Impact of Hepatic and Extrahepatic Insults on the Outcome of Acute-on-Chronic Liver Failure

Tarana Gupta, Radha K. Dhiman, Sahaj Rath, Swastik Agrawal, Ajay Duseja, Sunil Taneja, Yogesh Chawla

Department of Hepatology, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India

Background: To study the differences in outcome and predictors of mortality in acute-on-chronic liver failure (ACLF) precipitated by hepatic or extrahepatic insults. **Methods:** Consecutive patients of cirrhosis with acute decompensation were prospectively included and followed up for 90 days from admission. ACLF was defined based on chronic liver failure (CLIF) acute-on-chronic liver failure in cirrhosis (CANONIC study) criteria. Acute worsening due to acute viral hepatitis A and E, hepatitis B flare, alcoholic hepatitis, autoimmune hepatitis flare, or drug-induced liver injury were categorized as hepatic ACLF and that due to bacterial infection, upper gastrointestinal bleed or surgery as extrahepatic ACLF. Patients with both hepatic and extrahepatic insults were included in combined insult group. **Results:** Of 179 patients of acute decompensation, 122 had ACLF (hepatic insults 47 and extrahepatic insults 51). Alcohol (64.8%) was the most common etiology of cirrhosis while infection (36%) was the most common acute insult followed by alcoholic hepatitis (24.6%). Higher proportion of extrahepatic ACLF patients had history of prior decompensation than hepatic ACLF patients (62.7% vs. 27.7%, $P < 0.001$). There was no difference in mortality among hepatic and extrahepatic ACLF groups at 28 and 90 days (53.2% vs. 56.9%, $P = 0.715$ and 85% vs. 74.5%, $P = 0.193$, respectively). Area under receiver-operating curve (AUROC) for 28-day mortality in extrahepatic ACLF group was 0.788, 0.724, 0.718, 0.634, and 0.726 and in hepatic-ACLF group was 0.786, 0.625, 0.802, 0.761, and 0.648 for chronic liver failure-sequential organ failure assessment (CLIF-SOFA), model for end stage liver disease (MELD), integrated MELD score (iMELD), acute physiology and chronic health evaluation score (APACHE-II), and Child-Turcotte-Pugh score scores, respectively. **Conclusion:** There is no difference in mortality among hepatic and extrahepatic ACLF groups at 28 and 90 days. iMELD and CLIF-SOFA have highest AUROC to predict 28-day mortality in hepatic and extrahepatic ACLF groups, respectively. (J CLIN EXP HEPATOL 2017;7:9–15)

Acute-on-chronic liver failure (ACLF) is a clinical scenario wherein an acute insult leads to deterioration of underlying chronic liver disease. Asian Pacific Association for the Study of Liver (APASL)¹ and European Association for the Study of Liver (EASL)^{2,3} have given different criteria for diagnosing ACLF. The APASL group considers only hepatic insults/injury as acute

precipitating event, whereas EASL also includes extrahepatic insult such as the sepsis and upper gastrointestinal bleeding as a cause of acute insult.^{2,4–7} The chronic liver failure (CLIF) acute-on-chronic liver failure in cirrhosis (CANONIC) study has defined ACLF based on increased 28-day mortality in patients with liver cirrhosis and acute decompensation. In a previous study, we have demonstrated chronic liver failure-sequential organ failure assessment (CLIF-SOFA) criteria to be better than APASL criteria in defining ACLF.⁸ Various scoring systems like Child-Turcotte-Pugh (CTP),⁹ model for end-stage liver disease (MELD),¹⁰ integrated MELD (iMELD) score,¹¹ acute physiology and chronic health evaluation (APACHE II),¹² and CLIF-SOFA score⁸ have been used for prediction of mortality in ACLF. Studies across the globe have shown increased mortality and worse prognosis in patients of cirrhosis presenting as ACLF. The severity of ACLF depends on severity of chronic liver disease, the severity of acute insult and the induced systemic inflammatory response syndrome (SIRS), and finally resulting organ failure. There is ongoing effort to identify whether the cause of acute insult apart from its severity is also important in determining the final outcome of patients. In this prospective study, we aimed to determine the difference in the clinical course of patients with ACLF due to hepatic

Keywords: acute-on-chronic liver failure, hepatic insult, extrahepatic insult, mortality, organ failure

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Address for correspondence: Radha K. Dhiman, Department of Hepatology, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India. Tel.: +91 7087009337/1722744401.

