ORIGINAL ARTICLE

Acute kidney injury and acute-on-chronic liver failure classifications in prognosis assessment of patients with acute decompensation of cirrhosis

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ABSTRACT

Objective Prognostic stratification of patients with cirrhosis is common clinical practice. This study compares the prognostic accuracy (28-day and 90-day transplant-free mortality) of the acute-on-chronic liver failure (ACLF) classification (no ACLF, ACLF grades 1, 2 and 3) with that of acute kidney injury (AKI) classification (no AKI, AKI stages 1, 2 and 3).

Design The study was performed in 510 patients with an acute decompensation of cirrhosis previously included in the European Association for the Study of the Liver–Chronic Liver Failure consortium CANONIC study. ACLF was evaluated at enrolment and 48 h after enrolment, and AKI was evaluated at 48 h according to Acute Kidney Injury Network criteria.

Results 240 patients (47.1%) met the criteria of ACLF at enrolment, while 98 patients (19.2%) developed AKI. The presence of ACLF and AKI was strongly associated with mortality. 28-day transplant-free mortality and 90-day transplant-free mortality of patients with ACLF (32% and 49.8%, respectively) were significantly higher with respect to those of patients without ACLF (6.2% and 16.4%, respectively; both p<0.001). Corresponding values in patients with and without AKI were 46% and 59%, and 12% and 25.6%, respectively (p<0.0001 for both). ACLF classification was more accurate than AKI classification in predicting 90-day mortality (area under the receiving operating characteristic curve=0.72 vs 0.62; p<0.0001) in the whole series of patients. Moreover, assessment of ACLF classification at 48 h had significantly better prognostic accuracy compared with that of both AKI classification and ACLF classification at enrolment.

Conclusions ACLF stratification is more accurate than AKI stratification in the prediction of short-term mortality in patients with acute decompensation of cirrhosis.

Significance of this study

What is already known on this subject?

- Acute kidney injury (AKI) is a frequent complication of cirrhosis and a powerful predictor of death in hospitalised patients with liver cirrhosis.
- Acute-on-chronic liver failure (ACLF) is a clinical syndrome characterised by an acute deterioration of liver function and the development of organ failure in patients with chronic liver disease.
- The Chronic Liver Failure–Sequential Organ Failure Assessment (CLIF–SOFA) score has been shown to be a powerful predictor of death in hospitalised patients with cirrhosis.

What are the new findings?

- The development of ACLF according to CLIF–SOFA score was found to be more accurate than AKI classification in the prediction of short-term mortality in patients with cirrhosis who are hospitalised for an acute decompensation of the liver disease.
- The assessment of CLIF–SOFA score after 48 h further improved the prognostic accuracy of ACLF classification.
- ACLF classification is able to predict the prognosis of patients with cirrhosis in a stage-dependent fashion, stratifying the mortality risk.

How might it impact on clinical practice in the foreseeable future?

- The ACLF classification is a simple tool able to identify patients with cirrhosis with high risk of short-term mortality.
- The ACLF classification may be able to identify high-risk patients requiring an intensive care management.

INTRODUCTION

The assessment of patients at risk of poor outcome is a crucial point in clinical practice since it helps the physician to decide on the intensity of treatment and monitoring and the most appropriate setting for patients' management (intensive care unit or regular ward). For this reason, interest in assessing organ dysfunction and severity of illness in hospitalised patients with cirrhosis has increased in recent years. This interest has grown in parallel with the development of the concept of acute-on-chronic liver failure (ACLF) that, in its

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simplest terms, is characterised by the abrupt onset of organ failures in patients with cirrhosis hospitalised for an acute decompensation of liver disease.[1] The CLIF Acute-on-chronic liver failure in cirrhosis (CANONIC) study demonstrated that the presence of two (ACLF grade 2) or three organ failures (ACLF grade 3), which were defined by a Sequential Organ Failure Assessment (SOFA) score specifically adapted to patients with cirrhosis (CLIF-SOFA score) is associated with a high short-term mortality rate.[1]

In single-organ failure (ACLF grade 1), an increased mortality rate was observed for patients with kidney failure defined by a serum creatinine (sCr) >2 mg/dL or with a failure of an organ other than the kidney when it is associated with an sCr >1.5 mg/dL or with grade 1 or 2 hepatic encephalopathy.[1] For many years, a cut-off level of 1.5 mg/dL of sCr has been used for the diagnosis of impairment of kidney function in patients with cirrhosis even when an increase of sCr with respect to baseline was considered.[2–5] Consequently, the results of the CANONIC study have reinforced the concept that an impairment of kidney function has a marked negative impact on prognosis of hospitalised patients with cirrhosis, giving it a new dimension as a predictor of mortality.

