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Clinical profile of patients with acute-on-chronic liver failure (ACLF) and its prognostication

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Abstract
Background: Acute-on-chronic liver failure (ACLF) is a distinct clinical entity in the spectrum of chronic liver disease with a rapid downhill course and associated with poor outcome. The Asian Pacific Association for the Study of the Liver (APASL) consensus defined ACLF as "an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dL) and coagulopathy (INR ≥1.5) complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease". Data regarding ACLF are scarce, heterogeneous, and mostly retrospective specially in the Asian subcontinent. In accordance with these observations, this study was conducted to review clinical profile, primary etiologies, precipitating insults, laboratory parameters, outcome and predictor of mortality in patients with ACLF in a tertiary care hospital of North India.
Aim: To study the Clinical profile of patients with acute-on-chronic liver failure (ACLF) and its prognostication
Methods: In this prospective study, 178 consecutive patients of ACLF as per APASL definition were included. Etiology of cirrhosis, precipitating events, frequency of organ failure and predictor of mortality were assessed.
Results:A total of 178 patients were included with mean age 44 (range 18-42) years and139 were male (78%).Jaundice, followed by ascites with or without hepatic encephalopathy, was the most common presentation (162/178, 91%). Among patients who had esophageal varices (67.24%), approximately half (46%) had large esophageal varices. Hyponatremia was noted in 39% patients of ACLF. The most common causes of cirrhosis were alcohol (47%), cryptogenic (27%) followed by HBV (18%) and HCV infection (7%). Most common precipitating events were infection (47.6%) followed by active alcoholism (27.6%).Most of the patients had single precipitant (88.7%).Out of 114 patients of CLD because of alcohol and HBV (64% of total patients), ACLF was caused by reactivation of underlying disease itself in 65 patients (36.5%). 86.5% patients had organ failure, as per EASL CLIF-SOFA consortium. Among patients who qualified as ACLF by EASL-CLIF criteria, only a small percentage (≈17 %) are qualified as ACLF grade 1 whereas 56% had ACLF of grades 2 and 3 and associated with significantly higher mortality (56%). The presence of no organ failure, single organ failure and two organ failure carried a mortality rate 29.16%, 36.50% and 42.10% respectively. Whereas, more than 70% patients die within 28 days if had ≥ 3 organ failure. Overall 28-day and 3-months mortality was 43.82 % and 58.43%. Non survivors (n=78) had a significantly higher CTP score (p value=0.04), MELD score (p value=0.002), CLIF-SOFA score (p value=0.007), and ≥3 organ failure (p value=0.02) as compared to survivors (n=100).
Conclusion: Infections as acute precipitating events of ACLF are much more common in this region as compared to the west. ACLF patients have a high prevalence of organ failure and severity of organ failure as well as baseline severity of liver disease determines the high mortality.

Keywords: ACLF, APASL, CLD

Introduction
Acute-on-chronic liver failure (ACLF) is an increasingly recognized clinical entity encompassing an acute deterioration of liver function in patients with chronic liver disease, either secondary to superimposed liver injury or due to extra-hepatic precipitating factors such as infection, culminating in the end-organ dysfunction. ACLF is a dynamic syndrome with rapid downhill course and associated with very high short term mortality. In 2008, the Asian Pacific Association for the Study of Liver (APASL) defined ACLF as an "acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease [1]. The American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) also defined ACLF as an "acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at three months due to multi organ failure [2, 3] Systemic inflammatory response syndrome (SIRS) has been implicated in the pathogenesis of ACLF as well determining the outcome of patients with ACLF. The initial triggering event leads to profound cytokine storm leading to various micro and macro circulatory changes and finally culminating into multi organ dysfunction. Organ failure is the central component of ACLF and leads to the hypothesis that the organs may behave differently to the chronic decompensated liver disease [4]. Recently EASL-CLIF consortium prospectively analyzed a large cohort of patients to define various organ failures, to assess various factors predicting mortality and to develop a prognosticating model [3]. The consortium also modified the existing Sequential Organ Failure Assessment (SOFA) score mainly used in critical care setting and devised a new CLIF-SOFA

