Predictors of in-hospital mortality in Acute on Chronic Liver Failure

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ABSTRACT

Background and aim: Acute on chronic liver failure (ACLF) is a serious medical condition which results from acute derangement of liver function in preexisting liver cirrhosis and is accompanied by multi-organ failure. It must be differentiated from the acute decompensation of chronic liver disease and promptly treated as it carries a high short-term mortality. Our study aim was to determine the frequency of ACLF and risk factors of in hospital mortality of ACLF.

Methods: A total of 143 liver cirrhosis patients were enrolled in the study. Data on the ACLF grades and organ failure was recorded according to the EASL CLIF criteria. Predictors of ACLF were then determined based on regression analysis test.

Result: The mortality in the ACLF group was much higher (23.3%) than that of the non-ACLF group (12.4%). The most frequent organ failure, observed exclusively in the ACLF group, was found to be renal dysfunction (60.5%), which was followed by cerebral dysfunction (46.5%) in the same group. The deceased patients had much higher ratings overall. Among MELD, MELD-Na, CLIF-C Organ Failure and CLIF-C ACLF scores, the CLIF-C Organ Failure score was the strongest predictor of mortality (OR = 3.64, CI95% = 2.34–5.65, p = 0.01). On univariate analysis, positive odds ratio was seen with circulatory failure, MELD score, MELD Na score, CLIF-C ACLF score and EASL-CLIF OF score, whereas on multivariate analysis, creatinine, MELD score, circulatory failure and EASL-CLIF OF score (OR = 3.64, CI95% = 2.34–5.65, p = 0.01) were seen to be the independent predictors of mortality of ACLF.

Keywords: CLIF Organ Failure score CLIF C ACLF score MELD Na Child Turcotte Pugh Score

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INTRODUCTION:

In patients with liver cirrhosis, whether compensated or decompensated, abrupt liver function decline is the hallmark of acute on chronic liver failure (ACLF) [3], which is linked to a high short-term mortality (28 days) [1, 4]. To differentiate it from simple acute decompensation, ACLF is additionally marked by multi-organ failure and a strong systemic inflammatory response [2,4]. In the absence of infections, systemic inflammation can arise, leading to severe vasoconstriction and tissue hypoperfusion in several organs, including the brain and kidneys [4].

Over the past ten years, over thirteen definitions of ACLF have been proposed; however, three of these have gained the most traction. One of these definitions was put forth by the European Association for the Study of the Liver–Chronic Liver Failure (EASL-CLIF) Consortium, and it was based on a large prospective study [1,5].

Failure of one or more of the six major organ systems—liver, kidney, brain, coagulation, circulation, and respiration—is the basis for the definition of ACLF. The Chronic Liver Failure-Consortium Organ Failure scale is used to evaluate the failure of each organ system (CLIF C OF)

Compared to other criteria, it is observed that the EASL-CLIF criteria have a higher sensitivity in predicting the short-term mortality (>15%) of ACLF [3].ACLF can be precipitated by various factors, such as alcohol, drugs and viral infections, or it can be idiopathic as seen in most (40%) of the cases [7]. According to a recent meta-analysis, the prevalence of ACLF is 35% and the in-hospital mortality at 90 days is 58%. The most common cause of acute insult identified is alcohol however, regional, and cultural variations may exist. The most common trigger for ACLF was the infection of the gastrointestinal tract (35%) followed by gastrointestinal bleeding (22%), and the most common failure was the kidney (49%) [8].

Although ACLF is a fairly widespread phenomenon, there is still a dearth of research on it in resource-poor nations like Pakistan as well as the Middle East and North Africa. In a Pakistani tertiary care hospital, our goal was to investigate the incidence of ACLF based on EASL criteria, as well as its causative factors, triggers, and predictors of in-hospital mortality.

METHODS:

The Jinnah Postgraduate Medical Center's Ward 7 was the site of this prospective, cross-sectional investigation. The research project received approval from the Jinnah Postgraduate Medical Center's (JPMC) Institutional Review Board (IRB). Every patient who was enrolled before the commencement of the trial gave their informed consent. The study was conducted between October 2022 and March 2023, a period of six months. Patients with congestive heart failure, cirrhosis, and any underlying cancer, including hepatocellular carcinoma, were not allowed to participate in the trial. All cirrhosis patients who provided informed consent were included in the study.

