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

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Supplementary methods

Patients

The PREDICT study (ClinicalTrials.gov number, NCT03056612) is a European, investigator-initiated, multicenter, prospective, observational study performed in 48 university hospitals 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 [1]. Briefly, 1071 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. The diagnosis of cirrhosis was based on previous liver biopsy findings or a composite of clinical signs and laboratory test results and imaging. Diagnostic criteria of AD were based on the presence of ascites, encephalopathy, gastrointestinal hemorrhage or infections (the latter only in patients with prior decompensation) or any combination of these at non-elective hospital admission. Diagnosis of ACLF at enrolment or during follow-up was performed according to the EASL-CLIF criteria [2, 3]. Organ failure and organ dysfunction were defined according to the Chronic Liver Failure (CLIF)- Consortium organ failure (OF) score [4].

The stratification of patients with the AD-No ACLF phenotype into AD-pre-ACLF, AD-UDC and AD-SDC sub-phenotypes cohorts was performed using previously described criteria [1]. Therefore, patients included in the PREDICT study were stratified into four different groups (**Fig. 1**). 1. AD-ACLF: 202 patients with ACLF at enrolment; 2. AD-Pre ACLF: 218 patients without ACLF at enrolment who developed ACLF during a 3-month follow-up period after enrolment; 3. AD-UDC: 233 patients who did not develop ACLF during the 3-month follow-up period, but required at least one hospital readmission; 4. AD-

SDC: 620 patients who neither developed ACLF nor required hospital readmissions during the 3-month follow-up period.

Study Design

The PREDICT study [1] was designed to explore in detail two important time-periods during the clinical course of AD. The first period covered the first 90 days prior to hospital admission, with particular attention on the first two weeks prior to admission - the period in which most PEs can develop. The second period, the "follow-up period", covered the first three months after admission. During this period the early clinical course of patients with ACLF-phenotype and AD-No ACLF sub-phenotypes was assessed.

Pre-specified clinical and standard laboratory data were obtained at enrollment and during follow-up visits. The design of the PREDICT study is described in detail elsewhere [1].

Data obtained at enrollment.

Most patients were enrolled on the first or second day of hospital admission. Two categories of pre-specified information were obtained at enrolment. The first category included general characteristics and demographic data, specific data related to the AD episode, physical examination, standard laboratory analysis at enrollment, and results from the bacteriological cultures routinely performed in patients with suspected bacterial infections.

The second category of pre-specified data obtained at enrollment were related to the patient's medical history. The electronic case report form (eCRF) of the PREDICT study was specifically designed to capture the characteristics of any potential PE prior to enrollment, including severity and temporal

relationship to the onset of the AD.

Data obtained during follow-up

After enrollment, patients were closely followed-up for a period of three months with frequent pre-specified sequential visits and laboratory determinations. Data on liver transplantation or death and causes of death were prospectively collected three, six and 12 months after enrollment in all patients.

Identification of PEs of AD-No ACLF and AD-ACLF

In order to identify the PE an adjudication committee of the PREDICT study, which included JT, JF, RM and VA, was 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 relevant and "true" PEs (hereafter called PEs), which are highly likely to precipitate both phenotypes of AD according to the criteria defined below.

General principles for PE identification

To provide the PREDICT study with a reliable method to identify PEs, the following general principles were agreed upon:

1. PEs 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 cause).
2. When assessing the potential of hepatotoxic, nephrotoxic or neurotoxic drugs as PEs, the lack of liver, kidney or brain dysfunction or failure, respectively, as defined by the CLIF-C OF score [4] rule out drug-induced organ toxicity as a

PE.

3. As suggested by the results of the CANONIC study [2, 3], clinically identifiable, relevant and true PEs should have a higher prevalence in patients with AD-ACLF than in those with AD-no ACLF.
4. PEs should precede or coincide with the onset of AD-ACLF. The time period between the PE and the onset of AD-ACLF, however, is heterogeneous, depending on the PE.
5. Any event developing after the onset of AD-ACLF is a complication or a coincidental event but not a PE.

Specific criteria for the identification of PEs from the list proposed by the adjudication committee

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

Bacterial infections. Infections were considered to be potential PEs if they were diagnosed at the time of or solved within the 48-hour period that preceded the onset of AD. Infections which occurred before AD but were solved before this 48-hour time frame were considered unrelated events. Previous data have shown that the cytokine response to bacterial infections, even efficiently treated, may last up to 48 hours and may induce the onset of AD [5]. When infections were diagnosed between the first and the 10^{th} day after the onset of AD, they were considered complications of AD [6]. Proven bacterial infections were defined as previously described [6] and in accordance with the EASL guidelines [3].

Definitions of bacterial infection. Diagnostic criteria of proven bacterial infections included the following: spontaneous bacterial peritonitis (SBP): polymorphonuclear (PMN) cell count in ascitic fluid ≥250/mm^3; urinary tract infection (UTI): abnormal urinary sediment (>10 leukocytes/field) and positive urinary culture or uncountable leukocytes per field if negative cultures; spontaneous bacteremia: positive blood cultures and no cause of bacteremia; secondary bacteremia: a) catheter-related infection (positive blood and catheter cultures), b) bacteremia occurring within 24 hours after an invasive procedure; pneumonia: clinical signs of infection and new infiltrates on chest x-ray; bronchitis: clinical features of infection, no radiographic infiltrates and positive sputum culture; skin and soft tissue infections (SSTI): clinical signs of infection associated with swelling, erythema, heat and tenderness in the skin; cholangitis: cholestasis, right upper quadrant pain and/or jaundice and radiological data of biliary obstruction; spontaneous bacterial empyema (SBE): PMN count in pleural fluid ≥500/mm³ (250/mm³ if positive culture); secondary peritonitis: PMN count in ascitic fluid ≥250/mm³ and evidence (abdominal CT/ surgery) of an intraabdominal source of infection; *Clostridium difficile* infection (CDI): positive stool toxin in a patient with diarrhea.

Unproved bacterial infection: presence of fever (≥ 38ºC) and leukocytosis (white blood cell count ≥12.000/mm^3) requiring antibiotic therapy without any identifiable source.

