Acute on Chronic Liver Failure—In-Hospital Predictors of Mortality in ICU

Sujay Kulkarni, Mithun Sharma, Padaki N. Rao, Rajesh Gupta, Duvvuru N. Reddy

Department of Gastroenterology and Hepatology, Asian Institute of Gastroenterology, Hyderabad, India

Aims: We studied in-hospital predictors of mortality of acute on chronic liver failure (ACLF) in Indian patients. **Methods:** Patients admitted to the intensive care unit of our institute fulfilling the definition of ACLF based on the Asia-Pacific Association for Study of Liver Disease (APASL) consensus were included. Complete history and medical evaluation to assess the etiology of underlying liver cirrhosis and to identify the acute precipitating insult of worsening liver function was done. Data was prospectively recorded and various scoring systems and individual clinical and laboratory parameters were assessed to identify predictors of 28 days mortality. **Results:** 64 out of 240 patients screened for ACLF were analyzed in the study. Median age was 44 years and 53% were males. Alcohol was the primary cause of cirrhosis in 60.93%. Infections and active alcoholism was the main precipitating acute insult in 43% and 37% patients respectively. 28% patients had history of ingestion of hepatotoxic drugs as the acute insult. More than one acute insult was seen in 37.5% patients and type-II hepatic injury was the most common type. 28 days in hospital mortality was 43.75% and was highest in patients with sepsis (67.8%). Presence of hepato-renal syndrome and need for ventilation was associated with poor outcome. Though multiple variables were significant in predicting mortality on univariate analysis, yet on regression model only APACHE II and shock could significantly predict mortality with odds ratio of 3.18 and 9.14 respectively. Highest mortality was seen with cerebral and lung as organ failure and mortality increased as the number of organ failure worsened. CLIF-SOFA and APACHE-II scores having area under curve > 0.8 had higher ability to predict mortality. **Conclusion:** ACLF carries high short-term mortality and early intervention by liver transplantation should be considered in patients who shows high risk of mortality. (J CLIN EXP HEPATOL 2018;8:144–155)

Acute on chronic liver failure (ACLF) is a relatively new entity which was introduced to differentiate patients of chronic deterioration of liver cirrhosis as a part of natural history of the disease from those with deterioration due to a super-added acute hepatic or non-hepatic insult.

The definition of ACLF varies in the East from that followed in the West and have a different fundamental basis. The Asia-Pacific Association for Study of Liver Disease (APASL) defines ACLF as “an acute hepatic insult manifesting as jaundice (serum bilirubin > 5 mg/dl) and coagulopathy (INR > 1.5 or prothrombin activity < 40) complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease or cirrhosis and is

associated with high 28 days mortality”.¹ In contrast the working group from the American Association for Study of Liver Disease (AASLD) and the European Association for Study of Liver Disease (EASL) defines it as “an acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at three months due to multi-system organ failure”.^{2,3} While the EASL-AASLD consensus encompasses organ failure as the central component of ACLF, the key component in the APASL statement is liver injury. The need for this new entity was based on potential reversible nature of ACLF if the precipitating event can be controlled, failing which there is a high short term mortality of 50–90%.^{2–7} The acute insult in the Western world is usually alcohol and bacterial infections, while infections like reactivation of chronic hepatitis B predominate in the East.^{1,8} Data from India is diverse and studies have identified reactivation of hepatitis B as well as non-hepatic insults as common acute precipitant factors.^{9,10} This shows that etiological differences exist not only from west to east but also between different centers of same country.

Data from both the APASL and the EASL consortium have yielded varied results due the basic difference in definition of ACLF used by the two groups.⁸ The EASL consortium has devised a new Chronic-Liver-Failure-Consortium

Keywords: acute on chronic liver failure, intensive care unit, predictors, mortality, CLIF-SOFA

Received: 28 July 2017; **Accepted:** 17 November 2017; **Available online:** 23 November 2017

Address for correspondence: Mithun Sharma, Department of Gastroenterology and Hepatology, Asian Institute of Gastroenterology, Hyderabad, India.

E-mail: drmithunsharma@gmail.com

Abbreviations: ACLF: acute on chronic liver failure; APASL: Asia-Pacific Association for Study of Liver Disease; EASL: European Association for Study of Liver Disease

<https://doi.org/10.1016/j.jceh.2017.11.008>

Sequential-Organ-failure-assessment (CLIF-SOFA) scoring system to help prognosticate these patients and identify those who need immediate liver transplantation. Similar studies have been done from the Indian subcontinent as well as by the Indian National Association for Study of the Liver (INASL) consortium which involved retrospective data and supported the fact that organ failure predicts outcome.¹⁰⁻¹⁸

Our current study was a prospective study to identify the acute insults in ACLF and to identify predictors of in-hospital mortality in these patients which may help in identifying patients in need of urgent liver transplantation coupled with aggressive medical management to rectify the precipitating cause.

AIMS AND OBJECTIVES

The primary aim of the study was to assess the in-hospital predictors of 28 days mortality in ACLF for patients admitted to the Medical-Intensive-Care-Unit (MICU) in a tertiary care hospital. The secondary outcome was to study the clinical profile of these ACLF patients and identify the common underlying chronic and acute causes of liver injury.

MATERIALS AND METHODS

This was a prospective observational study conducted at the Liver Unit of Asian Institute of Gastroenterology, Hyderabad, India. The study was conducted between February 2015 to February 2016 and included patients admitted to the MICU of the Institute. To define ACLF, the definition recommended by APASL was used.¹ However, patients with sepsis were also included and infection and sepsis was considered as an acute precipitating factor.

The sample size was calculated considering a mortality of 40–50% in ACLF based on previous studies from the region and it was found that a minimum of 64 patients were required to achieve this observational result with a power of 80 percent and 0.05 type 1 error.^{15,17,19,20}

Inclusion Criteria

Patients who were admitted to the MICU of the liver unit between 18 years and 79 years and fulfilling the APASL definition of ACLF which included presentation with jaundice (serum bilirubin > 5 mg/dl) and coagulopathy (INR > 1.5) with development of ascites and/or encephalopathy within 4 weeks of onset were included in the study.