In 2007, the Acute Kidney Injury Network (AKIN) developed a consensus definition of AKI, a new term to define acute renal failure according to AKIN criteria.[6] The main innovative aspects introduced by AKIN criteria are the following: (a) an absolute increase in sCr is considered without any final cut-off value and (b) a staging system of AKI based on changes of sCr within 48 h. These criteria are being used extensively in critically ill patients since they have been shown to be accurate in predicting prognosis.[7] However, the information about AKIN criteria for diagnosis and classification of AKI in patients with cirrhosis is still limited. Recently, four prospective studies have shown that the AKI classification based on AKIN criteria predicts short-term and mid-term mortality in a stage-dependent fashion in hospitalised patients with cirrhosis.[8–11] The results indicate that the AKI classification is useful in the prognostic stratification of patients with cirrhosis. Nevertheless, the AKI classification has so far not been compared with a more complete assessment of organ failures in these patients. Thus, the current study was designed to compare prospectively the AKI classification and the classification of ACLF in the prognostic stratification of hospitalised patients with acute decompensation of cirrhosis.

PATIENTS AND METHODS

Study population

The current study was performed in a population of patients included in the CANONIC study.[1] The CANONIC study was a multicentre study aimed at evaluating the frequency, characteristics and outcome of ACLF in patients with cirrhosis admitted for an acute decompensation of the disease in 29 liver units from 8 European countries. Patients included in the current investigation were patients belonging to groups 1 and 2 of the CANONIC study. The distribution of patients in the CANONIC study has been reported in detail elsewhere.[1] Briefly, patients in group 1 were patients admitted to hospital for an acute decompensation of cirrhosis who had at least one organ failure at admission to hospital, while patients in group 2 were patients admitted for an acute decompensation of cirrhosis but without organ failure that were chronologically enrolled after each patient with organ failure. In patients from both groups, clinical and laboratory data were collected at enrolment, 2 days after enrolment and at different time intervals throughout the hospitalisation, specifically 3–7, 8–14, 15–21 and 22–28 days after enrolment. Patients from group 3 of the CANONIC study were not included in the current investigation because laboratory data were collected at the time of enrolment but not throughout hospitalisation. A total of 639 patients from groups 1 and 2 were evaluated for inclusion in the current study. Of these patients, 129 were excluded because of at least one of the following reasons: lack of sCr values at day 2 (68 cases), lack of one or more variables included in the ACLF definition at day 2 (51 patients) and death or liver transplantation one day after enrolment (12 patients). Therefore, the current study was carried out in 510 patients. The distribution of patients is shown in online supplementary figure S1.

Main variables and definitions

The study was aimed at evaluating the AKI classification as well as the ACLF classification[1 12] in determining the outcome of patients hospitalised for an acute decompensation of cirrhosis.

AKI was defined using the new Kidney Disease Improving Global Outcomes AKIN criteria and patients were categorised into 4 groups: no AKI and AKI stages 1, 2 and 3 (see online supplementary table S1).[12] According to this classification, a patient was considered to developing AKI when there was an increase in sCr ≥0.3 mg/dL or ≥50% in two different measurements obtained 48 h apart. The baseline sCr used was that obtained at enrolment of patients in the study while the second measurement was collected 2 days after enrolment.

ACLF was defined according to the presence and severity of organ failures as described in the CANONIC study, and patients were classified into 4 different groups: (1) no ACLF, (2) ACLF grade 1, (3) ACLF grade 2 and (4) ACLF grade 3 (see online supplementary table S1).[1] Outcome was analysed as 28-day and 90-day mortality.

