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Original Article

Frequency, Clinical Presentation, and Outcome of Acute-on-Chronic Liver Failure among Decompensated Cirrhosis of Liver Patients in a Tertiary Care Hospital

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Abstract:

Background: *Acute-on-chronic liver failure (ACLF) is characterised by the presence of organ failure in patients with decompensated cirrhosis and is associated with high short-term mortality. Different international entities have taken initiatives to define the condition in different times but recommendations and definitions from The European Association for the Study of the Liver- Chronic Liver Failure (EASL-CLIF) Consortium Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study are most comprehensive and widely accepted till date. Only limited data are available on the prevalence, clinical characteristics, and short-term outcomes of ACLF in Bangladesh. It would be very useful for clinicians to identify patients with ACLF early and initiate focused therapy including referral to transplant centers if these data are available.*

Objective: *To evaluate frequency, clinical presentation, and outcome of acute-on-chronic liver failure among decompensated cirrhosis of liver patients.*

Materials and Methods: *This prospective observational study was carried out at the Department of Gastrointestinal, Hepatobiliary and Pancreatic Disorders (GHPD), BIRDEM General Hospital, Shahbagh, Dhaka, Bangladesh from July, 2019 to September, 2021. Total 175 patients with decompensated cirrhosis of liver were screened, out of which 22 patients were dropped out due to various reasons. Purposive type of non-probability sampling technique was used. Formal ethical clearance was taken from the Institutional Review Board and ethical measures were ensured in concordance with the Declaration of Helsinki. An informed written consent was taken from all participants. Diagnosis of decompensated cirrhosis was based on clinical, biochemical, radiological and endoscopic findings. Laboratory data sent within 24 hours were collected. Oxygen saturation was measured using fingertip pulse oximeter. Investigations for ACLF triggers were done as necessary which included but not limited to urine routine and microscopic examination, urine culture, blood culture, and Anti HEV IgM. Patients' prognosis and survivability were observed by follow up phone call at 30 days. All data were recorded in a separate case record form and finally, it was analyzed by SPSS 23.*

Results: *Out of 153 patients, 49 patients (32%) had ACLF: grade 1 ACLF in 26 (17%), grade 2 in 18 (11.8%), and grade 3 in 5 (3.3%) patients. Patients had an average age of 59.54±11.55 years with no significant difference between ACLF and no ACLF groups. Most patients in both groups had others (NAFLD, autoimmune hepatitis, secondary biliary cirrhosis, idiopathic) as the main underlying cause of cirrhosis. Bacterial infection, GI bleeding, HEV infection, reactivation of HBV were the precipitating events in 81.6% of patients with ACLF, with bacterial infection being the most common trigger (63.3%). Overall, 44.9% ACLF patients died within 30 days of admission. Older age, male sex, hepatic encephalopathy, GI bleeding, presence of any trigger and higher Child-Turcotte-Pugh (CTP) score were associated with increased risk of death in ACLF.*

Conclusion: *Follow up of 153 patients with decompensated cirrhosis of liver revealed that 1 in 3 patients had ACLF and 44% of them would die in 30 days. Bacterial infection and GI bleeding were the most common triggers of ACLF. Early identification and intervention with multidisciplinary approach and referral to transplant centers are likely to improve survival outcomes in this population.*

Key words: *Acute-on-Chronic Liver Failure (ACLF), Decompensated Cirrhosis of Liver*

Introduction

Liver failure can develop as acute liver failure (ALF) in the absence of a preexisting liver disease, or a chronic decompensation of an end-stage liver disease termed as chronic liver failure (CLF), or an acute deterioration of known or unknown chronic liver disease known as acute-on-chronic liver failure (ACLF).[1]The terminology ACLF was first used in 1995 to describe a condition in which two insults to liver are operating simultaneously, one is ongoing and chronic and the other one is acute.[2] Since then different international entities have taken initiatives to define the condition including Asian Pacific Association for the Study of the Liver (APASL), North American Consortium for the Study of End-Stage Liver Disease (NACSELD), and European Association for the Study of the Liver-chronic liver failure (EASL-CLIF), to name a few. In 2009, the APASL provided the first consensus on ACLF, defined as "an acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy".[1] The 2014 definition was further expanded to include 'high 28-day mortality'.[3] Such

