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# CLINICAL AND HISTOLOGICAL MARKERS OF POOR PROGNOSIS IN ACUTE ON CHRONIC LIVER FAILURE (ACLF) – AN INDIAN PERSPECTIVE

Gastroenterology

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## ABSTRACT

**Introduction:** Acute on Chronic Liver Failure (ACLF) is associated with high mortality and requires early recognition and aggressive management.

**Aim:** To evaluate the clinical profile of ACLF and study factors associated with a poor outcome

**Materials and Methods**: 61 cases of ACLF were e valuated. Etiological work up and Trans-jugular liver biopsy was done in all patients. Patients were followed up for a period of four weeks or till death (if earlier).

**Results**: The mean age of patients was 40.06 +/- 4.2 years. Encephalopathy and GI Bleed was noted in 91.8% and 27.9% patients. Alcohol was the commonest etiology of chronic disease. Acute events were alcoholic hepatitis and viral hepatitis. Non-survivors had a higher incidence of GI Bleed and encephalopathy.

**Conclusion**: ACLF is associated with alcohol and viral hepatitis. GI bleed, Hepatic encephalopathy and type I histology are associated with a poor prognosis.

## KEYWORDS

### Introduction

Acute on Chronic Liver Failure (ACLF) is a concept that has emerged over the past decade and half. It has been argued to be different from decompensated liver disease in terms of pathogenesis, presentation and outcome. An entity that is associated with a higher mortality, ACLF needs to be recognized early, monitored carefully and managed aggressively for optimal outcomes and better results. The primary reason why ACLF has been proposed and stratified as a separate entity being that while chronic decompensation of the end-stage liver disease usually results in an irreversible deterioration, ACLF (due to acute episodes) is potentially reversible. However, this reversibility depends on the severity and nature of the acute insult and the degree of underlying chronic liver disease.

### Aim

This study was carried out a tertiary care hospital to study the clinical profile of patients with Acute on Chronic Liver Failure, to determine the precipitating cause and etiology of underlying chronic liver disease. The study also aimed to evaluate complications of liver disease and the histological characteristics with the final outcome

### Materials and Methods

This study was a prospective observational study. 61 cases of ACLF were enrolled in the study over a period of 08 months. (Oct 2014 – May 2015). ACLF was defined as per definition of APASL (serum bilirubin $\geq$ 5 mg/dL and INR $\geq$ 1.5 in patients who develop ascites on physical examination and/or clinical encephalopathy within four weeks of jaundice) [1].

Patients with severe co-morbid conditions, concomitant HCC and sepsis were excluded. Patients less than 18 years of age and more than 70 were excluded. Informed consent was taken from all patients. A detailed history of jaundice, prodromal symptoms, cholestasis, coagulopathy, ascites, gastrointestinal bleed and encephalopathy were recorded. Any history of recent drug consumption or alcohol abuse was also taken in to account. All patients were subjected to a detailed clinical examination. Nutritional status was recorded with height, weight and BMI. Patients were examined for pallor, icterus, pedal edema, clubbing, skin changes, and stigmata of liver failure. A detailed systemic examination was done in all patients. All patients underwent baseline hematological and biochemical investigations, ultrasound abdomen and upper gastrointestinal endoscopy. Etiological work up was done for the cause of acute insult and underlying chronic liver disease. Viral markers included HBsAg, Anti HCV, IgM anti-HAV, IgM Anti-HEV, Total Anti HBc and IgM anti-HBc. HBsAg positive patients underwent quantification of HBeAg and HBV DNA. Similarly, in Anti-HCV positive patients, genotype and quantitative HCV RNA were done. Other tests included autoimmune markers (ANA, Anti LKM1, AMA and SMA), Serum Iron, Serum Ferritin, Total Iron Binding Capacity, Serum Ceruloplasmin, and Alpha Feto-Protein (AFP). Trans-jugular liver biopsy (TJLB) was done after taking consent using 18 G Cook needle. Liver histology was described into the two patterns: Type I (Marked ductular proliferation, coarse inspissated bile plugs higher stage of fibrosis and variable activity) and Type II (Hepatocyte ballooning, rosette formation, type I cholestasis, moderate to severe interface activity and variable fibrosis). All patients were followed up for a period of four weeks or till death (if earlier)

### Statistical Analysis

The statistical analysis was performed using SPSS version 20. The clinical profile of patients was analyzed by chi-square test for qualitative variables and student t test / one way ANOVA for quantitative variables. $p < 0.05$ was considered as statistically significant.

