrhage, infection, or any combination of these. Importantly, AD was not due to an isolated bacterial infection in any of the enrolled patients. Diagnosis of ACLF during follow-up was performed according to the CANONIC study criteria.[7] Organ failure and organ dysfunction were defined according to the CLIF consortium (CLIF-C) organ failure (OF) score.[11]

Study design

Pre-specified clinical data, standard laboratory data and biological samples for biobanking were obtained at enrollment and sequentially during the follow-up visits (Fig. 1). The electronic case-report form was designed to collect granularity in the clinical data and the detailed queries answered remaining issues in case of inconsistencies. Herein, only clinical and standard laboratory data are analyzed.

Data obtained at enrollment

Two categories of pre-specified information were obtained at enrollment. The first category included general characteristic and demographic data, specific data related to the AD episode at enrollment, results of physical examination and standard laboratory analysis, including differential white-cell blood count (WBC) and C-reactive protein (CRP) levels, as markers of systemic inflammation. Cultures were routinely performed in patients with suspected bacterial infections.

The second category of pre-specified data was related to the past medical history and included: a) the timepoint of the onset of decompensated cirrhosis (as defined by the first episode of AD); b) the complications of AD occurring within the last 3 months prior to enrollment; c) treatment of complications (including prior transjugular portosystemic shunt stent [TIPS] and its indication); and d) any hospitalization during the last 3 months prior to enrollment. Data regarding onset of decompensated cirrhosis could be obtained in 612 patients. Data

regarding the occurrence of ascites, gastrointestinal hemorrhage, hepatic encephalopathy, bacterial infections and hospitalizations within the last 3-month period prior to enrollment were obtained in 860, 796, 793, 791 and 831 patients, respectively.

Data obtained during follow-up
After enrollment, patients were prospectively followed-up for a period of 3 months. The scheme of visits and collection of data and samples at enrollment and during the 3-month follow-up period after enrollment is indicated in Fig. 1. Finally, data on liver transplantation or death and causes of death were prospectively collected 3, 6 and 12 months after enrollment in all patients.

Defining the 6-month observational period
Of note, according to the pattern of data collection described earlier, we defined a 6-month observational period, which included the 3-month period prior to enrollment, the enrollment visit and the 3-month follow-up period after enrollment (Fig. 1).

Amendment to the initial study protocol
During the first 8 months of the study, 720 patients were consecutively enrolled, and used for prevalence calculations. Subsequently, since the number of patients developing ACLF was low, we amended the study protocol to enroll only high-risk patients. After IRB approval of this amendment, the last 351 patients were enrolled in the study.

Statistical analysis
Patient stratification
Patient stratification was performed based on the clinical course during the 3-month follow-up period for several reasons: i) the main objective of the study was the characterization of the clinical course after enrollment; ii) a preliminary analysis of an incomplete set of consecutive patients included in the PREDICT study showed that AD consisted of a single complication (either ascites, encephalopathy or gastrointestinal hemorrhage) in only 50% of patients. The remaining patients had 2 or 3 simultaneous complications, making stratification based on complications at enrollment extremely complex. iii) By contrast, stratification of patients based on ACLF development (yes or no) and clinical course profile (unstable *vs.* stable, among ACLF-free patients) during the 3-month follow-up was simpler and more appropriate for addressing the main objective of the study.

Therefore, our patients were stratified into 3 groups for data analysis: i) pre-ACLF group: patients who developed ACLF within 90 days of enrollment; ii) unstable decompensated cirrhosis (UDC) group: patients who experienced at least 1 hospital readmission, but without ACLF development within the 90-day follow-up period; and iii) stable decompensated cirrhosis (SDC) group: patients without ACLF development or readmissions within the 90-day follow-up period.

Because bacterial infections are major precipitants of AD and ACLF, and systemic inflammation is the hallmark of AD and ACLF, infections and systemic inflammation were considered in detail when characterizing these groups.

Data analysis
Discrete variables are summarized as counts (percentages) and continuous variables as mean ± SD. Non-normally distributed variables are summarized as median (IQR) and were log-transformed for some statistical analyses and for graphical comparisons. In univariate statistical comparisons, the chi-square test was used for categorical variables, whereas the Student's t test or analysis of variance were used for normally distributed continuous variables and the Wilcoxon signed-rank test or the Kruskal-Wallis test were used for non-normally distributed continuous variables. In all statistical analyses, significance was set at p <0.05.

Tools to predict ACLF development
For the prediction of ACLF development during the 90-day follow-up period, the CLIF-C ACLF development score (CLIF-C ACLF-D score) was fitted according to the TRIPOD recommendations (see TRIPOD checklist). There were no missing data in most potential predictors of ACLF development at enrollment, except for serum albumin and plasma CRP levels, whose values were not available, respectively, in 5%, 9% and 8% of patients from the pre-ACLF, UDC, and SDC groups and in 20%, 13% and 11% of patients from the 3 groups (Table S2). Therefore, for multivariate analysis, we assumed that these missing values could be considered at random and carried out a multiple imputation based on a mixed model including all potential predictors significantly associated with ACLF in the univariate analysis.[13]

We used the proportional-hazards model for competing risks proposed by Fine and Gray to identify the best subset of independent predictors associated with the onset of ACLF and to develop a new predictive score (the CLIF-C ACLF-D score).[14] Liver transplantation and death could be considered as 'competing' events in the competing risks model. The initial model included the most relevant characteristics at enrollment found to be significantly associated (both clinically and statistically) with ACLF development at 3 months in the univariate analysis (Table S3). In the final CLIF-C ACLF-D score model, the best subset of independent predictors was selected based on a stepwise forward procedure with p-in <0.05 and p-out <0.10 for the change in model log-likelihood (Table S4). The coefficients estimated for each predictor were used as relative weights to compute the score.

Because the PREDICT study is the only thorough investigation on the factors leading to ACLF, no other cohort could be used for external validation. As a result, we had to carry out a random split-sample derivation and validation processes for the new score. The subset of patients used to derive the score included two-thirds of patients (n = 707) randomly selected from each patient group. The internal score validation was performed on the remaining third of patients (n = 364) and compared the predictive ability of the CLIF-C ACLF-D score with those of the CLIF-C AD score, MELD, MELD-sodium and Child-Pugh scores by estimating the corresponding Harrel' C-indexes and 95% CIs both in the derivation and validation sets.

