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Original Research Article

A study of clinical profile and factors affecting mortality in patients with acute on chronic liver failure in a tertiary hospital in north east India

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ABSTRACT

Background: Data regarding Acute on Chronic Liver Failure (ACLF) patients from North East India is scarce and presentation to hospital is often late. We aim to study their clinical profile, aetiology of underlying chronic liver disease, precipitating factors, predictors of mortality and their short term outcome (3 months).
Methods: Among 1000 consecutive patients of any form of acute decompensation, 245 patients diagnosed as ACLF were prospectively studied. Comparison was done between survivors versus non survivors of ACLF and between ACLF and Non ACLF patients.
Results: Mean age of ACLF patients was 44.2±10.3 years and male:female ratio was 13.4:1. Common causes of underlying cirrhosis in ACLF was alcoholic liver disease, 210 (85.7%), Hepatitis B virus related cirrhosis, 20 (8.2%), Hepatitis C virus related cirrhosis, 6 (2.4%) and cryptogenic in 8 (3.3%). Precipitating causes were alcoholic hepatitis in 98 (46.6%) among alcoholic cirrhosis, acute flare of Hepatitis B infection in 12 patients (60%) among Hepatitis B related cirrhosis, recent use of drugs in 110 (44.8%), sepsis in 71 (28.9%), spontaneous bacterial peritonitis (SBP) in 36 (14.7%), urinary tract infection in 36 (14.7%), acute hepatitis A in 5 (2%) and acute hepatitis E in 3 (1.2%). hepatic encephalopathy, low sodium, high International Normalised Ratio (INR) were found to be significantly associated with high mortality. Increasing number of organ failures is associated with increasing risk of death.
Conclusions: ACLF is characterized by rapid deterioration especially when multiorgan failure sets in due to certain precipitating factors in a previously diagnosed or undiagnosed chronic liver disease.

Keywords: Acute chronic liver failure, Chronic liver disease, Organ failure, MELD

INTRODUCTION

The term acute on chronic liver failure (ACLF) was first used by Japanese researchers in 1995 to describe a condition where two insults in liver occur simultaneously, one chronic and ongoing and the other acute.[1] At present, there are two main consensus working definitions of ACLF. The Asia Pacific Association for the Study of Liver (APASL) defined ACLF as "acute hepatic insult manifesting as jaundice (defined as serum bilirubin level >5 mg/dl) and coagulopathy (defined as international normalized ratio >1.5), complicated within 4 weeks by ascites and /or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.[2] The other definition by European Association for Study of Liver (EASL)-American Association for Study of Liver Disease (AASLD) in 2013, defines 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 multi- system organ failure.[3] ACLF occurs in about 30% of patients with an acute decompensation of cirrhosis and has a significantly higher short term mortality of 30-50% than expected with decompensated liver cirrhosis.[3-5] ACLF is usually associated with a precipitating event which can be reversed if diagnosed early, although the underlying cirrhosis is irreversible.

The primary aetiology of the underlying chronic liver disease is still Chronic HBV in the Asia-Pacific region, whereas in the West, Alcohol and NASH are a significant cause of cirrhosis.[2,6] The precipitating events in ACLF are variable and can be both infectious or non-infectious. Among the infectious aetiologies, reactivation of hepatitis B virus (HBV) infection especially in the Asian region super infection with hepatitis E virus, especially in the Indian subcontinent and HAV infection are common.[7-11] APASL definition per se excludes bacterial infection as a precipitating event, on the other hand it has been recognized as an integral cause for the development of ACLF in the West. Among the non-infectious aetiologies hepatotoxic drugs, herbal indigenous medicines, acute variceal bleeding, major surgical procedure are important causes of ACLF.[4,12,13] In some patients with ACLF there may be more than one acute insult simultaneously. Data on ACLF is scarce, heterogenous and mostly retrospective. The present study documents the various precipitating events, underlying chronic liver disease, the clinical and biochemical spectrum and also the factors predicting mortality in ACLF in North East India.

