

Original Research Article

Descriptive study of clinical profile and outcome in patients of acute on chronic liver failure, at a tertiary care center in Northern India

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ABSTRACT

Background: Acute-on-chronic liver failure (ACLF) is a recently described syndrome that is characterized by abrupt deterioration in patients with chronic liver disease (CLD) and has high short-term mortality. The aim of this study was to describe the clinical profile, causes and outcomes of ACLF at a tertiary care centre in Northern India.

Methods: In this descriptive study of 50 consecutive patients, were included, between August 2015 to January 2018, who were admitted and diagnosed as ACLF as defined by APASL. Causes of acute precipitating event and CLD and outcomes were assessed.

Occurrence and severity of organ failure was also assessed.

Results: 48 (96 %) were males and 2 (4%) were females with male to female ratio was 24:1. The mean age of male and female subjects was similar, 40.7±9.9 years and 39.2±9.4 years respectively. The most common cause of CLD was alcohol in 50% cases and next most common cause was hepato-tropic viruses HBV infection in 20%, HCV in 6% cases and there was unknown cause in 12 % cases. The most common precipitating factor of acute decompensation was alcohol in 50% cases, hepatotropic viruses in 30% cases. Excluded sepsis and GI bleed as precipitating events. The combined mortality at the end of 1-month and 3-months, in our study was 60%. CLIF-SOFA score was found to be the most reliable scoring system to discriminate between survivors and non survivors.

Conclusions: Alcohol was the commonest precipitating cause of ACLF. Organ failures (OFs) are independently predictive of mortality.

Keywords: ACLF, CLD, Cirrhosis, UGI Bleed, HBV infection, HCV Infection

INTRODUCTION

ACLF is a recently described syndrome that is characterized by abrupt deterioration in patients with CLD and has high short-term mortality.¹

It has become pertinent to distinguish ALF from ACLF and simultaneously to understand that decompensated

state of CLD are different entities which will require different approaches.

The Asian Pacific association for study of liver disease (APASL) defines Acute on chronic liver failure as acute hepatic insult manifesting as jaundice (bilirubin >5 mg/dl) and coagulopathy (INR>1.5), complicated within

4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed CLD.²

APASL includes hepatic insults as causes of acute decompensation, whereas European association for the study of the liver and American association for the study of liver diseases (EASL-AASLD) includes both hepatic and non-hepatic causes (like sepsis and variceal bleeding) as pre-capitating factors.

EASL-AASLD defined ACLF as ‘an acute deterioration of pre-existing CLD, usually related to a precipitating event and associated with increased mortality at three months due to multisystem organ failure.’

The EASL-AASLD definition includes only cirrhotic, whereas the APASL definition includes both cirrhotic and non-cirrhotic.

The world gastroenterology organization working party gave a unifying definition combining the EASL-AASLD and APASL criteria and categorized patients into different categories based on severity of underlying CLD, namely, no-cirrhosis, compensated cirrhosis, and decompensated cirrhosis.³ One of the largest published studies on ACLF has been by the Indian National Association for Study of the Liver (INASL).⁴

METHODS

In this descriptive, observational study, 50 consecutive ACLF patients, diagnosed as per the APASL criteria, admitted between August 2015 and January 2018, at Command hospital (Western command), Panchkula, Haryana, India, were included. The primary objective was to study the clinical profile, namely, precipitants, course and outcomes of ACLF patients.

Inclusion criteria included patients above 18 years of age, with hepatic insults, with or without prior decompensation, who were diagnosed as ACLF based on the APASL definition were included.

Exclusion criteria excluded patients who presented initially with Gastrointestinal haemorrhage, Patients who presented with septicemia at the onset, unless the primary infection involved the liver.

ACLF was diagnosed as per APASL definition. The diagnosis of cirrhosis was based on clinical, biochemical, imaging evidence, or prior liver biopsy with F4 changes.⁵

Acute hepatic insults included viral superinfection (hepatitis E virus/hepatitis A virus), viral reactivation (hepatitis B), continuous alcohol consumption, autoimmune flare, and drugs (anti-tuberculosis/anti-epileptics). Non-hepatic insults were classified as variceal bleeding, sepsis (spontaneous bacterial peritonitis, urinary tract infection, respiratory tract infection, cellulitis, and spontaneous bacteraemia).

