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A study on outcome of patients with acute-on-chronic liver failure at a tertiary care hospital

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Abstract
Acute-on-chronic liver failure (ACLF) is relatively recent entity and is not well described in the literature. The term acute-on-chronic liver failure was first used in 1995 to describe a condition in which two insults to the liver are operating simultaneously, one of them being ongoing and chronic and the other one acute. However, a clear definition of ACLF is still lacking, and this term is being used to mean different entities by different clinicians. Any patient who had underlying chronic liver disease with superimposed acute insult is being labeled as having ACLF. Whatsoever may be the case the most important is the denominator, the presence or absence of underlying liver disease. Prospectively collected data of all patients included demographics, clinical presentation, course in hospital and outcome. All patients had routine hematological biochemical and liver function tests. The etiology of superimposed acute event and chronic liver disease was investigated in detail and prognostic scores were calculated within 24hrs of admission. 60 patients included in our study were followed up for next three months, of which 30 patients died and 30 patients survived. All patients were classified in Child-Pugh class based on CTP score. There were only three patients Child-Pugh class A and none of them died. Child- Pugh class B had 10 patients, out of these 2 patients died & 8 patients survived. Total 47 patients were classified in Child-Pugh class C and 28 (59.57%) & this difference was statistically significant (p=0.013). According EASL-CLIF consortium grading, 23 out of 30 patients of Grade 3 ACLF, 5 out of 16 Grade 2 ACLF, 2 out of 11 Grade 1 ACLF & none of the Grade 0 ACLF patients died. These findings are statistically very much significant (P=0.0001). Even MELD score was significantly high among Non survivors when compared to the Survivors. (30.04 ± 2.37 Vs 25.53 ± 1.81) (p=0.0001).

Keywords: ACLF, child-Pugh class, liver function tests

Introduction
Liver failure can develop as an acute liver failure, acute-on-chronic liver failure (ACLF), or a chronic decompensation of an end stage liver disease. Acute and chronic liver failure are well understood and defined entities, whereas ACLF is an enigmatic entity because of considerable heterogeneity in its mode of presentation and also associated with variable mortality of about 40 to 66% (Falk forum). Acute-on-chronic liver failure (ACLF) is the result of an acute insult superimposed on previously symptomatic and asymptomatic chronic well compensated liver disease. The pathophysiological basis of ACLF is due to precipitating events, such as super added Hepatotropic infections, sepsis, hepatic inflammation, drugs or bleeding, which induce an inflammatory response of the liver with resultant end-organ failure of the circulatory system, brain, liver and kidney [1, 2].

Acute liver failure is a devastating multiorgan syndrome characterized by sudden and severe liver cell dysfunction in previously healthy individual. The first definition of acute liver failure was first introduced by Trey & Davidson in 1979, who described fulminant hepatitis as, “a potential reversible condition, the consequence of severe liver injury, in which the onset of hepatic encephalopathy was within 8 weeks of the first symptoms of illness, & in the absence of preexisting liver disease”. The most widely accepted definition of acute liver Disease in 2005 (AASLD) includes evidence of coagulation abnormality, usually an INR> 1.5, and any degree of mental alternation (encephalopathy) in a patient without preexisting cirrhosis and with an illness of <26 weeks duration [3, 4].

Acute-on-chronic liver failure (ACLF) is relatively recent entity and is not well described in the literature. The term acute-on-chronic liver failure was first used in 1995 to describe a condition in which two insults to the liver are operating simultaneously, one of them being

ongoing and chronic and the other one acute. However, a clear definition of ACLF is still lacking, and this term is being used to mean different entities by different clinicians. Any patient who had underlying chronic liver disease with superimposed acute insult is being labeled as having ACLF. Whatsoever may be the case the most important is the denominator, the presence or absence of underlying liver disease [5].

