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Acute-on-Chronic Liver Failure in Patients with Alcoholic Liver Cirrhosis

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Abstract- **Background acute-on-chronic liver failure is an abrupt deterioration of liver function in patients with preexisting chronic liver disease, usually related to a precipitating events.**
Aim to determine the prevalence, potential precipitating factors and to analyze the clinical-laboratory profile.
Methods A total of 149 patients with liver cirrhosis, all males, with average age of 50.5±9 and the long history (more than 15 years) of excessive alcohol consumption (more than 150-180 g/ethanol/day) were enrolled. The patients were randomly divided into two group according to the presence and absence of acute-on-chronic liver failure. The clinical, laboratory and MELD score were compared between the two groups.

Index Terms—**Acute-on-chronic liver failure, heavy alcohol consumption, reactivation of hepatitis B virus infection, spontaneous bacterial peritonitis.**

I. INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a dynamic clinical syndrome with high prevalence, characterized by an acute deterioration of liver failure and high short-term mortality rates [1]. The term of ACLF wa s introduced in 1995 to describe a condition where two hepatic insult simultaneously operate, one of them being chronic, and the other acute [2]. It may developed at any time during the course of chronic liver disease, from compensated to long-standing cirrhosis. In 2013 a definition has been proposed based on results of a large prospective observational European study by EASL as an " acute deterioration of pre-existing chronic liver disease, usually related to a precipitating events, and associated with increased mortality at 3 months due to multisystemic organ failure [3]. So, ACLF is a specific form of liver failure and different from the acute liver failure, a rapid deterioration of the liver function in the absence of pre-existing liver disease, and chronic liver failure, a progressive and slow deterioration over the course of pre-existing end stage liver disease [4]. Precipitating events, such as bacterial infection (spontaneous bacterial peritonitis, sepsis, pneumonia), active alcoholism, HBV reactivation (or HCV reactivation), gastrointestinal bleeding, drug induced liver injury, TIPS insertion or large volume paracentesis without intravenous albumin administration are always involved, even though they cannot ascertained in the 45-50% of the cases [4].

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The short-term mortality rate of the patients with ACLF is closely related to the severity and nature of acute insult, the degree of underlying chronic liver disease or the combination of the two.
Systemic inflammatory response characterized by a predominantly inflammatory cytochines profile, is believed to mediate hepatic inflammation and to causes the transition from the stable cirrhosis to ACLF [5,6,7]. It was demonstrated that patients with ACLF have immunological "defects" that are comparable with those in patients with sepsis [8]. The clinical picture of both ACLF and septic shock is strongly similar, characterized by progressive vasodilatation shock and multiple organ failure [9]. Unfortunately, there are no well-established prognostic indicators available for predicting ACLF progression. We aimed to determine the prevalence of ACLF in patients with alcoholic liver cirrhosis, potential precipitating factors and to analyze the clinical-laboratory profile.

II. METHODS

The study cohort consist of 149 patients with a decompensation of alcoholic liver cirrhosis admitted t the university service of gastro-hepatology between May 2012 and December 2014, all males, with an average age of 50.5±9 years. Patients were diagnosed to have alcoholic cirrhosis on the basis of composite of clinical, laboratory, ultrasound, endoscopy features and the long history (more than 15-20 years) of excessive alcohol consumption (> 150-180 g/ethanol/day). Patients with evidence for autoimmune chronic liver disease, toxic hepatitis, biliary obstruction or hepatocellular carcinoma were excluded. Enrollment into the trial was attempted within the first five days after admission. All enrolled patients were evaluated in detailed pertaining to their physical examination, laboratory parameters and presence of any precipitating events responsible for recent worsening of jaundice, coagulopathy, new onset significant ascites, new onset/new episode of encephalopathy, or any combination of these. Definition of ACLF per grading of severity was based on number and type of organ failure according to EASL study [3]. A formal consensus was obtained from all the patients or their caretakers.
The patients were randomly divided into two group according to the presence (Group 1) or absence (Group 2) of ACLF. Group 1 was composed of the patients presenting with single failure of the kidney, 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 patient with single cerebral failure who had a serum creatinine level ranging from 1.5 to 1.9 mg/dL

(ACLF Grade 1), patients with two organ failure (ACLF Grade 2) and those with three or more organ failure (ACLF Grade 3). Group 2 was composed of the alcoholic cirrhotic patients with no organ failure, those with a single failure of the liver, coagulation, circulation or respiratory who had a serum creatinine level < 1.5 mg/dL and no hepatic encephalopathy and patients with single hepatic encephalopathy who had a serum creatinine level < 1.5 mg/dL.