Statistical analysis

Data were collected using an electronic case report form. Quantitative variables are reported as mean and SD or median, minimum and maximum according to their nature. Categorical variables are reported as count and percentage in each category and total. Factors associated with the development of AKI, ACLF and mortality were identified in a bivariate analysis with Student t test and one-way analysis of variance for quantitative variables (depending on the number of categories), or the non-parametric corresponding tests, if needed. The 28-day and 90-day mortality rates were estimated as transplant-free mortality. In addition, since transplantation can be considered a competing event of death, curves showing the cumulative probability of failure were estimated with the cumulative incidence function proposed by Fine and Gray[13] due to the lack of validity of the Kaplan–Meier estimator in this context.

The accuracy of AKI and ACLF classifications in predicting 28-day and 90-day transplantation-free mortality was assessed estimating the area under the curve of the receiving operating characteristic (AUCROC). Furthermore, they were compared in order to establish the better classification in prognosis. In a similar way, classification's accuracy for the estimation of both mortalities under a competing risk approach was assessed with the C-index and compared with the integrated discrimination improvement index. Two-sided p values of <0.05 were considered to indicate statistical significance.

RESULTS

Baseline characteristics of the patients

The demographic, clinical and laboratory characteristics of patients at the time of enrolment in the study are shown in table 1.

Table 1 Baseline characteristics of patients at enrolment (n=510)

Age (years)	55±12	(22–95)
Male sex	331 (65)	
Aetiology of cirrhosis		
Alcohol	292 (60)	
Hepatitis C virus	67 (13)	
Alcohol plus hepatitis C virus	46 (9)	
Other causes	84 (18)	
Previous decompensation(s)		
Ascites	310 (60)	
Encephalopathy	152 (32)	
GI bleeding	114 (24)	
Spontaneous bacterial peritonitis	50 (11)	
Concomitant diseases		
Arterial hypertension	104 (21)	
Diabetes mellitus	108 (22)	
Chronic renal failure	45 (9)	
Cause(s) of admission		
Ascites	351 (70)	
Encephalopathy	190 (38)	
Bacterial infection	124 (25)	
GI bleeding	79 (16)	
Other	177 (35)	
Exploratory data		
Mean arterial pressure (mm Hg)	82±12	(46–122)
Heart rate (bpm)	83±17	(45–150)
Laboratory data		
White blood cells ($\times 10^9$/L)	9±5	(0.8–50)
Platelet count ($\times 10^9$/L)	102±7	(12–543)
Serum bilirubin (mg/dL)	8±9	(0.5–45.5)
Serum albumin (g/dL)	2.8±0.5	(1.3–4.5)
International normalised ratio	1.9±0.7	(1–7)
Plasma C-reactive protein (mg/L)	38±42	(0.6–326)
Serum creatinine (mg/dL)	1.6±1.3	(0.4–12.5)
Serum sodium (mmol/L)	134±6	(111–153)
Child-Pugh score	10±2	(5–15)
MELD	22±8	(6–40)

Data are expressed as mean±SD (min-max) or number of patients (percentage).
MELD, model for end-stage liver disease.

Table 2 Baseline characteristics of patients at enrolment according to the subsequent development of acute kidney injury (AKI) at 48 h after enrolment

	No AKI (n=412)	AKI (n=98)	p Value
Age (years)	56±11	53±14	0.09
Male sex	270 (65)	61 (62)	0.53
Aetiology of cirrhosis			
Alcohol	243 (61)	49 (52)	0.07
Hepatitis C virus	56 (14)	11 (12)	0.50
Alcohol plus hepatitis C virus	37 (9)	9 (9)	0.98
Other causes	58 (15)	26 (27)	0.003
Previous decompensation(s)			
Ascites	250 (65)	60 (63)	0.79
Encephalopathy	126 (33)	26 (28)	0.36
GI bleeding	98 (26)	16 (17)	0.09
Spontaneous bacterial peritonitis	41 (11)	9 (10)	0.74
Concomitant diseases			
Arterial hypertension	76 (19)	28 (29)	0.03
Diabetes mellitus	83 (20)	25 (25)	0.28
Chronic renal failure	36 (9)	9 (9)	0.93
Cause(s) of admission			
Ascites	274 (68)	77 (79)	0.02
Encephalopathy	142 (35)	48 (49)	0.01
Bacterial infection	95 (24)	29 (30)	0.23
GI bleeding	68 (17)	11 (11)	0.18
Other	147 (36)	30 (31)	0.27
Exploratory data			
Mean arterial pressure (mm Hg)	82±12	79±12	0.007
Heart rate (beats/min)	83±17	87±19	0.02
Laboratory data			
White blood cells ($\times 10^9$/L)	8.2±5.3	10.4±7.2	0.0005
Platelet count ($\times 10^9$/L)	103±72	99±65	0.84
Serum bilirubin (mg/dL)	7±8.2	12±12	0.0004
Serum albumin (g/dL)	2.8±0.6	2.7±0.6	0.26
International normalised ratio	1.8±1	2.2±1	<0.0001
Plasma C-reactive protein (mg/L)	35±39	52±50	0.0003
Serum creatinine (mg/dL)	1.4±1.1	2.5±2	<0.0001
Serum sodium (mmol/L)	135±6	133±6	0.06
Child–Pugh score	10±2	11±2	<0.0001
MELD	21±7	28±87	<0.0001