As a complementary tool to predict ACLF development, a decision tree model was fitted using the 980 patients with information about the development of ACLF. Patients, who died or were transplanted without presenting ACLF before 3 months were excluded. The clinical variables selected for the model were the independent predictors of ACLF development obtained in the multivariate analysis for the CLIF-C ACLF-D score. The decision tree algorithm selected the most relevant of these clinical variables, their position within the decision tree and their optimal cut-off values. The model was fitted using R software (version 3.6.3) rpart package with settings minsplit = 10 and maxdepth = 5. Also, the complexity parameter was set by default to 0.01. Model parameters were estimated using the function tune.rpart from the

Table 1. Patient characteristics prior to, at, and after enrollment.

Characteristic	Pre-ACLF (n = 218)	UDC (n = 233)	SDC (n = 620)	*p* value
Age, years, mean ± SD	61.1 ± 10.0	60.9 ± 10.6	57.9 ± 11.0[a]	<0.001
Female sex, n (%)	70 (32.1)	74 (31.8)	200 (32.3)	0.990
Etiology of cirrhosis, n (%)				
Alcohol	107 (49.1)	143 (61.4)[b]	346 (55.9)	0.032
HCV	14 (6.4)	12 (5.2)	41 (6.6)	0.727
Alcohol and HCV	10 (4.6)	8 (3.4)	33 (5.3)	0.506
Non-alcoholic steatohepatitis	16 (7.3)	17 (7.3)	48 (7.8)	0.965
Other etiologies	70 (32.1)	51 (21.9)[b]	150 (24.2)[b]	0.028
Events prior to enrollment, n (%)				
Ascites	130 (66.7)	122 (65.9)	229 (47.7)[a]	<0.001
Hepatic encephalopathy	46 (25.4)	54 (31.4)	75 (17.1)[a]	<0.001
Gastrointestinal hemorrhage	17 (9.6)	29 (17.1)[b]	62 (13.9)	0.125
Any hospitalization	106 (56.7)	119 (65.0)	210 (45.6)[a]	<0.001
Data at enrollment				
Clinical data, organ failures and organ dysfunctions, n (%)				
Ascites	173 (79.4)	170 (73.0)	415 (66.9)[b]	0.002
Hepatic encephalopathy	65 (29.8)	73 (31.3)	168 (27.1)	0.428
Gastrointestinal hemorrhage	16 (7.3)	39 (16.7)[b]	97 (15.6)[b]	0.005
No organ failure or dysfunction	50 (22.9)	80 (36.5)[b]	291 (46.9)[a]	<0.001
Liver failure	29 (13.3)	11 (4.7)[b]	30 (4.8)[b]	<0.001
Liver dysfunction	51 (23.4)	36 (15.5)[b]	84 (13.5)[b]	0.003
Circulatory dysfunction	20 (9.2)	43 (18.5)[b]	50 (8.1)[c]	<0.001
Renal dysfunction	51 (23.4)	17 (7.3)[b]	40 (6.5)[b]	<0.001
Coagulation failure	8 (3.7)	4 (1.7)	7 (1.1)[b]	0.050
Coagulation dysfunction	29 (13.3)	19 (8.2)	46 (7.4)[b]	0.029
Brain failure	4 (1.8)	4 (1.7)	16 (2.6)	0.676
Brain dysfunction	59 (27.1)	67 (28.8)	144 (23.2)	0.197
Respiratory dysfunction	10 (4.6)	8 (3.4)	29 (4.7)	0.722
Main reason for hospitalization				
Ascites	105 (48.4)	106 (45.5)	267 (43.1)	0.382
Hepatic encephalopathy	29 (13.4)	34 (14.6)	82 (13.2)	0.870
Gastrointestinal hemorrhage	13 (6.0)	37 (15.9)[b]	110 (17.7)[b]	<0.001
Bacterial infection	32 (14.7)	27 (11.6)	84 (13.5)	0.603
Other	38 (17.5)	29 (12.4)	77 (12.4)	0.147
Biomarkers of systemic inflammation, median (IQR)				
White-cell count, $\times 10^9$/L	7.2 (4.9–9.8)	6.1 (4.3–8.5)[b]	6.0 (4.2–8.7)[b]	0.002
Serum C-reactive protein, mg/L	23 (11–41)	16 (8–35)[b]	15 (6–36)[b]	<0.001
Measurements estimating organ function				
Serum bilirubin, mg/dl, median (IQR)	3.9 (1.9–9.0)	2.6 (1.3–5.4)[b]	2.3 (1.4–4.5)[b]	<0.001
Serum albumin, g/dl, mean ± SD	2.7 ± 0.7	2.8 ± 0.6	3.0 ± 0.6[a]	<0.001
INR, median (IQR)	1.6 (1.4–1.9)	1.4 (1.3–1.7)[b]	1.4 (1.2–1.7)[b]	<0.001
Serum creatinine, mg/dl, median (IQR)	1.1 (0.8–1.5)	0.9 (0.7–1.2)[b]	0.8 (0.7–1.1)[a]	<0.001
Plasma sodium, mEq/L, mean ± SD	134 ± 6	135 ± 5	136 ± 5[a]	<0.001
Severity scores, mean ± SD				
Child-Pugh	9.8 ± 1.8	9.2 ± 1.7[b]	8.7 ± 1.8[a]	<0.001
MELD	19 ± 5	16 ± 5[b]	15 ± 5[a]	<0.001
MELD-sodium	23 ± 5	19 ± 5[b]	18 ± 5[a]	<0.001
CLIF-C AD	57 ± 8	53 ± 8[b]	50 ± 8[a]	<0.001
Data after enrollment				
Mortality rates, n (%)				
90-day mortality rate	117 (53.7)	49 (21.0)	–	
1-year mortality rate	147 (67.4)	83 (35.6)	59 (9.5)	
Main causes of death, n (%)				
ACLF	130 (88.4)	25 (30.1)[b]	29 (49.2)[a]	<0.001
Hypovolemic shock	4 (2.7)	14 (16.9)[b]	3 (5.1)[c]	<0.001
Other causes of death	6 (4.1)	15 (18.1)[b]	15 (25.4)[b]	<0.001
Unknown	7 (4.8)	29 (34.9)[b]	12 (20.3)[b]	<0.001
Liver transplantation within 12 months after enrollment	33 (15.1)	39 (16.7)	73 (11.8)	0.125

(*continued on next page*)

Table 1. (*continued*)

Characteristic	Pre-ACLF (n = 218)	UDC (n = 233)	SDC (n = 620)	*p* value
Data after enrollment				
Indicators of severe portal hypertension, n (%)				
TIPS[d]	18 (8.3)	33 (14.2)[b]	63 (10.2)	0.107
TIPS for gastrointestinal hemorrhage	4 (1.8)	12 (5.4)	26 (4.2)	0.145
Any episode of gastrointestinal hemorrhage[d]	48 (22.0)	76 (32.6)[b]	155 (25.0)[c]	0.016

p values were obtained using chi-square test.
ACLF, acute-on-chronic liver failure; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; INR, international normalized ratio; MELD, model for end-stage liver disease; SDC, stable decompensated cirrhosis; TIPS, transjugular intrahepatic portosystemic shunt; UDC, unstable decompensated cirrhosis.
[a]Significantly different from the pre-ACLF group and UDC groups.
[b]Significantly different from the pre-ACLF group.
[c]Significantly different from the UDC group.
[d]At any time of the 6-month observational period, this being defined by the 3 months prior to, and the 3 months as of enrollment.

