Clinical Course of Acute-on-Chronic Liver Failure Syndrome and Effects on Prognosis

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Acute-on-chronic liver failure (ACLF) is characterized by acute decompensation (AD) of cirrhosis, organ failure(s), and high 28-day mortality. We investigated whether assessments of patients at specific time points predicted their need for liver transplantation (LT) or the potential futility of their care. We assessed clinical courses of 388 patients who had ACLF at enrollment, from February through September 2011, or during early (28-day) follow-up of the prospective multicenter European Chronic Liver Failure (CLIF) ACLF in Cirrhosis study. We assessed ACLF grades at different time points to define disease resolution, improvement, worsening, or steady or fluctuating course. ACLF resolved or improved in 49.2%, had a steady or fluctuating course in 30.4%, and worsened in 20.4%. The 28-day transplant-free mortality was low-to-moderate (6%-18%) in patients with nonsevere early course (final no ACLF or ACLF-1) and high-to-very high (42%-92%) in those with severe early course (final ACLF-2 or -3) independently of initial grades. Independent predictors of course severity were CLIF Consortium ACLF score (CLIF-C ACLFs) and presence of liver failure (total bilirubin ≥12 mg/dL) at ACLF diagnosis. Eighty-one percent had their final ACLF grade at 1 week, resulting in accurate prediction of short- (28-day) and mid-term (90-day) mortality by ACLF grade at 3-7 days. Among patients that underwent early LT, 75% survived for at least 1 year. Among patients with ≥4 organ failures, or CLIF-C ACLFs >64 at days 3-7 days, and did not undergo LT, mortality was 100% by 28 days. *Conclusions*: Assessment of ACLF patients at 3-7 days of the syndrome provides a tool to define the emergency of LT and a rational basis for intensive care discontinuation owing to futility. (HEPATOLOGY 2015;62:243-252)

Acute-on-chronic liver failure (ACLF) is an increasingly recognized entity characterized by an acute deterioration of a patient with compensated or relatively stable decompensated cirrhosis, frequent requirement of organ supports, and high short-term mortality.[1] Several diagnostic criteria have been proposed within the last decade for this syndrome, but they were based on a theoretical, rather than

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; ANOVA, analysis of variance; AUROC, areas under the receiver operating characteristic curve; CANONIC, Chronic Liver Failure (CLIF) Acute-on-Chronic Failure in Cirrhosis; CI, confidence interval; CLIF-C ACLFs, CLIF Consortium ACLF score; CRP, C-reactive protein; HE, hepatic encephalopathy; ICU, intensive care unit; INR, international normalized ratio; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; OR, odds ratio; PE, precipitating event; SOFA, Sequential Organ Failure Assessment.

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experimental, basis.[2,3] The ACLF definition and diagnostic criteria recently proposed by the Chronic Liver Failure (CLIF) ACLF in Cirrhosis (CANONIC) study, a European prospective, observational investigation performed in 1,343 patients admitted to 29 university hospitals for treatment of a cirrhosis complication, therefore represented the first approach in which the concept, epidemiology, diagnostic criteria, and prognosis of this syndrome have been defined based on prospective data.[4] According to the CANONIC study, ACLF is characterized by an acute decompensation (AD) of cirrhosis (ascites, encephalopathy, gastrointestinal hemorrhage, and/or bacterial infection) associated with organ/system failure(s) (liver, kidney, brain, coagulation, circulation, and/or lung), may develop at any time during the course of the disease (from compensated to long-standing decompensated cirrhosis), and is associated to a short-term (28-day) mortality rate ranging from 23% to 74%, depending on the number of organ failures despite standard supportive medical treatment. This condition is totally distinct from AD without ACLF, which is associated with a very low 28-day mortality rate (<2%). In Western countries, ACLF usually occurs in a context of systemic inflammatory response (characterized by higher leukocyte count and plasma C-reactive protein [CRP] level) as a result of bacterial infections, severe alcoholic hepatitis or to yet unidentified mechanisms.[4,5] The specific management (monitoring/management in intensive care unit [ICU], initiation of artificial organ support and indication of emergency liver transplantation [LT]) of patients with ACLF is still poorly defined.[6]

The prognostic models (i.e., CLIF-Sequential Organ Failure Assessment [SOFA] score or Model for End-Stage Liver Disease [MELD]), are mostly based on the variables measured at one time point, frequently at admission.[4] ACLF is a dynamic process with reversibility suggested in approximately one half of the cases or progress to life-threatening situation.[7] In the general ICU population, sequential assessment of organ failure scores clearly improves the prognostic performance of the admission-based model.[8] Dynamic assessments could more precisely reflect clinical courses of ACLF and better predict outcome of patients. To improve management and minimize futile and expensive care, description of clinical courses of ACLF during hospitalization and associated predicted prognosis is needed.[3]

The aim of the present study is to report on the clinical course of patients with ACLF included in the CANONIC study, relationships of clinical course with ACLF grade at diagnosis and short-term mortality, and predictors of course severity. This would help in identifying conditions either requiring early admission to ICU, organ support treatment and urgent LT, or rendering current medical interventions futile, and provide a rational basis for designing future studies on ACLF therapy.

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† The complete list of CANONIC Study Investigators is reported in the Appendix.