Exclusion Criteria

Patients with previously known hepatic decompensation in the form of ascites, encephalopathy or coagulopathy were excluded. Also patients with hepato-cellular

carcinoma and other malignancies, portal vein thrombosis were excluded.

The data collection was done in pre-designed format. A thorough history was taken with an intent to identify the cause of chronic liver disease as well as to find out the acute precipitating factor. The data recorded included complete demographic profile, details of clinical parameters (jaundice, ascites, gastro-intestinal bleed, grade of encephalopathy, records of vital parameters etc.). Laboratory investigations in all patients included complete hemogram, serum electrolytes, viral serology, autoimmune profile, liver function tests, serum creatinine, blood urea, prothrombin time, and INR. The patients were followed up till one month or in-hospital death at any point of time.

Diagnosis of underlying infection/sepsis which we included in our series was made by doing standard laboratory investigations which included blood, urine, sputum or ascitic fluid culture chest X-ray to identify any pulmonary infection, echocardiography to diagnose latent infective endocarditis and any other investigations as and when required. We considered the source of infection as unknown where all possible cultures did not show any bacterial growth at 48 h after collection in two consecutive sample.

The Child Turcotte Pugh (CTP) score, Model for end stage liver disease (MELD), Chronic liver failure consortium-sequential organ failure assessment (CLIF-SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score were calculated for all patients. MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium) was used for calculation of CTP, MELD and APACHE II score. SOFA calculator available online at www.clifconsortium.com was used to calculate CLIF-SOFA, number of organ failures and ACLF grade. Though the APASL definition was used for inclusion of patients, yet for sub-analysis, the organ failure and ACLF grading followed as per the CLIF consortium was used and is shown in Supplementary Table 1.

All patients received standard of medical care for liver cirrhosis as per protocol of the Institute. Patients presenting with acute variceal bleed underwent endoscopic variceal ligation (EVL) within 24 h of admission and also received medical care for gastro-intestinal bleed as per protocol. Spontaneous bacterial peritonitis and hepatorenal syndrome (HRS) were managed as per guidelines.^{21,22} Need for ventilator support and choice of antibiotics was based on the decision of the intensivist and based on the sensitivity profile of infections of the hospital. All patients were counseled for either living or deceased donor liver transplantation. However, due to paucity of organs coupled with financial constraints of the patients, transplantation could not be done in any of these patients (Table 1).

This study was reviewed and approved by the Asian Institute of Gastroenterology Institutional Review Board

Table 1 Clinical, Biochemical, Organ Failure Profile Among Survivors and Non-survivors: Univariate Analysis.

Variable		Non-survivors (n = 28)	Survivors (n = 36)	P value
Age in years [median (IQR)]		47.5 (37–54)	42 (37–52)	0.677
Sex (male: females)		25:3	30:6	0.720
Presense of ascites [n (%)]		27 (96.42%)	33 (91.66%)	0.411
Encephalopathy > 2[n (%)]		26 (92.85%)	10 (27.77%)	0.001
GI bleeding [n (%)]		6 (21.42%)	5 (16.12%)	0.435
Active alcohol abuse (only applicable to alcoholics) [n (%)]		16 (76.19%)	7 (36.84%)	0.006
Hemoglobin (gm/dl) [median (IQR)]		10.4 (7.2–11.8)	11 (9.7–11.9)	0.03
Total leukocyte count [median (IQR)]		13,200 (8850–15,925)	9250 (6700–11,675)	0.078
Platelet count (lakhs/mm ³) [median (IQR)]		1.5 (1.10–1.56)	1.58 (1.30–1.87)	0.364
Sodium, mEq/L [median (IQR)]		128 (120–134)	132 (128–135)	0.004
Potassium, mEq/L [median (IQR)]		4 (3.6–4.9)	3.6 (3.0–4.2)	0.006
Creatinine, mg/dl [median (IQR)]		2.5 (1.3–3.5)	1.1 (0.8–1.45)	0.001
Bilirubin level (mg/dl) [median (IQR)]		15.4 (7.8–25)	18.9 (14.3–23.9)	0.206
Albumin (g/dL) [median (IQR)]		2.15 (1.8–2.4)	2.4 (2.0–2.6)	0.135
International normalized ratio [median (IQR)]		2.56 (2.10–4.08)	1.81 (1.66–2.45)	0.001
Presence of SIRS on admission [n (%)]		24 (85.71%)	14 (38%)	0.001
Presence of sepsis [n (%)]		17/28 (68%)	9/36 (25%)	0.001
Shock on admission [n (%)]		11/28 (39.3%)	1/36 (2.8%)	0.011
MELD [median (IQR)]		36.15 (29.5–41.8)	26.8 (24.5–28.6)	0.001
CLIF-SOFA [median (IQR)]		15 (13–16)	10 (9–11)	0.001
APACHE II [median (IQR)]		23.5 (19–27)	13 (9–16)	0.001
CTP [median (IQR)]		14 (12–14)	12 (11–13)	0.001
ACLF grade ≥ 2[n (%)]		28 (100%)	15 (41.6)	0.001
Organ	Liver failure [n (%)]	15 (46.4%)	6 (16.7%)	0.001
	Kidney [n (%)]	24 (85.7%)	13 (36.1%)	0.001
	Cerebral [n (%)]	24 (85.7%)	0 (0%)	0.001
Failure	Circulatory [n (%)]	13 (46.4%)	1 (2.9%)	0.001
	Coagulation [n (%)]	13 (46.4%)	7 (19%)	0.001
	Respiratory [n (%)]	16 (57.1%)	1 (2.9%)	0.001

and the Institutional Ethics committee (AAIG/AHF IRB:36/2015). All participants or their legal guardian provided informed written consent prior to study enrolment. This study being non-randomized was not registered with clinicaltrials.gov.in.

