Section: Medicine

Original Research Article

TO STUDY CLINICAL PROFILE AND IN-HOSPITAL OUTCOME IN PATIENTS WITH ACUTE ON CHRONIC LIVER FAILURE

Thingbaijam Shanti Devi[1], Shehanaz N[2], Linda Marangmei[3], Thangjam Gautam Singh[4] ,Ningthoukhongjam Reema[5], Johnson Maibam[6], Sunil Kumar Leishangthem[7], Ksh. Birendra Singh[8]

[1]*Associate Professor, Department of Medicine, Regional institute of Medical Sciences, RIMS, Imphal, Manipur, India.*
[2]*Junior resident, Department of Medicine, RIMS, Imphal, India.*
[3]*Associate Professor, Department of Medicine, RIMS, Imphal, India.*
[4]*Associate Professor, Department of Radiodiagnosis, Shija Academy of Health Sciences, Imphal, India.*
[5]*Assistant Professor, Department of Medicine, RIMS, Imphal, India.*
[6]*Senior resident, Department of Medicine, RIMS, Imphal, India.*
[7]*Senior resident, Department of Medicine, RIMS, Imphal, India.*
[8]*Professor, Department of Medicine, RIMS, Imphal, India.*

Received *: XX/XX/2024*
Received in revised form *: XX/X /2024*
Accepted *: XX/X/2024*

Corresponding Author:
Dr.Thangjam Gautam Singh
Associate Professor, Department of Radiodiagnosis, Shija Academy of Health Sciences, Imphal, India.
Email: thangjamgautam@gmail.com

DOI: 10.70034/ijmedph.2024.4.133

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2024; 14 (4); 709-718

ABSTRACT

Background: Chronic liver disease (CLD) patients with abrupt deterioration of hepatic function with associated extrahepatic organ failures is defined as acute on chronic liver failure (ACLF). The triggering incidents most common being alcohol followed by drug-induced injury, viral hepatitis, bacterial infections, hypoxia-related injury and major surgical procedures. An acute triggering event inflicts damage upon hepatocytes, leading to the accumulation of inflammatory cytokines leading to cascade of events resulting in further injury to the liver when hepatocyte regeneration fails (liver decompensation), compromised immune function and render them to infections, multi-organ failure, and eventual mortality. Studies regarding in hospital course and mortality for ACLF patients are very few in this region. Hence, this study was conducted to evaluate the clinical profile of ACLF patients, assessment of the in-hospital course, mortality and outcome and to determine the factors affecting the outcome.

Materials and Methods: This study was conducted in Regional Institute of Medical Sciences (RIMS), Imphal from May 2022 to July 2024. All patients with chronic liver disease fulfilling the Asian Pacific Association for the Study of Liver criteria for ACLF, admitted in the Department of Medicine, were enrolled. On the day of admission (within 24hours), severity of liver disease was assessed and routine blood investigations, ultrasound whole abdomen, ascitic fluid analysis, upper GI endoscopy were done. Child Pugh Score, Model for End Stage Liver Disease-Na, Sequential Organ Failure Assessment and EASL- CLIF (European Association for the study of Liver-Chronic liver failure) consortium criteria were used. Outcome or mortality were compared among survivors and non – survivors of ACLF.A p value <0.05 was considered significant.

Results: A total of 70 ACLF patients were enrolled. The mean age of patients were 45.25±7.9 years with majority being males 63 (89.9%). Jaundice is detected in all patients (100%) and alcohol is the most common etiology of CLD found in 59 patients (84.1%).The most common acute insult precipitating ACLF was bacterial infection (34.3%){Spontaneous bacterial peritonitis followed by active alcoholism (32.9%)}. In our study, anemia and thrombocytopenia were present in 60(85.7%) and 52 (25.7%) patients respectively. Majority of patients belonged to Child Pugh class C (64%).There was significant association between a higher MELD score and mortality

(p<0.05), 58 patient (82.6%) survived and 12 (17.4%) died with the mean duration of hospital stay of 11.7±4 days. The most common organ failure was cerebral failure (25.7%) (grade II hepatic encephalopathy). ACLF grade 0,1,2,3 were present in 15(21.7%), 29(42%), and 19 (27.5%) patients respectively. There was significant association between ACLF grade and outcome, 66.7% of the non-survivors were in ACLF grade 3 (p<0.05).

Conclusions: Majority of the patients had multi-organ failure at the time of admission (42%) and was significantly associated with mortality (p<0.05). Higher grades of ACLF was associated with higher mortality. Parameters predicting poor outcome are low hemoglobin and platelet, high total leucocyte count, low serum albumin, elevated creatinine and high INR. Therefore, better characterization of the disease, vital signs and organ function will help in improving the patients' outcome and early implementation of organ-specific interventions.

Key Words: chronic liver disease, MELD –Na score, ACLF, in hospital, outcome, mortality.

