JGH Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.13340

HEPATOLOGY

Acute-on-chronic liver failure in India: The Indian National Association for Study of the Liver consortium experience

Shalimar,* Vivek Saraswat,† Shivaram P Singh,‡ Ajay Duseja,§ Akash Shukla,¶ Chundamannil E Eapen,** Dharmendra Kumar,†† Gaurav Pandey,† Jayanti Venkataraman,‡‡ Pankaj Puri,§§ Krishnasamy Narayanswami,†† Radha K Dhiman,§ Sandeep Thareja,†† Sandeep Nijhawan,¶¶ Shobna Bhatia,¶ Uday Zachariah,** Ujjwal Sonika,* Thomas Varghese*** and Subrat K Acharya*

*Department of Gastroenterology, All India Institute of Medical Sciences New Delhi, ††Army Hospital Research and Referral, †Sanjay Gandhi Postgraduate Institute of Medical Sciences Lucknow, ‡S.C.B Medical College, Cuttack, §Postgraduate Institute of Medical Education and Research, Chandigarh, ¶Seth GS Medical College and KEM Hospital, Mumbai, **Christian Medical College, Vellore, ‡‡Global hospital, §§Madras Medical College, Chennai, ¶¶SMS Medical College, Jaipur, and ***Medical College Hospital, Calicut, India

Key words
alcohol, hepatitis B, hepatitis E, organ failure, sepsis, variceal bleeding.

Accepted for publication 3 March 2016.

Correspondence
Subrat Kumar Acharya, Room No 3105, 3rd Floor, Teaching Block, Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi 110029, India. E-mail: subratacharya2004@yahoo.com

Declaration of conflict of interest: None.

Author contributions: Shalimar, Vivek Saraswat, and Subrat Acharya have performed acquisition of data, analysis and interpretation of data, drafting of manuscript, and critical revision of manuscript. Ajay Duseja, Akash Shukla, CE Eapen, Dharmendra Kumar, Gaurav Pandey, Jayanti Venkataraman, K. Nayayansamy, Pankaj Puri, R. K. Dhiman, Sandeep Nijhawan, Sandeep Thareja, Shivaram Singh, Shobna Bhatia, Uday Zachariah, and Varghese Thomas have performed acquisition of data, analysis and interpretation of data, and critical revision of manuscript. Ujjwal Sonika has performed acquisition of data.

Abstract

Background and Aim: The aim of this study was to analyze etiologies and frequency of hepatic and extrahepatic organ failures (OFs) and outcome of acute-on-chronic liver failure (ACLF) at 10 tertiary centers in India.

Methods: In this retrospective study (2011–2014), patients satisfying Asian Pacific Association for the Study of the Liver definition of ACLF were included. Etiology of acute precipitating insult and chronic liver disease and outcomes were assessed. Occurrence and severity of OF were assessed by chronic liver failure-sequential organ failure assessment score.

Results: The mean (±SD) age of 1049 consecutive ACLF patients was 44.7 ± 12.2 years; Eighty-two percent were men. Etiology of acute precipitants included alcohol 35.7%, hepatitis viruses (hepatitis A, hepatitis B, and hepatitis E) 21.4%, sepsis 16.6%, variceal bleeding 8.4%, drugs 5.7%, and cryptogenic 9.9%. Among causes of chronic liver disease, alcohol was commonest 56.7%, followed by cryptogenic and hepatitis viruses. Predictors of survival were analyzed for a subset of 381 ACLF patients; OF's liver, renal, coagulation, cerebral, respiratory, and failure were seen in 68%, 32%, 31.5%, 22.6%, 14.5%, and 15%, respectively. Fifty-seven patients had no OF, whereas 1, 2, 3, 4, and 5 OFs were recorded in 126, 86, 72, 28, and 12 patients, respectively. The mortality increased progressively with increasing number of OFs (12.3% with no OF, 83.3% with five OFs). During a median hospital stay of 8 days, 42.6% (447/1049) of patients died. On multivariate analysis by Cox proportional hazard model, elevated serum creatinine (hazard ratio [HR] 1.176), advanced hepatic encephalopathy (HR 2.698), and requirement of ventilator support (HR 2.484) were independent predictors of mortality.

Conclusions: Alcohol was the commonest etiology of ACLF. Within a mean hospital stay of 8 days, 42% patients died. OFs independently predicted survival.