R package e1071, to select the best decision tree model, according to accuracy, sensitivity and specificity. A decision tree plot was generated based on the model fitted. A 10-Fold cross validation was used to reduce over-fitting and to assess the discriminative ability of the model, by estimating the corresponding sensitivity and specificity of the model and computing the area under the receiver-operating-characteristic curve (AUC).

Results

Heterogeneity of the clinical course of AD

Clinical course of patients with AD

As expected, the pre-ACLF group, which included 218 patients who developed ACLF during the 3-month follow-up period after enrollment, had the highest 3-month and 1-year mortality rates (53.7% and 67.4%, respectively) (Table 1). Twenty-two patients with pre-ACLF were transplanted after ACLF developed within the 3-month follow-up period. The 233 patients included in the UDC group, who did not develop ACLF, but who died or required at least 1 hospital readmission within the 3-month follow-up period, had 3-month and 1-year mortality rates of 21.0% and 35.6%, respectively; 177 of these patients required 1 readmission, 32 patients 2 readmissions, and 17 patients ≥3 readmissions. Fourteen patients with UDC were transplanted after readmission for an AD episode within the 3-month follow-up period. Finally, the 620 patients included in the SDC group, who did not develop ACLF, require hospital readmission, nor die during the 3-month follow-up period after enrollment, showed very low mortality (9.5%) within the 1-year follow-up period after enrollment. Among the 720 patients consecutively enrolled during the first 8 months after the onset of the study, 425 (59%) were in SDC group. Twenty-eight patients with SDC were transplanted from the waitlist without ACLF or a new episode of AD within the 3-month follow-up period.

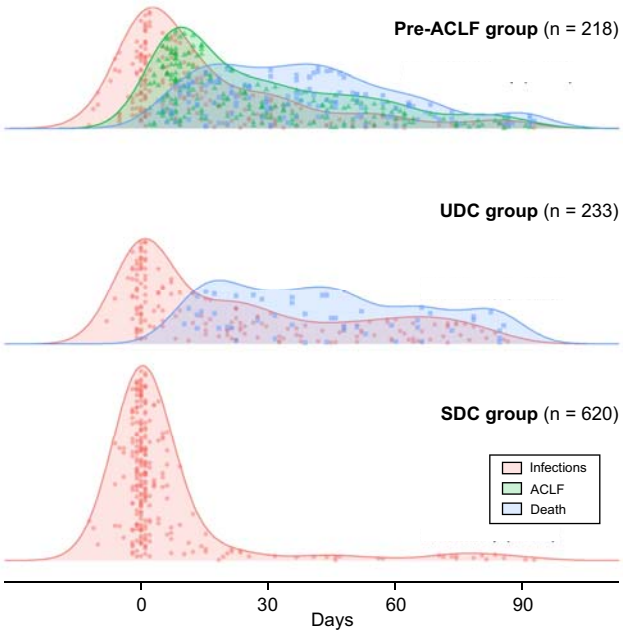

Fig. 2. Density curves of events during the 3-month follow-up period after enrollment in patients with pre-ACLF, UDC and SDC. The zero timepoint corresponds to enrollment into the study. Bacterial infections are represented in red, ACLF in green, and deaths in blue. ACLF, acute-on-chronic liver failure; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.

The clinical course of patients with pre-ACLF was characterized by a huge density of bacterial infections, episodes of ACLF and death, which are summarized as events (Fig. 2). A total of 120 patients (55% of this group) developed ACLF during the first hospitalization and 98 developed the syndrome from first discharge to the end of the 3-month follow-up period. The bacterial infection density curve chronologically preceded the ACLF density curve, and both curves preceded the mortality density curve, supporting a cause to effect relationship between the 3 events. The extreme proximity between the bacterial infection and ACLF density curves reflects that ACLF is a hyperacute process with a very short time period between precipitating events and the onset of the syndrome. Fig. 3A shows the cumulative rate of weekly occurrence of ACLF during the first 90 days after enrollment of patients with pre-ACLF. Fig. 3B shows that using the 90th day after enrollment as a landmark, the cumulative incidence of death 1 year after enrollment was also higher among patients assigned to the pre-ACLF group than among those assigned to 1 of the other 2 groups. The density of events in the UDC group was remarkably lower than the density of events in the pre-ACLF group. Although this feature was mainly due to the lack of ACLF episodes in the UDC group, the density of bacterial infections and deaths were also lower. Finally, although the density of bacterial infections at first presentation in the SDC group was as high as in the UDC group, it was remarkably lower during the rest of the 3-month follow-up period.

There were no significant differences between the 3 groups of patients regarding the etiology of cirrhosis (Table 1), prevalence of active alcoholism (26.6%, 23.2% and 27.6%, respectively) or presence of hepatocellular carcinoma (within Milan criteria) at enrollment (5.4%, 6.5% and 3%, respectively). Moreover, there was

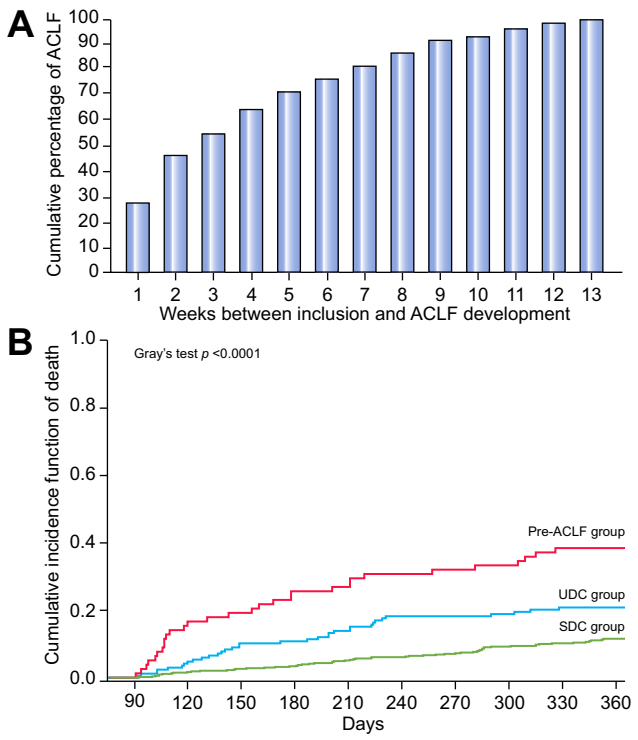

Fig. 3. Cumulative rates of ACLF and death. (A) Cumulative rate of ACLF per week during the 90-day follow-up period in patients with pre-ACLF. (B) Cumulative incidence of death between the 90-day (landmark) and 1 year after enrollment in patients with pre-ACLF, UDC and SDC. ACLF, acute-on-chronic liver failure; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.

