Acute-on-Chronic Liver Failure Is a Distinct Syndrome That Develops in Patients With Acute Decompensation of Cirrhosis

RICHARD MOREAU,[1] RAJIV JALAN,[2] PERE GINES,[3] MARCO PAVESI,[4] PAOLO ANGELI,[5] JUAN CORDOBA,[6] FRANCOIS DURAND,[1] THIERRY GUSTOT,[7] FAOUZI SALIBA,[8] MARCO DOMENICALI,[9] ALEXANDER GERBES,[10] JULIA WENDON,[11] CARLO ALESSANDRIA,[12] WIM LALEMAN,[13] STEFAN ZEUZEM,[14] JONEL TREBICKA,[15] MAURO BERNARDI,[9] and VICENTE ARROYO,[3] for the CANONIC Study Investigators of the EASL–CLIF Consortium

[1]Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy; Inserm Unité 773, Centre de Recherche Biomédicale Bichat-Beaujon CRB3, Clichy and Paris; and Université Paris Diderot-Paris 7, Paris, France; [2]Institute of Liver and Digestive Health, Liver Failure Group, Royal Free Campus, London, England; [3]Liver Unit, Hospital Clinic, University of Barcelona, IDIBAPS, [4]Data Management Centre, CLIF Consortium, Hospital Clinic, and [6]Servicio de Hepatologia, Hospital Vall d'Hebron, Universitat Autonoma de Barcelona, Centro de Investigacion Biomedica en Red Enfermedades Hepaticas y Digestivas (CIBERehd), Barcelona, Spain; [5]Department of Medicine, Unit of Hepatic Emergencies and Liver Transplantation, University of Padova, Padova, Italy; [7]Department of Gastroenterology and Hepato-Pancreatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium; [8]Centre Hépato-Biliaire, Hôpital Paul Brousse, Assistance Publique-Hôpitaux de Paris, Villejuif, France; [9]Semeiotica Medica, Policlinico S. Orsola-Malpighi, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [10]Liver Center Munich, Department of Medicine 2, Klinikum der LMU Munchen-Grosshadern, Munich, Germany; [11]Institute of Liver Studies and the Cellular Biology of Inflammation, King's College Hospital, London, England; [12]Division of Gastroenterology and Hepatology, San Giovanni Battista Hospital, University of Turin, Turin, Italy; [13]Department of Liver and Biliopancreatic Diseases, University Hospital Gasthuisberg, KU Leuven, Leuven, Belgium; [14]Department of Medicine I, JW Goethe University Hospital, Frankfurt, Germany; and [15]Department of Internal Medicine I, University Hospital of Bonn, Bonn, Germany

CLINICAL LIVER

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BACKGROUND & AIMS: Patients with cirrhosis hospitalized for an acute decompensation (AD) and organ failure are at risk for imminent death and considered to have acute-on-chronic liver failure (ACLF). However, there are no established diagnostic criteria for ACLF, so little is known about its development and progression. We aimed to identify diagnostic criteria of ACLF and describe the development of this syndrome in European patients with AD. **METHODS:** We collected data from 1343 hospitalized patients with cirrhosis and AD from February to September 2011 at 29 liver units in 8 European countries. We used the organ failure and mortality data to define ACLF grades, assess mortality, and identify differences between ACLF and AD. We established diagnostic criteria for ACLF based on analyses of patients with organ failure (defined by the chronic liver failure–sequential organ failure assessment [CLIF-SOFA] score) and high 28-day mortality rate (>15%). **RESULTS:** Of the patients assessed, 303 had ACLF when the study began, 112 developed ACLF, and 928 did not have ACLF. The 28-day mortality rate among patients who had ACLF when the study began was 33.9%, among those who developed ACLF was 29.7%, and among those who did not have ACLF was 1.9%. Patients with ACLF were younger and more frequently alcoholic, had more associated bacterial infections, and had higher numbers of leukocytes and higher plasma levels of C-reactive protein than patients without ACLF ($P < .001$). Higher CLIF-SOFA scores and leukocyte counts were independent predictors of mortality in patients with ACLF. In patients without a prior history of AD, ACLF was unexpectedly characterized by higher numbers of organ failures, leukocyte count, and mortality compared with ACLF in patients with a prior history of AD. **CONCLUSIONS: We analyzed data from patients with cirrhosis and AD to establish diagnostic criteria for ACLF and showed that it is distinct from AD, based not only on the presence of organ failure(s) and high mortality rate but also on age, precipitating events, and systemic inflammation. ACLF mortality is associated with loss of organ function and high leukocyte counts. ACLF is especially severe in patients with no prior history of AD.**

Keywords: Prospective Cohort; Chronic Liver Disease; Organ Failures; Prognosis.

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Acute decompensation (AD), defined by the acute development of one or more major complications of liver disease (ie, ascites, encephalopathy, gastrointestinal hemorrhage, bacterial infection),[1–5] is the main cause of hospitalization in patients with cirrhosis. AD develops in many cirrhotic patients in the absence of any other significant feature, while in others it is associated with organ failure(s) (ie, worsening of liver function and/or kidney failure and/or failure of other organs).[6–8] Patients with AD and organ failure(s) are at high risk for short-term death.[6–8] It has become customary to refer to these patients as patients with acute-on-chronic liver failure

Abbreviations used in this paper: ACLF, acute-on-chronic liver failure; AD, acute decompensation; CANONIC, chronic liver failure (CLIF) Acute-on-Chronic Liver Failure in Cirrhosis; EASL-CLIF, European Association for the Study of the Liver-chronic liver failure; SOFA, sequential organ failure assessment.

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(ACLF).[6–10] However, the current definitions of ACLF differ greatly from each other and have been developed on a theoretical rather than experimental basis.[10–19] A universally accepted and used definition of ACLF is still lacking.[10] Because of the lack of a definition, other important features of this syndrome remain unknown, including prevalence, frequency of precipitating factors, natural history, and pathogenic mechanism(s). Defining ACLF is not only a matter of nosology, but also is of great importance because it would allow early identification of patients at high risk for end-organ failure–related death, requiring specific treatments and/or intensive management. This large, prospective, observational study, performed within the context of the European Association for the Study of the Liver-chronic liver failure (EASL-CLIF) Consortium and called the EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study, was designed to develop a definition of ACLF able to identify cirrhotic patients with a high risk of short-term mortality. Other unknown features of ACLF were also investigated, including prevalence, precipitating factors, and main pathogenic mechanisms.

Patients and Methods

Study Design

Patients were screened and enrolled from February to September 2011 in 12 European countries after the appropriate approvals were obtained. Patients were screened at liver units in 29 university hospitals; each liver unit had a regular ward, intensive care facilities, and a liver transplantation program. The policy of allocation of liver transplants was similar among study centers. The diagnosis of cirrhosis was based on previous liver biopsy findings or a composite of clinical signs and findings provided by laboratory test results, endoscopy, and radiologic imaging. Written informed consent was obtained from patients or their legal surrogates before enrollment. The members of the writing committee assume responsibility for the accuracy and completeness of the data and for the fidelity of the study to the protocol. All authors had access to the study data and reviewed and approved the final manuscript. Grifols or Gambro did not play a role in the study design as well as analyses of the data.

Patients

We screened patients hospitalized for at least 1 day who had an AD of cirrhosis as defined by the acute development of large ascites, hepatic encephalopathy, gastrointestinal hemorrhage, bacterial infection, or any combination of these.[1–5] More details on the definition of AD are available in Supplementary Materials and Methods.

We enrolled patients who developed AD for the first time as well as those with a prior history of AD (one or more episodes) who recovered after specific treatment. Causes of exclusion are summarized in Figure 1.

Data Collection

We collected data from all enrolled patients on history (including previous episodes of AD), physical examination, lab-

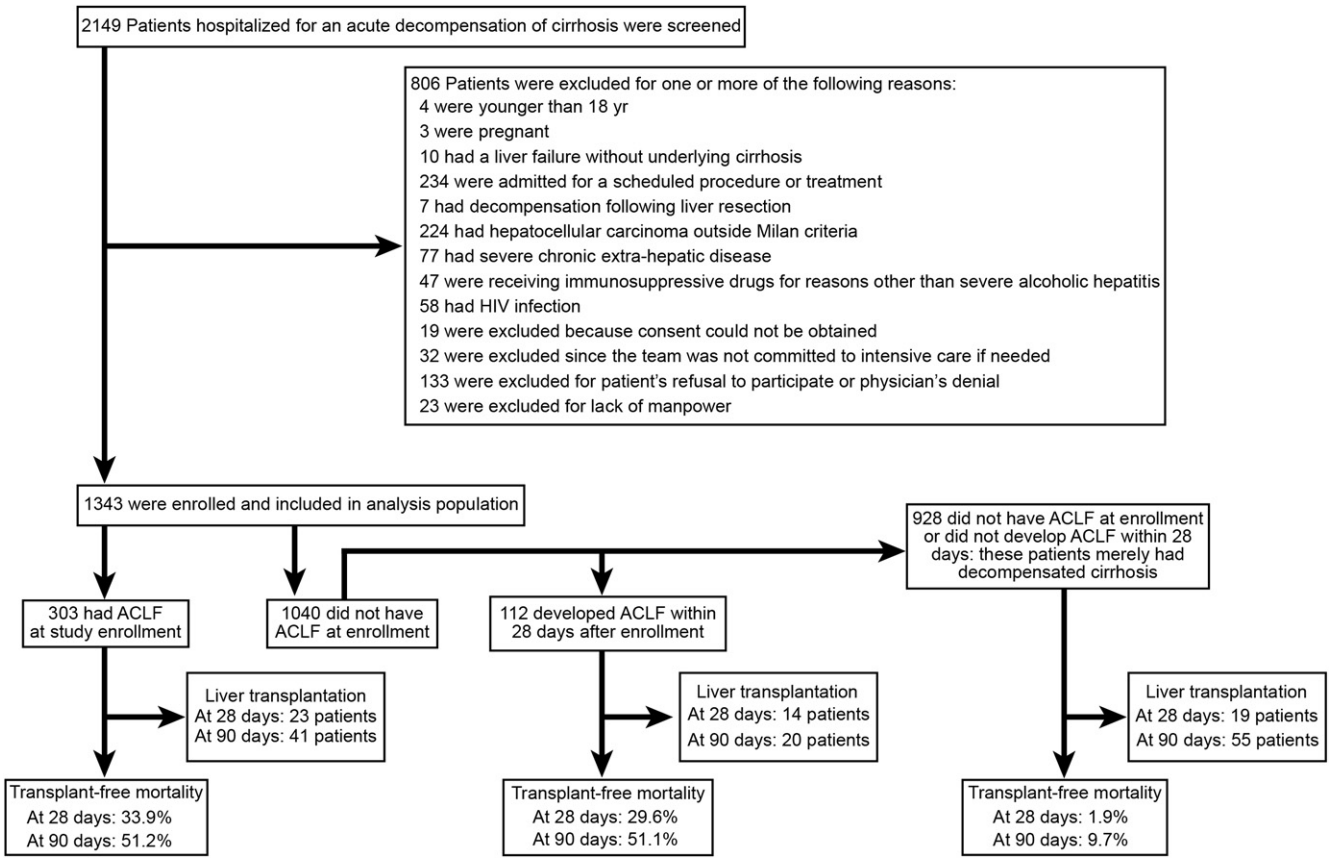

Figure 1. Screening, enrollment, and flow of patients according to the presence or absence of ACLF.

oratory measurements, and events that may be potential precipitating factors of both AD and ACLF: active alcoholism (more than 14 drinks per week in women and more than 21 drinks per week in men[20] within the previous 3 months), bacterial infection, gastrointestinal hemorrhage, therapeutic paracentesis without use of intravenous albumin, transjugular intrahepatic portosystemic shunting, major surgery, hepatitis, and alcoholic hepatitis (liver biopsy required).