A proforma was formulated that recorded the patient's demographics, the reason for admission, the aetiology of liver cirrhosis, and laboratory and radiographic investigations. All cirrhotic patients admitted during the study period were included in the study. There were 148 cirrhotic patients in total; 43 of the 148 patients had an ACLF diagnosis based on the EASL-CLIF criteria. The CLIF-C OF score was used to evaluate the organ failure. The Child-Pugh (CTP), Model for End Stage Liver Disease (MELD), and MELD sodium (Na) scores were used to determine the severity of cirrhosis.

The EASL CLIF criteria were applied to assess ACLF based on the number of organ failures.

ACLF Grade 1 was characterized by mild to moderate hepatic encephalopathy (HE) or brain failure with creatinine 1.5-1.9 mg/dl, as well as single kidney failure or liver failure, coagulopathy, circulatory failure, respiratory failure, and serum creatinine 1.5-1.9 mg/dl. ACLF Grade 2: Any two malfunctioning organs. Any three organ failures or more is ACLF Grade 3.

Statistical analysis:

Data were stored and analyzed in SPSS version 25. The frequency and in-hospital mortality of ACLF were calculated. Risk estimation of ACLF was done

using binary logistic regression testing using univariate and multivariate analysis.

RESULTS:

The mortality in the ACLF group was much higher (23.3%) than that of the non-ACLF group (12.4%). The most common reason for admission identified was infection followed by hepatic encephalopathy. Table 2 summarizes the relationship between death and organ failure in ACLF and non-ACLF patients. The EASL-CLIF organ failure scoring system indicated that all organ failures in the ACLF group were linked to a higher probability of death. The most frequent organ failure, observed exclusively in the ACLF group, was found to be renal dysfunction (60.5%), which was followed by cerebral dysfunction (46.5%) in the same group. The deceased patients had much higher ratings overall.

Among MELD, MELD-Na, CLIF-C Organ

TABLE 1: COMPARISON OF MORTALITY BETWEEN ACLF AND NON ACLF PATIENTS

Group	Non. survivors
ACLF	23.3%
Non ACLF	12.4%

Table 2: Association of ACLF with CTP, Mortality and Failure of Organs

Variables		Non ACLF (n=105)		ACLF (n=43)		p-value
		n	%	n	%	
CTP Score grade	A	20	19.0	2	4.7	0.04*
	B	46	43.8	18	41.9	
	C	39	37.1	23	53.5	
Liver Failure	Yes	5	2.9	7	16.3	<0.01*
	No	102	97.1	36	83.7	
Renal Failure	Yes	-	-	26	60.5	<0.01*
	No	105	100.0	17	39.5	
Cerebral Failure	Yes	25	23.8	20	46.5	<0.01*
	No	80	76.2	23	53.5	
Coagulation Failure	Yes	2	1.9	4	9.3	0.03*
	No	103	98.1	39	90.7	
Circulation Failure	Yes	2	1.9	7	16.3	<0.01*
	No	103	98.1	36	83.7	
Respiratory Failure	Yes	-	-	3	7.0	<0.01*
	No	105	100.0	40	93.0	
Outcomes	Discharged	92	87.6	33	76.7	0.09
	Expired	13	12.4	10	23.3	
*p<0.05 was considered statistically significant using the Pearson Chi-Square test						

Among MELD, MELD-Na, CLIF-C Organ Failure and CLIF-C ACLF scores, the CLIF-C Organ Failure score was the strongest predictor of mortality (OR = 3.64, CI95% = 2.34–5.65, p = 0.01) which has been summarised in Table 3.

Table 3: predictors of mortality

Test Result Variable(s)	Area	Std. Error	Asymptotic 95% Confidence Interval		p-value	sensitivity	specificity	Cut off value
MELD Score	0.620	0.06	0.48	0.75	0.06	40.5	70.6	7.5
MELD Na Score	0.646	0.06	0.52	0.77	0.02*	56.5	56.8	20.5
CLIF Consortium Organ Failure Score	0.668	0.06	0.53	0.79	0.01*	43.5	77.6	8.5
CLIF C ACLF SCORE	0.653	0.06	0.52	0.77	0.02*	60.9	56.8	39.8

