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ORIGINAL ARTICLE

Baseline characteristics, grading and mortality in acute on chronic liver failure using EASL CLIF CRITERIA.

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ABSTRACT… Objective: To observe baseline characteristics, ACLF (Acute on Chronic Liver Failure) grading and mortality in ACLF patients using EASL CLIF CRITERIA. **Study Design:** Prospective, Observational study. **Setting:** Medical unit III, ward 7, Jinnah Postgraduate Medical Centre, Karachi. **Period:** January 2022 to June 2022. **Material & Methods:** We prospectively analysed data of hospitalised liver cirrhosis patients at a tertiary care hospital in Karachi, Pakistan. The data was analysed in SPSS version 25. **Results:** There were a total of 43 ACLF patients, with the median age of IQR of 56(47-62) years, out of which 20 (46.5%) patients were male and 23 (53.5%) were females. The most common etiology of liver cirrhosis was hepatitis C 26(60.5%) followed by other etiologies nine (20.9%) and hepatitis B eight (18.6%). The most common precipitating factor was infection 19(44.2%) and the most frequent organ failure (OF) was renal failure (60.5%), followed by cerebral failure (46.5%) and other OFs. There were 24 patients in ACLF grade one, 13 in grade two and six in grade three ACLF. All six patients of ACLF grade three belonged to CTP C (Child-Turcotte-Pugh score) (100%) with 100% mortality. ACLF grade two had nine (69.2%) and ACLF grade one had eight (33.33%) CTP C patients. The in hospital mortality of ACLF was 23%. The median MELD Na of these patients was 28 (23-31), CLIF Consortium Organ Failure score was 9(8-10) and CLIF C ACLF Score was 45 (38-55). **Conclusion:** Highest mortality was observed in Child Pugh C and ACLF grade three in our patients. Such patients must be closely monitored and referred early for medical management and liver transplantation.

Key words: ACLF Grading, Precipitating Factors.

INTRODUCTION

Acute on chronic liver failure is a complex syndrome defined by the worsening of symptoms in pre-existing chronic liver disease. It is manifested by one or multiple organ failures and is associated with high mortality.[1] Many international consortia have suggested diagnostic criteria of ACLF, out of which EASL CLIF criteria is the most acceptable one as it has greater sensitivity in identifying ACLF patients and has better prognostic capability.[2]

According to EASL (European Association for the study of Liver) CLIF criteria, ACLF can occur in compensated as well as prior decompensated patients and can be triggered by any cause.

The most frequent triggering factors of ACLF in the west are bacterial infection and alcohol intake in contrast to viral infections like Hepatitis B, followed by sepsis and alcohol intake in the east.[3] However in 40% of these patients no triggering factor has been found for ACLF.[3]

Interestingly in patients awaiting transplantation, a retrospective study identified obesity grade III (BMI >40 kg/m2) as a risk factor leading to ACLF.[4] Other risk factors observed were old age, white race, hepatocellular carcinoma and high MELD Na score.[5]

In ACLF, the immune dysregulation is driven by systemic inflammation, caused by pathogen and damage-associated molecular patterns, leading to tissue damage and ultimately organ failure.[6]

ACLF can be complicated by upper

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gastrointestinal bleed due to varices, portosystemic encephalopathy, immune dysfunction, hepatorenal and hepatopulmonary syndrome.[7]

The overall transplant free mortality of ACLF has been estimated to range between 30%-40%, requiring immediate intervention and appropriate treatment.[8]

However, timely dialysis in case of renal failure and early liver transplant can lead to better outcomes.[9] In order to reduce mortality, empirical use of antibiotics should be rapidly initiated. Injection albumin which is considered to have a beneficial role in treating subacute bacterial peritonitis (SBP) should also be incorporated in the treatment of ACLF.[10]

The one year survival rate of post-transplant ACLF patients has exceeded 70%.[11]

Even with 3 organ failures, there is 84% one-year survival rate if timely transplantation is done.[12]

While observing an increased frequency of ACLF patients at our centre, we evaluated the demographic, clinical parameters and mortality of these patients in our study.

MATERIAL & METHODS

This is the prospective, observational study conducted in Ward 7, Jinnah Postgraduate Medical Center. The duration of the study was 6months from January 2022 till June 2022. A questionnaire was designed to collect patient's data, including demographics, reason for admission, baseline characteristics and laboratory values. 43 patients who were diagnosed as ACLF using EASL CLIF criteria were recruited in the study.