Silent CLD was defined as patients with undiagnosed pre-existing CLD and no previous history of decompensation, overt CLD was defined as patients previously diagnosed as cirrhosis with or without decompensation.

Data collection collected at admission: age, gender, clinical presentation, laboratory parameters (hemogram, liver function tests, INR), CTP score, MELD, MELD-Na, SOFA, and CLIF-SOFA score at baseline. In addition, cause of acute hepatic decompensation, etiology of underlying CLD and outcomes were noted.⁶⁻⁸ A detailed history was taken (alcohol consumption, drugs, hematemesis, melaena, previously diagnosed hepatitis B and C). Each patient was tested for hepatitis B surface antigen, immunoglobulin M (IgM) hepatitis B core antibody, IgM antibody against hepatitis A (HAV), and IgM antibody against hepatitis E virus (HEV). The etiology of CLD was diagnosed as per the standard defined criteria.^{9,10}

All patients were managed with standard of care therapy. Patients with hepatitis B were started on antiviral drugs (tenofovir or entecavir). Renal replacement therapy was provided as required. Patients with variceal bleeding underwent endoscopic variceal ligation. Spontaneous bacterial peritonitis and hepatorenal syndrome were managed as per recommendations. Rifaximin and lactulose were started in patients with hepatic encephalopathy. Need for ventilator support as well as the need for and choice of antibiotics were decided by the treating clinicians. Patients were followed up during hospital stay, and outcome was noted. None of the patients underwent liver transplantation.

The study was approved by the ethics committees of the institution. Statistical analysis was carried out using SPSS version 20.

RESULTS

Gender distribution: A male preponderance was noted in this study, 48 (96%) were males and 2 (4%) were females with male to female ratio was 24:1. Alcohol abuse is higher in males in our country which could also play a role in the skewed sex distribution.

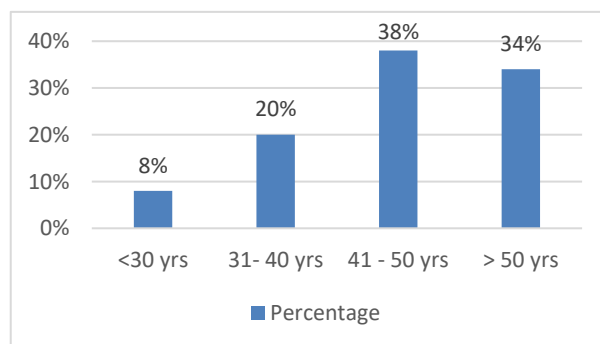


Figure 1: Age distribution.

Past history profile of patients with ACLF: Out of 50 patients, 8 (16%) patients had past history of viral hepatitis, 7 (14%) patient had history of surgery and 9 (18%) had prior history of blood transfusion. Only 13 (26%) patients were taking antiviral therapy while the rest of the patients were detected to have chronic viral hepatitis for the first time. History of decompensation in form of ascites or GI bleed was noted in 27 (54%) patients and 10 (20%).

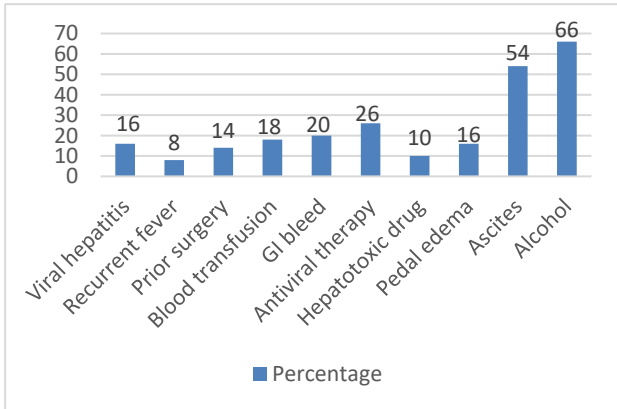


Figure 2: Past history profile of study population.