METHODS

This prospective observational study was conducted in the Department of Gastroenterology, Guwahati Medical College and Hospital, Guwahati. Among One thousand consecutive patients of any form of acute deterioration of chronic liver disease, 245 patients with ACLF were included in the study based on the APASL criteria with some deviations, from June 2016 to July 2019. The deviations were patients with past history of acute decompensation of liver cirrhosis 6 months prior to the present episode who had then recovered completely with treatment and patients with non-hepatic causes of sepsis as precipitating causes as modification to the APASL criteria for ACLF. Patients with age <18 years, pregnant, portal vein thrombosis, hepatocellular carcinoma, unwilling to participate in the study were not included in the study protocol. Written informed consent was obtained from the patients or their attendants.

All enrolled patients were evaluated regarding their clinical presentation, aetiology, precipitating factors, laboratory investigations, endoscopic features and received standard management and intensive care whenever required and treated conservatively. Nutritional status assessment was done using anthropometric measurements like the Body Mass Index (BMI) (in patients with ascites was checked after paracentesis) and Subjective Global Assessment (SGA) which is a tool that incorporates clinical findings and patient's history into a nutritional assessment score as follows- A: well nourished, B: moderately malnourished and C: severely malnourished. This score has been validated in a number of conditions.[14] Patients were followed up for a period of 3 months or till death whichever occurred earlier. Diagnosis of cirrhosis was based on composite clinical, laboratory, ultrasound (coarse liver architecture with irregular margins with evidences of portal hypertension, portal vein diameter >13mm, ascites, splenomegaly and presence of collaterals), varices (> grade 2) in endoscopy, Fibroscan whenever feasible (in patients with no or minimum ascites) and wherever previously available, liver biopsy. Patients diagnosed with ACLF were further evaluated for the presence of precipitating factors like, alcoholic hepatitis, infection, drug toxicity, acute infection with hepatitis A and E viruses, acute flare of chronic hepatitis B. Alcoholic hepatitis was diagnosed as acute onset of jaundice, malaise, anorexia in patients with alcohol abuse for last 4 weeks with signs of decompensated liver disease (eg. Ascites, hepatic encephalopathy) with AST/ALT characteristically <3xULN, AST>ALT. Diagnosis of infection was done by standard procedures utilizing blood cultures, urine and ascites culture and radiological evidence of pulmonary infection and presence of cellulitis if any. Recent use of toxic herbal drugs and hepatotoxic drugs were evaluated. Acute flare of Hepatitis B was diagnosed in patients with acute increase in ALT levels (>5 times ULN) in a background of chronic hepatitis B related cirrhosis. Organ failure was defined by the presence of SOFA score of 3 or more for the respective organ system. Presence of two or more extra hepatic organ failure is defined as multiorgan failure. First, the ACLF patients were described and then two sets of analysis was performed. In one set, comparison was made between survivors and non survivors of the ACLF group and in the second set the ACLF (cases) were compared with the Non ACLF patients (controls).

Statistical analysis

All the data were recorded in a predetermined proforma. The descriptive statistics for the various parameters for both control (non ACLF) and case (ACLF) group as well as the survivors and non-survivors are expressed as Mean±Standard deviation. The primary analysis compared the cases with controls and the survivors with non-survivors among ACLF patients. The comparison of the continuous variables (parameters) for the cases with controls and for the survivors with the non-survivors has been carried out using the Mann-Whitney U-test. For comparison of categorical variables (parameters), two proportions Z-test have been used. Multivariate logistic regression analysis has been employed to identify the factors (parameters) which significantly predict mortality. All the statistical tests used are two-tailed and a significance level of 0.05 has been used. The SPSS for

Windows version 24 (SPSS Inc., Chicago, IL) and R 3.5.3 software have been used to perform the analysis.

RESULTS

Patients

Out of one thousand consecutive patients with any form of decompensation, 245 (24.5%) patients were diagnosed as ACLF according to the APASL criteria. Past history of acute decompensation that recovered completely was seen in 82 (33.4%) of these patients and was included in the ACLF group, remaining 163 (66.5%) did not have any prior history of decompensation. Mean age in ACLF patients was 44.2±10.3 years. Majority were males (93%) with the Male: Female ratio 228:17 (13.4:1).

Table 1: Demographic features, clinical and prognostic variables in ACLF and non ACLF patients at admission.