score to address various issues specifically associated with liver failure and cirrhosis [5]. There are various similarities with end-stage liver cirrhosis; the most important difference between these entities is the potentially reversible nature of ACLF if the precipitating factor can be controlled. Furthermore, the most important difference between acute liver failure and ACLF is the presence of underlying chronic liver disease in patients with ACLF [1, 3]. ACLF usually results following a precipitating event in the background of established cirrhosis. The causes of acute insult (AI) in ACLF are variable and largely depends upon the geographical region and the population under study, and they can be either hepatic or non-hepatic as well as infectious and non-infectious. It has been always argued that ACLF of West differs from ACLF described in the East. The Simultaneous presence of more than one acute insult is also common. Alcohol and hepatotoxic drugs are the most common acute insults in Western countries, while infectious acute insults are more common in East subcontinent [6]. Of all infections, reactivation of hepatitis B virus infection is one of the major causes of ACLF in Asia [1, 4]. Other frequent causes of acute insults are variceal bleeding, sepsis, and surgery.

The main characteristic features of ACLF are its reversibility and a high rate of short-term mortality (50–90 %) due to multiorgan failure (MOF) in the absence of liver support devices and/or liver transplantation [7, 8]. That's why It is essential to diagnose ACLF as early as possible and to recognize at-risk patients and differentiate them from those that will survive only with intensive medical care. Therefore, attempts to characterize natural history, clinical profile and treatment in a better way are mandatory to optimized treatment and improve outcome. Most of the time it is very difficult to determine which patients will benefit from on-going aggressive treatment, which will benefit from on-going liver transplantation, and perhaps which require some form of mechanical liver support.

Data regarding ACLF are scarce, heterogeneous, and mostly retrospective specially in the Asian subcontinent. In accordance with these observations, this study was conducted to review clinical profile, primary etiologies, precipitating insults, laboratory parameters, outcome and predictor of mortality in patients with ACLF in Indian setting.

This prospective study describes the clinical profile and predictor of mortality in patients with ACLF in a tertiary care hospital of North India.

Methods

This prospective study was conducted in the Department of Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS), a tertiary level heath care centre in Lucknow.

The study was approved by the institute's ethical committee.

Study design: Prospective follow up study

Follow up: 6 months

Study duration: two year (December 2014-December 2016)

Study group: Consecutive patients of Acute-on-chronic liver failure (ACLF) admitted in the department of gastroenterology, SGPGI, Lucknow.

Inclusion criteria

Consecutive patients of ACLF admitted to the department of gastroenterology for more than one day (>1d) for the treatment of a complication of liver disease or for evaluation of suitability for liver transplantation

Exclusion criteria

- Pregnancy
- Age < 18 years
- Patients with acute liver failure without liver Cirrhosis
- Patients with cirrhosis admitted for more than one day for Schedule procedure {(e.g. band ligation, transjuglar intrahepatic portal systemic shunting(TIPS)}
- Hepatocellular carcinoma outside Milan criteria
- Previously known severe extra hepatic disease (chronic renal failure requiring Hemodialysis, severe heart disease, severe chronic pulmonary disease, psychiatry disorders)
- Immunosuppressive drugs other than corticosteroids at dose for severe alcoholic hepatitis
- HIV infection

Data collection and investigation

Data were collected, including complete demographic profile, clinical and laboratory variables, and assessment of the severity of liver disease on the day of admission (within 24 h) followed by a detailed evaluation during hospital stay.