E-mail: rkpsdhiman@hotmail.com

Abbreviations: ACLF: acute-on-chronic liver failure; APACHE-II: acute physiology and chronic health evaluation score; APASL: Asian Pacific Association for the Study of Liver; AUROC: area under receiver-operating characteristics; CANONIC study: chronic liver failure (CLIF) acute-on-chronic liver failure in cirrhosis; CLIF-SOFA: chronic liver failure-sequential organ failure assessment; CTP: Child-Turcotte-Pugh score; EASL: European Association for the Study of Liver; HE: hepatic encephalopathy; iMELD: integrated MELD score; MELD: model for end-stage liver disease; SBE: spontaneous bacterial empyema; SBP: spontaneous bacterial peritonitis; SIRS: systemic inflammatory response syndrome; UTI: urinary tract infection

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and extrahepatic insults, their 28- and 90-day mortalities, and the accuracy of different prognostic scores for predicting 28-day mortality.

METHODS

This was a prospective, observational cohort study, which screened inpatients of cirrhosis admitted in the Department of Hepatology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India from July 2013 to June 2015. The PGIMER, Chandigarh ethics committee approved the study (INT/IEC/2015/493, dated 11/09/2015). All study participants, or their legal guardian, provided informed written consent prior to study enrollment and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. All consecutive patients of cirrhosis of liver with acute decompensation were screened and patients fulfilling the criteria of ACLF as per CANONIC study were included. All patients were followed up for 90 days from inclusion or death, whichever was earlier. Patients with hepatocellular carcinoma, chronic kidney disease, cardiovascular disease, chronic respiratory disease, cerebrovascular disease, pregnancy, and age <18 years were excluded from the study.

DEFINITIONS

Acute Decompensation

The diagnosis of cirrhosis was based on clinical, biochemical, and ultrasonography or liver histological data.^{8,13} Acute decompensation of cirrhosis was defined as per the criteria of the CANONIC study as development of upper gastrointestinal bleeding, overt ascites over 2 weeks, new onset hepatic encephalopathy (HE), and/or bacterial infection.² Acute bacterial infection was diagnosed by presence of spontaneous bacterial peritonitis (SBP) (ascitic fluid polymorphonuclear leukocytes >250 cells/mm³), spontaneous bacterial empyema (SBE) (pleural fluid polymorphonuclear leukocytes >250 cells/mm³ with culture or >500 cells/mm³ without culture), urinary tract infection (UTI) (positive urine culture with or without presence of pus cells in urine), pneumonia (sputum culture positive or infiltrates on chest X-ray), cellulitis (with or without positive culture), and bacteremia (positive blood culture) on admission.

Acute-on-Chronic Liver Failure

ACLF was diagnosed as per CANONIC study.² The organ failures were considered as per CLIF-SOFA score. Liver failure was defined as bilirubin >12 mg/dL, coagulation failure as international normalized ratio (INR) >2.5, or platelet count <20,000/mm³; cerebral failure as presence of grade III/IV HE; renal failure as creatinine >2 mg/dL or need of renal replacement therapy; respiratory failure as

PaO₂/FiO₂ < 200 or SpO₂/FiO₂ < 214; and circulatory failure as mean arterial pressure (MAP) < 70 mmHg requiring inotropic support.²

The acute insult was considered hepatic if there was (1) recent alcohol intake leading to alcoholic hepatitis, (2) acute viral hepatitis A, B, or E, (3) hepatitis B virus (HBV) flare, or (4) drug-induced liver injury, and as extrahepatic if there was (1) bacterial infection, (2) surgery, or (3) upper gastrointestinal bleeding. If 2 insults were present simultaneously, patients were classified as having combined insult, and if no precipitating event could be identified, unknown insult was kept as a possibility.

