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Clinical profile of patients with acute-on-chronic liver failure

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Abstract

ACLF is a distinct clinical entity and different from acute liver failure or chronic liver disease as here two simultaneous but different insults are operating: acute insult and chronic insult. Like acute liver failure ACLF is also associated with high mortality rate, liver support device are important therapeutic options for these patients to provide them additional time for recovery or to serve as a “bridge” to transplantation, whereas orthotopic liver transplantation remains the only definitive therapy who do not improve with supportive measures. Patients with acute-on-chronic liver failure (ACLF) admitted in Medicine or Hepatology ward were enrolled for the study. The most frequent symptoms reported by the patients with ACLF in our study were Jaundice 60(100%) and abdominal distension (ascites) 55 (91%). Other symptoms were altered sensorium (encephalopathy) 36(60%), anorexia 34(56%), fatigue 25(41%), pedal edema 20(33.3%), clinically palpable spleen 22(36.6), fever 12(20%) abdominal pain & GI bleeding each 08(13.3%). Among the GI bleeding patients 2 patients had Hematemesis only, 6 patients had only malena & 1 patient had both. Among HE patients 13(21%) had grade 1-2 HE & remaining 23(38%) patients had grade 3-4 hepatic encephalopathy.

Keywords: Acute-On-Chronic Liver Failure, GI Bleeding Patients, Orthotopic Liver Transplantation

Introduction

Acute-on-chronic liver failure (ACLF) is an increasingly recognized distinct disease entity encompassing an acute deterioration of liver function in patients with chronic liver disease [1]. Scrutiny of the existing data indicates several important conclusions regarding ACLF. First, it results in significantly higher short-term mortality than expected with decompensated liver cirrhosis. Second, the occurrence of organ failure(s) in patients with cirrhosis indicates a poor prognosis with high mortality. It is not the severity of underlying liver disease that is important, but the severity of end-organ failure that determines prognosis. Third, it is usually associated with a precipitating event. And it has a reversible component to the acute deterioration, although the underlying cirrhosis is not reversible [1, 2]. Liver failure manifests as decreased synthetic liver function altered immune response, increased susceptibility to infection, abnormalities in splanchnic and systemic circulation, hepatic encephalopathy, renal failure and impairment of metabolic function such as metabolism of toxins [3]. Liver failure occurs as an acute liver failure (ALF), acute-on-chronic liver failure (ACLF), or as a chronic decompensation of end-stage liver failure. While ALF occurs without pre-existing liver disease, ACLF is defined as an acute deterioration of liver function in a patient with previously well or fairly well compensated chronic liver disease and chronic hepatic decompensation occurs in patients of cirrhosis as a result of relentless progression of underlying liver disease. Syndrome of ACLF has recently been described and remains poorly understood entity, largely because of considerable heterogeneity in its mode of presentation [4]. It is meant to encompass those patients with previously well compensated symptomatic or asymptomatic chronic liver disease in whom an acute de-compensation of liver function occurs due to the effects of a precipitating event such as complication of sepsis, upper gastrointestinal bleeding, ischemia, or superadded liver injury due to Hepatotropic virus, alcohol, hepatotoxic drugs or toxins. Studies have shown that factors responsible for acute decompensation of liver function in patients of ACLF vary in different parts of the world. Data from west have identified alcohol, sepsis and GI bleed as the most common cause responsible for hepatic decompensation, whereas studies from the Indian subcontinent and other parts of South East Asia have reported reactivation of HBV

and HEV super infection as common precipitating events [5]. ACLF is a distinct clinical entity and different from acute liver failure or chronic liver disease as here two simultaneous but different insults are operating: acute insult and chronic insult. Like acute liver failure ACLF is also associated with high mortality rate, liver support device are important therapeutic options for these patients to provide them additional time for recovery or to serve as a “bridge” to transplantation, whereas orthotopic liver transplantation remains the only definitive therapy who do not improve with supportive measures [6].

ACLF is frequently being recognized in clinical practice, so there is growing interest to understand the various aspects like the nature of acute insult, etiologies of underlying chronic liver diseases, pathophysiology, prognostic outcome and the role of supportive therapies. There is paucity of literature on this issue and those available are biased studies as patients with milder form of illness were not studied, so understanding is at a very premature level.

Methodology

Patients with acute-on-chronic liver failure (ACLF) admitted in Medicine or Hepatology ward were enrolled for the study.

Inclusion Criteria

- Patients of ACLF were selected based on the following criteria
- Acute deterioration in liver function (over a period of 4 weeks)
- Manifesting as jaundice (S. Bilirubin >5 mg/dl) with any of the following features
- Coagulopathy (INR >1.5)
- Ascites, or
- Hepatic encephalopathy,
- In patients of diagnosed or undiagnosed prior underlying chronic liver disease.

Exclusion Criteria

- Hepatocellular carcinoma (HCC).
- Portal vein thrombosis.
- Predominantly unconjugated hyperbilirubinemia.
- Lack of consent.