INTRODUCTION

The concept of acute on chronic liver failure (ACLF) was introduced by Jalan and Williams in 2002 to describe the acute deterioration in liver function over two to four weeks in a patient with well compensated cirrhosis associated with a precipitating event which could be hepatic or non-hepatic leading to severe deterioration in clinical status with jaundice and hepatic encephalopathy.[1]

Acute-on-chronic liver failure (ACLF) is a syndrome characterised by acute decompensation of CLD associated with organ failures and high short-term mortality.[2]The Asian Pacific Association for the Study of the Liver (APASL) generated a consensus ACLF definition in 2009. The revised APASL consensus defines ACLF as an acute hepatic insult, manifesting as jaundice (defined as serum bilirubin ≥5 mg/dL (≥85 μmol/L)) and coagulopathy (defined as international normalised ratio ≥1.5 or prothrombin activity <40%), complicated within 4 weeks by clinically detected ascites and/or encephalopathy, in a patient with or without a previous diagnosis of CLD or cirrhosis.[3]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 CLD, usually related to a precipitating event and associated with increased mortality at three months due to multi-organ failure.[4,5]

Current evidence shows that the pathophysiology of ACLF is closely associated with an intense systemic inflammation sustained by circulating pathogen-associated molecular patterns and damage-associated molecular patterns. The development of organ failures may be a result of a combination of tissue hypoperfusion, direct immune-mediated damage and mitochondrial dysfunction.[6]ACLF usually results following an acute precipitating event in the background of underlying cirrhosis. The causes of acute insult largely depend on the geographical variables and Western countries, while infectious acute insults are more common in East subcontinent.[7] Of all infections, reactivation of hepatitis B virus infection is one of the major causes of ACLF in Asia.[3,6,8] Other frequent causes of acute insults are variceal bleeding, sepsis, and surgery. The main characteristic feature of ACLF is its reversibility and high short term mortality (50-90%) due to multiorgan failure in the absence of liver support devices and/or liver transplantation.[9,10]

In general, patients with two or more extra hepatic organ failures have high mortality risk. Respiratory failure is the strongest predictor of death.[11] Liver function is not the main determinant of clinical outcome for patients with decompensated cirrhosis, thus liver specific scoring systems, such as CTP (Child Turcotte Pugh) and MELD (Model for end stage liver disease) have limitation in predicting the outcome in ACLF. Organ failure scores, such as the APACHE II (Acute physiology and chronic health evaluation) and CLIF SOFA(Chronic liver failure-sequential organ failure assessment) are more helpful in predicting survival.[12]Data regarding acute on chronic liver failure are scarce from North-east India. High mortality rates, prolonged period of hospitalization and profound burden on healthcare system associated with the condition, demonstrates the importance of improving our idea about ACLF.[13]With this background, the aim is to study the clinical profile and predictors of in-hospital outcome in ACLF patients.

MATERIALS AND METHODS

This is a hospital based longitudinal study conducted in Regional Institute of Medical Sciences (RIMS), Imphal from May 2022 to July 2024. All patients with CLD fulfilling the Asian Pacific Association for the Study of Liver criteria for ACLF, admitted in the Department of Medicine, were enrolled.

Inclusion Criteria: included all patients above 18 years diagnosed with ACLF on the basis of Asian Pacific Association for the Study of Liver criteria (APASL).

Exclusion Criteria: Included those patients diagnosed with hepatocellular carcinoma, portal vein thrombosis, post Liver Transplant patients and those not giving consent for the study.

Study procedure: The patients were recruited after obtaining an informed consent. Detailed history was taken, clinical examination and relevant investigations were performed after their approval. Severity of liver disease was assessed. Routine blood investigations included complete hemogram (Hb, Total count, Differential count, Platelet count), liver function test, kidney function test, prothrombin time (PT) and international normalised ratio (INR),serum Lipid profile with LDL, HDL, Triglyceride, T. Cholesterol, serology (HbsAg, anti HCV, HIV 1 & 2). Whenever indicated Hepatitis A, E serology, hepatitis B and C viral load, Ultrasound whole abdomen, chest xray, urine routine examination, urine /blood culture and sensitivity, antinuclear antibody test (if indicated), ascitic fluid analysis, upper gastrointestinal (UGI) endoscopy and CT (computed tomography) scan Abdomen were done.

Outcome Variables were clinical profile of ACLF patients, in-hospital course, mortality and outcome.

Operational Definitions

The etiology of underlying CLD

Diagnosis of cirrhosis: It was based on clinical findings, biochemistry (low serum albumin < 3.5g/ dL,aspartate-aminotransferase/alanine-amino transferase i.e AST/ALT ratio >1, elevated bilirubin), imaging (heterogeneous echotexture of liver with irregular outline, altered liver size, Portal vein >13mm, porto-systemic collateral), endoscopy (esophageal varices) or documentation suggestive of prior decompensation.[14]

Diagnosis of ACLF

Asian Pacific Association for the Study of Liver consensus defines ACLF as an acute hepatic insult, manifesting as jaundice (defined as serum bilirubin ≥5 mg/dL and coagulopathy (defined as INR ≥1.5 or prothrombin activity<40%), complicated within 4weeks by clinically detected ascites and/or encephalopathy, in a patient with or without a previous diagnosis of CLD or cirrhosis.[4]

Cause of acute insults

Alcohol: As per APASL 2009 consensus, alcohol should be considered as an acute insult in case of active drinking within the last 4 weeks[3].

Bacterial Infection: In case of suspected infection (history of fever and/or leucocytosis or neutrophilia), evaluated extensively to find the source of infection.

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 were excluded.

Hepatotropic Infections-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 investigation.

Non Hepatotropic Insults-Trauma, surgery,TIPS, variceal bleeding.