### Results

ACLF affected young patients with the mean age being 40.06 +/- 4.2 years. Fifty seven (93.4%) patients were males. The mean ages of male and female subjects were 40.7 +/- 3.4 years and 39.2 +/- 2.9 years respectively. Almost 70 % of the subjects (n = 43) were between 30 to 50 yrs of age. The most frequent symptom at admission was jaundice (100%) and distension of abdomen (90.1%). Other common symptoms at admission were anorexia, fatigue, swelling of feet and spontaneous bleeding and the lesser common were fever, pruritus, oliguria, and pain abdomen. The basic characteristics of the patients are shown in Table 01.

**Table 1: Patient Characteristics**

| Characteristics | Value | Characteristics | Value |
|---|---|---|---|
| Age (years) | 40.1 yrs | Oliguria | 13 (21.3%) |
| Females | 04 (6.6%) | Pain abdomen | 07 (11.5%) |
| Jaundice | 61 (100%) | Stigmata of liver disease | 45 (73.7%) |
| Distention | 51 (90.1%) | Ascites | 54 (90.9%) |
| Anorexia | 41 (66.4%) | Encephalopathy | 56 (91.0%) |
| Fatigue | 29 (47.5%) | Spontaneous bacterial peritonitis | 06 (9.8%) |
| GI bleeding | 21 (34.4%) | No varices | 08 (13.1%) |
| Fever | 11 (18.4%) | Small varices | 40 (65.6%) |
| Pruritus | 05 (8.2%) | Large varices | 13 (21.3%) |

On examination all patients were icteric and 90.9% patients had ascites. Forty-five (73.7%) patients had stigmata of liver disease with palmar erythema being the commonest. Splenomegaly was seen in forty one (66.4%) patients. Hepatic encephalopathy was common with low grade encephalopathy (Grade I and II) in 32 (52.5%) patients and higher levels of encephalopathy (Grade III – IV) in 24 (39.3%) patients. Seventeen (27.9%) patients had a GI bleed during the hospitalization. All the patients were evaluated as per guidelines and standard scores for prognosis were calculated. The average MELD, SOFA and CTP were 25.2 +/- 3.1, 7.27 +/- 1.3 and 11.2 +/- 3.4. The investigations of the cohort are summarized in Table 2.

**Table 2: Investigations**

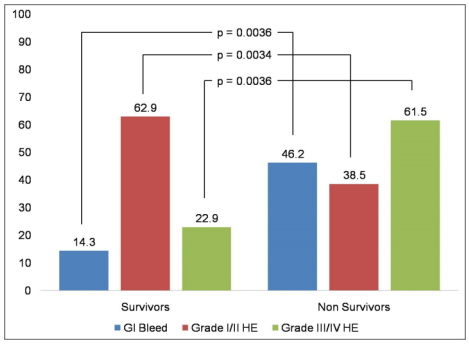
| Characteristics | Value | | |
|---|---|---|---|
| Hemoglobin (g/dl) | 10.84 | Serum Protein (g/dl) | 6.4 |
| Total Leucocytes Count (/mm3) | 11200 | Serum Albumin (g/dl) | 3.1 |
| Platelet count (/mm3) | 92000 | Blood Urea Nitrogen (mg/dl) | 35 |
| Bilirubin (mg/dl) | 14.1 | Serum Creatinine (mg/dl) | 1.42 |
| Aspartate Transaminase (IU/ml) | 114 | MELD | 25.2 +/- 3.1 |
| Alanine Transaminase (IU/ml) | 159 | SOFA | 7.27 +/- 1.3 |
| Alkaline Phosphatase (IU/ml) | 184 | CTP | 11.2 +/- 3.4 |

Legend MELD: Mortality in End stage Liver Disease score
SOFA: Sequential organ failure assessment
CTP: Child Turcott Pugh score

The etiology of the chronic liver disease could be identified in fifty three (86.8%) patients. Alcohol was the most common etiology seen in twenty seven (44.3%) patients followed by HBV infection (18.1%). Five patients (8.2%) had both HBV infection and significant alcohol intake contributing to the chronic liver disease. HBV-HCV co-infection was seen in one patient. Other etiologies detected were autoimmune hepatitis (3.2%), PSC (3.2%), PBC (1.6%) and Wilson's disease (1.6%). The etiology of the chronic liver disease could not be determined in 13.2% patients.