Statistical Analysis

This was done using the Statistical Package for Social Sciences (SPSS 20th version) and MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium). All the continuous variables were expressed as mean and standard deviation. Median and inter-quartile range (IQR) and percentage frequency distribution for continuous and categorical variables respectively was done. Student's *t* test and chi-square test were used for comparing quantitative and qualitative data respectively. Cox-proportional regression model was used to see the effect of various

independent variables which were significant in univariate analysis. A *P* value (2 tailed) of <0.05 was considered as statistically significant. The ability to discriminate between survivors and non-survivors using different scoring system was assessed by receiver operating characteristic (ROC) curve. Sensitivity, specificity and cut off values for all the scores were obtained and the population at risk of death was assessed by Kaplan–Meir curve which were then compared by long rank test.

RESULTS

Out of the 240 consecutive patients of liver cirrhosis admitted to the MICU of the Institute, 164 patients were excluded as they did not fulfill the criteria of ACLF.¹ Of the remaining 76 patients of ACLF, further 12 patients were excluded from the final analysis as 10 patients took

discharge against medical advice within 72 h of admission, while one patient died within 6 h and another patient refused to sign the informed consent form (Figure 1).

Forty (62.5%) of these patients were diagnosed as cirrhosis of liver for the first time. The median age at presentation was 44 years (range 13–65 years) and 53 (82.81%) were males.

The median duration of development of ascites and/or encephalopathy was 13 (range 6–28) days. Ascites was present in 60 (93.75%) and encephalopathy was evident in 52 (79.68%) patients. Upper gastro-intestinal bleed was present in 11 (17.18%) patients and 7/11 (63.3%) were managed with EVL and argon plasma coagulation for gastric antral vascular ectasia and haemorrhoidal banding for bleeding internal hemorrhoids was required in 3/11 (27.2%) and 1/11 (9.09%) of these patients respectively.

Chronic Insult

Alcohol was attributed as the etiology of cirrhosis in 39 (60.93%) of patients while cryptogenic/non-alcoholic fatty

liver related cirrhosis was found in 22 (35.37%) patients. Underlying chronic hepatitis B and C was found to be the cause in 2 and 1 patients respectively. Wilson's disease was found in 2 patients. There was no statistical difference in the outcome (survival at 28 days) based on the underlying chronic etiology (Table 2).

Acute Insult

Infection was the main precipitating acute insult in 28/64 (43%) followed by active alcoholism in 24/64 (37%) patients. The most common identifiable source of infection was spontaneous bacterial peritonitis in 13/28 (46%) followed by urinary tract infection (UTI) in 8/28 (28%), lobar pneumonia in 6/28 (21.4%) and lower limb cellulitis in 1/28 (3.5%). Culture positive bacterial peritonitis was found in 7 patients and all the UTI were bacterial culture positive; *E. coli* being the most common organism. A definite source of sepsis was not found in 6 (21.4%) patients.

Eighteen (28%) of the patients had only the ingestion of a hepatotoxic drug as the identifiable risk factor for acute

Figure 1 Consort diagram showing patient recruitment.

Table 2 Proportion of Mortality in Individual Chronic Etiologies in ACLF Patients.

Etiology	Non-survivors n (%)	Survivors n (%)	
Alcohol	20/28 (71.4%)	19/36 (52.8%)	Chi square 5.382 and P value 0.371
NASH	3/28 (10.7%)	8/36 (22.2%)	
Cryptogenic	3/28 (10.7%)	6/36 (16.7%)	
HBV	0/28 (0%)	2/36 (5.6%)	
Wilson	1/28 (3.6%)	1/36 (2.8%)	
HCV	1/28 (3.6%)	0/36 (0%)	

NASH: non-alcoholic steato-hepatitis; HBV: hepatitis B virus; HCV: hepatitis C virus.

insult. Out of these 4 (22.2%) were due to anti-tubercular drug toxicity and the remaining had history of ingestion of complementary and alternative medicines (CAM) for treatment of jaundice. The use of CAM for treatment of jaundice may have aggravated the bilirubin levels. However, it is difficult to attribute with certainty that CAM was the precipitating acute insult or CAM caused the progression.

Two (3.12%) patients had a flare of hepatitis B with sero-reversion from HBeAg negative to positive status. Super-added hepatitis E and A were identified as cause of acute insult in 4 (6.25%) and 3 (4.6%) patients.

Twenty four (37.5%) patients had more than one identifiable acute insult while in 7 (10.93%), no discernible precipitating factor was evident. There was no significant statistical difference between survivors and non-survivors based on the type of acute insult (Table 3).

Type of ACLF

29 (45.31%) had type II (hepatic injury) ACLF: alcoholic hepatitis followed by hepato-toxic drugs being the most common. 11 (17.18%) had type I ACLF (non-hepatic injury) of which sepsis was the most common cause. 16 (25%) had a combination of hepatic as well as non-hepatic injury.

Mortality in ACLF

The 28 days mortality in our study population was 28/64 (43.75%). 24 of these patients died during the same

admission while 4 died during the second admission which was within a median of 5 days after discharge.

Mortality was highest in those patients who had sepsis (67.85%) followed by alcohol as an underlying precipitating factor (66.6%). Active alcohol abuse was considered when the patient took >60 g/day of alcohol within 1 month of onset of symptoms. On univariate analysis active alcohol abuse was found to be associated with increased mortality. Most of these (62.5%) had associated sepsis which explains the possible increased susceptibility of alcoholics to infections. Patients with acute viral hepatitis had the least mortality in our series probably due to low number of patients with individual viral etiology in this study. On further adhoc analysis of impact of viral and non-viral etiologies as acute insult on survival, no significant difference was found (Supplementary Table 2).

HRS or acute kidney injury (AKI) was present in 37 (57.8%) patients. All 20 suspected type I HRS and 4 of 17 type 2 HRS patients did not respond to the regimen of albumin-terlipressin or hemo-dialysis and succumbed due to renal failure. The other 13 patients with HRS who did not require dialysis support succumbed to death because of other organ failure. All 16/64 (25%) patients of ACLF who required invasive ventilator support died during hospitalization and the mean ventilator days was 3 (range 1–8). Ventilator associated pneumonia was found in 4 patients while Acute respiratory distress syndrome

Table 3 Proportion of Mortality in Individual Acute Precipitating Factors Among Survivors and Non-survivors.

