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PREDICT identifies precipitating events associated with the clinical course of acutely decompensated cirrhosis

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Background & Aims: Acute decompensation (AD) of cirrhosis may present without acute-on-chronic liver failure (ACLF) (AD-No ACLF), or with ACLF (AD-ACLF), defined by organ failure(s). Herein, we aimed to analyze and characterize the precipitants leading to both of these AD phenotypes.
Methods: The multicenter, prospective, observational PREDICT study (NCT03056612) included 1,273 non-electively hospitalized

patients with AD (No ACLF = 1,071; ACLF = 202). Medical history, clinical data and laboratory data were collected at enrolment and during 90-day follow-up, with particular attention given to the following characteristics of precipitants: induction of organ dysfunction or failure, systemic inflammation, chronology, intensity, and relationship to outcome.

Results: Among various clinical events, 4 distinct events were precipitants consistently related to AD: proven bacterial infections, severe alcoholic hepatitis, gastrointestinal bleeding with shock and toxic encephalopathy. Among patients with precipitants in the AD-No ACLF cohort and the AD-ACLF cohort (38% and 71%, respectively), almost all (96% and 97%, respectively) showed proven bacterial infection and severe alcoholic hepatitis, either alone or in combination with other events. Survival was similar in patients with proven bacterial infections or severe alcoholic hepatitis in both AD phenotypes. The number of precipitants was associated with significantly increased 90-day mortality and was paralleled by increasing levels of surrogates for systemic inflammation. Importantly, adequate first-line antibiotic treatment of proven bacterial infections was associated with a lower ACLF development rate and lower 90-day mortality.

Conclusions: This study identified precipitants that are significantly associated with a distinct clinical course and prognosis in patients with AD. Specific preventive and therapeutic strategies targeting these events may improve outcomes in patients with decompensated cirrhosis.

Lay summary: Acute decompensation (AD) of cirrhosis is characterized by a rapid deterioration in patient health. Herein, we aimed to analyze the precipitating events that cause AD in patients with cirrhosis. Proven bacterial infections and severe alcoholic hepatitis, either alone or in combination, accounted for almost all (96-97%) cases of AD and acute-on-chronic liver failure. Whilst the type of precipitant was not associated with mortality, the number of precipitant(s) was. This study identified precipitants that are significantly associated with a distinct clinical course and prognosis of patients with AD. Specific preventive and therapeutic strategies targeting these events may improve patient outcomes.

Introduction

Acute decompensation of cirrhosis (hereafter called AD) defines the acute development of ascites, hepatic encephalopathy, gastrointestinal hemorrhage or bacterial infections, or any combination of these. In 2013, the CANONIC study identified the syndrome of acute-on-chronic liver failure (ACLF), the most severe phenotype of AD, in 20% of 1,343 consecutive patients non-electively hospitalized for the treatment of an episode of AD.[1] ACLF was characterized by single or multiple organ failure and high 28-day mortality rate (30%).

In 2020, the PREDICT study, a prospective observational investigation of 1,273 hospitalized patients with AD, showed that patients without ACLF (AD-No ACLF phenotype) comprised 3 distinct sub-phenotypes defined according to ACLF development and readmission within 3 months after AD.[2] In brief, pre-ACLF patients developed ACLF and showed high short-term (90-day) mortality (67%); unstable decompensated cirrhosis (UDC) patients did not develop ACLF, but required readmission(s) and showed significant short-term mortality (35%); stable decompensated cirrhosis (SDC) patients presented an uncomplicated course during the 3-month follow-up period and showed lower 1-year mortality (9%).

In the traditional view, the development of AD is initiated by an acute worsening of stable cirrhosis through different pathophysiological mechanisms considered as precipitants. Evidence from the CANONIC and the PREDICT studies challenges this view,[1,2] and suggests that AD manifests mainly as a result of systemic inflammation, inducing multiple organ dysfunction and presents with different clinical phenotypes.[3,4] Indeed, systemic inflammation increases across the sub-phenotypes of AD-no ACLF (SDC, UDC and pre-ACLF), and reaches its peak in patients with AD-ACLF.[5,6] Moreover, in AD-ACLF phenotype, the grade of systemic inflammation correlated with the number of organ failures, clinical course severity and prognosis.[3,4] Hence, for a precipitant to be of importance, it must have the ability to impair end-organ function.

Despite the fact that AD-ACLF phenotypes frequently develop in close chronological relationship with the precipitant(s), the critical time period prior to AD-ACLF has not yet been explored in detail. Moreover, no specific criteria for the diagnosis of precipitants have been identified to date. Consequently, many clinically relevant aspects of precipitants remain ill-defined.

The current study is the second investigation derived from the PREDICT study. Its aim was to provide the rationale for the diagnosis of precipitants and to investigate the association of type and number of precipitants with early clinical course and prognosis in patients hospitalized with AD-No ACLF and AD-ACLF phenotypes.

Patients and methods

Patients

The PREDICT study (ClinicalTrials.gov number, NCT03056612) is a European, investigator-initiated, multicenter, prospective, observational study performed in 48 university hospitals (approved by the respective ethics committees) from 15 countries and promoted by the European Foundation for the Study of Chronic Liver Failure. The design of the study has been reported in detail elsewhere.[2] Briefly, 1,071 cirrhosis patients with AD-No ACLF phenotype and 202 with AD-ACLF phenotype non-electively hospitalized for treatment were enrolled from March 2017 to July 2018 after providing their informed consent. AD was diagnosed as previously described[2] and ACLF according to the EASL-CLIF criteria.[1,7] Stratification of patients with the AD-No ACLF phenotype into the AD-pre-ACLF, AD-UDC and AD-SDC sub-phenotypes was performed using previously described criteria[2] and outlined inFig. 1 (for detailed description please see supplementary information).

Study design

The PREDICT study[2] was designed to explore the last 90 days prior to hospital admission (especially the last 2 weeks), and the first 3 months after admission (follow-up period), in which the early clinical course of patients was assessed. Pre-specified clinical and standard laboratory data were obtained at enrolment and during follow-up visits. The design of the PREDICT study is described in detail in the supplementary information and elsewhere.[2]

Identification of precipitants of AD-No ACLF and AD-ACLF

In order to identify the precipitants an adjudication committee of the PREDICT study, which included JT, JF, RM and VA, was