Infections diagnosed at admission or within two days after admission were classified as healthcare-associated (HCA) in patients with a prior contact with the healthcare environment (hospitalization or short term-admission for at least two days in the previous 90 days, residence in a nursing home or a long-

term care facility or chronic hemodialysis). The remaining infections were considered community-acquired when they were present at admission or developed within the first 48 hours after hospitalization and nosocomial when the diagnosis was made thereafter [6, 7]. MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Extensively drug resistant (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories and pandrug resistant (PDR) as non-susceptibility to all currently available agents [8]. The following bacteria were considered MDR in the current study: extended-spectrum beta-lactamase (ESBL, mainly *Escherichia coli* and *Klebsiella pneumoniae)* or desrepressed chromosomic AmpC ß-lactamase-producing *Enterobacteriaceae* (*Enterobacter or Citrobacter spp),* carbapenem-resistant *Klebsiella pneumoniae,* carbapenem-resistant *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia,* carbapenem-resistant *Acinetobacter baumanii*, *Burkholderia cepacia*, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-susceptible and vancomycin-resistant *Enterococcus faecium* (VSE, VRE).

Severe sepsis was defined by the presence of SIRS and at least one acute organ failure. Septic shock was diagnosed by the presence of data compatible with SIRS and need of vasopressor drugs in the setting of hypotension [9].

Infections were considered cured when all clinical signs of infection disappeared and on the presence of: a) urinary infections: normal urine sediment and negative urine culture; b) spontaneous or secondary bacteremia: negative control cultures after antibiotic treatment; c) pneumonia: normal chest X-ray and negative control cultures if positive at diagnosis; d) bronchitis:

negative bronchial aspirate/sputum culture; e) SSTI: normal physical exam of the skin and negative c ontrol cultures if positive at diagnosis; f) cholangitis: improvement of cholestasis, resolution of clinical symptoms and negative control cultures if positive at diagnosis; g) SBP and SBE: PMN cell count in ascitic/pleural fluid < 250/mm³ and negative control cultures if positive at diagnosis. Resolution of the rest of infections was based on conventional clinical criteria.

Definitions on antibiotic therapy

Three types of empirical antibiotic strategies were considered: 1) “classic” strategies including first to third-generation cephalosporins, amoxicillin clavulanic-acid/cloxacillin or quinolones, 2) regimens using piperacillin-tazobactam, and 3) broader MDR strategies including regimens using carbapenems or cefepime± glycopeptides (or linezolid/daptomycin) or tigecycline.

The criteria used to consider an initial antibiotic therapy appropriate included

1) microbiological: If an antibiotic with appropriate in vitro activity against isolated pathogen(s) was administered at diagnosis of infection.

2) clinical: a) culture-negative infection: antibiotic strategies administered at the time of diagnosis solving the infection without need for further escalation or b) culture-positive infections: antibiotic with appropriate in vitro activity against the isolated pathogen(s) administered at diagnosis of infection.

Otherwise, the initial therapy was considered inappropriate [6]. Time to antibiotic therapy administration after diagnosis of infection was not recorded.

Alcohol-related liver injury. Alcoholic hepatitis was diagnosed according to the clinical criteria of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) [10], which includes the presence of at least three of the following:

1. Active alcoholism, as defined by more than three consecutive months of an alcohol intake higher than 60 g/day for males and 40 g/day for females.

2. Serum bilirubin>3 mg/dl;

3. AST>50 IU/; 4. AST/ALT>1.5 (maximal value of AST or ALT not exceeding 400 U/l).

These criteria are in line with the clinical diagnosis of alcoholic hepatitis according to existing EASL guidelines [11]. Alcoholic hepatitis was considered severe if patients showed CLIF-Consortium AD score ≥ 50 points [12], ore presence of ACLF (**Table 1**).

Gastrointestinal bleeding. Gastrointestinal bleeding was considered a PE if occurring within seven days prior to the onset of AD-ACLF. Moreover, because hemorrhagic shock, which is a potential cause of organ damage, had not been previously analyzed as a PE [1], it was included in our list of candidates for PEs (**Table.1**).

Drug-induced organ injury.

1. *Drug-induced liver injury* was considered a potential PE when the hepatotoxic drug was administered within one month prior to the onset of AD-ACLF and the patient presented with hepatocellular (serum AST or ALT exceeding 3-fold the upper limit of normal), cholestatic (serum alkaline phosphatase exceeding 2-fold the upper limit of normal) or mixed liver injury as defined by Hy´s law and FDA guidance as described in the recent EASL guidelines [13] as well as liver dysfunction (for patients with AD-No ACLF,

bilirubin > 6 mg/dl) or liver failure (for patients with AD-ACLF, bilirubin > 12 mg/dl). Potential hepatotoxic drugs were classified as described elsewhere [14]. Only drugs from groups A and B of this classification were considered potential candidates for liver toxicity.

2. *Drug-induced kidney injury* was considered a potential PE when the nephrotoxic drug was administered within seven days prior to the onset of AD-ACLF and patients presented with either renal dysfunction or renal failure according to the CLIF-C OF score. Diuretic-induced renal dysfunction or renal failure was not considered as a nephrotoxic condition.

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

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

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

The adjudication committee assessed nine additional, infrequent conditions (viral hepatitis and other viral infections, decompensated cardiopulmonary diseases, dehydration, large hematomas, acute pancreatitis, acute portomesenteric vein thrombosis, autoimmune diseases, cerebrovascular accident and intestinal occlusion) that were considered by the attending investigators as potential PEs.

Supplementary results

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

Bacterial infections:

Overall bacterial infections and infections caused by MDROs

Table S6 shows prevalence, type, clinical and epidemiological characteristics of proven bacterial infections diagnosed in the whole series and in patients with AD and ACLF. A total of 376 patients (29.5%) developed 440 bacterial infections. Prevalence of infection was significantly higher in ACLF than in AD patients (35.6% vs 22.3%). UTI (n=113), SBP (n=92) and pneumonia (n=87) were the most frequent proven infections in the whole series. Nosocomial episodes and severe sepsis or shock predominated in infections diagnosed as PE of ACLF during follow-up.

A total of 282 infections were culture-positive (66.2%). Isolation rate was similar in infections precipitating AD and ACLF. Prevalence of infections caused by resistant strains was 18.9% if all infections are considered and 29.4% in culture-positive episodes. Prevalence of MDR infections was significantly higher in infections precipitating ACLF during follow-up (all infections: 40.8%; culture-positive infections: 59.6%) than in those precipitating ACLF (26.3% and 39.4%, respectively) or AD at inclusion (9.8% and 15.8%, respectively; $p<0.0001$). MDR bacteria were also more frequently isolated in nosocomial infection than in HCA and CA episodes (29.1 % vs 21.8% and 13.6%, respectively). Finally, MDROs were more prevalent in infections causing severe sepsis/shock (33.3% vs. 15.1%, $p<0.001$).

