

# Acute-On-Chronic Liver Failure: Causes, Clinical Characteristics and Predictors of Mortality

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## ABSTRACT

**Objective:** To determine the causes, characteristics and predictors of mortality in patients with acute-on-chronic liver failure (ACLF).

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation, Karachi, from July 2014 to June 2016.

**Methodology:** All patients with acute-on-chronic liver disease (ACLD) with ages > 12 were included. Patients with ACLF, as defined by the Asian Pacific Association for the Study of Liver (APASL, 2014) were identified. Predictors of mortality were identified using chi-square or Fisher's exact test.

**Results:** Included in the study were 72 patients with mean age of 36.71 years, 46 (63.9%) being males. Among them, 61 developed ACLF. Commonest causes of chronic liver disease (CLD) were chronic viral hepatitis (37, 51.4%) and autoimmune hepatitis (14, 19.4%). Commonest causes of acute liver injury (ALI) were acute viral hepatitis (24, 33.3%) and drug induced liver injury (DILI) (17, 23.6%). Among those with ACLF, 24 (39.3%) patients died with median survival of 17.1 ±13.5 days. Mortality was significantly associated with Child Turcotte Pugh (CTP) score ≥13 (p=0.010), model for end-stage liver disease (MELD) score ≥30 (p=0.001), age >40 years (p=0.036), organ failures (OF) ≥3 (p <0.0001), portosystemic encephalopathy (PSE) (p <0.0001), renal failure (p <0.0001) and urosepsis (p <0.0001).

**Conclusion:** Acute viral hepatitis and DILI are commonest causes of ACLF. Mortality is high in ACLF patients having OF ≥3, CTP ≥13, MELD ≥30, age >40 years, PSE, renal failure and urosepsis.

**Key Words:** Liver failure. Acute-on-chronic liver failure. Acute liver injury. Acute viral hepatitis. Drug induced liver injury (DILI). Predictors. Mortality.

## INTRODUCTION

Chronic liver disease (CLD) is a serious problem in Pakistan, the major culprits being hepatitis C and hepatitis B virus related liver diseases.<sup>1</sup> Other causes include autoimmune hepatitis, metabolic liver diseases, alcoholic liver disease, cholestatic liver diseases, and cirrhosis associated with vascular diseases of the liver.<sup>2</sup> An acute insult to the liver, in any form, can lead to serious consequences in a patient with already existing chronic liver disease. This acute insult can be in the form of viral infection, drug induced liver injury or others, like alcoholic hepatitis.<sup>3</sup> The acute insult can lead to the condition called acute-on-chronic liver failure (ACLF) which is defined by the Asian Pacific Association for the Study of Liver (APASL, 2014) 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.<sup>4</sup> ACLF is a relatively common

syndrome occurring in 31% of hospitalised patients with cirrhosis who have an acute complication of their liver disease.<sup>5</sup> Patients with ACLF have a high short-term mortality of 50 - 90%.<sup>6</sup> The cause of this high mortality associated with ACLF is probably an inappropriate inflammatory response and immune dysfunction increasing the susceptibility to infections.<sup>7</sup> Both the severity of inflammation and the occurrence of new infection are associated with a higher risk of death.<sup>8</sup>

The severity of such complications can differ depending on various factors including those related to the host, the stage of the existing chronic liver disease, and the nature of the acute liver injury. Host related factors include the age of the patient and presence or absence of co-morbidities. Similarly, patients with decompensated liver disease are less likely to survive an acute hepatic insult compared to those with compensated disease. Also, the dose of the hepatotoxic agent determines the severity of injury that it may cause.

Extensive research work has been done worldwide in this regard in the past. However, little work has been done in our country to assess the factors associated with mortality in this group of patient population.

The aim of this study was, therefore, to identify the causes of acute and chronic liver diseases and identify the factors associated with mortality in this condition.

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## METHODOLOGY

This cross-sectional study was conducted in the Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation, Karachi from July 2014 to June 2016. Patients presenting with acute-on-chronic liver disease or failure were admitted in the gastroenterology ward. Acute-on-chronic liver failure (ACLF) was defined according to the Asian Pacific Association for the Study of Liver (APASL, 2014) as an acute hepatic insult manifesting as jaundice (total bilirubin >5 mg/dL) and coagulopathy (international normalised ratio >1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.<sup>4</sup> The liver disease characterised by acute insult over an already existing CLD but not meeting the above mentioned criteria was labelled as acute-on-chronic liver disease (ACLD).

