Prevalence and risk factors of acute-on-chronic liver failure in a single center from Argentina

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AIM
To study the prevalence, characteristics, risk factors and mortality at 28 d of acute-on-chronic liver failure (ACLF).

METHODS
A total of 100 cirrhotic patients admitted to our hospital for more than one day were included during the period between June 2013 and December 2015. We used the European Association for the Study of the Liver-Chronic Liver Failure-Consortium diagnostic criteria for ACLF, considering it as the acute decompensation of cirrhosis associated with the presence of one or more organ failure. For the diagnosis of organic failure the Chronic Liver Failure-Sequential Organ Failure Assessment score was used. Our population was divided into patients with and without ACLF. Clinical characteristics, presence of precipitating events, potential risk factors for developing ACLF and causes of mortality were analyzed. Mortality at 28 d was evaluated.

RESULTS
Twenty-nine patients (29%) developed ACLF criteria. Alcoholism, detected in 58 patients (58%), was the
major etiological agent of cirrhosis. Bacterial infections were recognized as a precipitating event in 41.3% of cases and gastrointestinal bleeding in 27.5%. No precipitating event was identifiable in 27.5% of patients with ACLF. Comparing patients with and without ACLF, statistically significant risk factors were: Child Pugh score 10.2 ± 2.1 vs 8.4 ± 1.6 (P < 0.0001), MELD score 20.7 ± 8.5 vs 12.3 ± 4 (P < 0.0001), presence of ascites 27 (93%) vs 43 (60.5%) (P = 0.001), leukocytosis 15300 ± 8033 per cubic millimeter vs 10770 ± 5601 per cubic millimeter (P < 0.0001), and high plasma levels of C reactive protein values 50.9 ± 46.4 mg/L vs 28.6 ± 23.4 mg/L (P < 0.0019). Mortality rate was 62% (18 patients) vs 5.6% (4 patients), respectively (P < 0.0001).

CONCLUSION
We observed that the ACLF is a frequent entity in this group of patients and has a significantly higher mortality rate.

Key words: Acute-on-chronic liver failure; Acute liver decompensation; Cirrhosis; Ascites; Mortality

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Core tip: Acute-on-chronic liver failure (ACLF) is an increasingly recognized entity that is gaining acceptance in recent times. It is characterized by an acute impairment of an underlying chronic liver disease with high short-term mortality, produced by the development of organic failures and associated with precipitating event. However, little is known about the development and progression of this syndrome. Guided by the European Association for the Study of the Liver (EASL) and the American Association for the Study of the Liver (AASLD), ACLF is an “acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event, and associated with increased mortality at three months due to multi-system organ failure”[4].

Recently, an European consortium exclusively dedicated to the study of liver failure in patients with chronic liver disease (EASL-CLIF-Consortium) conducted the CANONIC study with the aim to define the ACLF and be able to identify those cirrhotic patients with a high risk of short-term mortality. Based on the analysis of 1343 cirrhotic patients, the EASL-CLIF-Consortium proposed as diagnostic criteria the acute decompensation of the liver disease (defined by the development of ascites, encephalopathy, gastrointestinal bleeding or bacterial infection) associated with the presence of one or more organ failure. The organ failure was defined by the Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score (Table 1) and a mortality at 28 d higher than 15%[5,6].

Acute decompensation of cirrhosis is the leading cause of hospitalization in cirrhotic patients[7]. In many of these patients complications develop in the absence of organic failure, but in others they are associated with impaired function of kidneys, liver or other organs. The last group of patients, falling within the definition of ACLF, are those with a high risk of short term mortality.

The CANONIC study showed that ACLF is an extremely relevant and very common syndrome, with a prevalence of around 30%, differing from a mere acute decompensation by the presence of organ failure, the mortality rate 15 times higher, the clinical characteristics, the association with precipitating events and the parameters of systemic inflammation[8-10].

Due to the lack of a worldwide accepted definition and diagnostic criteria, many aspects of this syndrome, such as prevalence, natural history, precipitating factors, clinical features and pathophysiological mechanisms remain unknown[11,12].

The aims of our study were to determine the prevalence of ACLF in the cirrhotic patients of our institution using the diagnostic criteria established by the CANONIC study, to describe the clinical characteristics of ACLF, to assess the risk factors for developing ACLF, and to evaluate the mortality at 28 d, comparing the cases with and without ACLF.

