

Original Research Article

Acute on chronic liver failure- etiology, clinical profile, prognostic scores: experience from tertiary care centre of eastern India

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Received: 29 August 2021

Accepted: 30 September 2021

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ABSTRACT

Background: Acute on chronic liver failure (ACLF) is a recently recognised entity in chronic liver disease patients. Data regarding ACLF in terms of clinical presentation, etiology of underlying cirrhosis, precipitating factors, prognostic factors are lacking from eastern India. The present study was undertaken to evaluate the above factors along with the assessment of short-term mortality (4 weeks) in patients of ACLF.

Methods: In this prospective observational study, 120 patients diagnosed as ACLF were included. A comparison of complications, biochemical profiles and prognostic scores was made between the survivor and non-survivor groups.

Results: Of the 120 ACLF patients included, the mean age was 44.9±8.6 years and the male to female ratio was 2.5:1. Common clinical presentations were jaundice (100%), ascites (88.3%), hepatic encephalopathy (60%). The most common etiology for underlying CLD was alcohol (51.7%) followed by chronic hepatitis B (20%) and chronic hepatitis C (15%) infection. Alcohol hepatitis (40%) followed by hepatotropic viral infections (20%) and drug-induced liver injury (15%) were common identifiable precipitating agents. After a follow-up period of 4 weeks, 56 (46.6%) out of 120 patients died. The presence of sepsis, hyponatremia, renal failure, and coagulopathy was significantly associated with high mortality. Mortality was higher among patients having high Chronic liver failure consortium- acute on chronic liver failure (CLIF-ACLF) grade and closely related to the number of organ failures.

Conclusions: ACLF is a rapidly progressive syndrome in chronic liver disease patients, having high short-term mortality.

Keywords: Acute on chronic liver disease, Chronic liver disease, CLIF-ACLF, Cuttack

INTRODUCTION

Acute on chronic liver failure (ACLF) is a clinical syndrome, which occur in patients of Chronic liver disease (CLD), precipitated by acute insult and having high short term mortality.¹ More than 13 definitions of ACLF have been proposed.² In 2009, the Asian Pacific Association for the study of liver (APASL) provided the first consensus on ACLF, defined as ‘an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dl) and coagulopathy (INR ≥ 1.5 or prothrombin activity $<40\%$), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic

liver disease’.³ In 2014 this definition was further expanded and include ‘high 28 days mortality’.⁴ European association for study of liver (EASL)- American Association for study of liver disease (AASLD) defined ACLF as ‘Acute deterioration of pre-existing chronic liver disease usually related to a precipitating event and associated with increased mortality at 3 months due to multiorgan failure.’¹ EASL- Chronic liver failure (EASL-CLIF) consortium proposed another definition of ACLF based on prospective Canionic study. According to this ACLF was defined as Acute decompensation (AD) of cirrhosis associated with Organ failure (OF) and high short-term mortality (28 days mortality $\geq 15\%$).¹

Chronic hepatitis B infection remain most common cause of CLD and most common aetiology of cirrhosis is alcohol in India.⁵⁻⁷ On the other hand in western countries Non-alcoholic fatty liver disease (NAFLD) followed by alcohol become leading cause of CLD. Nature of acute insult that initiate development of ACLF also differ with geographical region. Hepatotropic viral infection and alcoholic hepatitis are the common acute insult in Asian countries.^{7,10-12} While bacterial infections and alcohol are common identifiable factors in west.^{1,13} More than one precipitating factor may be present in few patients.

Data on ACLF is scanty and mostly from retrospective studies. The aim of the study was to reveal aetiology of underlying CLD, precipitating factors, complications and short-term mortality rate in patients of ACLF from eastern India.

METHODS

This was a prospective observational study conducted in the department of hepatology, SCB Medical College and Hospital, Cuttack, Odisha. 120 patients of ACLF were included in study defined on the basis of APSAL criteria with some deviations, from March 2019 to November 2020. We included non-hepatic causes of sepsis and upper GI bleeding cases as acute insult in modification to APASL definition of ACLF. Patients with prior history of decompensation, portal vein thrombosis, hepatocellular carcinoma, metastatic liver disease, extrahepatic malignancy, retroviral disease, unwilling to participation in study were excluded.

