Original Research Article

Prevalence of acute on chronic liver failure, underlying etiology and precipitating factors

Premkumar K[1], Krishnasamy Narayanasamy[2*]

[1]Assistant Professor, [2]Director and Professor
Institute of Hepatobiliary Sciences, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India
[*]Corresponding author email: **drkns_1963@yahoo.com**

International Archives of Integrated Medicine, Vol. 6, Issue 4, April, 2019.
Copy right © 2019, IAIM, All Rights Reserved.
Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 14-03-2019 **Accepted on:** 19-03-2019
Source of support: Nil **Conflict of interest:** None declared.
How to cite this article: Premkumar K, Krishnasamy Narayanasamy. Prevalence of acute on chronic liver failure, underlying etiology and precipitating factors. IAIM, 2019; 6(4): 49-54.

Abstract

Background: Acute on chronic liver failure (ACLF) was first described in 1995 as a clinical syndrome distinct to classic acute decompensation. Characterized by complications of decompensation, ACLF occurs on a background of chronic liver disease and is associated with high rates of organ failure and significant short-term mortality estimated between 45% and 90%. Despite the clinical relevance of the condition, it still remains largely undefined with continued disagreement regarding its precise etiological factors, clinical course, prognostic criteria, and management pathways. It is concerning that, despite our relative lack of understanding of the condition, the burden of ACLF among cirrhotic patients remains significant with an estimated prevalence of 30.9%.

Aim of the study: The present study was aimed at estimating the prevalence of acute on chronic liver failure in our institute, etiology of underlying chronic liver disease, precipitating acute event and mortality rate.

Materials and methods: 150 patients admitted and treated with the diagnosis of ACLF in the Institute of Hepatobiliary Sciences, Rajiv Gandhi Government General Hospital during the period from December 2016 to November 2018 were included in the study. Their data regarding etiology of chronic liver disease, precipitating acute events and mortality were collected and analyzed.

Results: Out of 386 patients, 150 patients were admitted with acute on chronic liver failure with a prevalence of 39%. In 41% of patients, infection was the precipitating factor for ACLF either in the form of Sepsis, spontaneous bacterial peritonitis, Lower respiratory tract infection or skin, and soft tissue infections. Alcohol was the second most precipitating factor (32%), followed by upper gastrointestinal hemorrhage (12%) and drugs (2%). No precipitating cause could be identified in

12.7% of patients. Mortality rate was high in ACLF grade 3 (95%), followed by ACLF grade 2 (62%) and ACLF grade 1 (15%).

Conclusion: ACLF is a dynamic syndrome presenting with single, two or more organ failure in a patient with chronic liver disease following a triggering event and associated with high short term mortality. In our hospital, the prevalence of ACLF was 39% and the overall mortality rate was 83%. Infection and alcohol were found to be important precipitating factors. A multi-centre study involving a larger number of patients are needed to know the clinical characteristics, other precipitating factors and to form a standard treatment protocol for this dynamic syndrome.

Key words

Acute-on-chronic liver failure, Acute decompensation, Lower respiratory tract infection, Spontaneous Bacterial Peritonitis.

Introduction

Acute-on-chronic liver failure (ACLF) is an increasingly recognized entity that includes the acute deterioration of 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. There are more than thirteen different definitions. Two consensual definitions are commonly used [1]. 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 [2]. The second definition, developed by 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. 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 [3]. The EASL-CLIF-Consortium proposed 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 [4]. Acute decompensation of cirrhosis is the leading cause of hospitalization in cirrhotic patients. ACLF is a very common syndrome, with a prevalence of around 30%. It differs from acute decompensation by the presence of organ failure, associated with precipitating events, high mortality rate [5]. There is a lack of worldwide accepted definition. Many aspects of this disease, such as prevalence, natural history, precipitating factors, clinical features, and pathophysiological mechanisms remain unknown [6].

Materials and methods

This was a prospective observational study conducted between December 2016 and November 2018. A total of 386 patients with a diagnosis of cirrhosis / decompensated cirrhosis were admitted and treated as an inpatient in the Institute of Hepatobiliary Sciences, Rajiv Gandhi Government General Hospital, Chennai. Out of 386 patients, one hundred and fifty patients were diagnosed with ACLF presented with one / two or more organ failures were recruited and analyzed for our study. All patients' history including previous episodes of decompensation (ascites, encephalopathy, spontaneous bacterial peritonitis, esophageal varices, variceal bleeding or hepatocellular carcinoma), physical examination, laboratory analysis were done. All the patients were also analyzed for the potential precipitating factors (infections, active alcohol intake, gastrointestinal bleeding), and etiology of cirrhosis. ACLF patients were divided into 3

