

Prospective Study

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

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Abstract

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-Chronic Liver Failure-Consortium diagnostic criteria and the CANONIC study, we could establish that the prevalence of ACLF in our center was 29%, and that Child Pugh advanced stage, MELD score, presence of ascites and inflammation parameters were significant risk factors for ACLF.

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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].

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.

MATERIALS AND METHODS

In this prospective observational study we analyzed

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	Dopamine > 5 or E ≤ 0.1 or NE ≤ 0.1	Dopamine > 15 or E > 0.1 or NE > 0.1
Lungs (SpO ₂ /FiO ₂)	> 512	> 357 a ≤ 512	> 214 a ≤ 357	> 89 to ≤ 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.

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, active alcohol intake, gastrointestinal bleeding), and etiology of cirrhosis.

For the diagnosis of organic failure the CLIF-SOFA score was used (Table 1). Our population was divided into patients with and without ACLF. Within the group with ACLF the type and number of affected organs were analyzed and divided in 3 grades. ACLF grade 1 included patients with single kidney failure; patients with single failure of the liver, coagulation, circulation, or respiration who had a serum creatinine level ranging from 1.5 to 1.9 mg/dL and/or mild to moderate hepatic encephalopathy; and patients with single cerebral failure, who had a serum creatinine level ranging from 1.5 to 1.9 mg/dL. ACLF grade 2 included patients with failure of two organs and ACLF grade 3 included patients with failure of three or more organs.

After discharge, the mortality at 28 d was evaluated by monitoring on an outpatient basis or by telephone calls when patients did not attend the visit.

Clinical characteristics of each group, presence of precipitating events, potential risk factors for developing ACLF and causes of mortality were analyzed. Within the analyzed clinical parameters, the West-Haven scale for

encephalopathy grades was used^[13]; ascites was classified in mild (mild ascites only detectable by ultrasound), moderate (moderate ascites evident by moderate symmetrical distension of abdomen) and severe (large or gross ascites with marked abdominal distension)^[14]; circulation dysfunction implied arterial hypotension (mean arterial pressure below 70 mmHg) or requirement of inotropic drugs; and respiratory failure implied the need for mechanical ventilation.

Laboratory data included a complete blood analysis allowing the calculation of MELD and Child-Pugh scores. Inflammation parameters were evaluated by white blood cell count and C-reactive protein (CRP).

Both the clinical parameters and the laboratory results were recorded when patients were enrolled, when they showed some intercurrent or organic decompensation, and at discharge or previously to death.

Statistical analysis

For statistical analysis, the χ^2 test or the Fisher test were used for dichotomous variables as appropriate. For continuous variables the Student *t* test was used. For risk factors, the OR with their respective 95%CI were calculated as association measures.

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

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.

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%) [$P = 0.11$, OR = 2.36 (95%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%) [$P = 1$, OR = 1.00 (95%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%) [$P = 0.07$, OR = 2.37 (95%CI: 0.89-6.33)], previous episodes of encephalopathy 9 (31%) vs 10 (14%) [$P = 0.08$, OR = 2.74 (95%CI: 0.87-8.69)], presence of esophageal varices 18 (62%) vs 37 (52%) [$P = 0.38$, OR = 1.5 (95%CI: 0.57-3.99)], prior variceal hemorrhage 4 (13.7%) vs 10 (14%) [$P = 1.00$, OR = 0.97 (95%CI: 0.23-3.84)], presence of ascites during hospitalization 27 (93%) vs 43 (60.5%) [$P = 0.001$, OR = 8.79 (95%CI: 1.80-8.10)], white blood cell count 15300 ± 8.033 per cubic millimeter vs 10770 ± 5.601 per cubic millimeter ($P < 0.0001$), natremia 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

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

Organs failure	ACLF 1	ACLF 2	ACLF 3
Renal	7 (70)	2 (40)	10 (71)
Cerebral	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.

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^[5,10]. 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^[5].

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^[5]. 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

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

	ACLF	No ACLF	<i>P</i> vaule	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, <i>n</i> (%)	9 (31)	10 (14)	0.08	2.74	0.9-8.7
Esophageal varices	18 (62)	37 (52)	0.38	1.5	0.5-4
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 (<i>n</i> /mm ³ ± SD)	15.300 ± 10.770	8.033 ± 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.

may have been the trigger of irreversible pro- and anti-inflammatory mechanisms^[10,17,18]. The commonest organ failure was the kidney failure (66%)^[19,20]. 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^[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^[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 dysfunction, 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^[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*^[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^[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*^[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, to correct the precipitating factors and perhaps to install a more aggressive therapy, in order to reduce the high mortality^[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.

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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