no between-group difference in the number of patients with alcohol cessation (52 [23.9%] patients for pre-ACLF, 46 [19.7%] for UDC, and 146 [23.6%] for SDC; p = 0.456) and the number of those receiving HCV therapy (4 [1.9%] patients for pre-ACLF, 3 [1.3%] for UDC, and 14 [2.3%] for SDC; p = 0.650).

Duration of the decompensated phase of cirrhosis

The time-course density curves of liver transplantation or death in the 234 patients developing these events are shown in Fig. 4A. Time zero in this figure represents the onset of decompensated cirrhosis. Therefore, this analysis estimates the between-group differences in the length of the entire phase of decompensated cirrhosis. The pre-ACLF density curve preceded the UDC density curve, and both curves preceded the SDC density curve. These findings clearly indicate that ACLF development in patients with pre-ACLF significantly reduced the duration of the decompensated phase of the disease. Confirming these observations, the median time from the onset of decompensated cirrhosis to death or liver transplantation was 12 months (IQR 5.2–25.8) in patients with pre-ACLF, 14 months (9.6–24.3) in patients with UDC (p = 0.01 *vs.* patients with pre-ACLF), and 20 months (11.4–41.3) in patients with SDC (p = 0.04 *vs.* patients with UDC). These findings are confirmed by comparing individual values of the time period between the onset of decompensated cirrhosis and liver transplantation, death or end of follow-up between the 3 groups (Fig. 4B). Considering the between-group differences in mortality, the distinct duration of the decompensation phase would have been even more marked if follow-up had been longer than 1 year.

Prevalence and severity of bacterial infections

Table 2 provides information about infections during the 3 months before enrollment, at enrollment and during the 3 months after enrollment. Overall, 178 (22.4%) out of the 796 patients with data developed at least 1 bacterial infection during the 3-month period prior to enrollment. Of the 1,071 patients included in the analysis, 29.3% (n = 314) and 24% (n = 257) had infections at enrollment and during the 3-month follow-up period, respectively. These 571 patients with infections at enrollment or during follow-up (53.3%) presented a total of 674 infections.

Considering bacterial infections, Table 2 shows that the distinctive features of patients with pre-ACLF relative to patients of the 2 other groups included a higher proportion of patients with at least 1 infectious episode during the 6-month observational period (see also Fig. 4C); higher proportion of patients with sepsis at enrollment and during follow-up; higher proportion of patients with pneumonia during follow-up; and a higher proportion of patients receiving therapeutic antibiotics; all these differences being significant. During follow-up, the proportion of patients with community-acquired infection was significantly lower among patients with pre-ACLF than among the 2 other groups (Table 2). These findings are consistent with higher prevalence and severity of bacterial infections in the pre-ACLF group. At any time, the proportion of patients with infections caused by multi-drug-resistant bacteria was significantly higher between the pre-ACLF group and the UDC group (Table 2).

Clinical features prior to enrollment

By definition, patients with pre-ACLF and UDC exhibited greater clinical instability during the first 3 months after enrollment than patients with SDC. However, their clinical courses were also more unstable within the 3-month period prior to enrollment, as indicated by the significantly higher frequency of bacterial infections, ascites or hepatic encephalopathy and, consequently, hospital admissions in these groups of patients (Tables 1 and 2).

Clinical features and laboratory data at enrollment and during follow-up

Markers of systemic inflammation across groups

The WBC count and the CRP levels were significantly higher at enrollment in patients with pre-ACLF than in patients from the other 2 groups (Table 1). In contrast, there were no significant differences in these biomarkers between patients with UDC and SDC.

We compared the CRP levels and WBC measured at enrollment in patients with SDC, UDC and pre-ACLF, with those measured at the time of follow-up diagnosis of ACLF in 176 patients from the pre-ACLF group (including 103 patients with ACLF-1, 52 with ACLF-2, and 21 with ACLF-3), and those measured in a control group of 34 patients with compensated cirrhosis (no prior history of AD) (Fig. 4D) previously described.[5,6] Of note, the last 2 groups were included to facilitate the comparison of systemic inflammation throughout the whole spectrum of cirrhosis. There was a progressive increase in the grade of systemic inflammation across the different groups.

We also performed within-group comparisons of the levels of inflammatory markers measured at enrollment *vs.* those measured during follow-up (Table 3). The follow-up timepoint was the time of diagnosis of ACLF for the pre-ACLF group, while for the other 2 groups of patients, it was the last measurement prior to liver transplantation, or death, or the end of the 3-month