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Potential conflict of interest: Dr. Fernandez received lecture fees from Gambro and Grifols. Prof. Jalan consults for and received grants from Ocera, received research funding from Vital Therapies, has served on the scientific advisory board for Conatus Pharma, and received lecture fees from Gambro, has ongoing research collaboration with Gambro and Grifols, and is the principal investigator of an industry-sponsored study (Sequana Medical). He received grants and speaker fees from Grifols and Norgine. He consults for Conatus. He received grants from Gambro and Sequana. He is also inventor of a drug, L-ornithine phenyl acetate, that University College London has licensed to Ocera Therapeutics. Dr. Ginès consults for Ferring, Ikaria, and Noorik, has received speaker honorarium and research funding from Grifols, served on the scientific advisory board for Ferring and Sequena, and received research funding from Sequena and Ocera. Dr. Arroyo has received grant and research support from Grifols. Dr. Zeuzem consults for and is on the speakers' bureau for AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and Merck. Prof. Durand consults and received grants from Astellas, Novartis, and Gilead. He consults for Bristol-Myers Squibb. Dr. Welzel consults for AbbVie, Boehringer Ingelheim, Gilead, Janssen, and Novartis.

Table 1. Clinical Course Patterns and Types in Those Patients With ACLF Studied*

Initial Grade	Final Grade			
	No ACLF (n = 165)	ACLF-1 (n = 70)	ACLF-2 (n = 59)	ACLF-3 (n = 94)
ACLF-1 (%)				
Prevalence (n = 202)	110 (54.5)	49 (24.3)	18 (8.9)	25 (12.4)
28-day tx-free mortality (n = 190)	7/104 (6.7)	10/47 (21.3)	8/15 (53.3)	21/24 (87.5)
90-day tx-free mortality (n = 172)	19/95 (20.0)	17/41 (41.5)	10/13 (76.9)	23/23 (100)
ACLF-2 (%)				
Prevalence (n = 136)	47 (34.6)	19 (14.0)	35 (25.7)	35 (25.7)
28-day tx-free mortality (n = 118)	1/42 (2.4)	2/17 (11.8)	8/27 (29.6)	29/32 (90.63)
90-day tx-free mortality (n = 110)	5/39 (12.8)	5/16 (31.3)	18/23 (78.3)	32/32 (100)
ACLF-3 (%)				
Prevalence (n = 50)	8 (16.0)	2 (4.0)	6 (12)	34 (68)
28-day tx-free mortality (n = 45)	1/8 (12.5)	0/2 (0.0)	4/6 (66.7)	28/29 (96.6)
90-day tx-free mortality (n = 45)	1/8 (12.5)	1/2 (50.0)	4/6 (66.7)	28/29 (96.6)

ACLF: resolution or improvement (green boxes); steady *or* fluctuating course with unchanged final ACLF grade (uncolored boxes); and worsening (red boxes).
*Prevalence and associated 28- and 90-day transplant (tx)-free mortality.

Patients and Methods

Diagnostic Criteria of ACLF

Diagnostic criteria of ACLF grades were those previously described.[4] ACLF grade 1 (ACLF-1) at diagnosis was defined by presence of kidney failure (serum creatinine $\geq$2 mg/dL) or other single organ/system failure (liver: serum bilirubin $\geq$12 mg/dL; brain: grade III-IV hepatic encephalopathy [HE] based on West Haven criteria; coagulation: international normalized ratio [INR] $\geq$2.5 or platelet count $\leq 20 \times 10^9$/L; circulation: treatment with vasoconstrictors to maintain arterial pressure or inotropes to improve cardiac output; lungs: PaO_2/FiO_2 $\leq$200 or SpO_2/FiO_2 $\leq$214) if associated with kidney dysfunction (serum creatinine ranging from 1.5 to 1.9 mg/dL) and/or mild-to-moderate (grade I-II) HE. ACLF grade 2 (ACLF-2) and ACLF grade 3 (ACLF-3) were defined by the presence of 2 or $\geq$3 organ failures, respectively.

ACLF Clinical Course Definitions

For ACLF patients included in the CANONIC study, ACLF grade was assessed at least at the diagnosis, 3-7 days after diagnosis and then weekly during the 28-day follow-up, until death, LT, or discharge from hospital. All data were prospectively collected and missing data were notified.

The following definitions were used for the assessment of ACLF course.

Clinical Course Pattern. Clinical course pattern was assessed by comparing initial and final ACLF grades. Initial ACLF grade was that measured at diagnosis of the syndrome, either at enrollment of the CANONIC study or during follow-up. Final ACLF grade was that measured at the last available assessment of organ function within the first 28 days after diagnosis, before death, LT, or discharge from hospital. Because there are three initial ACLF grades (1, 2, or 3) and four final grades (no ACLF, ACLF-1, -2, or -3; Table 1), there were 12 different clinical early-course patterns of ACLF. Resolution was defined by changes from ACLF-3, -2, or -1 to no ACLF. Improvement was defined by changes from ACLF-3 to -2 or -1 and from ACLF-2 to -1. Worsening was defined by changes from ACLF-1 to -2 or -3 and from ACLF-2 to -3. Steady course was defined by absence of change of ACLF grades during follow-up. Finally, fluctuating course with unchanged final ACLF grade was defined by variations of ACLF grades during follow-up with similar initial and final grades. The time elapsed between the initial and final ACLF grade was recorded.

Time-Course Profile. We defined time-course profile (Fig. 1A) as very rapid, rapid, or slow resolution, improvement, or worsening when the final ACLF grade was reached within 48 hours, 3-7 days, or 8-28 days after diagnosis, respectively.