Data was collected with large number of variables including

- **The etiology of underlying chronic liver disease**

Diagnosis of cirrhosis

a. Cirrhosis were considered to be present if thrombocytopenia (platelet < 150 × 10^3/μL), splenomegaly, ascites (by cross sectional images), varices (by EGD, cross-sectional images, or history of variceal bleeding), and cirrhotic features of the liver (nodular surface or caudate lobe hypertrophy) in cross-sectional images and LSM ≥14kPa based on transient elastography (Fibroscan™, Echosense, France) were present.
b. The patients were labelled to have cryogenic CLD when the diagnosis was not reached after necessary work up for liver disease.(Referance)

Cause of acute insults

To identify the cause of acute insult, detailed clinical history of the disease was recorded, including fever, drugs, and alcohol intake. Reviewed (demographic profile, clinical history and laboratory parameters) and investigated thoroughly to find acute precipitating events.

- **Alcohol:** As per Asian Pacific Association for the Study of Liver (APASL) 2009 consensus, alcohol should be considered as an acute insult in case of active drinking within the last 4 weeks [1].
- **Infection:** In case of suspected infection (history of fever and/or leucocytosis or neutrophilia), evaluated extensively to find the source of infection.

The bacterial infection/sepsis was considered as an acute insult in the presence of definite evidence of infection and systemic inflammatory response syndrome (SIRS) and when all known common hepatic acute events such as acute viral hepatitis, viral or autoimmune hepatitis flare, other viral infection, parasitic infection, and exposure to drugs and toxins were excluded by appropriate history and investigations.

Criteria for Systemic inflammatory response syndrome (SIRS) as per American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM)-1992

SIRS is defined as 2 or more of the following variables

1. Temperature>38°C (100.4°F) or < 36°C (96.8°F)
2. Heart rate >90 beats per minute
3. Respiratory rate >20 breaths per minute or arterial carbon dioxide tension (PaCO 2) <32 mm Hg
4. Abnormal white blood cell count (>12,000/μL or < 000/μL or >10% immature [band] forms)

- **Hepatitis B flare/reactivation**- defined as APASL criteria [9]

A. Acute exacerbation/flare- defined as intermittent elevations of serum aminotransferase level to >five times the upper limit of normal and more than twice the baseline value.
B. Reactivation of hepatitis B- defined as a marked increase in HBV replication (≥2 log increase from baseline levels or a new appearance of HBV DNA to a level of ≥100 IU/ml) in a person with previously stable or undetectable levels, or detection of HBV DNA with a level ≥20,000 IU/ml in a person with no baseline HBV DNA.

- Liver severity scores as CTP score and MELD score
- Presence and grade of varices
- Presence and grade of ascites

As defined by the International Ascites Club [10]

Grade1 (mild): Ascites only detectable by ultrasound examination
Grade2 (moderate): Ascites causing moderate symmetrical distension of the abdomen
Grade 3 (large): Ascites causing marked abdominal distension
Presence and grade of hepatic encephalopathy according to

West Haven criteria for hepatic encephalopathy [11]

- Grade 1: trivial lack of awareness; euphoria or anxiety; shortened attention span; and impaired performance of addition or subtraction
- Grade 2: lethargy or apathy; minimal disorientation for time or place; subtle personality change; and inappropriate behavior
- Grade 3: somnolence to semi stupor, but responsive to verbal stimuli; confusion; and gross disorientation
- Grade 4: coma (unresponsive to verbal or noxious stimuli)

Presence and grade of organ failure as CLIF-SOFA score[3]

1. Liver failure: serum bilirubin level ≥12 mg/dl
2. Kidney failure: serum creatinine level of ≥2.0 mg/dl or the use of renal replacement therapy
3. Cerebral failure: grade III or IV hepatic encephalopathy as per West Haven classification
4. Coagulation failure: international normalized ratio (INR) >2.5 and/or platelet count of ≤20,000/dl
5. Circulatory failure: requirement of vasopressor
6. Respiratory failure: SpO2 to FiO2 ratio ≤200

After determining organ failure as per above criteria, enrolled patients of ACLF were further sub grouped as per EASL-CLIF consortium criteria [3]