Etiology ^a	Non-survivors n (%)	Survivors n (%)	
Alcohol	16 (57.14%)	8 (22.22%)	Chi square 29.824
Drug	6 (21.42%)	12 (33.33%)	
HEV	2 (7.14%)	2 (5.55%)	
HAV	1 (3.57%)	3 (8.33%)	
HBV	0 (0%)	2 (5.55%)	
Unknown	3 (10.71%)	4 (11.11%)	P = 0.324
Sepsis	19 (67.85%)	9 (25%)	

^aSome patient had more than one precipitant factor.

HAV: hepatitis A virus; HEV: hepatitis E virus; HBV: hepatitis B virus.

occurred in 3 and the remaining patients had high grade hepatic encephalopathy and progressive deterioration.

Predictors of Mortality

To find the individual predictors of mortality, a univariate analysis was done for all the clinical and laboratory parameters and for the scoring systems. In this analysis only median MELD, CLIF-SOFA, CTP, APACHE II scores were statistically higher and significant in non-survivors ($P = 0.001$). Also among non-survivors, hepatic encephalopathy of more than grade 2 and active alcohol abuse was significantly higher ($P = 0.001$ and 0.006 respectively). Lower sodium below 125 mmol/l ($P = 0.004$), higher potassium above 5.3 mmol/L ($P = 0.006$) and higher INR above 2.1 ($P = 0.001$) were significantly more among non-survivors. In addition presence of shock on admission ($P = 0.011$), sepsis ($P = 0.001$) and high systemic inflammatory response ($P = 0.001$) were significantly associated with increased mortality (Table 1).

Further to find independent predictors of mortality, regression analysis was done which revealed that APACHE II [Odds ratio 3.18 (95% CI; $1.01-9.98$)] and shock [odds ratio 9.14 (95% CI; $3.35-24.9$)] at presentation were significant predictors of mortality ($P < 0.05$). Though other variables were not statistically significant, yet the odd ratio indicates a higher risk of mortality for alcohol abuse (1.34), high MELD (1.68) and high CTP score (1.02). In addition, when an univariate analysis of the individual variables of the APACHE-II score was done, all parameters except age, serum potassium, respiratory rate and temperature were found to be statistically significant between survivors and non-survivors (Supplementary Table 3). However, when a multivariate Cox proportional regression model was done, only serum sodium was found to be statistically significant between

the two groups (chi-square 7.92 $P = 0.004$). The relative risk for serum sodium for predicting mortality was 1.08 (95% CI $1.02-1.15$).

Type of Organ Failure and Mortality

When the type of organ failure were considered and correlated with mortality, the highest mortality was associated with cerebral and circulatory/lung failure in $>95\%$ cases as shown in Figure 2. Further, when the number of organ failures were co-related with mortality, it was seen that mortality rose steeply when more than two organ failures were present and mortality reaching 80% and 94% when more than 3 and 4 organ failures were present respectively (Table 4).

When the ACLF grades were compared between survivors and non-survivors, 12.5% had no ACLF as per CLIF-consortium due to the basic difference in definition between CLIF consortium and APASL. The 28 days' mortality increased in patients who had grade 2 ACLF and there as a steep increase in mortality in grade 3 ACLF patients as shown in Table 5.

Receiver operating characteristics (ROC) was done to identify the ability of different scoring systems (MELD, CLIF-SOFA, CTP and APACHE II) in predicting mortality. The most sensitive scoring was APACHE II while the specificity was highest was highest for CLIF-SOFA. The area under curve ranges from 78.3% for MELD to 94.7% for SOFA. All the four scores were statistically significant for predicting mortality. Only CLIF-SOFA and APACHE II had an AUROC > 0.8 indicating their better ability to discriminate between survivors and non-survivors. CLIF-SOFA ≥ 11 had highest specificity while APACHE II (≥ 18) and CTP (≥ 13) had higher sensitivity as shown in Figure 3 and Table 6.

The cut off values of different scores were used to plot Kaplan-Meier curves for each score to assess risk of death.

Figure 2 Proportion of individual organs failures (as per CLIF-consortium) with eventual mortality.

Table 4 Organ Failures According to EASL-CLIF Consortium Criteria's and Associated Mortality.

No. of organ failure	Prevalence N (%)	Mortality n/N (%)
No OF	3 (4.6)	0 (0)
Any No. of OF ^a	61 (96.4)	28/61 (45)
1 OF	18 (28.12)	0/18 (0)
2 OF	16 (25)	4/16 (25)
3 OF	10 (15.62)	8/10 (80)
≥4 OF	17 (26.5)	16/17 (94.11)

^aMany patient had more than one organ failure; OF: organ failure; No.: number.

However, no statistical significant difference could be obtained. The curves however points toward a window for early intervention within first two weeks which may alter outcome based on the steep changes seen in all the curves after this window period (Figure 4).

DISCUSSION

ACLF is a relatively new entity⁷ and our study adds to the existing evidence and literature which is emerging and not yet exhaustive. The etiology of both the acute and the chronic insult varies in the East when compared to the West and most of the data from India are from Northern and Western India with one study from the east.^{10–17} Within the Indian subcontinent itself, there is significant difference in the etiology of chronic liver disease. The INASL consortium though has representation from all over the country, yet it was a retrospective study.¹⁶ Therefore, this being the first prospective study from southern India.

In our study, most common primary etiology of liver cirrhosis was alcohol related in 60.93% patients followed by cryptogenic/NASH related cirrhosis (35.37%). These findings add to the further diverse nature of underlying cause of cirrhosis in India and the results though are in tune with few other Indian studies^{11,13,17} yet are in contrast with other studies from India where the prevalence of alcoholic cirrhosis was only 10–30%.^{10,15,23} As the prevalence of chronic hepatitis B and C are higher in Northern India, these studies have reported chronic hepatitis B to be the most common cause of cirrhosis in 30–64% of patients with ACLF. Similarly, most data from China and Taiwan also had predominantly HBV as a primary etiological cause of cirrhosis in patients with ACLF.^{24,25} However, a large study by Moreau et al. had 50% of patients belonging to alcohol associated liver disease in the West.⁸ This shows that etiological differences exist not only from east to west world over, but also in between different centers of same country.