Impact of antibiotic resistance on clinical outcome

Table S7 shows the clinical outcome of infections caused by MDROs in comparison to that observed in infections caused by susceptible bacteria or with no microbiological isolation in the whole series and in infections precipitating AD and ACLF. As a whole, resolution of infection was significantly lower in episodes caused by MDROs (57.8% vs. 82.1%, p<0.0001). Infections caused by MDR strains showed higher prevalence of severe sepsis/shock (40.7% vs. 21.6%, p=0.0004), ACLF (72.3% vs. 42.0%, p<0.0001), 28-day (40.8% vs. 21.7%, p=0.0006) and 90-day mortality (48.7% vs. 30.7%, p= 0.003). The negative impact on clinical outcome of antibiotic resistance was observed in infections precipitating ACLF but not in those precipitating AD.

Type and adequacy of first line antibiotic strategies

Two main factors influenced first line antibiotic schemes: the site of acquisition of infection and severity (**Table 4 and S8**). Classic antibiotic strategies were used frequently in CA and HCA infections as first line therapy (69.6%). In contrast, nosocomial episodes were more frequently treated with piperacillin-tazobactam (20.4%) or with broader MDR covering strategies (38.8%). Remarkably, a relevant percentage of patients with severe sepsis/shock still received classic schemes not covering MDROs (40.5%).

The eCRF did not capture the time to antibiotic therapy administration after diagnosis of infection on detail. Variability on the duration of antibiotic therapy was remarkable, making it impossible to draw valid conclusions on the important point raised by the reviewer. Median of days of antibiotic therapy was nine days (Q1-Q3: 6-16); with no differences between infections caused by MDROs and those caused by susceptible strains or without isolation (see **Table S10A**.) Moreover, there were also marked differences in the duration of therapy

according to type and severity of bacterial infections, as outlined in **Table S10B**.

The efficacy of classic antibiotics, piperacillin-tazobactam and broader MDR empirical strategies is shown in **Tables 4 and S8**. In the whole series, empirical MDR covering strategies were more effective (higher infection resolution rate or higher adequacy to the microbiological susceptibility) than classic schemes in almost all clinical scenarios. Adequacy of classic antibiotics was extremely low in nosocomial infections (30.9% and 35.7% according to clinical and microbiological criteria, respectively) and in severe sepsis/shock (20.6% and 30.8%, respectively). Inadequacy of first line antibiotic strategies increased the cumulative incidence of developing ACLF in patients with AD (39.2% vs 21.3%, p=0.004) and 90-day mortality in both AD (36.5% vs. 16.9%; p=0.0009) and ACLF patients (66.2% vs. 44.2%) (**Figure 4**).

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Table S1. Differences in demographic data and etiology, clinical and laboratory data at enrollment, specific treatments during follow-up and mortality between patients with AD-No ACLF and with AD-ACLF.

	AD-No ACLF (n = 1071)	AD-ACLF (n = 202)	*p value*
Demographic data and etiology			
Age, yr, mean ± SD	59.2 +/- 10.78	57.0 +/- 13.08	0.0282
Male sex, n (%)	727 (67.9)	140 (69.3)	0.68
Alcoholic cirrhosis, n (%)	748 (69.9)	156 (77.2)	0.0353
Clinical and laboratory data			
Systemic hemodynamics, mean ± SD			
Mean arterial pressure (mmHg)	84.4 +/- 12.57	80.5 +/- 13.05	<.0001
Heart rate (bpm)	81.0 +/- 15.41	85.1 +/- 19.19	0.0053
Complications, n (%)			
Ascites	758 (70.8)	158 (78.2)	0.0308
Hepatic encephalopathy	306 (28.6)	133 (65.8)	<.0001
Gastrointestinal hemorrhage	152 (14.2)	34 (16.8)	0.33
Organ failures, n (%)			
Liver failure	69 (6.4)	83 (41.1)	<.0001
Renal failure	0 (0.0)	105 (52.0)	<.0001
Brain failure	23 (2.1)	40 (19.8)	<.0001
Coagulation failure	20 (1.9)	60 (29.7)	<.0001
Cardiovascular failure	3 (0.3)	29 (14.4)	<.0001
Respiratory failure	1 (0.1)	12 (5.9)	<.0001
Biomarkers of systemic inflammation, median (IQR)			
White blood cell count, $x10^9$/L	6.36 (4.36 - 8.98)	9.05 (6.73 - 13.38)	<.0001
Neutrophil count, $x10^9$/L	4.50 (2.60 - 6.75)	7.50 (4.60 - 11.00)	<.0001
Lymphocyte count, $x10^9$/L	1.20 (0.70 - 1.55)	1.00 (0.50 - 1.45)	0.15
Monocyte count, $x10^9$/L	0.55 (0.41 - 0.95)	0.95 (0.55 - 1.30)	<.0001
Serum C-reactive protein, mg/L	17.20 (6.90 - 37.30)	26.00 (10.10 - 53.08)	<.0001
Measurements estimating organ function			
Serum bilirubin, mg/dL, median (IQR)	2.63 (1.40 - 5.57)	6.92 (2.04 - 19.94)	<.0001
Serum albumin, g/dL, mean ± SD	2.9 +/- 0.62	2.9 +/- 0.66	0.54
Total cholesterol, mg/dL, median (IQR)	113.15 (89.23 - 147.50)	78.30 (52.75 - 110.25)	<.0001
International normalized ratio, median (IQR)	1.45 (1.26 - 1.70)	1.80 (1.44 - 2.60)	<.0001
Serum creatinine, mg/dL, median (IQR)	0.89 (0.69 - 1.20)	1.96 (1.01 - 2.61)	<.0001
Serum sodium, mEq/L, mean ± SD	135.1 +/- 5.26	133.7 +/- 6.96	0.0092
Prognostic scores, mean ± SD			
Child-Pugh score	9.0 +/- 1.84	10.6 +/- 2.34	<.0001
MELD score*	16.0 +/- 5.14	26.4 +/- 6.82	<.0001
MELD-Na score*	19.0 +/- 5.60	28.5 +/- 6.38	<.0001
CLIF-C organ failure score**	6.9 +/- 0.98	9.9 +/- 2.16	<.0001
CLIF-C AD score**	52.3 +/- 8.06	-	
Specific treatments during follow-up and mortality			
Specific treatments, n (%)			
Intensive care	101 (9.40)	42 (20.8)	<.0001
Renal replacement	19 (1.80)	17 (8.40)	<.0001
Mechanical ventilation	24 (2.20)	25 (12.40)	<.0001
Vasopressors	183 (17.10)	85 (42.10)	<.0001
90-day liver transplantation	64 (6.28)	25 (12.95)	0.0011
Mortality from enrollment, n (%)			
90-day mortality	166 (15.50)	81 (40.10)	<.0001

* MELD: Model for End-Stage Liver Disease score

** CLIF-C: Chronic Liver Failure Consortium

Chi-square or Fisher's tests performed in percentages comparisons.

