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Research Article

Prevalence and Predictors of Acute on Chronic Liver Failure in Cirrhotic Patients Hospitalized for Acute Decompensation

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Abstract

Background: Acute on chronic liver failure (ACLF) is associated with organ failures and high short-term mortality. Our objective was to determine the prevalence and the predictors of ACLF in cirrhotic patients hospitalized for acute decompensation.

Methods: Consecutive cirrhotic patients hospitalized for acute decompensation were recruited from January 2012 to December 2019. Logistic regression analyses were performed to identify clinical and epidemiological predictors of ACLF.

Results: In total, 195 patients were included. The mean age was 65.4 ± 13.1 years and the sex-ratio was 1.7. During follow-up, these patients were admitted to our department 460 times. ACLF occurred in 28.6% of admissions. Grade 1 was the most common (55.3%) followed by Grade 2 (22.7%) and Grade 3 (21.9%). The predictors of ACLF occurrence in our series were: bacterial infection ($p < 0.001$), CHILD-pugh score ($p = 0.001$), high MELD score on admission ($p = 0,001$), advanced age > 50 years ($p = 0,02$) and history of high blood pressure ($p = 0,04$). In multivariate analysis, only bacterial infection ($p < 0.001$, OR = 23.6), CHILD-pugh score ($p = 0.02$, OR = 20.3) MELD-Na and MELD score ($p = 0.003$, OR = 10.2) were independent predictors of ACLF.

Conclusion: In our study, the prevalence of ACLF was 28.6% of admissions. As a major precipitating factor, Bacterial infections would require rapid and effective management as well as close monitoring.

Keywords: *Liver Cirrhosis; ACLF; Bacterial Infection; Prevalence; Predictors*

Abbreviations

ACLF: Acute on Chronic Liver Failure; AD: Acute Decompensation; EASL: European Association for the Study of the Liver; EASL-CLIF: European Association for the Study of the Liver-Chronic Liver Failure; SOFA: Sequential Organ Failure Assessment; SBP: Spontaneous Bacterial Peritonitis; MELD: Model for End-Stage Liver Disease; MELD-Na: Model for End-Stage Liver Disease Sodium; AKI: Acute Kidney Injury; HCA: Healthcare-Associated

Introduction

ACLF is a recently individualized clinical entity defined by the European Association for the Study of the Liver (EASL) Chronic Liver Failure Consortium (CLIF) as acute deterioration of chronic liver disease and associated with organ failures and high short-term mortality [1-3]. According to studies, its prevalence in cirrhotic patients hospitalized for acute decompensation (AD) varies between 22 and 40% [3-5].

This particular form of decompensation usually occurs in the context of an immunosuppression and inappropriate inflammatory reaction as a result of precipitating event such as bacterial infection, excessive alcohol consumption, viral reactivation… [1,3,6]. However, the triggering event is not identified in about 20 to 40% of cases [1,3,6].

Aim of the Study

The aim of this study was to determine the prevalence as well as the predictors of this new entity in cirrhotic patients hospitalized for acute decompensation in order to improve their management.

Materials and Methods

Study population

In the current investigation, we performed a retrospective analysis of data from consecutive cirrhotic patients hospitalized in our department for acute decompensation recruited from January 2012 to December 2019. The non-inclusion criteria were the age below 18 years and Pregnancy. The demographic, clinical, and paraclinical data of the patients were collected (age, gender, medical history, smoking, alcohol consumption, drug intake, BMI, laboratory results...). CHILD, MELD and MELD-Na scores were also calculated on admission.

Definitions

The diagnosis of cirrhosis was established by the combination of clinical, imaging, endoscopic and laboratory findings. Acute decompensation was defined by acute development of any of the flowing complications: hepatic encephalopathy, ascites, acute variceal bleeding, bacterial infection, or a combination of these [1,3,7]. Acute on chronic liver failure was defined according to the EASL-CLIF Consortium definition and based on CLIF-ACLF score [1,7]. This score can be calculated online at the following link: https://www.clifresearch.com/ToolsCalculators.aspx. Similarly, the definition of organ failure was based on CLIF-C-OFs, simplified scale of CLIF-SOFA score [1,3]. In addition, patients with ACLF were classified according to the prognostic grades of ACLF as defined in the CANONIC study; Grade 1: Isolated kidney failure or isolated organ failure associated with renal dysfunction (creatinine ≥ 15 mg and < 20 mg) and/or hepatic encephalopathy grade 1 or 2, or cerebral failure associated with renal dysfunction (creatinine ≥ 15 mg and < 20 mg); Grade 2: two organ failures; Grade 3: Three organ failures or more [1,3,7].