Clinical profile: The most frequent symptoms reported by the patients with ACLF in our study were jaundice (100%) and ascites (90%). Other symptoms were anorexia (60%), fatigue (24%), fever (30%), pruritus (12%), pedal oedema (36%) and pain abdomen (16%), oliguria (22%), weight loss (10%) and spontaneous bleeding (30%). Patients with history of alcohol binge within 4 weeks were 10 (20%). In this study 13 subjects (26%) developed gastrointestinal (GI) bleed during hospitalization.

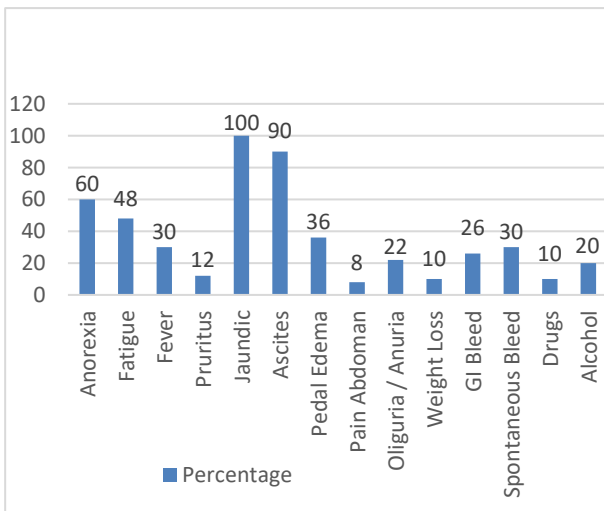


Figure 3: Symptom profile of study patients.

Clinical examination profile: On clinical examination all patients were icteric and 90% patients had ascites. Grade I-II and grade III-IV encephalopathy were noted in 28

(56%) and 18 (36%) patients respectively. Stigmata of CLD were seen in 76% patients, 52% had splenomegaly and 50% patients had pallor.

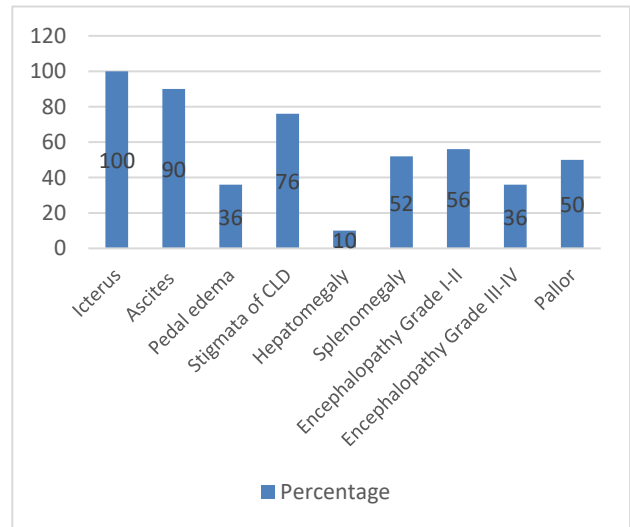


Figure 4: Clinical examination profile.

Precipitants of acute event: Precipitating factors of acute events leading to decompensation could be identified in 44 (88%) cases. Alcohol was responsible for hepatic decompensation in almost half of the cases 25 (50%). After alcohol, next most common etiology was hepatotropic viruses in 15 (30%) and drugs in 4 (8%).

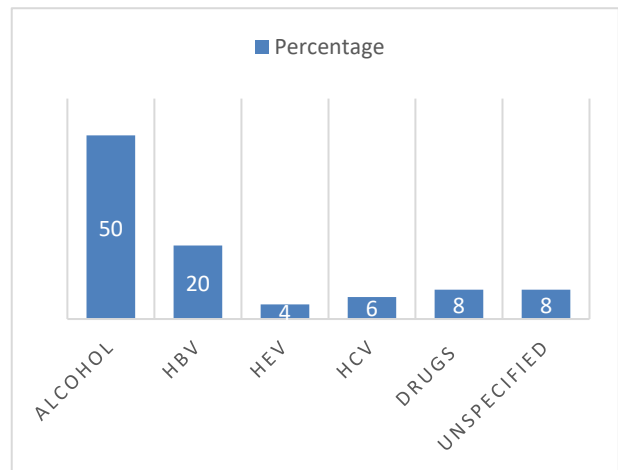


Figure 5: Precipitating factors of acute events.