Data regarding clinical presentation, demographics, laboratory parameters, endoscopic findings was recorded in predefined format. The aetiology of CLD, precipitating factor was investigated and prognostic scores (CTP/MELD/ACLF grade) were calculated. Organ failure was defined by CLIF- Sequential organ failure assessment (SOFA) score which included renal failure (serum creatinine ≥ 2 mg/dl), liver failure (serum bilirubin ≥ 12 mg/dl), cerebral failure (HE grade 3 or 4 as per West Heaven criteria), circulatory failure (patient requiring ionotropic support to maintain blood pressure), coagulation failure (INR ≥ 2.5 mg/dl), and respiratory failure (SpO₂/FiO₂ ≤ 200 or requiring mechanical ventilation). ACLF grading calculated on the basis of EASL-CLIF definition. Patients were managed conservatively, provided standard care or intensive care whenever required and followed up to 4 weeks or till death whichever occurred earlier.

Statistical analysis

All the data were recorded in predefine format. The descriptive statistics for various parameters are expressed as mean \pm standard deviation. Comparison of data was made between survivors and non-survivors. Comparison between continuous variables was carried out using Mann-Whitney U-test. All the statistical tests used are two tailed

and significant level of 0.05 has been used. The SPSS windows version 24 has been used for data analysis.

RESULTS

A total 120 patients of ACLF defined according to APASL criteria were included in our study. Majority of patients were in age group of 41-50 years (46.4%) and 44.9 \pm 8.6 years was the mean age of study group. Male to female ratio was 2.5:1.

All the patients had jaundice (100%) at the time of presentation. Ascites was found in 88.3% of cases. Hepatic encephalopathy was present in 78 (65%) patients; of which, 28 (23.3%) patients had grade 1 to 2 HE, whereas 50 (41.7%) patients had grade 3 to 4 HE. Ascites was present in 192 (92.23%) patients. Other presentations were anorexia (56%), fatigue (41%), fever (20%), GI bleeding (16.6%) and pain abdomen (13.3%). Coagulopathy was present in all patients. 68 (56.6%) patients had INR (International normalized ratio) between 1.5-2.5 and remaining 52 (43.3%) had INR more than 2.5. Prevalence of hyponatremia, renal failure, Spontaneous bacterial peritonitis (SBP) and sepsis was 67.5%, 37.5%, 39% and 38.3% respectively. Most common organ failure according to CLIF-SOFA score was coagulation (43.3%) followed by cerebral (41.7%), renal (37.5%), liver (30%) and cardiovascular (12%). 72 (85.7%) out of 84 patients had oesophageal varices who underwent endoscopy.

Chronic alcohol use was most common cause of underlying CLD found in 51.7% of patients. Other causes of CLD were chronic hepatitis B (20%), chronic hepatitis C (15%), Non-alcoholic steatohepatitis (NASH) (8%), cryptogenic cirrhosis (5%) and autoimmune causes (1.7%) (Figure 1). Alcoholic hepatitis was most common acute insult leading to ACLF, found in 48 (40%) of patients. Hepatotropic viral infection was found in 24 (20%) patients. Hepatitis A, hepatitis E and reactivation of hepatitis B as a precipitating event was found in 4 (3.3%), 12 (10%) and 8 (6.7%) of patients. Drug induced liver injury (DILI) was identified as precursor of ACLF in 18 (15%) patients. ATT (10%) and Complementary medicines (5%) were common offenders. GI bleeding (14.2%), Pneumonia (6.7%) and UTI (4.2%) were other precipitating factors (Figure 2).