Bacterial infections were diagnosed according to the following criteria: (i) SBP: a neutrophil count in ascites fluid greater than 250/mm^3 with no obvious source of infection that can be treated surgically; (ii) Urinary tract infection: the combination of a urine leukocyte count > 10/high power field with a positive culture or in the presence of significant leukocyturia with symptoms of urinary irritation, fever, and/or elements of biological inflammatory syndrome; (iii) Respiratory infection: the combination of respiratory symptoms (sputum, dyspnea, etc.), typical signs on auscultation, signs of infection (fever, leukocytosis) with radiological alveolar and/or interstitial syndrome or radiological bronchial syndrome; (iv) bacteraemia: positive blood culture without another source of infection; (v) Skin and soft tissue infection: clinical signs of infection associated with swelling, erythema, warmth and tenderness of the skin; The other bacterial infections were diagnosed according to conventional clinical, laboratory and radiological criteria [2,8-11]. The infection was considered presumed in the presence of fever and/or one or more elements of the biological inflammatory syndrome, indicating a prescription for antibiotics despite the negativity of the diagnosis of the site of the infection [2]. MDR bacteria were defined as nonsusceptibility to at least 1 agent in at least 3 antimicrobial categories. Extensively drug-resistant (XDR) bacteria were defined as nonsusceptibility to at least 1 agent in all but less than 2 antimicrobial categories. Pandrug-resistant bacteria (PDR) were defined as a bacteria resistant to all categories of antibiotics [12]. The infection was classified as nosocomial when the diagnosis of infection is made after 48 hours of admission. Infection was classified as healthcare-associated (HCA) if the diagnosis was made within 48 hours of hospitalization in a patient who met any of the following criteria: (1) had visited a hospital or hemodialysis clinic or had undergone intravenous chemotherapy during the 30 days before infection;

(2) was hospitalized for at least 2 days or had undergone surgery within 6 months prior to the infection; (3) had resided in a retirement home or long-term care facility. The infection was classified as community-acquired if the symptoms of infection had appeared before admission or within 48 hours after hospitalization and if the infection did not meet any criteria for HCA elicited [13]. Bacterial infection was considered an acute precipitant event when the onset of ACLF occurred after the infection was detected [2].

Statistical analysis

Statistical analysis was performed using 25th version of SPSS. Student t test and ANOVA test were performed to compare 2 or more means on independent series, respectively. Pearson's Chi-square test and Fisher's exact test (in case of small numbers) were used to compare the percentages on independent series.

A multivariate logistic regression study to identify factors independently linked to the occurrence of ACLF was performed. The ROC curve was established to determine the threshold of the quantitative variables which corresponded to the best "sensitivity-specificity" pair. The significance level was set at 5% for the statistical tests.

Results

In total, 195 cirrhotic patients with AD were included. The mean age was 65.4 ± 13.1 years and the sex-ratio was 1.7. Diabetes (50.2%), arterial hypertension (34.7%) and coronary artery disease (10.5%) were the predominant comorbidities. Nearly half of the patients were smokers while excessive alcohol consumption was not reported in only 3.2%. The average BMI was 27,9%. Hepatitis C viral infection (30,8%) was the most common cause of cirrhosis followed by hepatitis B viral infection (23,1%) and nonalcoholic steatohepatitis (13,3%). Most of the patients had advanced liver disease as shown by MELD score (15,7 ± 7), MELD sodium (MELD-Na) score (19,1 ± 8), and CHILD score (9,3 ± 2). The majority of patients had significant HTP (88.12%). The characteristics of the study population are listed in table 1.