INTRODUCTION
Acute-on-chronic liver failure (ACLF) is an increasingly recognized entity that includes the acute deterioration of a chronic liver disease, usually associated with a precipitating event, the development of one or more organ failure and high short-term mortality.

The term ACLF was initially coined in 1995[1]. There are more than thirteen different definitions up to date. Until worldwide diagnostic criteria are accepted, two consensual definitions are commonly used[2]. The first, belonging to the Asian Pacific Association for the Study of the Liver, considers that the ACLF is an “acute hepatic insult manifesting as jaundice and coagulopathy, complicated within four weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease”[3]. According to the second definition, developed in a joint symposium of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases, ACLF is an “acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event, and associated with increased mortality at three months due to multi-system organ failure”[4].

We observed that the ACLF is a frequent entity in this group of patients and has a significantly higher mortality rate.

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MATERIALS AND METHODS
In this prospective observational study we analyzed
patients with cirrhosis, diagnosed by a previous liver biopsy or by indirect signs (clinical examination, laboratory, imaging and endoscopy), who were hospitalized for more than one day in the Sanatorio Güemes, which is one of the biggest high complexity medical centers in Argentina, located in Buenos Aires City, with a capacity of 480 beds.

The protocol was approved by our institutional review board and patients gave the usual written informed consent for hospitalization, no additional procedures other than those indicated by the physicians, based on routine practice and international standards, were performed. Considering this fact, our institutional reviewers considered that another special consent was not required.

Patients were recruited between June 2013 and December 2015. Data were obtained from medical records, including previous episodes of decompensation (ascites, encephalopathy, spontaneous bacterial peritonitis, esophageal varices, variceal bleeding or hepatocellular carcinoma), physical examination, laboratory analysis, presence of potential precipitating factors (infections, carcinoma), physical examination, laboratory analysis, and at discharge or previously to death.

For statistical analysis, the χ² test or the Fisher test was used. For continuous variables the Student t test was used. For dichotomous variables as appropriate. For statistical analysis, the χ² test or the Fisher test were used for dichotomous variables as appropriate. For continuous variables the Student t test was used. For dichotomous variables as appropriate. For continuous variables the Student t test was used. For dichotomous variables as appropriate.

RESULTS

A total of 100 patients were included, of which 67 were male (67%) and 33 female (33%). The mean age was 60 ± 11 years and mean Child-Pugh score was 9 ± 1.9. Regarding to the etiology of cirrhosis, alcohol was found in 58 patients (58%), followed by hepatitis C infection and cryptogenic disease (Table 2).

The total of patients who fulfilled criteria for ACLF was 29 (29%), 10 of them (34.4%) were grade 1, 5 (17.3%) grade 2 and 14 (48.3%) grade 3 (Table 3). Seventeen patients (59%) had criteria for ACLF at admission to the hospital and 12 (41%) developed it during hospitalization, with an average time of presentation of 10 d. Renal failure was the prevalent organ failure for ACLF grade 1. For ACLF grade 2, coagulation failure was the prevalent finding followed by renal and respiratory failure. For ACLF grade 3, the prevalence of all organ failures was high with a significant impact in the circulatory and respiratory systems.

Table 1 Chronic liver failure-sequential organ failure assessment score

| Organ/system            | 0     | 1          | 2          | 3          | 4          |
|-------------------------|-------|------------|------------|------------|------------|
| Liver (bilirubin, mg/dL)| < 1.2 | ≥ 1.2 to < 2 | ≥ 2 to < 6 | ≥ 6 to < 12 | ≥ 12       |
| Kidney (creatinine, mg/dL)| < 1.2 | ≥ 1.2 to < 2 | ≥ 2 to < 3.5 | ≥ 3.5 to < 5 or dialysis | ≥ 5 or dialysis |
| Cerebral (HE grade)     | No HE | I          | II         | III        | IV         |
| Coagulation (RIN, platelet count) | < 1.1 | ≥ 1.1 to < 1.25 | ≥ 1.25 to < 1.5 | ≥ 1.5 to < 2.5 | ≥ 2.5 or platelet count ≤ 20000 per cubic millimeter |
| Circulation (mean arterial pressure, mmHg), inotropic drugs (μg/kg per minute)| > 70 | < 70 | Dopamine ≤ 5 or dobutamine or terlipressin | NE ≥ 0.1 or Dopamine > 15 or E > 0.1 | NE > 0.1 |
| Lungs (SpO₂/FiO₂)       | > 512 | ≤ 357 a ≤ 512 | > 214 a ≤ 357 | > 89 a ≤ 214 | ≤ 89 |

The text in bold indicates the diagnostic criteria for organ failure. HE: Hepatic encephalopathy; E: Epinephrine; NE: Norepinephrine; FiO₂: Fraction of inspired oxygen; SpO₂: Pulse oximetric saturation.
system (Table 4).