All patients with age greater than 12 years and presenting with either acute-on-chronic liver disease or failure were included in the study. Patients with already existing organ failures, e.g. end stage renal disease or congestive heart failure were excluded. The study was performed after approval from the ethical review committee (ERC) of the institution. Written informed consent was taken from all patients. A thorough history was taken and complete physical examination of all patients was performed, and the findings recorded in the structured proforma. The patients were specifically questioned about the prior use of alcohol or herbal and ayurvedic medicines. All baseline investigations were performed, including blood complete picture, liver and renal function tests. Ultrasound abdomen was done to identify the features of chronic liver disease. To identify the cause of the chronic liver disease, specific tests were done including viral serologies (hepatitis B surface antigen and anti-hepatitis C virus antibody); and where indicated, autoimmune serology, metabolic profile, doppler ultrasound and CT scan of abdomen were performed. To identify the cause of acute hepatic insult, a history of prior use of any hepatotoxic agents was taken. Besides, various tests were performed including serologies for hepatotropic viruses (hepatitis A and E, and where indicated hepatitis D, B and C), cytomegalovirus and herpes virus. The organ failures, other than liver failure, that developed in patients with ACLF, were defined as follows: renal failure (creatinine >2 mg/dL, cerebral failure (grade III or IV hepatic encephalopathy according to West Haven classification), coagulation failure (international normalised ratio >2.5), circulatory failure (need of vasoconstrictors to treat severe arterial hypotension), respiratory failure (arterial partial pressure of oxygen to fraction of inspired oxygen ratio  $[PaO_2/FiO_2] < 200$  or saturation of oxygen to fraction of inspired oxygen ratio  $[SpO_2/FiO_2] < 214$ ).

All data were collected on a structured proforma and results were analysed using SPSS version 20.

Continuous variables were expressed as mean and standard deviation. Frequencies and percentages were computed for different categorical variables and chi-square test or Fisher's exact test were used for data analysis. A p-value of less than 0.05 was considered as statistically significant. Odds ratios and confidence interval for predictors of mortality were calculated.

## RESULTS

A total of 72 patients were included in the study, of which 46 (63.9%) were males. The mean age was 36.71 years. Thirty-nine (54.2%) patients were of age less than 40 years. Among these, 61 (84.7%) had acute-on-chronic liver failure, while the remaining 11 had only acute-on-chronic liver disease without liver failure. At the time of admission, more than half of the patients, i.e. 41 (56.9%)

**Table I:** Causes of chronic liver disease and acute liver injury in the study population (n=72).

	Number of patients	Percentage (%)
<b>Chronic liver disease</b>		
Chronic viral hepatitis	37	51.4
HBV CLD*	18	
HCV CLD	17	
HBV + HCV CLD	2	
AIH** CLD	14	19.4
Cryptogenic CLD	6	8.3
Alcoholic CLD	6	8.3
Wilson's disease related CLD	6	8.3
NASH*** CLD	1	1.4
Portal biliopathy related CLD	1	1.4
Indian childhood cirrhosis	1	1.4
<b>Acute liver injury</b>		
Hepatotropic viral infections	24	33.3
Acute HEV	14	
HBV reactivation	4	
HDV superinfection	3	
Acute HAV	2	
HCV relapse	1	
Drug induced liver injury (DILI)	17	23.6
Anaesthetic agent	6	
Herbal medication	5	
Anti-tubercular therapy	3	
Interferon treatment	3	
Alcoholic hepatitis	6	8.3
Autoimmune hepatitis flare	4	5.5
Cholangitis	4	5.5
Hepatocellular carcinoma	4	5.5
Ischemic hepatitis	3	4.1
Wilsonian crisis	3	4.1
Other infective hepatitis	3	4.1
Dengue hepatitis	1	
Malarial hepatitis	1	
Enteric hepatitis	1	
Other hepatic malignancies	3	4.1
Hepatic metastasis	2	
Lymphoma	1	
Hepatic venous outflow tract obstruction (HVOTO)	1	1.4

\*Chronic liver disease; \*\*Autoimmune hepatitis; \*\*\*Non-alcoholic steatohepatitis.

patients, were previously diagnosed as CLD while the remaining 31 (43.1%) were found to have CLD for the first time.

Hepatitis B related cirrhosis was the most common cause of CLD seen in 18 (25%) patients, followed by Hepatitis C related cirrhosis in 17 (23.6%, Table I).