Criteria for Systemic inflammatory response syndrome (SIRS) as per American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM)-1992,[15]

SIRS is defined as presence of 2 or more of the following variables:

Temperature>38°C (100.4°F) or < 36°C (96.8°F)

Heart rate >90 beats per minute

Respiratory rate >20 breaths per minute or arterial carbon dioxide tension ($PaCO_2$) <32mmHg

Abnormal white blood cell count (>12,000/µL or < 4000/µL or >10% immature [band] forms)

Hepatitis B flare/reactivation- defined as APASL criteria,[16]

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

The International Ascites Club,[17] defines

Grade 1 (mild): Ascites detectable only with ultrasound examination.

Grade 2 (moderate): Moderate symmetrical abdominal distension due to ascites

Grade 3 (large): Gross abdominal distension due to ascites

Presence and grade of hepatic encephalopathy according to **West Haven criteria for hepatic encephalopathy,[18]**

Grade 1: insignificant lack of awareness; euphoria or anxiety; short attention span; and impaired addition or subtraction skills.

Grade 2: sluggishness or indifference; mild disorientation for time or place; slight personality change; and inappropriate behaviour

Grade 3: drowsiness to semi stupor, respond to verbal stimuli; confusion; and absolute disorientation

Grade 4: coma (unresponsive to verbal or noxious stimuli)

Presence and grade of organ failure as CLIF-SOFA score,[4]

Liver failure: serum bilirubin level ≥12 mg/dl

Kidney failure: serum creatinine level ≥2.0 mg/dl or patient requiring renal replacement therapy

Cerebral failure: Hepatic encephalopathy grade III or IV (West Haven classification)

Coagulation failure: international normalized ratio (INR) >2.5 and/or platelet count of ≤20,000/dl

Circulatory failure: requirement of vasopressor

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 (European Association for the study of Liver-Chronic liver failure) consortium criteria[(1)]:

No ACLF: This group comprise of

Patients with no organ failure

Patients with failure of any single organ(hepatic, circulatory, or respiratory) with normal serum creatinine and no HE

Patients with cerebral failure and serum creatinine <1.5 mg/dl

(2) ACLF 1: This group will comprise

Patients with renal failure

Patients with other single organ failure with serum creatinine between (1.5- 1.9) mg/dl and HE grades 1–2

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

CHILD PUGH TURCOTTE SCORE,[19]

Child Pugh classification score of cirrhosis was used to assess the prognosis in liver disease

PARAMETERS	SCORE		
	1	2	3
Serum bilirubin (mg/dl)	<2	2-3	>3
Serum Albumin (g/dl)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3
Ascites	None	Mild to moderate	Severe
Hepatic Encephalopathy	NIL	Grade 1-2	Grade 3-4

	Class A	Class B	Class C
Total Points	5-6	7-9	10-15
1 Year Survival	100	80	45

Kidney function test

Parameter	Normal range
Serum urea	18-40 mg/dl
Serum creatinine	0.6-1 mg/dl
Serum sodium	135-145 mEq/L

Liver function test

Parameters	Normal range
Total bilirubin	0.1-1 mg%
Direct Bilirubin	0.1-0.4mg%
Total Protein	6-8 g%
Alkaline phosphatise /ALP	98-279 IU
Gamma glutamyl transferase/GGT	1-15 IU (Males),7-32 IU (Females)
AST	5-40 IU
ALT	5-30IU
Serum albumin	3.5-5.5g/dl

INR evaluates the extrinsic and common pathway of coagulation. Normal range INR: 0.9 -1.2.

MELD-Na Score

MELD-Na score of cirrhosis was used to assess the prognosis in liver disease

MELD = 3.78×ln [serum bilirubin (mg/dL)] + 11.2×ln [INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43·

MELD-Na = MELD +1.32×(137- Na) – [0.033 × MELD (137-Na)]

3-Month Mortality Based on MELD Scores

The estimated 3-month mortality is based on the MELD score.[20]

MELD Score	Mortality Probability
40 and above	71.3% mortality
30-39	52.6% mortality
20-29	19.6% mortality
10-19	6.0% mortality
9 or less	1.9% mortality

-Thrombocytopenia–platelet <1.5 lakhs cells/mm^3

-**WHO (World health organization) criteria for anemia**: Hemoglobin<12g/dl in women and <13g/dl in men [21]

Mild anemia: 11-12.9g/dl in males, 11-11.9g/dl in females

Moderate anemia: 8-10.9 in males, 8-10.9g/dl in females

Severe anemia: < 8g/dl in males and females

Study Tools: Complete Hemogram, done by Haematology automated analyser.

Blood sugar by glucose oxidase method using Glucose liquicolor kit**.**

Liver Function test was done by enzymatic analyser.

PT and INR were done by Haemostatics analyser.

Kidney function test was done using Kinetic method for serum urea and jaffe's method for creatinine.

Ascitic fluid analysis-Total count was done by Neubauer chamber method and differential count by manual analysis Giemsa stain.

Hepatitis C serology was done by Flaviscreen method

Hepatitis B serology was done by Viruschek rapid test

HIV I & II serology was done by Retrogine HIV kit

Statistical Analysis

Statistical package for social sciences version 26 (SPSS V.26) was used for statistical analysis. Data was summarized using descriptive statistics like mean, standard deviation, percentages. Paired t- test and ANOVA was used to check for significance of the continuous variables and chi square test was used to check the significance of categorical variables. P value of <0.05 was considered significant (with CI 95%).

Approval of Research Ethics Board and Informed Consent: The study was approved by Research Ethics Board Regional Institute of Medical Sciences, Imphal (REB No: A/206/REB – Comm(SP)/RIMS/2015/920/258/2022).Confidentiality was maintained during the study procedure.