Among biochemical profile, mean of serum bilirubin, creatinine, albumin and sodium were 21.84 mg/dl, 1.53 mg/dl, 2.20 g/dl and 125 meq/l (Table 1). Significant difference was observed on comparing above laboratory values between survivor and non-survivor groups (Table 2). 56 (46.6%) out of 120 patients died within 4 weeks of diagnosis of ACLF. In non-survivor group 26 (92.8%) out of 56 patients had Child-Turcot-Pugh (CTP) class-C. Mean MELD score of survivor and non-survivor group was 25.53 \pm 1.81 and 30.04 \pm 2.37 respectively and difference was statistically significant. CLIF-ACLF grading was calculated for all patients. 6 (5%), 24 (20%), 32 (26.7%) and 58 (48.3%) patients had grade 0, 1, 2 and

3 respectively. In survivors, 50 (78.12%) out of 64 patients developed either two or less organ failures. On the other

side, 44 (78.5%) out of 56 patients in non-survivor group had multiorgan failure (>2 OF) (Table 3).

Table 1: Baseline parameters of patients.

Baseline parameters	Descriptive statistics
Age (years)	44.9±8.6
Haemoglobin (g/dl, mean±SD)	8.8±2.13
Total leucocyte count (x10 ⁹ /l)	10.6 (6.5-29.6)
Total platelet count (x10 ⁹ /l)	88.4 (78-312)
Total bilirubin (mg/dl)	21.84±5.51
AST (IU/dl)	236.6 (122-2423)
ALT (IU/dl)	149.5 (98.4-2664)
Alkaline phosphatase (IU/dl)	256.8 (196.3-356)
Serum albumin (g/dl, mean±SD)	2.20±0.52
INR (mean±SD)	2.25±0.32
Serum creatinine (mg/dl, mean±SD)	1.53±0.59
Serum sodium (meq/l, mean±SD)	125±4.76
CTP	11.2±2.7
MELD	27.48±3.1

Table 2: Comparison of baseline parameters between survivors and non-survivors.

Baseline parameters	Survivors (N=64)	Non-survivors (N=56)	P value
Haemoglobin (g/dl, mean±SD)	9.1±1.3	8.6±1.5	0.074
Total leucocyte count (x10 ⁹ /l)	8.1 (4.2-16.3)	16.4 (2.5-29.6)	0.00001
Total platelet count (x10 ⁹ /l)	89.3 (94.3-312)	67.6 (24.3-221)	0.093
Total bilirubin (mg/dl, mean±SD)	16.1±6.01	24.12±3.81	0.00001
AST (IU/dl)	193 (122-482)	468 (261-865)	0.112
ALT (IU/dl)	113 (62-326)	356 (76-584)	0.237
Alkaline phosphatase (IU/dl)	324 (193-564)	312 (186-482)	0.091
Serum albumin (g/dl, mean±SD)	2.36±0.31	2.1±0.26	0.00001
INR (mean±SD)	2.26±0.44	2.88±0.58	0.00001
Serum creatinine (mg/dl, mean±SD)	1.20±0.50	1.90±0.71	0.00001
Serum sodium (meq/l, mean±SD)	128±5.4	122±6.7	0.00001
CTP class	9.7+ 2.4	12.9+ 1.8	0.0001
MELD score	25.53±1.81	30.04 +2.37	0.0001

Table 3: Comparison of prognostic scores between survivors and non-survivors.

Prognostic score	Survivors (N=64)		Non-survivors (N=56)		P value
CTP score	9.7±2.4		12.9±1.8		0.0001
CTP	N	%	N	%	
Class A	8	12.5	0	0	
Class B	16	25	06	10.7	0.0433
Class C	40	62.5	50	89.3	0.0007
MELD score	25.53±1.81		30.04±2.37		0.0001
CLIF-ACLF (grading)	N	%	N	%	
Grade 0	06	9.3	0	0	
Grade 1	20	31.2	04	7.2	0.001
Grade 2	24	37.5	08	14.3	0.004
Grade 3	14	21.8	44	78.5	0.00001

Table 4: Comparison of present study with previous studies.

Patient characteristics	Present study	Canonic study ¹	Study by Duseja et al ¹⁰	Study by Shalimar et al ¹⁶
Total cases	120	303	102	1049

Continued.