In terms of acute precipitating events, 11 (17.18%) patients had type I ACLF (non-hepatic injury) sepsis being

Table 5 Mortality Prevalence as per ACLF Grading.

Definition (as per CLIF consortium)	Prevalence (n = 64)	28 days mortality rate
NO ACLF	9 (14.06%)	0 (0%)
ACLF Grade 1	12 (18.75%)	0 (0%)
ACLF Grade 2	16 (25%)	4 (25%)
ACLF Grade 3	27 (42.18%)	24 (88.88%)

ACLF: acute-on-chronic liver failure; CLIF: chronic liver failure consortium.

the most common acute insult. 16 (25%) patients had hepatic as well as non-hepatic injury. Similar demonstration of importance of non-hepatic insults in ACLF, even more profoundly, was shown by Duseja et al.⁹ where sepsis among the non-hepatic insults was the most common acute insult.

Bacterial infections were responsible as precipitating events in almost 43% of patients which is comparable to other Indian studies where prevalence of infection ranges from 32% to 66%.^{11,27} Traditionally, the APASL consortium excludes infections as an acute precipitating event, though infections and sepsis had been reported as a cause of acute de compensation in other studies where APASL definition was used.^{13,23} In our study, we found 28 (43.75%) patients with ACLF had bacterial infection and, of these 28 patients, bacterial infection was identified at the time of admission in 64% (18/28) patients and 36% of patients (10/28 cases) acquired bacterial infections during hospitalization and were considered as complication. Among 28 patients with bacterial infections, in 5 patients, bacterial infection/sepsis was the sole identifiable acute insult. These results were comparable with the data published by Jha et al.¹² However, in contrast to their study, we did not find malarial infections as the precipitating cause.

Spontaneous bacterial peritonitis ($n = 13$, 46% of infections) and UTI ($n = 8$, 28% of infections) were the commonest infections. Culture positive (including blood, ascitic fluid, urine, sputum etc.) bacterial infections were found in 70% patients with sepsis. Culture were not positive in remaining in view of antibiotics they received though many more patients would have been harboring bacterial infections as indicated by high procalcitonin levels found in these patients.

Mortality was highest in patients with sepsis (67.85%) similar to results by Khot et al.¹⁵ Though presence of sepsis was statistically significant on univariate analysis, yet it did not turn out to be independent predictor of mortality emphasizing again role of multi organ failure rather than a single acute precipitant influencing the outcome. The predominance of active alcoholism could explain the high frequency of sepsis in our study as it has been demonstrated in prior studies.^{26,27} Possible neutrophil dysfunction in alcoholics which causes

Figure 3 (A) AUROC of APACHE II score. APACHE II: acute physiology and chronic health evaluation; AUROC: area under receiver operating characteristic. (B) AUROC of CTP. CTP: Child-Turcotte-Pugh; AUROC: area under receiver operating characteristic. (C) AUROC of MELD score. MELD: model for end-stage liver disease; AUROC: area under receiver operating characteristic curve. (D) AUROC for SOFA. SOFA: sequential organ failure assessment; AUROC: area under receiver operating characteristics curve.

increased reactive oxidative bursts and impaired phagocytosis coupled with defective bacterial killing despite been in a pro-inflammatory state may make them more susceptible for infection and further worse prognosis.²⁶ Infections were similarly common in the original CANONIC study⁸ which had a high prevalence of patients with alcohol related cirrhosis and alcoholic hepatitis, while it is possible that in some cases infections are a consequence of ACLF rather than a cause. The CANONIC study also

demonstrated that non-ACLF patients who had infections at admission were more likely to develop ACLF in the same hospitalization.²⁸ This suggests a role for infections in the development of ACLF.³³⁻³⁵ However, this is still a debatable point and further research in this field would be needed.

Active alcoholism was present in more than one third (35.9%) of our patients presenting as ACLF, which correlates well with another Indian studies where alcohol

Table 6 Comparison of Different Scores as per Receiver Operating Characteristic Curve.

Type of score	AUC	SE	95% CI	P value	Sensitivity (95%CI)	Specificity (95%CI)	Cut off value ^a
MELD	0.783	0.0647	0.663–0.876	<0.0001	75 (57.8–87.9)	82.1 (63.1–93.9)	28.6
CLIFSOFA	0.947	0.0248	0.860–0.987	<0.0001	83.3 (67.2–93.6)	96.4 (81.7–99.9)	11
CTP	0.795	0.0575	0.675–0.885	<0.0001	94.4 (81.3–99.3)	57.1 (37.2–75.5)	13
APACHE-II	0.876	0.0485	0.770–0.945	<0.0001	91.6 (77.5–98.2)	78.5 (59–91.7)	18

^aCut off value derived from receiver operating characteristic curve. APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: sequential organ failure assessment; CTP: Child-Turcotte-Pugh; MELD: model for end-stage liver disease.

Figure 4 Comparison of different scoring systems for survival assessment. CTP: Child-Turcotte-Pugh, MELD: model for end stage liver disease; SOFA: sequential organ failure assessment; APACHE II: acute physiology and chronic health evaluation.

hepatitis was present in 27% and 25% of their patients.^{10,13} Active alcohol abuse was significantly associated with mortality on univariate analysis. Though it was not statistically significant on multivariate analysis, yet an odds ratio of 1.34 indicate higher risk of death.

Drug induced liver injury formed a significant number of our study population (28.12%) most of which were because of indigenous/herbal medications. This incidence is much more than previous Indian literature in ACLF.

Reactivation of HBV has been a predominant cause of acute-on-chronic liver failure presentation in most studies from Asia-Pacific region. However, we had only a couple of cases of HBV reactivation on a background of HBV cirrhosis, though our study was limited by a small number of enrolled patients. Similarly, acute viral hepatitis insults like HEV and HAV were very low (total 8 cases of HAV/HEV related viral hepatitis), though they have been well reported in literature.^{18,29,32} This can be explained by referral bias.