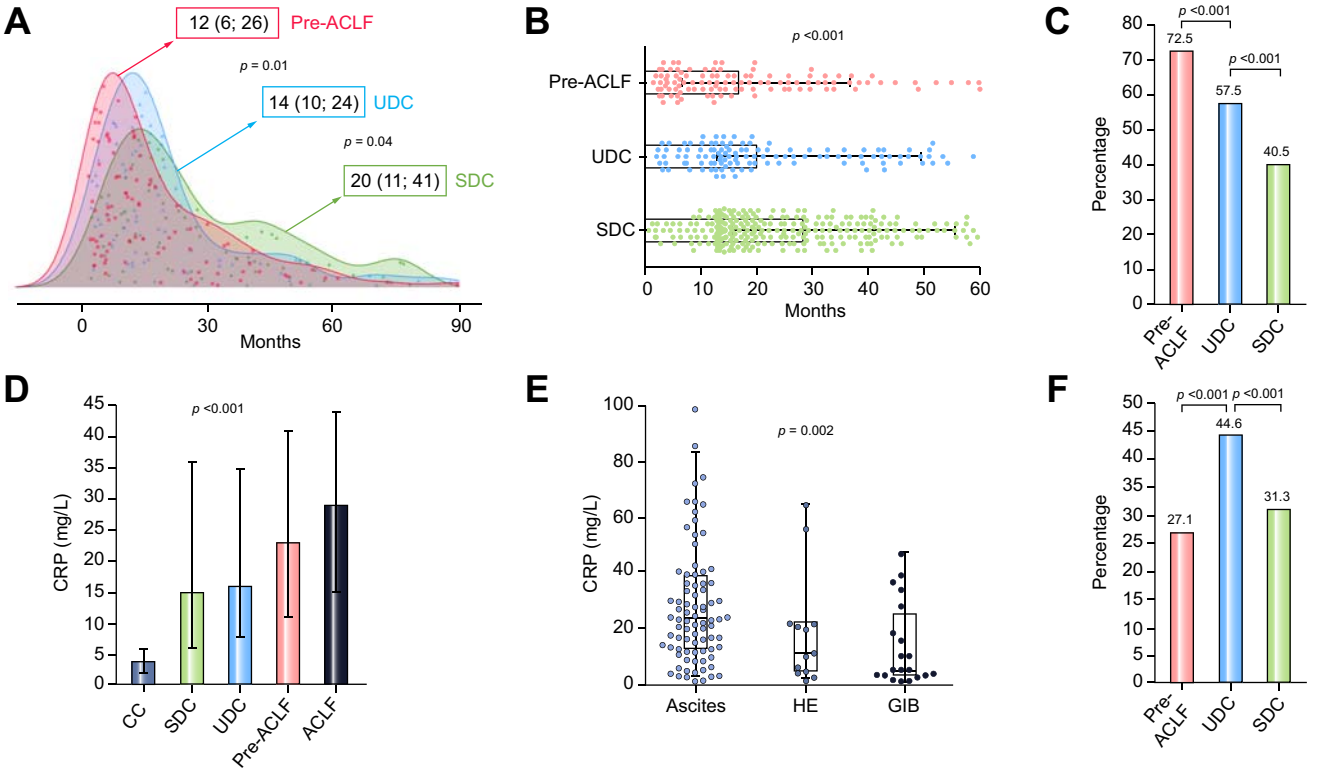

Fig. 4. Liver transplantation or death, as well as surrogates of systemic inflammation and portal hypertension in patients with pre-ACLF, UDC and SDC. (A) Density curves of liver transplantation or death during the 1-year follow-up period after enrollment in patients with pre-ACLF (in red), UDC (in blue) and SDC (in green) taking the zero-point as the onset of acute decompensation. The median time (IQR) from the onset of clinically decompensated cirrhosis (as defined by the date of first the episode of acute decompensation) to death or liver transplantation (duration of the decompensated phase of cirrhosis) was significantly shorter in patients with pre-ACLF than in those with UDC, and in patients with UDC than in those with SDC. *p* values were obtained using Mann-Whitney *U* test. (B) Individual time period between the onset of decompensated cirrhosis and liver transplantation, death or the end of the 1-year follow-up period after enrollment in the 3 groups of patients. For clarity, the figure does not include patients with values over the 75% IQR. Differences between groups were highly significant ($p < 0.001$). *p* values were obtained using Kruskal-Wallis test. (C) The percentage of patients developing at least 1 bacterial infection during the 6-month observational period in patients with pre-ACLF, UDC and SDC. *p* values were obtained using chi-square test. (D) Plasma levels of CRP (median and 75% CI) in a control group of 34 patients with compensated cirrhosis (CC, no prior history of AD), SDC, UDC, pre-ACLF and ACLF. Patients with CC were studied previously.[5,6] The ACLF group includes 176 patients from the pre-ACLF group who develop ACLF during the 3-month follow-up period. Samples for PCR measurements in these patients were obtained at the time of ACLF development, *p* values were obtained using Kruskal-Wallis test. (E) Serum concentration of C-reactive protein in 134 patients without prior history of AD who were enrolled only for ascites, encephalopathy or gastrointestinal hemorrhage. *p* values were obtained using Kruskal-Wallis test. (F) Percentage of patients presenting at least one surrogate of severe portal hypertension during the 6-month observational period in the Pre-ACLF, UDC and SDC groups. *P* values were obtained using chi-square test. ACLF, acute-on-chronic liver failure; AD, acute decompensation; CC, compensated cirrhosis; CRP, C-reactive protein; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.

follow-up period. Within each group, there was a close relationship between changes in inflammatory markers and the clinical course (Table 3). Progression of AD to ACLF in the pre-ACLF group occurred in the setting of a significant increase in WBC count and serum concentration of CRP. In patients with UDC there were no significant changes in WBC count and a small, but significant decrease in CRP, suggesting minor improvement of systemic inflammation. Finally, patients with SDC had a significant reduction in WBC and PCR.

Association between systemic inflammation and complications that define AD

In order to assess the association between systemic inflammation and the 3 major complications that define AD, we explored 134 patients who had no prior history of AD and were enrolled only for ascites (n = 99), encephalopathy (n = 14) or gastrointestinal hemorrhage (n = 21). The median (IQR) levels of plasma CRP was remarkably higher ($p < 0.002$) in patients with ascites (23.4 [12.5–38.0]) than in those with encephalopathy (11.0 [4.4–21.6]) and gastrointestinal hemorrhage (5.0 [3.0–22.4]) (Fig. 4E).

Organ function and scores

The prevalence of liver failure, liver dysfunction and renal dysfunction (as defined by the CLIF-C OF score[11]) at enrollment was significantly higher among patients with pre-ACLF group than among those with UDC and SDC (Table 1). Moreover, laboratory measurements estimating liver and renal function at enrollment were significantly more impaired among patients with pre-ACLF than among those with UDC and SDC, suggesting that a significant deterioration of organ function existed prior to enrollment in patients with pre-ACLF.

CLIF-C AD and MELD-sodium scores significantly worsened during the progression of pre-ACLF to ACLF and improved in

Table 2. Characteristics of infections at enrollment and during the 90-day follow-up period.