The study protocol was approved by Jinnah Postgraduate Medical Center (JPMC) Institutional Review Board (IRB) (F.2-81/2022-GENL/280/JPMC). All the patients meeting criteria were enrolled in the study after taking the informed consent.

Sample Size

The sample size was calculated by estimating the prevalence of ACLF in Pakistan using OpenEpi calculator, with the confidence interval of 95% and margin of error ±5.

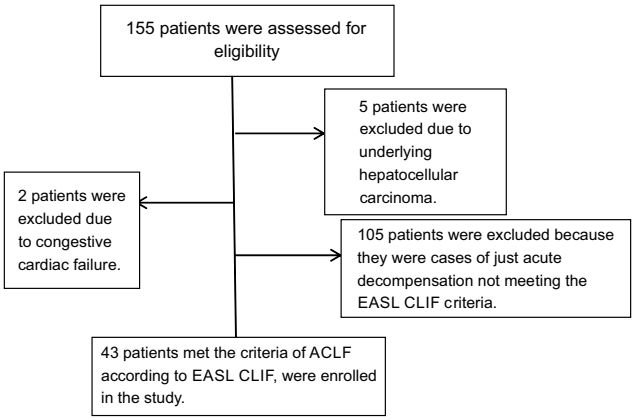

Chart-1. Shows selection of ACLF patients.

SPSS version 25 was used to store and analyse data. It was expressed either as mean ± standard deviation or median [inter-quartile range (25%-75%)] or as percentage with a P value<0.05 considered statistically significant.

Inclusion Criteria

Patients meeting the criteria of ACLF according to EASL CLIF were included.

Exclusion Criteria

Patients on renal replacement therapy at the time of diagnosis.

Patients with multiple major co-morbidities like coronary artery disease, congestive cardiac failure or any underlying malignancy including hepatocellular carcinoma.

The admitted patients were given standard protocol treatment and were followed till they got discharged or expired.

DEFINITIONS

ACLF

ACLF is a specific syndrome characterized by acute decompensation (AD) of cirrhosis, organ failures (OFs), and high short-term mortality according to EASL CLIF consortium.[13]

Acute Decompensation
Was the presence of ascites, hepatic encephalopathy (HE), gastrointestinal haemorrhage, and/or infections not meeting ACLF criteria

Organ Failure
Is defined by the Chronic Liver Failure Scale assessing 6 organ systems (liver, kidney, brain, coagulation, respiration and circulation)[13]
Liver Failure was defined as total bilirubin ≥12mg/dl
Kidney Failure was recognised when serum creatinine level was ≥2mg/dl or required renal replacement therapy
Cerebral failure was defined by grade III or IV hepatic encephalopathy as per the West Haven classification.
Coagulation Failure was acknowledged if the INR was ≥2.5
Respiratory Failure was defined by a PaO2 to FiO_2 ratio of ≤ 200 or a SpO_2 to FiO_2 ratio of ≤ 214 or use of mechanical ventilation.
Circulatory Failure was labelled by the use of vasopressors like dopamine, dobutamine or terlipressin
The EASL CLIF criteria was used to assess the grade of ACLF depending on the number of organ failures.
ACLF Grade 1: was determined by single kidney failure or liver failure, coagulopathy, circulatory failure, respiratory failure, serum creatinine 1.5-1.9mg/dl and/or mild to moderate hepatic encephalopathy OR brain failure with creatinine 1.5-1.9mg/dl
ACLF Grade 2: Any two organ failures
ACLF Grade 3: Any three or more organ failures

The CLIF-C ACLF score was calculated by combining the CLIF-C OF score, age, and WBC count with the following formula:[14]
CLIF-C ACLF = 10 × (0.33 × CLIF-OFs + 0.04 x Age + 0.63 × ln (WBC count) − 2

The CLIF Organ Failure score consists of six subscores (ranging from 1-3) to evaluate organ dysfunction, used for predicting prognosis in ACLF patients.[15]

Child Pugh score: was used for determining the severity of liver disease of the patients and will be calculated out of 15 based on total bilirubin, albumin, prothrombin time, ascites and HE.

MELD-Na was also used to estimate the severity of liver disease and was estimated by the formula: MELD Score - Na - 0.025 x MELD x (140-Na) + 140

High short-term mortality means death of the patient within 28 days since AD.[14]

RESULTS
Table-I. depicts 43 ACLF patients of which 20 patients were male(46.5%) and 23 were females(53.5%). The median IQR for age was 56 years.

Hepatitis C (60.5%) was the most frequent etiology of underlying CLD, followed by other causes (20.9%) and then hepatitis B (18.6%).