Introduction

Acute-on-chronic liver failure (ACLF) is a recently described syndrome that is characterized by abrupt hepatic decompensation in patients with chronic liver disease (CLD) and has high short-term mortality.[1] There are differences in the definition of this entity as per the European Association for the Study of the Liver and American Association for the study of Liver diseases (EASL-AASLD) and Asian Pacific Association for the Study of the Liver (APASL).[2,3]

EASL-AASLD defined ACLF as "an acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure."[2] The APASL defines ACLF as "acute hepatic insult manifesting as jaundice (bilirubin > 5 mg/dL) and coagulopathy (international normalized ratio [INR] > 1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease."[3] The EASL-AASLD definition includes only cirrhotics, whereas the APASL definition includes both cirrhotics and non-cirrhotics. APASL includes hepatic insults as causes of acute decompensation, whereas EASL-AASLD includes both hepatic and non-hepatic causes (like sepsis and variceal bleeding) as precipitating factors. Recently, 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.[1] It also included both hepatic and non-hepatic insults as precipitating events. There may be regional differences in etiology, pathogenesis, and natural course of ACLF, which may in turn influence the overall outcome of this syndrome. There is paucity of data from India; most studies are single-center with small sample size.[4–13] Therefore, the Indian National Association for Study of the Liver (INASL) formed the INASL Consortium for ACLF Research in the East (ICARE) that included 10 tertiary care centers from all parts of India and planned the present study to assess etiologies, course, and outcomes of patients with ACLF seen across India.

Methods

In this retrospective study, data of ACLF patients diagnosed as per the APASL criteria were collated.[3] In addition, patients with extra-hepatic acute insults and decompensated cirrhosis were also included at some of the centers. A total of 10 centers distributed across India contributed to the data (2011–2014). These included centers from northern India (All India Institute of Medical Sciences, New Delhi; Army Research & Referral Center, New Delhi; Post Graduate Institute of Medical Education and Research, Chandigarh; Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow; and SMS Medical College, Jaipur), western (KEM Mumbai), southern (Christian Medical College, Vellore; Medical College Hospital, Calicut; Global Hospital, Chennai), and eastern India (SCB Medical College, Cuttack). Each of these centers had been prospectively collecting data of ACLF, which were collated for the purpose of the current study. The primary objective of the study was to evaluate the etiologies, course, and outcome of ACLF patients.

Inclusion and exclusion criteria. Patients with age >18 years, with hepatic or extrahepatic insults, with or without prior decompensation, and satisfying APASL criteria were included. We excluded patients with hepatocellular carcinoma, incomplete data, or where the diagnosis was in doubt.

Definitions. ACLF was diagnosed as per the APASL definition—"acute hepatic insult manifesting as jaundice (bilirubin >5 mg/dL) and coagulopathy (international normalized ratio [INR] >1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease."[3] The diagnosis of cirrhosis was based on clinical, biochemical, imaging evidence, or prior liver biopsy with F4 changes.[5,14]

Organ failures (OFs) were defined as per the Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA).[15] Prognostic scores including Child Turcotte Pugh (CTP) score,[16] model of end-stage liver disease (MELD),[17] and acute physiology and chronic health evaluation score (APACHE II)[18] were calculated as per previously defined criteria.

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

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

Data collection. The data of the following variables were collected at admission: age, gender, clinical presentation, laboratory parameters (hemogram, liver function tests, INR), CTP score, MELD, APACHE II score, and CLIF-SOFA score at baseline. In addition, cause of acute hepatic decompensation, etiology of underlying CLD and outcomes were noted. Data of all patients ($n=1049$) is presented for the description of baseline characteristics, while predictors of survival were analyzed in a subset of patients ($n=381$), who had data available for all variables.

Etiology of acute insult and underlying chronic liver disease. A detailed history was taken (alcohol consumption, drugs, hematemesis, melena, 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.[2,5,19,20]

Management protocol. 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 contributing institutions.

Statistical analysis. The data were expressed as mean $\pm$ standard deviation when normally distributed and as mean (range) for those with skewed distribution. Categorical data were presented as proportions. The univariate analysis was performed to compare survivors and non-survivors using an independent *t*-test or Mann–Whitney *U*-test for continuous variables. Chi-square or Fisher's exact test for categorical variables was used. Receiver operating characteristic curves were drawn for significant variables with mortality as the outcome. Cox proportional hazard model was used to assess predictors of survival in a subset of patients in which complete data were available. A *P*-value of 0.05

was considered as statistically significant. SPSS version 17.0 (SPSS, Chicago, IL, USA) was used for statistical analysis.

Results

Of a total of 1270 patients, 1049 (81.3% men) ACLF patients were included. Two hundred and twenty-one patients were excluded as they did not satisfy the APASL criteria for ACLF. The median (IQR) age of patients was 45 (36–53) years, and one-third of patients were less than 40 years old. Ascites was present in 797/868 (91.8%). Hepatic encephalopathy was absent, early, or advanced in 388 (42.5%), 413 (45.2%), and 113 (12.3%) patients, respectively (Table 1). Forty percent of patients (312/780) had silent CLD, and 60% had overt CLD. The center-wise distribution of cases is shown in Figure 1.