Characteristic	Pre-ACLF (n = 218)	UDC (n = 233)	SDC (n = 620)	*p* value
Number of patients with infections n (%)*				
3 months prior to enrollment	58 (31.0)	45 (26.5)	75 (17.1)[a]	<0.001
At enrollment	74 (33.9)	61 (26.2)	178 (28.7)	0.176
3 months after enrollment	106 (48.6)	83 (35.6)[b]	68 (11.0)[a]	<0.001
Throughout the 6-month observational period	158 (72.5)	133 (57.1)[b]	251 (40.5)[a]	<0.001
Infections at enrollment				
Number of infections	83	67	189	
Site of infection, n/N (%)*				
Urinary tract	19/83 (22.9)	15/67 (22.4)	44/189 (23.2)	0.985
Spontaneous bacterial peritonitis	18/83 (21.7)	13/67 (19.4)	26/189 (13.8)	0.232
Pneumonia	10/83 (12.0)	14/67 (20.9)	24/189 (12.8)	0.213
Spontaneous bacteremia	9/83 (10.8)	5/67 (7.5)	9/189 (4.8)	0.184
Cellulitis	4/83 (4.8)	6/67 (9.0)	18/189 (9.6)	0.414
Suspected infections	6/83 (7.2)	8/67 (11.9)	35/189 (18.6)[b]	0.040
Other[c]	17/83 (20.5)	6/67 (9.0)	32/189 (17.0)	0.150
Severity of infection, n/N (%)*				
Community-acquired	52/83 (62.6)	35/67 (52.2)	149/189 (78.8)[a]	<0.001
Health-care- or hospital-acquired	31/83 (37.4)	32/67 (47.8)	40/189 (21.2)[a]	<0.001
Sepsis	26/83 (31.3)	11/67 (16.4)[b]	28/189 (15.1)[b]	0.005
Infection caused by MDR bacteria	6/83 (7.2)	3/67 (4.9)	18/189 (10.3)	0.379
Infections during the 3-month follow-up period				
Number of infections	140	117	76	
Site of infection, n/N (%)*				
Urinary tract	35/140 (25.0)	31/117 (26.5)	22/76 (28.9)	0.821
Spontaneous bacterial peritonitis	21/140 (15.0)	24/117 (20.5)	5/76 (6.6)[c]	0.030
Pneumonia	27/140 (19.3)	10/117 (8.5)[b]	10/76 (13.2)	0.047
Spontaneous bacteremia	10/140 (7.1)	9/117 (7.7)	2/76 (2.6)	0.319
Cellulitis	6/140 (4.3)	8/117 (6.8)	4/76 (5.3)	0.665
Suspected infections	16/140 (11.4)	13/117 (11.1)	16/76 (21.1)	0.091
Other[c]	25/140 (17.9)	22/117 (18.8)	17/76 (22.4)	0.717
Severity of infection, n/N (%)*				
Community-acquired	14/140 (10.0)	15/117 (12.8)[b]	15/76 (19.7)[b]	0.129
Health-care- or hospital-acquired	126/140 (90.0)	102/117 (87.2)	61/76 (80.3)[b]	0.129
Sepsis	70/140 (50.0)	21/117 (18.1)[b]	4/76 (5.3)[a]	<0.001
Infection caused by MDR bacteria	44/140 (33.8)	29/117 (28.2)	11/76 (16.2)[b]	0.031

p values were obtained using chi-square, * is calculated over the available data, no imputation was included in the table.
ACLF, acute-on-chronic liver failure; MDR, multidrug resistant; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.
[a]Significantly different from the pre-ACLF group and UDC groups.
[b]Significantly different from the pre-ACLF group.
[c]Other: catheter-related infection, cholecystitis, cholangitis, secondary peritonitis, pseudomembranous colitis, other gastrointestinal infection.

patients with SDC (Table 3). Scores also improved in patients with UDC, although to a lesser extent than in patients with SDC.

Increased prevalence of features suggesting severe portal hypertension in patients with UDC

Whereas severe systemic inflammation and organ failure or dysfunction were the most prominent features in patients from the pre-ACLF group, surrogates of severe portal hypertension were the hallmark of patients with UDC. First, the prevalence of circulatory dysfunction at enrollment (Table 1) and of gastrointestinal hemorrhage within the 6-month observational period (32% *vs.* 22% [$p = 0.01$] and 25% [$p = 0.03$], respectively) were significantly higher among patients with UDC than among those with pre-ACLF and those with SDC. Second, the percentage of patients who received TIPS during this period was also higher in the UDC group than in the other 2 groups (14.2% *vs.* 8.3% [$p = 0.04$] and 10.2% [$p = 0.1$], respectively). Finally, the prevalence of hypovolemic shock as the main cause of death was 6- and 3-times higher in patients with UDC group (16.9%) than in those with pre-ACLF (2.7%; $p < 0.001$) and SDC (5.1%; $p < 0.001$). Fig. 4F shows that the percentage of patients with at least 1 surrogate of severe portal hypertension was significantly higher in patients with UDC (44.6%) than in patients with pre-ACLF (27.1%) and SDC (31.3%).

Tools to predict development of ACLF

The CLIF-C ACLF-D score was developed to predict, at the time of hospital admission, the probability of a patient with AD developing ACLF during the following 3 months. The initial model was fitted including all the main characteristics at enrollment found to be associated with the development of ACLF in the univariate analysis (Table S3). Patients age (years), presence of ascites, WBC count ($\times 10^9$/L), serum albumin (g/dl), serum bilirubin (mg/dl), and serum creatinine (mg/dl) at study enrollment were subsequently identified as the best subset of independent predictors in the final model (Table S4) and their coefficients were used as relative weight to compute the corresponding score. The equation for CLIF-C ACLF-D score is as follows:

CLIF-C ACLF-D score = ((0.03 × Age) + (0.45 × Ascites) + (0.26 × ln(WBC)) − (0.37 × Albumin) + (0.57 × ln(Bilirubin)) + (1.72 × ln(Creatinine)) + 3 × 10.

The prognostic accuracy of CLIF-C ACLF-D score (Fig. 5A) was higher than those of CLIF-C AD, MELD, MELD-sodium and Child-

Table 3. Inflammatory markers and severity scores at enrollment and during the 90-day follow-up period.

	Enrollment	Follow-up	*p* value
Pre-ACLF (n = 218)			
Blood biomarkers of systemic inflammation, median (IQR)			
White-cell count, $\times10^9$/L	7.2 (4.9–9.8)	8.3 (5.7–12.9)	<0.001
Serum C-reactive protein, mg/L	23 (11–41)	29 (14–52)	0.033
Severity scores, mean ± SD			
MELD-sodium	23 ± 5	28 ± 6	<0.001
CLIF-C AD	57 ± 7	64 ± 9	<0.001
Unstable decompensated cirrhosis (n = 233)			
Blood biomarkers of systemic inflammation, median (IQR)			
White-cell count, $\times10^9$/L	6.1 (4.3–8.5)	5.9 (4.0–8.0)	0.343
Serum C-reactive protein, mg/L	16 (8–35)	12 (5–26)	0.004
Severity scores, mean ± SD			
MELD-sodium	19 ± 5	18 ± 6	0.006
CLIF-C AD	53 ± 7	51 ± 8	0.031
Stable decompensated cirrhosis (n = 620)			
Blood biomarkers of systemic inflammation, median (IQR)			
White-cell count, $\times10^9$/L	6.0 (4.2–8.7)	5.4 (3.9–7.3)	<0.001
Serum C-reactive protein, mg/L	15 (6–36)	8 (4–17)	<0.001
Severity scores, mean ± SD			
MELD-sodium	18 ± 5	16 ± 5	<0.001
CLIF-C AD	50 ± 8	48 ± 7	<0.001

p values were obtained using the Wilcoxon signed-rank test or the Student's *t* test where appropriate.
ACLF, acute-on-chronic liver failure; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; MELD, model for end-stage liver disease.