As prespecified in the study protocol, enrolled patients at each study site were divided into 3 groups: patients with organ failure (group I), patients without organ failure who were chronologically enrolled after each patient with organ failure (group II), and other enrolled patients without organ failure (group III). For logistical reasons, patients in groups I and II but not those in group III were subjected to an "intensive surveillance," which consisted of collection of an extensive set of data at days 2, 7, 14, 21, and 28 after enrollment that was similar to the data obtained at enrollment. Patients in group III had regular follow-up to allow detection of organ failure. When patients in group III developed organ failure, the intensive surveillance program was applied during the 28 days after detection of organ failure. Blood, serum, plasma, and urine samples were obtained from all patients at enrollment. Samples were also obtained during the 28-day follow-up from patients in groups I and II and from those in group III who developed organ failure. Finally, as prespecified in the study protocol, information on liver transplantation and mortality at 28 and 90 days following enrollment and causes of death were recorded for all enrolled patients.

Procedures

Diagnostic criteria for organ failure were defined before the start of the study. The sequential organ failure assessment (SOFA) score, which is widely used to diagnose organ failure in general intensive care units,[21] has also been used for this purpose in patients with cirrhosis.[22–24] However, some components of this score do not take into account specific features of cirrhosis.[8] Thus, for the diagnosis of organ failure, our study protocol prespecified use of a modified SOFA score, called the CLIF-SOFA score (Table 1), which had been specifically developed for the present study and based on several references[2,12,22,25–28] and the clinical experience of the authors. The definition of each type of organ failure is provided in Supplementary Materials and Methods. In our cohort of patients, the CLIF-SOFA score was as accurate as the Model of End-Stage Liver Disease[27] score and more accurate than the Child–Pugh score[29] in predicting 28-day mortality (data not shown). In addition, the CLIF-SOFA score was internally validated by means of a bootstrap re-estimation of the corresponding coefficient in a logistic regression model for 28-day transplant-free mortality fitted on 1000 samples obtained with replacement from the study population. Bootstrap estimates of the odds ratio for a 1-point increase in CLIF-SOFA score (odds ratio, 1.557; 95% confidence interval, 1.459–1.672) and for the corresponding area under the receiver operating characteristic curve (0.831) were very similar to those obtained from the original model (odds ratio, 1.552; area under the concentration-time curve receiver operating characteristic, 0.831).

Once data were collected, we followed a general strategy that was prespecified in the protocol. First, we defined ACLF and ACLF grades by investigating the association of organ failure(s) at enrollment with short-term mortality. Then, we assessed the prevalence and mortality associated with ACLF and ACLF grades at enrollment, for postenrollment ACLF (that occurring within the next 28-day follow-up period), and for the overall group of patients with ACLF. Finally, we searched for additional differences between ACLF and "mere" AD. This was performed by comparing clinical and laboratory characteristics of patients with and without ACLF.

Statistical Analyses

Data were collected using an electronic case report form. Estimation of study size was based on the assumption of a 9% to 10% 28-day mortality rate after enrollment in patients without organ failure and 18% for patients with one organ failure or more.[22,23] According to these estimations, a 15% mortality rate at 28 days after enrollment was the threshold selected for identifying subgroups of patients with high mortality in the process of definition of ACLF. Assuming that approximately one-third of patients would have ACLF at enrollment, a total study population of more than 1300 patients would allow an 80% power to detect a minimum relative risk of 1.5 (corresponding to a 28-day mortality rate of 15%) for patients with ACLF at enrollment. Twenty-eight–day and 90-day mortality rates were estimated as transplant-free mortality (patients who received a liver transplant were considered lost

Table 1. CLIF-SOFA Score

Organ/system	0	1	2	3	4
Liver (bilirubin, *mg/dL*)	<1.2	≥1.2 to ≤2.0	≥2.0 to <6.0	≥6.0 to <12.0	**≥12.0**
Kidney (creatinine, *mg/dL*)	<1.2	≥1.2 to <2.0	**≥2.0 to <3.5**	**≥3.5 to <5.0**	**≥5.0**
				or use of renal replacement therapy	
Cerebral (HE grade)	No HE	I	II	**III**	**IV**
Coagulation (international normalized ratio)	<1.1	≥1.1 to <1.25	≥1.25 to <1.5	≥1.5 to <2.5	**≥2.5 or platelet count ≤20×10⁹/L**
Circulation (mean arterial pressure, *mm Hg*)	≥70	<70	**Dopamine ≤5 or dobutamine or terlipressin**	**Dopamine >5 or E ≤0.1 or NE ≤0.1**	**Dopamine >15 or E >0.1 or NE >0.1**
Lungs					
PaO/FiO_2 or	>400	>300 to ≤400	>200 to ≤300	**>100 to ≤200**	**≤100**
SpO_2/FiO_2	>512	>357 to ≤512	>214 to ≤357	**>89 to ≤214**	**≤89**

NOTE. The original SOFA score is described by Vincent et al.[21] Like the SOFA score, the CLIF-SOFA score includes subscores ranging from 0 to 4 for each of 6 components (liver, kidneys, brain, coagulation, circulation, and lungs), with higher scores indicating more severe organ impairment. Aggregated scores range from 0 to 24 and provide information on overall severity. The text in bold indicates the diagnostic criteria for organ failures (see also Supplementary Materials and Methods).

HE, hepatic encephalopathy; E, epinephrine; NE, norepinephrine; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; SpO_2, pulse oximetric saturation.

Table 2. Twenty-Eight–Day Mortality According to the Number and Types of Organ Failures and the Presence of Kidney Dysfunction or Mild to Moderate Hepatic Encephalopathy at Enrollment

No. and types of organ failures	All patients	No kidney dysfunction or mild to moderate hepatic encephalopathy	Kidney dysfunction and/or mild to moderate hepatic encephalopathy
No organ failure	39/874 (4.5)	20/562 (3.6)	19/312 (6.2)
One organ failure	39/267 (14.6)	17/184 (9.2)	22/83 (26.5)
Single liver failure	14/101 (13.9)	4/68 (5.9)	**10/33 (30.3)**
Single cerebral failure	3/30 (10.0)	2/25 (8.0)	**1/5 (20.0)**
Single coagulation failure	3/28 (10.7)	1/19 (5.3)	**2/9 (22.2)**
Single circulation or lung failure	3/22 (13.6)	1/15 (6.7)	**2/7 (28.6)**
Single kidney failure	**16/86 (18.6)**	**9/57 (15.8)**	**7/29 (24.1)**
Two organ failures	**31/97 (32.0)**	**19/66 (28.8)**	**12/31 (38.7)**
Three organ failures or more	**33/42 (78.6)**	**25/29 (86.2)**	**8/13 (61.5)**

NOTE. Data are expressed as number of deaths/total number of patients (%). Among the 1343 enrolled patients, 1287 (95.8%) did not receive a liver transplant within 28 days of follow-up. Kidney dysfunction was defined by serum creatinine levels ranging from 1.5 to 1.9 mg/dL. Mild to moderate hepatic encephalopathy was grade I or II hepatic encephalopathy (CLIF-SOFA cerebral score of 1 or 2). The text in bold indicates the subgroups of patients defined as having ACLF.

to follow-up). Univariate analyses using χ^2 or Student t test and one-way analysis of variance were performed to assess the association between all potential factors and mortality or development of ACLF. Two logistic regression models were fitted to select the best subset of predictors for 28-day mortality and for development of ACLF after enrollment. Those factors showing a clinically and statistically significant association to the outcome in univariate analyses were selected for the initial models. The final models were fitted using a stepwise forward method based on model likelihood ratios with the same significance level ($P < .05$) for entering or dropping variables. Results are presented as frequencies and percentages or means and SDs. In all analyses, the significance level was set at $P < .05$.

Results

Patients

A total of 2149 consecutive patients were screened, of whom 1343 were enrolled. A majority of patients were enrolled during the first 4 days after hospital admission (Supplementary Figure 1). In total, 817 (60.8%), 1004 (74.8%), and 1185 (88.2%) patients were enrolled 1, 2, and 4 days after hospital admission, respectively. In 158 patients (11.7%), the elapsed time between hospital admission and enrollment was more than 4 days. Reasons for the delay between hospital admission and study enrollment are provided in Supplementary Results.

Supplementary Table 1 shows the characteristics at enrollment of the whole group; of note, 815 patients (60.7%) had at least a previous episode of ascites and 406 (32.7%) had a previous episode of hepatic encephalopathy. At enrollment, there were 330 patients (24.6%) in group I, 307 patients (22.8%) in group II, and 706 patients (52.6%) in group III. In group I, the most frequent organ failures (as defined by CLIF-SOFA score) were liver and kidney failures followed by coagulation and cerebral failures. Among patients with organ failure, a majority (64.9%) had a single organ failure, 24.4% had 2 organ failures, and 10.6% had 3 organ failures or more (Supplementary Table 2).

Diagnostic Criteria of ACLF and Prevalence of and Mortality Associated With ACLF at Enrollment

Definition of the diagnostic criteria of ACLF was obtained after analysis of the whole population of patients at enrollment. It was based on the presence of the 3 major characteristics of the syndrome: AD (inclusion criterion, present in all patients), organ failure (predefined by the SOFA-CLIF score), and high 28-day mortality rate (predefined threshold of 15%). The mortality rate within 28 days after enrollment was 32.0% in patients with 2 organ failures and 78.6% in those with 3 organ failures or more; it was only 14.6% in patients with one organ failure (Table 2, *first column*). To refine the prognostic assessment in patients with single organ failure, we looked for additional risk factors in these patients. The type of organ failure was clearly a risk factor of mortality. It was greater than 15% in the subgroup of patients with kidney failure; in contrast, it was less than 15% for single "non-kidney" organ failures (Table 2, *first column*). We further compared factors included in the SOFA-CLIF score between patients with single organ failure who did and did not die within 28 days after enrollment. Significant differences were found in serum creatinine level and in the prevalence of mild to moderate hepatic encephalopathy (grade I or II according to the West Haven classification) but not in serum bilirubin level, international normalized ratio, arterial pressure, and the ratio of pulse oximetric saturation to the fraction of inspired oxygen (Supplementary Table 3). In summary, 3 types of risk factors obtained from the CLIF-SOFA score at enrollment were found to be related to high 28-day mortality rate (Table 2): (1) the presence of 2 organ failures or more, (2) the presence of one organ failure when the organ that failed was the kidney, and (3) the coexistence of a single "non-kidney" organ failure with kidney dysfunction (ie, serum creatinine level ranging from 1.5 to 1.9 mg/dL) and/or mild to moderate hepatic encephalopathy. Based on these findings at enrollment, we defined 4 groups of patients.

1. **No ACLF.** This group comprises 3 subgroups: (1) patients with no organ failure, (2) patients with a single "non-kidney" organ failure (ie, single failure of

the liver, coagulation, circulation, or respiration) who had a serum creatinine level <1.5 mg/dL and no hepatic encephalopathy, and (3) patients with single cerebral failure who had a serum creatinine level <1.5 mg/dL. In total, 1040 of the 1343 enrolled patients (77.4%) had no ACLF at enrollment. The 28-day and 90-day mortality rates were 4.7% and 14%, respectively.