Patient characteristics	Present study	Canonic study ¹	Study by Duseja et al ¹⁰	Study by Shalimar et al ¹⁶
Mean age±SD (years)	44.9±8.6	57.2±12.2	44±12.5	44.7±12.2
Male: female	2.5:1	1.8:1	5:1	4.3:1
Mortality	46.6% (28 days)	33.9% (28 days)	46%	42.6% (8 days)
Acute precipitant	Case (%)			
Alcohol	40	24.5	29	35.7
Hepatotropic viruses	20	-	7	21.4
Sepsis	10.9	32.6	47	16.6
Variceal bleeding	14.2	13.2	12	8.4
Drugs	15.1	-	1	5.7

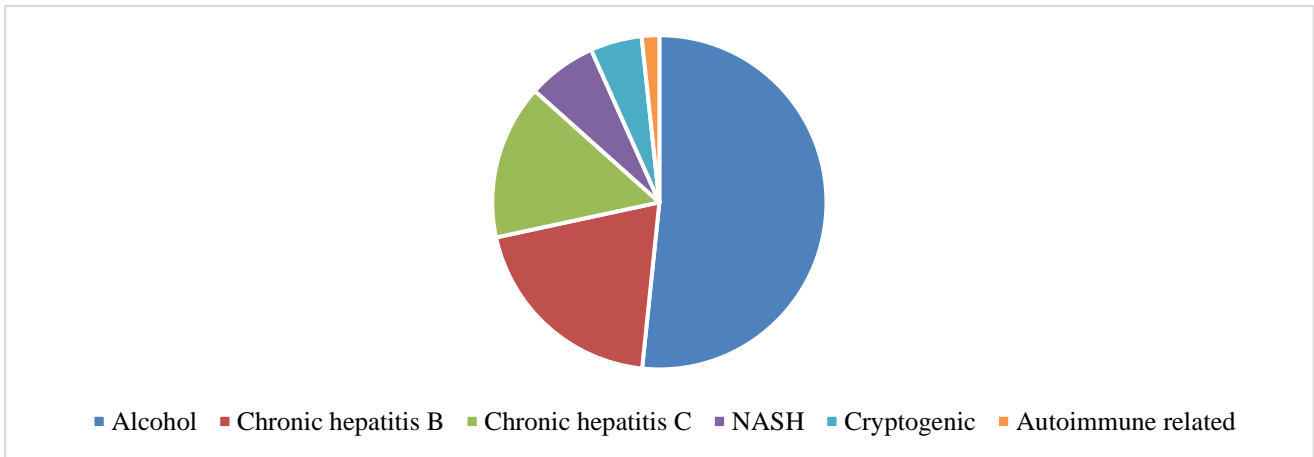


Figure 1: Aetiology of underlying CLD.