Table 1 Baseline clinical and laboratory characteristics of patients with ACLF ($n = 1049$)

Characteristic	All ACLF patients ($n = 1049$)	Patients with all available data ($n = 381$)	Patients with missing data ($n = 668$)	*P* value
Age ± SD (years)	45 (36–53)	42 (34.5–50)	45 (38–55)	< 0.001
Males	853 (81.3%),	299 (78.5%),	554 (82.9%),	0.162
Females	196 (18.7%)	82 (2.5%)	114 (17.1%)	
Ascites ($n = 868$)	798/868 (91.8%)	351 (92.1%)	447/487 (91.7%)	0.620
Hepatic encephalopathy grade ($n = 914$)				0.045
None	388/914 (42.4)	142 (37.3%)	246 (46.1%)	
Early (Grade I and II)	413/914 (45.2%)	184 (48.3%)	229 (42.9%)	
Advanced (Grade III and IV)	113/914 (12.4%)	55 (14.4%)	58 (10.9%)	
Hemoglobin, g/dL ($n = 815$)	9.5 (8.0–11.1)	9.8 (8.5–11.5)	9.3 (8.0–11.0)	0.001
Seizure ($n = 494$)	15/494 (3%)	9 (2.3%)	6 (5.3%)	0.797
Total leukocyte count, per mm^3	10 800 (7400–15 500)	11 600 (7900–17 237)	10 000 (7130–15 000)	0.002
Platelets ($\times 10^3/mm^3$) ($n = 844$)	109.5 (71–169)	104 (70–162)	110 (71–176)	0.506
Creatinine, mg/dL ($n = 996$)	1.2 (0.8–2.2)	1.4 (0.8–2.3)	1.1 (0.8–2.1)	0.125
Sodium, mEq/L ($n = 754$)	131 (126–136)	132 (127–138)	130.5 (125–135)	0.001
Potassium, mEq/L ($n = 637$)	3.9 (3.4–4.5)	3.9 (3.4–4.4)	4.0 (3.4–4.7)	0.081
Bilirubin, mg/dL ($n = 998$)	15 (7.7–24)	18 (10.5–26.0)	13 (7.1–23)	< 0.001
Aspartate aminotransferase, IU/L ($n = 772$)	116.5 (72–187)	132 (90–227)	112 (70–180)	< 0.001
Alanine aminotransferases, IU/L ($n = 770$)	63 (39–109)	80 (60–161)	55 (34–92)	< 0.001
Alkaline phosphatase, IU/L ($n = 654$)	188 (125–302)	226.5 (138–341)	175.5 (122–276)	0.001
Albumin, g/dL ($n = 826$)	2.5 (2.2–3.0)	2.6 (2.2–3.1)	2.5 (2.2–2.9)	0.268
International normalized ratio	2.1 (1.7–2.7)	2.1 (1.7–2.7)	2.2 (1.8–2.8)	0.031
CLIF-SOFA ($n = 544$)	8 (6–10)	8 (6–10)	8 (6–10)	0.091
APACHE II ($n = 469$)	14 (9–20)	14 (10–19)	15 (9–21)	0.240
MELD ($n = 917$)	27 (22–33)	28 (22–34)	27 (22–33)	0.348
CTP ($n = 974$)	12 (11–13)	12 (11–13)	12 (11–13)	0.720
Etiology (acute precipitating insult)				< 0.001
Continuous alcohol consumption	374 (35.7%)	154 (40.4%)	220 (32.9%)	
Viral superinfection/flare (HEV, HAV and HBV)	224 (21.4%)	117 (30.7%)	107 (16.0%)	
Sepsis	174 (16.6%)	36 (9.4%)	138 (20.6%)	
Cryptogenic	104 (9.9%)	52 (13.6%)	52 (7.8%)	
Variceal bleeding	88 (8.4%)	5 (1.3%)	83 (12.4%)	
Drugs	60 (5.7%)	17 (4.5%)	43 (6.4%)	
Others (AIH flare and surgery)	25 (2.4%)	0	25 (3.7%)	
Etiology (chronic liver disease)				0.034
Alcohol	595 (56.7%)	198 (52%)	397 (59.4%)	
Cryptogenic	204 (19.4%)	78 (20.5%)	126 (18.9%)	
Viral (HBV and HCV)	167 (15.9%)	62 (16.3%)	105 (15.7%)	
Autoimmune	51 (4.9%)	27 (7.1%)	24 (3.6%)	
Wilsons	10 (1.0%)	6 (1.6%)	4 (0.5%)	
HVOTO	5 (0.5%)	3 (0.8%)	2 (0.3%)	
Viral and alcohol	17 (1.6%)	7 (1.8%)	10 (1.5%)	
In hospital mortality ($n = 1049$)	447 (42.6%)	148 (38.8%)	299 (44.7%)	0.079
Hospital stay, median (range), days	8 (4–14)	9 (5–17)	8 (4–14)	0.092

All values are expressed as median (IQR), *n* (%) unless otherwise specified

CLIF-SOFA, chronic liver failure-sequential organ failure assessment score; APACHE, acute physiology and chronic health evaluation; MELD, model of end-stage liver disease; CTP, Child–Turcotte–Pugh score; HEV, hepatitis E virus; HAV, hepatitis A virus; HBV, hepatitis B virus; AIH, autoimmune hepatitis; HVOTO, hepatic venous outflow tract obstruction; HCV, hepatitis C virus; ACLF, acute-on-chronic liver failure.