Table 4: Risk Estimation of ACLF using Binary Logistic Regression

Parameters	Univariate analysis	Multivariate analysis
	Odds Ratio (95% C.I)	Odds Ratio (95% C.I)
Total Bilirubin	1.1* (1.0-1.2)	1.0 (0.9-1.2)
INR	2.8* (1.3-6.0)	1.7 (0.3-10)
Creatinine	5.0* (2.7-9.2)	3.7* (1.4-9.4)
MELD Score	1.31*(1.20-1.44)	1.20* (1.08-1.33)
CTP Score Grade C	5.8* (1.2-27.0)	9.5 (0.3-287)
Liver failure	6.6* (1.6-26.)	2.7(0.01-86)
Cerebral failure	2.7* (1.3-5.8)	2.1(0.5-8.8)
Circulation failure	10.0* (1.9-50.)	2.5* (2.2-285)
MELD-Na Score	1.25* (1.16-1.36)	
CLIF C OF Score	3.64* (2.34-5.65)	2.30*(1.45-3.65)
CLIF-C ACLF Score	1.12* (1.06-1.17)	
*Odds ratio considered significant with p<0.05, Dependent variable: ACLF		

Failure and CLIF-C ACLF scores, the CLIF-C Organ Failure score was the strongest predictor of mortality (OR = 3.64, CI95% = 2.34–5.65, p = 0.01) which has been summarised in Table 3.

Upon risk estimation of ACLF using binary logistic testing, it was seen that there was a positive odds ratio on univariate analysis with circulation failure, MELD score, MELD Na score, CLIF-C ACLF score and EASL-CLIF OF score, whereas on multivariate analysis, creatinine, MELD score, circulatory failure and EASL-CLIF OF score were independent predictors of mortality of ACLF as shown in table 4.

DISCUSSION:

ACLF is a complex clinical syndrome that remains a medical challenge due to its complex presentation with high short-term mortality [9]. Identification of the predictors of mortality is significant in predicting the outcomes of the patients and guiding early treatment [7]. In our present study, we identified the frequency of ACLF among our patients and the predictors of in-hospital mortality.

According to a meta-analysis by Mezzano G. et. al, the global prevalence of ACLF was 35% (95% CI 33% to 38%), the highest in South Asia at 65% [8]. In our study conducted on 148 participants, the frequency of ACLF was identified as 29.1% (n=43). ACLF was more commonly seen in the females (53.5%). The reason could be that female patients living in remote areas do not have early and easy access to tertiary care centres compared to their male counterparts and are more likely to present in an advanced stage of ACLF. ACLF is most often precipitated by sepsis, upper gastrointestinal bleeding or infections. [11] A Chinese study proved that HBV PC mutation was the most likely cause of ACLF among chronic Hepatitis B patients[12].

The in-hospital mortality rate of the enrolled cirrhotic patients was found to be 15.5% (n=23). The mortality in the ACLF (23.3%, n=10) group was observed to be almost twice that of the non-ACLF (12.4%, n=13) group. The highest mortality was seen in the ACLF grade 3 group (100%, n=6). This signifies that a higher ACLF grade is associated with higher mortality. Similar results were shown by Kulkarni et al in which the number of organ failures corresponded to the rising mortality [10]. Our findings are comparable to the study by Gawande A. et. al, in 2019, where the mortality in patients with ACLF grade 0 was 8.85%, ACLF grade 1 was 66.67%, ACLF grade 2 was 60.87%, and grade 3 was 83.75% [14]. Our findings are also consistent with the results of Verdelho et al. (68.97%) and Dominguez et al. (62.1%) both of which demonstrate the directly proportional relationship of grade of ACLF with mortality [15, 16]. These results suggest that prognosis is dependent on the stage of the disease at which it is detected. Hence, early detection and treatment ensure better outcomes. The high rate of short-term mortality may also be attributed to the fact that HCV infection is associated with higher short-term mortality which was identified as the most common etiological factor of ACLF in our population [17].

According to the EASL-CLIF OF scoring system, organ failures were associated with an increased risk of mortality in the ACLF group. Renal dysfunction (60.5%) was identified as the most common organ failure followed by cerebral dysfunction (46.5%) in the ACLF group in our study. All scores were significantly higher in the deceased patients. This finding is of utmost importance as most patients presented with acute kidney injury (AKI) or hepato-renal syndrome (HRS). Studies also show that the greater the number of organ failures at diagnosis, the greater the chance of mortality [18].