Parameter	ACLF (n:245)	Non ACLF (N:755)	P value
Mean age (years)	44.2±10.3	46.3±10.4	0.006
Sex Male	228	655	0.010
Female	17	100	0.010
Jaundice duration (days)	19.1±9.1	10±32.3	0.000
Ascites (days)	19.6±10.7	65.1±81.9	0.000
HE Grade 1	125	45	0.000
HE Grade 2	41	54	0.000
HE Grade 3	31	42	0.000
HE Grade 4	4	12	0.000
UGI bleed	61/144	276/632	0.728
Prev. decompensation	82	150	0.168
Nutrition	(n:224)	(n: 727)	
SGA: Grade A	37	172	0.013
SGA : Grade B	81	307	0.040
SGA : Grade C	106	248	0.003
BMI	21.5+ 3.6	22.3 + 3.5	0.010
CTP score	11.5+ 1.5	8.8+ 1.9	0.000
MELD score	25.9+ 7.6	15.2+ 5.2	0.000
Mortality	74	29	0.000
No. of failures (except liver failure)	1.8+ 1.1	0.0+ 0.7	0.000

HE: Hepatic Encephalopathy, UGI: Upper Gastrointestinal, SGA: Subjective Global Assessment, BMI: Body Mass Index, CTP: Child Turcot Pugh, MELD: Model End Stage Liver Disease

Clinical presentation

In the ACLF patients, cirrhosis was present in all underlying chronic liver disease. The common clinical presentations are summarized in Table 1. Jaundice was present in all (100%) cases and mean duration of jaundice was 19 days, acute onset ascites was seen in 231 (94.3%) patients. Mean duration of development of ascites from jaundice was 19.6±10.7 days. Hepatic encephalopathy was seen in 201 (82%) patients with ACLF. Out of 776 patients who underwent endoscopy (144 with ACLF, 632 without ACLF), esophageal varices (>grade 2) were seen in all patients with ACLF (100%) and 502 (79.4%) of Non ACLF of which 61 (42%) patients presented with acute variceal bleed in ACLF and 276 (43.6%) non ACLF had history of variceal bleeding. Thirty six patients (14.7%) presented with SBP and Hepatorenal syndrome was seen in 22 (9%) patients. Nutritional assessment could be done in 224 ACLF patients and 106 (47.3%) had severe malnutrition compared to 248 (34.1%) in non ACLF patients (Table 1).

Aetiology of underlying CLD

Major aetiology of the underlying cirrhosis was chronic alcohol use in 210 (85.7%), followed by HBV infection in 20 (8.2%) and cryptogenic in 8 (3.3%) patients (Table 2).

Table 2: Aetiology of the underlying chronic liver disease in all patients.

Aetiology	ACLF (n: 245)	Non ACLF (n: 755)	P value
Alcohol	210 (85.7%)	493 (65.3%)	0.000
HBV	20 (8.2%)	70 (9.2%)	0.690
HCV	6 (2.4%)	24 (3.2%)	0.714
AIH	1 (0.4%)	7 (0.9%)	0.704
Cryptogenic	8 (3.3%)	161 (21.3%)	0.000

HBV: Hepatitis B Virus related, HCV: Hepatitis C virus related, AIH: Autoimmune Hepatitis related.

Table 3: Precipitating factors in ACLF patients.

Precipitating factor	ACLF (n 245)	Percentage
SBP	36	14.7
UTI	36	14.7
Sepsis	71	28.9
HRS	22	9
Alcoholic Hepatitis	98/210	46.6
Acute flare of Hep B	12/20	60
Drugs	110	44.8
Acute Hepatitis A	5	2.04
Acute Hepatitis E	3	1.2

SBP: Spontaneous Bacterial Peritonitis, UTI: Urinary Tract Infection, HRS: Hepatorenal Syndrome, UGIB: Upper Gastrointestinal Bleed. For all precipitating factors denominator was 245 except with Alcoholic hepatitis and Acute flare of Hepatitis B

Precipitating insults

In the ACLF patients, cause of acute insult among Chronic Hepatitis B related cirrhosis was acute flare of Hepatitis B in 12 patients (60%), alcohol hepatitis in 98