For continuous variables comparisons, Student T-test for normally distributed variables or Wilcoxon rank sum test for not-normally distributed variables were used.

Table S2. Demographic data and etiology, clinical and laboratory data at inclusion, specific treatments during study and mortality in patients included in the AD-No ACLF cohort with proven bacterial infection or severe alcoholic hepatitis as unique precipitant.

	Proven Bacterial Infections (n = 188)	Severe Alcoholic Hepatitis (n = 151)
Demographic data and etiology		
Age, yr, mean ± SD	59.6 +/- 11.20	56.5 +/- 9.55
Male sex, n (%)	124 (66.0)	103 (68.2)
Alcoholic cirrhosis, n (%)	107 (56.9)	151 (100.0)
Clinical and laboratory data		
Systemic hemodynamics, mean ± SD		
Mean arterial pressure (mmHg)	82.2 +/- 12.95	84.6 +/- 12.35
Heart rate (bpm)	81.2 +/- 14.71	86.6 +/- 15.43
Complications, n (%)		
Ascites	128 (68.1)	113 (74.8)
Hepatic encephalopathy	58 (30.9)	34 (22.5)
Gastrointestinal hemorrhage	6 (3.2)	16 (10.6)
Organ failures, n (%)		
Liver failure	9 (4.8)	27 (17.9)
Renal failure	0 (0.0)	0 (0.0)
Brain failure	4 (2.1)	1 (0.7)
Coagulation failure	3 (1.6)	3 (2.0)
Cardiovascular failure	1 (0.5)	1 (0.7)
Respiratory failure	0 (0.0)	0 (0.0)
Biomarkers of systemic inflammation, median (IQR)		
White blood cell count, $x10^9$/L	6.99 (4.14 - 10.26)	8.55 (6.70 - 11.31)
Neutrophil count, $x10^9$/L	4.35 (2.50 - 7.70)	5.85 (4.20 - 7.70)
Lymphocyte count, $x10^9$/L	0.88 (0.69 - 1.34)	1.57 (1.00 - 1.87)
Monocyte count, $x10^9$/L	0.62 (0.45 - 0.96)	0.87 (0.63 - 1.22)
Serum C-reactive protein, mg/L	36.65 (19.80 - 75.40)	21.50 (10.10 - 38.34)
Measurements estimating organ function		
Serum bilirubin, mg/dL, median (IQR)	2.98 (1.46 - 5.68)	6.50 (3.85 - 10.20)
Serum albumin, g/dL, mean ± SD	2.8 +/- 0.63	2.7 +/- 0.48
Total cholesterol, mg/dL, median (IQR)	98.24 (68.54 - 137.40)	124.05 (93.2 - 156.70)
International normalized ratio, median (IQR)	1.47 (1.30 - 1.70)	1.67 (1.47 - 1.96)
Serum creatinine, mg/dL, median (IQR)	0.90 (0.70 - 1.19)	0.81 (0.63 - 1.15)
Serum sodium, mEq/L, mean ± SD	134.2 +/- 5.11	133.0 +/- 5.02
Prognostic scores, mean ± SD		
Child-Pugh score	9.1 +/- 1.84	10.2 +/- 1.38
MELD score*	16.1 +/- 5.03	20.1 +/- 4.59
MELD-Na score*	19.7 +/- 5.17	23.6 +/- 4.32
CLIF-C organ failure score**	7.0 +/- 1.05	7.3 +/- 1.09
CLIF-C AD score**	53.4 +/- 8.68	57.3 +/- 5.67
Specific treatments and mortality		
Specific treatments from inclusion, n (%)		
Intensive care	22 (11.7)	14 (9.3)
Renal replacement	5 (2.7)	3 (2.0)
Mechanical ventilation	5 (2.7)	3 (2.0)
Vasopressors	30 (16.0)	29 (19.2)
90-day liver transplantation	19 (10.56)	7 (4.9)
Mortality from inclusion, n (%)		
90-day mortality	38 (20.21)	29 (19.21)

* MELD: Model for End-Stage Liver Disease score; ** CLIF-C: Chronic Liver Failure Consortium

Chi-square or Fisher's tests performed in percentages comparisons. For continuous variables comparisons, Student T-test for normally distributed variables or Wilcoxon rank sum test for not-normally distributed variables were used.

Table S3. Demographic data and etiology, clinical and laboratory data at inclusion, specific treatments during study and mortality in patients included in the AD-No ACLF cohort according to the number of precipitants