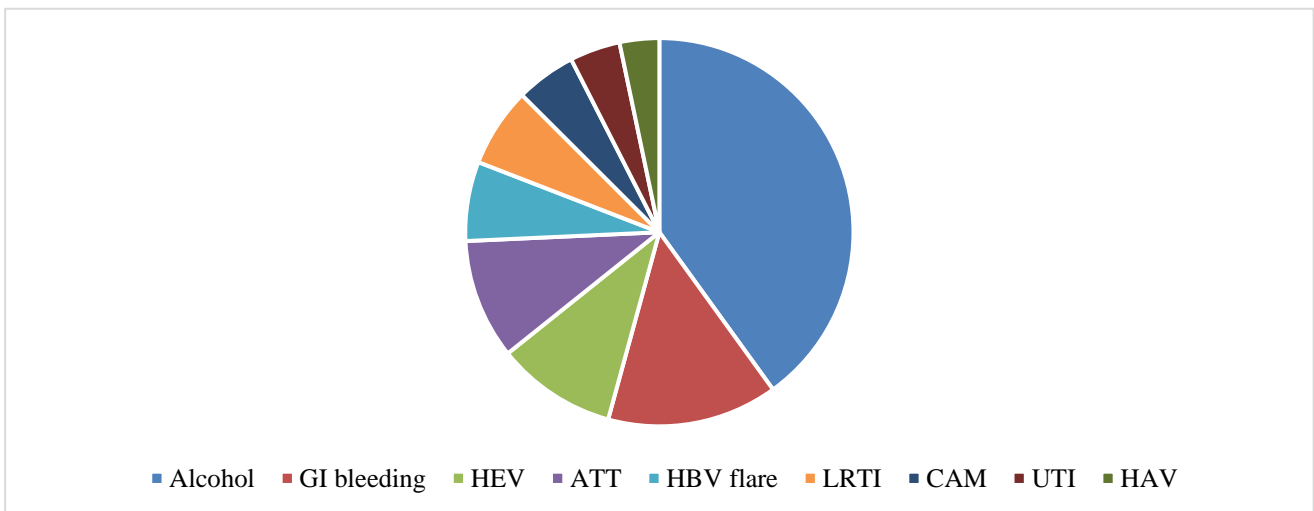


Figure 2: Aetiology of acute precipitating event.

DISCUSSION

Concept of ACLF in the management of cirrhosis is comparatively new and evolving. Significant differences are there between definitions of various societies from all over the globe. APASL criteria didn't include previously decompensated cirrhotic patients and extrahepatic organ failure in absence of liver failure while defining ACLF. They didn't consider sepsis and GI bleeding as acute

precipitating event.^{3,14} In our study we also excluded previously decompensated cases of cirrhosis. But we consider bacterial infections, GI bleeding as triggering events in deviation of APASL criteria.

Mean age of presentation in our study was 44.9±8.6 years and majority were males, 86 (71.7%) out of 120 patients. Similar results were observed in study by Sen et al and Shalimar et al.^{15,16}Alcohol abuse was most common

aetiology of underlying CLD in our study, followed by chronic hepatitis B (20%). Previous studies from Asian subcontinent documented chronic hepatitis B as most common aetiology of chronic liver disease.^{7,17,18} But recent studies have suggested alcohol as commonest cause of underlying CLD in Indian population.^{16,19}

We consider both hepatic and extrahepatic insults as precipitant of ACLF in our study. Bacterial infection was documented as commonest precipitating factor in studies from west, followed by GI bleeding and alcohol.¹ Alcohol (35%) followed by sepsis (16.6%), hepatotropic viruses (21.4%), variceal bleeding (8.4%) and drugs (5.7%) were reported as common precipitating factors in a multicentric study from India.¹⁶ Similar results were observed in our study except sepsis was less common and contribution of GI bleeding, drugs was more as acute precipitant. Commonest drug identified was combination ATT (10%), followed by Complementary and alternative medications (CAM). Devarbhavi et al documented drugs as a cause in 10.5%.²⁰ CAM were the commonest insult, followed by combination anti-tuberculosis therapy drugs in that study. Comparison of present study with previous studies is showing in Table 4.

Most common organ failure in our study was coagulation (43.3%) followed by cerebral (41.4%). In Canonic study, liver failure was present in 43.6% patients as compared with 30% in our study.¹ Mortality was low in patients with lower ACLF grading whereas higher ACLF grading was associated with high mortality (7.2% v/s 78.5%) and difference was statistically significant.

Limitation of this study were small sample size, short follow-up period and non-availability of liver transplantation.

CONCLUSION

ACLF is rapidly progressive syndrome with high short-term mortality. Alcohol is commonest identifiable acute precipitating agent for ACLF and also most common cause of underlying CLD in our study. Mortality was higher in patients having high leucocyte count, high total bilirubin, high serum creatinine, high MELD score, Higher CTP class, higher ACLF grade, low serum albumin and low serum sodium. Early recognition of these factors and prompt treatment may be helpful in decreasing the mortality.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Behera S, Prakash V, Bajpai S, Patra UC, Jena SK. Acute on chronic liver failure- etiology, clinical profile, prognostic scores: experience from tertiary care centre of eastern India. *Int J Res Med Sci* 2021;9:3405-10.