RESULTS

A total of 70 ACLF patients were enrolled. The baseline characteristics of the study subjects were given in table 1. The mean age of patients was 45.25±7.9 years with male preponderance 63 (89.9%) and 7 (10.1%) were females. The most common presenting symptom was jaundice (100%), followed by abdominal distension (94.3%) and altered sensorium (71.4%). The most common etiology of CLD was found to be alcohol in 59 patients (84.1%), followed by alcohol combined with Hepatitis C infection. Bacterial infection was the most common acute insult precipitating ACLF among the patients studied (34.3%) followed by active alcoholism (32.9%). Among the bacterial infections, most common was spontaneous bacterial peritonitis (67.9%) followed by urinary tract infections (17.9%).

Laboratory parameters of the study subjects were given in table 2. In our study, 60 patients were found to have anemia (85.7%), with severe anemia in 29 patients (41.4%) and moderate anemia in 22 patients (31.4%). Thrombocytopenia was observed in 52 (25.7%) patients and both having significant association with mortality (p<0.05). Comparison of baseline parameters between Survivors and Non-survivors was shown in table 3.There was significant coagulopathy, determined by mean INR of 2.2±0.5. On comparing the mean INR between survivors and non-survivors, significant association was noted between raised INR and mortality (p<0.05). In our study, hyponatremia was seen in 24 (35%) patients. The mean serum sodium was 134.4±12.6 mg/dl. But there was no significant association between low serum sodium and in-hospital outcome of patients (p=0.31). On comparing the various laboratory parameters with outcome of the patients, low hemoglobin and platelet, high total leucocyte count, low serum albumin, elevated creatinine and high INR predicted poor outcome(p<0.05). There was significant renal dysfunction in the patients studied, with 50% patients having serum creatinine >1.5mg/dl. Several severity scores like Child Pugh, Model for End Stage Liver Disease-Na, EASL- CLIF consortium criteria were used. In our study, 35 patients (50%) had MELD-Na score above 20, followed by 32 patients (45.7%) with score between 30-39. There was significant association between a higher MELD score and mortality (p<0.05). Majority of patients belonged to Child Pugh class C (64%). Among the total 70 patients included in the study, 58 (82.6%) survived and 12 (17.4%) died in the hospital. The mean duration of hospital stay was 11.7±4 days with a median of 9 days. Based on CLIF-SOFA score for organ failure as shown in figure 1, most common organ failure was cerebral failure (25.7%) with majority of patients having grade II hepatic encephalopathy, followed by renal failure (24.3%), liver and coagulation failure (20%). Organ failure is an important predictor of mortality.

ACLF Grade based on EASL CLIF Consortium criteria as given in figure 2 (and then subdivided into no ACLF and ACLF grade 1, 2 and 3. Twenty-nine patients (42%) were in ACLF grade 2 and 19 patients (27.5%) were in grade 3, out of which patients (66.7%) of the 19 patients died in hospital. However, 15 patients (21.7%) qualified as no ACLF. There was significant association between ACLF grade and outcome as shown in figure 3, 66.7% of the non-survivors were in ACLF grade 3 (p<0.05). At the time of admission, most of study subjects had multi-organ failure (42%) which had significant association with mortality (p<0.05). Higher mortality was observed in patients with higher grades of ACLF. Patients in ACLF grade 3 had higher mortality when compared to those in

grade 1 and 2. There was significant association between the ACLF grade and outcome of patients ($p<0.05$).

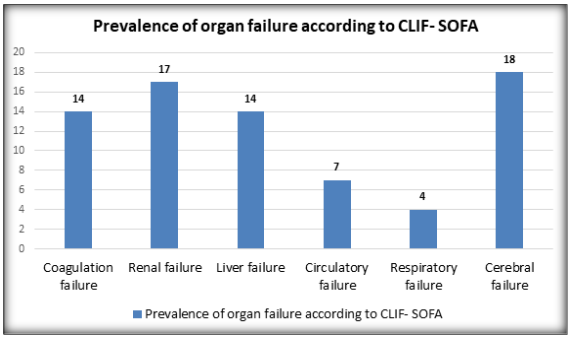

Figure 1: Prevalence of organ failure according to CLIF –SOFA score (n = 70)

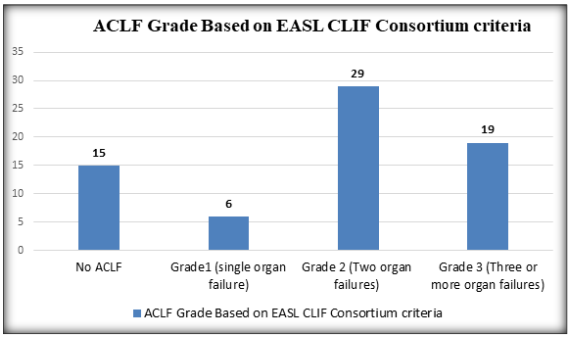

Figure 2: ACLF Grade based on EASL CLIF Consortium criteria (n = 70)