Patients

In the prospective, observational CANONIC study, informed consent in writing was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in approval by the institutional review committee. Three hundred eighty-eight patients of the CANONIC study were included in the present study because they had: (1) ACLF at enrollment (n = 291) or developed this syndrome during follow-up (n = 97) and (2) complete clinical and laboratory data at diagnosis and last assessment of ACLF during the 28-day follow-up

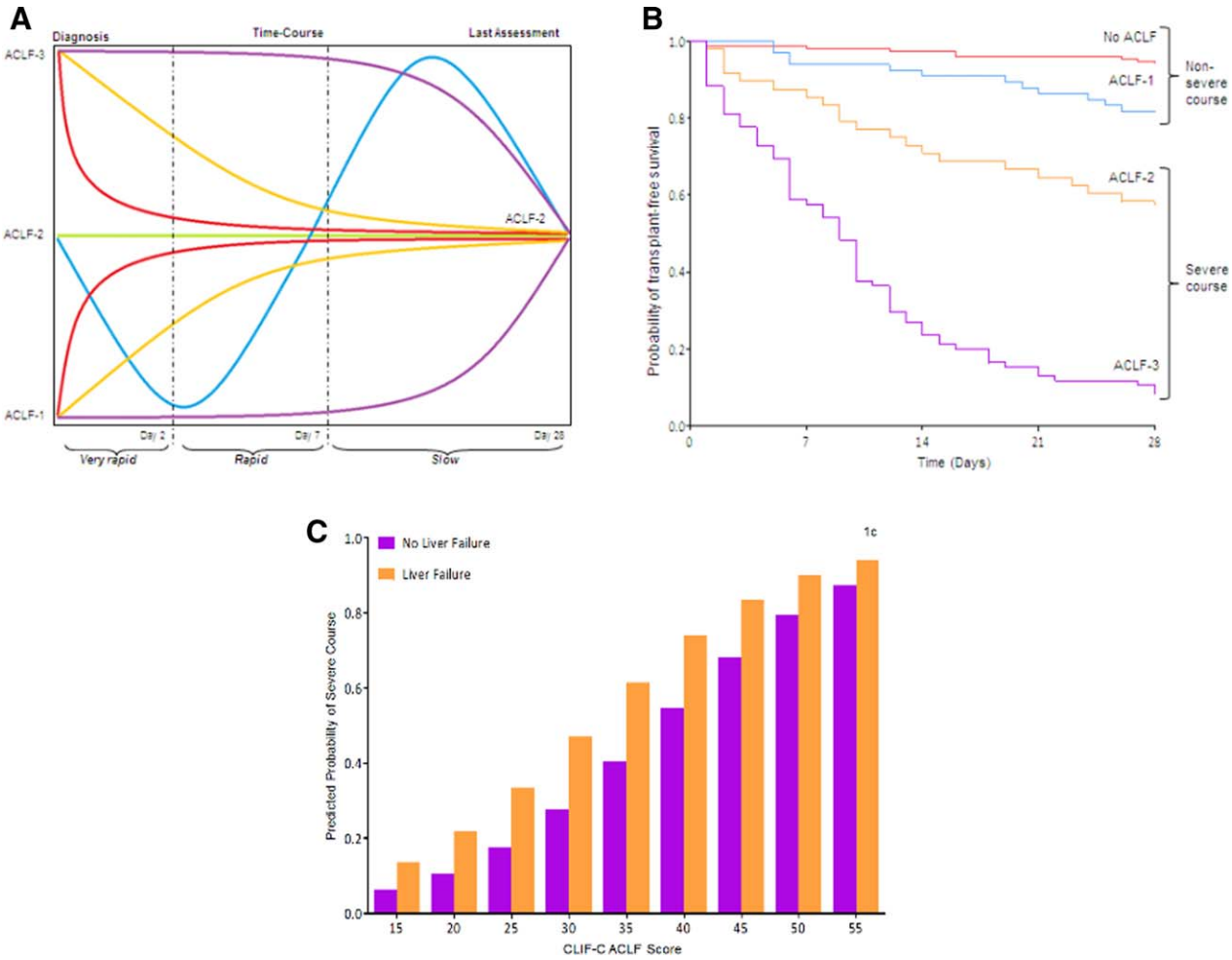

Fig. 1. (A) Examples of time-course profile: very rapid (within 48 hours, red lines), rapid (between 3 and 7 days, yellow lines), and slow (between 8 and 28 days, purple lines) improvement or worsening; steady (green line) and fluctuating course with unchanged final grade (blue line). (B) Kaplan-Meier's 28-day transplant-free survival curves of patients based on their final ACLF grade. (C) Estimated probability of severe early course of ACLF based on CLIF-Consortium ACLF score (CLIF-C ACLFs) and absence or presence of liver failure (defined by total bilirubin $\geq$12 mg/dL).

period. Twenty-nine patients were excluded because of lack of sufficient data; however, similar short- and mid-term mortality rates were found (data not shown). Among the 388 included patients, 35 were transplanted in 28 days after ACLF diagnosis. Donor organs were obtained in no case from executed prisoners or other institutionalized persons.

Analysis of Potential Futility

To investigate whether there is a particular group of patients with ACLF in which current medical interventions are likely to be futile, two types of analysis were performed in patients with ACLF-3 at enrollment or at any time of the 28-day follow-up. The first assessed the relationship between the number of organ failures or the CLIF Consortium ACLF score (CLIF-C ACLFs) at diagnosis of ACLF-3 and mortality at 28 and 90 days.[9] The second type of analysis assessed the relationship between the number of organ failures or the CLIF-C ACLFs at days 3-7 after diagnosis of ACLF-3 and mortality at 28 and 90 days. These analysis were performed in patients with complete set of clinical and laboratory data at days 3-7 after diagnosis of ACLF-3.

Risk Factors of Severe Clinical Course and Other Statistical Analysis

Univariate analyses using chi-square or Fisher's exact tests, Student *t*, or Mann-Whitney's U tests and one-way analyses of variance (ANOVAs) or Kruskall-Wallis' non-parametric ANOVAs were performed to assess the association between patients' characteristics at diagnosis of initial and final ACLF grade and clinical course severity. A logistic regression model was fitted to select the best subset of predictors of a severe course. Those factors showing a clinically, statistically significant association in univariate analysis were selected for the initial model. The final model was fitted using a step-wise forward method based on improvement in model likelihood

ratios. Significance levels to enter and drop model variables were adopted as 5% and 10%, respectively. In all analyses, with the exception of assessment of LT, transplant-free mortality was taken into account. Survival probabilities were estimated by means of Kaplan-Meier's method and were compared using the log-rank test. Accuracy of ACLF grade (at diagnosis and at days 3-7) to predict clinical course severity was assessed by estimating and comparing the corresponding areas under the receiver operating characteristic curves (AUROCs). Results are presented as frequencies and percentages with 95% confidence interval (CI), means and standard deviations, or median (min-max). Significance level was set at $P < 0.05$.