Characteristics	Study population
Age (mean-years)	65.4 ± 13.1
Sex-ratio	1,7
Excessive alcohol consumption (%)	3,6
Smoking (%)	54,7
BMI (mean-kg/m^2)	27,9
Medical history	
Diabetes (%)	50,2
Arterial hypertension (%)	34,7
Coronary artery disease (%)	10,9
Etiology	
Hepatitis C (%)	30,8
Hepatitis B (%)	23,1
NASH (%)	13,3
Alcohol (%)	3,6

Undetermined (%)	6
Other (%)	23,2
Acute decompensation	
Ascites (%)	30
Hepatic encephalopathy (%)	20
variceal bleeding (%)	21
Laboratory results	
C-reactive protein (mg/dL)	20,18 [0 - 222]
White blood count (/nL)	6165,84 [1400 - 56500]
Haemoglobin (g/dL)	10,74 [3 - 17,4]
Platelet count (/mm^3)	113514 [11300 - 580000]
TP (%)	60,08 [14 - 99]
Albuminc (g/dL)	30,47 [13,4 - 47,4]
Creatinine (mg/dL)	92,55 [25 - 1159]
Urea (mg/dL)	7,38 [0,7 - 49,2]
Sodium (mmol/L)	134,37 [116 - 148]
Aspartate aminotransferase (U/L)	80,28 [7 - 3380]
Alanine aminotransferase (U/L)	51,68 [6 - 1990]
γ-Glutamyltransferase (U/L)	94,74 [7 - 1138]
Bilirubin (mg/dL)	53,57 [2 - 647]
Scores	
CHILD (mean)	9,3
MELD (mean)	15,7
MELD-Na (mean)	19,1

Table 1: *Characteristics of study population.*

During the study period, patients were admitted to our department 460 times. The prevalence of ACLF was 28,6% of admissions. Grade 1 was the most common (55.3%). The prevalence of Grade 2 and Grade 3 was 22,7% and 21,9% respectively. Hepatic encephalopathy was the most common organ failure (21,52%). The prevalence of AKI was 16,51%. The coagulation failure, circulatory failure, and respiratory impairment were reported in 15,21%, 10,24%, and 8,04% respectively. In case of ACLF, the prevalence of bacterial infection at admission was 31%. The most common infections were urinary tract infection (44,8%) and respiratory infection (15,5%). The prevalence of SBP, bacteraemia, and Skin and soft tissue infection was 13,9%, 9,7% and 6,6% respectively. No site was found and infection was considered presumed in 8% of cases. Infection was classified as community-acquired, healthcare-associated, and nosocomial in 39%, 44%, and 17%, respectively. This infection has been documented in 44.2% of cases. Gram-negative bacteria were the main strains isolated (74%). The bacteria isolated were MDR in 33% and XDR in 5,2%. Table 2 summarizes the characteristics of bacterial infections.

Bacterial infections	Prevalence
Site	
Urinary tract infection (%)	44,8
Respiratory infection (%)	15,5
SBP (%)	13,9
Bacteraemia (%)	9,7
Skin and soft tissue infection (%)	6,6
Other (%)	9,5
Type	
community-acquired (%)	39
healthcare-associated (%)	44
Nosocomial (%)	17
Bacteria	
Gram-negative (%)	74
Escherichia coli (%)	51
Klebsiella spp. (%)	9
Pseudomonas spp. (%)	3,6
Stenotrophomonas maltophilia (%)	1,8
Other (%)	8,6
Gram-positive (%)	26
Staphylococcus (%)	8
Enterococcus spp. (%)	16
Others (%)	2
MDR (%)	33
XDR (%)	5,2

Table 2: *Characteristics of bacterial infections.*

ACLF was more common in people over 50 years of age with a history of high blood pressure. In addition, the advanced stage of liver disease estimated by the CHILD and MELD score was significantly associated with an increased risk of developing ACLF. Furthermore, ACLF was more commonly observed in the case of bacterial infection.

In multivariate analysis, only bacterial infection (OR = 23.6), CHILD-pugh score (OR = 20.3), MELD-Na and MELD score (OR = 10.2) were independent predictors of ACLF occurrence. Table 3 presents a comparison between patients with and without ACLF.

Characteristics	ACLF	No-ACLF	P value
Age > 50 years (%)	88	81,4	0,029
Gender (male)	72,3	66,5	0,103
Excessive alcohol consumption (%)	2,9	0,9	0,093
Smoking (%)	55,2	48,6	0,118
BMI (mean-kg/m^2)	27,74	27,48	0,632
Medical history			
Diabetes (%)	46,2	49,2	0,317
Arterial hypertension (%)	41	32,5	0,049
Coronary artery disease (%)	13,4	11,2	0,304
Etiology			0,486
Hepatitis C (%)	23,8	31,6	
Hepatitis B (%)	22,3	23,4	
NASH (%)	21,6	19,4	
Alcohol (%)	2,9	0,9	
Undetermined (%)	3	6,38	
Bacterial infection (%)	31	9,7	< 0,001
Scores			
CHILD (mean)	10,1	7,3	< 0,001
MELD (mean)	20,9	13,6	< 0,001
MELD-Na (mean)	24,2	16,8	< 0,001