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initiatives led the scientific community to find out new fields of research of a syndrome with extrahepatic organ failure associated with short-term mortality. The EASL-CLIF Consortium Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study is a comprehensive registry to understand outcomes on hospitalized patients with cirrhosis.[4] Unlike NACSELD which only considered infections as triggers of ACLF, there was no restrictive inclusion criteria, and operational definitions for organ failure in EASL-CLIF were clearly outlined. The CANONIC investigators adapted the Sequential Organ Failure Assessment (SOFA) to their cohort to predict short-term mortality (CLIF-C ACLF).[5] On the other hand, APASL ACLF Research Consortium (AARC) 2019 definition considers patients with compensated cirrhosis (diagnosed or undiagnosed) and those with non-cirrhotic chronic liver disease only. Patients who have extrahepatic precipitants and those with kidney, circulatory, or respiratory failures are excluded from the definition.[6] Finally, the World Gastroenterology Organization (WGO), considering the differences between Western and Eastern definitions, has recently provided some suggestions to improve the operational definition of ACLF and its validity remains to be determined using prospective studies.

Current recommendation by EASL-CLIF is defining ACLF as- absence of ACLF (patients with: No organ failure, Single organ failure in patients with a serum creatinine level of <1.5 mg/dL and no hepatic encephalopathy, Cerebral failure in patients with a serum creatinine level of <1.5 mg/dL), ACLF grade 1 (patients with: single kidney failure, single liver, coagulation, circulatory or lung failure that is associated with a serum creatinine level of 1.5–1.9 mg/dL and/or hepatic encephalopathy grade 1 or grade 2, single brain failure with a serum creatinine level of 1.5– 1.9 mg/dL), ACLF grade 2 (patients with: two organs failures), ACLF grade 3 (patients with: three organ failures or more).[4]

Due to the variety of definitions it is quite difficult to predict an accurate proportion of patients with cirrhosis who would meet criteria for ACLF. However, based on previous studies it is reasonable to estimate that ACLF is present in between 24% and 40% of patients with decompensated cirrhosis admitted to the hospital.[7] Viral hepatitis, alcohol or a combination of both are the predominant causes of underlying chronic liver disease in ACLF in the world.[9]The change in dietary patterns and lifestyle will likely lead to a shift on the ACLF predisposing disease and, as other areas in hepatology, it would not be surprising if non-alcoholic steatohepatitis took the lead in years to come.[10]The nature of potential triggers also varies depending on the geographical locations and population under study.

Hence, only limited data are available on the prevalence, clinical characteristics, and short-term outcomes of ACLF in patients with cirrhosis seen in Bangladesh. It would be very useful for clinicians to identify patients with ACLF early and initiate focused therapy if these data are available. In Bangladesh liver transplantation program is going to be done regularly in near future. For selection of liver transplant cases, the etiology and comorbid conditions play a vital role. Systemic infection is a relative contraindication for liver transplantation. So the aims of this study were to explore frequency, clinical presentation and outcome of ACLF among decompensated cirrhosis of liver patients in a tertiary care hospital in Bangladesh.

Materials and Methods

This was a prospective observational study carried out at the department of Gastrointestinal, Hepatobiliary and Pancreatic Disorders (GHPD), BIRDEM General Hospital, Shahbagh, Dhaka, Bangladesh during the period of July, 2019 to September, 2021.Sample size is calculated at 5% level of significance and confidence interval at 95% level.Purposive type of non-probability sampling technique was applied to enroll the patients with decompensated cirrhosis of liver admitted in the department of GHPD of BIRDEM General Hospital, Dhaka, were included in this study.