2. **ACLF grade 1.** This group includes 3 subgroups: (1) patients with single kidney failure, (2) patients with single failure of the liver, coagulation, circulation, or respiration who had a serum creatinine level ranging from 1.5 to 1.9 mg/dL and/or mild to moderate hepatic encephalopathy, and (3) patients with single cerebral failure who had a serum creatinine level ranging from 1.5 and 1.9 mg/dL. In total, 148 patients (11.0%) had ACLF grade 1 at enrollment. The 28-day and 90-day mortality rates were 22.1% and 40.7%, respectively.
3. **ACLF grade 2.** This group includes patients with 2 organ failures; 108 patients (8.0%) had ACLF grade 2 at enrollment. The 28-day and 90-day mortality rates were 32.0% and 52.3%, respectively.
4. **ACLF grade 3.** This group includes patients with 3 organ failures or more; 47 patients (3.5%) had ACLF grade 3 at enrollment. The 28-day and 90-day mortality rates were 76.7% and 79.1%, respectively.

Overall, 303 patients (22.6%) had ACLF at enrollment; their 28-day and 90-day mortality rates were 33.9% and 51.2%, respectively.

Clinical Characteristics of ACLF at Enrollment

Patients with ACLF were younger and more frequently alcoholic (Table 3). Bacterial infection, active alcoholism, and a composite of other precipitating events (including therapeutic paracentesis without use of intravenous albumin, transjugular intrahepatic portosystemic shunting, major surgery, and hepatitis) were more frequent in patients with ACLF than in those without. Supplementary Table 4 shows that the higher prevalence of bacterial infection in the ACLF group was related to spontaneous bacterial peritonitis and pneumonia; it also shows that sepsis and septic shock were more frequent in patients with ACLF than in those without. Gastrointestinal hemorrhage was not more frequent in the ACLF group. Reactivation of the hepatitis B virus, which is a common cause of ACLF in other continents,[16–18] was extremely infrequent in our European cohort. No precipitating event was identifiable in 43.6% of patients with ACLF (Table 3). Among patients with ACLF, the presence or the type of precipitating events was not related to mortality (Supplementary Table 5). Kidney failure was the most prevalent organ failure for ACLF grade 1. For ACLF grade 2, liver failure was the most prevalent organ failure, followed by kidney, cerebral, and coagulation failures. For ACLF grade 3, the prevalence of all organ failures was high or moderately high (respiratory failure). Previous episodes of AD were absent in 23.2% of patients with ACLF at enrollment, indicating a relatively frequent development of AD of cirrhosis in the form of ACLF (Table 3).

Postenrollment ACLF

Among the 1040 patients without ACLF at enrollment, 112 (10.8%) developed ACLF within 28 days (median, 5 days) after enrollment (postenrollment ACLF) (Figure 1). In 110 patients, ACLF developed at the same hospitalization of study enrollment. The remaining 928 patients (89.2%) did not develop postenrollment ACLF (Figure 1). Mortality rates at 28 and 90 days after enrollment in patients with and without postenrollment ACLF were 29.6% versus 1.9% ($P < .001$) and 51.1% versus 9.7% ($P < .001$), respectively (Figure 1). The prevalence of postenrollment ACLF grades 1, 2, and 3 was 6.7%, 3.9%, and 0.9% and the 28-day and 90-day mortality rates were 25.8%, 28.6%, and 62.6% and 41.1%, 65.4%, and 75.0%, respectively. Bacterial infections (before diagnosis of ACLF) were more frequent in patients with postenrollment ACLF (57% vs 41% in patients who remained free of ACLF; $P < .01$). Among patients with postenrollment ACLF, 21.5% did not have any identifiable precipitating factor and 31.3% had no previous episode of AD. Factors that were independently and significantly associated with the development of postenrollment ACLF included higher CLIF-SOFA score, increased leukocyte count, and the presence of ascites, all 3 at enrollment (Supplementary Table 6).

Analysis of the Whole Group of Patients With ACLF

A total of 415 patients (30.9%) had ACLF either at enrollment or during the 28-day follow-up period (Figure 1); 213 (15.8%) were defined as having ACLF grade 1, 146 (10.9%) as grade 2, and 56 (4.4%) as grade 3. Supplementary Figure 2 shows that 28-day and 90-day mortality rates in patients with ACLF were 32.8% (23.3% for grade 1, 31.3% for grade 2, and 74.5% for grade 3) and 51.2% (40.8% for grade 1, 55.2% for grade 2, 78.4% for grade 3), respectively. The 28-day and 90-day mortality rates in patients without ACLF at enrollment or within 28 days after enrollment were 1.9% and 9.8%, respectively. Multiple organ failure without septic or hypovolemic shock was the main cause of death in the whole group of patients (37% at 90 days), followed by septic shock (23.4%) and hypovolemic shock (7.2%) (Supplementary Table 7).

Patients with ACLF had a significantly higher white cell count ($9.7 \pm 6.1 \times 10^9$ vs $6.6 \pm 4.0 \times 10^9$/L; $P < .001$) and plasma C-reactive protein level (40.3 ± 41.1 vs 24.9 ± 32.7 mg/L; $P < .001$) than the group without ACLF. Significant differences in leukocyte count and C-reactive protein level were also observed between these groups when analyses were restricted to noninfected patients only. There was a clear trend for an increase in leukocyte count and plasma C-reactive protein level in parallel to the increase in ACLF grade (Supplementary Table 8). Higher CLIF-SOFA score and increased leukocyte count, both obtained at diagnosis of ACLF (ie, at enrollment or during the 28-day follow-up period), were

Table 3. Patient Characteristics at Enrollment

Characteristic	No ACLF (n = 1040)	ACLF all grades (n = 303)	*P* value[a]	ACLF grade 1 (n = 148)	ACLF grade 2 (n = 108)	ACLF grade 3 (n = 47)	*P* value[b]
Age (*y*)	58 ± 12	56 ± 11	.02	58 ± 12	54 ± 11	52 ± 12	<.01
Male sex	655 (63.0)	195 (64.4)	.66	104 (70.3)	66 (61.1)	25 (53.2)	.14
Ascites	656 (63.4)	236 (78.7)	<.001	112 (76.2)	87 (82.1)	37 (78.7)	.08
Mean arterial pressure (*mm Hg*)	85 ± 12	79 ± 13	<.001	81 ± 13	79 ± 13	72 ± 10	<.001
Cause of cirrhosis							
Alcohol	483 (49.2)	170 (60.3)	<.01	86 (61.9)	64(59.8)	26 (56.5)	<.01
Hepatitis C virus	210 (21.4)	38 (13.0)	<.01	15 (10.8)	17 (15.9)	6 (13.0)	.01
Alcohol plus hepatitis C virus	95 (9.7)	27 (9.3)	.83	14 (10.1)	9 (8.5)	4 (8.7)	.97
Potential precipitating events of ACLF							
Bacterial infection	226 (21.8)	98 (32.6)	<.001	44 (29.9)	33 (30.8)	21 (44.7)	<.001
Gastrointestinal hemorrhage	180 (17.3)	40 (13.2)	.09	15 (10.1)	14 (13.0)	11 (23.4)	.06
Active alcoholism within the past 3 months	147 (14.9)	69 (24.5)	<.001	22 (16.1)	28 (28.6)	19 (40.4)	<.001
Other precipitating event[c]	34 (3.5)	25 (8.6)	<.001	12 (8.5)	10 (9.6)	3 (6.7)	<.01
No precipitating event[d]	584 (58.9)	126 (43.6)	<.001	73 (51.4)	40 (40.0)	13 (27.3)	<.001
More than one precipitating event[e]	56 (5.7)	39 (13.5)	<.001	17 (12.0)	14 (14.0)	8 (17.0)	<.001
Organ failures							
Liver	75 (7.2)	132 (43.6)	<.001	37 (25.2)	65 (60.2)	30 (63.8)	<.001
Kidney	0 (0)	169 (55.8)	<.001	87 (58.8)	49 (45.4)	33 (70.2)	<.001
Cerebral	26 (2.5)	73 (24.1)	<.001	5 (3.4)	35 (32.4)	33 (70.2)	<.001
Coagulation	21 (2.0)	84 (27.7)	<.001	11 (7.4)	42 (38.9)	31 (66.0)	<.001
Circulation	13 (1.3)	51 (16.8)	<.001	3 (2.0)	18 (16.7)	30 (63.8)	<.001
Lungs	4 (0.4)	28 (9.2)	<.001	5 (3.4)	7 (6.5)	16 (34.0)	<.001
Kidney dysfunction	96 (9.2)	40 (13.2)	.04	26 (17.6)	8 (7.4)	6 (12.8)	.01
Mild to moderate hepatic encephalopathy	254 (24.6)	108 (35.9)	<.001	74 (50.3)	25 (23.1)	9 (19.6)	<.001
Laboratory data							
Hematocrit (*%*)	31 ± 6	29 ± 6	<.001	29 ± 6	29 ± 5	27 ± 7	<.001
Platelet count ($\times 10^9$/*L*)	110 ± 76	100 ± 69	.02	107 ± 73	98 ± 67	77 ± 56	.01
Serum bilirubin (*mg/dL*)	4.8 ± 6.8	12.8 ± 17.7	<.001	7.7 ± 9.2	15.2 ± 11.1	23.2 ± 35.9	<.001
International normalized ratio	1.5 ± 0.4	2.1 ± 0.9	<.001	1.7 ± 0.6	2.3 ± 0.9	2.8 ± 1.0	<.001
Alanine aminotransferase (*U/L*)	55 ± 123	67 ± 118	.14	44 ± 53	65 ± 121	169 ± 217	<.001
Aspartate aminotransferase (*U/L*)	93 ± 148	143 ± 268	<.01	80 ± 70	132 ± 174	377 ± 580	<.001
γ-Glutamyltransferase (*U/L*)	177 ± 296	141 ± 160	.01	154 ± 176	120 ± 124	145 ± 178	.22
Serum creatinine (*mg/dL*)	1.0 ± 0.4	2.3 ± 1.6	<.001	2.4 ± 1.4	2.1 ± 1.8	2.6 ± 1.7	<.001
Serum sodium (*mmol/L*)	135 ± 6	133 ± 6	<.001	133 ± 7	133 ± 6	134 ± 7	<.001
Time from first previous decompensation							
No previous decompensation	279 (27.8)	66 (23.2)	.12	21 (16.5)	27 (27.6)	18 (42.9)	<.01
Less than 3 mo	102 (10.8)	47 (17.6)	.02	23 (18.1)	14 (14.3)	10 (23.8)	<.01
From 3 to 12 mo	165 (17.4)	43 (17.1)		21 (16.5)	19 (19.4)	3 (7.1)	
More than 12 mo	402 (42.8)	111 (41.6)		62 (48.8)	38 (38.8)	11 (26.2)	

NOTE. Data are expressed as means ± SD or number of patients (%).
[a]*P* value of comparisons between patients with and without ACLF.
[b]*P* value of comparisons across ACLF grades (no ACLF, ACLF grade 1, ACLF grade 2, and ACLF grade 3).
[c]Other precipitating event was defined by the presence of one of the following: transjugular intrahepatic portosystemic shunting, major surgery, therapeutic paracentesis without use of intravenous albumin, hepatitis, or alcoholic hepatitis (liver biopsy required for diagnosis).
[d]No precipitating event denotes the absence of bacterial infection, active alcoholism, or other precipitating event.
[e]More than one precipitating event denotes the presence of at least 2 of the following: bacterial infection, active alcoholism, or other precipitating event.

independently and significantly associated with mortality (Supplementary Table 6).