(46.6%) among alcohol related cirrhosis. Sepsis was diagnosed as precipitating factor in 71 (28.9%). Recent use of drugs was attributed to 110 (44.8%) patients, of which Herbal medicines of unknown composition in 103 (93.6 %) cases and ATT in 7 (6.3%). Hepatitis A was seen in 5 (2%) and Acute Hepatitis E in 3 (1.2%) (Table 3). In ninety eight (40%) patients, multiple acute predisposing insults were identified of which 79 (32.2%) had 2 simultaneous insults and 19 (7.7%) patients had 3 or more insults. Ninety eight patients (40%) had single acute insult. In forty nine patients (20%) no precipitating factor could be identified. Mortality in patients with multiple insults was significantly higher than patients with single insult.

Table 4: Biochemistry in patients with ACLF and Non ACLF.

Parameters	ACLF (n:245)	Non ACLF (n:755)	P value
Total Bilirubin (mg/dl)	11.4± 6.8	1.9±1.1	0.000
AST (U/l)	175.8±192.7	100.4±90.4	0.000
ALT(U/l)	96.5±148.4	56.9±58.5	0.000
ALK hos(U/l)	227±139	217.9±183.3	0.021
Albumin (gm/dl)	2.5±0.5	2.7±0.6	0.000
Prothrombin time (sec)	23.6±9	17.8±6.6	0.000
INR	2.2±1.1	1.7±4.7	0.000
TLC (10^3 /ul)	10.4±6.6	6.8 ± 5.8	0.000
Haemoglobin (gm/dl)	8.8± 2.1	8.7± 2.3	0.530
Platelet count(10^3/ul)	128± 5	144±325	0.054
Sodium (mmol/l)	133.3± 7.7	134.9±9	0.000
Pottasium (mmol/l)	3.8± 0.8	4.4±7.4	0.101
Creatinine (mg/dl)	2.1±1.1	1.1±0.8	0.000
FBS(mg/dl)	105.8±53.3	111.7±58.4	0.050
PPBS (mg/dl)	134.3±57.1	141.5±69.7	0.207

AST: Aspartate Transaminase, ALT: Alanine Transaminase, ALK phos: Alkaline phosphatase, INR: International Normalized Ratio, TLC: Total Leukocyte count, FBS: Fasting Blood Sugar, PPBS: Post Prandial Blood sugar

Biochemistry

Among the laboratory parameters, significantly high mean bilirubin level was seen among ACLF 11.4±6.8 mg/dl. Seventy one patients (28.9%) had leukocytosis (>12 x 103/ uL) blood, mean leukocyte count 10.4 6.6 (103/ uL) blood, but infection was documented in only 17/71patients (23.9%), 8/71 patients (11.2%) had positive ascites culture, 3/71 (4.2%) had positive sputum culture, 6/71 patients (8.4%) had positive urine culture and no patients had positive blood culture.

Table 5: Clinical features and biochemical parameters of ACLF patients and difference between survivors and non survivors.

Parameters	Surv (n: 171)	Nonsurv (n: 74)	P value
Mean age (years)	44.7±10.7	42.3±8.3	0.192
Sex Male	175	53	0.008*
Female	15	2	0.274
Jaundice duration (mean)	19±9.4	19.3±8.3	0.645
Ascites duration (mean)	19.5±10.8	19.8±10.5	0.825
HE Grade 0	20	5	0.005*
Grade1	99	26	0.000*
Grade 2	30	11	0.004*
Grade 3	9	33	0.000*
Grade 4	4	8	0.386
Nutrition SGA GradeA	29	8	0.001*
GradeB	70	11	0.000*
GradeC	77	29	0.000*
Body mass index	21.6±3.7	21.3±3.3	0.489
s/bilirubin (mg/dl)	10.7±6.3	13.8±8	0.008*
AST (U/l)	153.9±139.3	255.6±303.8	0.005*
ALT (U/l)	85.8±108.1	133.5±238.5	0.070
Alk Phos (U/l)	229±142.5	220.1±127.4	0.555
Albumin (gm/dl)	2.5±0.5	2.4±0.7	0.058
Prothrombin Time (sec)	21.9±7.7	27.8±11.6	0.000*
INR	2±1.1	2.5±1.1	0.001*
TLC (10^3 /ul)	10.2±6. 4	11.1±7.4	0.675
Haemoglobin (gm/dl)	8.9±2.3	8.6± 2	0.339
Platelet count (10^3 /ul)	131±59	120±48	0.223
Sodium (mmol/l)	133.8±7.3	131.4±8.6	0.015*
Pottasium (mmol/L)	3.8±0.8	3.9±0.9	0.346
Creatinine (mg/dl)	2±0.9	2.6±1.6	0.005*
Fasting BS (mg/dl)	105.9±45	105.5±76	0.066
Post Prandial BS (mg/dl)	134.9±56.0	132.4±61.4	0.740