Diagnosis of cirrhosis was based on clinical, biochemical, radiological and endoscopic findings. The primary outcome was transplant-free survivability within the 30 days after the date of admission for decompensated cirrhosis. Age, sex, blood pressure, and laboratory values from patient's admission form were obtained. Hepatitis C virus (HCV) was defined based on a positive HCV RNA test or positive Anti HCV antibody test, hepatitis B virus (HBV) based on a positive HBV DNA test or positive HBsAg test or Anti HBc total test, and alcohol-related liver disease based on previous diagnosis of alcohol use disorders or an Alcohol Use

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Disorders Identification Test-Consumption (AUDIT-C) ≥4, at any point prior to the first admission for cirrhosis. AUDIT-C questionnaire was used only when patient gives history of alcohol consumption. The following injury/trigger factors were defined: infection including HEV superinfection and relapse of hepatitis B, gastrointestinal bleeding, active alcohol use, hepatotoxic drugs, and herbal indigenous medicines. Active alcohol use was further defined when the patient had any alcohol use disorder and/or AUDIT-C ≥4 within 1 year prior to the admission. The model for end-stage liver disease sodium corrected (MELD-Na) was calculated using laboratory values for bilirubin, creatinine, INR, and serum sodium on the first value within 24 hours. If several values were present within 24 hours, the maximum bilirubin, creatinine, and INR, and lowest sodium values were taken.

Inclusion criteria were all patients of decompensated cirrhosis of liver (acute decompensation as well as prior decompensation), newly and previously diagnosed Cirrhosis patients were included, duration of hospital stay at least 24 hours, and age ≥ 18 years. Exclusion criteria were admission for scheduled procedure or treatment, hepatocellular carcinoma beyond Milan criteria, severe comorbid conditions like stroke, Chronic Kidney Disease (CKD) including End-stage renal disease (ESRD), Chronic Obstructive Pulmonary Disease (COPD), and chronic heart failure, ongoing immunosuppressive treatments, jaundice due to biliary obstruction.

A questionnaire was filled up by the investigator which would contain information regarding past history of CLD, previous admission for decompensation, alcohol intake, viral hepatitis, hepatic encephalopathy, ascites, variceal bleeding and jaundice, drug history and other co-morbidities. Physical examination was done systematically. Blood sample for serum albumin, bilirubin, prothrombin time, serum electrolytes, serum creatinine and CBC sent within 24 hours were collected. Oxygen saturation was measured using fingertip pulse oximeter. Investigations for ACLF triggers were done as necessary which included but not limited to urine routine and microscopic examination, urine culture, blood culture, and Anti HEV IgM. Patients' prognosis and survivability were observed by follow up phone call at 30 days.

After editing & coding, the coded data were entered into the computer by using the SPSS (Statistical Package for Social Sciences) version-23.0 software. For statistical analysis chi-square test for categorical variables and parametric and non-parametric tests for continuous variables were used depending whether the variables were normally distributed or not. Logistic regression models were constructed to evaluate the possible predictors/associations with mortality of ACLF. Statistical significance was set at 0.05 level and confidence interval at 95% level. Ethical clearance was obtained from the ethical review committee.

Results

A total of 175 patients were screened, of whom 10 patients were found to have CKD, 7 patients had a diagnosis of Hepatocellular carcinoma (HCC) outside Milan criteria, 1 patient was younger than 18 year, and 4 patients were lost to follow up. So 153 patients were taken for analysis.

Table 1: Baseline characteristics of study subjects (N=153)

Characteristics	ACLF all grades	No ACLF	P value
Sample, n(%)	49 (32)	104 (68)	
Age(years)	59.20± 10.19	59.69± 12.19	0.808
Gender			
Male	28 (57.1)	57 (54.8)	0.862
Female	21 (42.9)	47 (45.2)	
Cause of cirrhosis			0.518
HBV	12 (24.5)	37 (35.6)	
HCV	4 (8.2)	10 (9.6)	
Alcohol	2 (4.1)	3 (2.9)	
Others	31 (63.3)	54 (51.9)	
Clinical features			
Ascites	39 (79.6)	90 (86.5)	0.192
Hepatic encephalopathy	28 (57.1)	16 (15.4)	**0.000**
GI bleeding	8 (16.3)	16 (15.4)	0.527
SBP	2 (4.1)	4 (3.8)	0.627
Laboratory data			
Serum bilirubin (mg/dL)	3.9±4.2	2.2±2.5	**0.005**
INR	1.5±0.4	1.4±1.4	**0.001**
Serum Albumin (g/L)	25.4±5.0	27.8±6.1	**0.016**
Serum Creatinine (mg/dL)	2.0±1.1	1.0±0.3	**0.000**
Serum Sodium (mmol/L)	129.5±16.9	131.3±17.4	**0.025**
WBC count (/cmm)	9340±4873	7520±3832	**0.023**
CTP score	10.78±2.16	9.12±1.97	**0.000**
MELD-Na score	23.18 ±5.34	14.96 ±5.34	**0.000**