Patients with ACLF without previous AD were younger, were more frequently active alcohol drinkers, had a more severe grade of ACLF, and had a higher prevalence of liver, cerebral, coagulation, and respiratory failure; higher leukocyte count; and higher serum levels of C-reactive protein and mortality at 28 days (42.2% vs 29.6%; $P = .03$) than patients with ACLF and prior AD (Table 4). The probability of death in patients with ACLF increased with the rise in the leukocyte count (Figure 2). However, for any given value of leukocyte count, the probability of death was significantly higher in patients without prior AD than in those with prior AD.

Comparison of Patients With Alcoholic Versus Nonalcoholic Cirrhosis

Patients who did not receive a liver transplant during the first 28 days after enrollment were divided into 3 groups: nonalcoholic cirrhosis, alcoholic cirrhosis without active alcoholism, and alcoholic cirrhosis associated with active alcoholism during the past 3 months (Table 5). There were no major differences between patients with nonalcoholic cirrhosis and those with alcoholic cirrhosis and no active alcoholism. In contrast, patients with alcoholic cirrhosis and active alcoholism significantly differed from those of the other 2 groups in that they were

Table 4. Characteristics of Patients at the Onset of ACLF According to Prior History of AD

Characteristic	Any prior AD (n = 294)	No prior AD (n = 98)	*P* value
Age (*y*)	56.2 ± 11.6	54.6 ± 11.8	.28
Male sex	190 (64.6)	60 (61.2)	.54
Cause of cirrhosis			
Alcohol	161 (56.9)	59 (62.8)	.32
Hepatitis C virus	45 (15.9)	11 (11.7)	.32
Alcohol plus hepatitis C virus	25 (8.9)	9 (9.6)	.84
Potential precipitating events of ACLF			
Bacterial infection	110 (38.1)	44 (45.8)	.18
Active alcoholism within the past 3 mo	47 (17.1)	36 (37.5)	<.0001
Other precipitating event	31 (11.0)	7 (7.4)	.31
Any precipitating event	168 (59.8)	69 (71.9)	.03
More than one precipitating event	18 (31.6)	6 (23.1)	.42
Organ failures			
Liver	99 (35.7)	45 (47.9)	.04
Kidney	141 (50.9)	43 (45.7)	.39
Cerebral	55 (19.9)	27 (28.7)	.07
Coagulation	80 (28.9)	37 (39.4)	.06
Circulation	65 (23.5)	22 (23.4)	.99
Lungs	26 (9.4)	22 (23.4)	<.001
ACLF grade			
Grade 1	161 (54.8)	40 (40.8)	.02
Grade 2	100 (34.0)	38 (38.8)	
Grade 3	33 (11.2)	20 (20.4)	
Laboratory data			
Leukocyte count ($\times 10^9$/L)	8.9 ± 5.8	11.9 ± 6.1	<.001
Platelet count ($\times 10^9$/L)	89 ± 66	113 ± 83	.02
Serum bilirubin (μmol/L)	10.9 ± 11.1	14.0 ± 12.1	.03
International normalized ratio	2.1 ± 1.0	2.2 ± 1.0	.25
Alanine aminotransferase (U/L)	66 ± 127	79 ± 117	.43
Aspartate aminotransferase (U/L)	145 ± 386	233 ± 468	.13
γ-Glutamyltransferase (U/L)	112 ± 154	180 ± 166	<.01
Serum creatinine (μmol/L)	2.0 ± 1.2	1.9 ± 1.4	.38
C-reactive protein (mg/L)[a]	38 ± 40	51 ± 44	.03

NOTE. Data about previous AD were missing in 23 patients. Data are presented as means ± SD or number of patients (%).
[a]The upper limit of normal values for C-reactive protein was 5 mg/L.

younger and had more marked laboratory alterations (Table 5). They also had a higher prevalence of corticosteroid therapy. Although the prevalence and severity of ACLF were higher in patients with alcoholic cirrhosis and active alcoholism than in the rest of the patients, there were not significant differences in mortality between groups (Table 5).

Supplementary Results provides information on the site of hospitalization (Supplementary Table 9), therapies used for kidney failure and ascites, and relationships of regional variation in prevalence of ACLF with outcomes (Supplementary Table 10 and Supplementary Figure 3).

Discussion

The aim of the current study was to establish the diagnostic criteria of ACLF and subsequently to assess the natural history of this syndrome. There was no "evidence-based" definition of ACLF at the time of this study, so we had to assume several important issues. First, the study was performed in patients with AD because this is an essential component of the syndrome. Here, we assumed that organ failure detected at study enrollment developed simultaneously with AD and not before. This assumption was probably correct because the thresholds used for the diagnosis of organ failure were very restrictive, and hence organ failures were unlikely to be present in patients with compensated or moderately decompensated cirrhosis. The second component of ACLF was the presence of organ failure. We decided to include organ failure considered in the SOFA score because it has already been used in cirrhosis,[22–24] but we modified definitions of SOFA subscores according to the authors' experience. Finally, the third component of the syndrome was high short-term mortality. We predefined a 28-day mortality rate greater than 15% as a threshold. This assumption was confirmed with the results shown in patients with single organ failure (Table 2).

Using easily available parameters included in the CLIF-SOFA score, we were able to differentiate patients with ACLF from those without ACLF (ie, with "mere" AD) (Figure 1). Interestingly, we found that cirrhotic patients with AD and single liver failure (or any other single "non-kidney" organ failure) had a low risk of death unless they also had kidney dysfunction and/or mild to moderate hepatic encephalopathy (Table 2). These findings indicate that, when isolated, liver failure (as defined by the CLIF-SOFA score) is dispensable for the diagnosis of ACLF.

In addition to the presence of organ failure and very high risk of short-term mortality, patients with ACLF exhibited other differential characteristics from patients without ACLF. They were younger, more frequently had alcoholic cirrhosis, and less frequently had hepatitis C virus–related cirrhosis and exhibited a higher prevalence of associated potential precipitating events, particularly active alcoholism and severe bacterial infections, and data consistent with an intense systemic inflammatory response (ie, high leukocyte count and plasma C-reactive protein concentration). The intensity of this inflammatory response paralleled the severity of ACLF. Our data do not confirm the generally accepted paradigm that organ failure in cirrhosis is a terminal event that develops at the latest phases in the clinical course of the disease. In half of our patients with ACLF, this syndrome developed in the absence of a prior history of AD or a few weeks (less than 3 months) after the first AD.

Our study indicates that ACLF is an extremely relevant syndrome. First, it is very frequent. The overall prevalence in our patients was 30.9%. Second, it is associated with a very high mortality rate in comparison with that in patients without ACLF; the 28-day mortality rate was 15 times higher in patients with ACLF. Finally, it is an important cause of death in patients with cirrhosis. In fact, the most frequent cause of death in our patients was multiple organ failure without septic or hypovolemic shock.

An outstanding observation was that 43% of patients with ACLF at enrollment did not have any identifiable potential precipitating event of the syndrome and that the presence or absence or the type of precipitating event was

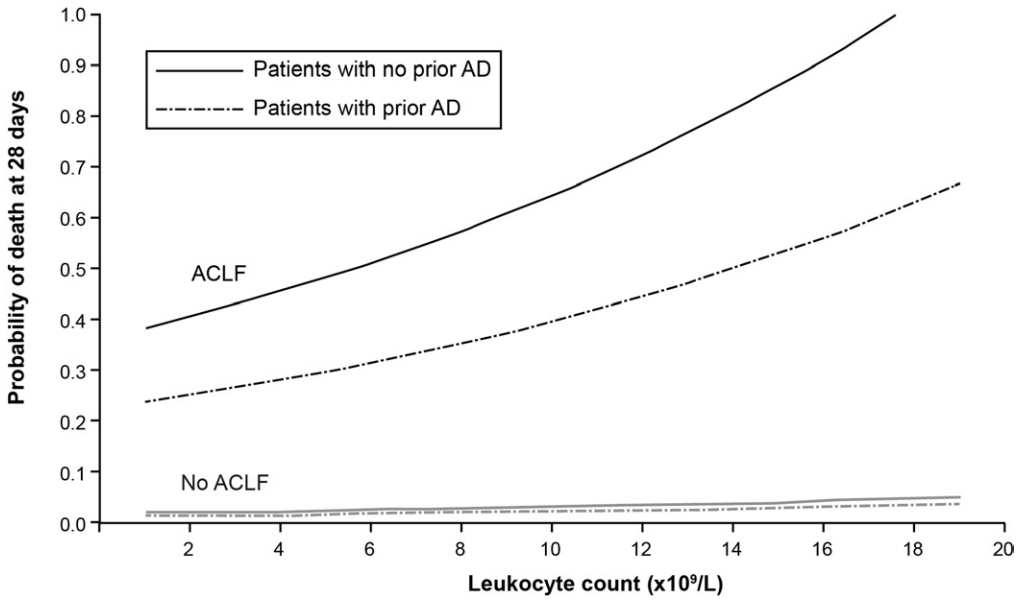

Figure 2. Relationship between the estimated probability of death at 28 days and leukocyte count according to the presence of ACLF and prior history of AD.

unrelated to the severity of ACLF and 28-day mortality rate. Together these results indicate that there is no clear explanation of ACLF development in a significant number of patients and that although precipitating events are triggers for ACLF in a proportion of patients, they are not major determinants of the number of failing organs and short-term mortality. In our study, the diagnosis of bacterial infection was based on standard routine procedures (see study protocol). It cannot be excluded that the prevalence of bacterial infections would have been higher if more sensitive diagnostic techniques had been used. Alternatively, the release of pathogen-associated molecular patterns (resulting from "aseptic" intestinal bacterial translocation) or that of danger-associated molecular patterns (resulting from tissue injury) might be unrecognized "precipitating events."[5] In addition, it is possible that some precipitating events were not diagnosed because of their nature (eg, drug-induced liver injury) or due to the large study scale.

As expected, the CLIF-SOFA scores measured at enrollment and at diagnosis of ACLF were independent risk factors of postenrollment development of ACLF and ACLF-associated mortality, respectively. It was also not surprising that ascites at enrollment was a risk factor of postenrollment development of ACLF because it is an independent predictive factor of kidney failure following bacterial infection.[25,26]

However, in our study, 2 other unexpected predictors of development of ACLF and associated mortality were identified. The first was the degree of inflammatory reaction as estimated by the leukocyte count, which was an independent predictor of postenrollment development of ACLF and ACLF-associated mortality. The second was the prior history of AD. Contrary to what could be expected, patients without previous AD developed a more severe form of ACLF, higher levels of inflammatory mediators, and higher rates of mortality than patients with previous AD.

An excessive inflammatory response, as observed in patients with ACLF, may induce tissue damage (a process called immunopathology) and organ failure.[30] On the other hand, it has been suggested that inflammation-induced tissue damage depends not only on the intensity of the inflammatory response per se but also on the intrinsic capacity of host organs to tolerate (ie, endure) the effects of the inflammatory response.[30] A decrease in the capacity of tolerance of vital organs can sensitize these organs to tissue damage caused by moderate increases in the inflammatory response.[30] Here, we found that for any given value of white blood cell count (and presumably inflammation), the probability of mortality was high in patients with ACLF and no previous AD, intermediate with ACLF and no previous AD, intermediate in patients with ACLF and previous AD, and very low in patients without ACLF irrespective of the past history of AD. Thus, patients with ACLF may be characterized by a decrease in the capacity of tolerance of different end-organs to the inflammatory response of the host; this decrease appeared to be more marked in patients without previous AD than in those with previous AD.

In this study, liver biopsy was performed in very few patients with AD. Therefore, it is not possible to know the exact frequency of alcoholic hepatitis. Nevertheless, we found features consistent with the potential diagnosis of alcoholic hepatitis in the subset of patients with active alcoholism during the past 3 months (which represented only 30% of patients with alcoholic cirrhosis). Interestingly, there were no major differences between the group of patients with alcoholic cirrhosis and no active alcoholism and those with nonalcoholic cirrhosis (which were considered as "negative controls"). Together these findings suggest that there was no overrepresentation of alcoholic hepatitis in our study.