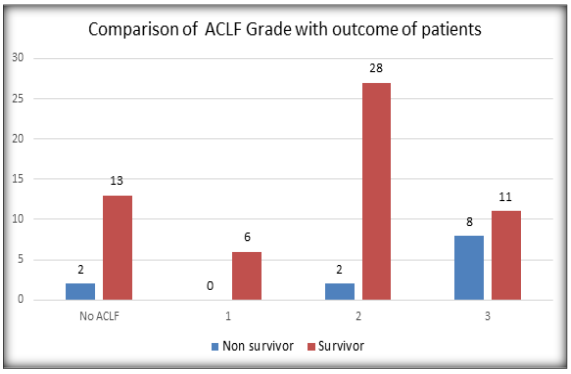

Figure 3: Comparison of ACLF Grade with outcome of the patients (n = 70)

Table 1: Baseline characteristics of the study subjects (n = 70)

Characteristics	Study patients n (%)
Age (in years)	
Mean + SD	45.25+7.9
Gender	
Male	63(89.9%)
Female	7(10.1%)
Clinical symptoms	
Jaundice	70(100%)
Abdominal distension	66(94.3%)
Altered sensorium	50(71.4%)
Malena	19(27.1%)
Hematemesis	11(15.7%)
Fever	10(14.3%)
Reduced urine output	13(18.6%)
Etiology of CLD	
Autoimmune hepatitis	1(1.4%)
Alcohol	59(84.1%)
Alcohol + hepatitis B	1(1.4%)
Alcohol + hepatitis C	5(7.2%)
Hepatitis C	1(1.4%)
NASH	3(4.3%)
Severity of Anemia	
No anemia	10(14.3%)
Mild	9(12.9%)
Moderate	22(31.4%)
Severe	29(41.4%)
Thrombocytopenia	
Present	52(74.3%)
Absent	18(25.7%)
Etiology of acute insult of ACLF	
Alcohol	23(32.8%)
Bacterial infection	24(34.3%)
UGI bleed	13(18.8%)
Alcohol + bacterial infection	4(5.6%)
Alcohol + UGI bleed	6(8.5%)
Causes of bacterial infection triggering ACLF	
Spontaneous bacterial peritonitis	19(67.9%)
Urinary tract infection	5(17.9%)
Lower respiratory tract infection	2(7.1%)

Sepsis (unknown source)	2(7.1%)
INR	
1-5-1.7	9(12.9%)
1.7-2.3	46 (65.7%)
>2.3	15(21.4%)
Serum creatinine (mg/dl)	
<1.1	6(8.6%)
1.1-1.5	29(41.4%)
>1.5	35((50%)
Hepatic encephalopathy	
Grade I	12(17.1%)
Grade II	40(57.1%)
Grade III	15(21.4%)
Grade IV	3(4.2%)
UGI endoscopy	
No varix	13(18.6%)
Grade I varix	11(15.7%)
Grade II varix	16(22.9%)
Grade III varix	12(17.1%)
Not done	18(25.7%)
MELD-Na score	
≤9	0(0%)
10-19	0(0%)
20-29	35(50%)
30-39	32(45.7%)
≥ 40	3(4.3%)
Child Pugh Turcotte score	
Class A	0(0%)
Class B	6(8.6%)
Class C	64(91.4%)
In hospital mortality	
Survived	58(82.6%)
Died	12(17.4%)
Mean duration of hospital stay (Days)	11.7±4
Median (days)	9

Table 2: Baseline characteristics of laboratory parameters (n = 70)

Laboratory parameters	Mean	SD
Hemoglobin(g/dl)	8.7	1.9
Total leucocyte count (per litre)	16.1	5.5
Platelet count (lakh)	1.16	0.58
Total Bilirubin (g/dl)	17.9	7.5
AST (U/L)	144	95
ALT (U/L)	69	65
ALP (U/L)	96	48
Creatinine (mg/dl)	1.9	1.1
Serum Albumin (mg/dl)	2.2	0.3
INR	2.1	0.5
Prothrombin time	26.3	5.0
Sodium (mEq/l)	134.4	12.6
Potassium (mEq/l)	3.7	0.7
Random blood sugar (mg/dl)	106	32.1

Table 3: Comparison of baseline parameters between Survivors and Non-survivors (n=70)

Parameters	Non-survivors		Survivors		
	Mean	SD	Mean	SD	p-value
Age	46.1	7.1	45.2	7.7	0.35
Hemoglobin (g/dl)	8.0	1.7	8.8	1.9	0.01*
Platelet(lakh)	0.96	0.42	1.20	0.60	0.01*
TLC (per litre)	20.3	3.0	16.1	5.5	0.01*
Total Bilirubin (mg/dl)	17.6	7.9	17.9	7.5	0.32
AST (U/L)	143	74	145	99	0.52
ALT (U/L)	63	21	71	71	0.21
ALP (U/L)	79	22	100	51	0.11
Creatinine (mg/dl)	3.0	1.7	1.7	0.7	0.01*
PT	27.3	5.7	26.1	4.9	0.21
INR	2.2	0.5	2.1	0.5	0.32
S. Potassium (mEq/l)	4.1	1.1	3.6	0.5	0.12
S. Sodium (mEq/l)	135.3	2.8	134.2	13.8	0.31
S. Albumin	2.0	0.3	2.6	0.3	0.01*
MELD-NA score	31.5	5.3	29.7	4.4	0.01*

DISCUSSION

Acute-on-chronic liver failure (ACLF) is a complex syndrome characterized by an acute deterioration of pre-existing chronic liver disease (CLD) and associated with high short-term mortality.[2] This condition often presents with multi-organ failure and requires intensive medical management. The present study aimed to evaluate the clinical profile and in-hospital course and outcome of patients with ACLF, offering insight into the demographic patterns, etiological factors and severity indicators in the study population.

