

## Acute-On-Chronic Liver Failure-Outcome and Its Predictors in A Tertiary Care Hospital

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### ABSTRACT

**Objective:** To determine the characteristics and outcome of acute-on-chronic liver failure patients being managed at Pak-Emirates Military Hospital Rawalpindi.

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

**Place and Duration of Study:** Department of Gastroenterology at Pak-Emirates Military Hospital, Rawalpindi, from Sep 2018 to Jan 2021.

**Methodology:** In this study, 1559 patients diagnosed with cirrhosis were studied. Patients with pre-existing chronic kidney disease, chronic obstructive pulmonary disease, cardiac failure, dementia, and stroke were excluded. All the relevant features of each case were recorded in the proforma.

**Results:** Out of 1559 patients, 67 had Acute-on-chronic liver failure. The majority of patients who presented with acute-on-chronic liver failure were in grade Ib (55%), followed by grade II (30%). Hepatitis C virus related liver cirrhosis was the commonest underlying liver disease (78.4%). Drugs were the commonest triggering factor (33%), followed by acute viral hepatitis (27%). However, a large number of patients had no identifiable cause (25.4%).

**Conclusion:** Acute-chronic-liver failure is common in patients presenting with acute decompensation of liver cirrhosis. Patients undergoing liver transplantation in the correct window period, have good prognosis.

**Keywords:** Acute-on-chronic liver failure, Hepatitis C, Viral hepatitis.

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### INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a condition that is characterized by acute decompensation of chronic liver disease associated with organ failures and elevated short-term mortality. There is no single accepted definition and numerous societies/organizations have given their own working definitions.<sup>1</sup> Asian Pacific Association for Study of Liver Diseases (APASL) provided the first consensus,<sup>2</sup> on ACLF in 2009 and later on modified the definition in 2014. In the study by APASL, patients with already decompensated cirrhosis who deteriorated due to acute insult were excluded but other organizations e.g., European Association for Study of Liver Diseases (EASL),<sup>3</sup> and North American Consortium for Study of End-stage Liver Disease (NACSELD)<sup>4</sup> included such patients in their definitions of ACLF.

According to literature, 24-40% of the patients admitted to hospitals with cirrhosis have ACLF.<sup>5</sup> An excessive systemic inflammatory response seems to play a crucial role in the development of ACLF.<sup>6</sup> Using

a liver-adapted sequential organ assessment failure score (SOFA), it is possible to triage and prognosticate the outcome of patients with ACLF. The course of ACLF is dynamic and keeps changing during hospital admission. For most of the patients, the prognosis can be predicted between day 3 and 7 of hospital admission and clinical decisions such as evaluation for a liver transplant or discussion over the goals of care, can be tailored using clinical scores.

Exact data on the incidence of ACLF in Pakistan is not available and it remains one of the less well-studied syndromes in this country. However, due to the high burden of chronic liver disease, it can be quite reasonably inferred that ACLF is fairly common among the admitted patients of cirrhosis. The aim of this study was to determine the short-term prognosis of patients with ACLF and to see if and how it correlates with the stage of ACLF in our setting.

### METHODOLOGY

This cross-sectional study was carried out at the Department of Gastroenterology Pak-Emirates Military Hospital (PEMH) Rawalpindi, from September 2018 to January 2021 through consecutive sampling technique. Approval from the Institutional Review Board was taken (A/28/EC/256/2021). Patients or their next of

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kin were informed about the study and consent was obtained for data collection. The sample size was calculated with margin of error set at 2.5%, confidence level at 95% and an anticipated frequency (response distribution) of 50% using OpenEpi sample size calculator.

**Inclusion Criteria:** Patients diagnosed and admitted with cirrhosis were included in the study.

**Exclusion Criteria:** Patients with pre-existing chronic kidney disease, chronic obstructive pulmonary disease (COPD), cardiac failure, dementia and stroke were excluded.

We studied the data of patients diagnosed and admitted with cirrhosis in the Gastroenterology unit of one of the largest tertiary care hospital in Pakistan. We used laboratory results, ICD-9 codes to identify underlying etiologies. Cirrhosis was diagnosed according to clinical findings, radiological results, biochemical as well as histological parameters. Along with hemogram values, liver function tests, renal function tests, values of prothrombin time, blood sugar levels in fasting state, or  $\alpha$ -fetoprotein levels were evaluated. Virus markers, such as hepatitis B surface antigen and HCV RNA, were noted in each patient. Serological markers such as antinuclear antibodies, antibody against liver/kidney microsomes, anti-smooth muscle antibodies and immunoglobulin A tissue transglutaminase antibody were noted in non- alcoholic patients and who were negative to viral markers. Wilson disease investigations (serum ceruloplasmin, 24-hour urinary copper and Kayser–Fleischer ring slit-lamp examination), hemochromatoses and venous Doppler, etc. were conducted where implied. The etiology was called cryptogenic because there was no identifiable cause of cirrhosis. When there was a possibility of hepatocellular carcinoma on ultrasound, computed tomography was performed. Upper gastrointestinal endoscopy was carried out in all the cases, unless contraindicated.