The CLIF-C Organ Failure score was the strongest predictor of mortality (OR = 3.64, CI95% = 2.34–5.65, p = 0.01) followed by CLIF-C ACLF and MELD Na scores with significant p values found to be superior to MELD score. Our results were similar to a study conducted in Islamabad where CLIF C ACLF was found to be more accurate than MELD [19]. A Korean study also proved CLIF C ACLF, CLIF C OF and CLIF SOFA to be useful scores in predicting mortality[20]. The CLIF-C OF score has been widely used to assess the number of organ dysfunctions and failures and is also the main constituent of the CLIF-C-ACLF score, designed to predict mortality in ACLF patients. Tongluk et al in a Thai study also highlighted the CLIF C OF score to be the best predictor of mortality of ACLF patients.[13]

In our study, on univariate analysis, serum creatinine, circulatory failure, MELD score, MELD

Na score, CLIF-C ACLF score and CLIF-C OF score were identified as positive predictors, out of which on multivariate analysis creatinine, circulatory failure, MELD score, and CLIF-C OF score were identified as independent predictors of mortality. Circulatory failure is an important component of ACLF criteria and can result in high mortality of these patients as proven by our study. However, in contrast, renal and cerebral failure were shown to be the predictors of mortality in a Mexican study [21]. The addition of circulatory failure either in the form of the use of vasopressors or the mean arterial pressure (MAP, mmHg) may enhance the sensitivity of a prognostic score in predicting mortality in ACLF patients. This can be attributed to the fact that ACLF comprises severe hemodynamic instability and the MELD score does not contain the as
Asessment of abnormal hemodynamic states [18].

CONCLUSION:

It is imperative to identify ACLF early and distinguish it from acute decompensation as the management and prognosis of the two differ significantly. It is seen that patients identified early with two or more organ failures at presentation with the CLIF C OF score in resource-poor settings can be planned for aggressive management and early referral for a liver transplant to reduce mortality. It is seen that the MELD Na, CLIF-C ACLF score, and EASL-CLIF OF are superior to the MELD score and highly significant in predicting mortality in patients with ACLF. CLIF C OF score, serum creatinine, MELD and circulatory failure were the independent predictors of mortality.

REFERENCES:

[1] Arroyo V, Moreau R, Kamath PS, et al. Acute-on-chronic liver failure in cirrhosis. Nat Rev Dis Primers. 2016 Jun 9;2:16041. doi: 10.1038/nrdp.2016.41. PMID: 27277335.

[2] Moreau R, Jalan R, Gines P, et al; CANONIC Study Investigators of the EASL–CLIF Consortium. 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. doi: 10.1053/j.gastro.2013.02.042. Epub 2013 Mar 6. PMID: 23474284.

[3 Kim TY, Kim DJ. Acute-on-chronic liver failure. Clin Mol Hepatol. 2013 Dec;19(4):349-59. doi: 10.3350/cmh.2013.19.4.349. Epub 2013 Dec 28. PMID: 24459638; PMCID: PMC3894433.

[4] Zaccherini G, Weiss E, Moreau R. Acute-on-chronic liver failure: Definitions, pathophysiology and principles of treatment. JHEP Rep. 2020 Sep 2;3(1):100176. doi: 10.1016/j.jhepr.2020.100176. PMID: 33205036; PMCID: PMC7652714.

[5] Thuluvath PJ, Li F. Modified EASL-CLIF criteria that is easier to use and perform better to prognosticate acute-on-chronic liver failure. World J Hepatol. 2022 Feb 27;14(2):420-428. doi: 10.4254/wjh.v14.i2.420. PMID: 35317179; PMCID: PMC8891672.

[6] Sarin SK, Choudhury A, Sharma MK, et al. APASL ACLF Research Consortium (AARC) for APASL ACLF working Party.. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL): an update. Hepatol Int. 2019 Jul;13(4):353-390. doi: 10.1007/s12072-019-09946-3. Epub 2019 Jun 6. Erratum in: Hepatol Int. 2019 Nov;13(6):826-828. PMID: 31172417; PMCID: PMC6728300.

[7] Abudeif A, Sayed EKA, Galal GM. Characteristics and predictors of short-term mortality in decompensated cirrhotic patients with acute-on-chronic liver failure. Clin Exp Hepatol. 2022 Dec;8(4):300-308. doi: 10.5114/ceh.2022.122332. Epub 2022 Dec 28. PMID: 36683875; PMCID: PMC9850305.

[8] Mezzano G, Juanola A, Cardenas A, et al. Global burden of disease: acute-on-chronic liver failure, a systematic review and meta-analysis. Gut. 2022 Jan;71(1):148-155. doi: 10.1136/gutjnl-2020-322161. Epub 2021 Jan 12. PMID: 33436495.