Various prognostic scores including CTP, MELD, CLIF-SOFA, APACHE II, and iMELD were calculated from the patient data on admission.^{9–12}

MANAGEMENT OF PATIENTS

All patients were clinically evaluated including history, physical examination, and routine biochemical and imaging parameters. Work-up for the cause of cirrhosis and acute insult(s) was done for each case. The diagnosis of acute viral hepatitis was based on a positive serology for hepatitis E virus (IgM anti-HEV) or hepatitis A virus (IgM anti-HAV) by ELISA. HBV flare, autoimmune hepatitis (AIH), and Wilson disease were diagnosed based on American Association for the Study of Liver Diseases practice guidelines.^{14–16}

All patients were screened for presence of infection by procalcitonin assay, blood cultures, urine and ascitic fluid culture, blood fungal culture, and galactomannan assays on admission and later as required clinically. All patients with suspected infection were given intravenous antibiotics against gram-negative organisms empirically on admission, and later on, this was modified based on culture sensitivity pattern. In case of worsening sepsis, antibiotics against gram-positive organisms followed by antifungals were also given as required. Acute kidney injury was managed with intravenous 20% human albumin for 48 h followed by vasoactive drugs if needed and dialysis if indicated. Ascites was managed using diuretics and HE was treated with lactulose and rifaximin. Patients with circulatory failure were started on inotropes and those with respiratory failure were put on mechanical ventilation. Specific therapy included pentoxifylline 400 mg three times per day orally and tenofovir 300 mg once daily, modified by renal function, for alcoholic hepatitis and HBV flare, respectively. None of the patients were eligible for administration of steroid therapy. None of the patients underwent any experimental therapy or liver transplantation.

Statistical Analysis

The quantitative variables were presented as mean with standard deviation and/or range and qualitative variables

as proportions with percentages. Comparison between groups was done using Student's *t*-test and Mann-Whitney test for parametric and nonparametric variables, respectively, and χ^2 and Fisher exact test were used for categorical variables. Accuracy of prediction of 28-day mortality by MELD, iMELD, CTP, CLIF-SOFA, and APACHE-II in hepatic and extrahepatic ACLF groups was evaluated using area under receiver-operating curve (AUROC). A *P* value ≤ 0.05 was considered significant. Statistical analysis was performed using SPSS software version 21.0 (SPSS Inc., Chicago, IL).

RESULTS

Patients

Out of 480 patients with cirrhosis, 179 were found to have acute decompensation. ACLF was diagnosed in 122 patients on admission (Figure 1). Among 122 patients of ACLF, acute insult was hepatic in 47 (38.5%),

extrahepatic in 51 (41.8%), combined hepatic and extrahepatic in 15 (12.3%), and was unknown in 9 (7.4%) patients (Figure 1). Alcohol was the most common etiology of cirrhosis in 79 (64.8%) patients followed by cryptogenic, hepatitis C, hepatitis B, AIH, Wilson disease, and primary biliary cirrhosis (Table 1).

Clinical Characteristics

Overall, bacterial infection was the most common acute precipitating event in 44 (36%) patients followed by alcoholic hepatitis in 29 (23.8%) (Table 2). In hepatic ACLF group, alcoholic hepatitis was the most common acute insult followed by HBV flare, AIH flare, acute viral hepatitis, and Wilson disease (Table 1). In extrahepatic ACLF group, bacterial infection was the most common acute insult followed by upper gastrointestinal bleed and surgery (Table 3).

History of prior decompensation of liver disease was more common in patients of extrahepatic ACLF than

Figure 1 Flow chart of patients screened in the study.

Table 1 Etiology of Chronic Liver Disease.

Etiology	Overall (n = 179)	ACLF (n = 122)	Extrahepatic ACLF (n = 51)	Hepatic (n = 47)
Alcohol	118 (66%)	79 (64.8%)	26 (51%)	31 (66%)
Chronic hepatitis B	10 (5.6%)	7 (5.7%)	0	7 (15%)
Chronic hepatitis C	10 (5.6%)	8 (6.6%)	7 (13.7%)	1 (2.1%)
Alcohol and chronic hepatitis B/C	6 (3.4%)	5 (4.1%)	3 (5.8%)	1 (2.1%)
Cryptogenic	17 (9.5%)	11 (9%)	8 (15.7%)	1 (2.1%)
Wilson disease	5 (2.8%)	4 (3.3%)	2 (3.9%)	2 (4.3%)
Autoimmune hepatitis	8 (4.5%)	7 (5.7%)	4 (7.8%)	2 (4.3%)
Primary biliary cirrhosis	1 (0.6%)	1 (0.8%)	1 (1.9%)	0

ACLF: acute-on-chronic liver failure.

Table 2 Etiology of Acute Insult.