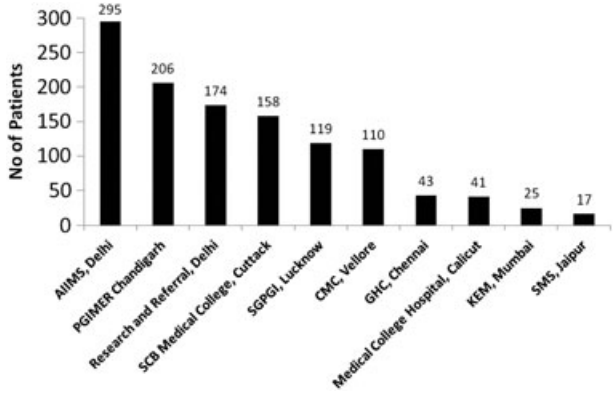

Figure 1 Center-wise distribution of acute-on-chronic liver failure patients.

The baseline clinical and laboratory parameters of all ACLF patients ($n = 1049$), ACLF patients with complete data available ($n = 381$), and those with missing data ($n = 668$) are shown in Table 1. All (1049) patients had jaundice (total bilirubin > 5 mg/dL) with INR value > 1.5. Most patients had significant derangement of liver functions tests. The median (range) bilirubin was 15 (5–59) mg/dL. Approximately 42% (415) of patients had creatinine > 1.5 mg/dL. The median CTP and MELD scores were 12 (6–15) and 27 (6–40), respectively.

All data required for calculation of individual CLIF-SOFA score and categorization of various OFs were available in 381 patients—the characteristics of this group are shown in Table 1. These patients were younger and had higher hemoglobin, total leukocyte count, sodium, bilirubin, aspartate aminotransferase, and alanine aminotransferase levels when compared with the group of 668 patients who had some data missing. There were differences between the two groups in proportions of patients with early and advanced hepatic encephalopathy, INR, etiologies of acute precipitating events, and causes of CLD. There were no differences in age, platelet count, and serum creatinine. The various prognostic scores like CLIF-SOFA, APACHE-II, MELD, and CTP were similar between the two groups.

Etiology of acute hepatic and extra-hepatic insults (Fig. 2a). The most common etiology of acute hepatic insult was continuous alcohol consumption in 35.7% (374), followed by hepatotropic viral infections (superinfection [HAV/HEV] or reactivation [HBV]) and drugs (including antituberculosis drugs) in 21.4% (224) and 5.7% (60) patients, respectively. There were significant differences in relative proportions of these etiologies across various centers. Continuous alcohol consumption was the commonest acute precipitating event at all centers contributing more than 100 patients, varying from 23.5–49% of cases across different centers. Of the viral etiologies, significantly higher proportion was reported from AIIMS, New Delhi (101/295, 34.2%), as compared with other centers (11.7% to 25.7%).

The commonest etiology of acute extra-hepatic insult was sepsis (bacterial infection) in 16.6%, followed by variceal bleeding in 8.4%. Similar to hepatic insults, there were significant differences among extrahepatic precipitating events across various centers. Of the 174 patients with sepsis as the acute insult, 59.2% were reported from two centers together—Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, and Post Graduate Institute of Medical Education and Research, Chandigarh, had 55 and 48 patients each with sepsis as acute events. Of the 88 patients with variceal bleeding, 64.8% (57) were reported from SCB Medical College, Cuttack, which was significantly higher as compared with other centers ($P = 0.001$).

Etiology of chronic liver disease (Table 1 and Fig. 2b). Alcohol was the most common etiology of CLD in 56.7%, followed by viral (HBV and HCV) in 16%. In addition, 1.6% had combined alcohol and viral etiology. Autoimmune, Wilsons, and hepatic venous outflow tract obstruction accounted for 4.9%, 4.9%, and 1.6% of the CLD. The etiology was cryptogenic (including non-alcoholic steatohepatitis) in 19.4% of patients. Among all the causes of CLD at various centers, alcohol was responsible for 44–68% of cases.

Organ failure and outcome (n = 381). Among the 381 ACLF patients, liver failure, renal failure, coagulation failure, cerebral failure, respiratory failure, and circulatory failure were seen