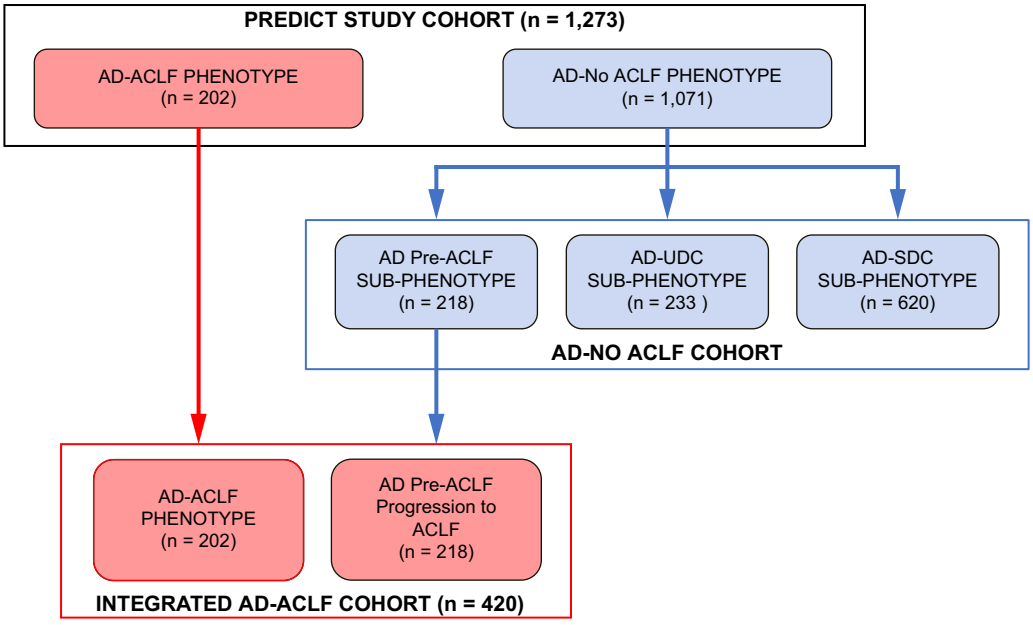

Fig. 1. Schematic outline of the study. AD phenotype groups and subgroups included in each of the AD cohorts used for the study analysis. For more explanation see the text. ACLF, acute-on-chronic liver failure; AD, acute decompensation; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.

nominated to elaborate a list of clinical events with the potential to precipitate AD or ACLF, and also the general principles and specific criteria for diagnosis. This committee identified precipitants according to the criteria defined below.

General principles for precipitant identification

- Precipitants should consist of events that have the potential to induce impairment in the function of the liver and/or other organs, either by direct organ injury (*e.g.* tissue hypoperfusion) or, indirectly, through significant dysregulation of important pathophysiological mechanisms (*e.g.* immune responses to microbial or endogenous factors).
- When assessing the potential of hepatotoxic, nephrotoxic or neurotoxic drugs as precipitants, the lack of liver, kidney or brain dysfunction or failure, respectively, as defined by the CLIF-C organ failure score[8] rule out drug-induced organ toxicity as a precipitant.
- As suggested by the results of the CANONIC study,[1,7] clinically identifiable, relevant and true precipitants should have a higher prevalence in patients with AD-ACLF than in those with AD-no ACLF.
- Precipitants should precede or coincide with the onset of AD-ACLF. The time period between the precipitants and the onset of AD-ACLF, however, is heterogeneous, depending on the precipitants.
- Any event developing after the onset of AD-ACLF is a complication or a coincidental event but not a precipitant.

Specific criteria for the identification of precipitants from the list proposed by the adjudication committee (for detailed description see supplementary appendix)

The adjudication committee evaluated the following events as potential precipitants as proposed by the CANONIC study and other investigations: bacterial infections, alcoholic hepatitis, gastrointestinal (GI) bleeding, drug-induced organ injury, therapeutic interventions.

Bacterial infections (details in supplementary information). Infections were considered to be potential precipitants if they were diagnosed at the time of or solved within the 48-hour period that preceded the onset of AD. Proven bacterial infections were defined as previously described[9] and in accordance with the EASL guidelines[7] (detailed definition in the supplementary information).

Alcohol-related liver injury (details in the supplementary information). Alcoholic hepatitis was diagnosed according to the clinical criteria of the NIAAA.[10] These criteria are in line with the clinical diagnosis of alcoholic hepatitis according to the existing EASL guidelines.[11] Alcoholic hepatitis was considered severe if patients had CLIF-C acute decompensation scores of ≥50 points,[12] or ACLF (Table 1).

GI bleeding (details in the supplementary information). GI bleeding was considered a precipitant if occurring within 7 days prior to the onset of AD-ACLF. Moreover, hemorrhagic shock was indicative of severe bleeding (Table 1).

Drug-induced liver injury was considered a potential precipitant when the hepatotoxic drug was administered within 1 month prior to the onset of AD-ACLF and the patient presented with liver injury as defined by Hy's law and FDA guidance as described in the recent EASL guidelines;[13] as well as liver dysfunction (in patients with AD-No ACLF, bilirubin >6 mg/dl) or liver failure (in patients with AD-ACLF, bilirubin >12 mg/dl). Only drugs from groups A and B of potential hepatotoxic drugs, described elsewhere,[14] were considered potential candidates for liver toxicity.

Drug-induced kidney injury was considered a potential precipitant when the nephrotoxic drug was administered within 7 days prior to the onset of AD-ACLF and patients presented with

Table 1. Clinical events, precipitants and combinations of precipitants in patients with AD-No ACLF and with AD-ACLF.

	AD-No ACLF (n = 1,071)	AD-ACLF (n = 202)	*p* value[a]
Clinical events, precipitants, n (%)			
Bacterial infections			
Any infection	314 (29.32)	101 (50.00)	<0.0001
Suspected bacterial infection	74 (6.91)	12 (5.94)	0.61
Proven bacterial infections[b]	239 (22.32)	89 (44.06)	<0.0001
Alcohol-related liver injury			
Alcoholic hepatitis	275 (25.68)	88 (43.56)	<0.0001
Severe alcoholic hepatitis[b]	200 (18.67)	88 (43.56)	<0.0001
GI bleeding			
Any GI bleeding	176 (16.43)	40 (19.80)	0.24
GI bleeding with hypovolemic shock[b]	13 (1.21)	12 (5.94)	<0.0001
Drug-induced brain injury			
Patients treated with neurotoxic drugs	84 (7.84)	17 (8.42)	0.78
Toxic encephalopathy[b]	13 (1.21)	12 (5.94)	<0.0001
Other candidates, n (%)			
Paracentesis without albumin	110 (10.28)	21 (10.40)	0.96
TIPS	49 (4.58)	8 (3.96)	0.69
Drug-induced liver injury	16 (1.49)	4 (1.98)	0.54
Viral hepatitis or other viral Infections	13 (1.21)	3 (1.49)	0.72
Drug-induced kidney injury	3 (0.28)	1 (0.50)	-
Surgery	3 (0.28)	0 (0.00)	-
Decompensated cardiopulmonary disease	4 (0.37)	3 (1.49)	-
Dehydration	3 (0.28)	1 (0.50)	-
Large hematomas	3 (0.28)	0 (0.00)	-
Acute pancreatitis	1 (0.09)	1 (0.50)	-
Portomesenteric vein thrombosis	2 (0.19)	1 (0.50)	-
Extrahepatic autoimmune disease	2 (0.19)	0 (0.00)	-
Cerebrovascular accident	0 (0.00)	1 (0.50)	-
Bowel occlusion	1 (0.09)	0 (0.00)	-
Number of precipitants			
Indeterminate	662 (61.81)	59 (29.21)	<0.0001
1	354 (33.05)	93 (46.04)	
≥2	55 (5.14)	50 (24.75)	

Chi-square or Fisher's tests performed in percentages comparisons. ACLF, acute-on-chronic liver failure; AD, acute decompensation; GI, gastrointestinal; TIPS, transjugular intrahepatic portosystemic shunt.
[a]Certain *p* value were not determined because of the low number of patients.
[b]Underlined precipitants are those considered as precipitants of AD-ACLF.

either renal dysfunction or renal failure according to the CLIF-C organ failure score. Diuretic-induced renal dysfunction or renal failure was not considered a nephrotoxic condition.