Acute insult	Cause	n (%)
Hepatic (n = 47)	Alcoholic hepatitis	30 (24.6%)
	HBV flare	8 (6.6%)
	AIH flare	3 (2.5%)
	Wilson disease	2 (1.6%)
	Viral hepatitis (A/B/E)	4 (3.3%)
Extrahepatic (n = 51)	Bacterial infection	44 (36%)
	Gastrointestinal bleed	6 (4.9%)
	Surgery	1 (0.8%)
Combined (n = 15)	Both hepatic and extrahepatic	15 (12.3%)
Unknown (n = 9)	Cause not identified	9 (7.4%)

HBV: hepatitis B; AIH: autoimmune hepatitis.

hepatic ACLF group (62.7% vs. 27.7%, $P < 0.001$). Extrahepatic ACLF group had low hemoglobin and platelet count as compared to hepatic ACLF group (Table 3). Hepatic ACLF group had higher serum bilirubin (mean 23.0 vs. 13.1 mg/dL, $P < 0.001$) than extrahepatic ACLF group resulting in higher prevalence of liver failure (85% vs. 49%, $P < 0.001$). There was no significant difference in prevalence of other organ failures (Table 3). Hepatic ACLF group had higher MELD (33.7 vs. 29.9; $P = 0.026$) and higher CLIF-SOFA (10.9 vs. 9.9; $P = 0.047$) than extrahepatic ACLF group (Table 4).

Mortality and Prognostic Models

There was no difference in 28- and 90-day mortalities among hepatic and extrahepatic ACLF groups (53.2% vs.

56.9%, $P = 0.715$ and 85% vs. 74.5%, $P = 0.193$, respectively) (Figure 3). Within the hepatic ACLF group, 28-day mortality was significantly lower if the acute insult was acute hepatitis B or hepatitis B flare ($n = 9$) compared to any other cause ($n = 38$) (11.1% vs. 52.6%, $P = 0.030$). The 90-day mortality was also lower, though not reaching statistical significance (55.6% vs. 84.2%, $P = 0.081$).

In extrahepatic ACLF group, CLIF-SOFA had highest AUROC for prediction of mortality at 28 days (0.788, 95% CI: 0.655–0.922). In hepatic ACLF group, iMELD has highest AUROC for prediction of mortality at 28 days (0.802, 95% CI: 0.674–0.930) (Table 5 and Figure 2A and B).

DISCUSSION

This study demonstrated that patients with ACLF have higher mortality than patients with acute decompensation not amounting to ACLF; however, there is no difference in 28- and 90-day mortalities based on whether the acute insult was hepatic or extrahepatic. The best prognostic score for hepatic group is iMELD and for extrahepatic group is CLIF-SOFA. Similar to our previous data,^{7,8} in the present study, alcohol was the predominant cause of chronic liver disease, alcoholic hepatitis was the most common hepatic insult, and infection was the most common extrahepatic insult. This is in contrast to studies from East Asia where hepatitis B is the predominant cause of chronic liver disease as well as acute insult in patients with ACLF.¹⁷

Patients with hepatic ACLF had higher bilirubin values and higher proportion of liver failure when compared to extrahepatic ACLF. In addition, hepatic ACLF group had

Table 3 Demographic, Clinical, and Laboratory Data at Admission.

Variable	Overall (n = 179)	ACLF (n = 122)	No ACLF (n = 57)	Hepatic ACLF ^a (n = 47)	Extrahepatic ACLF ^b (n = 51)	P ^{a,b} value
Age (years)	44.4 (18–78)	43.2 (21–70)	46.8 (16–78)	41.0 (25–70)	45.1 (21–70)	0.069
Males	154 (86%)	106 (86.9%)	48 (84.2%)	42 (89%)	40 (78%)	0.144
Prior decompensation	95 (53%)	57 (46.7%)	38 (66.7%)	13 (27.7%)	32 (62.7%)	0.000
Total leukocyte count ($\times 10^3/\text{mm}^3$)	13.1 (2.3–44.9)	14.4 (2.3–44.9)	10.3 (3–28)	14.9 (2.3–34.7)	12.5 (2.7–36.4)	0.032
Hemoglobin (g/dL)	9.1 (3.7–14.6)	9.2 (4–14)	9 (4.7–14.6)	9.9 (5.4–14.6)	8.8 (3.7–14)	0.007
Platelet count ($\times 10^3/\text{mm}^3$)	115.8 (9.4–444)	118.6 (9.4–444)	109.7 (14.4–393)	137.8 (9.4–444)	99.5 (17.3–369)	0.033
Bilirubin (mg/dL)	14.2 (0.5–45)	17.4 (1–45)	7.3 (1–30)	23 (7.3–45)	13.1 (0.6–45)	<0.001
INR	2.4 (1.2–7)	2.7 (1.2–7)	1.85 (1.2–4.1)	2.7 (1.2–5.8)	2.6 (1.2–7)	0.724
Albumin (g/dL)	2.8 (1.5–4.4)	2.7 (2–4)	2.8 (1.7–4.4)	2.7 (2–4)	2.8 (2–4)	0.715
Blood urea (mg/dL)	75.4 (10–286)	88.6 (10–286)	47.2 (11–151)	72.7 (10–255)	102 (17–286)	0.157
Creatinine (mg/dL)	2.1 (0.6–9.4)	2.6 (0.6–9.4)	1.19 (0.8–4.9)	2.5 (0.6–8)	2.7 (0.9–9.4)	0.697
Sodium (mEq/L)	131 (108–153)	129 (108–145)	133.2 (114–153)	130 (113–140)	130 (112–145)	0.934
Potassium (mEq/L)	4.1 (2.1–6.3)	4.1 (2–6)	4 (2.5–5.8)	3.8 (2–6)	4.2 (2–6)	0.064