(1) No ACLF: This group comprised

a. Patients with no organ failure
b. Patients with single hepatic, coagulation, circulatory, or respiratory failure with serum creatinine
c. <1.5 mg/dl, and no HE
d. Patients with cerebral failure and serum creatinine <1.5 mg/dl

(2) ACLF 1: This group comprised

a. Patients with renal failure
b. Patients with other single organ failure with serum creatinine between (1.5- 1.9) mg/dl and HE
c. grades 1–2
d. Patients with single cerebral failure and serum creatinine between (1.5- 1.9) mg/dl

(3) ACLF 2: patients with two organ failures

(4) ACLF 3: patients with three or more organ failures

Subgroups: Subdivided into different group based upon underlying severity of Chronic liver disease as well as acute insults.

Based on the underlying severity of Chronic liver disease as per world gastroenterology organization (WGO) [10]

1. Chronic liver disease -Type A
2. Compensated cirrhotic-Type B
3. Decompensated cirrhotic or 2nd episode of ACLF-Type C

Based on Acute Insult

1. Hepatic Insult
2. (Different in nature from the underlying etiology of CLD)
3. Non-Hepatic\ Insult
4. Both Hepatic insult and underlying etiology are the same

All patients were investigated with
Complete blood count-Hemoglobin (g/dl), TLC ($x10^3$ cells/mm^3), Platelet count ($x10^3$ cells/mm^3)
Renal function test and electrolyte-Urea (mg/dl), Serum creatinine (mg/dl), Sodium (meq/dl), Potassium (meq/dl)
Liver function test-Total bilirubin (mg/dl), Albumin (mg/dl), Globulin (mg/dl), AST (IU/L), ALT (IU/L), ALP (IU/L), GGT (IU/L)
Coagulation-INR
Lactate
Alpha fetoprotein (ng/ml)
Urine analysis:
Routine and microscopy, C/S, Urine protein: creatinine (mg/mmol),
24 hour urine sodium and Creatinine, Fractional excretion of sodium
Ascitic fluid analysis (AFA):
Cell counts (TLC and DLC), protein, albumin, c/s, ADA and cytology as indicated
Tests to r/o Sepsis –if required
Cultures – blood/urine/ascetic fluid/plural fluid/wound
Chest X ray

Other investigations

USG abdomen
Triple phase CT scan –If suspecting HCC
Fibroscan (after control of ascites)
Transjuglar liver biopsy (TJLB) -If indicated

Statistical analysis

All results are expressed as a mean±standard deviation (SD), median (range), or frequency (in percent).

Quantitative variables, expressed as means±SD, were compared with the use of the Student's t test. Qualitative variables, expressed as percentages, were compared with the use of a chi-square test.

Ap value of <0.05 was considered statistically significant.

Results

A total of 178 patients of acute-on-chronic liver failure as per defined by the Asian Pacific Association for the Study of the Liver (APASL) criteria (ACLF as an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dl) and coagulopathy (INR ≥1.5) complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease) with the exception that those with evidence of infection were also was enrolled in this study between December 2014 to July 2016.They were followed till December 2016. Out of 178, 139 were male (78%). The mean age was 44 (range 18-82) years.

Table 1: Baseline characteristics of 178 patients qualifying as acute-on-chronic-liver failure by The Asian Pacific Association for the Study of the Liver (APASL) criteria