Results

Clinical Course Patterns: Prevalences and Relationship to the Initial ACLF Grade and Mortality at 28 and 90 Days. Overall, ACLF resolved or improved in 192 patients (49.5%; green boxes in Table 1), followed a steady or fluctuating course with unchanged final ACLF grade in 118 (30.4%; uncolored boxes), and worsened in 78 (20.1%; red boxes). Among the 202 patients with initial ACLF-1, the most frequent clinical course was resolution of the syndrome (54.5%), followed by a steady or fluctuating course pattern (24.3%) and worsening (21.2%; Table 1). Among the 136 patients with initial ACLF-2, the most frequent clinical course was also ACLF resolution (34.6%); improvement was found in 14% of patients with initial ACLF-2, steady or fluctuating course in 25.7%, and worsening in 25.7% (Table 1). Finally, in most patients with initial ACLF-3 (68%), the syndrome remained steady or fluctuating. Interestingly, among patients with initial ACLF-3, there was resolution in 16% or improvement in 16% (Table 1). Median time between initial and last ACLF grade assessment was 14 (1-28) days.

Overall, resolution of ACLF was observed in 165 patients (42.5%). In the remaining patients, the final grade was ACLF-1 in 70 (18%), ACLF-2 in 59 (15.2%), and ACLF-3 in 94 (24.3%). There was a relationship between initial and final ACLF grade. Frequency of ACLF resolution was high in patients with initial ACLF-1 and low in those with initial ACLF-3. In contrast, the proportion of patients with final ACLF-3 was low in patients with initial ACLF-1 and very high in those with ACLF-3 (Table 1).

The 28-day mortality rate was low in patients with ACLF resolution (5.8%), moderate in those with final ACLF-1 (18.2%), high in those with final ACLF-2 (41.7%), and very high in those with final ACLF-3 (91.8%), independently of whether they presented ACLF-1, -2, or -3 at diagnosis (Tables 1 and 2). Figure 1B shows 28-day survival probability curves according to the four final ACLF grades. The 28- and 90-day mortality rates in patients with initial ACLF-2 or -3 who achieved ACLF resolution (4% and 12.8%, respectively) were not significantly different ($P = 0.4987$ and $P = 0.2868$, respectively) with regard to corresponding rates observed in those with initial ACLF-1 (6.7% and 20%, respectively). Supporting Table 1 compares clinical characteristics, laboratory values, and treatment at ACLF diagnosis of these two groups of patients (initial ACLF-1 vs. ACLF-2 or -3) who recovered. Active alcoholism as a precipitating event (PE) and the lack of previous decompensations were significantly more frequent in patients with ACLF-2 or -3 than in those with ACLF-1 who resolved ACLF during hospitalization. As expected, presence of all organ failures (except for renal failure) and intensity of treatment were significantly higher in patients with initial ACLF-2 or -3.

Given that bacterial infection and active alcoholism were the more frequent PEs of ACLF in our cohort, we compared the short- and mid-term prognosis based on clinical course patterns and main PE, and we did not find any statistical difference (Supporting Table 2). The 28- and 90-day mortality rates in patients with and without bacterial infections as PEs were 35.0% versus 28.6% ($P = 0.2437$) and 47.5% versus 40.5% ($P = 0.2285$), respectively. The corresponding rates in patients with or without active alcoholism were 32.9% versus 30.5% ($P = 0.7772$) and 45.2% versus 42.6% ($P = 0.7695$), respectively.

Predictors of Clinical Course Severity. The 28-day mortality rates of patients with ACLF resolution or final ACLF-1 were relatively low (Table 2). Moreover, they had similar clinical and laboratory data at diagnosis. The only relevant difference between patients with ACLF resolution and those with final ACLF-1 was a higher prevalence of renal failure and a lower prevalence of respiratory, circulatory, coagulation, and liver failure at diagnosis in those with final ACLF-1. Renal replacement therapy during hospitalization was more frequent in patients with final ACLF-1, but there were no major differences in other therapeutic procedures. According to homogeneity of patients with ACLF resolution and those with final ACLF-1, they were grouped as patients with nonsevere early course.

The 28-day mortality rates of patients with final ACLF-2 or -3 were high or very high. Moreover, these patients were younger than those with nonsevere early course and had higher prevalence of ascites at diagnosis and bacterial infections and active alcoholism as PEs. Accordingly, patients with final ACLF-2 or -3 were grouped as those with severe early course.