The patients who progressed to ACLF, after acquiring the acute liver injury, developed subsequent systemic infections and various organ failures including renal, circulatory, hematologic and cerebral failure. Among the 61 patients who developed ACLF, the subsequently acquired infections included urinary tract infections in 20 (32.8%) and spontaneous bacterial peritonitis in 9 (14.8%) patients. The commonest organisms isolated in blood culture were *Escherichia coli* and *Enterococcus*; while those in urine culture included *Escherichia coli*, *Enterococcus*, *Klebsiella* and yeast; and those identified in ascitic fluid culture were *Enterococcus* and *Klebsiella* species. The organ failures that developed subsequent to the acute-on-chronic hepatic insult included cerebral failure in the form of portosystemic encephalopathy in 28

(45.9%) patients, while renal failure and circulatory failure in 19 (31.1%) patients each. Patients with ACLF who developed three or more organ failures were 23 (37.7%), those with two organ failures were 8 (13.1%), while all the remaining had liver failure only. Among those with ACLF, the Child Turcotte Pugh (CTP) score was 13 or more in 19 (31.1%) patients, while the model for end-stage liver disease (MELD) score was 30 or more in 25 (41%) patients.

Among the 61 patients with acute-on-chronic liver failure, 24 (39.3%) patients died with a median survival of 17.1 ±13.5 days. Univariate analysis results are shown in Table II.

## DISCUSSION

The commonest cause of chronic liver disease in our study was hepatitis B or hepatitis C virus related cirrhosis. This is in contrast to the Western countries and neighbouring country India, where alcoholic cirrhosis is the commonest cause.<sup>9,10</sup> This reflects the comparatively lesser use of alcohol in Pakistan compared to the West

**Table II:** Association of various clinical parameters with mortality in patients with acute-on-chronic liver failure (n=61).

	Expired N (%)	Discharged N (%)	p-value	Odds ratio	95% Confidence Interval
Age					
≤40	9 (37.5)	24 (64.9)	0.036*	0.325	0.112-0.945
>40	15 (62.5)	13 (35.1)			
Gender					
M	15 (62.5)	26 (70.3)	0.528	1.418	0.479-4.202
F	9 (37.5)	11 (29.7)			
Ascites					
Yes	21(87.5)	35 (94.6)	0.324	2.500	0.386-16.208
No	3 (12.5)	2 (5.4)			
Portosystemic encephalopathy					
Yes	19 (79.2)	9 (24.3)	<0.0001*	11.822	3.425-40.802
No	5 (20.8)	28 (75.7)			
Albumin					
<2.8	20 (83.3)	24 (64.9)	0.116	2.708	0.762-9.625
>2.8	4 (16.7)	13 (35.1)			
INR					
≥2	14 (58.3)	13 (35.1)	0.075	2.585	0.899-7.427
<2	10 (41.7)	24 (64.9)			
CTP					
≥13	12 (50.0)	7 (18.9)	0.010*	4.286	1.360-13.503
<13	12 (50.0)	30 (81.1)			
MELD					
≥30	16 (66.7)	9 (24.3)	0.001*	6.222	2.003-19.325
<30	8 (33.3)	28 (75.7)			
Renal failure					
Yes	15 (62.5)	4 (10.8)	<0.0001*	13.750	3.649-51.810
No	9 (37.5)	33 (89.1)			
Urosepsis					
Yes	15(62.5)	5 (13.5)	<0.0001*	10.667	3.045-37.361
No	9 (37.5)	32 (86.4)			
Organ failures					
≥3	21(87.5)	2 (5.4)	<0.0001*	122.500	18.895-794.18
<3	3 (12.5)	35 (94.6)			

\*p value <0.05; INR = International normalised ratio; CTP = Child turcotte pugh; MELD = Model for end stage liver disease; UTI = Urinary tract infection

and India. The second most common cause of CLD observed in our study was autoimmune hepatitis. Also, more than 40% of the patients included in this study had presented to their physician with ACLF, and were found to have an already existing chronic liver disease for the first time. This indicates that a large proportion of the apparently healthy people in Pakistan have chronic liver disease and remain undiagnosed until they acquire an acute insult, which causes significant deterioration in liver function necessitating them to seek medical advice. Therefore, in Pakistan, screening of the apparently healthy population is essential on a large scale to identify this undiagnosed disease burden.

The commonest causes of acute hepatic insult noted in our study were hepatic viral infections and drug induced liver injury followed by alcoholic hepatitis, flare of autoimmune hepatitis, hepatic malignancies and other less common causes. Among the viral infections, the most commonly encountered cause was acute hepatitis E and less commonly hepatitis A virus infection. This indicates that lifestyle measures like hand washing, use of boiled water for drinking, and proper cooking of food should be strictly advised to patients with CLD to avoid acquiring this preventable cause of ACLF. Also, vaccination for hepatitis A should be recommended to all cirrhotic patients if non-immune to HAV (i.e. negative anti HAV IgG). Similarly, vaccination against HEV should be offered to all patients with CLD as soon as it becomes available in our country. Among those with drug induced liver injury (DILI), the commonest inciting agents were hepatotoxic anaesthetic drugs used during surgery performed under general anaesthesia, followed by herbal and ayurvedic medicines, hepatotoxic drugs like anti-tubercular therapy, and use of interferon for chronic hepatitis C. This indicates that in our part of the world where use of alternative and complementary medicine is quite common, educating CLD patients regarding the toxicity potential of herbal and ayurvedic medications is important. Also, while treating tuberculosis, it is essential to rule out liver cirrhosis first; and if the patient is found to have evidence of advanced liver fibrosis, a regimen consisting of least hepatotoxic drugs should be selected. With the advent of directly acting antiviral agents for hepatitis C, it can be expected that the incidence of interferon induced liver injury, as a cause of ACLF, will be reduced in the future.