Patients characteristic		All (n=178)
Age (years); median (range)		44(18-82)
Gender (Male); N (%)		139 (78%)
Etiology of cirrhosis (N, %)	Alcohol	85 (47.7%)
	Cryptogenic	48 (27%)
	Hepatitis B	33 (18.5%)
	Hepatitis C	13 (7.5%)
	Autoimmune hepatitis (AIH)	3 (1.5%)
	Others	3 (1.5%)
Precipitating events (N, %)	Infection	85 (47.6%)
	Active alcoholism	49 (27.6%)
	Hepatitis B reactivation/flare	19 (10.7%)
	Drug (Herbal,ATT, etc.)	15 (8.4%)
	Gastrointestinal bleed	15 (8.4%)
	Unknown	4 (2.24%)
	Acute HEV	1 (0.56%)
Laboratory parameters; median (range)		
Hb (g/dl)		9.6 (1.4-35.3)
TLC (per mm3)		93 (15-307)
Platelets (×103)		132 (100-172)
Na (mEq/L)		3.9 (2.5-6.6)
K (mmol/L)		1.0 (0.3-5.6)
Creatinine (mg/Dl)		13.05(5.1-42)
Total bilirubin (mg/dl)		121.5(18-1927)
AST (U/L)		55(12-1174)
ALT (U/L)		2.5 (0.9-5.6)
Serum albumin (g/dl)		2.56 (1.07-9.18)
INR		2.71 ± 1.23

AST-aspartate aminotransferase, ALT alanine aminotransferase, INR international normalize ratio

Severity assessment

Severity of liver disease was assessed within 24 hours of admission in all patients (table 2,2A and 2B). Baseline severity of liver disease was high as suggested by the high CTP score (median 12) and high MELD score (median 28) score. The median number of organ failure was 2.

Table 2: Assessment of baseline severity of ACLF patients within 24 hours of admission

Severity score	Median, range
CTP score	12 (8-15)
MELD score	28 (15-40)
CLIP-SOFA score	10 (6-15)
No of organ failure	2 (0-6)

Child-Turcotte-Pugh (CTP) score

Median CTP was 12 (range 8-15); most of the patients had CTP-C (163/178, 91.6%).

Table 2A: CTP scores of ACLF patients within 24 hours of admission

CTP score	Prevalence
B	15
C	163

Model of end stage liver disease (MELD) score

Median MELD was 28 (range 15-40), 92.7% ACLF patients had a MELD score (>20), including 15 patients with MELD score 40 or more.

Table 2B: MELD scores of ACLF patients within 24 hours of admission

MELD Score		
<40	**MELD score 163**	**Number**
	<9	No
	10-19	13
	20-29	83
	30-39	67
40 or more	15	

CTP- Child-Turcotte-Pugh (CTP) score, MELD- Model of end stage liver disease (MELD) score, CLIF-SOFA chronic liver failure-sequential organ failure assessment (CLIF-SOFA)

Clinical presentation

Jaundice, followed shortly by ascites with or without hepatic encephalopathy, was the most common presentation in all patients (162/178, 91%). Mean duration of development of ascites from the onset of jaundice was 16 days. Jaundice with hepatic encephalopathy only, but no ascites was present in 16 (9%) patients only. Encephalopathy was present in 96 (53.93%) patients.

91 patients had a past history of decompensation in form of ascites (68) or gastrointestinal bleed (41). Upper GI endoscopy was performed in 116 patients; 78 patients (67.2 %) had oesophageal varices, and in 36 (31%) patients had large varices, although only 14 patients presented with GI bleeding on admission. Among patients who had varices, approximately half (46%) had large esophageal varices. Acute kidney injury (AKI) was seen in 1/4th of patients. Hyponatremia (defined as the serum sodium concentration < 130 meq/dl) was noted in 39 % patients of ACLF.

Table 3: Presentation of ACLF patients at admission

Parameters	Prevalence (N, %)
Ascites	162 (91%)
Encephalopathy	96 (53.9%)
Acute kidney injury (AKI)	48 (26.96%)
Hyponatremia	69 (38.8%)
Varices	78 (67.2%)

Etiology of liver disease and acute insults

Most common etiology of cirrhosis was alcohol (47.7%) and cryptogenic (27%) followed by hepatitis B (18.5%) and hepatitis C (7.5%) comprised 97% overall. Dual etiology {(such as alcohol and HBV (n=4), alcohol and HCV (n=2) and confection of HBV and HCV (n=1)} were seen in a few patients. 3 patients had Autoimmune hepatitis.