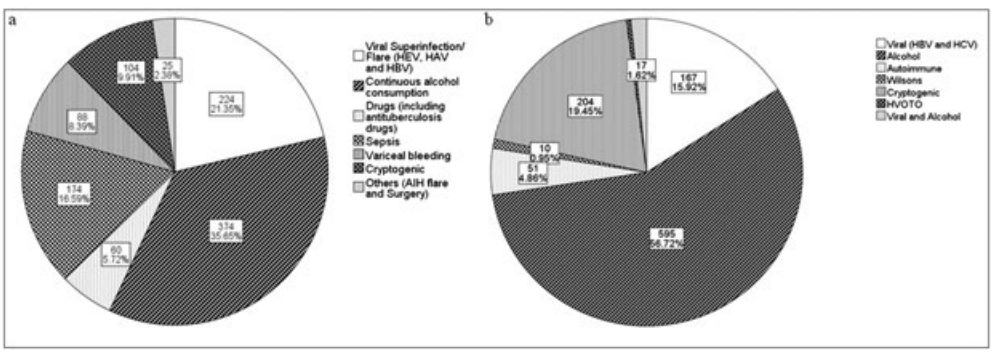

Figure 2 (a) Etiology of acute hepatic and extrahepatic precipitating events in patients with acute-on-chronic liver failure (ACLF) ($n = 1049$). (b) Etiology of chronic liver disease in ACLF patients (n = 1049). □ Viral Superinfection/Flare (HEV, HAV and HBV); ▨ Continuous alcohol consumption; ▫ Drugs (including antituberculosis drugs); ▩ Sepsis; ▪ Variceal bleeding; ▪Cryptogenic; ▫ Others (AIH flare and Surgery); ▫ Viral (HBV and HCV); ▪ Alcohol; ▫ Autoimmune; ▪ Wilsons; ▪ Cryptogenic; ■ HVOTO; ▫ Viral and Alcohol.

in 68%, 32%, 31.5%, 22.6%, 14.5%, and 15%, respectively. Fifty-seven patients had no OF, whereas 1, 2, 3, 4, and 5 OFs were recorded in 126, 86, 72, 28, and 12 patients, respectively. The mortality in patients increased progressively from 12.3% in patients with no OF to 83.3% in patients with five OFs (Fig. 3). The mortality increased in patients with increasing grade of ACLF as shown in Figure 4. Mortality in patients with ACLF 0 was 15.3% (22/144), ACLF 1–33.3% (13/39), ACLF 2–47.7% (41/86), and ACLF 3–64.3% (72/112).

Comparison of survivors and non-survivors (Table 2). Non-survivors had significantly elevated total leukocyte count, INR, serum creatinine, serum bilirubin, and serum potassium. Albumin levels were significantly lower in non-survivors as compared with survivors. Continuous alcohol consumption as an acute precipitating event was seen in a significantly higher proportion of non-survivors, and infection was more frequent. On the other hand, viral superinfection/reactivation was present in a significantly higher proportion of survivors as compared with non-survivors.

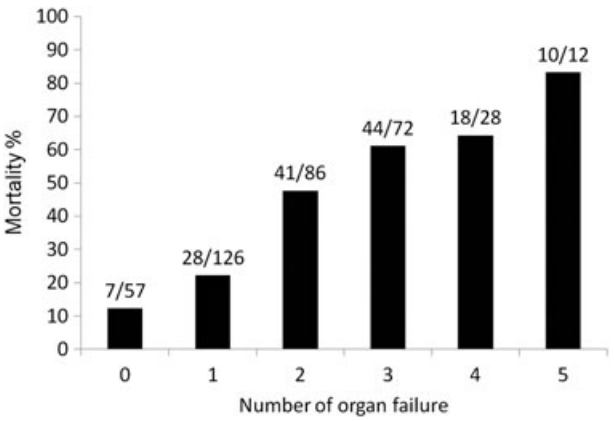

Figure 3 In-hospital mortality as per the number of organ failures ($n = 381$). The numbers on the top of the bars represent the number of deaths/total number of patients.

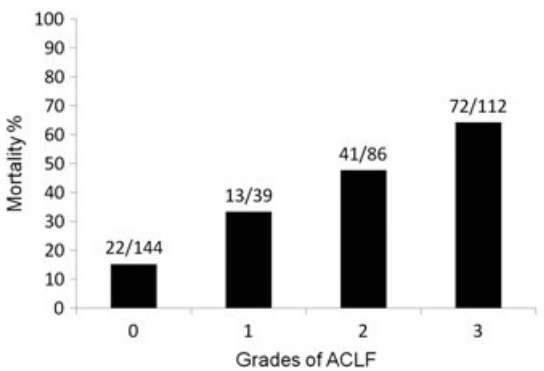

Figure 4 In-hospital mortality as per the grade of acute-on-chronic liver failure (ACLF) ($n = 381$). The numbers on the top of the bars represent the number of deaths/total number of patients.

The various prognostic scores—CLIF-SOFA, APACHE-II, MELD, and CTP scores—were significantly higher in non-survivors.

There were no significant differences in age, sex, hemoglobin, platelet count, serum sodium, aspartate aminotransferase, and alanine aminotransferase values. The etiology of CLD was similar in survivors and non-survivors. Multiple regression analysis using the Cox proportional hazard model showed that raised serum creatinine (hazard ratio [HR] 1.176, 95% CI 1.037–1.332, $P = 0.011$), advanced hepatic encephalopathy (grades III and IV) (HR 2.698, 95% CI 1.551–4.693, $P < .001$), and requirement of ventilator support (HR 2.484, 1.423–4.262, $P = 0.001$) were independent predictors of mortality.