HE: Hepatic Encephalopathy, SGA: Subjective Global Assessment, AST: Aspartate Transaminase, ALT: Alanine transaminase, Alk Phos: Alkaline Phosphatase, INR: International Normalized Ratio, TLC: Total Leukocyte count, BS: Blood Sugar, *: significant p value.

Documentation of infection was low perhaps due to starting antibiotics before documenting infection in many patients (Table 4).

Comparison of ACLF and Non ACLF patients

Out of 1000 patients of acute decompensation, 245 patients were diagnosed as ACLF according to the APASL criteria and the remaining 755 patients were considered as non ACLF. Mean age and gender was similar in both groups (p value: 0.006 and 0.010 respectively). Hepatic Encephalopathy (HE) was significantly higher in ACLF patients across all grades (p value: 0.000). History of previous decompensation was similar in both groups. Patients with ACLF had significantly higher grades of malnutrition (Grade C) (p: 0.003). Among precipitating factors, infections (SBP, UTI, sepsis) and alcoholic hepatitis was significantly higher in ACLF patients (p: 0.000). Among laboratory parameters, significantly high bilirubin levels, INR, Total leukocyte count, Sodium, Creatinine and low albumin was seen in ACLF patients. Presence of all organ failures except liver failure was significantly higher in ACLF (p: 0.000). Significantly higher values of CTP and MELD scores and mortality were seen in ACLF patients (p: 0.000).

Organ failure

Patients with 2 or more organ failure besides liver failure, were said to have multi organ failure. 108/245 patients (44.1%) had single organ failure and 137 (55.9%) had multiorgan failure of which 79 (57.6%) had 2 organ failure, 59 (43.1%) had 3 or more organ failures. Almost 53/59 (90%) of patients with 3 or more organ failure died in comparison to 17.7% (14/79) patients with 2 organ failure and only 6.5% (7/108) patients with single organ failure.

Mortality and its predictors

Mortality at 30 days was 32.4% and 50/74 (67.5%) in 90 days. Most common cause of mortality was multi organ failure. On univariate analysis, presence of hepatic encephalopathy, low sodium, high INR, high creatinine were found to be significantly associated with mortality (Table 5). On multivariate analysis of these significant variables by Cox Regression analysis, only hepatic encephalopathy, low serum Sodium and high INR were found to be independent baseline predictors of mortality.

Scoring systems

The various scoring systems like Child-Turcot-Pugh (CTP), Model for End Stage Liver Disease MELD, SOFA were analyzed to compare survivors and non survivors by using Area under Receiver Operating Characteristics curve (AUROC). AUROC of CTP score, SOFA and MELD score against mortality in ACLF patients was 0.6365 (95% CI: 0.5640 to 0.7089) and p value 0.0006951, 0.7271 (95% CI: 0.6590 to 0.7952),p value <0.0001 and 0.6959 (95% CI: 0.6200 to 0.7719) p value <0.0001 respectively. This showed that SOFA had an edge over the other 2 scoring systems. (Fig).

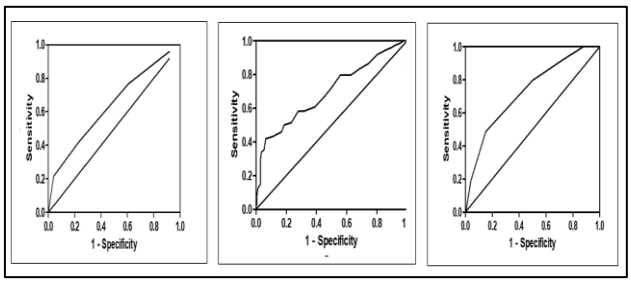

Figure 1: Receiver operating characteristic (roc) curves of CTP (child turcot pugh), meld and sofa scores in relation to predicting mortality in ACLF patients.