Table 4: Etiology of cirrhosis

Etiology of cirrhosis (%)	Prevalence (N, %)
Alcoholic Liver disease	85 (47.7%)
Cryptogenic	48 (27%)
Hepatitis B	33 (18.5%)
Hepatitis C	13 (7.5%)
Autoimmune hepatitis (AIH)	3 (1.5%)
Others	3 (1.5%)

Acute insults

Most of the ACLF patients had single precipitant (158/178, 88.7%), 13 had more than one precipitant whereas in 7 patients precipitating events were not identified.

Most common precipitating events were infections (47.6 %) and active alcoholism (27.6%) followed by reactivation/flare of hepatitis B infection, medication (herbal as well as ATT) and gastrointestinal bleeding.

Out of 114 patients of CLD because of alcohol and HBV (64% of total patients), ACLF was caused by reactivation of underlying disease itself in 65 patients (36.5%).

Table 5: Precipitating events of ACLF patients

Precipitating events (%)	Prevalence (N, %)
Infection	85 (47.6%)
Active alcoholism	49 (27.6%)
Hepatitis B reactivation/flare	19 (10.7%)
Drug	15 (8.4%)
Gastrointestinal bleed	14 (7.8%)
Unknown	7 (3.9%)
Acute HEV	2 (1.16%)

Infection as an acute insult

Among various infections, SBP was most common (45%) followed by pneumonia (24%) and UTI (13%). Few patients had cellulitis, cholecystitis and Cholangitis etc. In 7 patients, source of infection was not identified. 8 patients had more than one infections.

Table 5A: Various infections as a precipitating events of ACLF patients

Source of infection	Prevalence (N, %)
SBP	38 (44.7%)
Pneumonia	20 (23.5%)
UTI	11 (12.9%)
Cellulitis	6 (7.0%)
Cholecystitis	5 (5.9%)
Cholangitis	2 (2.4%)
Boils	1 (1.1%)
Gastroenteritis	1 (1.1%)
Liver abscess	1 (1.1%)
Gluteal abscess	1 (1.1%)
Unknown	7 (8.2%)

Assessment of Organ failure as per EASL CLIF-SOFA score

Most of the patients had organ failure (86.5%, 154/178) as per EASL CLIF-SOFA score.

Although all patients had serum bilirubin levels >5 mg/dl and INR >1.5, by CLIF-SOFA definition, 52.8 % had serum bilirubin >12 mg/dl and qualified as liver failure.

Similarly, all patients had INR >1.5, by CLIF-SOFA definition, 53.9 % had either INR > 2.5 and or Platelets < 20 thousands and qualified as coagulation failure.

Out of 98 hepatic encephalopathy, only 38 patients qualified cerebral failure in view of presence of grade III/IV encephalopathy.

Although renal dysfunction was observed in (28.6 %, 51/178) patients of ACLF, the prevalence of renal failure was 19.6 % as per criteria defined by EASL-CLIF-SOFA consortium.

Prevalence of cardiorespiratory failure was comparable to renal failure (19.1 % vs. 19.7 %, respectively).

Table 6: Prevalence of Various organ failure as per EASL CLIF-SOFA score

Organ failure	Prevalence (%)
Coagulation failure	96 (53.9%)
Liver failure	94 (52.8%)
Cerebral failure	38 (21.3%)
Renal failure	35 (19.7%)
Circulatory failure	27 (15.2%)
Respiratory failure	7 (3.9%)

Grading of ACLF as per EASL-CLIF consortium criteria

After determining organ failure, enrolled patients of ACLF were further graded as per EASL-CLIF consortium criteria.

Around 1/4th of patients qualified as no ACLF by EASL-CLIF criteria.The patients who qualified as ACLF by the above criteria, only a small percentage (≈17 %) qualified as ACLF grade 1. More than half of the patients (56%) were classified as ACLF grades 2 and 3.

Patients with ACLF grades 2 and 3 had a significantly higher mortality (56%) as compared to those patients who qualified as "no ACLF" as per above criteria.