Table 3: *Predictors of ACLF in cirrhotic patients hospitalized for AD.*

Discussion

In 2011, the EASL-CLIFF consortium conducted a prospective, multicenter study (CANONIC study), which included 1343 cirrhotic patients hospitalized for AD in 29 expert centers for liver disease in 12 European countries. The main objective of this study was to objectively define ACLF. Therefore, the study investigated short-term mortality caused by organ failures in cirrhotic patients hospitalized for AD. The minimum 28-day mortality threshold was set at 15% and organ failures were defined according to the CLIF-SOFA scale, which was subsequently simplified to CLIF-C-OF. Analysis of the data from this study allowed not only to define ACLF objectively, but also to classify it in prognostic grades [3]. Using this definition, the prevalence of ACLF in our study was 28.6% of admissions. Our results were comparable to data from previous studies in which the prevalence of ACLF varied between 22 and 40% of cases [3-5]. Indeed, in a Chinese study using the definition of EASL-CLIF consortium and including 3004 patients, the prevalence of ACLF was 33.7% of cases [4]. Nevertheless, a recent national American study including 72,316 patients hospitalized for AD has shown that this prevalence is clearly decreasing, probably due to earlier management of AD [5]. Furthermore, in the CANONIC study, grade 1 was the most common (51.5%) followed by grade 2 (35%) and grade 3 (13.5%) [3]. However, the prevalence of different grades of ACLF varies widely across studies [3-5,14]. Remarkably, the peculiarity of our study was the relatively high prevalence of grade 3 (21.9%).

Regarding organ failure, renal failure was the most common (55.8%) in the Canonic study, followed by liver failure (43.6%), coagulation failure (27.7%), neurological failure (24.1%), circulatory failure (16.8%) and respiratory impairment (9.2%) [3]. In our study, neurological (21,5%) and renal failure (16,5%) were the most common.

Another main aim of the study was to determine the predictors of ACLF in cirrhotic patients hospitalized for AD. It was reported by the CANONIC study as well as an Asian prospective cohort that young subjects were significantly more at risk of developing ACLF [3,15]. This may be explained by the more intense immune response in young subjects compared to older subjects. However, this finding has not been confirmed by other studies [16]. Our results were totally in contrast with these findings, advanced age was significantly correlated with ACLF.

In the CANONIC study, where the prevalence of alcoholic cirrhosis was predominant, the alcoholic etiology of cirrhosis was significantly associated with ACLF [3]. Piano., *et al*. also showed similar results [16]. However, in our study, alcohol etiology is not associated with ACLF. The particularity of our study population was the low rate of alcohol consumption and the clear predominance of the viral cause of cirrhosis.

Furthermore, we found that bacterial infections were the strongest predictor of ACLF. This is the most striking result of our study which confirms the data of the previous studies [17,18]. Indeed, in the CANONIC study, the prevalence of infection in patients with ACLF at admission (32.6%) was significantly higher than that in patients without ACLF [3]. A recent retrospective Asian cohort which included 1281 patients hospitalized for AD of viral B cirrhosis showed that the prevalence of bacterial infections during this syndrome was 28.1% [18]. In case of ACLF, the prevalence of bacterial infection at admission, in our study, was 31% with the predominance of urinary tract infections and pneumonia. In the Fernandez J., *et al*. series, ascitic fluid infection was the most common (27.1%) followed by urinary tract (20%) and respiratory (19.3%) infection [2].

In addition, it has also been shown that multi-resistant organisms are more frequent during ACLF than during classical decompensation [2]. In our study, 38,2% of isolated strains were multi-resistant.

The higher prevalence of multi-resistant germs and Gram-positive bacteria during ACLF is explained by the higher frequency of intrahospital and care-associated infections as well as the more frequent use of invasive procedures during this syndrome [2].

Conclusion

Our study confirmed the major role of bacterial infection as the main precipitating event of ACLF. For this, rapid diagnosis and adequate management of any bacterial infection, as well as close monitoring, are indicated in order to avoid this severe complication.

Conflict of Interest

Nothing to declare.

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