There were 44% patients who were admitted with impression of HE, 21% were with jaundice and upper GI bleed each, 9% with infection and 5% had ascites. 55.8% of these patients had previous history of hospital admission.

Infection (18.6%) was the most frequent triggering factor, followed by upper GI bleed (18.6%) and SBP (11.6%). There was one patient of Hepatitis A, E and reactivation of Hepatitis B each. In 16.3% of the patients the triggering factor for ACLF was unknown. Figure-1. Illustrates renal failure (60.5%) to be the most common organ failure, followed by cerebral failure (46.3%). 16.3% had circulation failure, 16.3% liver failure, 9.3% had coagulation failure and 7% had respiratory failure. Most patients 23 (53.5%) had CTP grade C.

Table-II shows the laboratory parameters and scores of ACLF patients. The median MELD Na sore was 28 (23-31), CLIF Organ Failure score was 9 (8-10) and CLIF C ACLF score was 45 (38-55)

Table-III shows that highest number of ACLF patients 24 (55.8%), out of which most were males 14 (58.3%), were in grade 1. 13 (30.2%) patients were in grade 2 ACLF with female predominance of 9(69.2%). Although only 6 (14%) patients were in grade 3 but again had a higher percentage of female patients 4 (66.7%).

CTP grade A patients 2(8.3%)were found only in ACLF grade 1. 14 (58.3%) patients with CTP B were found in ACLF grade 1 and 4 (30.8%) in ACLF grade 2 whereas ACLF grade 3 comprised only of CTP C patients 6(100%).

In hospital mortality was 10 (23.3%) while 33(76.77%) patients were discharged. 4 patients out of 20 (16.7%) among ACLF grade A patients got expired. No expiry seen in ACLF grade 2 and 100 % mortality seen in ACLF grade 3.

Pearson Chi Square test showed a statistically significant association of ACLF samples with CTP grade and organ failures ($p<0.05$).

Characteristics		ACLF (n=43)	
		N	%
Gender	Male	20	46.5
	Female	23	53.5
Etiology of cirrhosis	Hepatitis B	8	18.6
	Hepatitis C	26	60.5
	Others	9	20.9
Cause of admission	Ascites	2	4.7
	Hepatic Encephalopathy	19	44.2
	Infection	4	9.3
	Jaundice	9	20.9
	Upper GI bleed	9	20.9
Previous history of hospital admission due to complication of liver diseases	Yes	24	55.8
	No	19	44.2
Acute precipitating factors	Hep E	1	2.3
	Hep A	1	2.3
	Infection	19	44.2
	Reactivation of Hep B	1	2.3
	SBP	5	11.6
	Upper GI Bleed	8	18.6
	Autoimmune Hepatitis	1	2.3
	Unknown	7	16.3

Table-I. Baseline characteristics of ACLF patients

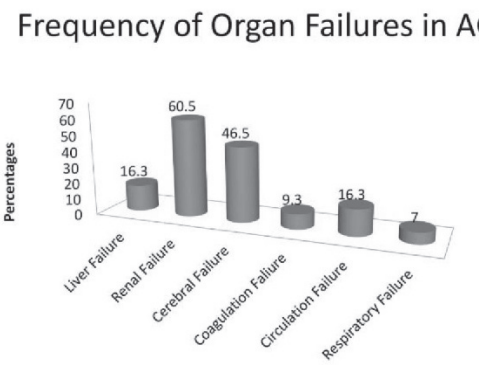

Figure-1.

Parameters	ACLF
	Median (IQR)
Age (years)	56(47-62)
Mean Arterial Pressure	83(73-93)
Pulse	92(84-103)
Respiratory Rate	20(19-22)
Hemoglobin	9.3(8-10.6)
TLC	8.9(6.3-11.8)
Platelets	112(52-147)
Total Bilirubin	2.7(1-8.27)
SGPT	44(26-99)
INR Day1	1.65(1.3-2)
Serum Albumin	2.1(1.9-2.7)
Sodium (Na)	134(129-139)
Potassium (K)	4.5(3.6-5.1)
Creatinine	2.12(1.5-3.04)
MELD Na Score	28 (23-31)
CLIF Consortium Organ Failure Score	9(8 – 10)
Clif C ACLF SCORE	45 (38 – 55)

Table-II. Clinical characteristics and laboratory parameters of the patients

DISCUSSION

ACLF is a life-threatening condition which occurs in patients with pre-existing chronic liver disease. In our study, Hepatitis C 26 (60.5%) was the most common etiology of chronic liver disease compared to the alcoholic cirrhosis reported in a study conducted in Europe by Moreau R etal[15] and in a small study conducted in Pune, India.[16] The difference in etiologies can be attributed to the social, religious and cultural norms of a particular country.