grades according to the type and number of organs affected. 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. Organ failures were defined as per the CANONIC study criteria [16]. Diagnosis of liver failure was by a serum bilirubin level of ≥ 12.0 mg/dL. Kidney failure was defined if the serum creatinine level was ≥ 2.0 mg/dL or the need for renal replacement therapy. Cerebral failure was defined by grade III or IV hepatic encephalopathy as per the West Haven classification. Coagulation failure included an international normalized ratio of ≥ 2.5 and/or platelet count of ≤ 20000/cc. Circulatory failure was defined by the need for the use of vasopressors like dopamine, dobutamine, or terlipressin at any dose. Respiratory failure was defined by a PaO_2 to FiO_2 ratio of ≤ 200 or a SpO_2 to FiO_2ratio of ≤ 214 [17]. Clinical characteristics of each group, the presence of precipitating events, potential risk factors for developing ACLF and causes of mortality were analyzed.

Statistical analysis

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

Results

Out of 386 patients admitted during the period from December 2016 to November 2018, 150 patients with ACLF were included for the study and analyzed for their underlying cause for chronic liver disease, the precipitating acute event, and the organ failures.

Male was the predominant gender presented with ACLF (n=128). The mean age was 50+/- 12 and mean Child-Pugh score was 9+/- 2.2. Among the etiology for underlying chronic liver disease, most cases were alcoholics (n=87) followed by HBV infection (n=22), cryptogenic (n=18) and NASH (7) as per **Table - 1**.

Table - 1: Etiology of cirrhosis.

Agent	No. of Patients	Percentage
Alcohol	87	58%
Alcohol + Virus	11	7.3%
HBV	22	14.6%
HCV	5	3.3%
NASH	7	4.6%
Cryptogenic	18	12%

Table - 2: Prevalence of ACLF.

ACLF	Grade 1	Grade 2	Grade 3
No. of Patients	15 (10%)	18 (12%)	117 (78%)
Mortality	3 (15%)	11 (62%)	111 (95%)

Table - 3: Precipitating factors for ACLF.

Cause	No. of patients
SBP	10
Sepsis	30
LRTI	10
Skin and soft tissue infection	12
GI hemorrhage	18
Drug-induced	3
Alcohol	48
No precipitating cause	19

Table - 4: Organ failure.

Organ Failure	ACLF		
	Grade 1	Grade 2	Grade 3
Renal	7	12	102
Cerebral	2	6	104
Coagulation	4	10	46
Liver	6	11	58
Circulatory	0	3	110
Respiration	3	5	111

Patients with ACLF grade 1 were 15, ACLF grade 2 was 18 and with ACLF grade 3 were 117 (**Table – 2**).

Infective etiology was the predominant trigger for acute events (n=62), SBP, Sepsis, Lower respiratory tract infections, skin, and soft tissue infections. Active alcoholism was the second most triggering factor, followed by upper gastrointestinal hemorrhage. No cause for precipitating acute event could be identified in 19 patients. All the patients were admitted in liver intensive care unit. Most of the patients with grade 3 ACLF required inotropic support and ventilatory support. ACLF resolved in 12 patients with ACLF grade 1, 7 patients with ACLF grade 2 and only in 6 patients with ACLF grade 3.Mortality rate was high in ACLF grade 3 (95%), followed by ACLF grade 2 (62%) and ACLF grade 1 (15%) as per **Table - 3**.

The commonest organ failure was a renal failure (80.7%). Circulatory and respiratory failure was observed in 95% of cases with ACLF grade 3. Another observation was patients admitted with lower respiratory infection with ACLF grade 1 or 2 had higher mortality (24%) as per **Table - 4**.