	indeterminate PE (n=662)	One PE (n=354)	Two or more PEs (n=55)	*p* value
Demographic data and etiology of cirrhosis				
Age, yr, mean ± SD	59.9 +/- 10.91	58.1 +/- 10.55[b]	58.8 +/- 10.15	0.0384
Male sex, n (%)	452 (68.3)	237 (66.9)	38 (69.1)	0.89
Alcoholic cirrhosis, n (%)	425 (64.3)	270 (76.3)[b]	53 (96.4)[a]	<.0001
Data at inclusion				
Systemic hemodynamics, mean ± SD				
Mean arterial pressure (mmHg)	85.1 +/- 12.55	83.1 +/- 12.75[b]	83.9 +/- 10.89	0.0428
Heart rate (bpm)	79.2 +/- 15.27	83.6 +/- 15.26[b]	86.0 +/- 14.77[b]	<.0001
Complications, n (%)				
Ascites	463 (69.9)	251 (70.9)	44 (80.0)	0.28
Hepatic encephalopathy	181 (27.3)	101 (28.5)	24 (43.6)[a]	0.0367
Gastrointestinal hemorrhage	117 (17.7)	31 (8.8)[b]	4 (7.3)[b]	0.0002
Organ failures, n (%)				
Liver failure	25 (3.8)	36 (10.2)[b]	8 (14.5)[b]	<.0001
Renal failure	0 (0.0)	0 (0.0)	0 (0.0)	.
Brain failure	17 (2.6)	5 (1.4)	1 (1.8)	0.47
Coagulation failure	10 (1.5)	7 (2.0)	3 (5.5)	0.11
Cardiovascular failure	1 (0.2)	2 (0.6)	0 (0.0)	.
Respiratory failure	1 (0.2)	0 (0.0)	0 (0.0)	.
Biomarkers of systemic inflammation, median (IQR)				
White blood cell count, x10^9/L	5.41 (4.05 - 7.60)	7.58 (5.30 - 10.32)[b]	8.33 (6.58 - 13.49)[a]	<.0001
Neutrophil count, x10^9/L	3.24 (2.40 - 5.35)	5.21 (3.15 - 7.67)[b]	6.30 (4.27 - 10.29)[a]	<.0001
Lymphocyte count, x10^9/L	0.95 (0.65 - 1.45)	1.22 (0.68 - 1.97)[b]	1.15 (0.85 - 1.70)	0.0040
Monocyte count, x10^9/L	0.53 (0.36 - 0.75)	0.79 (0.55 - 1.11)[b]	0.99 (0.77 - 1.44)[a]	<.0001
Serum C-reactive protein, mg/L	12.10 (5.00 - 24.50)	27.00 (13.18 - 56.33)[b]	46.75 (19.00 - 73.95)[a]	<.0001
Measurements estimating organ function				
Serum bilirubin, mg/dL, median (IQR)	2.05 (1.20 - 3.62)	4.04 (2.05 - 7.78)[b]	7.10 (4.00 - 9.89)[a]	<.0001
Serum albumin, g/dL, mean ± SD	3.0 +/- 0.63	2.8 +/- 0.57[b]	2.7 +/- 0.55[b]	<.0001
Total cholesterol, mg/dL, median (IQR)	117.0 (95.00 - 143.00)	109.00 (80.00 - 143.00)	114.00 (73.66 - 159.06)	0.44
International normalized ratio, median (IQR)	1.40 (1.21 - 1.60)	1.56 (1.35 - 1.80)[b]	1.70 (1.48 - 1.90)[a]	<.0001
Serum creatinine, mg/dL, median (IQR)	0.90 (0.69 - 1.20)	0.86 (0.67 - 1.18)	0.86 (0.70 - 1.10)	0.26
Serum sodium, mEq/L, mean ± SD	135.9 +/- 5.17	133.8 +/- 5.13[b]	133.5 +/- 5.37[b]	<.0001
Prognostic scores, mean ± SD				
Child-Pugh score	8.6 +/- 1.77	9.5 +/- 1.74[b]	10.6 +/- 1.52[a]	<.0001
MELD score*	14.6 +/- 4.64	17.8 +/- 5.20[b]	20.1 +/- 4.54[a]	<.0001
MELD-Na score*	17.4 +/- 5.24	21.3 +/- 5.24[b]	23.4 +/- 4.47[a]	<.0001
CLIF-C organ failure score**	6.7 +/- 0.86	7.2 +/- 1.07[b]	7.5 +/- 1.05[a]	<.0001
CLIF-C AD score**	50.4 +/- 7.64	54.9 +/- 7.76[b]	58.9 +/- 6.63[a]	<.0001
Specific treatments and mortality				
Specific treatments from inclusion, n (%)				
Intensive care	50 (7.6)	41 (11.6)[b]	10 (18.2)[b]	0.0083
Renal replacement	9 (1.4)	8 (2.3)	2 (3.6)	0.32
Mechanical ventilation	12 (1.8)	8 (2.3)	4 (7.3)[b]	0.0316
Vasopressors	106 (16.0)	67 (18.9)	10 (18.2)	0.48
90-day liver transplantation	36 (5.7)	27 (8.0)	1 (2.0)	0.16
Mortality after inclusion, n (%)				
90-day mortality	80 (12.1)	69 (19.5)	17 (30.9)	<.0001

* MELD: Model for End-Stage Liver Disease score; ** CLIF-C: Chronic Liver Failure Consortium

[a] Significantly different from the group with inderteminate PE and group with 1 PE; [b] Significantly different from the group with inderteminate PE; [c] Significantly different from the group with 1 PE.

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.

Table S4. Demographic data and etiology, types and number of precipitants (PEs), clinical and laboratory data at diagnosis, specific treatments during follow-up and mortality in the integrated ACLF cohort (n = 420)

Demographic data and etiology	
Age, yr, mean ± SD	59.1 +/- 11.74
Male sex, n (%)	288 (68.6)
Alcoholic cirrhosis, n (%)	302 (71.9)
Precipitants at diagnosis*	
Type of PEs, n (%)	
Proven bacterial infections	186 (44.3)
Severe alcoholic hepatitis	145 (34.5)
GI bleeding with shock	20 (4.8)
Toxic encephalopathy	16 (3.8)
Number of PEs, n (%)	
Indeterminate PE	147 (35.0)
One PE	191 (45.5)
Two or more PEs	82 (19.5)
Clinical and laboratory data	
Systemic hemodynamics, mean ± SD	
Mean arterial pressure (mmHg)	79.0 +/- 13.08
Heart rate (bpm)	83.4 +/- 18.06
Complications, n (%)	
Ascites	295 (77.2)
Hepatic encephalopathy	235 (61.5)
GI bleeding	51 (13.4)
Organ failures, n (%)	
Liver failure	138 (36.1)
Renal failure	215 (56.3)
Brain failure	71 (18.6)
Coagulation failure	94 (24.7)
Cardiovascular failure	58 (15.3)
Respiratory failure	37 (9.7)
Biomarkers of systemic inflammation, median (IQR)	
White blood cell count, x109/L	8.69 (6.10 - 13.14)
Neutrophil count, $x10^9$/L	6.68 (4.20 - 11.05)
Lymphocyte count, $x10^9$/L	0.92 (0.51 - 1.45)
Monocyte count, $x10^9$/L	0.83 (0.51 - 1.24)
Serum C-reactive protein, mg/L	26.75 (12.40 - 52.00)
Measurements estimating organ function	
Serum bilirubin, mg/dL, median (IQR)	5.65 (2.00 - 15.95)
Serum albumin, g/dL, mean ± SD	2.9 +/- 0.72
Total cholesterol, mg/dL, median (IQR)	75.09 (50.10 - 109.41)
International normalized ratio, median (IQR)	1.78 (1.44 - 2.40)
Serum creatinine, mg/dL, median (IQR)	2.04 (1.05 - 2.61)
Serum sodium, mEq/L, mean ± SD	133.8 +/- 7.03
Scores at diagnosis	
Prognostic scores, mean ± SD	
Child-Pugh score	10.5 +/- 2.28
MELD score*	26.0 +/- 6.58
MELD-Na score*	28.2 +/- 6.13
CLIF-C organ failure score**	9.8 +/- 2.12
CLIF-C ACLF score**	49.5 +/- 9.05
ACLF grade	
ACLF grade I	222 (58.7)
ACLF grade II	110 (29.1)
ACLF grade III	46 (12.2)
Specific treatments and mortality	
Specificl treatments from ACLF, n (%)	

Intensive Care	88 (21.0)
Renal replacement therapy	35 (8.3)
Mechanical ventilation	47 (12.3)
Vasopressors	159 (37.9)
90-day liver transplantation	49 (11.67)
Mortality from diagnosis	
90-day mortality, n (%)	209 (49.76)

* MELD: Model for End-Stage Liver Disease score

** CLIF-C: Chronic Liver Failure Consortium

The number of precipitants reflects the sum of the numbers of the respective precipitant in Figure 3A.