Predictors of clinical course severity were then assessed by comparing patients with nonsevere and

Table 2. Clinical and Laboratory Data at Diagnosis of ACLF, Treatment During Hospitalization, and 28- and 90-Day Transplant (tx)-Free Survival According to Clinical Course Patterns of ACLF

Final ACLF Grade	No ACLF (n = 165)	ACLF-1 (n = 70)	ACLF-2 (n = 59)	ACLF-3 (n = 94)	*P* Value
28-day tx-free mortality (%)	9/154 (5.8)	12/66 (18.2)	20/48 (41.7)	78/85 (91.8)	<0.0001
90-day tx-free mortality (%)	25/142 (17.6)	23/59 (39)	32/42 (76.2)	83/84 (98.8)	<0.0001
Clinical data					
Age, years	56.0 ± 12.0	58.9 ± 12.0	53.1 ± 10.2	53.3 ± 11.4	0.0073
Alcohol, %				58.7	0.9814
HCV, %	59.1	59.4	56.1	16.3	0.8536
No previous decompensation, %	12.6	15.6	14.0	32.6	0.0803
Ascites at ACLF diagnosis, %	24.4	14.5	28.8	86.2	0.0926
Bacterial infection as PE*, %	34.4	31.3	45.6	48.9	0.0446
Active alcoholism as PE, %	26.0	9.5	30.4	25.3	0.0298
Laboratory data, organ failures, and scores at diagnosis of ACLF					
Leucocyte, $\times 10^9$/L	9.1 ± 5.3	8.9 ± 5.8	9.5 ± 5.9	12.3 ± 7.8	0.0007
CRP, mg/L	39.2 ± 41.3	36.0 ± 51.1	27.2 ± 19.3	53.8 ± 42.1	0.0002
Bilirubin, mg/dL	8.6 ± 10.0	6.0 ± 7.4	14.4 ± 11.0	16.4 ± 11.6	<0.0001
INR	1.9 ± 0.7	1.8 ± 0.7	2.4 ± 1.0	2.5 ± 1.0	<0.0001
Creatinine, mg/dL	1.9 ± 1.1	2.6 ± 1.7	1.9 ± 1.3	2.5 ± 1.8	0.0005
Na, mEq/L	133.9 ± 6.7	134.1 ± 7.3	133.1 ± 6.1	132.6 ± 6.2	0.3653
Renal failure, %	46.1	72.9	40.7	53.2	0.0005
Cerebral failure, %	16.4	14.3	23.7	35.1	0.0017
Respiratory failure, %	10.9	5.7	10.2	17.0	0.1490
Circulatory failure, %	15.8	8.6	10.2	31.9	0.0002
Coagulation failure, %	20.6	15.7	37.3	45.7	<0.0001
Liver failure, %	29.1	15.7	57.6	57.5	<0.0001
Child-Pugh score	10.4 ± 2.0	10.0 ± 2.2	11.6 ± 1.6	12.4 ± 1.4	<0.0001
MELD score	24.1 ± 6.6	24.7 ± 5.6	29.0 ± 5.9	31.7 ± 6.3	<0.0001
CLIF-C ACLF score	46.4 ± 7.1	45.1 ± 7.1	49.3 ± 8.8	55.7 ± 9.0	<0.0001
ACLF-1, %	66.7	70.0	30.5	26.6	<0.0001
ACLF-2, %	28.5	27.1	59.3	37.2	0.0001
ACLF-3, %	4.9	2.9	10.0	36.2	<0.0001
Treatments, %†					
ICU admission	33.3	42.9	59.3	85.1	<0.0001
Variceal bleeding‡	21.2	20.0	25.4	27.7	0.5763
Antibiotics	73.3	78.6	86.4	92.5	0.0012
Transfusion§	35.8	54.3	55.9	69.2	<0.0001
Vasoactive agents¶	38.2	44.3	54.2	90.4	<0.0001
Mechanical ventilation	13.9	12.9	20.3	66.0	<0.0001
Renal replacement	10.3	24.3	18.6	58.5	<0.0001

*Active alcohol as PE means within the last 3 months before diagnosis and bacterial infection as PE means from admission to ACLF diagnosis.
†At any time during the follow-up.
‡Includes vasoactive (somatostatin/terlipressin), endoscopic therapy, and transjugular intrahepatic portosystemic shunt insertion.
§Includes transfusion of red cells package, fresh-frozen plasma, platelets, and cryoprecipitates.
¶They include any vasoactive drug used for circulatory support or hepatorenal syndrome.
Abbreviation: HCV, hepatitis C virus.

severe early course (Supporting Table 3). Of the clinical and laboratory parameters introduced in the final regression model (age, CLIF-C ACLFs, initial ACLF grade, ascites, bacterial infection, white cell count, and presence of individual organ failures at diagnosis of initial ACLF), only the CLIF-C ACLFs (odds ratio [OR] = 1.11; 95% CI: 1.07-1.15; $P < 0.0001$) and presence of liver failure (OR = 2.82; 95% CI: 1.72-4.63; $P < 0.0001$) were independently and significantly associated with severe early course. Based on this model, the probability (P) of developing a severe early course was estimated by means of the following formulae:

- Patients without liver failure: $P = 1/(1+\exp\ [5.8709-0.1028*\text{CLIF-C ACLFs}])$
- Patients with liver failure: $P = 1/(1+\exp[4.8347-0.1028*\text{CLIF-C ACLFs}])$

Figure 1C shows that liver failure significantly contributed to increase the corresponding probability overall and particularly at the lower CLIF-C ACLFs values.

Time-Course Profiles: Day 3-7 ACLF Grade. Overall, resolution, improvement or worsening of ACLF occurred very rapidly, rapidly, or slowly in 40.2%, 14.7%, and 14.7% of patients, respectively. Time-course profiles were not related to prognosis