Prognostic scores. The Area Under Receiver Operating Characteristic curves (AUROC) curves for various prognostic indices, CLIF-SOFA, MELD, APACHE II, and CTP, were 0.659 (0.596–0.722), 0.624 (0.559–0.690), 0.624 (0.559–0.689), and 0.588 (0.522–0.654), respectively (Fig. 5). On multivariate analysis, only CLIF-SOFA predicted the mortality (odds ratio [95% CI] 1.088 [1.006–1.176]).

Discussion

This retrospective multicenter study is the largest series of ACLF patients reported from India. In this study, alcohol was found to be the commonest etiology of ACLF across all centers. Acute precipitants included both hepatic and extrahepatic insults in varying proportions at different centers. The in-hospital mortality in the index admission was quite high (42%), over a short period of 8 days.

ACLF is characterized by an acute insult leading to decompensation of underlying CLD, previously diagnosed or undiagnosed. Precipitating factors include both hepatic and extrahepatic insults. In the CANONIC trial—which included 303 ACLF patients with hepatic or extrahepatic acute precipitants—bacterial infection (32.6%), gastrointestinal bleeding (13.2%), and active alcoholism (24.5%) were common acute precipitants, while no precipitating event was found in 43.6% of patients.[15] In the present ICARE cohort, a higher proportion of hepatitis viral infections were found as the acute precipitating event, which is not unexpected because both HAV and HEV are endemic in India and are major causes of both sporadic and epidemic forms of acute hepatitis. The frequency of sepsis and of variceal bleeding as acute events was lower—with the majority of such cases being reported from only three centers. Interestingly, the mortality in the extrahepatic insults in our cohort was 42.3%, similar to the overall mortality in the cohort. This is in coherence with the EASL-AASLD definition that includes extrahepatic insults as the acute precipitating events in the definition of ACLF. However, it is in contrast to the APASL definition of ACLF that includes only acute hepatic causes as precipitants of ACLF.[3] Our data suggest that extrahepatic insults should be included as acute precipitants of ACLF. It is also important that uniform definitions and predefined criteria should be used to categorize patients across all centers, to allow for comparisons.

Alcohol was reported as the most common etiology of cirrhosis in the CANONIC study (49.2%). In India, the average consumption of alcohol has increased, and the average age of consumption of alcohol has decreased.[21] Even in the ICARE cohort, alcohol

Table 2 Comparison of variables between survivors and non-survivors in patients with ACLF

Variable	Non-survivors ($n = 148$)	Survivors ($n = 233$)	P value
Age ± SD (years)	42.68 ± 11.84	42.47 ± 11.97	0.867
Sex (males : females)	124:24	175:58	0.055
Hemoglobin, g/dL	9.8 (8.4–11.0)	10.1 (8.5–11.9)	0.222
Total leukocyte count (per mm^3)	13 400 (9600–19 025)	10 200 (7400–14 500)	< 0.001
Platelet count ($\times 10^3/mm^3$)	102 (66–165.7)	108.5 (75–162)	0.295
International normalized ratio	2.29 (1.8–3.0)	2 (1.6–2.5)	< 0.001
Creatinine, mg/dL	1.9 (1.2–3.3)	1.1 (0.8–1.8)	< 0.001
Sodium, mEq/L	132 (126–141)	132 (128–138)	0.410
Potassium, mEq/L	4.2 (3.5–4.6)	3.6 (3.3–4.2)	0.001
Bilirubin level (mg/dL)	21.4 (12.1–27.1)	16.8 (9.4–24.5)	0.005
Aspartate aminotransferase (IU/L)	127 (85–229)	137.5 (90–226)	0.807
Alanine aminotransferase (IU/L)	75.5 (60–150)	80 (58–164)	0.855
Alkaline phosphatase, IU/L	244.5 (166–350)	209 (129–329)	0.067
Albumin (g/dL)	2.5 (2.1–2.9)	2.7 (2.3–3.2)	0.006
MELD	32 (26–37)	26 (21–31)	< 0.001
CLIF-SOFA	9 (7–11)	7 (5–9)	< 0.001
APACHE II	15 (11–21)	12 (10–13)	< 0.001
CTP	12 (11–13.7)	12 (10–13)	< 0.001
Ventilatory support	59 (39.6%)	27 (11.6%)	< 0.001
Etiology—acute precipitating insult			0.003
HEV, HAV, HBV	28 (18.9%)	89 (38.2%)	
Alcohol	72 (48.6%)	82 (35.2%)	
Drug	6 (4.1%)	11 (4.7%)	
Sepsis	14 (9.5%)	22 (9.4%)	
Variceal bleeding	3 (2.0%)	2 (0.9%)	
Cryptogenic	25 (16.9%)	27 (11.6%)	
Etiology—chronic liver disease			0.408
Viral	22 (14.9%)	40 (17.2%)	
Alcohol	86 (58.1%)	112 (48.1%)	
Autoimmune	8 (5.4%)	19 (8.2%)	
Wilsons	3 (2.0%)	3 (1.3%)	
Cryptogenic	27 (18.2%)	51 (21.9%)	
HVOTO	0	3 (1.3%)	
Viral and alcohol	2 (1.4%)	5 (2.1%)	
Infection	88 (59.5%)	63 (27%)	< 0.001
Organ failure			
Liver failure	111 (75%)	148 (63.5%)	0.024
Cerebral failure	35 (23.6%)	20 (8.6%)	< 0.001
Renal failure	74 (50%)	47 (20.2%)	< 0.001
Coagulation failure	60 (41.1%)	60 (26.4%)	0.004
Circulatory failure	31 (20.9%)	26 (11.2%)	0.012
Respiratory failure	59 (39.6%)	27 (11.6%)	< 0.001