Table S5. 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 with proven bacterial infection or severe alcoholic hepatitis as unique precipitant

	Proven bacterial infections (n = 111)	Severe alcoholic hepatitis (n = 73)
Demographic data and etiology		
Age, yr, mean ± SD	63.5 +/- 10.08	56.3 +/- 11.21
Male sex, n (%)	81 (73.0)	50(68.5)
Alcoholic cirrhosis, n (%)	68 (61.3)	73 (100.0)
Clinical and laboratory data		
Systemic hemodynamics, mean ± SD		
Mean arterial pressure (mmHg)	77.2 +/- 12.89	82.6 +/- 12.56
Heart rate (bpm)	79.7 +/- 16.72	84.8 +/- 17.17
Complications, n (%)		
Ascites	78 (75.0)	54 (79.4)
Hepatic encephalopathy	63 (60.6)	44 (64.7)
GI bleeding	8 (7.7)	2 (2.9)
Organ failures, n (%)		
Liver failure	22 (21.2)	38 (55.9)
Renal failure	68 (65.4)	26 (38.2)
Brain failure	20 (19.2)	8 (11.8)
Coagulation failure	18 (17.5)	23 (33.8)
Cardiovascular failure	20 (19.4)	2 (2.9)
Respiratory failure	17 (16.5)	3 (4.5)
Biomarkers of systemic inflammation, median (IQR)		
White blood cell count, $x10^9$/L	9.21 (6.33 - 13.35)	10.36 (7.61 - 13.60)
Neutrophil count, $x10^9$/L	7.22 (4.77 - 11.04)	7.87 (5.19 - 9.53)
Lymphocyte count, $x10^9$/L	0.70 (0.34 - 1.44)	1.25 (0.88 - 1.90)
Monocyte count, $x10^9$/L	0.85 (0.65 - 1.21)	1.00 (0.75 - 1.52)
Serum C-reactive protein, mg/L	40.50 (18.00 - 83.50)	24.46 (11.00 - 41.60)
Measurements estimating organ function		
Serum bilirubin, mg/dL, median (IQR)	3.24 (1.89 - 9.87)	13.30 (4.71 - 20.82)
Serum albumin, g/dL, mean ± SD	3.0 +/- 0.67	2.8 +/- 0.72
Total cholesterol, mg/dL, median (IQR)	49.00 (38.90 - 93.86)	91.50 (68.00 - 125.00)
International normalized ratio, median (IQR)	1.70 (1.40 - 2.18)	1.98 (1.52 - 2.67)
Serum creatinine, mg/dL, median (IQR)	2.15 (1.29 - 2.68)	1.39 (0.79 - 2.13)
Serum sodium, mEq/L, mean ± SD	134.0 +/- 6.41	132.6 +/- 6.03
Prognostic scores, mean ± SD		
Child-Pugh score	10.2 +/- 2.23	11.1 +/- 1.96
MELD score*	24.8 +/- 6.72	27.2 +/- 5.39
MELD-Na score*	27.3 +/- 5.93	29.5 +/- 5.19
CLIF-C organ failure score**	9.8 +/- 2.21	9.7 +/- 1.55
CLIF-C ACLF score**	51.2 +/- 8.75	48.6 +/- 6.54
ACLF grades, n (%)		
ACLF grade I	61 (59.8)	41 (61.2)
ACLF grade II	27 (26.5)	22 (32.8)
ACLF grade III	14 (13.7)	4 (6.0)
Special treatments and mortality		
Special treatments from ACLF, n (%)		
Intensive care	26 (23.4)	11 (15.1)
Renal replacement	10 (9.0)	3 (4.1)
Mechanical ventilation	17 (16.3)	4 (5.9)
Vasopressors	47 (42.3)	19 (26.0)
90-day Liver transplantation	15 (13.89)	9 (12.68)
Mortality from ACLF diagnosis, n (%)		
90-day mortality	58 (52.25)	36 (49.32)

*MELD: Model for End-Stage Liver Disease score; ** CLIF-C: Chronic Liver Failure Consortium,
Chi-square or Fisher's tests performed in percentages comparisons. For continuous variables comparisons, Student T-test for normally distributed variables or Wilcoxon rank sum test for not-normally distributed variables were used.

Table S6. Prevalence, type, epidemiological characteristics and severity of proven bacterial infections in the whole series and in patients with AD and with ACLF