Grade

- None or minimal portal inflammation, no necrosis.
- Portal inflammation (chronic persistent hepatitis) without necrosis and/or lobular inflammation without evidence of necrosis.
- Mild limiting plate necrosis (mild chronic active hepatitis) and/or focal lobular necrosis.
- Moderate limiting plate necrosis (moderate CAH) and/or severe focal cell damage.
- Severe limiting plate necrosis (severe CAH) and/or bridging necrosis.

Stage

- No fibrosis
- No fibrosis or confined to enlarged portal zones
- Periportal or portal-portal septa but intact architecture.
- Septal-fibrosis with architectural distortion; no obvious cirrhosis.
- Probable or definite cirrhosis.

Study variables

- Coagulopathy–Coagulopathy was defined as prolonged prothrombin time, as indicated by an international normalized ratio (INR) of > 1.5.
- Hepatic Encephalopathy – Hepatic encephalopathy was graded based on the change in consciousness, intellectual function, and behavior.

Results

There was overall preponderance in our study, 43(71.7%) were males and 17 (28.3%) were females and male to female ratio was 2.5: 1. The mean age of all subjects was 43.4 ±9.2, the mean age of male and female subjects were approximately equal, 41.44 ±10.2 yrs and 45.77 ±7.11 years respectively. More than 76 % of the subjects were below 50 years of age in both male and female groups, with most common age group being 41 to 50 years (46%).

Table 1: Age and Sex wise distribution of the patients with ACLF

Age group	Male	Female	Total
16 - 30 yrs	0	5	5
31 - 40 yrs	10	3	13
41 - 50 yrs	21	7	28
51 - 60 yrs	12	2	14
Total	43 (71.7%)	17 (28.3%)	60 (100%)

The most frequent symptoms reported by the patients with ACLF in our study were Jaundice 60(100%) and abdominal distension (ascites) 55(91%). Other symptoms were altered sensorium (encephalopathy) 36(60%), anorexia 34(56 %), fatigue 25(41%), pedal edema 20(33.3 %), clinically palpable spleen 22(36.6), fever 12(20 %) abdominal pain & GI bleeding each 08 (13.3%). Among the GI bleeding patients 2 patients had Hematemesis only, 6 patients had only malena & 1 patient had both. Among HE patients 13(21%) had grade 1-2 HE & remaining 23(38 %) patients had grade 3-4 hepatic encephalopathy.

Table 2: Clinical Profile of patients with ACLF (n=60)

Symptom	Frequency	Percent
Anorexia	34	56%
Fatigue	25	41%
Fever	12	20%
Pain abdomen	08	13.3%
GI bleeding	08	13.3%
Hematemesis	03	5%
Malena	07	11.6%
Jaundice	60	100%
Pedal edema	20	33.3%
Hepatic Encephalopathy	36	60%
Grade 1-2	13	21%
Grade 3-4	23	38 %
Clinical Ascites	55	91%
Palpable spleen	22	36.6%

In our study the mean ± SD hemoglobin level was 9.8 ± 2.13, the median (range) total leukocyte count was 9.6 ×10⁹/L (6.5 -29.6 ×10⁹/L) and median (range) total platelet count was 88.4×10⁹/L (78- 312×10⁹). The median (range) serum total bilirubin was 21.84 ± 5.51 mg%. Median (range) AST was found greater than median ALT level in our study population, 236.6 IU/L (122 -2423 IU/L) and 149.5 (98.4-2664IU/L) respectively. The median (range)

ALP was within normal limits 256.8 IU/L(196.3-356.0 IU/L).The mean \pm SD serum albumin was below the lower limit of normal, 2.20 ± 0.52 gm /dl and the mean \pm SD INR

was 2.25 ± 0.32 . The mean \pm SD serum creatinine was 2.53 ± 0.59 mg/dl and mean \pm SD serum sodium was 127 ± 4.76 mEq/L.

Table 3: Laboratory parameters at admission in patients with ACLF (n=60)

Lab parameter	Descriptive statistics
Haemoglobin (gm/dl, Mean \pm SD)	9.8 \pm 2.13
Total Leucocyte count ($\times 10^9$ /L, Median, Q1-Q3)	9.6(6.5-29.6)
Total Platelet count ($\times 10^9$ /L, Median, Q1-Q3)	88.4(78-312)
Total Bilirubin (mg/dl, Median, Q1-Q3)	21.84 \pm 5.51
AST (IU/dl, Median, Q1-Q3)	236.6(122-2423)
ALT (IU/dl, Median, Q1-Q3)	149.5(98.4-2664)
Alkaline Phosphatase (IU/dl, Median, Q1-Q3)	256.8(196.3-356.0)
Serum Albumin (gm/dl, Mean \pm SD)	2.20 \pm 0.52
INR (Mean \pm SD)	2.25 \pm 0.32
Serum Creatinine (mg/dl, Mean \pm SD)	2.53 \pm 0.59
Serum Sodium (mEq/L, Mean \pm SD)	127 \pm 4.76