Data are expressed as means ± SD or number of patients (%).P value determined by Chi-Square test, independent sample t test, and Wilcoxon Rank-Sum tests as appropriate.

Table 2: Baseline characteristics of study subjects according to ACLF grades (N=49)

Characteristics	ACLF grade 1	ACLF grade 2	ACLF grade 3	P value
Sample, n(%)	26 (53.1)	18 (36.7)	5 (10.2)	
Age(years)	60.12±8.47	57.72±12.86	59.8± 8.87	0.747
Gender				
Male	13 (50)	12 (66.7)	3 (60)	0.542
Female	13 (50)	6 (33.3)	2 (40)	
Cause of cirrhosis				0.885
HBV	6 (23.1)	4 (22.2)	2 (40)	
HCV	2 (7.7)	1 (5.6)	1 (20)	
Alcohol	1 (3.8)	1 (5.6)	0 (0)	
Others	17 (65.4)	12 (66.7)	2 (40)	
Clinical features				
Ascites	20 (76.9)	14 (77.8)	5 (100)	0.396
Hepatic encephalopathy	12 (46.2)	11 (61.1)	5 (100)	0.000
GI bleeding	3 (11.5)	5 (27.8)	0 (0)	0.352
SBP	2 (7.7)	0 (0)	0 (0)	0.589
Laboratory data				
Serum bilirubin (mg/dL)	3.2±3.3	4.7±5.3	4.5±4.6	0.734
INR	1.4±0.4	1.6±0.4	1.9±0.5	**0.009**
Serum Albumin (g/L)	26.4±4.4	23.8±5.8	26.4±3.9	0.238
Serum Creatinine (mg/dL)	1.92±0.61	1.94±1.63	2.52±1.15	0.256
Serum Sodium (mmol/L)	126.1±21.8	132.1±5.6	137.6±12.3	0.250
WBC count (/cmm)	8835±8355	1040±6023	8152±5435	0.616
CTP score	10.19±2.00	11.00±2.09	13.00±2.00	**0.036**
MELD-Na score	22.54±5.95	23.17±5.47	26.60±5.41	0.369

Data are expressed as means ± SD or number of patients (%).

P value determined by Chi-Square test, One way ANOVA test, and Kruskal-Wallis H tests as appropriate.

Of these, 49 patients (32%) met the criteria for ACLF: grade 1 ACLF in 26 (53.1%), grade 2 in 18 (36.7%), and grade 3 in 5 (10.2%) patients. Patients had an average age of 59.54±11.55 years. Those who developed ACLF had a mean age of 59.20±10.19 and who did not develop ACLF had a mean age of 59.69±12.19 years. The difference was statistically non-significant (p>0.05). Similar result was also observed for different grades of ACLF. Majority patients were aged between 61-70 years (39.2%). However, among ACLF group 38.8% were between 51-60 years.

Among all 55.6% were male and 44.4% were female. Among no ACLF group, 54.8% and among ACLF group 57.1% were male. The distribution was statistically non-significant (p>0.05). Similar result was also observed for different grades of ACLF.

Most patients in both groups had others (NAFLD, autoimmune hepatitis, secondary biliary cirrhosis, idiopathic) as the main underlying cause of cirrhosis. HBV accounted for 32% and HCV 9.2% of the cirrhosis cases. The distribution was similar in relation to presence of ACLF or ACLF grades (p>0.05).