Whether patients with ACLF should be admitted or not to the intensive care unit is controversial.[23] Our study was not designed to address this question. Nevertheless, our results can serve as a resource for designing studies aimed

Table 5. Characteristics of Patients According to the Etiology of Cirrhosis and the Presence or Absence of Active Alcohol Consumption Within the Prior 3 Months Before Enrollment

Characteristic	Patients with nonalcoholic cirrhosis (n = 461)	Patients with alcoholic cirrhosis without active alcohol consumption (n = 492)	Patients with alcoholic cirrhosis and active alcohol consumption (n = 198)
Age (*y*)	61 ± 14	57 ± 10	52 ± 9[a]
No previous decompensation	122 (27.5)	117 (24.4)	72 (37.9)[a]
Any previous hospitalization	226 (49.9)	209 (43.5)	77 (39.5)
Any precipitating event[c]	202 (45.0)	215 (44.0)	198 (100)[a]
More than one precipitating event[c]	30 (6.7)	24 (4.9)	102 (51.5)[a]
Categories of precipitating events			
Bacterial infection	128 (27.9)	113 (23.0)	38 (19.2)
Spontaneous bacterial peritonitis	36 (8.0)	32 (6.7)	6 (3.1)[b]
Gastrointestinal hemorrhage	73 (15.8)	75 (15.2)	47 (23.7)[a]
Other precipitating events	11 (2.5)	19 (3.9)	25 (13.4)[b]
Ascites at enrollment	296 (64.4)	325 (66.5)	130 (65.7)
Hepatic encephalopathy at enrollment	149 (32.3)	163 (33.2)	74 (37.6)
Mean arterial pressure at enrollment	83 ± 12	84 ± 12	84 ± 15
Administration of corticosteroids during hospitalization	33 (7.2)	39 (7.9)	47 (23.7)[a]
ACLF during hospitalization			
No ACLF	349 (75.7)	337 (68.5)	113 (57.1)[a]
All ACLF	112 (24.3)	155 (31.5)	85 (42.9)[a]
ACLF grade I	63 (13.7)	93 (18.9)	31 (15.6)
ACLF grade II	34 (7.4)	46 (9.4)	35 (17.7)
ACLF grade III	15 (3.2)	16 (3.3)	19 (9.6)
Laboratory data			
Hematocrit (*%*)	31 ± 6	31 ± 6	30 ± 6
Platelet count ($\times 10^9$/*L*)	103 ± 70	114 ± 78	110 ± 73
Serum bilirubin (*mg/dL*)	5.5 ± 8.1	5.3 ± 8.0	9.8 ± 9.1[a]
International normalized ratio	1.6 ± 0.5	1.7 ± 0.6	1.8 ± 0.7[a]
Aspartate aminotransferase (*U/L*)	97 ± 160	90 ± 202	142 ± 171[a]
Alanine aminotransferase (*U/L*)	61 ± 146	50 ± 113	59 ± 74
γ-Glutamyltransferase (*U/L*)	116 ± 137	152 ± 211	340 ± 522[a]
Serum creatinine (*mg/dL*)	1.2 ± 0.9	1.3 ± 1.1	1.2 ± 1.1
Serum sodium (*mmol/L*)	136 ± 6	135 ± 6	135 ± 6
Leukocyte count ($\times 10^9$/*L*)	6.6 ± 4.2	7.6 ± 5.0	9.1 ± 5.5[a]
C-reactive protein (*mg/L*)	27 ± 36	29 ± 36	33 ± 38
28-Day mortality	48 (10.4)	54 (11.0)	29 (14.6)

NOTE. Data are expressed as means ± SD or number of patients (%).
[a]$P < .01$ vs the other 2 groups.
[b]$P < .05$ vs the other 2 groups.

to investigate the appropriate site of hospitalization for patients with ACLF.

In this study, enrolled patients from Belgium, France, and the United Kingdom had more severe cases than those from Italy, Spain, or Germany. The reasons for these differences are unclear. However, we found a close correlation between the prevalence of ACLF in each country on one hand and short-term mortality and the prevalence of liver transplantation on the other, suggesting homogeneous management of ACLF across the European countries involved in the study.

In conclusion, our study provides robust diagnostic criteria for ACLF. Using these diagnostic criteria allowed us to provide evidence that ACLF is distinct from "mere" AD. The prevalence of ACLF in patients with AD is 30%; it is associated with a short-term mortality rate 15 times higher than that in patients with AD alone. Patients with ACLF may or may not have a prior history of AD. Besides the alteration of end-organ functions, mortality associated with ACLF is related to high leukocyte count but not to causes of inflammation. ACLF is especially severe in patients without a prior history of AD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of GASTROENTEROLOGY at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2013.02.042.

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Reprint requests

Address requests for reprints to: Pere Gines, Liver Unit, Hospital Clinic, University of Barcelona, Catalonia, Spain. e-mail: pgines@clinic.ub.es; fax: (34) 93 2271779.

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A list of CANONIC study investigators is provided in the Appendix.

Conflicts of interest

The authors disclose the following: This is the first result of an initiative of several European and American investigators to potentiate research in chronic liver failure (CLIF). An assembly of European hepatologists proposed the European Association for the Study of the Liver (EASL) to endorse a consortium aimed to promote research on CLIF, to stimulate the formation of research groups in this field in Europe, and to identify potential areas of common interest with European industry. The Executive Committee of EASL accepted to endorse the consortium on June 2009 and elected V.A. and M.B. as chairman and vice-chairman, respectively, for 5 years. Twelve other EASL members proposed by the assembly were elected to form the Steering Committee. From 2009 to 2012, the EASL-CLIF Consortium received unrestricted grants from Grifols and Gambro. Grifols has prolonged its unrestricted grant for an additional 4 years. There is no other support for the consortium. The Fundació Clinic, a foundation ruled by the Hospital Clinic and University of Barcelona, administers the EASL-CLIF Consortium grants. V.A., M.B., and members of the Steering Committee have no relationship with Grifols or Gambro other than conferences in international meetings (from which they may receive an honorarium) or as investigators on specific projects unrelated to the consortium. Until now the EASL-CLIF Consortium has not performed any study promoted by pharmaceutical companies. The scientific agenda of the EASL-CLIF Consortium and the specific research protocols are made exclusively by the Steering Committee members without any participation of pharmaceutical companies. R.J. received research funding from Vital Therapies, has served on a scientific advisory board for Conatus Pharma, and received lecture fees from Gambro. P.G. has received speaker honorarium and research funding from Grifols, served on the scientific advisory board for Ferring and Sequana, and received research funding from Sequana. J.C. has served as a consultant to Ocera. A.G. has served as a consultant to CSL Behring. S.Z. has served as a consultant to Abbott, Achillion, AstraZeneca, Bristol Myers-Squibb, Boehringer Ingelheim, Gilead, Janssen Cilag, Merck, Novartis, Presidio, Roche, Santaris, and Vertex. V.A. has received grant and research support from Grifols. The remaining authors disclose no conflicts.

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Appendix. Alphabetical List of CANONIC Study Investigators

Patricia Aguilar Melero, Hospital Universitario Reina Sofía, Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Córdoba, Spain

Agustin Albillos, Servicio de Gastroenterología, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, CIBERehd, Madrid, Spain

Carlo Alessandria, Division of Gastroenterology and Hepatology, San Giovanni Battista Hospital, University of Turin, Turin, Italy

Paolo Angeli, Department of Medicine, Unit of Hepatic Emergencies and Liver Transplantation, University of Padova, Padova, Italy

Vicente Arroyo, Liver Unit, Hospital Clinic, University of Barcelona, CLIF Consortium, CIBERehd, Barcelona, Spain

Rafael Bañares, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), CIBERehd, School of Medicine, Universidad Complutense, Madrid, Spain

Daniel Benten, Department of Gastroenterology and Hepatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Mauro Bernardi, Semeiotica Medica, Policlinico S. Orsola-Malpighi, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Massimo Bocci, Department of Gastroenterology and Hepato-Pancreatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

Paolo Caraceni, Semeiotica Medica, Policlinico S. Orsola-Malpighi, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

María-Vega Catalina, Hospital General Universitario Gregorio Marañón, IiSGM, CIBERehd, Madrid, Spain

Jun Liong Chin, Liver Unit, St Vincent's University Hospital, Dublin, Ireland

Minneke J. Coenraad, Department of Gastroenterology-Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

Audrey Coilly, Centre Hépato-Biliaire, Hôpital Paul-Brousse, Assistance Publique-Hôpitaux de Paris, Villejuif, France

Mar Concepción, Department of Gastroenterology, Hospital de la Santa Creu i Sant Pau, Barcelona, Universitat Autònoma de Barcelona, Barcelona, Spain

Juan Cordoba, Servicio de Hepatologia, Hospital Vall d'Hebron, Universitat Autònoma de Barcelona, CIBERehd, Barcelona, Spain

Andrea de Gottardi, University Clinic of Visceral Surgery and Medicine of Berne, Berne, Switzerland

Manuel de la Mata, García Hospital Universitario Reina Sofía, CIBERehd, IMIBIC, Córdoba, Spain

Carme Deulofeu, Data Management Centre, CLIF Consortium, Hospital Clinic, Barcelona, Spain

Marco Domenicali, Semeiotica Medica, Policlinico S. Orsola-Malpighi, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Livia Dorn, Department of Gastroenterology and Hepatology, Innsbruck Medical University, Innsbruck, Austria

François Durand, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique Hôpitaux de Paris, Clichy; Inserm U773, Centre de Recherche Biomédicale Bichat-Beaujon CRB3, Clichy and Paris; and Université Paris Diderot-Paris 7, Paris, France

Laure Elkrief, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique Hôpitaux de Paris, Clichy; Inserm U773, Centre de Recherche Biomédicale Bichat-Beaujon CRB3, Clichy and Paris; and Université Paris Diderot-Paris 7, Paris, France

Javier Fernandez, Liver Unit, Hospital Clinic, University of Barcelona, CLIF Consortium, CIBERehd, Barcelona, Spain

Elisabet Garcia, Data Management Centre, CLIF Consortium, Hospital Clinic, Barcelona, Spain

Angelo Gatta, Department of Medicine, University of Padova, Padova, Italy

Ludmila Gerber, Department of Medicine I, JW Goethe University Hospital, Frankfurt, Germany

Alexander Gerbes, Liver Center Munich, Department of Medicine 2, Klinikum der LMU München-Grosshadern, Munich, Germany

Pere Ginès, Liver Unit, Hospital Clinic, University of Barcelona, CIBERehd, Barcelona, Spain

Henning Grøenbæk, Department of Medicine V, Unit of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

Monica Guevara, Liver Unit, Hospital Clinic, University of Barcelona, CIBERehd, Barcelona, Spain

Thierry Gustot, Department of Gastroenterology and Hepato-Pancreatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

AnneKristin Hausen, Department of Internal Medicine I, University Hospital of Bonn, Bonn, Germany

Corinna Hopf, Liver Center Munich, Department of Medicine 2, Klinikum der LMU München-Grosshadern, Munich, Germany

Rajiv Jalan, Institute of Liver and Digestive Health, Liver Failure Group, Royal Free Campus, London, England

Stine Karlsen, Department of Medicine V, Unit of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

Wim Laleman, Department of Liver and Biliopancreatic Diseases, University Hospital Gasthuisberg, KU Leuven, Leuven, Belgium