Toxic encephalopathy was considered a potential precipitant when the neurotoxic drug was administered within 48 hours prior to the onset of AD-ACLF and the patient presented with encephalopathy in severity similar to brain dysfunction or brain failure according to the CLIF-C organ failure score.

Therapeutic interventions including transjugular intrahepatic portosystemic shunt (TIPS), major surgical procedures and large volume paracentesis without albumin administration were considered as potential precipitants if performed within 7 days prior to the onset of AD-ACLF.

Other potential precipitants identified by the investigators in the individual patients eCRF

The adjudication committee assessed 9 additional, infrequent clinical events (details in the supplementary information).

Statistical analysis

Discrete variables are shown as counts (percentage) and continuous variables as mean ± SD. Non-normally distributed variables are summarized by the median (IQR). In univariate statistical comparisons, the chi-square test or Fisher's exact test, when at least 25% of expected counts were below 5, were used for categorical variables, whereas the Student's *t* test or analysis of variance were used for normally distributed continuous variables and the Wilcoxon rank-sum test or the Kruskal-Wallis test for continuous variables not normally distributed. For comparisons at different time-points in the same patients, paired tests were used: McNemar test was applied for dichotomic variables and a test of symmetry was performed for variables with 3 categories. In all statistical analyses, significance was set at $p<0.05$.

Overall, the proportion of missing values in the main reported characteristics (demographics, clinical variables, laboratory values, precipitants and clinical outcomes) rounded 1% at most. Only complete clinical blood counts and total cholesterol showed higher proportions of missing data, which were mainly due to common problems with sample availability or with technical laboratory processes that occurred in several site laboratories and can be considered to be completely random. A simple imputation approach was used to impute the missing values for each of the 4 variables mentioned above (neutrophil, lymphocyte and monocyte counts and total cholesterol). SAS PROC MI was used assuming an arbitrary pattern for missing values and adopting a fully conditional specification (FCS) regression method. Model covariates included age, sex, CLIF-C organ failure score and number of precipitants or presence of bacterial infections or alcoholism or ACLF at inclusion, depending on the

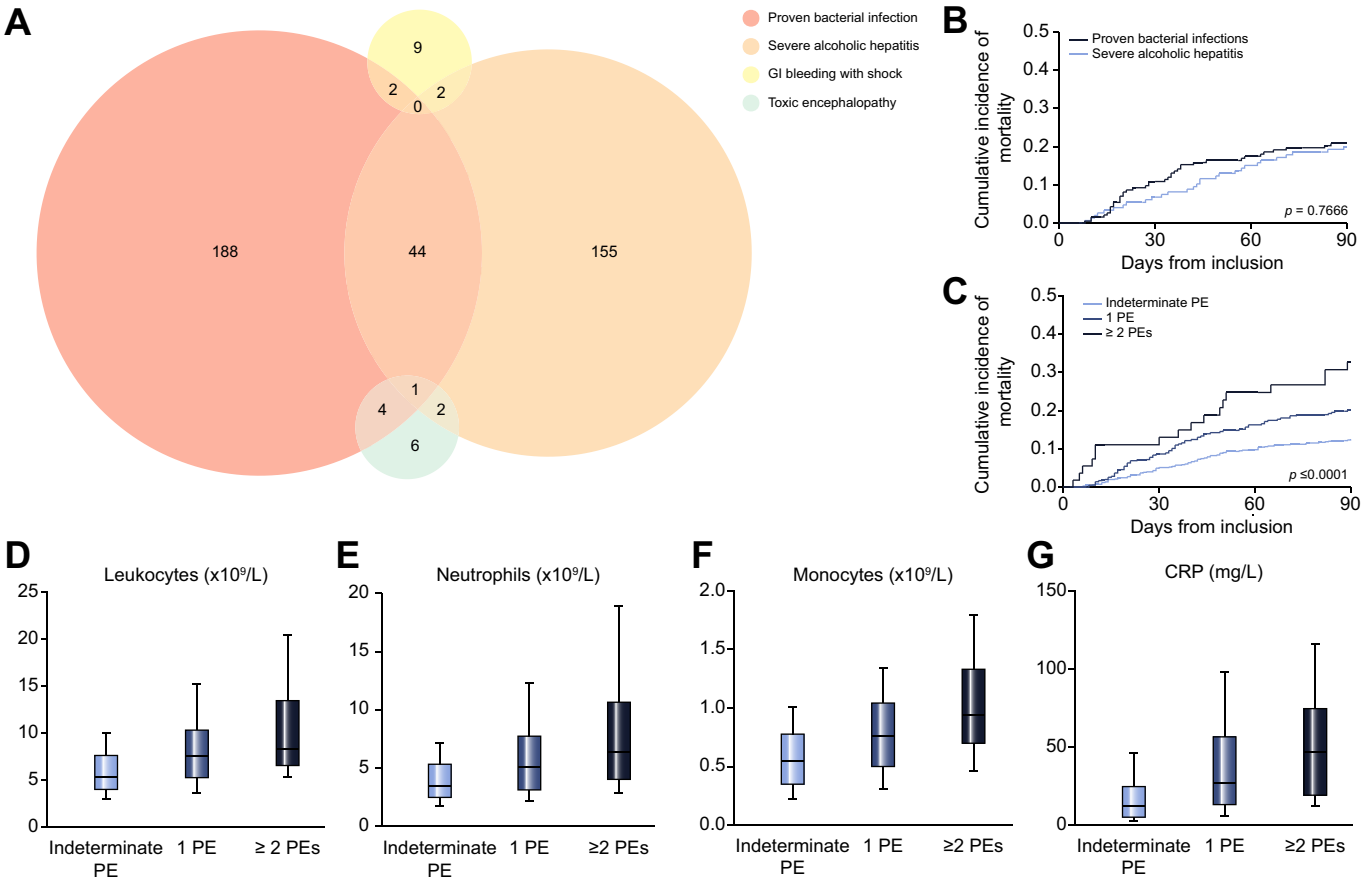

Fig. 2. Precipitants in AD-No ACLF. Combinations of PEs in the AD-No ACLF cohort shown in a 4-set circle Venn diagram (panel A). Cumulative incidence of mortality in patients with AD-No ACLF according to the type of precipitant (proven infections alone *vs.* severe alcoholic hepatitis alone; panel B) and the number of precipitants (indeterminate PE, 1 PE, and ≥2 PEs; panel C) *p* values were obtained from Gray's test. Blood levels of leukocytes (panel D), neutrophils (panel E), monocytes (panel F) and the serum concentration of CRP (panel G) in patients with AD-No ACLF and indeterminate PE, 1 PE and ≥2 PEs. Boxes show median and IQR and whiskers show 10-90 percentiles. Kruskal-Wallis test was performed with all values in each comparison. Differences were statistically significant ($p<0.0001$) for all biomarkers. ACLF, acute-on-chronic liver failure; AD, acute decompensation; CRP, C-reactive protein; PE(s), precipitant(s).