	Total (N=1273)	AD at inclusion (N=1071)	ACLF at inclusion (N=202)	ACLF during follow-up (N=218)
Prevalence (infected patients/%)	376 (29.5%)	239 (22.32%)	89 (44.06%)	68 (31.20%)
Overall infections (n)	440	265*	99	76
Overall culture-positive infections (n/n infections/%)	282/426 (66.20%)	164/256 (64.06 %)	66/94 (70.21%)	52/76 (68.42 %)
Prevalence of patients infected by MDROs (n/%)	76/376 (20.21%)	25/239 (10.46%)	23/89 (25.84%)	28/68 (41.18%)
Overall MDR infections (n/ n infections/%)	83/440 (18.86 %)	26/265 (9.81 %)	26/99 (26.26 %)	31/76 (40.79 %)
Culture-positive MDR infections (n /n infections/%)	83/282 (29.43 %)	26/164 (15.85 %)	26/66 (39.39%)	31/52 (59.62 %)
Type of infection (n/%)				
Spontaneous bacterial peritonitis	92 (20.91%)	56/265 (21.13%)	21/99 (21.21%)	15/76 (19.74%)
Urinary tract infection	113 (25.68%)	72/265 (27.17%)	23/99 (23.23%)	18/76 (23.68%)
Skin and soft tissue infections	38 (8.64%)	27/265 (10.19%)	8/99 (8.08%)	3/76 (3.95%)
Pneumonia	87 (19.77%)	48/265 (18.11%)	18/99 (18.18%)	21/76 (27.63%)
Secondary bacterial peritonitis	5 (1.14%)	2/265 (0.75%)	1/99 (1.01%)	2/76 (2.63%)
Spontaneous or secondary bacteremia	43 (9.77%)	24/265 (9.06%)	14/99 (14.14%)	5/76 (6.58%)
Other	62 (14.09%)	36/265 (13.58%)	14/99 (14.14%)	12/76 (15.79%)
Site of acquisition				
Community-acquired (n/n infections/%)	250/440 (56.82%)	185/265 (69.81%)	55/99 (55.56%)	10/76 (13.16%)
MDR infections (n /%)	34/250 (13.60 %)	16/185 (8.65%)	13/55 (23.64%)	5/10 (50.00%)
HCA (n/n infections/%)	87/440 (19.77%)	48/265 (18.11%)	22/99 (22.22%)	17/76 (22.37%)
MDR infections (n /%)	19/87 (21.84%)	6/48 (12.50%)	6/22 (27.27%)	7/17 (41.18%)
Nosocomial (n/n infections/%)	103/440 (23.41%)	32/265 (12.08%)	22/99 (22.22%)	49/76 (64.47%)
MDR infections (n /%)	30/103 (29.13 %)	4/32 (12.50%)	7/22 (31.82%)	19/49 (38.78%)
Severity at infection diagnosis				
No sepsis (n/n infections/%)	277/422 (65.64%)	196/255 (76.86%)	52/97 (53.61%)	29/70 (41.43%)
MDR infections (n /%)	36/277 (13.00%)	17/196 (8.67%)	9/52 (17.31%)	10/29 (34.48%)
Sepsis (n/n infections/%)	61/422 (14.45%)	44/255 (17.25%)	9/97 (9.28%)	8/70 (11.43%)
MDR infections (n /%)	15/61 (24.59%)	6/44 (13.64%)	4/9 (44.44%)	5/8 (62.50%)
Severe sepsis or shock (n/n infections/%)	84/421 (19.91%)	15/255 (5.88%)	36/97 (37.11%)	33/70 (47.14%)
MDR infections (n /%)	28/84 (33.33%)	2/15 (13.33%)	12/36 (33.33%)	14/33 (42.42%)

AD: acute decompensation; ACLF: acute-on-chronic liver failure; HCA: healthcare-associated; MDR: multidrug resistance; *35 infections that precipitated both, AD and ACLF were included in the AD at Inclusion group.

Table S7. Clinical outcome of proven infections according to the antibiotic resistant profile of the responsible bacteria

	Total	No isolation/ susceptible bacteria	Multiresistant bacteria	p-value
Overall Infections (n)	**440**	**357**	**83**	
Resolution of infection (n/%)	341/440 (77.50%)	293/357 (82.07%)	48/83 (57.83%)	<.0001
Precipitant of ACLF (n/%)	210/440 (47.27%)	150/357 (42.02%)	60/83 (72.30%)	<.0001
Severe sepsis/shock (n/%)	109/432 (25.23%)	76/351 (21.65%)	33/81 (40.74%)	0.0004
Infections precipitating AD (n)	**265**	**239**	**26**	
Resolution of infection (n/%)	236/265 (89.06%)	214/239 (89.54%)	22/26 (84.62%)	0.50
Severe sepsis/shock (n/%)	26/261 (9.96%)	24/235 (10.21%)	2/26 (7.69%)	0.68
Precipitant of ACLF (n/%)	35	32/239 (9.73%)	3/23 (13.04%)	1.0000
Infections precipitating ACLF (n)	**175**	**118**	**57**	
Resolution of infection (n/%)	105/175 (60.00%)	79/118 (66.95%)	26/57 (45.61%)	0.0069
Severe sepsis/shock (n/%)	83/171 (48.54%)	52/116 (44.83%)	31/55 (56.36%)	0.15
Patients with bacterial infections (n)	**376**	**300**	**76**	
Mortality at 28 days (n/%)	96/376 (25.53%)	65/300 (21.67%)	31/76 (40.79%)	0.0006
Mortality at 90 days (n/%)	129/376 (34.31%)	92/300 (30.67%)	37/76 (48.68%)	0.0031

AD: acute decompensation; ACLF: acute-on-chronic liver failure; Chi-square or Fisher's tests performed in percentages comparisons.

Table S8. Adequacy of initial antibiotic strategies in the whole series of proven infections and in infections precipitating AD and ACLF, according to strategies and different contexts

Variable	All proven bacterial infections				Infections precipitating AD				Infections precipitating ACLF			
Type of empirical antibiotic strategies	Total (n=440)	Classic* (n=273)	Piperacillin-tazobactam (n=70)	MDR Coverage** (n=92)	Total (n=265)	Classic (n=187)	Piperacillin-tazobactam (n=34)	MDR Coverage (n=39)	Total (n=175)	Classic (n=86)	Piperacillin-tazobactam (n=36)	MDR coverage (n=53)
	Community-acquired or healthcare-associated acquisition											
No. of infections/total no. **(%)**	**337/337 (100)**	**231/332 (69.6)**	**49/332 (14.8)**	**52/332 (15.7)**	**233/233 (100)**	**170/228 (74.6)**	**30/228 (13.2)**	**28/228 (12.3)**	**104/104 (100)**	**61/104 (58.6)**	**19/104 (18.3)**	**24/104 (23.1)**
Adequacy,%:												
- Clinical criteria	65.1	58.4	69.4	90.4	71.1	64.7	80.0	100.0	51.9	41.0	52.6	79.2
- Microbiological criterion	61.2	50.7	73.1	97.1	65.2	55.9	87.5	100.0	53.5	38.6	50.0	94.1
	Nosocomial acquisition											
No. of infections/total no. **(%)**	**103/103 (100)**	**42/103 (40.8)**	**21/103 (20.4)**	**40/103 (38.8)**	**32/32 (100)**	**17/32 (53.1)**	**3/32 (12.5)**	**11/32 (34.4)**	**71/71 (100)**	**25/71 (35.2)**	**17/71 (23.9)**	**29/71 (40.9)**
Adequacy,%												
- Clinical criteria	54.4	30.9	66.7	72.5	46.9	35.3	25.0	72.7 100.0	57.7	28.0	76.5	72.4
- Microbiological criterion	62.9	35.7	66.7	88.9	56.5	41.7	25.0		66.0	31.3	81.8	85.0
	No sepsis or sepsis											
No. of infections/total no. **(%)**	**338/338 (100)**	**230/333 (69.1)**	**46/333 (13.8)**	**57/33 (17.1)**	**240/240 (100)**	**175/235 (74.5)**	**29/235 (12.3)**	**31/235 (13.2)**	**98/98 (100)**	**55/98 (56.1)**	**17/98 (17.4)**	**26/98 (26.5)**
Adequacy,%:												
- Clinical criteria	65.8	60.4	69.6	84.2	69.8	64.6	75.9	93.6	56.1	47.3	58.8	73.1
- Microbiological criterion	62.2	52.9	67.9	90.2	64.8	55.8	76.5	100.0	56.7	44.4	54.6	80.0
	Severe sepsis/shock											