There was a significantly high 28-day mortality rate of 43.75% in patients with ACLF, which was comparable to similar studies by Shalimar et al. (43.6%), Amarapurkar et al. (43%) and INASL consortium experience (42%), Agarwal et al. (48%) many of which had a heterogeneous study population.^{13,14,16,18}

In a sub-analysis, we reclassified our patients into ACLF grades as defined by the recent EASL-CLIF consortium under the CANONIC study.²⁸ By utilizing CLIF-SOFA definitions of organ failures, we found that 96.4% of our enrolled patients had at least one organ failure. By definition, liver failure was present in around half of the enrolled population which necessarily meant that quite significant proportion of our patients had serum bilirubin levels > 12 mg/dl as opposed to study by Amarapurkar et al. where around 20% were satisfied CLIF SOFA definition of liver failure.¹³

As per the EASL-CLIF criteria, we also divided the patients into NO ACLF and ACLF grades 1–3. There

was no mortality in the No ACLF and ACLF grade 1, while the mortality rate climbed steeply from grade 2 onwards. Prevalence of mortality increased significantly according to ACLF grade. This corresponds very well to previous studies^{8,12} and indicates importance of multi-organ failure in predicting outcome.

In our study, no discernible precipitating event was found in only 7 patients (10.93%), which is similar to other studies from India reporting no identifiable cause in 10% cases¹³ but contrasting to study from the West where 43% of patients had no discernible precipitating event.⁸

Further, higher number of acute precipitating insults were associated with higher mortality. This is similar to previous Indian studies Jha et al. and Pati et al. but the results were not statistically significant in those reports.^{12,17} Many of our patients were having alcohol as an acute as well as underlying chronic insult making increased susceptibility to sepsis which makes patients more prone to death.

In terms of organ failure, mortality rates were 88.88% in ACLF 3 patients, signifying significantly high mortality as number of organ failures which is similar to existing literature.^{8,13,27} Though prevalence of liver, respiratory failure exceeded prevalence of other organ failures by definition in these patients, mortality rate was lowest in liver failure, indicating involvement of other organ playing important role in mortality as compared to liver failure. This further enlightens importance of multi-organ failure in outcome.

HRS was found in 57.8% (37/64) of patients with almost 100% mortality even with the use of standard treatment for HRS as well with the use of slow low efficient dialysis. Though continuous renal replacement therapy might offer several advantages like less fluctuation in the mean arterial pressure; maintenance of stable cerebral perfusion pressure without a rise in intracranial pressure; and a reduction in cerebral edema by preventing rapid osmolar shifts or fluctuations in the mean arterial pressure, yet the benefits in HRS of ACLF are not promising.^{29,30}

All patients ($n = 16$) requiring ventilator support died during hospitalization. INASL consortium experience found ventilator support as an important predictor of mortality.¹⁶

Presence of shock and higher APACHE II were found to be independent predictors of mortality which is similar to a Canadian study which also found APACHE II as an independent predictor. In contrast Indian study by Dhi-man et al. also found CLIF-SOFA score an independent predictor of mortality.^{27,31}

Mortality rate with shock was 91.66% (11/12) in our study. Though not well defined in ACLF, cirrhosis of liver presenting as shock has high mortality rate of about 60–100%.^{33–35} With the inception of the concept of ACLF, studies have shown that patients with ACLF and shock are extremely sick with mortality exceeding 80%.^{36,37} Only 1 patient who recovered from shock within 48 h of

admission survived, probably indicating importance of initial response of shock to resuscitative measures in predicting outcome.

Limited studies have been published from India on the use of prognostic scores in patients defined strictly as ACLF. In a study by Northern India, that generated a prognostic model based on hepatic encephalopathy, hyponatremia and renal failure, including patients with ACLF resulting from cirrhosis of varied etiologies and a super-added acute insult with hepatitis E virus or hepatitis A virus, found it to be superior in predicting 3-month mortality to MELD and CTP scores (AUROC: 0.952 vs. 0.941 [MELD] and 0.636 [CTP]).³⁸ In another study,¹⁰ MELD, CLIF-SOFA and APACHE II scores (all with AUROC > 0.8) performed better than the CTP score in predicting 3-month mortality. In contrast, a study from Canada where one-third of patients had bacteremia at admission showed that both APACHE II and MELD performed similarly (both with an AUROC 0.86) in predicting mortality, but a high APACHE II score was an independent predictor of in-hospital mortality in 184 patients with ACLF.

Our results in patients with ACLF (in whom the predominant acute insult was alcoholic hepatitis or non-hepatotropic infection) also favor the superiority of APACHE II and CLIF-SOFA (both having AUROC > 0.8) in relation to other scores for predicting short-term mortality; APACHE II being an independent predictor of mortality in our study.

At admission patients with ACLF have not only hepatic insufficiency but most patients have multi-organ dysfunction. Survival assessment by Kaplan–Meir also showed that the initial two weeks may be crucial for intervention as graph rises steeply after the first two weeks and flattens after that. This might indicate that emerging therapies role of emerging therapies like liver assist devices or consideration of early liver transplantation during this window period.

The current study had some limitations in the form of not having a large enough patient group for a meaningful subgroup analysis in a wide context considering regional variations. Also short term mortality prediction was based on various predictors only once in this study. Serial data might have been more useful in predicting the outcome in critically ill patients like ACLF.

In addition we had very few viral hepatitis cases were found as a precipitating factor. Finally, patients in this study, received standard intensive care with limited regional access to hepatic support systems (as bridge) or liver transplantation.

CONCLUSION

ACLF is an emerging entity which shows very high short term mortality. There is a wide variation in both the underlying chronic as well as acute precipitating cause

in various parts of the world and even within a big country like India. The use of various prognostic scores in patients with ACLF may help in categorizing these patients to limited ICU resources and evolving therapies. The CLIF-SOFA and APACHE II scoring system are superior to other prognostic scores in predicting short term mortality in these patients. Further studies are required to throw more light on this evolving concept of ACLF and will guide us for better management of these patients.