Liver failure was defined by a serum level of bilirubin >12 mg/dL; kidney failure by a serum creatinine level of >2 mg/dL; cerebral failure by grade III or IV hepatic encephalopathy; coagulation failure by an INR ratio > 2.5 and/or a platelet count of < $20X10^9$/L; circular failure by the need for the use of tirlipressin or dopamine and respiratory failure by a PaO_2 to FiO_2 ratio of < 200or a SpO_2 to FiO_2 ratio of <214 [3]. Blood samples were collected to cheek liver function, renal function, INR, respiratory situation and routine blood tests. Diagnosis of spontaneous bacterial peritonitis was based on the presence of polymorphonuclear leukocytes more than 250 cells mm^3 in ascitic fluid. Reactivation of hepatitis B virus infection was defined as elevated ALT and HBV-DNA > 2.000 IU/mL. MELD score calculated according to the original formula proposed by the Mayo Clinic Group [10] was used to assess the severity of disease.

The clinical, biochemical characteristics and MELD score of the patients were expressed as mean ±SD. Comparison between groups was done by using X^2 test for categorical variable and student t test for parametric variables. For all analysis a P value less than 0.005 was considered statistically significant.

III. RESULTS

A total of 149 patients with alcoholic liver cirrhosis, all males, with average age of 50.52±9 years were enrolled. A majority of the patients 122 (81.7%) were enrolled during the first three days after hospital admission, 27 (18.3%) of them during the first five days. The main cause of admission was tense ascites, followed by spontaneous bacterial peritonitis, gastrointestinal bleeding from esophagus varices rupture, hepatic encephalopathy or combination of any of these. At enrollment 89 patients,with an average of age of 44.6±8.2 years met the criteria for ACLF and 60 with an average of 53.7±10.3 years were patients without ACLF. The overall prevalence of ACLF in our study in patients with alcoholic liver cirrhosis was 59.7%.

Among patients with ACLF, 62 (69%) were defined as having ACLF Grade 1, 22 (25%) as Grade 2, 5 (6%) as Grade 3, while in the group of the cirrhotic patients without ACLF, 20 (34 %) as Grade 1 and 5 (9%) as Grade 2. In the patients of the first group (with ACLF), the most frequent organ failure were kidney and liver failure, followed by hepatic encephalopathy, while in the second group (without ACLF) was kidney failure. The most important precipitating event was heavy alcohol consumption (more than 80-100 mL ethanol within the last 4-8 weeks), followed by spontaneous bacterial peritonitis, reactivation of hepatitis B virus infection, gastrointestinal bleeding from the esophageal varices rubture and the combination of alcohol consumption and hepatitis B virus infection, respectively in 40.4%, 21.3%, 8,5%, 14.9% and 14.9%.

Mean values of clinical-laboratory parameters of patients with and without ACLF are shown on the following table.

Parameters	With ACL (n=89)	Without ACLF (n= 60)	P value
Age (year)	44.6±9.2	53.7±10.3	0.0001*
Temperature >38°C	26 (61.9%)	46 (42.9%)	0.0001**
Leucocyte ($X10^9$ c)	9.8±4.5	7.4±4.9	0.002
Bilirubin (mg/dL)	12.1±4.1	4.8±5.5	0.0001
AST (UI/L)	184±4.6	106±34	0.0001
ALT (UI/L)	68±33	53±29	0.005
Albumin (g/L)	26.4±3.7	25.9±4.6	0.4
INR ratio	2.6±0.8	1.9±0/7	0.0001
Platelet (1000/mm^3)	122±68	144±78	0.07
Creatinine (mg/dL)	2.2±1.1	1.9±1.6	0.17
Serum sodium (mEq/L)	132±5	134±6	0.07
Meld score	41±3	26±3	0.0001

Compared to the patients without ACLF (Group 2), ACLF patients were distinctly younger (p=0.0001). They had significantly higher white cell count (9.8±4.5 vs 7.4±4.9, p=0.002), bilirubin level (12.1±4.1 vs 4.8±5.5, p=0.0001), serum level of AST and ALT, respectively 184±46 vs 106±34 (p=0.0001) and 68±33 vs. 53±29 (p=0.005) and much more number of patients with temperature higher than 38^0 (p=0.0001). Patients with ACLF (Group 1) had also higher level of international normalized ratio (2.6±08 vs 1.9±1.6), creatinine (2.2±1.1 vs 1.9±1.6) and lower platelet count (122±68 vs 144±7.8). Finally, our data clearly demonstrate that liver dysfunction (MELD-Score) was much more severe in patients with ACLF than those without ACLF, 41±3 vs 26± 2 (p=0.0001).