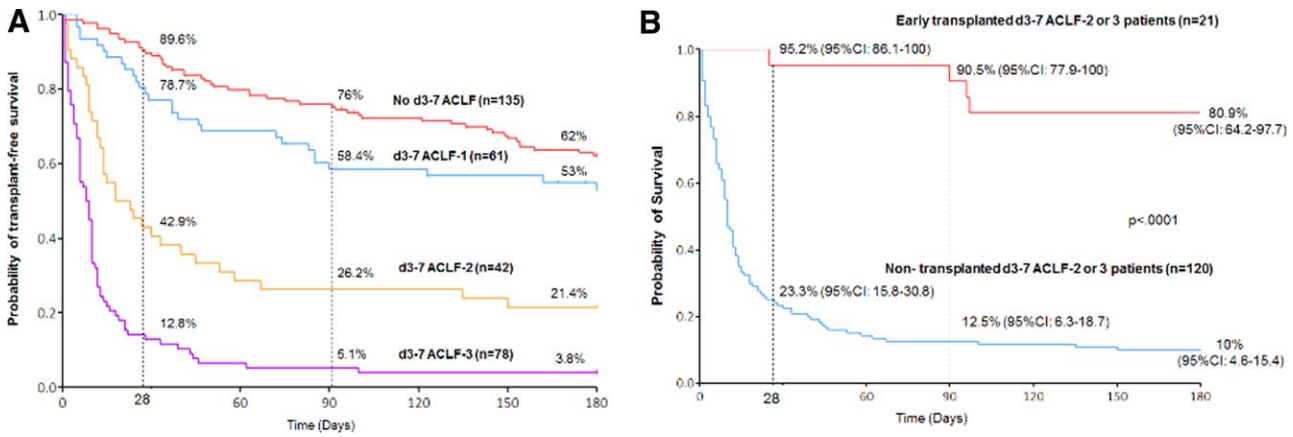

Fig. 2. (A) Kaplan-Meier's 180-day transplant-free survival curves of patients based on their ACLF grade at days 3-7 (d3-7 ACLF). (B) Probability (180-day) of survival in patients with d3-7 ACLF-2 or -3 not transplanted and in patients undergoing early (28-day) LT. Kaplan-Meier's curves were compared using log-rank test.

(Supporting Table 4). Owing to the fact that final ACLF grade was already defined at days 3-7 in 81% patients, ACLF-grade at days 3-7 after diagnosis (d3-7 ACLF) predicted significantly better 28- and 90-day mortality rates than ACLF grade at diagnosis (AUROC [95% CI] 0.85 [0.8-0.89] vs. 0.65 [0.59-0.71] and 0.81 [0.76-0.85] vs. 0.62 [0.57-0.68], respectively; $P < 0.0001$).

The Possibility and Timing of LT in ACLF. Figure 2A shows the 180-day transplant-free probability of survival in patients according to d3-7 ACLF grade. The probability of 28-day transplant-free survival was high for patients with no d3-7 ACLF and with d3-7 ACLF-1 (89.6% and 78.7%, respectively) and low to very low for patients with d3-7 ACLF-2 and -3 (42.9% and 12.8%, respectively). These differences were maintained at 90 and 180 days.

Twenty-five of thirty-five patients who were transplanted during the 28-day follow-up, had ACLF at the time of transplantation (ACLF-1, 5; ACLF-2, 11; ACLF-3, 9; Supporting Table 5). Median delay between ACLF diagnosis and LT was 11 (1-28) days. Prevalences of organ failure among these patients were 64% for renal, 60% for coagulation, 56% for liver, 36% for circulatory, 22% for cerebral, and 0% for respiratory failure. Thirty-eight percent had ACLF-3 (19% with 3 organ failures and 19% with 4 organ failures). Renal replacement therapy and mechanical ventilation were required in 40% and 28% of patients, respectively. The 1-year probability of survival in these patients was 75.3% (ACLF-1, 80% [95% CI: 71.4-100]; ACLF-2, 71.6% [95% CI: 44.2-99]; ACLF-3, 77.8% [95% CI: 50.6-100]), compared to 90% (95% CI: 71.4-100) for the 10 patients with ACLF resolution before LT.

Figure 2B shows the 180-day probability of survival of d3-7 ACLF-2 or -3 patients undergoing LT within the 28-day follow-up, compared to transplant-free survival probability in d3-7 ACLF-2 or -3 patients not transplanted. The 28- and 180-day probability of survival was 95.2% and 80.9% in patients receiving early LT and 23.3% and 10% in those not transplanted.

Analysis of Potential Futility in Patients With ACLF-3. Fifty patients with ACLF-3 at diagnosis and 71 additional patients with ACLF-1 or -2 at diagnosis who worsened to ACLF-3 at any time during the 28-day follow-up period were included in this analysis.

Table 3. Number of Organ Failures (OFs) and CLIF-C ACLFs in Patients With ACLF-3 at Days 3-7 After ACLF-3 Diagnosis*

No. of OFs at 3-7 Days	28-Day Tx-Free Mortality (%; 95% CI)	90-Day Tx-Free Mortality (%; 95% CI)	CLIF-C ACLFs at 3-7 Days	28-Day Tx-Free Mortality (%; 95% CI)	90-Day Tx-Free Mortality (%; 95% CI)
0	1/7 (14.3; 2.6-51.3)	1/7 (14.3; 2.6-51.3)	>20-30	0/1 (0)	0/1 (0)
1	0/7 (0%)	1/7 (14.3; 2.6-51.3)	>30-40	1/4 (25.0; 4.6-69.9)	1/4 (25.0; 4.6-69.9)
2	7/12 (58.3; 32.0-80.7)	9/11 (81.8; 52.3-94.9)	>40-50	1/11 (9.1; 1.6-37.7)	4/10 (40.0; 16.8-68.7)
3	9/17 (52.9; 31.0-73.8)	13/17 (76.5; 52.7-90.4)	>50-60	11/18 (61.1; 38.6-79.7)	13/18 (72.2; 49.1-87.5)
4	9/10 (90.0; 59.6-98.2)	10/10 (100; 72.3-100)	>60-70	11/14 (78.6; 52.4-92.4)	13/14 (92.9; 68.5-98.7)
5	10/10 (100; 72.3-100)	10/10 (100; 72.3-100)	>70-80	12/12 (100; 75.8-100)	12/12 (100; 75.8-100)
6	5/5 (100; 56.6-100)	5/5 (100; 56.6-100)	>80-90	3/3 (100; 43.9-100)	3/3 (100; 43.9-100)
Total	41/68 (60.3; 48.4-71.1)	49/67 (73.1; 61.5-82.3)	Total	39/63 (61.9; 50.0-72.9)	46/62 (74.2; 62.1-83.5)

*Relationships to 28- and 90-day transplant (tx)-free mortality.