CONFLICTS OF INTEREST

The authors have none to declare.

APPENDIX A SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.jceh.2017.11.008](https://doi.org/10.1016/j.jceh.2017.11.008).

REFERENCES

1. Sarin SK, Kumar A, Almeida JA, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int*. 2009;3:269–282. <http://dx.doi.org/10.1007/s12072-008-9106-x> [PMID:19669378].
2. Jalan R, Gines P, Olson JC, et al. Acute-on chronic liver failure. *J Hepatol*. 2012;57(December (6)):1336–1348. <http://dx.doi.org/10.1016/j.jhep.2012.06.026> [PMID:22750750].
3. Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. *Curr Opin Crit Care*. 2011;17(April (2)):165–169. <http://dx.doi.org/10.1097/MCC.0b013e328344b42d> [PMID:21326095].
4. Laleman W, Verbeke L, Meersseman P, et al. Acute-on-chronic liver failure: current concepts on definition, pathogenesis, clinical manifestations and potential therapeutic interventions. *Expert Rev Gastroenterol Hepatol*. (January)2014;(January). <http://dx.doi.org/10.1586/egh.11.47> [PMID:21780899].
5. Chan AC, Fan ST, Lo CM, et al. Liver transplantation for acute-on-chronic liver failure. *Hepatol Int*. 2009;3(December (4)):571–581. <http://dx.doi.org/10.1007/s12072-009-9148-8> [PMID:19680733, PMCID:PMC2790588].
6. Mikolasevic I, Milic S, Radic M, Orlic L, Bagic Z, Stimac D. Clinical profile, natural history, and predictors of mortality in patients with acute-on-chronic liver failure (ACLF). *Wien Klin Wochenschr*. 2015;127(April (7–8)):283–289. <http://dx.doi.org/10.1007/s00508-015-0707-9> [PMID:25821053].
7. Mikolasevic I, Radić M, Milić S, Stimac D. Acute-on-chronic liver failure (ACLF) – a new entity in hepatology? *Lijec Vjesn*. 2013;135 (November–December (11–12)):322–325 [PMID:24490333].
8. Moreau R, Gines P, Jalan R, et al. 1404 Diagnosis, prevalence, and prognosis of acute-on-chronic liver failure (ACLF): results of the EASL-chronic liver failure (CLIF) consortium canonic study. *J Hepatol*. 2012;56(April):S552–S553. [http://dx.doi.org/10.1016/S0168-8278\(12\)61415-9](http://dx.doi.org/10.1016/S0168-8278(12)61415-9).
9. Duseja A, Chawla YK, Dhiman RK, Kumar A, Choudhary N, Taneja S. Non-hepatic insults are common acute precipitants in patients with acute on chronic liver failure (ACLF). *Dig Dis Sci*. 2010;55 (November (11)):3188–3192. <http://dx.doi.org/10.1007/s10620-010-1377-0> [PMID:20721624].
10. Garg H, Kumar A, Garg V, Sharma P, Sharma BC, Sarin SK. Clinical profile and predictors of mortality in patients of acute-on-chronic liver failure. *Dig Liver Dis*. 2012;44(February (2)):166–171. <http://dx.doi.org/10.1016/j.dld.2011.08.029> [PMID:21978580].
11. Duseja A, Choudhary NS, Gupta S, Dhiman RK, Chawla Y. APACHE II score is superior to SOFA, CTP and MELD in predicting the short-term mortality in patients with acute-on-chronic liver failure (ACLF). *J Dig Dis*. 2013;14(September (9)):484–490. <http://dx.doi.org/10.1111/1751-2980.12074> [PMID:23692973].
12. Jha AK, Nijhawan S, Rai RR, Nepalia S, Jain P, Suchismita A. Etiology, clinical profile, and inhospital mortality of acute-on-chronic liver failure: a prospective study. *Indian J Gastroenterol*. 2013;32(March (2)):108–114. <http://dx.doi.org/10.1007/s12664-012-0295-9> [PMID:23526372].
13. Amarapurkar D, Dharod MV, Chandnani M, et al. Acute-on-chronic liver failure: a prospective study to determine the clinical profile, outcome, and factors predicting mortality. *Indian J Gastroenterol*. 2015;34(May (3)):216–224. <http://dx.doi.org/10.1007/s12664-015-0574-3> [PMID:26080655].
14. Agrawal S, Duseja A, Gupta T, Dhiman RK, Chawla Y. Simple organ failure count versus CANONIC grading system for predicting mortality in acute-on-chronic liver failure. *J Gastroenterol Hepatol*. 2015;30(3):575–581. <http://dx.doi.org/10.1111/jgh.12778> [PMID:25251968].
15. Khot AA, Somani P, Rath P, Amarapurkar A. Prognostic factors in acute-on-chronic liver failure: a prospective study from western India. *Indian J Gastroenterol*. 2014;33(2):119–124. <http://dx.doi.org/10.1007/s12664-013-0409-z> [PMID:24122317].
16. Shalimar. Saraswat V, Singh S, et al. Acute on chronic liver failure in India: the INASL Consortium experience. *J Gastroenterol Hepatol*. 2016;31(October (10)):1742–1749. <http://dx.doi.org/10.1111/jgh.13340> [PMID:26989861].
17. Pati GK, Singh A, Misra B, et al. Acute-on-chronic liver failure (ACLF) in coastal eastern India: “a single-center experience”. *J Clin Exp Hepatol*. 2016;6(March (1)):26–32. <http://dx.doi.org/10.1016/j.jceh.2015.08.002> [PMID:27194893, PMCID:PMC4862011].
18. Shalimar. Kumar D, Vadraj PK, et al. Acute on chronic liver failure due to acute hepatic insults: etiologies, course, extrahepatic organ failure and predictors of mortality. *J Gastroenterol Hepatol*. 2016;31(April (4)):856–864. <http://dx.doi.org/10.1111/jgh.13213> [PMID:26519215].
19. Kim TY, Kim DJ. Acute-on-chronic liver failure. *Clin Mol Hepatol*. 2013;19(4):349–359. <http://dx.doi.org/10.3350/cmh.2013.19.4.349> [PMID:24459638, PMCID:PMC3894433].
20. Sarin SK, Choudhury A. Acute-on-chronic liver failure: terminology, mechanisms and management. *Nat Rev Gastroenterol Hepatol*. 2016;13(March (3)):131–149. <http://dx.doi.org/10.1038/nrgastro.2015.219> [PMID:26837712].
21. Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology*. 2013;57(April (4)):1651–1653. <http://dx.doi.org/10.1002/hep.26359> [PMID:23463403].
22. European Association For The Study Of The Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol*. 2010;53(3):397–417. <http://dx.doi.org/10.1016/j.jhep.2010.05.004> [PMID:20633946].
23. Rastogi A, Kumar A, Sakhuja P, et al. Liver histology as predictor of outcome in patients with acute-on-chronic liver failure (ACLF). *Virchows Arch*. 2011;459:121–127. <http://dx.doi.org/10.1007/s00428-011-1115-9> [PMID:21744153].
24. Huang K, Hu JH, Wang HF, et al. Survival and prognostic factors in hepatitis B virus-related acute-on-chronic liver failure. *World J*