A high mortality rate (39.3%) was observed in patients presenting with ACLF in our study. This was similar to the previously reported data stating a short- and medium-term mortality of 50 - 90%.<sup>11</sup> The predictors of mortality in the setting of acute-on-chronic liver failure that we observed in our study were CTP  $\geq 13$ , MELD  $\geq 30$ , age  $>40$  years, presence of 3 or more organ failures (OF), presence of portosystemic encephalopathy (PSE), renal failure, and urosepsis. Similar results were noted in a study performed in western India which showed that in

patients with ACLF, a MELD score of 27 or more was associated with high mortality.<sup>12</sup> In this study, we observed that when the MELD score of patients with ACLF was  $\geq 30$ , the mortality was significantly high. Besides, in a systematic review of 74 published studies, the overall mortality for patients with cirrhosis and associated renal failure was found to be as high as 67%.<sup>13</sup> In this study too, the presence of renal failure was strongly associated with mortality in ACLF patients. In a study by Garg, hepatic encephalopathy together with low serum sodium were found to be associated with high mortality.<sup>14</sup> This finding again conformed to the present results, where PSE showed statistically significant association with mortality. Furthermore, Agarwal found that simply counting the number of organ failures developing during hepatic decompensation may be as effective in determining mortality risk in ACLF as using the CLIF-SOFA score.<sup>15</sup> In this study too, greater than 3 organ failures was found to be a strong predictor of mortality. The commonest organ failures (other than liver) encountered in our study were renal and circulatory. This finding is consistent with that of Bajaj who also observed that cardiovascular failure can develop in ACLF, especially in those with concurrent renal failure.<sup>16</sup> Additionally, patients with cirrhosis may have an underlying cirrhotic cardiomyopathy, which may make them more susceptible to cardiovascular collapse during an acute inflammatory insult.<sup>17</sup>

In this study, among patients with ACLF, mortality was found to be high if the patient had associated sepsis related to urinary tract infection. Among the causes of sepsis, urosepsis was the most common, followed by sepsis associated with spontaneous bacterial peritonitis and pneumosepsis. Linderoth too, noted in his study that infection is a common feature of ACLF, which complicates the natural history and is associated with significant morbidity and mortality.<sup>18</sup> In the present study, low serum albumin did not predict mortality ( $p=0.188$ ). This can be explained by the fact that serum albumin drops in settings of acute inflammatory reaction and improves after correction of the underlying cause. Hence, in presence of ACLF, albumin is not a good predictor of mortality.

Various therapeutic interventions have shown improved survival in patients with ACLF. These include the use of granulocyte colony stimulating factor, antivirals for hepatitis B in cases where the acute insult is due to hepatitis B, and liver transplantation.<sup>19</sup> The role of granulocyte colony stimulating factor as a promoter of hepatic regeneration was reported in a small group of patients with ACLF and in a larger group of subjects with decompensated cirrhosis. In a single-center study, use of darbopoietin  $\alpha$  was associated with improved survival at 1 year.<sup>20</sup> Besides, the use of antiviral agents for the treatment of hepatitis B virus infection as a cause of ALI, has been shown to improve survival in patients with



ACLF.<sup>21</sup> The role of liver assisting devices remains unclear.<sup>22</sup> Molecular adsorbent recirculating system (MARS) has been examined among persons with ACLF, but no survival difference was observed between patients randomised to MARS or standard therapy.<sup>23</sup> However, liver transplantation for management of ACLF due to various etiologies has shown good results.<sup>24</sup>

One of the limitations of this study contributing to the high mortality was that the Institute was not readily offering the facility of liver transplantation to its patients. It was performed only in the presence of an assisting foreign team of transplant surgeons who visited the institute only once or twice a year.

### CONCLUSION

Commonest causes of chronic liver injury are hepatitis B or C virus infection followed by autoimmune hepatitis; while those of acute hepatic insult are viral hepatitis and drug induced liver injury. In patients with ACLF, mortality is high, and death is more likely to occur in the presence of  $\geq 3$  organ failures, CTP score of  $\geq 13$ , MELD score of  $\geq 30$ , age  $> 40$  years, portosystemic encephalopathy, renal failure, and urosepsis.

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