ORIGINAL ARTICLE

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

Paolo Angeli,1,2 Ezequiel Rodríguez,3,4,5 Salvatore Piano,1,2 Xavier Ariza,3,4,5 Filippo Morando,1,2 Elsa Solà,3,4,5,6 Antonietta Romano,1,2 Elisabet García,7 Marco Pavesi,6,7 Alessandro Risso,8 Alexander Gerbes,9 Chris Willars,10 Mauro Bernardi,11 Vicente Arroyo,3,4,6 Pere Ginès,3,4,5,6 for the CANONIC Study Investigators of the EASL-CLIF Consortium

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.

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
simplest terms, is characterised by the abrupt onset of organ fail-
ures in patients with cirrhosis hospitalised for an acute de-
compensation of liver disease. 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.

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. 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. Consequently, the results of the
CANONIC study have reinforced the concept that an impair-
ment of kidney function has a marked negative impact on prog-
nosis of hospitalised patients with cirrhosis, giving it a new
dimension as a predictor of mortality.

In 2007, the Acute Kidney Injury Network (AKIN) de-
veloped a consensus definition of AKI, a new term to define acute
renal failure according to AKIN criteria. 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 critical-
ally ill patients since they have been shown to be accurate in predicting prognosis. 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 pre-
dicts short-term and mid-term mortality in a stage-dependent
fashion in hospitalised patients with cirrhosis. 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 com-
plete 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 decompen-
sation of cirrhosis.

PATIENTS AND METHODS
Study population
The current study was performed in a population of patients
included in the CANONIC study. The CANONIC study was a
multicentre study aimed at evaluating the frequency, character-
ostiics 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 investiga-
tion 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. 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 differ-
ent 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 de-
finition 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 in determining the outcome of
cases 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). 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 measure-
ments 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). Outcome was analysed as 28-day and
90-day mortality.

Statistical analysis
Data were collected using an electronic case report form. Quan-
titative 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 mortal-
ity. In addition, since transplantation can be considered a com-
peting event of death, curves showing the cumulative
probability of failure were estimated with the cumulative inci-
dence function proposed by Fine and Gray 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 consid-
ered 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.
The majority of patients had advanced cirrhosis as indicated by markedly impaired liver function tests and high Child–Pugh and MELD, model for end-stage liver disease. 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 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 at 48 h after enrolment. 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.²⁹ 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...
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>
<thead>
<tr>
<th>Table 3</th>
<th>Potential causes of acute kidney injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume depletion</td>
<td>21 (17)</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>16</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3</td>
</tr>
<tr>
<td>Diuretic overdose</td>
<td>2</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>47 (39)</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>17</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7</td>
</tr>
<tr>
<td>Skin infection</td>
<td>4</td>
</tr>
<tr>
<td>Other infections</td>
<td>4</td>
</tr>
<tr>
<td>Unproved suspected infection</td>
<td>6</td>
</tr>
<tr>
<td>Type 1 hepatorenal syndrome</td>
<td>15 (12)</td>
</tr>
<tr>
<td>Surgery</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>37 (30)</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Baseline characteristics of patients according to the presence of acute-on-chronic liver failure (ACLF) at enrolment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No ACLF (n=270)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55±12</td>
</tr>
<tr>
<td>Male sex</td>
<td>173 (64)</td>
</tr>
<tr>
<td>Aetiology of cirrhosis</td>
<td>151 (58)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>39 (15)</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>24 (9)</td>
</tr>
<tr>
<td>Other causes</td>
<td>45 (17)</td>
</tr>
<tr>
<td>Previous decompensation(s)</td>
<td>161 (63)</td>
</tr>
<tr>
<td>Ascites</td>
<td>79 (31)</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>62 (24)</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>26 (10)</td>
</tr>
<tr>
<td>Concomitant diseases</td>
<td>46 (17)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>54 (20)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>14 (5)</td>
</tr>
<tr>
<td>Cause(s) of admission</td>
<td>170 (64)</td>
</tr>
<tr>
<td>Ascites</td>
<td>81 (30)</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>59 (23)</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>51 (19)</td>
</tr>
<tr>
<td>Other</td>
<td>94 (35)</td>
</tr>
<tr>
<td>Exploratory data</td>
<td>84±11</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>84±16</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>7.3±4.4</td>
</tr>
<tr>
<td>Platelet count (×10^9/L)</td>
<td>104±70</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>5.6±6.3</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>2.7±0.6</td>
</tr>
<tr>
<td>International normalised ratio</td>
<td>1.7±0.6</td>
</tr>
<tr>
<td>Plasma C-reactive protein (mg/L)</td>
<td>33±39</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.0±0.4</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>135±6</td>
</tr>
<tr>
<td>Child–Pugh score</td>
<td>10±2</td>
</tr>
<tr>
<td>MELD</td>
<td>18±6</td>
</tr>
</tbody>
</table>

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

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

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

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.
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 AKI 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.