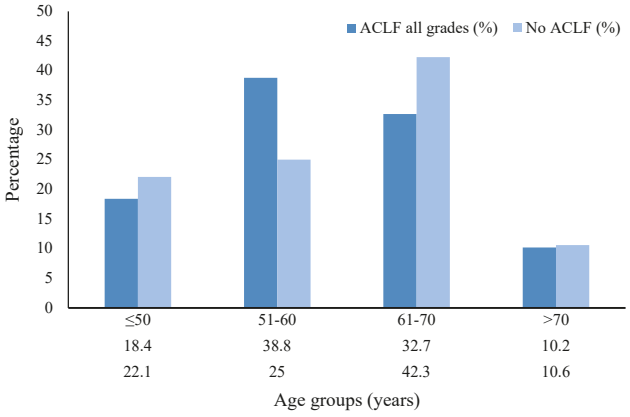

Figure 1: Age groups of patients with and without ACLF

Among all 84.3, 28.8, 15.7 and 3.9% patients had ascites, hepatic encephalopathy, GI bleeding and SBP respectively. Hepatic encephalopathy was significantly more common among ACLF group (p<0.05).

As expected, patients with ACLF had higher levels of serum bilirubin, INR, creatinine, WBC count, CTP score and end-stage liver disease (MELD-Na) score and lower levels of serum albumin and serum sodium than patients without. When laboratory data were compared across ACLF grades, only INR and CTP score were found to be higher with increasing severity of ACLF. Distribution of other laboratory parameters did not show significant differences across different grades of ACLF.

Table 3: Potential precipitating events among study subjects (N= 153)

	ACLF all grades (n=49) n(%)	No ACLF (n=104) n(%)	P value
Bacterial infections	31 (63.3)	36 (34.6)	**0.001**
GI bleeding	8 (16.3)	16 (15.4)	0.527
HEV	3 (6.1)	4 (3.8)	0.399
HBV reactivation	4 (8.4)	8 (7.7)	0.574
No precipitating event	9 (18.4)	50 (48.1)	**0.000**
More than one event	6 (12.2)	10 (9.6)	0.406

P value determined by Chi-Square test

Bacterial infections, GI bleeding, Hepatitis E, reactivation of HBV were the precipitating events in 81.6% of patients with ACLF, with bacterial infections being the most common trigger (63.3%). No precipitating event was found in 18.4% patients with ACLF. 51.9% of patients in no ACLF group also had these precipitating events that were the possible causes of acute decompensation. However, frequency of bacterial infection was higher in ACLF group compared to no ACLF ($p<0.05$).

Table 4: Types of infection identified among study subjects (N= 153)

	ACLFall grades (n=49) n(%)	No ACLF (n=104) n(%)	P value
Pneumonia	5 (10.2)	3 (2.9)	0.070
UTI	18 (36.7)	22 (21.2)	**0.034**
Sepsis	0 (0)	2 (1.9)	0.461
SBP	2 (4.1)	4 (3.8)	0.627
Multiple sites	6 (12.2)	4 (3.8)	0.058

P value determined by Chi-Square test

Higher frequency of bacterial infection in ACLF group was mainly related to UTI (36.7%) and pneumonia (10.2%). Multiple sites infection was present in 12.2%.

Table 5: Distribution of organ failures among study subjects (N= 153)

	ACLFall grades (n=49) n(%)	No ACLF (n=104) n(%)	P value
Liver	5 (10.2)	2 (1.9)	**0.035**
Kidney	18 (36.7)	0 (0)	**0.000**
Cerebral	21 (42.9)	3 (2.9)	**0.000**
Coagulation	4 (8.2)	0 (0)	**0.010**
Circulation	12 (24.5)	1 (1)	**0.000**
Lungs	20 (40.8)	1 (1)	**0.000**

P value determined by Chi-Square test

In patients with ACLF, cerebral failure (42.9%), respiratory failure (40.8%) and kidney failure (36.7%) were the most common organ failures.