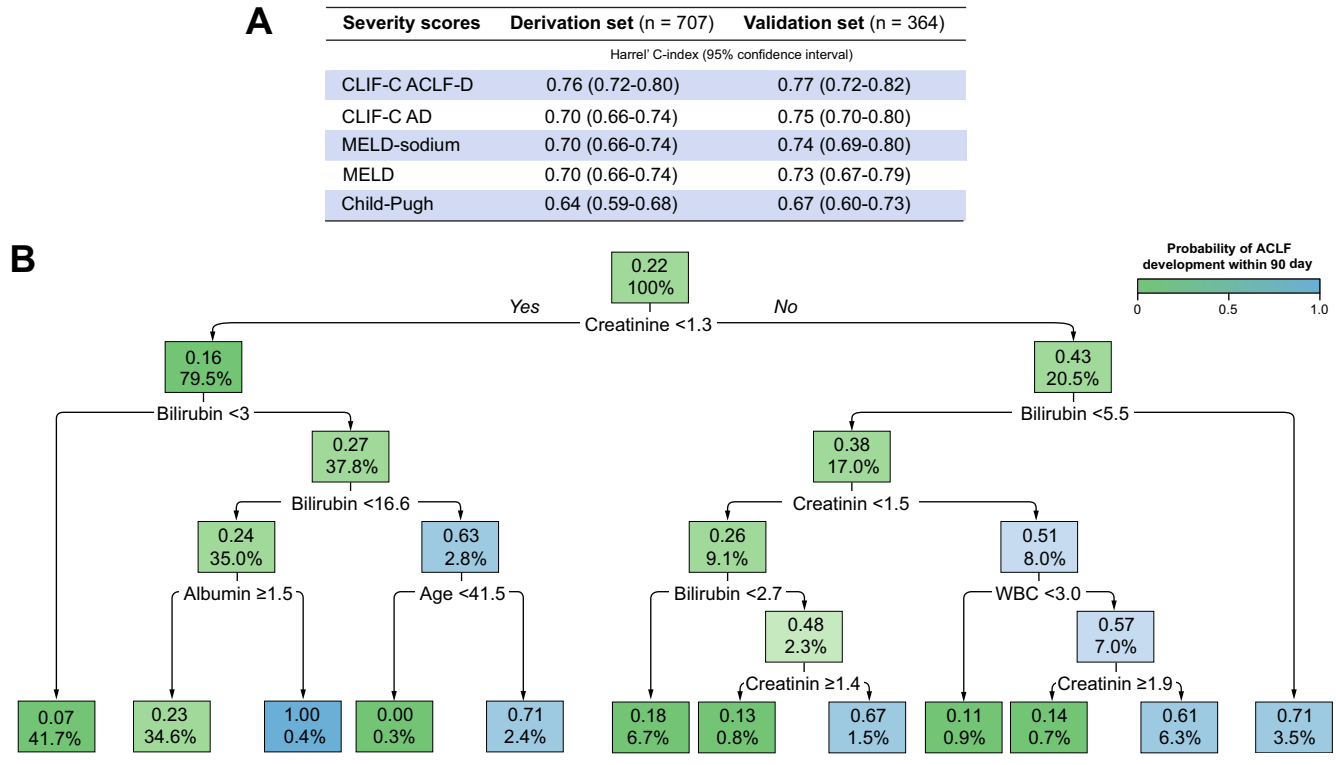

Fig. 5. Predictive ability of the CLIF-C ACLF-D score. (A) Comparison between the predictive ability of the CLIF-C ACLF-D score with those of the CLIF-C AD, MELD, MELD-sodium and Child-Pugh scores using Harrel' C-indexes and 95% CIs both in the derivation and validation sets. (B) Decision tree plot for the prediction of ACLF development during the 90-day follow-up period after enrollment. Each node shows the percentage of patients classified and their probability of ACLF development within the 90-day follow-up period after enrollment (also represented by the colors and color intensity). The blue color represents a probability of ACLF development >0.5. The green color represents a probability of ACLF development ACLF <0.5. The intensity of the color represents the estimated probability value. The upper node (root node) represents the entire population of patients (980 patients, 100%) included in the analysis and its corresponding probability of ACLF development before entering the model (0.22). Each node includes the estimated probability of subsequent subsets of patients. ACLF, acute-on-chronic liver failure; CLIF-C ACLF-D, Chronic Liver Failure Consortium acute-on-chronic liver failure development; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; MELD, model for end-stage liver disease.

Pugh scores in the derivation set. In the validation set, the CLIF-C ACLF-D showed a similar accuracy but smaller differences with regards to the other scores. Therefore, we were unable to design a new score to predict ACLF development more accurately than the traditional clinical scores.

The most relevant clinical variable selected by the decision tree model was creatinine, with a threshold of 1.3 mg/dl (Fig. 5B). Bilirubin, albumin, age and WBC were also selected to subsequently discriminate patients. The terminal nodes with a probability of ACLF higher than 0.5, classifying patients likely to develop ACLF, included 14.1% of the patients. The model achieved a discriminating ability (AUC) of 0.76 (0.72–0.79), with high specificity (95%) but low sensitivity (38%), indicating an important misclassification among those patients who actually developed ACLF.

Discussion

The most noteworthy finding of the current study was the identification of 3 different clinical courses with distinct pathophysiology and prognosis in patients hospitalized for the treatment of an episode of AD. These 3 clinical courses were unrelated to the etiology of cirrhosis, or to active alcoholism in patients with alcohol-related cirrhosis, indicating that they were largely dependent on other mechanisms.