^{a, b} ACLF: acute-on-chronic liver failure; INR: international normalized ratio.

Table 4 Organ Failures, Prognostic Scores, and Mortality in Hepatic and Extrahepatic ACLF.

Variable	Overall (n = 179)	ACLF (n = 122)	Hepatic ACLF ^a (n = 47)	Extrahepatic ACLF ^b (n = 51)	P ^{a,b} value
Liver failure	90 (50%)	79 (64.8%)	40 (85%)	25 (49%)	<0.001
Coagulation failure	69 (38.5%)	69 (56.6%)	26 (55%)	30 (58.8%)	0.726
Cerebral failure	21 (12%)	21 (17.2%)	10 (21%)	9 (17.6%)	0.650
Renal failure	73 (40.1%)	73 (59.8%)	27 (57%)	32 (62%)	0.592
Circulatory failure	13 (7.3%)	14 (11.5%)	5 (10.6%)	6 (11.8%)	0.860
Respiratory failure	2 (1%)	2 (1.6%)	1 (2.1%)	1 (1.9%)	0.953
CTP	11.3 (5–15)	11.7 (7–15)	11.7 (8–14)	11.8 (8–15)	0.760
APACHE II	12.4 (1–41)	13.3 (3–27)	14.4 (4–27)	13.2 (3–24)	0.337
MELD	28 (8–40)	31.6 (12–40)	33.7 (18–40)	29.9 (12–40)	0.026
iMELD	6.4 (1.8–12.6)	7.2 (3–13)	7.4 (3–13)	7.2 (3–12)	0.714
CLIF-SOFA	9.1 (1–18)	10.4 (4–18)	10.9 (8–17)	9.9 (5–15)	0.047
28-day mortality	76 (42.4%)	68 (55.7%)	25 (53.2%)	29 (56.9%)	0.715
90-day mortality	107 (59.8%)	96 (78.7%)	40 (85%)	38 (74.5%)	0.193

a, b ACLF: acute-on-chronic liver failure; CTP: Child–Turcotte–Pugh score; MELD: model for end-stage liver disease; APACHE II: acute physiology and chronic health evaluation score; iMELD: integrated MELD score; CLIF-SOFA: chronic liver failure-sequential organ failure assessment.

higher MELD and CLIF-SOFA score at admission. There was higher prevalence of prior decompensation and lower platelet counts in extrahepatic ACLF group. This illustrates the basic difference between the two groups in that there is poor hepatic reserve in extrahepatic ACLF group due to more advanced underlying liver disease. Failure may be precipitated by relatively minor extrahepatic insult, which does not result in very high bilirubin values or development of liver failure.¹⁸ High prevalence of infection in this group may be due to a more immunocompromised state due to underlying advanced liver disease. In hepatic ACLF group, the hepatic reserve is relatively maintained and ACLF develops when a severe hepatic insult leads to acute hepatic failure-like situation leading to high prevalence of liver failure with high MELD scores.

Table 5 Predictive Value of Prognostic Scores in Hepatic and Extrahepatic ACLF Groups.