Mortality of ACLF

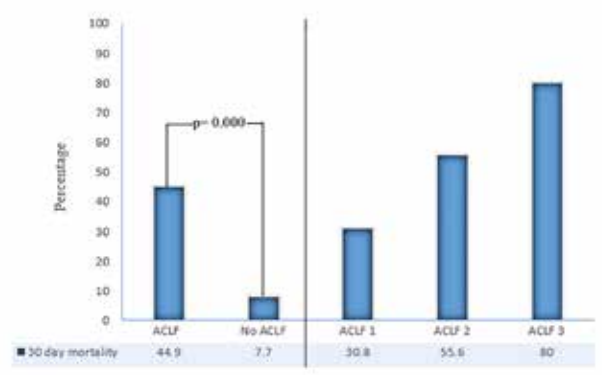

Figure 2: Mortality rate at 30 days in patients with and without ACLF and by grades (N=153).

To examine the difference between ACLF and ACLF grades, the independent Chi-square analysis was used. Mortality rate was compared to no ACLF for all comparison, Chi-square tests, $p<0.01$.

In total, 30 (19.6%) patients died within 30 days. The 30-day mortality was higher in patients with ACLF than in those without (44.9% vs. 7.7%, $p<0.01$). The risk of 30- day mortality was increased with severity of ACLF; this risk was 30.8% in patients with ACLF-1, 55.6% in patients with ACLF-2, and 80% in patients with ACLF-3, respectively.

Table 6: Predictors of mortality (N= 153)

Predictors	30-day mortality OR (95% CI)
ACLF grades (reference- No ACLF)	
ACLF grade 1	2.06 (0.48-8.79)
ACLF grade 2	3.38 (0.69-16.54)
ACLF grade 3	7.62 (0.49-117.71)
Demographics	
Age (years)	1.02 (0.97-1.07)
Male vs. female	0.83 (0.23-2.95)
Etiology (reference- Others)	
HBV	0.93 (0.22-3.77)
HCV	2.86 (.52-15.70)
Alcohol	12.74 (1.09-149.43)

Cirrhosis complication	
Ascites	0.76 (0.19-3.15)
Hepatic encephalopathy	3.69 (0.86-15.88)
Triggers	
GI bleeding	24.63 (3.09-196.56)
Any	0.85 (0.20-3.65)
MELD-Na score	1.18 (1.03-1.35)
CTP score	1.10 (0.77-1.56)

Results of multivariate logistic regression model.

For all patients, the presence of ACLF-1, ACLF-2 or ACLF-3 had a 2.06 (95% CI 0.48-8.79), 3.38 (95% CI 0.69-16.54) and 7.62 (95% CI 0.49-117.71) higher odds of 30-day mortality compared with no ACLF. Increasing age (adjusted odds ratio [OR] 1.02, 95% CI 0.97-1.07), presence of hepatic encephalopathy (adjusted OR 3.69, 95% CI 0.86-15.88), GI bleeding (adjusted OR 24.63, 95% CI 3.09-196.56), higher MELD-Na (adjusted OR 1.18, 95% CI 1.03-1.35) and CTP (adjusted OR 1.10, 95% CI 0.77-1.56) score were associated with higher odds of mortality. Males were less likely to die compared to females (adjusted OR 0.83, 95% CI 0.23-2.95). Ascites or presence of any trigger (GI bleeding or infections or HBV reactivation or Hepatitis E) was associated with lower likelihood of mortality. As for underlying diagnosis, HCV and alcoholism were associated with higher odds of 30-day mortality compared with others, while HBV infection was associated with lowers likelihood of mortality.

Table 7: Predictors of mortality for patients with ACLF (n= 49)

Predictors	30-day mortality OR (95% CI)
ACLF grades (reference- ACLF grade 1)	
ACLF grade 2	2.81 (0.81-9.80)
ACLF grade 3	9.00 (0.86-93.82)
Demographics	
Age (years)	1.01 (0.95-1.06)
Male vs. female	3.33 (1.00-11.14)
Cirrhosis complication	
Hepatic encephalopathy	2.31 (0.71-7.45)
Triggers	
GI bleeding	12.13 (1.36-108.36)
Any	3.50 (0.65-18.95)
MELD-Na score	1.00 (0.90-1.10)
CTP score	1.09 (0.84-1.43)

Results of multivariate logistic regression model.