Analyzing the possible precipitating factors in patients with ACLF, an infectious cause was recognized in 12 (41.3%), being pneumonia the main source of infection, and gastrointestinal bleeding in 8 (27.5%). One patient (3.4%) developed ACLF after a renal failure secondary to acute diarrhea. There was not an evident precipitating factor in 8 cases (27.5%) (Table 5). In the group of patients without ACLF, we observed the following clinical events: Gastrointestinal bleeding in 27 patients (38%), bacterial infections in 20 (29%), other causes such as constipation in 5 (7%) and no event in 19 (26%).

When patients with and without ACLF were compared, we observed, respectively: Male 23 (79%) vs 44 (62%) \(P = 0.11, \text{OR} = 2.36 (95\% \text{CI}: 0.78-7.43)\), age 60 ± 11 years vs 60 ± 11 years \(P = 1.00\), active alcohol intake in the last 3 mo 9 (31%) vs 22 (31%) \(P = 1, \text{OR} = 1.00 (95\% \text{CI}: 0.23-2.79)\), Child Pugh 10.2 ± 2.1 vs 8.4 ± 1.6 \(P < 0.0001\), MELD score 20.7 ± 8.5 vs 12.3 ± 4 \(P < 0.0001\), previous episodes of ascites 18 (62%) vs 29 (41%) \(P = 0.07, \text{OR} = 2.37 (95\% \text{CI}: 0.89-6.33)\), previous episodes of encephalopathy 9 (31%) vs 10 (14%) \(P = 0.08, \text{OR} = 2.74 (95\% \text{CI}: 0.87-8.69)\), presence of esophageal varices 18 (62%) vs 37 (52%) \(P = 0.38, \text{OR} = 1.5 (95\% \text{CI}: 0.57-3.99)\), prior variceal hemorrhage 4 (13.7%) vs 10 (14%) \(P = 1.00, \text{OR} = 0.97 (95\% \text{CI}: 0.23-3.84)\), presence of ascites during hospitalization 27 (93%) vs 43 (60.5%) \(P = 0.001, \text{OR} = 8.79 (95\% \text{CI}: 1.80-8.10)\), white blood cell count 15300 ± 8.033 per cubic millimeter vs 10770 ± 5.601 per cubic millimeter \(P < 0.0001\), natriemia 133.3 ± 6.9 mEq/L vs 135.1 ± 5.3 mEq/L \(P = 0.16\), and CRP values 50.9 ± 46.4 mg/L vs 28.6 ± 23.4 mg/L \(P < 0.0019\) (Table 6).

Twenty patients were hospitalized in the intensive care unit, 14 received mechanical ventilation and none had artificial liver support because it is not available at our center. ACLF resolved or improved in 11 patients (38%) during hospitalization: 7 patients (70%) in grade 1, 3 (60%) in grade 2 and only 1 (7%) in grade 3. In the group of ACLF, 18 patients (62%) died, due to septic shock 10, type 1 hepatorenal syndrome 3, shock without focus 3, upper gastrointestinal bleeding 1 and bronchoaspiration 1. The mortality was 30% in ACLF grade 1, 40% in grade 2 and 92% in grade 3. In the group without ACLF, 4 patients (5.6%) died, due to infection 3 and cardiac failure 1.

**DISCUSSION**

ACLF is a syndrome different from traditional decompensated cirrhosis, not only because of the presence of organ failure and high mortality rate but also because of the alcoholic etiology of cirrhosis, the prevalence of some specific triggers such as bacterial infection and the higher level of systemic inflammation\(^{[15,16]}\). To recognize ACLF allows to identify those patients at high risk for death due to organ failure and the CANONIC study provided much more precise diagnostic criteria\(^{[4,5,15]}\). So, we followed these criteria in our center and we found a prevalence of 29%, similar to the 30.9% found in the CANONIC study\(^{[6,10]}\). It is interesting to point out that cirrhotic patients may develop ACLF during their stay in the hospital, with an incidence of 14.4%. This figure is quite higher than the 10.8% observed in the CANONIC study\(^{[6]}\).