IV. DISCUSSION

We studied the patients with a decompensation of alcoholic liver cirrhosis, considering this clinical situation as a very important background for development of ACLF. In the Western countries alcoholic cirrhosis is the cause of 50%-70% of all predisposing liver disease of ACLF, comparing to the 10%-30% caused by chronic viral infection [2, 11]. As the above-mentioned authors the overall prevalence of ACLF in our patients was 59.7%.

Alcohol consumption is a huge international problem and one of the most frequent causes of liver cirrhosis in the Western world, although there is variation across countries. It is estimated that alcohol consumption is responsible for 5.9% of global mortality world-wide [12] and for 2.5 million death per year [13]. In the last decades a dramatically increase of mortality rate due to end-stage liver disease has been reported in same European countries, mostly related to the increased prevalence of alcohol consumption [14]. The pattern of alcohol use is strongly related to age, culture, education, religion and other socio-demographic characteristics. Europeans are, in fact, the world's top consumers of alcohol in the world. Rapid political, economic, social and cultural transformation in Albania during the last twenty-five years, has deeply changed habits of alcohol use and alcohol-related problems. Albania is a country where use of alcohol beverages with high ethanol content (rake) is a very diffused habit.

ACLF is an acute deterioration of liver function, potentially reversible, usually associated with a precipitating event.

The reversibility depends on the severity and nature of acute insult and the degree of the underlying chronic liver disease [2]. The precipitating events are different and vary according to the geographic region, including both infection and non-infection causes.

In this study we found that severe alcoholic hepatitis presenting with jaundice, fever, AST level more than twice the upper limit of normal range, ratio of AST/ALT greater than 2 and leucocytosis, resulting from the heavy alcohol intake (daily consumption more than 80-100 mL ethanol) within the 4-8 weeks was the most common precipitating factor (40.4% of the cases). In this occasion it was underlined that severe alcoholic hepatitis accounts for only part both cases of ACLF in patients with alcoholic cirrhosis [15]. The dramatic liver damage is result of the complex interplay between ethanol metabolism, inflammation and innate immunity [16].

In concordance with others bacterial infection such as spontaneous bacterial peritonitis, urinary tract infection or sepsis, are significantly more common in patients with ACLF than in those without ACLF [3]. In this study is shown clearly that spontaneous bacterial peritonitis was one of the principal precipitating event (21.3% of the patients). Moreover, taking into account the release of pathogen-associated molecular patterns (resulting from "aseptic" intestinal bacterial translocation) or of danger-association molecular patterns (resulting from tissue injury), it was judged that spontaneous bacterial peritonitis may be more frequent [17]. The "cirrhosis-associated immune dysphunction", which include the main syndromic abnormalities of immune function, immuno-deficiency and systemic inflammation, seems to play a predominant role in developing of ACLF [18,19].

Reactivation of hepatitis B virus infection, either spontaneous or due to antiretroviral therapy, through the massive immune-mediated cytotoxicity in liver parenchyma, is obviously important cause of ACLF, particularly in regions with high prevalence of HBV infection. Despite the estimated two-fold reduction of HBsAg prevalence during the last two decades (from 18% in 1994 to 8.5% in 2009) Albania remains an endemic country [20, 21, 22]. Nevertheless, in our study we found the reactivation of hepatitis B virus infection as a cause of ACLF in 8.5% of patients. On the other hand, it is well known the important role of the association between heavy alcohol consumption and hepatitis B virus infection. This combination was seen in 14.9 % of our cases.

There are extensively debate regarding to the role of varices bleeding as the acute insult of ACLF [2]. Anyhow, we believe that gastrointestinal bleeding after the esophagus varices rupture, through the protein load, anemia, hypotension, hypoxia and azotemia in patients with end-stage liver disease, should be set in line as the potential precipitating event for ACLF. In this study 14.9 % of the patients with ACLF were admitted in fact consequently of the gastrointestinal bleeding from the esophagus varices rupture. Finally, in 47 % of our patients ACLF developed in the absence of a clearly responsible precipitating events.

This study showed clearly that ACLF is a distinct from "mere" acute decompensation of liver cirrhosis. There were, in fact, significant differences between cirrhotic patients with and without ACLF in that they were younger, had higher level of serum bilirubine, AST and ALT levels and international ratio, had more market systematic inflammatory response, expressed by higher temperature and leucocyte count, and disease severity outcome testified by MELD-Score.