Data are expressed as mean±SD or number of patients (percentage).
MELD, model for end-stage liver disease.

The majority of patients had advanced cirrhosis as indicated by markedly impaired liver function tests and high Child–Pugh and model for end-stage liver disease (MELD) scores.

Frequency and characteristics of AKI and relationship with outcome

In total, 98 of the 510 patients (19.2%) developed AKI during the first 48 h after enrolment. In these patients, sCr concentration increased from 2.5±1.9 at baseline to 2.7±1.9 mg/dL at day 2 (p=0.0064). Corresponding values of sCr in the 412 patients who did not develop AKI were 1.4±1.1 and 1.2 ±0.9 mg/dL, respectively (p<0.0001). In total, 34 of 98 patients (34.7%) who developed AKI had AKI stage 1, 4 (4.1%) stage 2 and 60 (61.2%) stage 3. The relatively high proportion of patients with AKI stage 3 was largely due to the need for renal replacement therapy in 50 of 60 patients (83.3%) who had AKI stage 3. Values of sCr according to the different AKI stages are shown in online supplementary figure S2.

Table 2 shows the comparison of baseline characteristics of patients categorised according to the subsequent development of AKI within the 48 h time frame. Patients who developed AKI had more frequent history of arterial hypertension, higher frequency of ascites and hepatic encephalopathy, and lower mean arterial pressure and higher heart rate compared with patients who did not develop AKI. Moreover, patients who developed AKI had more severe impairment of liver function, higher sCr levels and higher leucocyte count and C-reactive protein levels compared with those of patients who did not develop AKI. The frequency of ascites and encephalopathy and the magnitude of changes in laboratory tests paralleled the presence and severity of AKI (see online supplementary table S2).

The development of AKI was associated with precipitating factors in most patients, particularly bacterial infections and volume depletion. In addition, 15 of 98 patients had type 1 hepatorenal syndrome, according to the International Ascites Club[14 15] (table 3).

The presence of AKI at 48 h after enrolment had a strong association with prognosis in a stage-dependent manner. Twenty-eight-day transplant-free mortality in patients with AKI

Table 3 Potential causes of acute kidney injury

Volume depletion	21 (17)
GI bleeding	16
Diarrhoea	3
Diuretic overdose	2
Bacterial infection	47 (39)
Spontaneous bacterial peritonitis	17
Pneumonia	9
Urinary tract infection	7
Skin infection	4
Other infections	4
Unproved suspected infection	6
Type 1 hepatorenal syndrome	15 (12)
Surgery	2 (2)
Unknown	37 (30)

Values are number of patients and percentages (in parentheses).
Patients could have more than one potential cause: 41 patients had one, 19 had two and 1 had three. The cause was unknown in 37 patients.

stage 2–3 was 55.9% compared with 25% in patients with AKI stage 1 and 12% in patients without AKI (p<0.0001). Corresponding values of 90-day transplant-free mortality were 67.3%, 40% and 25.6%, respectively (p<0.0001). During the 90-day period after enrolment, 63 patients (12.5%) were transplanted, 17 with AKI and 46 without AKI (17.5% and 11.4% from the AKI and non-AKI groups, respectively; p=0.09).