Table 7: Grading of ACLF as per EASL CLIF consortium and associated mortality

ACLF grading	Number (%)	Mortality
No ACLF	48 (26.96%)	11 (22.91%)
ACLF grade 1	30 (16.85%)	11 (36.67%)
ACLF grade 2	54 (30.34%)	27 (50.0%)
ACLF grade 3	46 (25.84%)	29 (63.04%)

Prevalence of organ failures, according to EASL-CLIF consortium criteria and associated mortality

All 178 patients of ACLF were evaluated to determine organ failure as per organ failure criteria defined by EASL-CLIF consortium.

Mortality was assessed at 28- days and 3-months.

Overall 28-days and 3-months mortality was 43.82 % and 58.43%.

The presence of no organ failure, single organ failure and two organ failure carried a mortality rate 29.16%, 36.50% and 42.10% respectively. Whereas, more than 70% patients die within 28 days if had ≥ 3 organ failure.

Table 8: Prevalence of number of organ failure (as per EASL CLIF-SOFA score) and associated mortality

Number of organ failure	Prevalence (N, %)	28- day mortality (N, %)	3 months mortality (N, %)
No organ failure	24 (13.48)	7 (29.16)	12 (50%)
1 organ failure	63(35.39)	23 (36.50)	37 (58.73%)
2 organ failure	57(32.02)	24 (42.10)	28 (49.12%)
3 organ failure	10(5.61)	7 (70.0)	7 (70.0%)
4 organ failure	17(13.48)	11 (64.70)	14 (82.35%)
5 organ failure	6(9.55)	5 (83.33)	5 (83.33%)
6 organ failure	1(0.56)	1 (100)	1 (100%)

Predictor of mortality

The 28-daysmortality rates, according to different etiology are, 53%, 43% and 29 % for alcohol, hepatitis B and cryptogenic cirrhosis respectively. Probably due tothe more severe presentation of alcohol related ACLF and relatively fewer number of hepatitis B patients.

No significant difference was observed in laboratory parameters among survivors and non survivors (shown in table). Non survivors had a significantly higher CTP score, MELD score and CLIF-SOFA score as compared to non survivors (p value 0.0399, 0.0025 and 0.0067 respectively).Non survivors had a significantly higher proportion of 3 or more organ failure (p=0. 0219). Although no significant difference was observed between survivors and non survivors with no, one and two organ failure (p value 1.0, 0.1582 and 0.8715 respectively).

Table 9: Comparison of ACLF patients between survivors and non survivors

Parameters	Survivors (n=100)	Non survivors (n=78)	P value
Age	**44.34±12.56**	**44.38±11.30**	0.9804
Gender female	26	13	0.1482
Precipitant	51	34	0.3657
Infection	25	24	0.4034
Active alcoholism	10	9	0.8091
Hep B reactivation/flare Drug	11	4	0.1852
GI bleeds	9	6	0.3939
Unknown	4	NIL	NA
Acute HEV	1	NIL	NA
Lab parameters			
Hb (g/dl)	9.5 ±2.23	9.45 ±2.42	0.9107
TLC (per mm3)	10.627 ±5.72	12.14 ±7.47	0.3611
Platelets (×103)	109.72 ±67.86	103.58 ±60.72	0.5325
Na (mEq/L)	132.71±8.08	130.31±8.43	0.0551
K (mmol/L)	4.49±3.76	3.95±0.99	0.2642
Creatinine (mg/Dl)	1.29±0.91	1.57±1.27	0.0903
Total bilirubin (mg/dl)	17.33±9.76	17.33±9.76	0.3956
AST (U/L)	182.39±249.51	208.32±243.86	0.4881
ALT (U/L)	105.34±166.0	102.61±123.68	0.9038
Serum albumin (g/dl)	2.61±0.62	2.56±0.40	0.6884
PT/INR	2.71±1.23	3.13±1.66	0.0518
CTP	11.75±1.49	12.21±1.50	0.0399
MELD	27.83 ±7.02	31.49±8.88	0.0025
CLIF-SOFA score	9.72 ±1.66	10.49±2.07	0.0067
No of organ failure			
0	14	10	1.0000
1	40	23	0.1582
2	33	24	0.8715
≥3	13	21	0.0219