DISCUSSION

The incidence of ACLF in this prospective observational study was 24.5%. Among precipitating factors, non-hepatotropic infections/sepsis were considered as deviation to the APASL 2009 criteria as it has been thought to be relevant and considered in a number of other studies from the West. It was suggested that non hepatic insults like sepsis may initiate a cascade resulting in end-organ dysfunction and liver failure in patients with stable cirrhotic status.[15] As in our study, Pati et al 2015, noted prior history of acute decompensation in 45.53% ACLF patients with no significant difference in mortality in those without history of previous decompensation.[17] Similiar mean age at presentation (44.2+ 10.3 years) and male (93%) majority were observed by many other studies.[16] In our study, all cases had underlying cirrhosis and the commonest aetiology of underlying cirrhosis was alcohol abuse in 85.7% patients followed by chronic HBV infection in 8.1%. Studies from the West document alcoholic cirrhosis as the most frequent aetiology of chronic liver disease and viral hepatitis in the studies from Asian subcontinent.[18-24] Recent trends have shown Alcohol as the commonest cause of underlying cirrhosis in the Indian subcontinent too.[17,25] Most common precipitating factors in our study was flare of hepatitis B which was seen in 60% of the Hepatitis B infection patients followed by alcoholic hepatitis (46.6%) and drugs (45%) and sepsis in 29% patients. A study by Garg et al showed that 85% of the cases was due to flare of Hepatitis B.[26] Similar findings were seen in most of the Asian studies.[23,26] Most Western literature however documents alcoholic hepatitis, sepsis and Upper GI bleed as the common precipitating factors.[28-30] Alcoholic Hepatitis was responsible for acute insult in 46% of our patients with ACLF similar to studies by Dhiman et al.[31] We considered alcohol as acute insult when last drink was in 28 days because after acute injury, immunological injury declines after 28 days.[32] Drugs as precipitating factor was seen in 45% patients mostly due to unknown

herbal medicine intake. Intake of herbal medications is a very common occurrence with patients with jaundice in this part of the country due to unregulated medicines prescribed by quacks as is demonstrated by Das et al in a study that herbal drugs was the cause of Acute liver failure in 78% patients in North East India.[33] Although, this was a study done in Acute Liver Failure patients it is possible that use of unregulated herbal medicines can be a cause of severe liver dysfunction among ACLF patients too. Sepsis was seen in 29% patients, Fever in 24.5% and mean Total Leukocyte count was 10373.5/cub mm blood in our patients. Due to hyperdynamic circulation and portal hypertension, the current clinical definition of SIRS and sepsis may not be entirely acceptable, therefore careful consideration and high index of suspicion was used to diagnose sepsis in our patients. High Total leukocyte count, fever and SIRS was taken into account. Infection was documented in only 24% patients. Kumar et al (2016) showed similar findings of 32% patients with sepsis in their study.[34] High mortality was seen in our patients, (67.5%) 90 day mortality. Similar findings were observed in other Indian studies, Garg 63% and Pati 71.26%. Hepatic encephalopathy, low serum Sodium and high INR were found to be independent baseline predictors of mortality on multivariate analysis which was similar to other studies.[26,35] Occurrence of multi organ failure especially with 3 or more failures resulted in a very bad prognosis causing almost 90% mortality in all patients and this is in concordance to findings in other studies in critically ill patients.[36]

CONCLUSION

ACLF is a serious condition that often leads to high mortality because acute precipitating insults causes further damage to the liver which has underlying chronic liver disease besides causing multi organ failure. As presence of multiorgan failure was associated with near 90% mortality it is extremely important to identify the modifiable precipitating events and organ failure at the earliest in order to improve patient outcomes. Current treatment strategies are symptomatic therefore better characterization of the disease will assist in developing new management strategies in the future.

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