Table 2. Type and number of precipitants in patients with pre-ACLF, unstable decompensated cirrhosis and stable decompensated cirrhosis.

	Pre-ACLF (n = 218)			
	At enrolment	At ACLF development	UDC (n = 233)	SDC (n = 620)
Type of precipitant, n (%)				
Proven bacterial infections	64 (29.4)	97 (44.5)**	49 (21.0) *,##	126 (20.3) **,##
Severe alcoholic hepatitis	58 (26.6)	57 (26.1)	45 (19.3) +	97 (15.6) **,#
GI bleeding with shock $	2 (0.9)	8 (3.7)	2 (0.9)	9 (1.5)
Toxic encephalopathy $	3 (1.4)	4 (1.8)	3 (1.3)	7 (1.1)
Number of precipitants, n (%)				
Indeterminate	111 (50.9)	88 (40.4)**	142 (60.9) *,##	409 (66.0) **,##
One	88 (40.4)	98 (45.0)**	83 (35.6) ##	183 (29.5) ##
Two or more	19 (8.7)	32 (14.7)**	8 (3.4) ##	28 (4.5) ##

Comparison between all groups to the pre-ACLF group at enrolment is displayed by the following symbols:
+$p<0.07$, *$p<0.05$ and **$p<0.01$ *vs.* the pre-ACLF group at enrolment.
Comparison between all groups to the pre-ACLF group at ACLF development is displayed by the following symbols:
#$p<0.001$ and ##$p<0.0001$ *vs.* pre-ACLF group at ACLF development.
Chi-square or Fisher's tests performed in percentages comparisons among groups.
McNemar test used in paired comparisons for the types of precipitant between the 2 time-points in pre-ACLF group.
Symmetry test used in paired comparisons for the number of precipitant between the 2 time-points in pre-ACLF group.
$*p* value not determined due to the low number of patients.
ACLF, acute-on-chronic liver failure; AD, acute decompensation; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.

analysis that was to be performed. For each variable, missing values were imputed by computing the median of the values obtained by fitting the model on 100 repetitions generated from the original dataset.

Cumulative incidence functions (CIF's) were used to estimate survival curves accounting for liver transplantation as an event 'competing' with mortality, as well as to estimate ACLF development accounting for both mortality and liver transplantation as events "competing" with ACLF development, using common non-parametric methods. The equality of CIFs across groups was evaluated by means of the Gray's test.[15] Statistical analysis was performed using SAS v9.4 and plots were performed with R v1.2.5042 and GraphPad Prism v5 software.

Results

Identification of precipitants for AD at enrolment in the PREDICT study cohort

The PREDICT study cohort includes 1,273 patients, of whom 202 patients presented with AD-ACLF and 1,071 patients with AD-No ACLF (Fig. 1). There were 4 main precipitants: bacterial infections, alcohol-related liver injury, GI bleeding and toxic encephalopathy (Table 1).

The prevalence of patients with proven bacterial infections was significantly higher in AD-ACLF than in AD-No ACLF cases, while prevalence of suspected bacterial infections was very low and similar in both groups. Therefore, only proven bacterial infections were considered as precipitants of AD-ACLF, and this was the most common precipitant (44% in AD-ACLF and in 22.3% in AD-No ACLF [$p<0.0001$]).

Prevalence of severe alcoholic hepatitis (alcoholic hepatitis associated with CLIF-C AD score ≥50 or ACLF) was significantly higher in patients with AD-ACLF (43.6% *vs.* 18.7% in AD-No ACLF). Overall, alcoholic hepatitis was not always associated with organ dysfunction. Therefore, only severe alcoholic hepatitis was identified as a precipitant, and was the second most frequent.

Severe GI bleeding associated with hypovolemic shock was the third most frequent precipitant, although its prevalence in the AD-ACLF and the AD-No ACLF group (5.9% and 1.2%, respectively, $p<0.0001$) was low.