Among these patients, 28-day mortality rate was 67.5% (95% CI: 54.5-76.9%) in patients with 3 organ failures at the diagnosis of ACLF-3 (n = 77), 76.7% (95% CI: 59.1-88.2) in those with 4 organ failures (n = 30), and 85.7% (95% CI: 60.1-96.0) in those with 5-6 organ failures (n = 14). Corresponding 90-day mortality rates were 76.6% (95% CI: 66.1-84.7), 90.0% (95% CI: 74.4-96.5), and 85.7% (95% CI: 60.1-96.0), respectively. There was also no critical cut-off level of CLIF-C ACLFs at diagnosis over which there were a significant number of patients with a mortality rate of 100% (data not shown).

For 68 from these 121 patients with ACLF-3, we had information about the evolution of ACLF grade during the subsequent week. In the remaining 53 patients, there were no available follow-up data because they died within 7 days after diagnosis of ACLF-3 (40 patients) or had incomplete data to assess the number of organ failures or the CLIF-C ACLFs (13 patients). Table 3 shows the relationship between the number of organ failures or CLIF-C ACLFs at days 3-7 after ACLF-3 diagnosis and 28- and 90-day mortality rates in those patients with ACLF-3 and complete set of clinical and laboratory data. In the 25 patients with 4 organ failures or more, 28- and 90-day mortality rates were 90% (95% CI: 71-96) and 100%. In the 24 patients with CLIF-C ACLFs over 64, 28- and 90-day mortality rates were 100%.

Discussion

Four major findings about the ACLF syndrome were found in our study. The first is that ACLF is an extraordinarily dynamic syndrome with a resolution observed in 42.5% of patients. Second, short-term mortality of ACLF patients was accurately predicted by the clinical course of the syndrome defined by the evolution between the initial and final ACLF grades independently of the initial grade. The best time point to define the clinical course of ACLF was between the third and seventh day after ACLF diagnosis (d3-7 ACLF). Together, these findings suggest that intensive care of patients with ACLF should be continued during the first 7 days after ACLF diagnosis and that assessment at day 7 could help to make decisions regarding subsequent management: continuation and potential LT, or discontinuation owing to futility.

According to our data, the main goal for any therapeutic approach for ACLF should be the resolution of the syndrome because it is associated with the lowest short- (28-day) and mid-term (90-day) mortality rates (5.8% and 17.6%, respectively). Resolution of ACLF is not an uncommon feature. It occurred in 165 of our patients, and although it was more frequently observed in those with ACLF-1 at diagnosis (53.5%), it was relatively common in those with ACLF-2 (34.6%) and not exceptional in patients with ACLF-3 (16%). The 28- and 90-day mortality rates observed in our patients with resolution of ACLF were similar to those reported by Moreau et al. in patients admitted to the hospital with AD of cirrhosis, but without ACLF (4.7% and 14%, respectively).[4] A limitation of our study is that the small number of patients in the subgroups of patients with initial ACLF grade 3 who experienced resolution or improvement are very small (8 and 8, respectively), making conclusions about outcomes uncertain. Although showing a mortality rate higher than patients with resolution of ACLF (18.2% at 28 days), patients with final ACLF-1 had short- and mid-term prognosis remarkably better than patients with final ACLF-2 or -3 (41.7% and 91.8% at 28 days). Based on these data, ACLF patients could have a severe early course (final ACLF-2 or -3) and nonsevere early course (final ACLF-1 or resolution of ACLF). Therefore, patients with severe early course constitute a particular homogenous population to test specific therapeutic procedures for ACLF, such as artificial liver support systems.[10,11] An important observation was that in 51% of patients with severe early course, this was a result of worsening of an initial ACLF-1 or -2; in the rest of the patients, it was the result of a lack of improvement of the initial ACLF-2 or -3 (45%) or improvement of an initial ACLF-3 to -2 (4%). These findings indicate that therapeutic intervention in patients with ACLF should be directed not only to improve the organ failures present at diagnosis, but also to prevent impairment of function of the other organs during hospitalization. This concept was already suggested by the survival benefit of albumin administration in the prevention of renal impairment in spontaneous bacterial peritonitis.[12]

Another goal for adequate management is to predict, early and precisely, the course and prognosis of the syndrome. First, patients with severe early course presented, at diagnosis, most of the risk factors of mortality included in the CLIF-C ACLFs. They were younger than patients with nonsevere early course, more frequently compensated before development of the syndrome, with higher prevalence of ascites at diagnosis, a more intense systemic inflammatory reaction (higher white cell count), and higher prevalence of cerebral, circulatory, coagulation, and liver failure. Therefore, it is not surprising that the CLIF-C ACLFs, together with the presence of liver failure at diagnosis, were the only independent predictors of clinical course severity found in our series.