The 3 distinct types of clinical courses coincided with specific changes in the grade of systemic inflammation. Patients with pre-ACLF showed significantly higher grade of systemic inflammation at enrollment than patients with UDC and SDC. By contrast, there was no significant difference in systemic inflammation between patients with UDC and SDC. Moreover, whereas the levels of inflammatory markers increased significantly during follow-up, accompanying the progression of AD to ACLF in patients with pre-ACLF, they decreased intensely in patients with SDC, while they did not show clear changes in patients with UDC. Therefore, a distinct progression of systemic inflammation is likely a major pathogenetic mechanism underlying the 3 clinical courses of patients with AD. This finding is a key feature in the new comprehensive hypothesis for AD presented in the current article.

Thus, patients with SDC developed the index episode of AD in the context of moderate systemic inflammation. In addition, systemic inflammation decreased rapidly and remained at low intensity during the 3-month follow-up. Probably due to this, all patients recovered from the index episode of AD, most presented a long-term relatively benign clinical course and only 9.5% died within the 1-year follow-up. Around half of the few patients who died within the 1-year follow-up period reproduced the clinical course of the pre-ACLF group and developed multiorgan failure. In contrast, hypovolemic shock was reported as the main cause of death in only 5% of cases.

In contrast, patients with pre-ACLF developed AD in the context of more intense systemic inflammation, which further increased with ACLF development during follow-up. These patients differed significantly from patients with SDC in many other features reported at enrollment, clearly supporting that they were in a pre-ACLF stage. They exhibited a significantly higher prevalence of liver failure, liver dysfunction, renal dysfunction, ascites, encephalopathy and bacterial infections and significantly worse prognostic scores than patients with SDC and UDC.

The median time between the onset of decompensated cirrhosis to liver transplantation or death, which covers the complete phase of clinically decompensated cirrhosis, was remarkably shorter in patients in the pre-ACLF group (12 months) than in those with SDC (20 months), indicating an accelerated clinical course of the decompensated phase of the disease towards death in patients with pre-ACLF.

Finally, the clinical course during the first 3-month period prior to admission, as estimated by the prevalence of ascites, encephalopathy and bacterial infections, was significantly more unstable in the pre-ACLF group than in the SDC group. This finding suggests that patients with pre-ACLF were already more severely ill than patients with SDC months before reaching the pre-ACLF status. We presume that the intensity of systemic inflammation during this period was probably sufficient to induce this frequent development of complications requiring hospital admission, but not enough to reach the critical threshold beyond which ACLF develops.[15] Therefore, pre-ACLF should be suspected in patients hospitalized for AD with prior unstable clinical course, very high levels of inflammatory markers and liver failure or liver or kidney dysfunction. Unfortunately, we were unable to design new specific tools that improve the accuracy of the CLIF-C AD and MELD-sodium scores for predicting ACLF development.

Patients with UDC shared many characteristics with patients with pre-ACLF and SDC. Like patients with pre-ACLF, they presented clinical course instability within the 3-month period prior to and after enrollment. However, they did not present severe systemic inflammation at enrollment or a clear increase of systemic inflammation level during follow-up. This probably explains the lack of development of ACLF in this group of patients. A second important finding in patients with UDC was their significantly higher prevalence of features suggestive of severe portal hypertension. This finding supports that the second major pathophysiological mechanism of AD is likely related to changes in portal hypertension.

Therefore, the most severe course of AD corresponds to patients with pre-ACLF who develop rapid progression of systemic inflammation leading to ACLF development and death. The second course corresponds to patients with UDC, who have an increased incidence of complications related to severe portal hypertension, such as circulatory dysfunction at enrollment, increased incidence of gastrointestinal hemorrhage and TIPS placement during the 6-month observational period and higher mortality due to hypovolemic shock. However, since the grade of systemic inflammation did not progress to the critical threshold level to induce extrahepatic organ failure, only a minority of patients with UDC developed ACLF. Consequently, they lived longer than patients with pre-ACLF. Finally, the third course of AD, which is by far the most frequent, corresponds to patients with SDC and is likely the consequence of a slow progression of these 2 pathophysiological mechanisms, leading to a relatively benign course and much longer survival.

This hypothesis is further supported by our findings showing that ascites, which is the complication associated with the most extensive organ dysfunction (liver, kidney, heart and systemic circulation),[16,17] was associated with the most intense systemic inflammation in comparison with hepatic encephalopathy and gastrointestinal hemorrhage.

Bacterial infections were frequently associated with AD. Roughly, 1 in every 3-4 patients included in each group were

infected at the time of AD development. Two mechanisms have been proposed for this association. The first is that bacterial infections, by increasing the intensity of systemic inflammation, precipitate the development of AD.[2,5,6] The second is that bacterial infections would be the consequence of a compensatory immunomodulatory reaction to systemic inflammation, which impairs the antibacterial activity of immune cells (immunoparalysis).[18–20] Our findings suggest that these 2 mechanisms are not mutually exclusive.

In summary, the PREDICT study suggests that AD in cirrhosis is a clinical condition with 3 different courses and 2 major pathophysiological mechanisms. Pre-ACLF is predominantly related to rapid progression of systemic inflammation, ACLF development and an extremely high short-term mortality rate. UDC occurs in the context of rapid progression of portal hypertension and is associated with a less severe clinical course and lower short-term mortality. Finally, both mechanisms progress slowly in SDC, and patients follow a relatively benign course with longer survival. Predicting the outcome of patients who present with AD is a major future research challenge.

Abbreviations

ACLF, acute-on-chronic liver failure; AD, acute decompensation; AUC, area under the receiver-operating characteristic curve; CLIF-C ACLF-D, Chronic Liver Failure Consortium acute-on-chronic liver failure development; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; CLIF-C OF, Chronic Liver Failure Consortium organ failure; CRP, C-reactive protein; HR, hazard ratio; MELD, model for end-stage liver disease; SDC, stable decompensated cirrhosis; TIPS, transjugular intrahepatic portosystemic shunt; UDC, unstable decompensated cirrhosis; WBC, white blood cell count.

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Conflict of interest

None of the authors have conflicts of interest for the reported study.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

JT, JF, WL, JC, RJ, RM, PG, PA, VA: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, funding recipient, administrative, technical and material support, study supervision; EG, AA, AC, CP, MP, CS, AC, AM, FA: acquisition of data, analysis of data, technical and material support; TT, MB, PA, CA, FEU, CJ, MST, TG, AA, WL, ES, RB, MJ, CS, TR, JA, PG, WB, SZ, CR, TB, AS, LLG, MC, OR, RS, HZ, AC, GSP, AdG, HG, FS, CT, OCÖ, FS, SR, RA, MRG, HVV, CF, MM, MP, PC, SP, IG, MP, VV, RM, ZV, MB, EB: acquisition of data, interpretation of data, critical revision of the manuscript regarding important intellectual content.

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Supplementary data

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