Because transplantation can be considered a competing event of death, the cumulative incidence function of mortality during follow-up was assessed using a competing risk approach (see the Methods section). As shown in figure 1, presence and severity of AKI was clearly associated with 28-day and 90-day cumulative mortality risk.

ACLF at enrolment and relationship with outcome

In total, 240 of 510 patients (47.1%) met the criteria of ACLF at enrolment in the study: 110 had ACLF grade 1 (45.8%), 96 grade 2 (40%) and 34 (14.2%) grade 3. The comparison of the baseline characteristics of patients with and without ACLF is shown in table 4. Patients with ACLF at enrolment had higher frequency of ascites and hepatic encephalopathy at admission and lower frequency of GI bleeding compared with patients without ACLF. Surprisingly, there were no significant differences between the two groups with respect to the frequency of bacterial infections. Patients with ACLF had more frequent history of arterial hypertension and chronic kidney disease, and more severe impairment of liver function tests, higher sCr, lower serum sodium and arterial pressure, and higher white blood cell count and plasma C-reactive protein levels at enrolment with respect to patients without ACLF (table 4). The frequency of

Table 4 Baseline characteristics of patients according to the presence of acute-on-chronic liver failure (ACLF) at enrolment

	No ACLF (n=270)	ACLF (n=240)	p Value
Age (years)	55±12	55±11	0.46
Male sex	173 (64)	158 (34)	0.68
Aetiology of cirrhosis			
Alcohol	151 (58)	141 (61)	0.49
Hepatitis C virus	39 (15)	28 (12)	0.35
Alcohol plus hepatitis C virus	24 (9)	22 (0.4)	0.91
Other causes	45 (17)	39 (17)	0.90
Previous decompensation(s)			
Ascites	161 (63)	149 (66)	0.49
Encephalopathy	79 (31)	73 (33)	0.62
GI bleeding	62 (24)	52 (24)	0.81
Spontaneous bacterial peritonitis	26 (10)	24 (11)	0.83
Concomitant diseases			
Arterial hypertension	46 (17)	58 (24)	0.04
Diabetes mellitus	54 (20)	54 (23)	0.48
Chronic renal failure	14 (5)	31 (13)	0.002
Cause(s) of admission			
Ascites	170 (64)	181 (76)	0.003
Encephalopathy	81 (30)	109 (46)	0.0003
Bacterial infection	59 (23)	65 (29)	0.13
GI bleeding	51 (19)	28 (12)	0.02
Other	94 (35)	83 (35)	0.99
Exploratory data			
Mean arterial pressure (mm Hg)	84±11	79±13	<0.0001
Heart rate (beats/min)	84±16	83±18	0.63
Laboratory data			
White blood cells (×10^9/L)	7.3±4.4	10.1±6.7	<0.0001
Platelet count (×10^9/L)	104±70	101±73	0.35
Serum bilirubin (mg/dL)	5.6±6.3	11±11	<0.0001
Serum albumin (g/dL)	2.7±0.6	2.8±0.6	0.14
International normalised ratio	1.7±0.6	2.1±0.9	<0.0001
Plasma C-reactive protein (mg/L)	33±39	45±0.6	0.0009
Serum creatinine (mg/dL)	1.0±0.4	2.4±1.6	<0.0001
Serum sodium (mmol/L)	135±6	134±6	0.004
Child–Pugh score	10±2	11±2	<0.0001
MELD	18±6	27±7	<0.0001

Data are expressed as mean±SD or number of patients (percentage).
MELD, model for end-stage liver disease.