Causes of CLD: Causes for CLD could be identified in 88% cases. Most common cause of CLD was alcohol in 50% of cases.

Complication in ACLF patients: Oesophageal varices was documented in nearly 40% of cases, hyponatremia in 23% cases followed by clinical coagulopathy in 18% cases. Sepsis was detected during course of hospitalization in 16% cases.

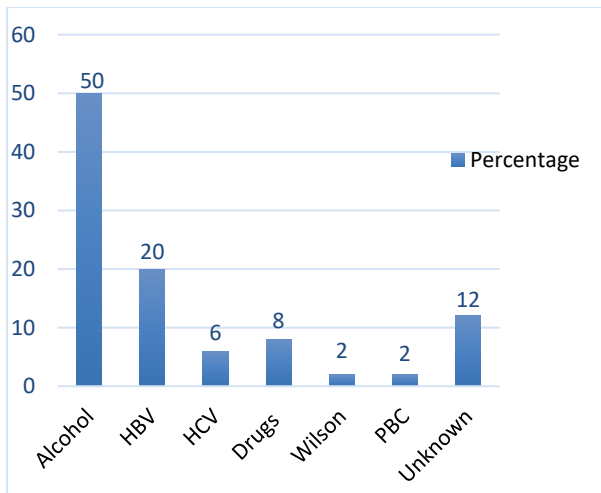


Figure 6: Causes for CLD.

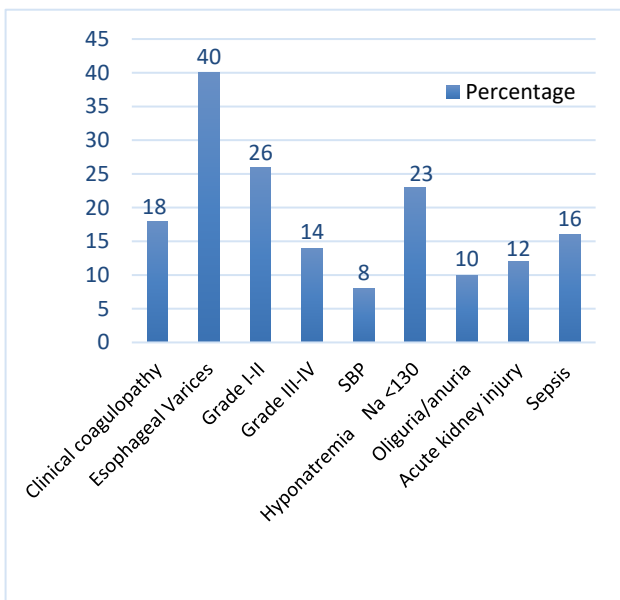


Figure 7: Complications.

Outcome of ACLF patients

Clinical profile of survivors Vs non-survivors: In this study 30 (60%) patients died during 1 month and 3 months follow-up. During follow-up male patients died were 29 and female patient 1. Among other parameters, fever, GI bleed and grade 3-4 hepatic encephalopathy were significantly higher in the non-survival group.

Comparison of laboratory parameters between survivors and non-survivors: Haemoglobin: Mean Haemoglobin for the non-survivor patients were highly significantly lower 9.7 gm% compared to survivors (11.2 gm%) (p<0.01). TLC: TLC, mean was higher among non-survivors 13513.33/cmm compared to survivors

(8734/cmm) and this difference was very highly significant with (p=0.001).

Table 1: Comparison of clinical profile between survivors and non-survivors.