Ansgar W. Lohse, Department of Gastroenterology and Hepatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Caterina Maggioli, Semeiotica Medica, Policlinico S. Orsola-Malpighi, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Daniel Markwardt, Liver Center Munich, Department of Medicine 2, Klinikum der LMU München-Grosshadern, Munich, Germany

Javier Martinez, Servicio de Gastroenterología, Hospital Universitario Ramón y Cajal, Madrid, Spain

Alfredo Marzano, Division of Gastroenterology and Hepatology, San Giovanni Battista Hospital, University of Turin, Turin, Italy

P. Aiden McCormick, Liver Unit, St Vincent's University Hospital, Dublin, Ireland

Francisco Mesonero, Servicio de Gastroenterología, Hospital Universitario Ramón y Cajal, Madrid, Spain

José Luis Montero Álvarez, Hospital Universitario Reina Sofía, CIBERehd, IMIBIC, Córdoba, Spain

Rajeshwar P. Mookerjee, Institute of Liver and Digestive Health, Liver Failure Group, Royal Free Campus, London, England

Filippo Morando, Department of Medicine, University of Padova, Padova, Italy

Richard Moreau, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique Hôpitaux de Paris, Clichy; Inserm U773, Centre de Recherche Biomédicale Bichat-Beaujon CRB3, Clichy and Paris; and Université Paris Diderot-Paris 7, Paris, France

Christophe Moreno, Department of Gastroenterology and Hepato-Pancreatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

Bernhard Morrell, University Clinic of Visceral Surgery and Medicine of Berne, Berne, Switzerland

Christian Mortensen, Department of Gastroenterology, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark

Frederik Nevens, Department of Liver and Biliopancreatic Diseases, University Hospital Gasthuisberg, KU Leuven, Leuven, Belgium

Marco Pavesi, Data Management Centre, CLIF Consortium, Hospital Clinic, CIBERehd, Barcelona, Spain

Markus Peck-Radosavljevic, Department of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria

Gustavo Pereira, Liver Unit, Hospital Clinic, University of Barcelona, CIBERehd, Barcelona, Spain

Alessandro Risso, Division of Gastroenterology and Hepatology, San Giovanni Battista Hospital, University of Turin, Turin, Italy

Mario Rizzetto, Division of Gastroenterology and Hepatology, San Giovanni Battista Hospital, University of Turin, Turin, Italy

Ezequiel Rodriguez, Liver Unit, Hospital Clinic, University of Barcelona, CIBERehd, Barcelona, Spain

Antonietta Romano, Department of Medicine, University of Padova, Padova, Italy

Faouzi Saliba, Centre Hépato-Biliaire, Hôpital Paul-Brousse, Assistance Publique-Hôpitaux de Paris, Villejuif, France

Didier Samuel, Centre Hépato-Biliaire, Hôpital Paul Brousse, Assistance Publique-Hôpitaux de Paris, Villejuif, France

Tilman Sauerbruch, Department of Internal Medicine I, University Hospital of Bonn, Bonn, Germany

Macarena Simon-Talero, Servicio de Hepatologia, Hospital Vall d'Hebron, Universitat Autònoma de Barcelona, CIBERehd, Barcelona, Spain

Pablo Solis-Muñoz, Institute of Liver Studies and the Cellular Biology of Inflammation, King's College London, London, England

German Soriano, Department of Gastroenterology, Hospital de la Santa Creu i Sant Pau, Barcelona, Universitat Autònoma de Barcelona, CIBERehd, Instituto de Salud Carlos III, Barcelona, Spain

Jan Sperl, Department of Hepatogastroenterology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Walter Spindelboeck, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Graz, Austria

Rudolf Stauber, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Graz, Austria

Christian Steib, Liver Center Munich, Department of Medicine 2, Klinikum der LMU München-Grosshadern, Munich, Germany

Jonel Trebicka, Department of Internal Medicine I, University Hospital of Bonn, Bonn, Germany

Dominique Valla, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique Hôpitaux de Paris, Clichy; Inserm U773, Centre de Recherche Biomédicale Bichat-Beaujon CRB3, Clichy and Paris; and Université Paris Diderot-Paris 7, Paris, France

Hans Van Vlierberghe, Department of Gastroenterology and Hepatology, Ghent University Hospital, Ghent, Belgium

Len Verbeke, Department of Liver and Biliopancreatic Diseases, University Hospital Gasthuisberg, KU Leuven, Leuven, Belgium

Wolfgang Vogel, Department of Gastroenterology and Hepatology, Innsbruck Medical University, Innsbruck, Austria

Henninge Wege, Department of Gastroenterology and Hepatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Tania Welzel, Department of Medicine I, JW Goethe University Hospital, Frankfurt, Germany

Julia Wendon, Institute of Liver Studies and the Cellular Biology of Inflammation, King's College London, London, England

Chris Willars, Liver Intensive Care Unit, King's College Hospital, London, England

Maria Yago Baenas, Institute of Liver and Digestive Health, Liver Failure Group, Royal Free Campus, London, England

Giacomo Zaccherini, Semeiotica Medica, Policlinico S. Orsola-Malpighi, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Stefan Zeuzem, Department of Medicine I, JW Goethe University Hospital, Frankfurt, Germany

Supplementary Materials and Methods

Definitions of AD

Acute development of large ascites was defined by the development of grade 2 to 3 ascites, according to the International Ascites Club Classification,[1] within less than 2 weeks; it could be a first episode of ascites or a new episode. Patients with chronic refractory ascites who were admitted to the hospital frequently for therapeutic paracentesis due to rapid reaccumulation of large ascites were not included in this definition.

Acute hepatic encephalopathy was defined by the acute development of a change in mental status in a patient with previous normal consciousness and no evidence of an acute neurologic disease.[2] It could be the first episode of hepatic encephalopathy or a new episode. Patients with chronic hepatic encephalopathy were not included in this definition.

Acute gastrointestinal hemorrhage was defined by the development of an upper and/or lower gastrointestinal bleeding of any etiology.[3]

Although bacterial infections are not specific complications of cirrhosis, they were considered as such because of their high prevalence and association to abnormalities related to cirrhosis, including bacterial translocation and impaired leukocyte functions.[4,5] Spontaneous bacterial peritonitis, spontaneous bacteremia, urinary tract infection, pneumonia, and cellulitis, the most frequent infections in cirrhosis,[5] as well as any other type of acute bacterial infection were included in this definition.

Definitions of Organ Failures

Liver failure was defined by a serum bilirubin level of $\geq$12.0 mg/dL.[6]

Kidney failure was defined by a serum creatinine level of $\geq$2.0 mg/dL or the use of renal replacement therapy. The reason for using this serum creatinine threshold is that relatively low increases of serum creatinine levels in cirrhosis indicate marked reductions in glomerular filtration rate, and there is a large body of evidence indicating that serum creatinine levels $\geq$2 mg/dL are associated with poor prognosis.[7,8]

Cerebral failure was defined by grade III or IV hepatic encephalopathy, according to the West Haven classification.[2]

Coagulation failure was defined by an international normalized ratio$>$2.5 and/or a platelet count of $\leq 20 \times 10^9$/L. International normalized ratio was included because it is commonly used in cirrhosis and has been validated as a prognostic factor.[9]

Circulatory failure was defined by the use of dopamine, dobutamine, or terlipressin. The use of terlipressin was included in the assessment because it is frequently used as a vasoconstrictor in cirrhosis.[7,8] Any dose of dobutamine or terlipressin was taken into account; doses for dopamine, E and NE vasoconstrictors were in micrograms per kilogram per minute.

Respiratory failure was defined by a ratio of partial pressure of arterial oxygen to FiO_2 of $\leq$200 (by analogy with the SOFA score)[10] or an SpO_2 to FiO_2 ratio of $\leq$200.[11] The possibility of using the SpO_2 to FiO_2 ratio was offered because arterial catheterization is not a standard procedure in patients with cirrhosis admitted to regular wards.

Supplementary Results

Study enrollment did not coincide with hospital admission because (1) the study protocol prespecified that patients should be hospitalized for at least 1 day before enrollment, (2) admission occurred during the weekend, (3) patient's transfer to the liver unit was from another ward of the same hospital, (4) patient's transfer was from another hospital (this was the case for 308 patients [22.9%]), or (5) AD that led to enrollment occurred late during the hospital stay in patients admitted to the hospital for a scheduled procedure (eg, band ligation, radiofrequency, transjugular intrahepatic portosystemic shunting) or reasons unrelated to cirrhosis (eg, surgery, trauma, symptomatic renal stones). Clinical and laboratory data were obtained at enrollment in all patients (data were used to define organ failure at enrollment) and at the time of diagnosis of organ failure in those without organ failure at enrollment but developing organ failure during the 28 day follow-up (data were used to define postenrollment organ failure). Potential precipitating events (other than active alcoholism) of organ failure at enrollment were those present at admission or developing between admission and enrollment. In patients without organ failure at enrollment but developing organ failure during follow-up, potential precipitating events were those present at admission or developing between admission and diagnosis of postenrollment organ failure.

Site of Hospitalization

Supplementary Table 9 shows that 23.9% of patients were admitted to the intensive care unit at enrollment or during hospitalization. Patients who were admitted to the intensive care unit had more severe conditions than those not admitted in terms of CLIF-SOFA and Model of End-Stage Liver Disease (MELD) scores, presence of ACLF, grade of ACLF, and 28-day mortality rate.

Therapies Used for Kidney Failure and Ascites in the 699 Patients With 28-Day Follow-up

Among the 425 patients with kidney failure, 136 (31.8%) were treated with vasoconstrictors (91 [21.4%] with terlipressin, 17 [4.0%] with noradrenaline, and 28 [6.7%] with other drugs [including midodrine]). A total of 101 patients (23.8%) received renal replacement therapy.

Among the 291 patients treated with paracentesis, 225 (77.3%) received intravenous albumin. This solution was

given in 67.7% of the 158 patients with a volume of removed ascitic fluid of <5 L and 90% of the 192 patients with a volume of ascitic fluid of ≥5 L (there were 59 patients receiving more than one paracentesis treatment).

Regional Variation in Prevalence of ACLF and Outcomes

We analyzed these features in the 6 countries that enrolled 90 patients or more (ie, Germany, Italy, Spain, Belgium, France, and the United Kingdom) (Supplementary Table 10). Patients were more severely ill in Belgium, France, and the United Kingdom than in the other 3 countries, for example, in terms of MELD and CLIF-SOFA sores measured at enrollment, prevalence and severity of ACLF, 28-day mortality rate, and liver transplantation within the first 28 days after enrollment. Nevertheless, there was a significant direct correlation between the prevalence of ACLF in each country and corresponding 28-day transplant-free mortality (Supplementary Figure 3*A*) or the prevalence of liver transplantation within the first 28 days after enrollment (Supplementary Figure 3*B*).