There is a lack of uniformity in diagnostic criteria of ACLF with many unresolved and contentious issues as well; for example, what constitutes the chronic liver disease in ACLF. The spectrum of underlying chronic liver disease can range from bland steatosis to hepatitis to compensated cirrhosis to decompensated cirrhosis. Similarly, what constitutes the acute insult; Hepatotropic viruses, toxins, sepsis, or even a variceal bleed? Moreover, the definition of liver failure in ACLF has been imprecise in terms of which criteria to include; level of bilirubin and the time period of deterioration from the onset, initiating event to be accepted as jaundice, or any symptom pertaining to hepatic dysfunction. There is no consistent definition of ACLF in the literature and studies done earlier on ACLF have used their own definitions and inclusion criterion. The first working definition of ACLF was proposed by Sen *et al*. in 2002, which defines ACLF as; 'Acute deterioration in liver function over a period of 2-4 weeks, usually associated with a precipitating event, leading to severe deterioration in clinical status, with jaundice and hepatic encephalopathy and/or hepatorenal syndrome, with a high SOFA/APACHE II score'. However even Sen *et al*. have not defined the precise level of serum bilirubin and the coagulopathy has not been included in the definition. The cut-off level of serum bilirubin for inclusion in different studies varies widely. Arbitrarily cut-off levels of serum bilirubin ranging from 6-20 mg/dL have been employed. Similarly criteria vary when defining the components of liver failure like ascites, coagulopathy, hepatic encephalopathy, hepatorenal syndrome and variceal bleeding [6].

Methodology

The diagnosis of CLD will be based on

1. Supportive history along with clinical findings,
2. Biochemical (low serum albumin, A/G reversal),
3. Ultrasonography imaging (heterogeneous echo texture of liver with irregular outline, altered liver size depending on the etiology, dilated portal vein with Porto- systemic collaterals), &
4. UGI endoscopy revealing esophageal varices grade ≥ II.

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.

Methods

Prospectively collected data of all patients included demographics, clinical presentation, course in hospital and outcome. All patients had routine hematological biochemical and liver function tests. The etiology of superimposed acute event and chronic liver disease was investigated in detail and prognostic scores were calculated within 24hrs of admission.

Results

There was no significant difference among survivors survivors and non survivors with respect to the development of ascites, esophageal varices or SBP, but there was highly significant difference in terms of INR, most of the patients with higher INR (>2.5) were died 22 out of 27, whereas only 8 out of the 33 died with INR 1.5 to 2.5 (*P*=<0.0001).Higher number of patients developed sepsis in the non-survivors (60%), as compared to the survivors (16%) and this difference was also statistically highly significant (*p*=<0.001). Similar results are seen in terms of Renal failure, 20 (66.6%) out of 30 of non survivors developed renal failure, whereas only 5 (16.6%) out of 30, developed renal failure (*p*=0.001). Most of the non survivors also developed 95 ero prevalen (<130 mEq/L) as compared to Survivors. This difference was also statistically significant (*p*=0.001).

Table 1: Complications in patients with ACLF (n=60)

Complication		Survivors (n=30)	Non survivors (n=30)	*P* value
Ascites		22 (73.3)	23 (76.6)	0.902
Hepatocellular carcinoma		0 (0)	1 (3.3)	0.912
Coagulopathy				
	INR < 1.5	0 (0)	0 (0)	
	INR 1.5 – 2.5	25 (83.3)	08 (26.6)	<0.0001
	INR > 2.5	5 (16.6)	22 (73.3)	
Esophageal varices		27 (90.0)	29 (96.6)	0.319
	Grade I – II	13 (48.1)	09 (31.03)	0.285
	Grade III – IV	14 (51.8)	20 (68.9)	0.118
Sepsis		5 (14.7)	18 (69.2)	< 0.001
SBP		4 (33.3)	8 (66.6)	0.197
Hyponatremia				
	Na > 130	16 (53.3)	02 (6.6)	<0.001
	Na <130	14 (46.6)	28 (93.3)	
Renal failure		5(20)	20 (80)	<0.001
Hepato-renal syndrome		1 (3.3)	2 (7.7)	0.402

60 patients included in our study were followed up for next three months, of which 30 patients died and 30 patients survived. All patients were classified in Child- Pugh class based on CTP score. There were only three patients Child-Pugh class A and none of them died. Child- Pugh class B had 10 patients, out of these 2 patients died & 8 patients survived. Total 47 patients were classified in Child-Pugh class C and 28 (59.57 %) & this difference was statistically significant (p=0.013). According EASL-CLIF consortium grading,23 out of 30 patients of Grade 3 ACLF, 5 out of 16 Grade 2 ACLF, 2 out of 11 Grade 1 ACLF & none of the Grade 0 ACLF patients died. These findings are statistically very much significant (P=0.0001).Even MELD score was significantly high among Non survivors when compared to the Survivors. (30.04 ± 2.37 Vs 25.53 ± 1.81) (p=0.0001).