Parameter	Survivors (%)	Non-survivors (%)	P (%)
Age (Years)	36±7	40±6	NS
Sex			
Male	19	29	0.02
Female	1	1	
Anorexia	12 (40)	18 (60)	NS
Fatigue	10 (41.6)	14 (58.3)	NS
Fever	5 (33.3)	10 (66.6)	<0.001
Pain Abdomen	3 (37.5)	3 (37.5)	NS
GI Bleed	4 (30.7)	9 (69.2)	<0.001
Hepatic encephalopathy			
Grade 1-2	10 (35.7)	18 (64.2)	NS
Grade 3-4	4 (22.2)	14 (77.7)	<0.01
Pedal oedema	8 (44.4)	10 (55.5)	NS
Ascites	20 (44.4)	25 (55.5)	NS

Comparison of predictive values of various scoring systems: The relative ability of various scoring systems to discriminate between survivors and non-survivors was assessed using the area under ROC curve. In general, concordant zee statistic of 0.05 is associated with chance alone. Whereas values greater than 0.7 was accepted as an indicator of useful test. Among all five scores, CLIF-SOFA, was found to be the most reliable scoring system to discriminate between survivors and non-survivors.

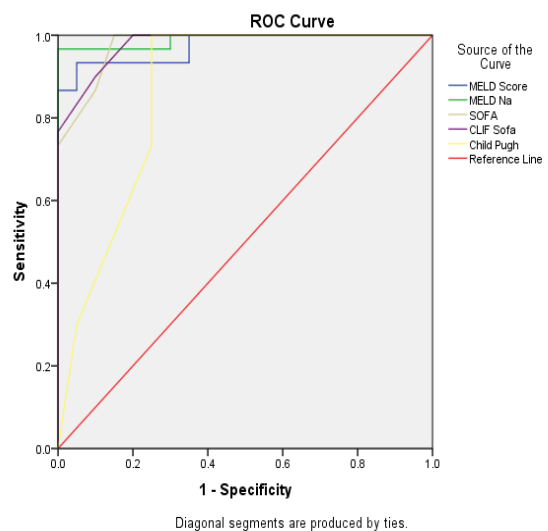


Figure 8: ROC for prognostic scoring systems.

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

Characteristics	Survival status		P value
	Survivors No. of cases (n=20) *	Non- Survivors No. of cases (n=30) *	
HB (gm%)	11.2	9.7	<0.01
TLC	8734	13513.37	0.001
Platelet (/cmm)	96500.00 (67500.00-110000.00)	76400.00 (62988.11-87000.00)	0.052
T. bilirubin (mg/dl)	11.45 (6.50-13.35)	16.60 (12.70-18.63)	0.002
Direct bilirubin (mg/dl)	7.80 (4.20-10.40)	8.70 (8.50-12.10)	0.038
AST	158	310	0.034
ALT	87	141	0.053
Urea (mg/dl)	28.50 (18.50-43.50)	93.50 (73.00-144.91)	0.001
Creatinine (mg/dl)	0.90 (0.75-1.10)	1.85 (1.60-2.20)	0.001
INR	1.77 (1.65-1.78)	2.32 (2.13-2.89)	0.001
Ascitic Fluid WBC (cell/cmm)	268.00 (150.00-350.00)	450.00 (340.25-590.00)	0.003
Ascitic Fluid Protein(gm/dl)	2.15 (1.80-2.40)	2.10 (1.90-2.30)	0.637
Ascitic Fluid Albumin (mg/dl)	1.10 (0.90-1.30)	0.95 (0.65-1.20)	0.280
Ascitic Fluid SAAG	2.10 (1.85-2.60)	1.90 (1.40-2.29)	0.419

DISCUSSION

ACLF is characterized by liver cell dysfunction as a result of an acute insult superimposed on previously symptomatic and asymptomatic chronic well compensated liver disease and can be a devastating illness. The present study was carried out to evaluate the clinical profile of patients with ACLF; to study the outcomes of ACLF patients at 4 weeks and 3 months, to study the prognostic markers for predicting mortality at 4 weeks and 3 months. In the study, we included patient who fulfilled criteria for ACLF according to APASL guideline. Excluded sepsis and GI bleed as precipitating events and prospectively followed patients for 1 month and 3 months.