***No. of infections/total no.* (%)**	**84/84**	**34/84**	**22/84**	**28/84**	**15/15**	**7/15**	**4/15**	**4/15**	**69/69**	**27/69**	**18/69**	**24/69**
	(100)	**(40.5)**	**(26.2)**	**(33.3)**	**(100)**	**(46.7)**	**(26.7)**	**(26.7)**	**(100)**	**(39.1)**	**(26.1)**	**(34.8)**
Adequacy,(%:												
- Clinical criteria	51.2	20.6	68.2	75.0	46.7	14.3	75.0	75.0	52.2	22.2	66.7	75.0
- Microbiological criterion	63.0	30.8	81.8	100.0	62.5	40.0	100.0	100.0	63.0	28.6	77.8	100.0

CA: community-acquired; HCA: healthcare-associated: AD: acute decompensation; ACLF: acute-on-chronic liver failure; Chi-square or Fisher's tests performed in percentage comparisons.
*One to third generation cephalosporins, amoxicillin-clavulanic acid, quinolones; **carbapenem±glycopeptide/linezolid/daptomycin or tigecycline;
Resolution of infection without further escalation/bacterial susceptibility to initial antibiotics in culture positive infections; ## Bacterial susceptibility to initial antibiotics in culture positive infections

Table S9. Comparison between the outcome of patients with severe alcoholic hepatitis at inclusion (N=288) receiving or not receiving steroids

	No steroids (N=210)	Steroids (N=49)	p-value
28-day mortality from inclusion	31/210 (14.76%)	9/49 (18.37%)	0.52
Main cause of death			
Hypovolemic shock	1/31 (3.23%)	0/9 (0%)	
ACLF	25/31 (80.65%)	7/9 (77.78%)	
Other	1/31 (3.23%)	2/9 (22.22%)	
Unknown	4/31 (12.90%)	0/9 (0%)	
90-day mortality from inclusion	55/210 (26.19%)	18/49 (36.73%)	0.13
Main cause of death			
Hypovolemic shock	2/55 (3.64%)	2/18 (11.11%)	
ACLF	40/55 (72.73%)	12/18 (66.67%)	
Other	3/55 (5.45%)	3/18 (16.67%)	
Unknown	10/55 (18.18%)	1/18 (5.56%)	
Patients with severe alcoholic hepatitis at inclusion - AD patients at Inclusion - (N=200)			
	No steroids (N=151)	Steroids (N=30)	
28-day mortality from inclusion	9/151 (5.96%)	4/30 (13.33%)	0.23
Main cause of death			
Hypovolemic shock	0/9 (0%)	0/4 (0%)	
ACLF	7/9 (77.78%)	4/4 (100.00%)	
Other	0/9 (0%)	0/4 (0%)	
Unknown	2/9 (22.22%)	0/4 (0%)	
90-day mortality from inclusion	30/151 (19.87%)	8/30 (26.67%)	0.40
Main cause of death			
Hypovolemic shock	1/30 (3.33%)	1/8 (12.50%)	
ACLF	20/30 (66.67%)	7/8 (87.50%)	
Other	2/30 (6.67%)	0/8 (0%)	
Unknown	7/30 (23.33%)	0/8 (0%)	

Patients with severe alcoholic hepatitis at inclusion - ACLF at Inclusion - (N=88)			
	No steroids (N=59)	Steroids (N=19)	
28-day mortality from inclusion	22/59 (37.29%)	5/19 (26.32%)	0.38
Main cause of death			
Hypovolemic shock	1/22 (4.55%)	0/5 (0%)	
ACLF	18/22 (81.82%)	3/5 (60.00%)	
Other	1/22 (4.55%)	2/5 (40.00%)	
Unknown	2/22 (9.09%)	0/5 (0%)	
90-day mortality from inclusion	25/59 (42.37%)	10/19 (52.63%)	0.43
Main cause of death			
Hypovolemic shock	1/25 (4.00%)	1/10 (10.00%)	
ACLF	20/25 (80.00%)	5/10 (50.00%)	
Other	1/25 (4.00%)	3/10 (30.00%)	
Unknown	3/25 (12.00%)	1/10 (10.00%)	

Table S10. Duration of antibiotic treatment according to multi-drug resistant (MDR) bacterial infection (A) and site of infection (B).

A	**Total (N=1273)**	**MDR infection**	**No MDR infection**	**p-value**
Overall infections (n)	440	83	357	
Antibiotic duration (n);	(434)	(81)	(353)	
Median (Q1 - Q3) in days	9.00 (6.00 - 16.00)	10.00 (6.00 - 19.00)	9.00 (7.00 - 16.00)	0.45

B	Antibiotic duration (N) Me (Q1 - Q3) in days	**p-value**
Type of infection		*0.0033*
Spontaneous bacterial peritonitis	(91) 9.00 (7.00 - 15.00)	
Urinary tract infection	(109) 8.00 (5.00 - 13.00)	
Skin and soft tissue infections	(38) 9.50 (7.00 - 22.00)	
Pneumonia	(87) 9.00 (7.00 - 18.00)	
Secondary bacterial peritonitis	(5) 15.00 (12.00 - 25.00)	
Spontaneous or secondary bacteremia	(43) 11.00 (7.00 - 15.00)	
Other	(61) 14.00 (8.00 - 24.00)	
Severity at infection diagnosis		*0.0233*
No sepsis	(271) 9.00 (6.00 - 14.00)	
Sepsis	(61) 14.00 (7.00 - 21.00)	
Severe sepsis or shock	(84) 10.00 (7.00 - 17.00)	

AD: acute decompensation; ACLF: acute-on-chronic liver failure; Kruskal-Wallis test was used for comparisons.