Table 2: Comparison of prognostic factors between survivors and non survivors

Prognostic factor	Survivors (n=30)	Non survivors (n=30)	*P* value
CPT score class			
A	3 (10)	0 (0)	
B	8 (26.6)	2(6.6)	0.013
C	19(63.3)	28(93.3)	
EASL-CLIF grading			
Grade 0	03 (10)	0(0)	
Grade 1	09 (30)	2 (6.6)	0.0001
Grade 2	11 (36.6)	5 (16.6)	
Grade 3	07 (23.3)	23 (76.6)	
MELD score (Mean ± SD)			
	25.53 ± 1.81	30.04 ± 2.37	0.0001

Discussion

In this study the mean Serum albumin, Creatinine and sodium has been significantly differ among survivors and non-survivors. This findings are in accordance with other studies, underlies the fact that patients with ACLF have common pathophysiological alteration irrespective of other factors like nature of acute insult, age, etiology of underlying cirrhosis etc.

Sepsis was noted in a 23 out of 60 (38.3%) of ACLF cases and it was 3.6 times more frequent (60%) in fatal cases than survivors (16%). Other studies from our country as well as western countries have reported sepsis varying from 25-54%. The frequent occurrence of sepsis in our study as well as in other reports highlights fact that the patient with ACLF as with those of ALF are highly susceptible to infections. Investigators have even demonstrated that patients with ACLF have immunological defects similar to that seen in sepsis, the TNF-α production and HLA-DR expression were severely decreased compared to subjects with stable cirrhosis. SBP was detected in 20% of the cases in the present study, other study have also reported almost similar figures ranging from 7 to 20%.

In this study 41% and 5% patients developed renal failure and HRS respectively, and most of them not survived. However a recent Indian study reports similar figure, where 35% developed renal failure and it was shown to be an independent predictor of mortality. Studies from China on acute on chronic hepatitis B liver failure reported higher incidence of HRS ranging widely from 16% to 63%. Considering the data from our study and from other studies it can be concluded that occurrence of renal failure or HRS portends poor prognosis.

Most frequent acute evet leading to ACLF was hepatotrophic viral infections (HEV/HAV/HBV reactivation) studies from the Indian subcontinent have reported superadded HEV infection as a frequent cause of acute decompensation in patients with ACLF. In the present study super imposed HEV infection was identified in 16.7% (10 out of 60) of patients as the most common etiological agent leading to acute hepatic compensation. Recently in a largest series from our country on retrospectively analyzing 3220 patients of cirrhosis with superimposed acute viral hepatitis due to HEV or HAV, 80 patient were identified to have HEV related ACLF with mortality rate of 43.80%. This study has few drawbacks as they have especially sought patients of ACLF which were due to superadded HEV or HAV infection and have excluded patients with ACLF due to other causes like acute HBV infection or reactivation, alcohol, hepatotoxic drugs, HCC and other. They have retrospectively studied patients who were diagnosed cases of cirrhosis. Other studies from the Indian subcontinent have identified HEV as a cause of ACLF ranging from 20-43%. The higher rates of HEV as reported by these studies may be due to the fact they have only studied HEV related ACLF. A recent study from another South East Asian country has reported HEV as a cause of ACLF in 21% of cases [7, 8].

In terms of mortality rate in patients with HEV related ACLF our data is similar to other previous studies. Out of 10 patients of HEV related ACLF 4 patients died in our study (40%). Most of the other studies from South East Asia have also reported higher mortality rates ranging from 43% to 66% in HEV related ACLF. However Kumar *et al*. (2007) [3, 4, 12] observed only 14% mortality in such cases, which differs with our observation. This discrepancy in the mortality rates might be due to heterogeneous population of patients with CLD included in various studies. The higher the mortality rate (43.8%) as perported by Radhakrishna *et al*. may be due to the fact that they have retrospectively studied already diagnosed cases of cirrhosis, these findings suggest for the need for the larger, multi-centre studies with similar cohort and universal protocols. It is clearly evident from the available data that HEV is emerging as an important cause of compensation in patients with CLD, this is especially true in countries like India where the standards of water hygiene and sanitation are poor. The prevalence of IgG anti-HEV antibodies in patients of chronic liver disease varies from 17.5% to 56%, so these patients are good candidates for HEV vaccination. A recent trial on safety and efficacy of recombinant protein HEV (rHEV) vaccine by Shreshtha *et al*. (2007) from Nepal, has demonstrated rHEV vaccine to be 95.5% efficacious. Therefore it will be

judicious to consider HEV vaccination of patients with CLD once this vaccine is freely available, especially in endemic countries like India [9].