The patients in this study, 72.1%, patients, were between 30-50 years of age, suggesting that the syndrome usually affects and results in significant morbidity and mortality in the prime and productive years of the life of cirrhotic patients. Other studies from our country have noted similar mean age of presentation ranging from 36 to 45 years.^{11,12} Males predominated in our study by 24 times and similar male predominance has been observed in other Indian reports.¹²

The most frequent acute event leading to ACLF was alcohol 25 (50%) hepatotropic viral infections [HBV infection/reactivation in 10 (20%), HEV 2 (4%), and HCV 3 (6%) patients].

Studies from the Indian subcontinent have reported superadded HEV infection as a frequent cause of acute decompensation in patients with ACLF, ranging from 20-43%.¹³⁻¹⁵ The higher rates of HEV as reported by these studies may be due to the fact that they have only studied

HEV related ACLF. Most studies from South East Asia have reported high mortality rates ranging from 43% to 66% in HEV related CLD.^{15,16}

The prevalence of IgG anti-HEV antibodies in patients of CLD varies from 17.5% to 56%, so these patients are good candidates for HEV vaccination.^{15,16} A recent trial on safety and efficacy of recombinant protein HEV (rHEV) vaccine by Shreshtha et al from Nepal, has demonstrated rHEV vaccine to be 95.5% efficacious.¹⁷ 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.

So far only one study from India has identified large number of HAV related ACLF cases, but this study has retrospectively analysed 3220 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.¹² Otherwise HAV related ACLF has been infrequently reported from India, Kumar et al had reported HAV in 2/48 (4%) of patients, which is similar to our study.¹³ In India HAV seroprevalence in healthy adult population ranges from 26.2 to 92%.^{18,19}

Published literature supports the recommendation that HAV vaccine be administered early in the natural history of CLD when immunogenicity rates are high. However, it may be more cost effective to do anti HAV serology rather than across the board vaccination strategy.

In this study identified HBV reactivation in 7.38% and superimposed acute HBV infection in 8.31% of cases, with no significance difference among survivors and non-survivors. Data on HBV superinfection in patients with

CLD is very scarce and limited to few case reports only, but a report from India by Garg et al has documented HBV reactivation in 2/48 (28%) of cases.²⁰ Although it is difficult to distinguish acute HBV infection from reactivation, relied on IgM anti-HBc levels and disappearance of HBsAg to distinguish between the two. Moreover, presence of IgG Anti HBc also supports reactivation. In our laboratory IgM anti-HBc is being reported as ratio of sample to cut off (S/CO), and as suggested by Rodella et al a threshold of 10 S/CO seems best suited for differentiating acute from chronic hepatitis (higher titer in acute infection).²¹ 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 antivirals in management of HBV reactivation is limited. In a recent randomized placebo-controlled trial, Garg et al, from Delhi, have found better survival in tenofovir group as compared to placebo (64% vs. 15%, $p=0.03$). Besides, there was significant decline in the HBV DNA levels, improvement in CTP and MELD scores in the tenofovir group.²⁰

Alcoholic hepatitis has been frequently reported in western studies as a cause of acute decompensation in patients of CLD. Identified 25 (50%) patients with alcoholic hepatitis to account for acute deterioration, out of which 16 (32%) patients died. Other studies have reported alcoholic hepatitis as an etiology of ACLF ranging from 12.5% to 50%.²²

Sepsis is a well-recognized complication of ACLF but whether it itself acts as an initial precipitating event is still debatable. Wasmuth et al in their study identified infection as a precipitating factor in 13 out of 27 cases of ACLF.²³ However, it is of note that these patients did not have septicaemia, rather had a cytokine profile similar to patients with sepsis, therefore they reported as sepsis like immune paralysis. Sepsis plays an important role in the progression and management decisions of ACLF, but whether it itself acts as an initial precipitating event was debatable. The existing literature from the United Kingdom and the United States has included sepsis as an integral cause for the development of ACLF. However, it was argued that sepsis alone might not directly cause an acute hepatic insult but could result in worsening of the condition of the patient. Furthermore, sepsis per se can cause organ failure in cirrhotic patients without direct hepatic derangements. It was therefore not considered as a cause of acute insult. To bring homogeneity of the population under consideration of the hepatorenal syndrome of ACLF, it was proposed that any infectious agent directly afflicting the liver leading to acute derangement in its function should be included.² So therefore excluded sepsis as an acute insult in this study.