Characteristics		ACLF Grade 1 (n=24)		ACLF Grade 2 (n=13)		ACLF Grade 3 (n=6)		P-Value
		N	%	n	%	N	%	
Gender	Male	14	58.3	4	30.8	2	33.3	0.17
	Female	10	41.7	9	69.2	4	66.7	
Etiology of cirrhosis	Hepatitis B	7	29.2	1	7.7	-	-	0.04*
	Hepatitis C	13	54.2	11	84.6	2	33.3	
	Others	4	16.7	1	7.7	4	66.7	
Cause of admission	Ascites (not SBP)	2	8.3	-	-	-	-	0.38
	Hepatic Encephalopathy	10	41.7	4	30.8	5	83.3	
	Infection	2	8.3	1	7.7	1	16.7	
	Jaundice	6	25.0	3	23.1	-	-	
	Upper GI bleed	4	16.7	5	38.5	-	-	
Previous history of hospital admission due to complication of liver diseases	Yes	13	54.2	9	69.2	2	33.3	0.26
	No	11	45.8	4	30.8	4	66.7	
CTP Score grade	A	2	8.3	-	-	-	-	<0.01*
	B	14	58.3	4	30.8	-	-	
	C	8	33.3	9	69.2	6	100	
Outcome	Discharged	20	83.3	13	100	-	-	<0.01*
	Expired	4	16.7	-	-	6	100	

Table-III. Characteristics of samples with ACLF grade

The median age of our patients was 56 years with the male patients (46.5%) outnumbering the female patients. Consistently, Bhatti etal[17] reported male predominance of (73.5%) among ACLF patients having mean age 40.90+_13.93 years.

ACLF is considered to be triggered by a precipitating factor in CLD patients which results in acute deterioration of their clinical state. Most of the patients (44.2%) in our study had infection as the underlying cause of ACLF followed by upper GI bleed and SBP. Interestingly in 16.3% of the patients, no triggering factor was identified. However according to a review article on Canonic study by Vicenti Arroyo etal[18], there were mostly 30% infection related ACLF cases with 40 % of ACLF cases had no precipitating factor. On the contrary, acute viral hepatitis was reported to be the most frequent cause of ACLF by Tasneem.[19]

The compromised liver function and impaired immunity make these patients more susceptible to infections, accounting for its highest percentage in our study. Underlying infections also explain the presentation of HE in the majority of our patients (44.2%), especially in grade 3 ACLF.

Renal failure was the most frequent OF (60.5%) seen among these patients which was consistent with Vincentis' study who also reported renal failure (56%) to be the commonest OF.[18] On the contrary, Bhatti etal reported hepatic failure to be the commonest OF in his study.[17]

Our study showed 23.3% mortality among ACLF patients with 100% mortality in ACLF grade 3 patients. Another study conducted in Pakistan by Sarfaraz etal reported mortality of 43.2% with its highest association with more than 3 OFs[20,11] whereas Rao etal study showed 30% mortality among ACLF.[21] According to Harnaez and an Indian study, ACLF grade 3 at the time of admission shows worst prognosis compared to grade 1 and 2 showing consistency with our results.[22,23]

On the contrary, an Egyptian study showed in hospital mortality of 74.3%.[24]

The multi organ failures in ACLF grade 3 of our patients, including high frequency of renal failure

made their prognosis poor and unsuitable to undergo liver transplantation.

As the transplant window with living donor setting is small, decision for liver transplantation must be taken in the first week to improve survival of these patients.[25]

Single centre study with a small sample size are the limitations of our study, therefore the results of this study cannot be generalised for the whole population of the area.

CONCLUSION

Our results showed highest mortality in Child Pugh C with ACLF grade three. Therefore risk stratification in terms of Child Pugh Score, OFs and ACLF grading of such patients must be done at the time of admission. These measures will help to provide them with immediate appropriate medical management and early referral for liver transplantation to reduce mortality.

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2	Falak Naz	Literature review and contribution in manuscript writing.	
3	Zeeshan Ali	Concept, Design statistical analysis, Editing of manuscript.	
4	Shabnam Naveed	Reviewed manuscript.	
5	Syed Masroor Ahmed	Final review, approval and editing of manuscript.	
6	Sulhera Khan	Data collection and reviewed manuscript.	