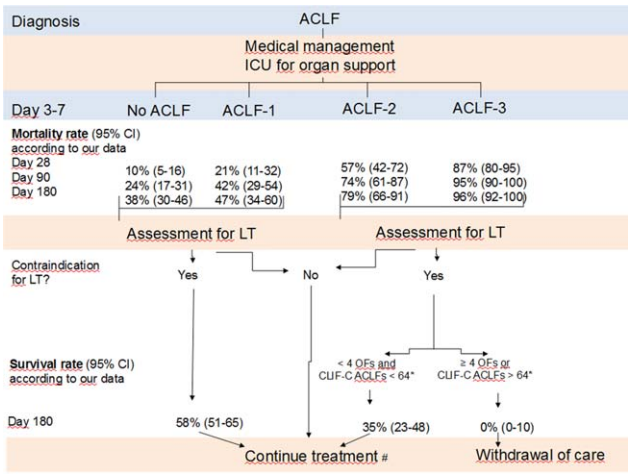

Fig. 3. Proposed algorithm for management and further research studies of ACLF patients based on mortality rate (95% CI). The first step is the assessment of ACLF grade at days 3-7 of medical management and potential organ support(s). LT should be assessed in all ACLF patients because of high 90-day mortality rates (>20%). In the case of contraindication to LT, the presence of 4 or more organ failures (OFs) or CLIF-C ACLFs >64 at days 3-7 from ACLF-3 diagnosis (*) could indicate the futility of care. #Moreover, withdrawal of care may be considered in LT candidates if LT is considered futile by the local team (i.e., patients too sick to be transplanted).

The current study highlights the benefits obtained from studies focusing on a strategy integrating the impact of early treatment on the outcome. As an example, the response to corticosteroids assessed by the Lille model at day 7 improves to accuracy of prognosis prediction of patients with severe alcoholic hepatitis, compared to baseline scores (Maddrey or MELD scores).[13] In a parallel manner, we observed that ACLF grades between the third and seventh day after ACLF diagnosis (d3-7 ACLF) predicted more accurately the short- and mid-term prognosis than initial grades. Then, care and evolution of ACLF during the first week and its assessment at the end of this period could be a good strategy to decide after management or, on the other hand, to define potentially the futility of care.

The high risk of early death in patients with d3-7 ACLF-2 or -3 makes it necessary to consider all available treatment options, including LT. Based on our study, early LT (during the first month after diagnosis) is feasible for ACLF patients, as demonstrated by acceptable 1-year survival rate (75.3%). However, this result was lower than the 88% 1-year survival rate measured in the overall population of patients who received an LT. It is difficult to draw conclusions about transplantation survival rates owing to low number of transplanted ACLF patients (n = 25). Interestingly, a recent study by Mathurin et al. showed similar probability of survival post-LT in 26 patients with severe acute alcoholic hepatitis nonresponders to corticosteroids, many of them with ACLF.[14] Because of very high 28-day mortality rate of patients with d3-7 ACLF-2 or -3 (45% and 86.1%), assessment and indication of LT should potentially be made on an emergency basis. Currently, in most countries, graft allocation is based on MELD score and does not take into account cerebral, circulatory, and pulmonary failures, giving no priority for ACLF patients.[15] Another point is that some ACLF patients are potentially too sick for LT, and the good result of LT in our cohort may overestimate the success rate by a potential strict selection of patients.[16] In the context of scarcity of donor livers, the potential benefit of ACLF patients with LT must be also balanced with the rationing.[17] An allocation system should aim to maximize outcome after LT. Development of a large international database collecting information on long-term survival post-LT is warranted to confirm that severe course of ACLF is a reasonable indication of LT and to define the associated strict selection criteria.

Treatment futility is always a complex and controversial issue.[18-20] In many patients with ACLF, decisions to withdraw or withhold life-sustaining treatment are clearly dependent on the possibility of a short-term LT. We did not identify, at diagnosis, any subset of patients in which current medical interventions might be considered as futile. Moreover, the CLIF-C ACLFs alone or associated with presence of liver failure at diagnosis did not show any critical cut-off level over which there was a significant proportion of patients reaching a mortality rate close to 100%. ICU refusal of patients merely because of ACLF diagnosis, even if the grade is high, is no longer supported. Therefore, assessment of potential medical futility has to be done after diagnosis and medical management. The number of organ failures or the CLIF-C ACLFs at 3-7 days after ACLF-3 diagnosis were useful to define futility. The 28- and 90-day mortality rates were 90% and 100% in the 25 patients with 4 organ failures or more and of 100% in the 24 with CLIF-C ACLFs greater than 64. Then, if LT is contraindicated or not available for patients with ≥4 organ failures or CLIF-C ACLFs >64 at days 3-7 after diagnosis of ACLF-3, the intensive organ support should be discontinued owing to futility. Then, based on our prognostic data, we propose an algorithm for management of patients with ACLF considering potential LT or futility of care (Fig. 3). Owing to the small number of patients in the subgroups, cautions must be taken about the generalization of the data, and this algorithm must be considered more as a basis for further research studies on the management of ACLF than a proposed clinical practice. Moreover, the definition and grades of ACLF are still difficult to apply in clinical practice, and future

studies are required to clearly and easily identify the syndrome. Moreover, some factors not assessed in the present study, such as relapse or continuation of alcohol intake, could influence the outcome of patients.

In summary, ACLF patients require extensive and expensive clinical resources. Their intensive management needs time points to provide clinical decision about continuation or discontinuation owing to futility. With this in mind, our study demonstrates that ACLF is a very dynamic syndrome that may resolve, improve, or worsen within a timeframe ranging from 1-2 days to 2-4 weeks. Prognosis correlates better with clinical course than with ACLF grade at diagnosis. Clinical course severity can be predicted by the CLIF-C ACLFs and the presence of liver failure at diagnosis. Given that resolution, improvement, or worsening of ACLF occur very rapidly or rapidly after diagnosis in most patients, survival can be accurately predicted at 3-7 days after diagnosis by ACLF grade (d3-7 ACLF). Moreover, d3-7 ACLF could be a good assessment to define the need and timing of potential LT. In the same manner, the number of organ failures and CLIF-C ACLFs at days 3-7 after ACLF-3 diagnosis could provide a rational basis for discontinuation of intensive care owing to futility.

Appendix: CANONIC Study Investigators

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