It is noteworthy that 65.8% of our patients who developed ACLF had more than one organ involved (grades 2 and 3). This finding differs from the results of the CANONIC study showing that 64.3% of patients had only one organ involvement\(^{[10]}\). A possible explanation for this discrepancy may be that our patients had advanced stages of cirrhosis (Child-Pugh C 72%) and high prevalence of alcoholism as etiology of the cirrhosis (58% vs 48.6% in the CANONIC study). An advanced disease

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Table 2  Cirrhosis etiology

| Etiology                                      | n (%)  |
|----------------------------------------------|--------|
| Alcohol                                      | 58 (58)|
| Alcohol + hepatitis C virus                  | 5 (5)  |
| Hepatitis C Virus                            | 13 (13)|
| Nonalcoholic steatohepatitis                 | 4 (4)  |
| Cryptogenic                                  | 12 (12)|
| Autoimmune hepatitis                         | 4 (4)  |
| Primary biliary cirrhosis                    | 1 (1)  |
| Primary biliary cirrhosis + autoimmune hepatitis | 1 (1) |
| Hepatitis B virus + alcohol                  | 1 (1)  |
| Hemochromatosis                              | 1 (1)  |

Table 3  Prevalence of acute on chronic liver failure n (%)

| ACLF                  | Grade 1 | Grade 2 | Grade 3 |
|-----------------------|---------|---------|---------|
| Patients              | 10 (34.4) | 5 (17.3) | 14 (48.3) |
| Mortality             | 3 (30)  | 2 (40)  | 13 (92)  |

ACLF: Acute-on-chronic liver failure.

Table 4  Type and number of organ failure n (%)

| Organs failure                                   | ACLF 1 | ACLF 2 | ACLF 3 |
|--------------------------------------------------|--------|--------|--------|
| Renal failure                                    | 7 (70) | 2 (40) | 10 (71) |
| Cerebral failure                                 | 1 (10) | 1 (20) | 12 (85) |
| Coagulation                                      | 1 (10) | 3 (60) | 8 (57)  |
| Liver                                            | 1 (10) | 1 (20) | 2 (14)  |
| Circulatory                                      | 0 (0)  | 1 (20) | 14 (100) |
| Respiratory                                      | 1 (10) | 2 (40) | 14 (100) |

ACLF: Acute-on-chronic liver failure.

Table 5  Precipitating events of acute-on-chronic liver failure

| Potential precipitating events of ACLF | n (%) |
|---------------------------------------|-------|
| Bacterial infection                   | 12 (41.3) |
| Gastrointestinal hemorrhage           | 8 (27.5) |
| Renal failure secondary to acute diarrhea | 1 (3.4) |
| No precipitating event                | 8 (27.5) |

ACLF: Acute-on-chronic liver failure.
may have been the trigger of irreversible pro- and anti-inflammatory mechanisms\cite{10,17,18}. The commonest organ failure was the kidney failure (66%)\cite{10,20}. The prevalence of circulatory and respiratory failure was high (51% and 58%) but significant only in patients with ACLF grade 3.

As expected by previous references, bacterial infections primarily and gastrointestinal bleeding secondly were the main precipitating events\cite{5,21}. It is important to note that in 27.5% of cases we did not identify an evident precipitating factor to explain ACLF in 27.5% of cases, a fact that was previously observed by other authors\cite{5}.

We found that Child-Pugh score, MELD score, presence of ascites, elevated leukocyte count and high CRP values parameters were significant risk factors for the development of ACLF. Although Child-Pugh and MELD scores were not considered as risk factors, the statistical significance of ascites, kidney disfunction, hepatic encephalopathy, bilirubin, serum creatinine and international normalized ratio in the CANONIC study allows us to infer that our findings agree with these observations. The role of leukocyte count and CRP as inflammatory parameters were also emphasized by these authors\cite{5,9}.

As it was previously observed, mortality was significantly higher in our patients with ACLF. Mortality in our patients with ACLF grade 1 was higher when compared with the figures reported by Gustot et al\cite{22} (30% vs 6% to 18%), but it was similar in patients with ACLF grade 2 and 3 (40% to 92% vs 42% to 92%). As it was also observed by these authors, mortality increased significantly when three or more organs were involved\cite{5,10,22}.