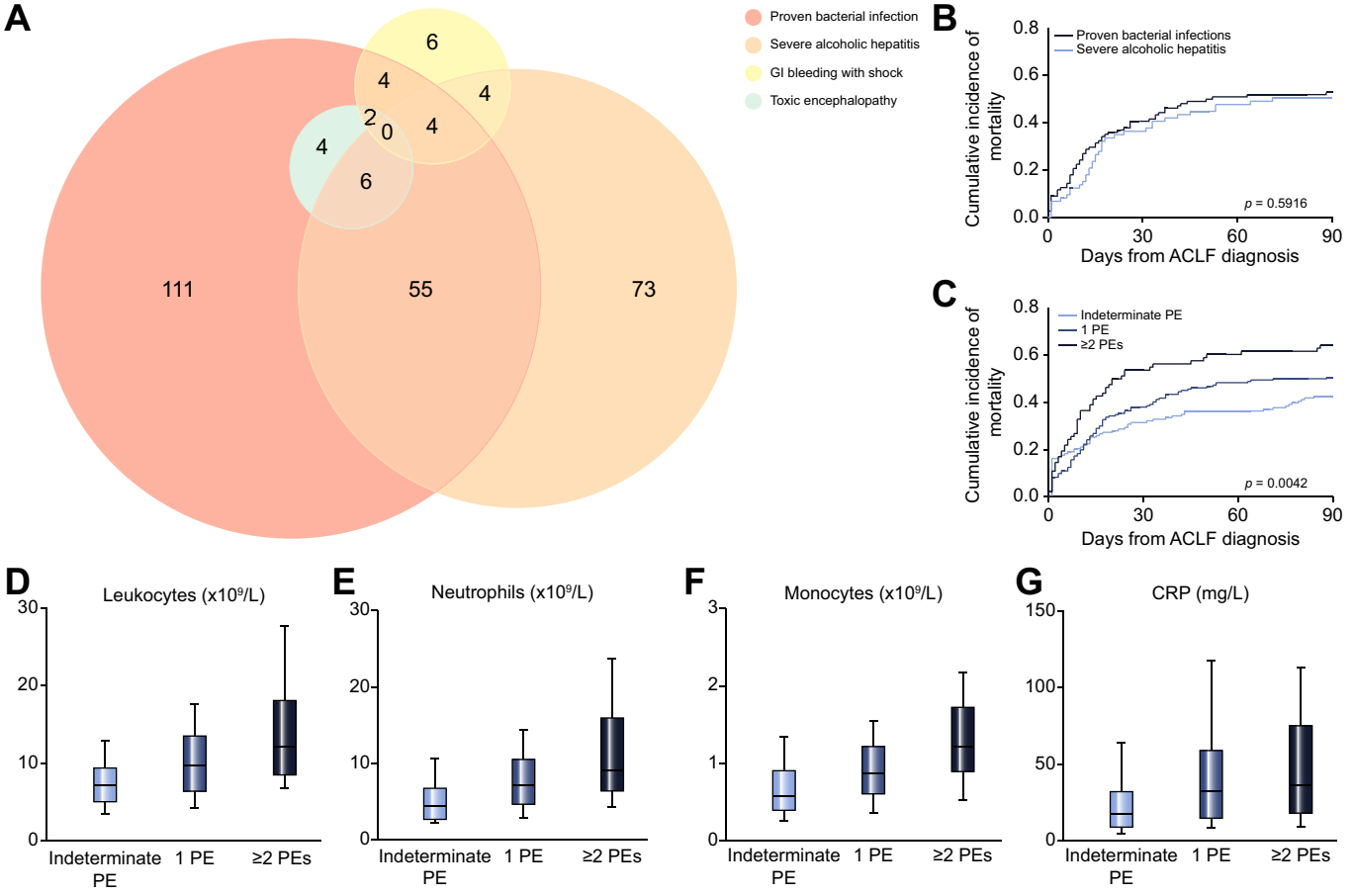

Fig. 3. Precipitants in AD-ACLF. Combinations of PEs in the integrated AD-ACLF cohort shown in a 4-set circle Venn diagram (panel A). Cumulative incidence of mortality in patients with AD-ACLF according to the type of PE (proven infections alone *vs.* severe alcoholic hepatitis alone; panel B) and the number of PEs (indeterminate PE, 1 PE, and ≥2 PEs; panel C); p-values were obtained from Gray's test. Blood levels of leukocytes (panel D), neutrophils (panel E), monocytes (panel F) and the serum concentration of CRP (panel G) in patients with AD-ACLF and indeterminate PE, 1 PE and ≥2 PEs. Boxes show median and IQR and whiskers show 10-90 percentiles. Kruskal-Wallis test was performed with all values in each comparison. Differences were statistically significant ($p<0.0001$) for all biomarkers. ACLF, acute-on-chronic liver failure; AD, acute decompensation; CRP, C-reactive protein; PE(s), precipitant(s).

Finally, of the 3 examined types of drug-induced organ injury, only the prevalence of toxic encephalopathy was significantly higher in the AD-ACLF group than in the AD-No ACLF group (5.9% and 1.2%, respectively, $p<0.0001$) and it thus qualified as a precipitant. All drugs associated with severe toxic encephalopathy were opioids or benzodiazepines.

Neither therapeutic paracentesis without intravenous albumin nor TIPS qualified as precipitants, since their prevalence was not significantly higher in patients with AD-ACLF than in patients with AC-no ACLF.

Table 3. Demographic data and etiology, clinical and laboratory data at diagnosis, specific treatments during follow-up and mortality in patients included in the integrated AD-ACLF cohort according to the number of precipitants.

	Indeterminate precipitant (n = 147)	1 precipitant (n = 191)	≥2 precipitants (n = 82)	*p* value
Demographic data and etiology of cirrhosis				
Age, year, mean ± SD	61.2 ± 11.38	60.5 ± 11.06	52.1 ± 11.41[a]	<0.0001
Male sex, n (%)	99 (67.3)	137 (71.7)	52 (63.4)	0.36
Alcohol-related cirrhosis, n (%)	81 (55.1)	144 (75.4)[b]	77 (93.9)[a]	<0.0001
Data at ACLF diagnosis				
Systemic hemodynamics, mean ± SD				
Mean arterial pressure (mmHg)	80.8 ± 12.51	79.0 ± 13.05	76.1 ± 13.65[b]	0.0419
Heart rate (bpm)	79.4 ± 15.80	82.0 ± 17.26	92.9 ± 19.93[a]	<0.0001
Complications, n (%)				
Ascites	90 (73.2)	134 (74.9)	71 (88.8)[a]	0.0206
Hepatic encephalopathy	61 (49.6)	112 (62.6)[b]	62 (77.5)[a]	0.0003
GI bleeding	16 (13.1)	16 (8.9)	19 (23.8)[c]	0.0053
Organ failures, n (%)				
Liver failure	29 (23.6)	60 (33.5)	49 (61.3)[a]	<0.0001
Renal failure	84 (68.3)	98 (54.7)[b]	33 (41.3)[a]	0.0006
Brain failure	13 (10.6)	31 (17.3)	27 (33.8)[a]	0.0002
Coagulation failure	25 (20.3)	41 (23.0)	28 (35.0)[a]	0.0474
Cardiovascular failure	6 (4.9)	25 (14.0)[b]	27 (33.8)[a]	<0.0001
Respiratory failure	3 (2.4)	21 (11.9)[b]	13 (16.3)[b]	0.0022
Biomarkers of systemic inflammation, median (IQR)				
White blood cell count, $x10^9$/L	7.19 (5.03–9.40)	9.72 (6.39–13.50)[b]	12.14 (8.57–18.10)[a]	<0.0001
Neutrophil count, $x10^9$/L	4.23 (2.25–6.85)	7.32 (4.60–10.45)[b]	9.56 (6.44–15.50)[a]	<0.0001
Lymphocyte count, $x10^9$/L	0.85 (0.65–1.40)	0.94 (0.56–1.56)	1.20 (0.73–1.97)[b]	0.0794
Monocyte count, $x10^9$/L	0.60 (0.40–0.92)	0.92 (0.65–1.22)[b]	1.32 (0.95–1.77)[a]	<0.0001
Serum C-reactive protein, mg/L	17.60 (8.80–32.00)	32.30 (15.00–58.90)[b]	36.15 (18.00–75.00)[b]	<0.0001
Measurements estimating organ function				
Serum bilirubin, mg/dl, median (IQR)	2.29 (1.12–11.04)	5.70 (2.12–14.80)[b]	14.53 (6.55–23.08)[a]	<0.0001
Serum albumin, g/dl, mean ± SD	3.0 ± 0.82	2.9 ± 0.68	2.9 ± 0.65	0.45
Total cholesterol, mg/dl, median (IQR)	86.70 (57.75–123.80)	70.50 (48.50–104.00)[b]	64.50 (42.00–83.50)[b]	0.0145
International normalized ratio, median (IQR)	1.53 (1.32–2.13)	1.75 (1.45–2.34)[b]	2.18 (1.80–2.78)[a]	<0.0001
Serum creatinine, mg/dl, median (IQR)	2.15 (1.54–2.80)	2.00 (1.04–2.50)[b]	1.55 (0.82–2.81)[b]	0.0024
Serum sodium, mEq/L, mean ± SD	133.6 ± 6.77	133.6 ± 6.36	134.4 ± 8.71	0.70
Prognostic scores, mean ± SD				
Child-Pugh score	9.5 ± 2.41	10.5 ± 2.18[b]	11.8 ± 1.50[a]	<0.0001
MELD score	24.3 ± 6.21	25.6 ± 6.41	29.8 ± 6.13[a]	<0.0001
MELD-Na score	26.6 ± 6.11	27.9 ± 5.81	31.2 ± 5.83[a]	<0.0001
CLIF-C organ failure score	8.9 ± 1.70	9.7 ± 1.97[b]	11.3 ± 2.20[a]	<0.0001
CLIF-C ACLF score	45.7 ± 7.45	50.1 ± 8.05[b]	54.1 ± 10.86[a]	<0.0001
ACLF grades, n (%)				
ACLF grade I	93 (76.2)	105 (59.7)[b]	24 (30.0)[a]	<0.0001
ACLF grade II	23 (18.9)	53 (30.1)[b]	34 (42.5)[a]	
ACLF grade III	6 (4.9)	18 (10.2)[b]	22 (27.5)[a]	
Specific treatments and mortality				
Specific treatments from ACLF, n (%)				
Intensive care	15 (10.2)	41 (21.5)[b]	32 (39.0)[a]	<0.0001
Renal replacement	8 (5.4)	13 (6.8)	14 (17.1)[a]	0.0055
Mechanical ventilation	3 (2.4)	22 (12.3)[b]	22 (27.5)[a]	<0.0001
Vasopressors	35 (23.8)	72 (37.7)[b]	52 (63.4)[a]	<0.0001
90-day liver transplantation	19 (13.1)	25 (13.4)	5 (6.3)	0.22
Mortality after ACLF diagnosis, n (%)				
90-day mortality	62 (42.2)	95 (49.7)	52 (63.4)[a]	0.0087