Discussion

Acute decompensation occurs due to complications of portal hypertension and chronic liver disease, presenting as variceal bleeding, infection, hepatic encephalopathy and ascites. With recent improvements in the medical management of acute decompensation, many patients are able to return to a compensated state. However, a proportion of patients suffer from significant pathological sequelae, characterized by hepatic and/or extrahepatic organ failure or multi-organ failure requiring management in intensive care and significant life support [7]. ACLF is a distinct syndrome which usually presents with organ failure following a triggering event and associated with high short term mortality. While the precise pathophysiology of ACLF remains to be elucidated, amplified and unopposed inflammation seems to play a vital role. Due to profound inflammation that occurs with ACLF, as well as its rapid progression, multiple organ supportive therapy is often required and is associated with a short-term mortality rate of 45%-90%. Although the underlying cirrhosis in ACLF remains irreversible, the condition itself is thought to possess a reversible component, as it is often associated with a specific precipitating factor [8]. There is currently a scarcity of data regarding the epidemiology of ACLF; however, the high mortality rates, prolonged periods of hospitalization and the profound burden on healthcare systems associated with the condition demonstrate the importance in improving our understanding of the condition [9]. In our center, we found a prevalence of 39% which is slightly higher than the CANONIC study. In our study, 90% of patients admitted with ACLF had more than one organ involved (grades 2 and 3), but the results of the CANONIC study showed only 64.3% of patients had only one organ involvement [10]. Most of the patients admitted in our hospital had the advanced liver disease at presentation. The commonest precipitating factor for ACLF was an infection (41%) Sepsis, spontaneous bacterial peritonitis, Lower respiratory tract infection, skin, and soft tissue infections [11]. Alcohol was the second most precipitating factor (32%), followed by upper gastrointestinal hemorrhage (12%) and drugs (2%). No precipitating cause could be identified in 12.7% of patients. Mortality rate was higher in patients with ACLF grade 2(62% vs 32%) and lower in patients with ACF grade 1 (15% vs 22.1%) in our center compared to other studies [12]. This could be due to the lesser number of patients in this category. Mortality rate was slightly higher in ACLF grade 3, compared to other studies. Most of the patients were with advanced liver disease at presentation. This could explain the higher mortality rate associated with grade 2 and 3 ACLF [13, 14, 15].

Conclusion

ACLF is an increasingly recognized condition in a patient with chronic liver disease presenting

with single, two or more organ failure following a triggering event associated with high short term mortality. In our hospital, the prevalence of ACLF was 39% and the overall mortality rate was 83%. Infection and alcohol were found to be important precipitating factors. Limitations of this study being a single-center study with a small number of patients. A multicentre study involving larger numbers of patients are needed to know the clinical characteristics, other precipitating factors and to form a standard treatment protocol for this dynamic syndrome.

References

1. Ohnishi H, Sugihara J, Moriwaki H, Muto Y. Acute-on-chronic liver failure. Ryoikibetsu Shokogun Shirizu., 1995; 7: 217–219.
2. Singh H, Pai C. Defining acute-on-chronic liver failure: East, West or middle ground? World J Hepatol., 2015; 7: 2571-2577.
3. Sarin SK, Kumar A, Almeida JA, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). Hepatol Int., 2009; 3: 269–282.
4. Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, Arroyo V, Kamath PS. Acute-on-chronic liver failure. J Hepatol., 2012; 57: 1336–1348.
5. Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, et al. Acute-on-chronic acute decompensation of cirrhosis. Gastroenterology, 2013; 144: 1426–1137.
6. Younossi ZM, Henry L, Stepanova M. A new comorbidity model for predicting mortality in patients with cirrhosis: does it work? Gastroenterology, 2014; 146: 19–24.
7. Ginès P, Cárdenas A, Arroyo V, Rodés J. Management of cirrhosis and ascites. N Engl J Med., 2004; 350: 1646–1654.
8. Kim TY, Kim DJ. Acute-on-chronic liver failure. Clinton. Hepatol., 2013; 19: 349–359.
9. Arroyo V, Moreau R, Jalan R, Gines P. Acute-on-chronic liver failure: a new syndrome that will re-classify cirrhosis. J Hepatol., 2015; (Suppl 1; 62): S131–S143.
10. Blasco-Algora S, Masegoza-Ataz J, Gutierrez-Garcia ML, Alonso-Lopez S, Fernandez-Rodriguez CM. Acute-on-chronic liver failure: pathogenesis, prognostic factors, and management. World J Gastroenterol., 2015; 21: 12125–12140.
11. Jalan R, Yurdaydin C, Bajaj JS, Acharya SK, Arroyo V, Lin HC, Gines P, Kim WR, Kamath PS. Toward an improved definition of acute-on-chronic liver failure. Gastroenterology, 2014; 147: 4–10.
12. Jalan R, Stdlbauer V, Sean S, Cheshire L, Chang YM, Mookerjee RP. Role of predisposition, injury, response and organ failure in the prognosis of patients with acute-on-chronic liver failure: a prospective cohort study. Crit Care, 2012; 16: R227.
13. Moreau R, Arroyo V. Acute-on-chronic liver failure: a new clinical entity. Clin Gastroenterol Hepatol., 2015; 13: 836–841.
14. Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. Curr Opin Crit Care, 2011; 17: 165–169.
15. Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, Laleman W, Trebicka J, Elkrief L, Hopf C, et al. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology, 2015; 62: 243–252.
16. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver

failure. Hepatology, 2012, 55(3): 965–967.

17. Marciano S, Mauro E, Carena A, Gadano A. Fallahepáticaagudasombercrónica. Actualizaciones en Hepatología., 2013; 5: 17–24.