The mean age of patients was found to be 45.25±7.9 years. Among them, 63 (89.9%) were males and 7 (10.1%) were females which was similar to the studies done by Tasneem AA et al,[22] {mean age of 36.71 years, 46 (63.9%) males} and Shalimar et al,[23] (mean age 44.7±12.2 years and majority were men).Male preponderance was observed in most studies on ACLF. The commonest presenting symptom was jaundice (100%), followed by abdominal distension in 66 (94.3%) and altered sensorium in 50 (71.4%) patients, which was similar to the studies by Supriya et al,[24] and Garg G et al.[25] In our study, UGI bleed in the form of malena and hematemesis were seen in 19 patients (27%) and was one of the major precipitating factor for ACLF and also occured as a complication of ACLF. Upper gastrointestinal endoscopy done in 52 patients revealed mostly grade II esophageal varix in 16 (22.9%) while there was no significant association between the grades of varix and outcome. The most common etiology of underlying CLD was found to be alcohol in 59 (84.1%) patients which was consistent with the studies by Khatua C et al,[26] and Pati GK et al,[27] in contrast to hepatitis B infection (37%) in a study by Garg G et al [25]. In our study, the most common acute insult precipitating ACLF was bacterial infection in 24 patients (34.3%) and active alcoholism in 23 patients (32.9%) which was at par with the studies conducted by Khatua et al,[26]Pati GK et al,[27] and Kulkarni S et al.[28] The incidence of ACLF triggered by alcohol is increasing in the Asian region.[29] This change in trend attributed to the growing westernisation of Asia with alcohol being the most common acute insult in Asian region.

In our study, the mean total leucocyte count was 16100±5.5 cells per mm.[3] This corresponds to the fact that the pathological hallmark of ACLF is systemic inflammation leading to raised TLC,[30] which serves an independent predicator of mortality and was at par with studies by Amarapurkar D et al,[31] and Wang C et al.[32]In our study, 60 (85.7%) patients were found to have anemia. Anemia was not only a trigger but also a predictor of short-term mortality($p<0.05$) in patients with ACLF which was similar to the study done by Piano S et al,[33] who studied the incidence, predictors and outcomes of ACLF in outpatients with cirrhosis. There was significantly lower serum albumin level among the non-survivor group compared to survivor group ($p<0.05$) while not significant in a study done by Tasneem AA et al.[22] Castro-Narro G et al,[34] described that low serum albumin level in cirrhotic patients are known to progress to ACLF and develop complications like circulatory dysfunction and hepatorenal syndrome. Out of the total 70 patients in our study, 29 patients (41.4%) had significant renal dysfunction and there was significantly high mean creatinine value was observed in the non-survivors ($p<0.05$) which was consistent with the study done by Amarapurkar D et al.[31] Similarly, Lotfi M et al,[35]documented renal failure as the most common organ failure in ACLF. In a study conducted by Mikolasevic I et al,[10] serum creatinine higher than 90µ/L was an independent predictor of mortality. In our study, 52(74.3%) patients had thrombocytopenia. There was significant association between thrombocytopenia and mortality ($p<0.05$) which was similar to the studies done by Ouyang R et al.[36]ACLF patients have substantial alterations in the hemostasis due to liver failure contributing to higher risk of bleeding.[36]The mean INR of patients was found to be 2.2±0.5. There was significant association between high INR and mortality ($p<0.05$) which was consistent with the study done by Garg G et al,[34] and Amarapurkar et al.[36] In our study, hyponatremia was seen in 24 (35%) patients. However, there was no significant association between low serum sodium and in-hospital outcome of patients ($p=0.31$). But in a study by Pereira G et al, hyponatremia at the time of admission was associated with low survival (35%) whereas survival was higher in patients without hyponatremia (70%).[37]

Various scoring systems like Child Pugh score (CTP), Model for End Stage Liver disease-Na (MELD-Na) and EASL-CLIF consortium criteria were used to assess the severity and to compare the non-survivors and survivors. In our study, 64 (91.4%) patients belonged to Child Pugh class C and 6 patients (8.6%) belonged to Child Pugh class B. But Child Pugh score did not differ significantly between the survivors and non-survivors, which was at par with Pati GK et al,[27] in his study. In our study, 35 (50%) patients had a MELD-Na score above 20 and 32 (45.7%) had a score between 30 – 39, conveying the higher short-term mortality in ACLF patients. Mean MELD-Na score was 31.4±5.3 in the non-survivor group and 29.7±4.4 in the survivor group ($p<0.05$). Hence MELD score is a predictor of severity and mortality in patients with ACLF.Mahmud N et al,[38] reported that models for ACLF mortality also had good discrimination at 28 and 90-days and were superior to MELD, MELD-sodium and the CLIF-C ACLF score. Gawande A et al,[39] found that higher MELD score and high CTP score were significantly associated with mortality. In his study, higher ACLF grade was also associated with higher mortality.