Discussion

This syndrome of acute-on-chronic liver failure (ACLF) has recently been recognized which has considerable heterogeneity in the mode of presentation and carries high mortality rate. There was no universally accepted definition for ACLF till now, but recently many study groups have proposed many definitions. Among these definitions what we considered for defining ACLF patients in our study was APASL (Asia Pacific Association for the Study of Liver) consensus -acute hepatic insult manifesting as jaundice (total serum bilirubin ≥ 5 mg %) and coagulopathy (INR ≥ 1.5), complicated within 4 weeks by ascites and encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease. In this study we also classified our patients according to EASL-CLIF 2013 (European Association for Study of the Liver Consortium – Chronic Liver Failure) the only available grading system for ACLF as of now, in to 4 grades based on the organ failure in ACLF patients. Total study population was 60 patients [7-8]. Most of the patients in this study were middle aged, below 50 years (76%), between 30 -50 years, near to half of the patients were in the age group of 41-50 years, suggesting that syndrome usually affects young cirrhotics and results in significant morbidity and mortality in the prime years of life of cirrhotic patients. In confirmatory to our observations, other studies from our country have noted similar mean age of presentation ranging from 36 to 45 years. Male predominated in our study by 2.5 times and male predominance from 2.3 to 3 times has been observed in other Indian studies. This male predominance observed in ACLF patients may be related to the underlying liver disease like chronic hepatitis B and alcoholic liver disease, which are more commoner in males. However a study from European country report older median age of presentation (57 years.), This might be related to late onset of cirrhosis in their population, moreover in this study the gender ratio was equal.

Apart from jaundice (inclusion criteria) the most frequent presentation in our study was Coagulopathy. Almost all of the patients in our study had an INR > 1.5 , with a mean INR of 2.25 and INR ≥ 2.5 was associated with poor outcome. This was in concordance with other studies from South East Asia, that higher Prothrobine time is a significant risk factor for mortality. The other ACLF defining features in the present study were Ascites (clinically 76 % and sonographically 91%) and Hepatic encephalopathy 36 (60

%). Other studies have also reported ascites ranging from 50 %-80%, HE ranging from 22%- 60%, which are consistence with our study results. Although ACLF and Acute Liver failure (ALF) manifest more or less in the similar fashion and affect previously asymptomatic individuals. However, ascites appears helpful in identifying ACLF as it was present in 91% cases, in this study and in 62% - 80% in previous reports, where as published reports could detect ascites in < 16 % of ALF cases. Hepatic encephalopathy is a universal feature of ACLF (due to defining criteria) but in ACLF it is observed less frequently (60% in this study and 22%- 60% in other previous reports).

Upper GI bleeding was less frequently reported by our patients but esophageal varices could be identified in more than 93% patients. Studies have reported frequency of GI bleeding ranging from 11%- 24%, also presence of bleed and grade of varices were found to affect the outcome of patients with ACLF. Even though most of our patients had grade 3-4 esophageal varices (34 out of 56) bleeding was in frequent in our patients.

More than half of the patients in this study had bilirubin > 15 mg % with mean serum bilirubin level 21.84 mg%. Other studies from our country have reported mean bilirubin levels ranging from 8.52 to 19.50mg%. Bilirubin levels were found to be significantly higher in the non-survivors in the present study as well as in other studies. This was substantiated by various studies employing MARS in management of patients with ACLF which found improvement in encephalopathy, CTP scores and short term mortality and hypothesized that improvement in this parameters could be partly due to the decline in levels of serum bilirubin after MARS. Thus it can be assumed that bilirubin levels may affect the prognosis of patients with ACLF. In this study median AST and median ALT levels were 236.60 and 149.50 respectively, with AST to ALT ratio of 1.58:1. The median AST was found to be 2.42 times greater than the median ALT levels among survivors and about 3.15 times in nonsurvivors in this study. However serum levels of liver enzymes did not found to affect survival of patients in our's as well as other studies [9-10].

Conclusion

- A total of 60 patients were enrolled in our study, most of the patients were below 50 years (73.3%) of age and males out numbered females by 2.7 times.

- The Median (range) of hospital stay was 12 days (4-36). Three months mortality was 50 %. In hospital mortality rate was 38.33% (n=23), 7(11.66%) patients died on follow-up within three months.
- The presenting features were Ascites (91%), Hepatic encephalopathy (60%) and less than 50% of patients reported constitutional symptoms like anorexia being the most common, followed by fatigue, pedal edema, fever and GI bleeding.
- The median TLC was $9.6 \times 10^9/L$, median platelet count was $88.4 \times 10^9/L$, median total bilirubin was 21.84mg%, with more than half of the patients having bilirubin >15 mg%. Nearly half of the patients had an INR of >2.5(48.3%). Mean serum Serum Creatinine was 2.53 mg% and mean serum sodium was 127mEq/L.

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