The main strength of our investigation is the prospective design that allowed a rigorous collection of data and its main weakness is that it was performed in a single center with a limited number of patients. Despite this limitation, we can draw several conclusions from our results. ACLF is a syndrome that occurs with high frequency in cirrhotic patients hospitalized for decompensated liver disease, reaching a prevalence of 29% in our centre. As noted in the literature, ACLF is a very dynamic syndrome. It resolved or improved in 38% of our patients, a figure lower than the 49% observed by Gustot et al\cite{22}. Patients may enter the hospital with ACLF but they may also develop it during their stay, there are risk factors that may predict its development and mortality significantly increases when it occurs. Consequently, it is important to recognize this entity, to be aware of its development and to install supportive measures in order to reduce the high mortality\cite{15,23-25}. To overcome the limitations of our study and to achieve a better knowledge of the epidemiology and clinical characteristics of ACLF in our country, it would be desirable to transfer our bounded experience to a multicenter prolonged study.

### Table 6 Comparative results between groups with and without acute on chronic liver failure n (%)

|                  | ACLF    | No ACLF | P value | OR   | 95%CI |
|------------------|---------|---------|---------|------|-------|
| Age (yr ± SD)    | 60 ± 11 | 60 ± 11 | 1.00    |      |       |
| Male             | 23 (79) | 44 (62) | 0.11    | 2.3  | 0.78-7.43 |
| Child Pugh (score ± DS) | 10.2 ± 2.1 | 8.4 ± 1.6 | < 0.0001 |      |       |
| MELD (score ± DS) | 20.7 ± 8.5 | 12.3 ± 4 | < 0.0001 |      |       |
| Active alcoholism | 9 (31)  | 22 (31) | 1.00    | 1    | 0.3-2.8 |
| Prior ascites     | 18 (62) | 29 (41) | 0.07    | 2.3  | 0.9-6.3 |
| Prior encephalopathy, n (%) | 9 (31) | 10 (14) | 0.08    | 2.74 | 0.9-8.7 |
| Esophageal varices | 18 (62) | 37 (52) | 0.38    | 1.5  | 0.5-5.4 |
| Ascites           | 27 (93) | 43 (60.5)| 0.001   | 8.8  | 1.8-58.1 |
| Variceal hemorrhage | 4 (13.7)| 10 (14) | 1       | 0.97 | 0.2-3.8 |
| White cell count (n/mm³ ± SD) | 15.30 ± 10.770 | 8.03 ± 5.601 | < 0.0001 |      |       |
| Serum sodium (mEq/L ± SD) | 133.3 ± 6.9 | 135.1 ± 5.3 | 0.16 |      |       |
| CRP (mg/L ± SD)  | 50.9 ± 46.4 | 28.6 ± 23.4 | 0.002 |      |       |
| Mortality        | 18 (62) | 4 (5.6) | < 0.0001 |      |       |

OR: Odds ratio; 95%CI: Confidence interval 95%; SD: Standard deviation; CRP: C-reactive protein; ACLF: Acute-on-chronic liver failure.

### Comments

#### Background

Acute-on-chronic liver failure (ACLF) is an increasingly recognized entity that includes the acute deterioration of a chronic liver disease, usually associated with a precipitating event, the development of one or more organ failure and high short-term mortality. However, little is known about the development and progression of this syndrome. This study aimed to determine the prevalence of ACLF and describe the characteristics of this syndrome; assess the risk factors and analyze the mortality at 28 d.

#### Research Frontiers

Until the development of the CANONIC study there was no established definition of ACLF and the published definition were based only on expert opinions. In this study using the CANONIC diagnostic criteria, the authors describe the clinical characteristics, the prevalence and natural history of ACLF in cirrhotic patients of the authors’ institution.

#### Innovations and Breakthroughs

As suggested in the literature, the authors observed that the ACLF is a frequent entity in this group of patients and has a significantly higher mortality rate.

#### Applications

As ACLF is a frequent syndrome, it is important to recognize this entity, to be aware of its development and to install supportive measures in order to reduce the high mortality.
**Terminology**

Acute-on-chronic liver failure: Acute deterioration of cirrhosis associated with organ's failure and short term mortality.

**Peer-review**

The paper is well written and includes information about a relevant topic.

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