All values are expressed as median (IQR), n (%) unless otherwise specified.
MELD, model of end-stage liver disease; CLIF-SOFA, chronic liver failure-sequential organ failure assessment score; APACHE, acute physiology and chronic health evaluation; CTP, Child–Turcotte–Pugh score; HEV, hepatitis E virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HVOTO, hepatic venous outflow tract obstruction; ACLF, acute-on-chronic liver failure.

was found to be the most common etiology of CLD across all centers (56.7%). Furthermore, half of the patients with active alcohol consumption died. This rising proportion of alcohol-induced liver disease is a matter of concern. It is vital to tackle this growing public health menace through education and social awareness.

The better survival rates seen in the viral superin fection/reactivation group may be explained by the fact that the number of OFs (2, 3, and 4)—which is directly related to outcome—was proportionally less in the viral precipitants as compared with other etiologies. Secondly, patients with HBV were treated with antiviral drugs, which are known to improve the outcome.[22]

The importance of OF as a defining criteria of ACLF was highlighted in the CANONIC study.[15] Presence of OF (defined as per CLIF-SOFA cut-off values) has been used in the CANONIC study to categorize patients into different grades. While in-hospital mortality was not reported in the CANONIC study, mortality at 28 and 90 days was reported to increase with

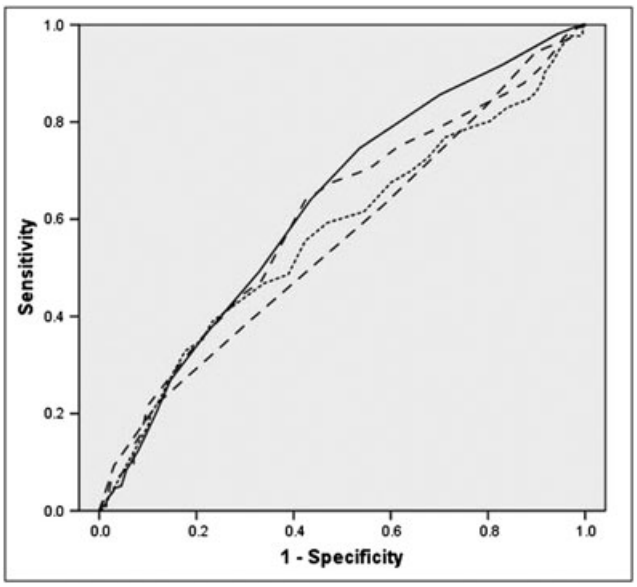

Figure 5 Receiver operating characteristic curves for various prognostic indices. The AUROC for various prognostic indices: chronic liver failure-sequential organ failure assessment, model of end-stage liver disease, acute physiology and chronic health evaluation score, and Child–Turcotte–Pugh were 0.659 (0.596–0.722), 0.624 (0.559–0.690), 0.624 (0.559–0.689), and 0.588 (0.522–0.654), respectively. — CLIF-SOFA; ···· MELD; – - APACHEII; – - CTP.

increasing grades of ACLF. In the ICARE cohort, only in-hospital mortality was assessed. A subset of 381 ACLF patients from the present cohort, for whom complete data for all parameters were available, was included in the Cox proportional hazard model in order to assess predictors of survival. In the ICARE cohort, liver failure alone was documented in 68%, which was fourfold more than that in the CANONIC study, whereas respiratory failure was present in 22.6%, compared with 2.4% in the CANONIC study. The frequencies of various OFs were twofold to ninefold more than that reported in the CANONIC study.[15] The higher frequency of OF suggests that patients in the ICARE cohort were much more sick. In accordance with the CANONIC study, mortality increased with increasing number of OFs, that is, in higher grades of ACLF, even within the short duration of hospital stay in our patients (8–10 days). Even after patients were categorized as ACLF grade 0, 1, 2, or 3, the mortality in our cohort was higher than that reported in the CANONIC study (Figs 3, 4). These differences may be possibly due to differences in etiologies of ACLF and ethnicity between the patient populations.