Variables	28-day mortality			
	Hepatic ACLF		Extrahepatic ACLF	
	AUROC	95% CI	AUROC	95% CI
MELD	0.625	0.457–0.704	0.724	0.581–0.867
iMELD	0.802	0.674–0.930	0.718	0.576–0.86
APACHE II	0.761	0.619–0.903	0.634	0.471–0.797
CLIF-SOFA	0.786	0.648–0.904	0.788	0.655–0.922
CTP	0.648	0.489–0.808	0.726	0.586–0.866

ACLF: acute-on-chronic liver failure; CTP: Child–Turcotte–Pugh score; MELD: model for end-stage liver disease; APACHE II: acute physiology and chronic health evaluation score; iMELD: integrated MELD score; CLIF-SOFA: chronic liver failure-sequential organ failure assessment.

The fact that the prevalence of extrahepatic organ failure is not higher in the extrahepatic insult group emphasizes that the final common pathway of deterioration and mortality in ACLF is systemic inflammation and subsequent circulatory dysfunction resulting in multiorgan failure^{19,20} irrespective of the cause of acute insult. In our previous study, we reported increasing in-hospital mortality with increasing numbers of organ failures (26% with single organ failure and 58%, 71%, and 100% with two, three, and four organ failures, respectively) in ACLF.²¹ The CANONIC investigators also gave importance to 28-day mortality to define ACLF and demonstrated increasing 28-day mortality with worsening ACLF grades.² iMELD, rather than multiorgan failure scores, was the best predictor of 28-day mortality in hepatic ACLF group. Since most patients of hepatic ACLF were compensated prior to acute worsening, the liver failure in them is more synonymous to acute liver failure where an acute hepatic insult leads to rapid deterioration of liver functions. Hence, iMELD encompassing core liver functions like bilirubin, INR, and encephalopathy is most affected. In contrast, CLIF-SOFA was the best predictor of mortality in extrahepatic ACLF group. Most of the patients in this group were already decompensated and infection was the most common extrahepatic insult resulting in systemic inflammation and predominant extrahepatic organ involvement with less liver failures. CLIF-SOFA score, which has good representation of extrahepatic organs, is hence best in determining 28-day mortality in extrahepatic ACLF. This is similar to CANONIC study where multiorgan failure was determinant of mortality in ACLF in a population where majority of acute insults were extrahepatic.^{2,22}

Figure 2 AUROC of various prognostic scores for 28-day mortality in (A) extrahepatic ACLF and (B) hepatic ACLF.

Despite these differences, the 28- and 90-day mortalities were comparable between the groups. In contrast, a Chinese study showed comparable 28-day mortality (50.7% vs. 48.3%, $P = 0.22$) but increased 90-day mortality in extrahepatic ACLF than hepatic ACLF group (68.3% vs. 58.9%, $P = 0.035$).¹⁷ This difference could be explained by the fact that the majority of hepatic ACLF in the Chinese study was due to HBV flare on underlying HBV cirrhosis, which is an imminently treatable condition by use of potent antivirals, unlike severe alcoholic hepatitis, which was the most common cause of hepatic ACLF in our study. Hence, 90-day mortality in hepatic ACLF group was high in our study compared to the previous study, and we did not find any difference in mortality between hepatic and extrahepatic ACLF. Since both these groups have similar clinical course

and outcome, it does not seem reasonable to exclude extrahepatic insults from the purview of ACLF as per the APASL definition.¹

The importance of this study is that by further stratifying ACLF based on the nature of acute insult and understanding the pathophysiological differences we may be able to devise better-targeted therapies for different types of ACLF. Also, determining the best prognostic score for each subtype of ACLF may further help us to optimize the decision regarding need for liver transplantation in this high-risk group.²³

CONCLUSION

This study demonstrates that while there are differences in severity of underlying liver disease and occurrence of liver failure after the acute insult, there is no difference in extrahepatic organ failure or mortality between ACLF caused by hepatic or extrahepatic insults.

AUTHORS' CONTRIBUTION

RKD conceived the idea for the study, wrote the protocol, performed analyses, interpreted data, and prepared the manuscript. TG wrote the protocol, performed analyses, interpreted data, and prepared the manuscript. SR assisted in data collection and patient care management. SA assisted in data analyses, interpreting data, and in preparing the manuscript. ST, AD, and YKC were involved in patient care management and assisted in the interpretation of the data and in preparing the manuscript.

Figure 3 Mortality at 28 and 90 days in various groups of acute-on-chronic liver failure (ACLF).

CONFLICTS OF INTEREST

The authors have none to declare.

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