As per the EASL- CLIF criteria, patients were divided into ACLF and no ACLF, which was further subdivided into grade 1, 2 and 3 based on the number of organ failures and severity of renal and cerebral failure. Approximately 15 patients (21.7%) qualified as no ACLF in our study. ACLF grade 2 and 3 comprises of 29 (42%) and 19 (27.5%) patients respectively. In our study 66.7% of non-survivors were having ACLF grade 3. There was significant association between higher ACLF grade and mortality ($p<0.05$) which was similar to the study conducted by Sarin SK et al.[3] Yu Shi et al [40] compared the clinical characteristics and prognosis between hepatic and extrahepatic group. Hepatic-ACLF was precipitated by hepatic insults and extrahepatic-ACLF was precipitated by extrahepatic insults. In their study, CLIF-Consortium scores for ACLF had the highest predictive value in the extrahepatic group.

In patients with ACLF, systemic inflammation characterized by elevated leucocytosis, cytokines, and chemokines (including IL-6 and IL-8) is commonly observed, a phenomenon typically absent in cirrhotic patients without ACLF. Bacteria-induced pathogen-associated molecular patterns (PAMPs) and virulence factors trigger the activation of transcription factors responsible for encoding cytokines in the inflammatory cascade. Additionally, endogenous inducers of inflammation, known as damage-associated molecular patterns (DAMPs), are generated due to hepatocyte denaturation. These DAMPs cooperate with Toll-like receptors (TLRs) to activate inflammatory cascades, contributing to tissue and organ damage, ultimately leading to organ failure. Outcome of the systemic inflammation include- Tissue hypoperfusion, immune mediated tissue damage, mitochondrial dysfunction, immunosuppression in ACLF [6].

In our study, the mean duration of hospital stay was 11.7±4 days with a median of 9 days and 12 patients (17.4%) died in the hospital. In this study, most common organ failure was found to be cerebral failure in 18 patients (25.7%), renal failure in 17 (24.3%) followed by liver and coagulation failure in 14 (20%) patients according to CLIF-SOFA score. Respiratory failure was seen only in 4 (5.7%) patients. In our study, 29 patients (41.4%) had multiple organ failures at the time of admission and was significantly associated with mortality ($p<0.05$). Similarly, Gawande A et al[39] ,in a prospective study with 208 patients, documented in-hospital mortality of 37.5%. In their study cerebral failure was the most common organ failure (41.34%) followed by coagulation failure (29.8%). Moreover, patients with multiple organ failure had higher mortality ($p<0.001$).

CONCLUSION

Fifty percent of patients had MELD-Na scores above 20. There was significant association between MELD-Na score, anemia, leucocytosis, thrombocytopenia, hypoalbuminemia, coagulopathy, raised creatinine with mortality ($p<0.05$) and poor outcome. There was no significant association between hepatic encephalopathy and ACLF grades. This study underscores the critical need for early identification and management of risk factors and acute insults to treat promptly subsequently improving outcomes in ACLF patients. Treatment objectives also include providing support for failing organs, and considering liver transplantation for eligible candidates, swiftly restoring metabolic and hemodynamic stability, administering nutritional support, and utilizing agents to safeguard hepatocytes and encourage regeneration.

Limitations: The present study has limitations inherent to lack of follow up as we assessed only in-hospital outcome and mortality. Mortality at 28-days and 90-days were not assessed. APASL criteria was used for diagnosis of ACLF, there would have been cases that did not satisfy the APASL criteria but might have had organ failures. Lastly, EASL-CLIF criteria is dependent on the number of organ failures. Some patients (21.7%) in our study fall in the category of no ACLF according to this criteria.

REFERENCES

1. Arroyo V, Jalan R. Acute-on-Chronic Liver Failure: Definition, Diagnosis, and Clinical Characteristics. Semin Liver Dis. 2016 May;36(2):109–16.
2. Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. Gut. 2017 Mar;66(3):541–53.
3. Sarin SK, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update. Hepatol Int. 2019; 13:353–90.
4. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013 Jun;144(7):1426–37, 1437.e1-9.
5. Kumar R, Mehta G, Jalan R. Acute-on-chronic liver failure. Clin Med. 2020 Sep;20(5):501–4.
6. Zaccherini G, Weiss E, Moreau R. Acute-on-chronic liver failure: Definitions, pathophysiology and principles of treatment. JHEP Reports [Internet]. 2021;3(1):100176. Available from: https://www.sciencedirect.com/science/article/pii/S2589555920301105
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 Nov;55(11):3188–92.
8. Sen S, Williams R, Jalan R. The pathophysiological basis of acute-on-chronic liver failure. Liver. 2002;22 Suppl 2:5–13.
9. Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, et al. Acute-on chronic liver failure. J Hepatol [Internet]. 2012 Dec;57(6):1336–48. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168827812005193
10. Mikolasevic I, Milic S, Radic M, Orlic L, Bagic Z, Stimac D. Clinical profile, natural history, and predictors of mortality in patients with acute-on-chronic liver failure (ACLF). Wien Klin Wochenschr. 2015; 127:283–9.