The mortality in patients with a serum bilirubin of 5–10 mg/dL (irrespective of other OFs) was 33% (30/90), similar to that reported by the APASL ACLF Research Consortium,[23]which predominantly included data from India. This is in contrast to the CANONIC study that defined a level of 12 mg/dL for 15% mortality at 28 days.[15] This discrepancy is best explained by the severity of acute hepatic insult in the ICARE cohort, which is illustrated by the observation that over 40% of the ICARE cohort had previously undiagnosed, "silent CLD," and decompensated from this compensated threshold to a level of decompensation that resulted in over 40% mortality within 8 days of hospitalization.

The most striking differences were seen in TLC, serum creatinine, INR, APACHE II, and CLIF-SOFA scores between survivors and non-survivors. Also, hepatic causes of acute insult were significantly higher in survivors, probably implying that systemic inflammation in these patients may have been lesser (significantly lower TLC). Overall, as expected, the non-survivors had higher CLIF-SOFA and APACHE II scores compared with the survivors. On multivariate analysis, raised serum creatinine, advanced hepatic encephalopathy, and respiratory failure with need for ventilator support were independent predictors. In addition, CLIF-SOFA score was superior to APACHE II, MELD, and CTP scores. This data reiterate the importance of OFs in determining the prognosis.

Limitations of this study include the fact that, being a retrospective study from tertiary care centers, there is inherent referral bias influencing the patient population. Also, some data were missing, which limited the number of cases (those with complete data available) for accurate assessment of OF and categorization into different grades of ACLF. We assessed the in-hospital mortality only; the mortality at 28 days and long-term mortality were not assessed. Another limitation was that patients were diagnosed as ACLF according to the APASL criteria and were thereafter assessed for OF as per the CANONIC study; there would have been cases that did not satisfy the APASL criteria but might have had OF, and these patients were excluded from the analysis. Also, although we found that infection was present in a significantly higher proportion of non-survivors as compared with survivors, we could not assess the impact of baseline infection as compared with a second attack of infection.

This study raises important issues that need to be evaluated further in future prospective studies: (i) differences in the natural course among different etiologies of ACLF (hepatic and non-hepatic precipitants); (ii) pathogenic differences in ACLF due to hepatic and non-hepatic insults; and (3) indications and timing of liver transplantation.

In conclusion, this study highlights that alcohol is the most common etiology of ACLF across India. The high mortality is a matter of concern. OFs predict outcome in ACLF. There is a need for further research into the prognostic factors, and future efforts are needed to define patients who are going to best benefit from liver transplantation.

References

1 Jalan R, Yurdaydin C, Bajaj JS *et al.* Toward an improved definition of acute-on-chronic liver failure. *Gastroenterology* 2014; **147** (1): 4–10.
2 Jalan R, Gines P, Olson JC *et al.* Acute-on chronic liver failure. *J. Hepatol.* 2012; **57** (6): 1336–48.
3 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** (1): 269–82.
4 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. *Liv. Int.: Off. J. Int. Assoc. Study Liv.* 2009; **29** (3): 392–8.
5 Kumar Acharya S, Kumar Sharma P, 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): 387–94.
6 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: Off. J. Indian Soc. Gastroenterol.* 2013; **32** (2): 108–14.

7 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** (11): 3188–92.

8 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** (9): 484–90.

9 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.: Off. J. Indian Soc. Gastroenterol.* 2015; **34** (3): 216–24.

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. Liv. Dis.: Off. J. Ital. Soc. Gastroenterol. Ital. Assoc. Study Liv.* 2012; **44** (2): 166–71.

11 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): 575–81.

12 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.* 2015. DOI:10.1016/j.jceh.2015.08.002.

13 Shalimar, Kumar D, Vadiraj 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.* 2015. DOI:10.1111/jgh.13213.

14 Brown JJ, Naylor MJ, Yagan N. Imaging of hepatic cirrhosis. *Radiology* 1997; **202** (1): 1–16.

15 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** (7): 1426–37, e1-9.

16 Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br. J. Surg.* 1973; **60** (8): 646–9.

17 Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31** (4): 864–71.

18 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit. Care Med.* 1985; **13** (10): 818–29.

19 Buchel E, Van Steenbergen W, Nevens F, Fevery J. Improvement of autoimmune hepatitis during pregnancy followed by flare-up after delivery. *Am. J. Gastroenterol.* 2002; **97** (12): 3160–5.

20 Chu CM, Liaw YF. Genotype C hepatitis B virus infection is associated with a higher risk of reactivation of hepatitis B and progression to cirrhosis than genotype B: a longitudinal study of hepatitis B e antigen-positive patients with normal aminotransferase levels at baseline. *J. Hepatol.* 2005; **43** (3): 411–7.

21 Prasad R. Alcohol use on the rise in India. *Lancet* 2009; **373** (9657): 17–8.

22 Garg H, Sarin SK, Kumar M, Garg V, Sharma BC, Kumar A. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. *Hepatology* 2011; **53** (3): 774–80.

23 Sarin SK, Kedarisetty CK, Abbas Z *et al.* Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. *Hepatol. Int.* 2014; **8** (4): 453–71.