In conclusion, ACLF as a very serious clinical condition with high prevalence in patients with alcoholic liver cirrhosis. Heavy alcohol intake within the last 4-8 weeks followed by spontaneous bacterial peritonitis, gastrointestinal bleeding from the esophageal varices rubture and reactivation of hepatitis B virus infection were the most common precipitating events for the development of ACLF. Nearly half of the patients with ACLF did not have any identifiable potential precipitating events. The main differences between ACLF and "mere" decompensation of alcoholic liver cirrhosis was based on the age, systematic inflammatory parameters, serum level of bilirubin, AST and AST/ALT ratio, INR ratio and MELD-Score.

REFERENCES

[1] Olson JC, Kamath PS. Acute-on-chronicliver failure: concept, natural history and prognosis. Curr Opin CritCare 2011;17:165-169.
[2] Sarin K.SH, Kumar A, Almeida JA et al. Acute-on-chronic liver failure: consensus recomandations of the Asian Pacific Association for the Study of the Liver APASL). Hepatol Int 2009; 3:296-282.
[3] Moreau R, Jalan R, Gines P et al. Acute-on-chronic liver failure is a distinct syndrome that develop in patients with acute decompensation of cirrhosis. Gastroenterology 2013; 144: 1426-1437.
[4] Lee WM. Etiologies of acute liver failure. Sem Liv Dis 2008;28:142-152.
[5] Rolando N, Wade J, Davalos M, Wendom J, Philpott-Howard R. The systemic inflammatory response syndrome in acute liver failure. Hepatology 2000;32:734-739.
[6] Tilg H, Diehl AM. Cytichines in alcoholic and nonalcoholic steathepatitis. NEJMed 2000; 343:1467-1476.
[7] Ambrosino G, Naso A, Feltracco P et al. Cytochines and liver failure: modification of TNF-alpha and IL-6in acute on chronic liver decompensation treatment with molecularadsorbent recycling system (MARS). Acta Biomedica 2003;74 (suppl.2):7-9.
[8] Wassmuth HE, Kunz D, Juagmur E et al. Patients with acute-on-chronic liver failure display "sepsis-like" immune paralysis. J Hepat 2005; 42:195-201.
[9] Sarin SK, Kumar A, Almeida J et al. Acute-on-chronic live failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver. Hepatol Int 2009;3(1):169-182.
[10] Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology 2007; 45: 797-805.
[11] Jalan R, Gines P, Olsen JC et al. Acute-on-chronic liver failure. J Hepatol 2012; 57:1396-1348.
[12] World Health Organization. Global Status Report on Alcohol and Health 2014.
[13] Dungum M, Cullough A. Diagnosis and management of alcohol liver disease. J Clin Transl Hepatol 2015; 3: 109-116.
[14] Haseldine s, Hydes T, Sheron N. Alcohol liver disease-the extend of the problem and what You can do about it. Clin Med 2015:15:179-195.
[15] Moreau R, JalanR, Arroyo V. Acute-on-chronic liver failure: recent concepts. Journal of Clinical and Experimental Hepatology 2015, 5;1:81-85.
[16] Gao B, Bataller R. Alcohol liver disease: pathogenesis and new therapeutic targets. Gastroenterology 2011:141:1572-1565.
[17] Gustot T, Durand F, Lebrec D et al. Severe sepsis in cirrhosis. Hepatology 2009:50:2022-2033.
[18] Sipeki N, Antal-Szalmas P, Lacates DC, Popp M. Immune dysphunction in cirrhosis. WJG 2014;20:2564-2577.
[19] Albillos A, Lario M, Alvares-Mon M. Cirrhosis-associated immune dysphunction: distinctive features and clinical relevance. J Hepatol 2014;61:1385-1396.

[20] Santantonio T, Lo Caputo S, Germinario Cet al. Prevalence of hepatitis viral infection in Albanian refugees. Eur J Epidemiol 1993, 9:537-540.
[21] Dalekos GN, Zervou E, Karabini F, Tasianos EV. Prevalence of viral markers among refugees from southern Albania: increased incidence of infection with hepatitis A, B and D viruses. Eur J gastroenterol Hepatol 1995; 7:553-558.
[22] Resuli B, Prifti S, Kraja B. et al. Epidemiology of hepatitis B virus infection in Albania. WJG 2009; 21:15 (7): 849-852.