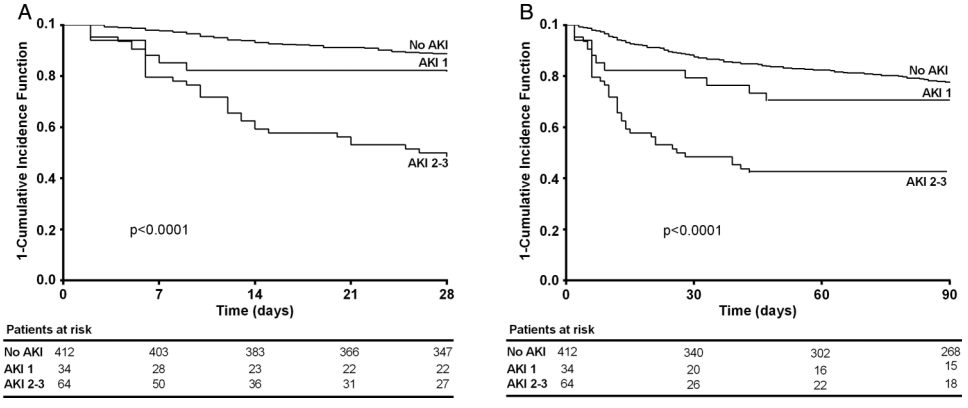

Figure 1 Probability of survival of all patients included, categorised according to the presence and severity of acute kidney injury (AKI) 48 h after enrolment. Calculations were performed using competing risks approach (see text). (A) 28-day survival; (B) 90-day survival.

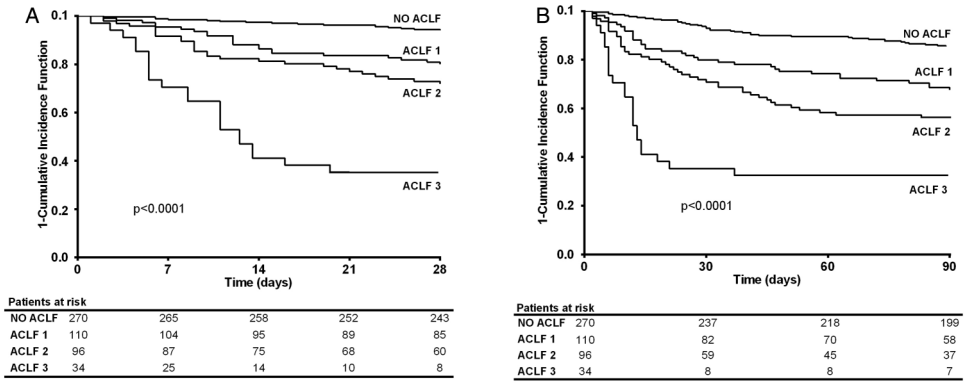

Figure 2 Probability of survival of all patients included, categorised according to the presence and severity of acute-on-chronic-liver-failure (ACLF) at enrolment. Calculations were performed using competing risks approach (see text). (A) 28-day survival; (B) 90-day survival.

ascites and encephalopathy and the magnitude of changes in laboratory tests changed in parallel with severity of ACLF (see online supplementary table S3).

The frequency and stages of ACLF in patients categorised according to the absence or presence of AKI and its stage are shown in online supplementary figure S3.

The presence of ACLF at enrolment was strongly associated with mortality. Twenty-eight-day transplant-free mortality in patients with ACLF was 32% compared with only 6.2% in patients without ACLF (p<0.0001). Corresponding values of 90-day transplant-free mortality were 49.8% and 16.4%, respectively (p<0.001). During the 3-month period after enrolment, 35 (14.6%) patients with ACLF and 28 (10.4%) patients without ACLF were transplanted (p=0.15). In a way similar to the analysis performed with AKI, the cumulative incidence function of mortality during follow-up of all patients categorised according to the presence and severity of ACLF was assessed using risk estimates adjusted to the competing risk of transplantation. As shown in figure 2, presence and severity of ACLF was clearly associated with 28-day and 90-day cumulative mortality risk.

Comparison of the prognostic value of AKI classification vs ACLF classification

We then compared the accuracy of the two classifications in predicting 28-day and 90-day mortality in the whole series of patients admitted to hospital for management of an acute decompensation of cirrhosis. The AUCROC for predicting transplant-free mortality was significantly better for the ACLF classification compared with that of the AKI classification, both at 28 and 90 days (table 5). Likewise, the comparison of the two classifications under a competing risk analysis approach was also better for ACLF compared with AKI.