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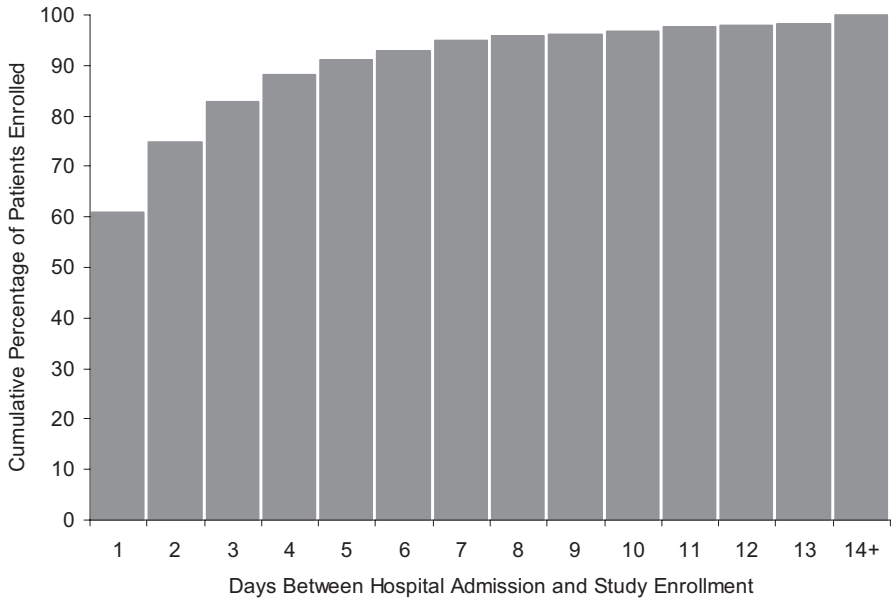


Supplementary Figure 1. Elapsed time between hospital admission and enrollment in the study.

Supplementary Table 1. Characteristics of Patients at Enrollment

Characteristics	
Age (*y*)	57.2 ± 12.2
Male sex	850 (63.3)
Patients on waiting list for liver transplantation	181 (13.5)
Etiology of cirrhosis	
Alcohol	659 (51.9)
Hepatitis C virus	248 (19.5)
Alcohol + hepatitis C virus	122 (9.6)
Other	240 (18.9)
No previous decompensation	345 (26.8)
Any previous decompensation	942 (73.2)
Type of previous decompensation	
Ascites	815 (60.7)
Hepatic encephalopathy	406 (32.7)
Gastrointestinal hemorrhage	326 (35.5)
Bacterial infections	128 (11.4)
No previous hospitalization[a]	700 (53.5)
Any previous hospitalization[a]	608 (46.5)
Cause of previous hospitalization[a]	
Ascites	332 (25.7)
Hepatic encephalopathy	189 (14.6)
Bacterial infections	133 (10.3)
Gastrointestinal hemorrhage	106 (8.2)
Hepatorenal syndrome	51 (3.9)
Surgery	52 (4.0)
Other	188 (14.5)
Previous admission to intensive care unit[a]	88 (6.8)
Site of hospitalization at enrollment	
Intensive care unit	196 (14.6)
Ward	1139 (84.8)
Cause of hospitalization at enrollment	
Ascites	892 (66.8)
Hepatic encephalopathy	459 (34.3)
Gastrointestinal hemorrhage	220 (16.4)
Bacterial infection	324 (24.2)
Laboratory data at enrollment	
Hematocrit (*%*)	31 ± 6
Platelet count (×10^9/*L*)	108 ± 75
Serum bilirubin (*mg/dL*)	6.6 ± 10.8
International normalized ratio	1.7 ± 0.6
Aspartate aminotransferase (*U/L*)	104 ± 182
Alanine aminotransferase (*U/L*)	57 ± 122
γ-Glutamyltranspeptidase (*U/L*)	169 ± 272
Serum creatinine (*mg/dL*)	1.3 ± 1.0
Serum sodium (*mmol/L*)	135 ± 6
Leukocyte count (×10^9/*L*)	7.5 ± 4.9
C-reactive protein (*mg/L*)	28.9 ± 35.4
MELD score at enrollment	18.8 ± 7.5
Child–Pugh score at enrollment	9.7 ± 2.1

NOTE. Data are expressed as means ± SD or number of patients (%).
[a]Within the prior 3 months before the hospital admission related to study enrollment.

Supplementary Table 2. Prevalence and Number of Organ Failures at Study Enrollment of the 1343 Patients

	No. of patients	Prevalence
No. of organ failures		
No organ failure	901	67.1%
One organ failure	287	21.4%
2 organ failures	108	8.0%
3 to 6 organ failures	47	3.5%
Type of organ failure		
Liver failure	207	15.4%
Kidney failure	169	12.6%
Coagulation failure	105	7.8%
Cerebral failure	99	7.4%
Circulatory failure	64	4.8%
Respiratory failure	32	2.4%

NOTE. Organ failures were identified according to the CLIF-SOFA scale (see Table 1). In these patients, at enrollment, the Child–Pugh score was 9.7 ± 2.1 (mean ± SD) and the MELD score was 18.8 ± 7.5. The Child–Pugh score can range from 5 to 15, with higher scores indicating more severe liver disease.[13] The MELD score ranges from 6 to 40, with higher scores indicating more severe disease.[10]

Supplementary Table 3. Association Between 28-Day Outcome After Enrollment in Patients With One Organ Failure and Measurements Included in the CLIF-SOFA Score

Measurements	Survivors (n = 229)	Deaths (n = 39)	*P* value
Hepatic encephalopathy grade I–II in patients without cerebral failure (*%*)	26.2	45.7	.0192
Serum creatinine in patients without renal failure (*mg/dL*)	0.9 ± 0.45	1.3 ± 0.48	<.0001
International normalized ratio in patients without coagulation failure	1.6 ± 0.45	1.7 ± 0.36	NS
Mean bilirubin in patients without liver failure (*mg/dL*)	3.5 ± 3.0	3.5 ± 3.0	NS
Mean arterial pressure in patients without circulatory failure (*mm Hg*)	82.2 ± 12.0	84.7 ± 12.0	NS
SpO_2 to FiO_2 ratio in patients without respiratory failure	442.5 ± 57	411.8 ± 89	NS

NOTE. Values are expressed as means ± SD.
NS, not significant; SpO_2, pulse oximetric saturation; FiO_2, fraction of inspired oxygen.

Supplementary Table 4. Severity and Site of Bacterial Infections in Patients Without or With ACLF at Study Enrollment

	No ACLF (n = 1040)	ACLF (n = 303)	*P* value
Bacterial infections	226 (21.8)	98 (32.6)	<.01
Severity			
Sepsis	36 (3.5)	35 (11.9)	<.01
Septic shock	1 (0.1)	10 (3.4)	<.01
Site			
Spontaneous bacterial peritonitis	57 (5.6)	31 (10.6)	<.01
Pneumonia	23 (2.2)	18 (6.1)	<.01
Urinary tract infection	46 (4.5)	18 (6.1)	.28
Skin infection	23 (2.3)	7 (2.4)	.92
Unproved	57 (5.5)	18 (6.1)	.76
Other	25 (2.4)	15 (5.2)	.02

NOTE. Data are expressed as number of patients (%).

Supplementary Table 6. Predictors of Development of Postenrollment ACLF in Patients Without ACLF at Enrollment and of 28-Day Transplant-Free Mortality for the Whole Group of Patients With ACLF[a]

	Odds ratio estimate	95% Confidence interval for the odds ratio	*P* value
Predictive model for the development of postenrollment ACLF[b]			
CLIF-SOFA score (per increase of 1 point)	1.39	1.24–1.57	<.001
Leukocyte count (per increase of 1 $\times 10^9$/L)	1.06	1.01–1.11	.01
Ascites at admission (yes vs no)	1.67	1.04–2.68	.03
Predictive model for 28-day transplant-free mortality in patients who had ACLF at enrollment or developed ACLF after enrollment[c]			
CLIF-SOFA score (per increase of 1 point)	1.34	1.21–1.49	<.001
Leukocyte count (per increase of 1 $\times 10^9$/L)	1.08	1.03–1.13	<.01

[a]The whole group of 415 patients with ACLF includes 303 patients with ACLF at enrollment and 112 patients who developed postenrollment ACLF. A stepwise forward selection method based on log-likelihood ratio was applied in both logistic regression models (*P* value in = *P* value out of less than .05).

[b]Measurements used to assess risk factors of ACLF development were those obtained at enrollment in patients without ACLF. Other potential predictors included in the initial model were any precipitating event, bacterial infection, excessive alcohol consumption, mean arterial pressure, aspartate aminotransferase level, serum sodium level, and prior episodes of decompensated cirrhosis.

[c]Measurements used to assess risk factors of mortality associated with ACLF were those obtained at diagnosis of ACLF (at enrollment or after enrollment in patients with postenrollment ACLF). Other potential predictors included in the initial model were the MELD score, alanine aminotransferase level, aspartate aminotransferase level, hepatic encephalopathy, ascites, serum sodium level, prior episode of decompensated cirrhosis, and mean arterial pressure.

Supplementary Table 5. Twenty-Eight–Day Mortality Rate in Patients With ACLF According to the Presence or Absence of Precipitating Events at Enrollment

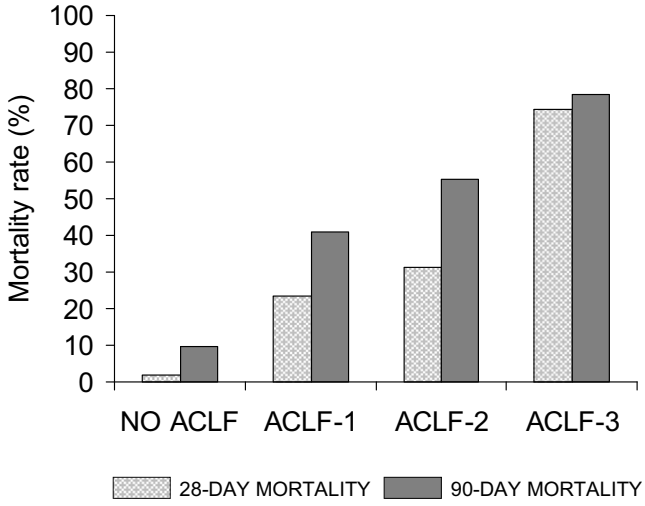
Characteristics	Patients with the characteristic	Patients without the characteristic	*P* value
One or more precipitating events[a]	52/153 (34.0)	39/114 (34.2)	.97
More than one precipitating event[a]	14/38 (36.8)	77/229 (33.6)	.70
Active alcoholism within the 3 months before hospital admission[b]	21/67 (31.3)	67/193 (34.7)	.62
Bacterial infection at enrollment	33/90 (36.7)	62/188 (33.0)	.54
Other precipitating events at enrollment[c]	10/25 (40.0)	82/244 (33.6)	.52

NOTE. Data are expressed as number of deaths/total number of patients (%).

[a]Excluding gastrointestinal hemorrhage.

[b]Active alcoholism was defined as more than 14 drinks per week in women and more than 21 drinks per week in men.

[c]Other precipitating events included therapeutic paracentesis without use of intravenous albumin, transjugular intrahepatic portosystemic shunting, major surgery, acute hepatitis, and alcoholic hepatitis.



Supplementary Figure 2. Mortality rate at 28 days and 90 days according to the grade of ACLF.

Supplementary Table 7. Main Causes of Death at 28 and 90 Days After Study Enrollment

Causes of death	Deaths at 28 days (n = 144)	Deaths at 90 days (n = 265)
Multiple organ failure without septic or hypovolemic shock	63 (43.8)	99 (37.4)
Septic shock	40 (27.8)	62 (23.4)
Hypovolemic shock	12 (8.3)	19 (7.2)
Cirrhosis[a]	0	7 (2.6)
Cerebral hemorrhage	2 (1.4)	4 (1.5)
Myocardial infarction	1 (0.7)	4 (1.5)
Hepatocellular carcinoma	1 (0.7)	4 (1.5)
Non-liver cancer	2 (1.4)	2 (0.8)
Massive pulmonary inhalation	1 (0.7)	2 (0.8)
Epileptic status	1 (0.7)	2 (0.8)
Pulmonary embolism	0	2 (0.8)
Other causes[b]	7 (4.9)	11 (4.2)
Cause unknown	11 (7.6)	42 (15.8)

NOTE. All values are expressed as n (%).