When analysis was restricted to patients with ACLF, higher 30-day mortality was found to be associated with increasing grades of ACLF (presence of 2 or 3+ organ failures had a 2.81 [95% CI 0.81-9.80] and 9.00 [95% CI 0.86-93.82] higher odds of 30-day mortality compared with ACLF-1), increasing age, male sex, hepatic encephalopathy, GI bleeding, any trigger and higher CTP score. MELD-Na score did not affect mortality in ACLF.

DISCUSSION

Total 153 patients were taken for the study. They were followed up at day 30 after admission. Two major findings are being reported for these patients admitted for an episode of decompensated cirrhosis. First, ACLF was present in 32% (n = 49) of patients admitted with decompensated cirrhosis between November, 2019 to May, 2021 in GHPD department of BIRDEM General Hospital. The most common underlying predisposing liver diseases in ACLF were NAFLD, autoimmune hepatitis, secondary biliary cirrhosis and idiopathic categorized as others (63.3%), followed by hepatitis B (24.5%). Infection, gastrointestinal bleeding, hepatitis E or reactivation of hepatitis B was identified in 81.6% as probable precipitating factors. Second, a significant number of these patients (44.9%, n = 22) died within 30 days of admission. The presence of 3 or more organ failures was associated with the highest 30-day mortality risk (80%). However, several patient-level factors were found to be associated with suboptimal outcomes in patients with ACLF. Particularly, in addition to older age, male sex, hepatic encephalopathy, GI bleeding and higher CTP score were associated with higher mortality risk at 30 days.

As for demographic factors, mean age of all patients was 59.54±11.55 years. Being a progressive disease hepatic decompensation in cirrhosis is expected to occur in later years of life. Thus a higher overall mean age was noticed.[11]in a study conducted in 2019 among decompensated cirrhosis patients found a mean age of 55.58±14.46 years which corresponds to this study. Mean age of patients with ACLF was 59.20±10.19 years which is concordant with CANONIC study (56±11 years).

Among all, majority of patients were male (55.6%) and the rest were female (44.4%). This is consistent with the findings of CANONIC study as well as[11-14] and a number of other studies. They reported a male proportion of 64 to 86% in their studies. A study conducted in Italy addressed the question of gender difference in cirrhosis patients and reported that gender-wise prevalence of cirrhosis depends on the causes and varies from time to time.[15]They observed a male preponderance in HBV-related cases and alcohol related cirrhosis cases. In HCV related cases they found a change in preponderance of gender over time. The gender distribution was statistically similar in ACLF group. But mortality in ACLF was higher among males than females which is concordant with CANONIC study.

Overall, ACLF was more common in this study population (32% vs. 22.6%) than data reported in the CANONIC study. Most of this difference was due to higher frequency of ACLF-1 (17% vs. 11% in the CANONIC study) and ACLF-2

(11.8% vs. 8%). Another national cohort study from the USA reported ACLF in 26.39% of patients admitted with decompensated cirrhosis.[16]Mortality in ACLF differs when it comes to region and study design. Barosa et al reported a 28-day mortality of 45.8% in ACLF patients which is concordant with this study.[17]Among patients with ACLF, mortality was higher in this study than in the CANONIC study (30-day mortality 44.9% vs. 28-day mortality 33.9%). Differences in demographic factors (race), underlying cause of cirrhosis, triggers, organ failure distribution, and higher ACLF-2 mortality (55.6% vs. 32%) likely explains the observed differences in mortality of ACLF. For example, patients of this study were non-White, and less likely to have alcohol as the cause of cirrhosis (4.1% vs.60.3%). Moreover, the precipitating trigger was more likely to be infectious (63.3% vs. 32.6%) and GI bleeding (16.3% vs. 13.2%) and unlikely to be recent alcohol abuse.