Fifty one patients (83.6%) had an identifiable event leading to the acute failure. Alcohol was responsible for hepatic decompensation in 25 (40.9%) cases. After alcohol, the next most common etiology was the hepatotropic viruses, seen in 22 (36.1%) patients. Among these patients, Hepatitis E Virus was the commonest affecting 14 patients (63.6%). Reactivation of HBV infection and Hepatitis A virus infection were seen in four (18.2%) patients each. Drugs contributed to the acute decompensation in four (6.6%) of the cases. Almost 10% of cases (n=06) had more than one cause with notable combinations being "HBV and alcohol" and "alternative medication with alcohol" in 04 (6.6%) and 02 (3.3%) patients respectively. No cause could be determined in 10 (16.4%) cases.

ACLF was associated with a high mortality with twenty six patients (43.4%) dying during hospitalization. The whole cohort was divided into two groups (survivor and non survivors). The mean age in both survivors and non survivors was similar (40.6 vs 39.4 yrs). As compared to the survivors, the non survivors had a significantly higher incidence of complications as shown in Figure 1.




There was a higher incidence of GI Bleed (46.2% vs 14.3%, p = 0.0036) amongst the non survivors. The grade of encephalopathy correlated with mortality. The incidence of encephalopathy was significantly higher amongst the non survivors as compared to survivors (100% vs 85.8%, p = 0.04). Higher grade of encephalopathy (Grade III or IV) was significantly higher amongst the non survivors (61.5% vs 22.9%, p = 0.0034) as compared to survivors. The reverse was true for lower grades of encephalopathy with survivors having a higher frequency (62.9% vs 38.5%, p = 0.074).

All the patients underwent trans-jugular liver biopsy. Liver histology was described in two patterns: Type I being characterized by marked ductular proliferation, coarse inspissated bile plugs, higher stage of fibrosis and variable activity and Type II showing hepatocyte ballooning, rosette formation, cholestasis, moderate to severe interface activity and variable fibrosis. Type II pattern was more common and was seen in thirty nine (63.9%) patients and the rest (36.1%) had type I pattern of histology pattern. When the type of histology was correlated with mortality it was seen that type I histology was significantly more common amongst the non-survivors (76.9% vs 5.7%, p = 0.001) and type II histology was more common amongst the survivors (94.3% vs 23.1%, p = 0.001). A significantly higher mortality was seen in type I histology as compared to type II (90.9% vs 15.4%, p = 0.0001).

## Discussion

ACLF is characterized by liver cell dysfunction as a result of an acute insult superimposed on chronic well compensated liver disease. This study was carried out to evaluate the clinical profile of patient with ACLF (with respect to the precipitating event and the etiology of chronic illness). We also attempted to analyze various factors contributing to the mortality of these patients. A total of 61 patients were enrolled with the major fraction (72.1%) within 30 – 50 years of age, indicating that the syndrome usually affects the prime and productive years in the life of a cirrhotic. Jha AK et al [2] and Pati GK et al [3] also noted a similar presentation. This observation bears great importance in the natural history of a cirrhotic with his prime years being the phase of threat.