Discussion

ACLF is a dynamic syndrome, which behaves differently from decompensated cirrhosis in view of rapid deterioration leading to multiorgan dysfunction, high mortality and potential reversibility [12]. Patients may revert back to the baseline status if the acute event and clinical consequences recover.

There are only a few prospective studies from northern India addressing the clinical profile, natural history and mortality in patients with ACLF.

This was single-center, prospective study to evaluate the clinical profile and to determine the predictor of mortality in patients with ACLF.

The most common presentation was Jaundice, followed by associates with or without hepatic encephalopathy (91%).

In the study, the most common cause of cirrhosis was alcohol, cryptogenic and HBV and HCV infection (overall 97%), almost similar to others Indian study [13, 15] Out of 114 patients of CLD because of alcohol and HBV (64% of total patients), ACLF was caused by reactivation of underlying disease itself in 65 patients (36.5%).

Acute precipitating events in ACLF are less well defined. Both hepatic and non-hepatic insults are implicated as acute precipitating events leading to ACLF in patients with stable cirrhosis or those with mild decompensation.

Hepatic viral infection, alcohol (active drinking within the last 4 weeks), use of hepatotoxic drugs, and flare of autoimmune hepatitis or Wilson's disease are well-accepted cause of acute insults[15]. However, the role of infectious agents (other than hepatitis viruses A–E) afflicting the liver, sepsis, surgical intervention, and variceal bleeding is not well defined.

In the present study, 89% patients had single precipitant, 7% had more than one precipitant whereas in 4% patients precipitating events were not identified.

Most common precipitating events were infection (47.6%) and active alcoholism (27.6%) followed by reactivation/flare of hepatitis B infection, medication (herbal as well as ATT) and gastrointestinal bleeding. Our results showed almost similar finding with Amprapurkar *et al*. study which showed infection followed by alcoholism was most common acute precipitating events [13]. Among various infections, the most common infections are SBP, pneumonia and urinary tract infection (82% overall). Prevalence of infection and active alcohol intake as a precipitating event was significantly higher in ACLF patients, this finding was almost similar to the study by Moreau *et al*. [3].

As per the EASL-CLIF criteria, we also divided the patients into no ACLF and ACLF, ACLF further graded as 1, 2, and 3 according to presence of organ failure and severity of renal and cerebral failure. Approximately 1/4th patients are qualified as no ACLF as per this criteria. ACLF grade 2 and 3 comprises 56 % overall. ACLF grade 2 and 3 had significantly higher mortality as compared to no ACLF or ACLF grade 1 ($p<0.05$).

Presence and number of Organ failure as defined by CLIF-SOFA consortium had significant impact on mortality. In this study prevalence of organ failure was Coagulation failure (53.9%), Liver failure (52.8%), Cerebral failure (21.2%), Renal failure (19.6%), Circulatory failure (15.2%) and, Respiratory failure (3.9%).

There was a significantly higher 28-days mortality rate of 43.8 % in patients with ACLF by APASL criteria, which was comparable to similar studies by Duseja *et al*. (Mortality of 46 %) and Rastogi *et al*. (Mortality 50 %) which had a heterogeneous studies population [17, 18].

The presence of no organ failure or single organ failure had an almost similar mortality rate (29.16% and 36.50 % respectively). 2 organ failure had 42% 28 day mortality. More than two (≥3) organ failurehad significantly high mortality rate >70 %.

In conclusion infections as acute precipitating events of ACLF are much more common in this region as compared to the west. ACLF patients have a high prevalence of organ failure and severity of organ failure as well as baseline severity of liver disease determines the high mortality.

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