We then analysed whether assessment of presence and severity of ACLF after 2 days of enrolment (that is, at the same day that the AKI classification was assessed) had better prognostic accuracy than assessment of ACLF at enrolment. During the 2-day period after enrolment, 28 of 270 patients (10.4%) who did not have ACLF at baseline developed ACLF (grade 1 in 16 patients, grade 2 in 11 patients and grade 3 in 1 patient). By contrast, 64 of 240 patients (26.7%) who had ACLF at enrolment improved and no longer met the criteria of ACLF at day 2 (previous ACLF grades were 1 in 43 patients, 2 in 18 patients and 3 in 3 patients). Assessment of ACLF classification at day 2 had significantly better prognostic accuracy compared with those of AKI classification and ACLF classification at enrolment, both using comparisons of standard AUCROC curves for transplant-free mortality as well as comparisons under a competing risk approach considering transplant as a competing event of death (table 5). The predictive accuracy of the model was similar according to the different aetiologies of cirrhosis (alcoholic cirrhosis vs hepatitis C or B infection).

Causes of death and effect of bacterial infections

Table 6 shows the causes of death during the 28-day period in patients classified according to the presence or absence of ACLF at 48 h after enrolment. As expected, mortality was markedly higher in patients with ACLF than in those without (p<0.0001). There were no significant differences between the two groups with respect to causes of death.

Among the 510 patients included, 150 developed a bacterial infection (29.4%). The prevalence of infection increased with the presence and severity of ACLF. More importantly, mortality in patients with infections correlated also with presence and severity of ACLF (table 7).

Table 5 Comparison of acute kidney injury (AKI) and acute-on-chronic liver failure (ACLF) classifications to predict 28-day and 90-day mortality

	AKI	ACLF at enrolment	ACLF at 48 h	AKI vs ACLF at enrolment	AKI vs ACLF at 48 h	ACLF at enrolment vs ACLF at 48 h
AUCROC*					p Value	
28-day	0.68 (0.62 to 0.73)	0.77 (0.71 to 0.82)	0.84 (0.80 to 0.89)	0.0049	<0.0001	0.0021
90-day	0.62 (0.57 to 0.66)	0.72 (0.67 to 0.77)	0.77 (0.73 to 0.82)	<0.0001	<0.0001	0.0092
C-index†					p Value	
28-day	0.66 (0.61 to 0.71)	0.74 (0.69 to 0.79)	0.81 (0.76 to 0.85)	0.09	<0.0001	0.0004
90-day	0.61 (0.57 to 0.65)	0.69 (0.65 to 0.73)	0.74 (0.70 to 0.77)	0.0028	<0.0001	0.0002

Values in parentheses are 95% CIs.
*Transplant-free mortality.
†Mortality considering transplantation as competing event.
AUCROC, area under the curve of the receiving operating characteristic.

Table 6 Causes of death in the whole series categorised according to the presence or absence of acute-on-chronic liver failure (ACLF) at 48 h after enrolment

Cause	No ACLF (n=306)	ACLF (n=204)
Septic shock	3 (25)	32 (42)
Multiorgan failure	3 (25)	22 (29)
Hypovolemic shock	2 (17)	12 (16)
Other	0 (0)	7 (9)
Unknown	4 (33)	3 (4)
Total	12 (4)	76 (37)

Data are expressed as number of patients (values in parentheses are percentages). Percentages in 'Total' refer to the number of patients in each group (no ACLF and ACLF). In the other rows percentages refer to the number of deaths in each group (no ACLF vc ACLF).

DISCUSSION

The purpose of the current study was to compare the accuracy of the AKI classification with that of the ACLF classification, recently proposed by the European Association for the Study of the Liver (EASL)–CLIF consortium on the basis of the CANONIC study, in the prediction of 28-day and 90-day mortality in patients hospitalised for an acute decompensation of cirrhosis.[1]

The main result of the study is that the ACLF classification has greater prognostic accuracy compared with that of the AKI classification in the prediction of 28-day and 90-day mortality. This holds true considering the ACLF classification at enrolment, but more especially when patients were stratified according to the ACLF classification at 48 h of enrolment. This greater prognostic accuracy of the ACLF system is first of all due to the fact that, in contrast to the AKIN criteria, it includes in its definition also non-kidney organ failures such as encephalopathy and cardiovascular dysfunction that are known to have a strong negative impact on prognosis of patients with cirrhosis. In addition, the diagnosis of ACLF also includes liver and coagulation failures, based on the use of serum bilirubin and international normalised ratio, respectively, that are known to have a strong predictive value on 90-day mortality in these patients.[16–18] The availability of a classification system, like the current one on ACLF, which is simple in its application and also able to provide an accurate prognostic assessment at the point of enrolment, is a key factor for planning the management of a severe clinical condition like acute decompensation of cirrhosis. In particular, the identification of patients with a high risk of mortality would be invaluable in deciding when and in which patients to intensify medical care, and in selecting those for liver transplantation. Recognition of high-risk patients with an acute decompensation of the liver disease could facilitate focused resource allocation by identifying those most likely to benefit. Finally, subsequent research in this field can help stratify diagnostic and therapeutic findings between high-risk and low-risk subsets of patients, thereby promoting a targeted evaluation and/or application of them.