[a]$p<0.05$ *vs.* no precipitant and 1 precipitant.
[b]$p<0.05$ *vs.* indeterminate precipitant.
[c]$p<0.05$ *vs.* 1 precipitant. Chi-square or Fisher's tests performed in percentages comparisons. For continuous variables comparisons, analysis of variance for normally distributed variables or Kruskal-Wallis test for not normally distributed variables were used. ACLF, acute-on-chronic liver failure; AD, acute decompensation; GI, gastrointestinal; MELD, model for end-stage liver disease.

In total, 721 patients (56.6%) included in the PREDICT study cohort did not present any identifiable precipitant (indeterminate precipitant), 447 (35.1%) presented 1 precipitant, and 105 (8.2%) presented ≥2 precipitants.

The clinical characteristics, laboratory data, prognostic scores, and 90-day mortality rate of patients with AD-No ACLF and AD-ACLF are presented in Table S1.

Prevalence and association of precipitants with characteristics, clinical course and prognosis of patients included in the AD-No ACLF cohort

Prevalence of precipitants and their combinations

AD-No ACLF (n = 1,071) was associated with 1 precipitant in 354 patients (33.0%), and with ≥2 precipitants in 55 patients (5.1%), as illustrated in Fig. 2A. In the AD-No ACLF cohort, 662 patients (61.8%) presented with indeterminate precipitants (Table 1). Therefore, in 394 patients (96.3%), AD-No ACLF was related to proven bacterial infections or severe acute alcoholic hepatitis, either alone or in combination. AD-No ACLF was unrelated to bacterial infections or alcoholic hepatitis in only 15 (3.7%) patients.

Precipitants are associated with the clinical course and survival of patients with AD-No ACLF.

Prevalence of patients with proven bacterial infections and severe alcoholic hepatitis at enrolment was higher in AD-pre-ACLF (29.4% and 26.6%, respectively) than in AD-UDC (21.0% and 19.3%) or AD-SDC (20.3%. and 15.6%) phenotypes. Moreover, the number of patients with indeterminate precipitants was significantly lower (50.9%) and the number of patients with 1 or ≥2 precipitants was higher (40.4% and 8.7%) in patients with AD-pre-ACLF than in those with AD-UDC (60.9%, 35.6% and 3.4%, respectively) and AD-SDC (66.0%, 29.5% and 4.5%). Moreover, these differences were even more pronounced, when UDC or SDC groups at baseline were compared with the AD-pre-ACLF group at the time point of ACLF development. These observations suggest that the presence and the number of precipitants at enrolment are important determinants in the development of AD-pre-ACLF, the most severe sub-phenotype in patients with AD-No ACLF (Table 2).

Interestingly, patients with a single precipitant of the 2 major groups of precipitants (proven bacterial infection and severe alcoholic hepatitis) showed a comparable 90-day mortality (Fig. 2B). This is the case, despite the significant differences in clinical and laboratory parameters between patients with either proven bacterial infection or severe alcoholic hepatitis as sole precipitant (Table S2), indicating that the type of precipitant is not crucial for outcome, if correctly defined.

As shown in Fig. 2C, 90-day mortality was highest in patients with ≥2 precipitants and lowest in patients without any identifiable precipitant (Fig. 2C). In parallel, levels of leukocytes, neutrophils, monocytes and C-reactive protein (CRP) (Fig. 2D-G), organ dysfunction and failures and overall scores increased with the number of precipitants (Table S3).

Results derived from the integrated ACLF cohort

This integrated cohort included 202 patients with AD-ACLF at the time of enrolment (AD-ACLF group) and 218 patients in AD-pre-ACLF group who developed AD-ACLF during the study and who were included at the time of development of ACLF (Fig. 1). The integrated AD-ACLF cohort was developed with 2 objectives: i) a further characterization of the AD-ACLF phenotype in patients with community-acquired and hospital-acquired ACLF; and ii) an analysis of precipitants in a sufficiently sized AD-ACLF cohort.

Prevalence of precipitants and their combinations

Of the 420 patients included in the integrated AD-ACLF cohort, AD-ACLF was triggered by 1 precipitant in 191 patients (45.5%), and by or ≥2 in 82 patients (19.5%), while precipitant was indeterminate in 147 patients (35.0%) (Table S4). Fig. 3A shows the different combinations of precipitants in the Integrated AD-ACLF cohort. Like the AD-No ACLF cohort, 266 (97.4%) of patients with identifiable precipitants had proven bacterial infections or severe acute alcoholic hepatitis as either a single or as combined precipitants.

Table 4. Adequacy of initial antibiotic strategies.