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

---

**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

<table>
<thead>
<tr>
<th>Cause</th>
<th>No ACLF (n=306)</th>
<th>ACLF (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock</td>
<td>3 (25)</td>
<td>32 (42)</td>
</tr>
<tr>
<td>Multigorgan failure</td>
<td>3 (25)</td>
<td>22 (29)</td>
</tr>
<tr>
<td>Hypovolemic shock</td>
<td>2 (17)</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (33)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>12 (4)</td>
<td>76 (37)</td>
</tr>
</tbody>
</table>

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 vs ACLF).

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

<table>
<thead>
<tr>
<th></th>
<th>No ACLF (n=306)</th>
<th>ACLF grade 1 (n=92)</th>
<th>ACLF grade 2 (n=86)</th>
<th>ACLF grade 3 (n=46)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial infection</td>
<td>82 (27)</td>
<td>30 (33)</td>
<td>16 (25)</td>
<td>22 (49)</td>
<td>0.017</td>
</tr>
<tr>
<td>Death</td>
<td>3 (4)</td>
<td>7 (23)</td>
<td>7 (44)</td>
<td>15 (68)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>28-day</td>
<td>14 (17)</td>
<td>10 (35)</td>
<td>9 (56)</td>
<td>17 (77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>90-day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

**Author affiliations**

1. Department of Medicine (DIMED), University of Padova, Italy
2. Unit of Hepatic Emergencies and Liver Transplantation, Padova, Italy
3. Liver Unit, Hospital Clinic de Barcelona, University of Barcelona, Spain
4. Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
5. Fundación Renal Ildefonso Alvarez de Toledo (FRIAT), Madrid, Spain
6. Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBERHD), Spain
7. Data Management Centre, CLIF Consortium, Barcelona, Spain
8. Hospital San Giovanni Battista Hospital, University of Torino, Italy
9. Liver Unit, Klinikum Munich, Ludwig Maximilian University of Munich, Germany
10. Intensive Care Unit, Hepatology Department, Kings College London, UK
11. Semeiotica Medica—Policlinico S. Orsola-Malpighi, University of Bologna, Italy

**Acknowledgements**

The work of physicians and nurses working in the different hospitals that participated in the CANONIC study is greatly appreciated. This is study number 3 of the CANONIC Project.

**Contributors**

Design of study: PA and PG. Data collection: ER, SP, XA, FM, ES, AR, AII, and CW. Analysis of data: PA, PG, EG, MP, ER, and XA. Drafting and writing of manuscript: PA, PG, ER, SP, and XA. Critical revision of data and manuscript revision: AG, CW, MB, VA, PA, and PG.

**Funding**

Ministerio de Economia y Competitividad, Fondo de Investigación Sanitaria Instituto de Saludos Carlos III (FIS 2012/ P112/00330).

**Competing interests**

This study did not receive any direct funding; however, the CLIF consortium is supported by an unconditional grant from GRIFOLS S.A. Spain. PG has received research funding from the Instituto de Salud Carlos III (FIS 2012/ P112/00330). PG has also worked on a consultancy basis for Sequana Medical AG and Grifols S.A. MB declares he has acted as speaker for the following companies entirely unrelated to this study: CLS Behring GmbH, PPTA Europe and Baxter Healthcare SA. He has worked on a consultancy basis for CLS Behring GmbH and Baxter Healthcare SA.

**Patient consent**

Obtained.

**Ethics approval**

Each hospital obtained approval.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data sharing statement**

This is an original research article. The data base from which the data were obtained for this study is available in the Data base Management Center of the EASL-CLIF consortium, University of Barcelona, Spain. The data base is available for all the investigators who are involved or who will be involved in research studies after the approval of the EASL-CLIF consortium Steering Committee.

**REFERENCES**

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

Paolo Angeli, Ezequiel Rodriguez, Salvatore Piano, Xavier Ariza, Filippo Morando, Elsa Solà, Antonietta Romano, Elisabet Garcia, Marco Pavesi, Alessandro Risso, Alexander Gerbes, Chris Willars, Mauro Bernardi, Vicente Arroyo and Pere Ginès

Gut 2015 64: 1616-1622 originally published online October 13, 2014
doi: 10.1136/gutjnl-2014-307526

Updated information and services can be found at:
http://gut.bmj.com/content/64/10/1616

These include:

Supplementary Material
Supplementary material can be found at:
http://gut.bmj.com/content/suppl/2014/10/13/gutjnl-2014-307526.DC1

References
This article cites 20 articles, 3 of which you can access for free at:
http://gut.bmj.com/content/64/10/1616#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Errata
An erratum has been published regarding this article. Please see next page or:
/content/65/8/1394.full.pdf

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/
Erratum: Acute kidney injury and acute-on-chronic liver failure classifications in prognosis assessment of patients with acute decompensation of cirrhosis

Angeli P, Rodríguez E, Piano S, et al. Acute kidney injury and acute-on-chronic liver failure classifications in prognosis assessment of patients with acute decompensation of cirrhosis. *Gut* 2015;64:1616–22. The funding statement has been updated to read: Part of the work reported in this study has been funded by the project PI12/00330, integrated in the Plan Nacional I+D+I and cofunded by ISCIII-Subdirección General de Evaluación and European Regional Development Fund (ERDF).

*Gut* 2016;65:1394. doi:10.1136/gutjnl-2014-307526corr1