[a]Patients died of cirrhosis, but no specific cause was indicated.

[b]One patient each had pneumonia, cardiomyopathy, cerebral thrombosis, pericarditis, cholangiocarcinoma, postoperative complication, respiratory failure (unknown etiology), acute neurologic disease (unknown etiology), and acute liver failure.

Supplementary Table 8. Leukocyte Count and Plasma C-Reactive Protein Level at Enrollment and After Enrollment in All Patients and in the Specific Group of Patients Without Bacterial Infection[a]

	No ACLF	ACLF (all grades)	ACLF grade 1	ACLF grade 2	ACLF grade 3
At enrollment (all patients)[b]					
Leukocyte count ($\times 10^9$/L)	6.8 ± 4.1	10.1 ± 0.4[c]	8.5 ± 4.7[c]	10.9 ± 6.4[c]	13.0 ± 9.4[c]
C-reactive protein (mg/L)	25.4 ± 31.9	39.4 ± 42.7[c]	33.1 ± 40.0[d]	38.6 ± 32.5[c]	60.6 ± 62.0[c]
At enrollment (patients without bacterial infection)[e]					
Leukocyte count ($\times 10^9$/L)	6.6 ± 3.8	9.4 ± 5.3[c]	8.2 ± 4.3[c]	10.2 ± 6.0[c]	11.7 ± 5.6[c]
C-reactive protein (mg/L)	20.9 ± 24.5	33.4 ± 38.5[c]	24.6 ± 23.3	38.0 ± 33.5[d]	54.8 ± 75.2[d]
After enrollment (all patients)[f]					
Leukocyte count ($\times 10^9$/L)	5.9 ± 4.0	9.3 ± 5.7[c]	8.3 ± 5.6[d]	11.1 ± 6.0[d]	9.3 ± 3.3[d]
C-reactive protein (mg/L)	18.1 ± 17.7	36.2 ± 35.9[c]	39.9 ± 41.8[d]	33.1 ± 28.7[d]	26.5 ± 20.0
After enrollment (patients without bacterial infection)[g]					
Leukocyte count ($\times 10^9$/L)	6.0 ± 3.9	9.0 ± 5.4[c]	7.8 ± 4.6[d]	10.8 ± 6.6[d]	9.2 ± 3.2
C-reactive protein (mg/L)	16.2 ± 14.6	34.4 ± 37.7[c]	36.1 ± 44.6[d]	33.7 ± 31.1[d]	27.3 ± 21.4

NOTE. Data are expressed as means ± SD.

[a]According to the protocol, sequential laboratory measurements after enrollment were performed in all patients with organ failure at enrollment or developing organ failure within 28 days after enrollment and in 262 patients without organ failure.

[b]Leukocyte count and plasma C-reactive protein levels were measured in 1037 and 762 patients without ACLF and in 302 and 249 patients with ACLF, respectively.

[c]$P < .001$ vs no ACLF.

[d]$P < .05$ vs no ACLF.

[e]Leukocyte count and plasma C-reactive protein level were measured in 759 and 550 patients without ACLF and in 176 and 142 patients with ACLF, respectively.

[f]Leukocyte count and plasma C-reactive protein level were measured in 216 and 183 patients without ACLF and in 112 and 85 patients with ACLF, respectively.

[g]Leukocyte count and plasma C-reactive protein level were measured in 158 and 130 patients without ACLF and in 82 and 64 patients with ACLF, respectively.

Supplementary Table 9. Characteristics of Patients Admitted to the Ward or the Intensive Care Unit

Outcomes	Patients hospitalized in the ward (n = 967)	Patients admitted to the intensive care unit either at enrollment or during hospitalization (n = 303)	All patients (n = 1270)
CLIF-SOFA score	6.1 ± 2.5	9.0 ± 3.8	6.9 ± 3.2
MELD score	17.3 ± 6.4	23.8 ± 8.7	18.9 ± 7.6
No ACLF	759 (78.5)	99 (32.7)	858 (67.6)
All ACLF[a]	208 (21.5)	204 (67.3)	412 (32.4)
ACLF grade I	144 (14.9)	69 (22.8)	213 (16.8)
ACLF grade II	56 (5.8)	87 (28.7)	143 (11.3)
ACLF grade III	8 (0.8)	48 (15.8)	56 (4.4)
28-day mortality	44 (4.6)	98 (32.3)	142 (11.2)
28-day liver transplantation	28 (2.9)	24 (7.9)	52 (4.1)

NOTE. Data are expressed as means ± SD or number of patients (%).

[a]Either at enrollment or during the 28-day follow-up.

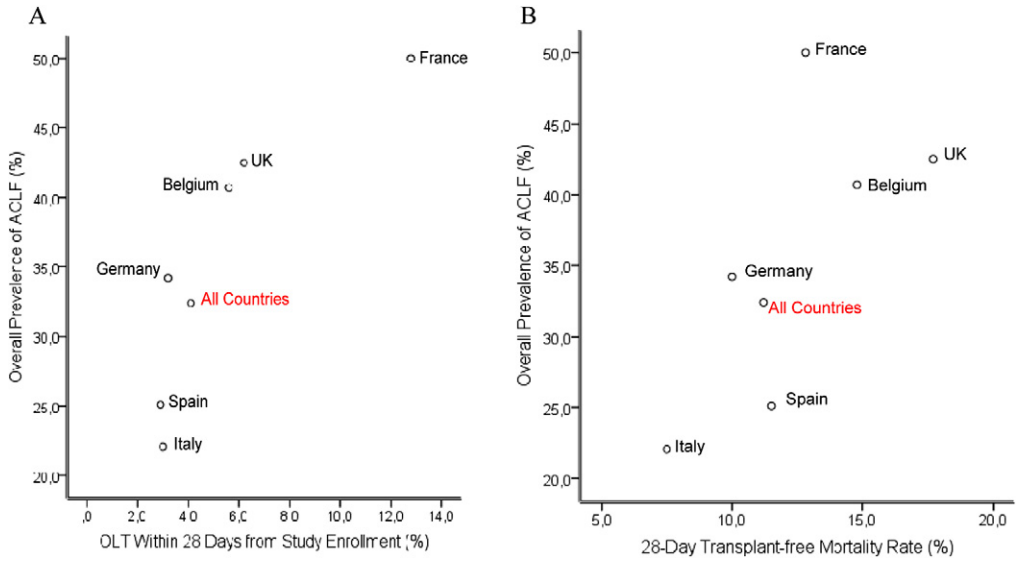
Supplementary Table 10. Characteristics of Patients in Countries That Enrolled 90 Patients or More

Outcomes	Germany (n = 219)	Italy (n = 335)	Spain (n = 279)	Belgium (n = 108)	France (n = 94)	United Kingdom (n = 113)	All (n = 1270)
Etiology of cirrhosis							
Alcohol	123 (60.0)	99 (31.7)	138 (53.5)	70 (65.4)	68 (72.3)	44 (38.9)	620 (51.5)
Hepatitis C virus	21 (10.2)	107 (34.3)	71 (27.5)	10 (9.4)	14 (14.9)	11 (9.7)	241 (20.0)
Alcohol + hepatitis C virus	11 (5.4)	43 (13.8)	19 (7.4)	5 (4.7)	5 (5.3)	14 (12.4)	110 (9.1)
Other	50 (24.4)	63 (20.2)	30 (11.6)	22 (20.6)	7 (7.5)	44 (38.9)	232 (19.3)
Precipitating events at study enrollment							
Any precipitating event	110 (53.4)	103 (33.1)	175 (63.9)	68 (63.0)	54 (61.4)	72 (64.3)	658 (54.1)
Active alcoholism[a]	36 (18.0)	14 (4.6)	35 (12.9)	41 (38.0)	21 (24.4)	31 (28.2)	201 (16.8)
Bacterial infection	48 (22.0)	58 (17.3)	97 (34.8)	31 (28.7)	25 (26.6)	24 (21.2)	308 (24.3)
Gastrointestinal bleeding	25 (11.4)	28 (8.4)	61 (21.9)	13 (12.0)	9 (9.6)	31 (27.4)	206 (16.2)
Other precipitating events	15 (7.3)	5 (1.6)	7 (2.6)	12 (11.2)	7 (7.8)	6 (5.5)	58 (4.8)
CLIF-SOFA score	7.0 ± 3.5	6.2 ± 2.8	6.5 ± 2.8	7.7 ± 3.6	8.3 ± 3.2	7.8 ± 3.4	6.9 ± 3.2
MELD score	18.8 ± 7.5	17.4 ± 7.4	17.7 ± 6.5	18.9 ± 7.9	24.1 ± 7.7	21.9 ± 8.3	18.9 ± 7.6
Prevalence of ACLF either at enrollment or during the 28-day follow-up period							
No ACLF	144 (63.8)	261 (77.9)	209 (74.9)	64 (59.3)	47 (50.0)	65 (57.5)	858 (67.6)
All ACLF	75 (34.2)	74 (22.1)	70 (25.1)	44 (40.7)	47 (50.0)	48 (42.5)	412 (32.4)
ACLF grade I	48 (21.9)	40 (11.9)	46 (16.5)	19 (17.6)	14 (14.9)	17 (15.0)	213 (16.8)
ACLF grade II	16 (7.3)	28 (8.4)	19 (6.8)	15 (13.9)	26 (27.7)	18 (15.9)	143 (11.3)
ACLF grade III	11 (5.0)	6 (1.8)	5 (1.8)	10 (9.3)	7 (7.5)	13 (11.5)	56 (4.4)
28-day liver transplantation	7 (3.2)	10 (3.0)	8 (2.9)	6 (5.6)	12 (12.8)	7 (6.2)	52 (4.1)
Overall 28-day mortality[b]	22 (10.0)	25 (7.5)	32 (11.5)	16 (14.8)	12 (12.8)	20 (17.7)	142 (11.2)
28-day mortality by ACLF							
No ACLF	3 (2.1)	7 (2.7)	5 (2.4)	1 (1.6)	0	1 (1.5)	17 (2.0)
All ACLF	19 (25.3)	19 (25.7)	27 (38.6)	15 (34.1)	12 (25.5)	19 (39.6)	125 (30.3)
90-day liver transplantation	15 (7.1)	27 (8.5)	18 (6.6)	10 (9.4)	16 (18.4)	11 (9.8)	107 (8.7)
Overall 90-day mortality[b]	45 (21.2)	63 (19.8)	54 (19.8)	29 (27.1)	24 (27.6)	23 (20.5)	257 (20.9)
90-day mortality by ACLF							
No ACLF	18 (12.9)	28 (11.4)	21 (10.3)	6 (9.4)	2 (4.8)	3 (4.7)	78 (9.4)
All ACLF	27 (37.5)	35 (48.6)	33 (47.8)	23 (53.5)	22 (48.9)	20 (41.7)	179 (44.4)
Leukocyte count ($\times 10^9/L$)	8.0 ± 5.7	6.4 ± 4.1	7.0 ± 4.3	8.2 ± 5.6	9.3 ± 6.1	8.1 ± 4.1	7.6 ± 4.9
C-reactive protein (*mg/L*)	26.5 ± 35.3	23.7 ± 31.9	20.8 ± 28.0	30.4 ± 39.2	36.6 ± 32.0	50.3 ± 49.1	29.0 ± 35.8

Data are expressed as means ± SD or number of patients (%).

[a]Within the last 3 months before the hospitalization related to study enrollment.

[b]Transplant-free mortality.



Supplementary Figure 3. Relationships between the prevalence of ACLF and prevalence of liver transplantation (*A*: Spearman's $r = 0.94$; $P = .005$) or short-term mortality (*B*: Spearman's $r = 0.77$; $P = .07$).