11. Reddy MS, Rajalingam R, Rela M. Liver transplantation in acute-on-chronic liver failure: lessons learnt from acute liver failure setting. Hepatol Int. 2015 Oct;9(4):508–13.
12. Moreau R. The Pathogenesis of ACLF: The Inflammatory Response and Immune Function. Semin Liver Dis. 2016 May;36(2):133–40.
13. Kamath PS. Acute on chronic liver failure. Clin liver Dis. 2017 Apr;9(4):86–8.
14. Smith A,Baumgartner K,Bositis C.Cirrhosis: Diagnosis and Management .Am Fam Physician.2019 Dec 15;100(12):759-770.PMID : 31845776.
15. Bone RC, Balk RA, Cerra FB et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest. 1992 Jun 1;101(6):1644-55.
16. Sarin SK, Kumar M, Lau GK et al. Asian Pacific clinical practice guidelines on the management of hepatitis B: a update: Hepatol Int, 2016-2015; 10:1 - 98
17. Arroyo V, Gines P, Gerbes AL. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology. 1996; 23:164-176
18. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification:final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology. 2002 Mar;35(3):716–21.
19. Tsoris A,Marlar CA.use of the Child Pugh Score in Liver Disease.(updated 2023 Mar 13).In : StatPearls (internet).Treasure Island(FL):StatPearls Publishing;2024Jan.Availablefrom :https://www.ncbi.nlm.gov/books /NBK542308/
20. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology. 2007 Mar;45(3):797–805.
21. World Health Organisation. Haemoglobin concentrations for the diagnosis of anemia and assessment of severity. Available at http://www.who.int/vmnis/indicators/hemoglobin
22. Tasneem AA, Luck NH. Acute-on-chronic liver failure: causes, clinical characteristics and predictors of mortality. J Coll Physicians Surg Pak. 2017;27(1):8–12.
23. Shalimar S, Vivek Saraswat VS, Singh SP et al. Acute-on-chronic liver failure in india: The Indian National Association for study of the Liver consortium experience (2016): 1742 - 1749.
24. Sharma S, Kumar K, Mohindra S. Clinical profile of patients with acute-on-chronic liver failure (ACLF) and its prognostication. Int J Med Heal Res. 2019;5(1):183–9.
25. Garg H, Kumar A, Garg V, Sharma P, Sharma BC, Sarin SK. Clinical profile and predictors of mortality in patients of acute-on-chronic liver failure. Dig Liver Dis. 2012;44(2):166–71.
26. Khatua CR, Senapati UK, Mohanty R, Singh SP. Profile of Acute-On-Chronic Liver Failure (ACLF) in Hospitalised Chronic Liver Disease (CLD) Patients: Experience from a Resource Constrained Region. J Clin Exp Hepatol. 2022;12: S51–2.
27. Pati GK, Singh A, Misra B, Misra D, Das HS, Panda C, et al. Acute-on-chronic liver failure (ACLF) in coastal eastern India:“a single-center experience.” J Clin Exp Hepatol. 2016;6(1):26–32.
28. Kulkarni S, Sharma M, Rao PN, Gupta R, Reddy DN. Acute on chronic liver failure—in-hospital predictors of mortality in ICU. J Clin Exp Hepatol. 2018;8(2):144–55.
29. Schulz M, Trebicka J. Acute-on-chronic liver failure: a global disease. Gut. 2022 Jan 1;71(1): 5-6
30. Casulleras M, Zhang IW, Lopez-Vicario C, et al. Leukocytes, systemic inflammation and immunopathology in acute-on-chronic liver failure. Cells. 2020 Dec 8;9(12):2632
31. Amarapurkar D, Dharod M V, Chandnani M, Baijal R, Kumar P, Jain M, et al. Acute-on-chronic liver failure: a prospective study to determine the clinical profile, outcome, and factors predicting mortality. Indian J Gastroenterol. 2015; 34:216–24.
32. Wang C, Ma D-Q, Luo S, Wang C-M, Ding D-P, Tian Y-Y, et al. Incidence of infectious complications is associated with a high mortality in patients with hepatitis B virus-related acute-on-chronic liver failure. World J Clin Cases. 2019;7(16):2204.
33. Piano S, Tonon M, Vettore E, et al. Incidence, predictors and outcome of acute-on-chronic liver failure in outpatients with cirrhosis. Journal of Hepatology. 2017 Dec 1:67(6):1177-84
34. Castro- Narro G, Moctezuma-Velazquez C, et al. Position statement on the use of albumin in liver cirrhosis. Annals of Hepatology. 2022 Jul 1;27(4):100708
35. El Sayed ML, Gouda TES, Khalil ELSAM, Al Arman MMES, Mohamed IE. Clinical profile and outcome among patients with acute-on-chronic liver failure admitted in the intensive care unit. Egypt J Intern Med. 2021; 33:1–11
36. Ouyang R, Li H, Xia J, et al. Lower platelet counts were associated with 90-day adverse outcomes in acute-on-chronic liver disease patients. Annals of Palliative Medicine. 2021 Sep;10(9): 9342353-9353
37. Pereira G, Baldin C, Piedade J, Reis V, Valdeolivas T, Victor L, et al. Combination and sequential evaluation of acute-on-chronic liver failure (ACLF) and hyponatremia and prognosis in cirrhotic patients. Dig Liver Dis. 2020;52(1):91–7.
38. Mahmud N, Hubbard RA, Kaplan DE, Taddei TH, Goldberg DS. Risk prediction scores for acute on chronic liver failure development and mortality. Liver Int. 2020;40(5):1159–67.
39. Gawande A, Gupta GK, Gupta A, Wanjari SJ, Goel V, Rathore V, et al. Acute-on-chronic liver failure: etiology of chronic and acute precipitating factors and their effect on mortality. J Clin Exp Hepatol. 2019;9(6):699–703.
40. Shi YU, Yang Y, Hu Y, Wu W, Yang Q, Zheng M, et al. Acute-on-chronic liver failure precipitated by hepatic injury is distinct from that precipitated by extrahepatic insults. Hepatology. 2015;62(1):232–42.