With regard to organ failures, ACLF cases of this study were more likely to have cerebral (42.9% vs. 24.1%), lung (40.8% vs. 9.2%) and circulatory failure (24.5% vs. 16.8%), but were less likely to have kidney (36.7% vs. 55.8%), liver (10.2% vs. 43.6%) and coagulation (8.2% vs. 27.7%) failures. Despite these differences, both studies underscore the prognostic significance of organ failure in cirrhosis by demonstrating a progressive increase in mortality risk with additional organ failures.

The prevalence of ACLF in patients with decompensated cirrhosis ranges widely in different reports from 24% to 65%.[18]Although there is advancements of inpatient medical care, our hospitals still lack services like sepsis bundles, rapid response teams, which may explain relative high ACLF mortality in this region. Lack of early recognition and intervention is another cause of high mortality particularly in ACLF-3. In addition, care of patients with cirrhosis may be different in centers with less advanced comprehensive care of critically ill patients with cirrhosis, which explains why transplant centers do better than non-transplant centers with regard to short-term mortality for both patients with and without ACLF.[19]Given the dismal outcomes of patients with ACLF-3, it is important that clinicians recognize this syndrome as a different entity, not as mere decompensation and start liver transplant evaluation.[20]

There are significant regional differences in the etiology and trigger factors of ACLF having a profound effect on the clinical management and outcome of this condition from one population to another. While comparing Asia and the West as a whole, the most common etiology of chronic insult in ACLF in both regions is alcohol and viral hepatitis, with hepatitis B being the predominant virus in Asia and hepatitis C in Europe and North America.[4,21,22] However, previous studies reported hepatitis B to be the most common cause of cirrhosis in Bangladesh which contradicts this study finding.[14,23] Widespread vaccination program might be the reason why hepatitis B prevalence is reducing day by day.[24] The acute precipitating event for ACLF is also reported differently according to the EASL-CLIF definition and the APASL ACLF Research Consortium (AARC) definition. While the EASL-CLIF criteria include both hepatic and nonhepatic insults, the AARC criteria accept only hepatic insults, thus making it difficult to make direct comparisons between the triggers for ACLF in Asia and the West. Currently, the most common acute insult in Asia is alcohol (50.3%) followed by viral hepatitis (22.6%: hepatitis B; 13.2%, hepatitis E virus; 9.4%) and DILI (9.3%), and no attributable cause was found in 4.8% of cases.[22] Relative low prevalence of alcohol use in Bangladesh may explain the difference in trigger factors found in this study.[25] Only one study was found in Bangladesh relating to etiological factors in ACLF.[14] It found hepatitis E super infection (20%), sepsis (16.67%), variceal bleeding (13.33%), and hepatotoxic drugs (3.33%) as the triggers of ACLF while no cause was found in 30% cases. However, the triggers were analyzed according to AARC criteria.

Despite the attempt to keep the study design as close to CANONIC study as possible, there were several pitfalls. All patients were followed up at day-30 by phone calls and it was not possible to obtain detailed history, physical examination results and laboratory parameters over phone calls. Therefore it is possible that some of these patients might have developed ACLF during that period. HBV DNA was not also done for all patients with hepatitis B cirrhosis and hence the frequency of hepatitis B reactivation obtained might be an underestimate. Due to social and cultural circumstances, some patients tend to conceal history of alcoholism. So the distribution of cirrhosis etiology might not be accurate. However, as all patients were selected from a single center (BIRDEM General Hospital), they were under the same healthcare model and benefits and, thus, the results were likely not affected by differential access to healthcare. This is one of the strengths of the study. This is a limitation of the study as well because the sample size was small for which the true image of ACLF might not be reflected. So further studies with large samples are required.

Conclusion

Acute on chronic liver disease is a separate clinical entity and is distinct from mere acute decompensation. Follow up of 153 patients with decompensated cirrhosis of liver admitted to GHPD department, BIRDEM General Hospital revealed that 1 in 3 patients had ACLF and 44% of them would die in 30 days. Bacterial infection and GI bleeding were the most common triggers of ACLF. Early identification and intervention with multidisciplinary approach and referral to transplant centers are likely to improve survival outcomes in this population. To get the true image of prevalence and mortality of ACLF in Bangladesh, further large and multicenter study is recommended.

Statement:

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Conflicts of interest: Nothing to declare

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