Table 7 Prevalence and mortality of bacterial infections in patients categorised according to acute-on-chronic liver failure (ACLF) grades

	No ACLF (n=306)	ACLF grade 1 (n=92)	ACLF grade 2 (n=66)	ACLF grade 3 (n=46)	p Value
Bacterial infection	82 (27)	30 (33)	16 (25)	22 (49)	0.017
Death					
28-day	3 (4)	7 (23)	7 (44)	15 (68)	<0.0001
90-day	14 (17)	10 (35)	9 (56)	17 (77)	<0.0001

Data are expressed as number of patients (values in parentheses are percentages).

Approximately 20% of the population of the current study developed AKI within the first 48 h after enrolment. The design of the CANONIC study may have favoured an underestimation of the actual prevalence of AKI in our series of patients. In fact, according to the definition of the AKIN criteria, only changes in sCr within the first 48 h after enrolment were considered for the definition of AKI. Therefore, patients who could theoretically have developed AKI before or after this interval of time were not considered. Looking at the baseline sCr in patients without AKI (see online supplementary figure S2) it is possible that some patients could have developed AKI before enrolment and probably before admission to hospital. It has been reported that a community-acquired AKI may account for at least one-third of all AKI episodes detected in general population.[19] However, the detection of community-acquired AKI criteria requires an sCr value to be evaluated just prior to hospital admission or a surrogate for it. Thus, the lack of this value represents more a limitation of applicability of the AKIN criteria than of the study design. As far as the possibility of development of AKI later during the hospitalisation, it should be taken into account that it has been observed that most AKI episodes occur during the first 48 h after admission.[20] On the other hand, the possibility that some patients could have developed ACLF more than 48 h after enrolment should also be taken into account. Thus, the comparison limited to the first 48 h, that is, at the same day that the AKI classification was assessed, puts the two classification systems in a condition of virtual equality. Despite this equality, the ACLF classification made it possible to stratify in prognostic terms 47.1% of patients at enrolment and 40% of patients after 48 h. A number of factors could have contributed to this high frequency of ACLF. First, among patients who had an organ failure at enrolment those with an organ failure other than the kidney were 41.7%. Second, the use of an absolute value of sCr ≥1.5 mg/dL, which has always shown a high prognostic value in hospitalised patients with cirrhosis, without suffering the methodological limitations of the AKIN criteria, has contributed to define an additional 10.4% of patients with ACLF. Finally, to fully understand the significance of this marked difference in frequency between AKI and ACLF in our patients, it is necessary to add that among the patients in whom AKI was diagnosed only 15.3% did not have ACLF (see online supplementary figure S3).

One downside of the study appeared when trying to analyse the prognostic accuracy of the model based on ACLF classification for prediction of adverse events. Unfortunately, this analysis could not be done because the number of patients without adverse events in the current series of patients was very low (only 10% of the series), which precluded a conclusive statistical analysis. Moreover, when adverse events related to organ failures were considered, there was a problem that organ failures were included in the definition of ACLF, which made the analysis not possible.

A final aspect of the study that should be emphasised is that the prognostic stratification of patients was done in the first 48 h after admission. However, this is an important period of time in which clinical decisions must be taken.

In conclusion, the ACLF classification provides a simple tool for an immediate stratification of patients with acute decompensation of cirrhosis on hospital admission. The prognostic accuracy of ACLF classification can be further enhanced when it is

applied 48 h after admission. The ACLF classification both at admission and at 48 h has better prognostic accuracy than the AKI classification, thus it should be used in the prognostic stratification of these patients.

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Acute kidney injury and acute-on-chronic liver failure classifications in prognosis assessment of patients with acute decompensation of cirrhosis

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