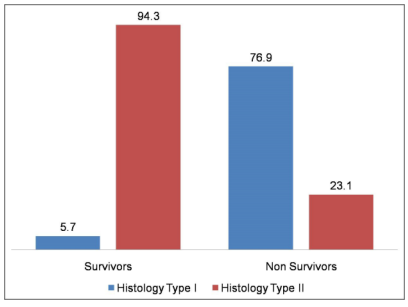
Studies from the Indian subcontinent have reported viral infection and alcohol as frequent causes of acute decompensation in patients with ACLF where as in the west alcohol was the commonest etiology. Jha et al [2] showed a high percentage of acute decompensation due to reactivation of hepatitis B virus infection (46.1 %) and bacterial infection (36.5 %) whereas Garg et al showed an almost equal prevalence of reactivation of chronic hepatitis B and alcoholic hepatitis as the acute event [4]. The studies done in the more recent past in India as well have detected alcohol as the commonest cause closely followed by viral illness [5]. Amongst the notable studies from the west Jalan et al have shown a significantly higher percentage of alcoholic hepatitis as the precipitating event [6]. In our study the most frequent acute event leading to ACLF was alcohol (40.9%) followed by hepatotropic viral infections like HEV (26.22%), HBV (6.5%), and HAV (6.55%). A possible contributor to this variation could have risen due to a higher recruitment of males in the study. A lesser prevalence of viral hepatitis may also be a result of an effective vaccination and screening program leading to a decrease in the prevalence of chronic viral hepatitis.

The etiology of the underlying CLD in patients with ACLF reflects the commonly prevailing etiologies of CLD in particular geographic locale. It could be identified in 86.8% cases. Most common cause of chronic liver disease was alcohol in 44.3% and the next common cause was HBV infection in 18.1%. It is also important to note that 9.8% patients had HBV-HCV co infection, thus showing the importance of testing for both viruses. Other reports from the Indian subcontinent have identified HBV as the most frequent CLD (30%) in patients with ACLF [7], whereas alcohol has been reported more commonly from the west, constituting more than half of the cases [8].

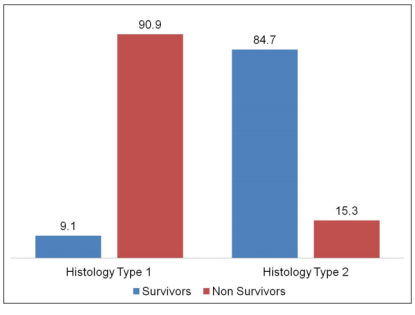
ACLF is associated with high short term mortality and complications like GI bleed and high grades of encephalopathy portend a poor prognosis for the patients. Garg et al have shown hepatic encephalopathy, low serum sodium, and high INR as markers of mortality [4]. A similar study has shown upper gastrointestinal bleeding, and respiratory or circulation dysfunction were predictors of early mortality in patients of ACLF [9]. In our study 42.6% died during hospitalized period. Various factors have been associated with high mortality the more common ones being high grade of encephalopathy and GI Bleed. The incidence of GI Bleed and Grade III – IV encephalopathy was significantly higher in the non-survival group. Among the patients with Gd I/II HE 62.9% survived whereas the survival was lesser in Gd III/IV group (22.9%) as shown in Figure 1. GI

Bleed and Hepatic encephalopathy may be major contributors to the prognosis of ACLF as they result in significant instability of the hemodynamic status (for GI Bleed) and cerebration (for encephalopathy).

Various patterns of hepatic histology have been described in patients of ACLF. Amongst the various patterns the two common patterns that have been described are - (a) Type I comprising of ductular billirubinostasis, extensive necrosis, eosinophilic degeneration with advanced fibrosis and nodule formation and (b) Type II which is characterised by ballooning degeneration with cellular cholestasis, acinar disarray with hepatocellular and canalicular bile and thin septa with mild fibrosis [10]. Type I histology has been proven to be associated with a higher mortality [11]. In our study we did liver biopsy by transjugular access. Twenty-two patients (36.1%) had type I pattern while 39 patients (63.9%) cases had type II pattern. Furthermore amongst all the patients with a favorable outcome (n=35), 94.3% patients had type II histology where as amongst the non survivor group (n=26), 76.9% patients had type I histology (Figure 2).




Among all patients with type I histology (n = 22), 20 patients (90.9%) died where as among patients with type II histology (n=39), 6 patients (15.3%) died (p=0.0001) (Figure 3).




## Conclusion

ACLF is a devastating event in the natural history of cirrhosis with a high rate of short term mortality. The clinical markers that are associated with a high mortality are GI bleed and high grade encephalopathy. The more common causes of acute deterioration of a cirrhotic include continued alcohol use and superadded viral hepatitis underscoring the importance of continued stress on abstinence and vaccination and hygiene to prevent viral hepatitis.

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