HAV infection has also been recognized as a cause of acute seroprevalence in ACLF. We found only five patients having superadded HAV infection leading to ACLF and out of them one died. HAV has been more often documented in western studies, since the 97s seroprevalence of HAV is low due to better hygienic conditions. In a landmark study by Vento *et al*. (1998) from Italy, 432 HAV seronegative chronic hepatitis C patients, were followed up for 7 year and found that 17 patients had superimposed HAV infection, of which 7 (41%) had fulminant hepatitis and six of them died. So far only one study from India has identified large number of HAV related ACLF cases, but this study has retrospectively analyzed 3320 patients of cirrhosis over 6 years duration with superadded HAV infection, so this may be reason for high rate of HAV related ACLF in their study. Otherwise HAV related ACLF has been infrequently reported from India, Kumar *et al*. (2008) [3, 4, 12] had reported HAV in 4% (2/48) of patients, which is similar to our study. India is considered hyper endemic for HAV and most of the adults have acquired protective anti-HAV antibodies through subclinical HAV exposure in childhood. During recent years, several reports from developing nations have suggested a shift in the HAV epidemiology from high to intermediate or low endemicity (Barzaget *et al*. 2000; Lee *et al*. 2000) [7]. In India HAV seroprevalence in healthy adult population ranges from 26.2% to 92%. Various studies from India has reported very high HAV seroprevalence in patients of CLD from 95% to 97% [10].

But the important issue is, whether there is need for vaccination against HAV in patients with CLD. The CDC recommends that all patients with CLD undergo hepatitis A vaccination (MMWR 1999). Although HAV vaccination in patients with chronic HBV or HCV infection showed seroconversion rates similar to healthy control but poor seroconversion rates in decompensated cirrhotics with lower anti-HAV geometric mean titers ranging from 0 to 103 published literature supports the recommendation that HAV vaccine be administered early in the natural history of CLD when immunogenicity rates are high. But strategy regarding routine HAV vaccination in patient with CLD in our country cannot be firmly delineated from the presently available studies. Since HAV is infrequent cause of ACLF and the number of IgG anti HAV negative patients is small, it will be more cost effective to perform serology prior to vaccinating them (the cost per test for lgG anti HAV is Rs.250/- whereas cost of vaccine is rs.1200/-). Therefore routine vaccination against HAV in patients with CLD in India will be failure exercise [11].

In our study we identified HBV reactivation in 3 cases (5%), with no significant difference among survivors and nonsurvivors. We could not find even single HBV super infection in our patients. Data on HBV super-infection in patient with CLD are very scarce and limited to few case reports only, but a recent report from India by Garg *et al*. have documented HBV reactivation in 28% (17/60) of cases. Although it is difficult to distinguish acute HBV infection from reactivation, we relied on lgM anti-HBC levels and disappearance of HBsAg to distinguish between the two. In our laboratory lgM anti-HBc is being reported as ratio of sample to cutoff (S/CO), and as suggested by Rodella *et al*. (2006) a threshold of 10 S/CO seems best suited for differentiating acute from chronic hepatitis (higher titer in acute infection), we took help of this criteria when the diagnosis was in doubt. Patients who cleared HBsAg from their serum after six months of follow up were considered to have acute HBV infection in the past. It is important to recognize and differentiate reactivation from acute HBV hepatitis since former frequently results in liver failure. Role of antiviral in management of HBV reactivation is limited. In a recent randomized placebo controlled trial by Garg *et al*. [9] Abstract from Delhi have found better survival in tenofovir group as compared to placebo (64% Vs 15%, p=0.03), also there was significant decline in the HEV DNA levels, improvement in CTP ad MELD scores in the tenofovir group [12].

Conclusion

- Most of the non survivors were also found to have higher MELD scores, which significantly co related with the mortality rate. (p=0.0001).
- We also classified our patients, according to the only available ACLF Grading system EASL-CLIF consortium 2013 grading. Mortality were found to be very high among the higher grades of ACLF when compared to lower grades. (76.6%, 31.2%,18.1% & 0% in Grade 3, Grade 2, Grade 1 & Grade 0 respectively).

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