Type of empirical antibiotic strategies	Total	Classic*	Piperacillin-tazobactam	MDR coverage**	*p* value
Number of all proven bacterial infections	440	273	70	92	
Resolution of infection without further escalation or bacterial susceptibility to initial antibiotics in culture positive infections (%)	62.5	54.2	68.6	82.6	<0.0001
Bacterial susceptibility to initial antibiotics in culture positive infections (%)	61.6	48.3	70.7	93.4	<0.0001
Number of proven bacterial infections precipitating AD	265	187	34	39	
Resolution of infection without further escalation or bacterial susceptibility to initial antibiotics in culture positive infections (%)	68.1	62.0	73.5	92.3	0.0008
Bacterial susceptibility to initial antibiotics in culture positive infections (%)	63.9	54.4	75.0	100.0	<0.0001
Number of proven bacterial infections precipitating ACLF	175	86	36	53	
Resolution of infection without further escalation or bacterial susceptibility to initial antibiotics in culture positive infections (%)	54.3	37.2	63.9	75.5	<0.0001
Bacterial susceptibility to initial antibiotics in culture positive infections (%)	58.5	36.7	66.7	89.2	<0.0001

Adequacy based on clinical criteria (resolution of infection without further escalation or bacterial susceptibility to initial antibiotics in culture positive infections) and the microbiological criterion (bacterial susceptibility to initial antibiotics in culture positive infections) in the whole series of proven infections and in infections precipitating AD and ACLF, according to empirical antibiotic strategies.

*One to third generation cephalosporins, amoxicillin-clavulanic acid, quinolones; **carbapenem±glycopeptide/linezolid/daptomycin or tigecycline; Chi-square or Fisher's tests used to compare percentages.

ACLF, acute-on-chronic liver failure; AD, acute decompensation; MDR, multidrug resistant.

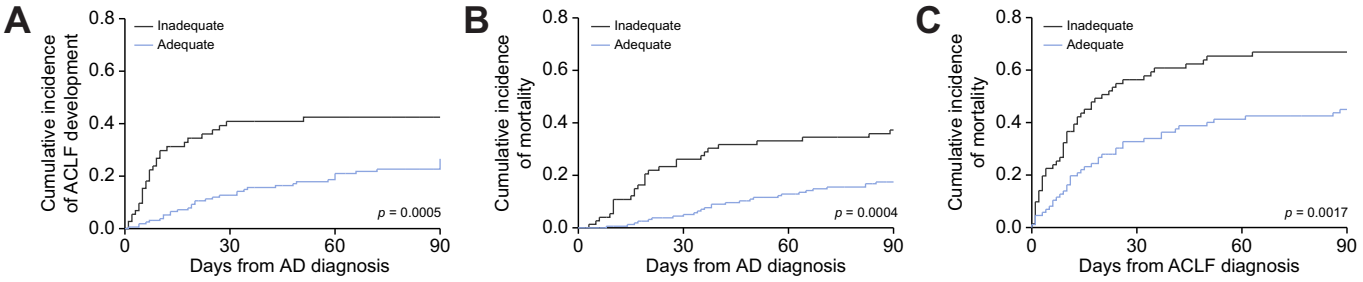

Fig. 4. Treatment of bacterial infections. Prognostic impact of inappropriate empirical antibiotic therapy in patients with AD and ACLF. (A) Probability of ACLF at day 90 in infected patients with AD receiving adequate or inadequate empirical antibiotic strategies (B-C) Probability of death at day 90 in patients with AD (B) and ACLF (C). Inadequacy of empirical strategies significantly increased the probability of ACLF and death in the different populations. *p* values were obtained from Gray's test. ACLF, acute-on-chronic liver failure; AD, acute decompensation.

The type of precipitant is significantly associated with clinical characteristics, but not clinical course and mortality of patients with AD-ACLF in the integrated cohort

As in AD-No ACLF patients (Table S2), patients with AD-ACLF had different clinical characteristics (among others higher bilirubin but lower CRP values in severe alcoholic hepatitis) depending on the type of single precipitant: proven bacterial infections or severe alcoholic hepatitis (Table S5). Similar to AD-No ACLF patients, these differences did not impact the clinical course and prognosis, as shown in Fig. 3B.

Number of precipitants is significantly associated with the clinical course and mortality of patients with AD-ACLF.

The number of precipitants in patients included in the integrated AD-ACLF cohort (indeterminate, 1 precipitant, and 2 or 3 precipitants) correlated positively with the prevalence of liver, brain, coagulation and cardio-circulatory failure and inversely with the prevalence of renal failure. These findings were due to differences in the predominance of specific organ failures among patients with a distinct number of precipitants. The predominant organ failure in patients with an indeterminate precipitant or with only 1 precipitant was renal failure. By contrast, liver failure was the predominant organ failure in patients with 2 or 3 precipitants. Moreover, the prevalence of other organ failures was also higher in patients with 2 or 3 precipitants. Consistent with these results, the number of precipitants at diagnosis also correlated directly with the grade of severity of ACLF (I, II or III), the severity of prognostic scores, the need for intensive care, the frequency of treatment with mechanical ventilation or renal replacement therapy, and the 90-day cumulative incidence of mortality (Table 3, Fig. 3C). Systemic inflammation, as estimated by the white blood cell count and blood levels of neutrophils and monocytes, increased in parallel with the number of precipitants (Table 3, Fig. 3D-G). Serum levels of CRP were also significantly higher in patients with 1 or ≥2 precipitants than in patients with indeterminate precipitants.

Role of treatment of precipitant in prevention of AD-ACLF and improvement of survival

Proven bacterial infections (details in the supplementary information)

A total of 376 patients (29.5%) developed 440 bacterial infections, of which 66.2% were culture positive. Nosocomial episodes and severe sepsis or shock predominated in infections diagnosed as a precipitant of ACLF during follow-up, while multidrug resistant (MDR) strains were involved in 18.9% of all infections and 29.4% of culture positive episodes. Also, prevalence of infections caused by MDR strains was significantly higher in infections precipitating ACLF during follow-up and in those causing severe sepsis/shock (Table S6). Overall, resolution of infection was significantly lower in episodes caused by MDR bacteria (57.8% *vs.* 82.1%, $p<0.0001$). The lower resolution rate of MDR-infections was associated with higher 28-day and 90-day mortality in patients with AD-ACLF, but not in infections precipitating AD (Table S7).

Classic antibiotic strategies were used frequently as first-line therapy in community-acquired and healthcare-associated infections (Table 4). In contrast, nosocomial episodes were more frequently treated with piperacillin-tazobactam (20.4%) or with broader MDR-covering strategies (38.8%). Remarkably, a significant percentage of patients with severe sepsis/shock still received classic schemes not covering MDR strains (40.5%). Empirical MDR-covering strategies were more effective in infection resolution (with regard to clinical response and microbiological susceptibility) than classic schemes (Table 4, Table S8). Adequacy of empirical antibiotic therapy was defined as resolution of infection without further escalation or bacterial susceptibility to initial antibiotics in culture positive infections. Importantly, adequacy of first-line antibiotic strategies decreased the cumulative incidence of developing ACLF in patients with AD (21.3% *vs.* 39.2%, Fig. 4A) and 90-day mortality in both AD (16.9% *vs.* 36.5%, Fig. 4B) and ACLF patients (44.2% *vs.* 66.2%, Fig. 4C).