- Gastroenterol.* 2011;17(29):3448–3452. <http://dx.doi.org/10.3748/wjg.v17.i29.3448> [PMCID: PMC3160571].
25. Xu Z, Ren X, Liu Y, et al. Association of hepatitis B virus mutations in basal core promoter and precore regions with severity of liver disease: an investigation of 793 Chinese patients with mild and severe chronic hepatitis B and acute-on-chronic liver failure. *J Gastroenterol.* 2011;46(March (3)):391–400. <http://dx.doi.org/10.1007/s00535-010-0315-4> [PMID:20848146].
 26. Mookerjee RP, Stadlbauer V, Lidder S, et al. Neutrophil dysfunction in alcoholic hepatitis superimposed on cirrhosis is reversible and predicts the outcome. *Hepatology.* 2007;46:831–840. <http://dx.doi.org/10.1002/hep.21737> [PMID:17670644].
 27. Dhiman RK, Agrawal S, Gupta T, Duseja A, Chawla Y. Chronic Liver Failure-Sequential Organ Failure Assessment is better than the Asia-Pacific Association for the Study of Liver criteria for defining acute-on-chronic liver failure and predicting outcome. *World J Gastroenterol.* 2014;20(October (40)):14934–14941. <http://dx.doi.org/10.3748/wjg.v20.i40.14934> [PMID:25356054, PMCID:PMC4209557].
 28. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology.* 2013;144(June (7)):1426–1437. <http://dx.doi.org/10.1053/j.gastro.2013.02.042> [PMID:23474284].
 29. Acharya SK, Sharma PK, Singh R, et al. Hepatitis E virus (HEV) infection in patients with cirrhosis is associated with rapid decompensation and death. *J Hepatol.* 2007;46(3):387–394. <http://dx.doi.org/10.1016/j.jhep.2006.09.016> [PMID:17125878].
 30. Gonwa TA, Wadei HM. The challenges of providing renal replacement therapy in decompensated liver cirrhosis. *Blood Purif.* 2012;33(1–3):144–148. <http://dx.doi.org/10.1159/000334149> [PMID:22269395].
 31. Karvellas CJ, Pink F, McPhail M. Bacteremia, acute physiology and chronic health evaluation II and modified end stage liver disease are independent predictors of mortality in critically ill non-transplanted patients with acute on chronic liver failure. *Crit Care Med.* 2010;38:121–126. <http://dx.doi.org/10.1097/CCM.0b013e3181b42a1c> [PMID:19770744].
 32. Kumar M, Sharma BC, Sarin SK. Hepatitis E virus as an etiology of acute exacerbation of previously unrecognized asymptomatic patients with hepatitis B virus-related chronic liver disease. *J Gastroenterol Hepatol.* 2008;23(June (6)):883–887. <http://dx.doi.org/10.1016/j.jceh.2013.08.013> [PMCID: PMC3940130].
 33. Montalto P, Vlachogiannakos J, Cox DJ, Pastacaldi S, Patch D, Burroughs AK. Bacterial infection in cirrhosis impairs coagulation by a heparin effect: a prospective study. *J Hepatol.* 2002;37(October (4)):463–470. [http://dx.doi.org/10.1016/S0168-8278\(02\)00208-8](http://dx.doi.org/10.1016/S0168-8278(02)00208-8) [PMID:12217599].
 34. Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology.* 2010;139(4):1246–1256. <http://dx.doi.org/10.3748/wjg.v20.i23.7252> [PMCID: PMC4064071].
 35. Gustot T, Durand F, Lebrech D, Vincent JL, Moreau R. Severe sepsis in cirrhosis. *Hepatology.* 2009;50(6):2022–2033. <http://dx.doi.org/10.1002/hep.23264> [PMID:19885876].
 36. Choudhury AK, Vashishtha C, Kedarisetty CK, Sarin SK. Systemic inflammatory response syndrome (SIRS) — a potential clinical marker for early sepsis and survival in acute on chronic liver failure (ACLF) [abstract 580]. *Hepatology.* 2014;60(suppl 1):A476A.
 37. Choudhury AK, Vasistha C, Kumar S, Sarin SK. A prospective open label randomized noninferiority trial to compare the efficacy and safety of monotherapy with noradrenaline and terlipressin in patients of cirrhosis with septic shock admitted to the intensive care unit. *Hepatology.* 2014;60(suppl 1):A252A.
 38. Radha Krishna Y, Saraswat VA, Das K, et al. Clinical features and predictors of outcome in acute hepatitis A and hepatitis E virus hepatitis on cirrhosis. *Liver Int.* 2009;29(3):392–398. <http://dx.doi.org/10.1111/j.1478-3231.2008.01887.x> [PMID:19267864].