[9] Rashed E, Soldera J. CLIF-SOFA and CLIF-C scores for the prognostication of acute-on-chronic liver failure and acute decompensation of cirrhosis: A systematic review. World J Hepatol. 2022 Dec 27;14(12):2025-2043. doi: 10.4254/wjh.v14.i12.2025. PMID: 36618331; PMCID: PMC9813844.

[10] Kulkarni S, Sharma M, Rao PN, et al. Acute on Chronic Liver Failure-In-Hospital Predictors of Mortality in ICU. J Clin Exp Hepatol. 2018

Jun;8(2):144-155. doi: 10.1016/j.jceh.2017.11.008. Epub 2017 Nov 23. PMID: 29892177; PMCID: PMC5992306.

[11] Huang K., Hu J.H., Wang H.F. Survival and prognostic factors in hepatitis B virus-related acute-on-chronic liver failure. World J Gastroenterol. 2011;17(29):3448–3452. [PMCID: PMC3160571]

[12] Xu Z., Ren X., Liu Y. Association of hepatitis B virus mutations in basal core promoter and precore regions with severity of liver disease: an investigation of 793 Chinese patients with mild and severe chronic hepatitis B and acute-on-chronic liver failure. J Gastroenterol. 2011;46(March (3)):391–400. [PMID: 20848146]

[13] Teerasarntipan T, Thanapirom K, Chirapongsathorn S, et al. Validation of prognostic scores predicting mortality in acute liver decompensation or acute-on-chronic liver failure: A Thailand multicenter study. PLoS One. 2022 Nov 22;17(11):e0277959. doi: 10.1371/journal.pone.0277959. PMID: 36413538; PMCID: PMC9681104.

[14] Gawande A, Gupta GK, Gupta A, et al. Acute-on-Chronic Liver Failure: Etiology of Chronic and Acute Precipitating Factors and Their Effect on Mortality. J Clin Exp Hepatol. 2019 Nov-Dec;9(6):699-703. doi: 10.1016/j.jceh.2019.04.050. Epub 2019 Apr 28. PMID: 31889750; PMCID: PMC6926243.

[**15]** Verdelho M, Perdigoto R, Machado J, et al.. Acute-on-chronic liver failure: a Portuguese single-centre reference review. GE Port J Gastroenterol 2018; 25: 18-23.

[16] Dominguez C, Romero E, Graciano J, et al.. Prevalence and risk factors of acute-on-chronic liver failure in a single centre from Argentina. World J Hepatol 2016; 8: 1529-1534.

[17] Mahmud N, Kaplan DE, Taddei TH, et al.. Incidence and mortality of acute-on-chronic liver failure using two definitions in patients with compensated cirrhosis. Hepatology 2019; 69: 2150-2163.

[18] Zhang Q, Li Y, Han T, Nie C, Cai J, Liu H, Liu Y. Comparison of current diagnostic criteria for acute-on-chronic liver failure. PLoS One. 2015 Mar 18;10(3):e0122158. doi: 10.1371/journal.pone.0122158. Erratum in: PLoS One. 2015;10(7):e0133817. PMID: 25785855; PMCID: PMC4364726.

19 Ramzan M, Iqbal A, Murtaza HG, Javed N, Rasheed G, Bano K. Comparison of CLIF-C ACLF Score and MELD Score in Predicting ICU Mortality in Patients with Acute-On-Chronic Liver Failure. Cureus. 2020 Feb 24;12(2):e7087. doi: 10.7759/cureus.7087. PMID: 32226688; PMCID: PMC7096002.

20 Song, D. S., Kim, T. Y., Kim, D. J., Kim, et al. (2018) Validation of prognostic scores to predict short-term mortality in patients with acute-on-chronic liver failure. Journal of Gastroenterology and Hepatology, 33: 900–909. doi: 10.1111/jgh.13991.

21 Méndez-Guerrero O, Calle-Rodas DA, Cervantes-Alvarez E, et al. Renal and brain failure predict mortality of patients with acute-on-chronic liver failure admitted to the intensive care unit. Annals of Hepatology. 2021 May 1;22:100270.

Our study has certain limitations. The first is a small sample size and the study being conducted at a single centre of the city. Also, the assessment of organ failures and prognostic scores was done at the time of admission only rather than serial evaluation multiple times during the study.

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