Severe alcoholic hepatitis

Steroids were administered in 49 patients with severe alcoholic hepatitis (18.9%), 30 patients with AD and 19 patients with ACLF at inclusion. The 28-day and 90-day mortality rates were not significantly different between patients receiving or not receiving steroids, neither in the whole population nor in patients with AD or ACLF at inclusion (Table S9).

Discussion

The PREDICT study offers a comprehensive investigation characterizing the precipitants of AD and demonstrating their impact on the development of AD-ACLF and prognosis.

The CANONIC study characterized the AD-ACLF phenotype and attributed an important role to precipitants in its development. The PREDICT study, designed to assess the period prior to ACLF,[2] identified 3 different clinical courses in AD-No ACLF: pre-ACLF, AD-UDC and AD-SDC. Moreover, the PREDICT study assessed how type and number of precipitants influence the

clinical course and the prognosis in patients with both AD-No ACLF and AD-ACLF. This prospective and detailed characterization offers diagnostic criteria for precipitants and rationalizes the identification of precipitants in patients with cirrhosis and AD. The criteria used for the diagnosis of precipitants considered the severity of the precipitant, the time interval between onset/resolution of the precipitant and onset of the AD episode, and their higher prevalence in patients with AD-ACLF than in patients with AD-No ACLF, which are more objective than the traditional principles of chronology and potential of organ injury.

Among the events recorded and evaluated in the PREDICT study, only 4 fulfilled the properties of precipitants (chronology, severe organ injury or higher prevalence in the AD-ACLF phenotype): proven bacterial infections, severe alcoholic hepatitis, GI bleeding with shock and toxic encephalopathy. While paracentesis without intravenous albumin administration and TIPS did not induce organ impairment (TIPS even improves survival in GI bleeding and ACLF[16,17]), the prevalence of drug-induced liver or renal injury and of other potential precipitants proposed by the investigators was extremely low, frequently below 1%, suggesting that they could be coincidental rather than precipitants.

Proven bacterial infections and severe alcoholic hepatitis were by far the most prevalent precipitants observed in the PREDICT study. Prevalence of GI bleeding associated with shock and toxic encephalopathy was considerably lower in both groups. In patients with AD-No ACLF, the prevalence of proven bacterial infections or severe alcoholic hepatitis and the number of precipitants present at enrolment were higher in patients with AD-Pre-ACLF than in patients with AD-UDC and AD-SDC. In contrast, no differences were found in the prevalence of these precipitants between patients with UDC or SDC. These findings suggest that precipitants are determinants of the development of the AD-Pre-ACLF sub-phenotype, which is associated with a worse clinical course and prognosis in patients with AD-No ACLF. Importantly, in >60% of the patients in the AD-No ACLF cohort, precipitating events were indetermined at enrolment, while this was the case in only 35% of the patients with AD-ACLF. These data suggest that AD-No ACLF develops more frequently in the context of endogenous mechanisms (e.g. progressive liver disease, bacterial translocation), confirming the CANONIC study and underlining the solidity of the PREDICT study.

The type of precipitant was associated with different clinical characteristics, but a similar clinical course and mortality. This finding is not surprising, since reactivation or superimposed hepatitis, also showed different prevalences of specific organ failures in AD-ACLF, but similar outcome as AD-ACLF triggered by extrahepatic precipitants (e.g GI bleeding).[18] The explanation may be due to the sequence of mechanisms. Bacterial infections would induce systemic inflammation as the primary mechanism, leading to predominantly circulatory and renal dysfunction or failure. In contrast, the direct insult of alcohol toxicity induces hepatic inflammation and cell death as primary mechanisms culminating in liver and coagulation dysfunction or failure. Importantly, systemic inflammation aggravates and leads to an identical syndrome through distinct pathophysiological pathways. For this reason, the criterion of severity (either systemic inflammation or organ injury) of the event is crucial to identify the precipitant.

Finally, our results show that the number of precipitants was an important determinant for the characteristics, the clinical course severity and the 90-day cumulative incidence of mortality. Not only that multiple (2 or more) precipitants trigger AD-ACLF (one in 5 patients) and is exceptional (one in 20 patients) in AD-No ACLF, but also the intensity of systemic inflammation, the prevalence of organ failures, the need for organ support, and the prognostic scores increased progressively from patients with indeterminate precipitants to patients with 1 and multiple precipitants. Therefore, when precipitants are defined according to these criteria, they are synergistic and additive in the worsening of outcome, despite different clinical characteristics.

Almost all (>96%) patients with precipitants showed proven bacterial infection and/or severe alcoholic hepatitis, either alone or in combination with other precipitants. This overwhelming prevalence of proven bacterial infections and/or severe alcoholic hepatitis as precipitants suggests that diagnosing, preventing and treating these precipitants is paramount to improve the prognosis of patients with decompensated cirrhosis.

PREDICT demonstrates that proven bacterial infections require specific and adequate treatment for prevention of AD-ACLF. This is of particular importance since MDR may challenge empirical treatments. The overall prevalence of MDR bacterial infections in PREDICT was in line with that reported in recently published multicenter investigations[19,20] and MDR bacterial infections were more severe (higher rate of severe sepsis/shock and of ACLF), associated with a lower resolution rate and higher 28-day and 90-day mortality,[19–21] underlining the importance of treatment of precipitants, thus confirming that definition and selection of precipitants has been chosen adequately. Importantly, classic antibiotics (1st-3rd generation cephalosporins, quinolones) have an unacceptable efficacy (<40%) in nosocomial infections, or in those with severe sepsis or shock. These findings support the current recommendations on the use of empirical broad schemes, according to specific epidemiological pattern of antibiotic resistance,[22–24] in the nosocomial setting and in severe sepsis/shock with rapid de-escalation strategies.[13]

In summary, of the clinical events explored as potential precipitants in the PREDICT study, only 4 (proven bacterial infections, severe acute alcoholic hepatitis, GI bleeding associated with shock and toxic encephalopathy) fulfilled the diagnostic criteria of precipitants. Proven bacterial infections and severe alcoholic hepatitis were present in the absolute majority (>96%) of patients. However, no precipitating event could be identified in 2/3 of AD-No ACLF patients and in 1/3 AD-ACLF patients. The prevalence and number of precipitants increased with severity of the AD-sub-phenotype form SDC/UDC to pre-ACLF and ACLF, which were also directly related with clinical course severity and short-term mortality in patients with AD. Our data, therefore, strongly suggest that precipitants are significantly associated with the clinical course and prognosis of patients with AD and specific preventive and therapeutic strategies for these precipitants are required to improve outcomes in decompensated cirrhosis.

Abbreviations

ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF, chronic liver failure; CIF, cumulative incidence of function; CRP, C-reactive protein; GI, gastrointestinal; OF, organ failure; MDR, multidrug resistant; MELD, model of end-stage liver disease; PE, precipitating event; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.

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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, DLS, AA, WL, ES, RB, MJ, CS, TR, JA, PG, WB, SZ, CR, TB, AS, KVD, 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

Data availability statement
While some of the data of this paper will be available upon request, the majority of the data are not suitable for posting as they are confidential.

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Supplementary data

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