In this study mean bilirubin was 14.1 mg%. Other studies from our country have reported mean bilirubin levels ranging from 8.5 to 19.5 mg%.^{13,26} 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 these parameters could be partly due to the decline in levels of serum bilirubin after MARS.^{24,25} However major contributory factors in MARS related improvement is due to change in inflammatory cytokines, bilirubin also play minor role. Thus, it can be assumed that bilirubin levels may affect the prognosis of patients with ACLF. In this study the mean AST, ALT levels were 317.8 ± 498.2 IU/L and 392.3 ± 587.4 IU/L respectively. However, serum levels of liver enzymes were not found to affect survival of patients in this as well as other studies.

In this study the mean serum albumin and creatinine, has been found significantly higher among non-survivors. This finding is in accordance with other studies

ACLF is a critical illness both in terms of very high mortality rates. In the patients 1 month and 3-month mortality was 60% Other studies have also reported a very high short term mortality rate ranging widely from 43% to 86%.^{26,11} However mortality rate in most of the Indian studies reported applies to the HEV related ACLF only, as other acute insults have not been considered, whereas in this study we have considered other acute insults as well. On univariate analysis we found higher grades of encephalopathy, clinical coagulopathy, higher grade of varices and type II pattern biopsy, bilirubin, INR, creatinine, acute kidney injury, CTP, MELD and CLIF SOFA score to be predictor of mortality. Platelet count have also been found to affect the prognosis, but we did not find them significant.^{12,27} However two factors that have been consistently shown to predict the outcome in this study as well other studies are, coagulopathy and renal impairment.^{28,12}

In this study 29.5% of patients developed acute kidney injury, and only 1 patient survived at 3 months. A recent Indian study reported that 35% developed renal failure and it was shown to be an independent predictor of mortality. Studies from the China on acute on chronic hepatitis B liver failure reported high incidence of HRS ranging widely from 16% to 63%.^{28,29} Considering the data from our study and other studies it can be concluded that occurrence of renal failure or HRS portends poor prognosis.

ACLF presents with liver failure and can mimic acute liver failure. Though both have common underlying pathophysiology i.e. sudden and severe liver cell dysfunction in a previously apparent healthy individual, the basic difference is the presence of underlying CLD in a patient of ACLF. This has leads to the recognition and need for this separate entity. Patient of ALF recovers fully but those with ACLF who had otherwise occult liver disease are left with manifest liver disease once they

overcome acute insult. Hepatotropic viruses have been identified as the common acute insults in most of the cases of ACLF, other acute insult being sepsis and hepatotoxins either in form of alcohol or drugs. Since ACLF is an evolving entity and there are still some lacunae in understanding the natural history, precipitating factors of acute insult and long-term outlook of these patients. Controversy still exists whether to consider sepsis and GI bleed as an acute insult, so this has to be studied with respect to its pathophysiological effects on liver to assign them as definite acute insults. Prediction of prognosis based on the scoring system especially CLIF-SOFA score is important in patients of ACLF. Moreover, this is a treatable condition. Multicentric studies are needed with large number of patients with homogeneous inclusion criteria regarding the level of bilirubin and components of liver failure. Similarly, acute insults should be predefined so that clinical course with respect to particular acute insult could be better delineated as well as mortality rates can be appropriately defined.

CONCLUSION

Believe that this study though small, will be amongst the one of many that will be further required to elucidate the entity of ACLF which will convert, into improved outcomes in the future. In this study fever, UGI bleed, lower haemoglobin, increased Sr creatinine, leucocytosis and organ failures, have clearly been associated with statistically significant poorer outcomes, and believe that intuitive and aggressive management of these variables will result in improved outcomes for the patients of ACLF. Also believe that a uniform definition of ACLF will help to better characterise and evolve our understanding of this entity across the globe.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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