For the ACLF patients, all of the cirrhotic patients receiving a diagnosis of ACLF were enrolled. Patients with pre-existing chronic kidney disease, COPD, cardiac failure, dementia, and stroke were excluded to avoid difficulty in attributing organ failure to the comorbidity or ACLF. Patients were categorized into stages of ACLF.<sup>7</sup> Treatment was given to all the patients as per the standard guidelines; however, a liver transplant was offered to only those patients who met the criteria for this procedure during the visit of the foreign transplant team to our hospital. Data collected included demographics, underlying liver

disease, precipitating factors, stage of ACLF, etc. All the participants were monitored for up to 3 months and survival and morbidity were recorded.

Data was analyzed by using Statistical Package for the Social Sciences version 23. Mean  $\pm$  SD were calculated for continuous variables. Frequency and percentages were calculated for categorical variables.

**RESULTS**

Fifteen-hundred and fifty-nine (1559) patients diagnosed with cirrhosis were studied. There were 1044 (67%) males and 515 (33%) female patients. The mean age of patients was  $62.4 \pm 7.2$  years.

Out of 1559 patients with liver cirrhosis, 67 (4.29%) had acute-on-chronic liver failure. Amongst those with acute-on-chronic liver failure, 51 (76%) were males and 16 (24%) were females with the mean age of  $38 \pm 3.5$  years. Out of 20% patients admitted to our hospital with AD (acute decompensation) of cirrhosis had ACLF on admission or developed it during their hospital stay, shown in Table-I & II.

**Table-I: Underlying etiology of cirrhosis in the study participants (n=1559).**

Etiology	Frequency	Percentage
Hepatitis C	1222	78.4
Hepatitis B	254	16.3
Autoimmune hepatitis	1	0.06
Primary sclerosing cholangitis	1	0.06
Wilson disease	2	0.12
Cryptogenic	79	5.06

**Table-II: Burden of complications in the sample population (n=1559).**

Complications	Frequency	Percentage
Variceal bleed	647	41.5
Spontaneous bacterial peritonitis	87	5.6
Porto-systemic encephalopathy	289	18.5
Grade 3 ascites requiring large volume paracentesis	231	15.0
Hepatorenal syndrome	163	10.4
Acute on chronic liver failure	67	4.3
Hepatocellular carcinoma	100	6.4

The majority of patients who presented with ACLF were in grade Ib, followed by grade II. HCV related liver cirrhosis was the most common underlying liver disease. Drugs were the commonest triggering factor, followed by acute viral hepatitis. However, a large number of patients had no identifiable cause. Mechanical ventilator support was provided to 9 patients who presented in ACLF grade II, out of which 3 were weaned off and recovered. However, none out of 4 in grade III could successfully be weaned off mechanical ventilation. Renal support in the form of

CRRT (Continuous Renal Replacement Therapy) was given to none shown in Table-III and IV. Liver transplantation was done in 4 patients, whose survival rate for the first 3 months was 100%. One patient was delisted from the liver transplant list after his grade progressed while being on the waiting list. Out of 20 patients who died while on supportive care, 15 died during the first 28 days (Table-V).

**Table -III: Frequency of precipitating events for ACLF (n=67).**

Aetiology	Frequency	Percentage
Drugs	22	33.0
Acute viral hepatitis	18	27.0
Alcoholic hepatitis	3	4.5
Bacterial infection	5	7.5
Exacerbation of existing viral infection (HBV)	2	3.0
Non-identifiable	17	25.4

**Table-IV: Underlying liver disease in the ACLF patients**

Aetiology	Frequency	Percentage
Chronic hepatitis C	31	46.3
Chronic hepatitis B	14	21.0
Alcoholic liver disease	5	7.5
Cryptogenic liver disease	17	25.4

**Table-V: Outcome among the ACLF patients during the first three months.**

ACLF Grade	Total n (%)	Outcome During the First Three Months		
		Recovery with Supportive care n (%)	Recovery after liver transplant, n (%)	Mortality n (%)
Ia	4 (6)	4 (100)	-	-
Ib	37 (55)	34 (92)	-	3 (8)
II	20 (30)	6 (30)	4 (20)	10 (50)
III	7 (10.5)	-	-	7 (100)

**DISCUSSION**

Previous study carried out at the tertiary treatment facilities in Pakistan, had demonstrated that for the 3,570 hospital admitted patients, 27% had gastroenterological pathologies, 68% had decompensated chronic liver disease (DCLD) and 10% had reported cases for liver disease with DCLD at 92% in the emergency ward.<sup>7</sup> From January to December 2009, a prospective study in 95 patients was carried out. The most prevalent cause of cirrhosis in the study was HCV infection (61.66%), followed by HBV, hepatitis B and C virus co-infection, and hepatitis B and D virus superinfection in 18.94%, 5.3% and 4.2% patients respectively. Other causes of liver cirrhosis were alcoholic liver disease in 3.2% of patients, PBC in 2.1%, and Wilson disease in 1.05% of patients, while no cause of cirrhosis was present in 3.15% patients.<sup>8</sup> However, a study was performed on 100 patients from April 2005 to April 2007 to evaluate the etiological causes, complications and pro-

gnosis of patients with cirrhosis of the liver and found that 52% patients reported with HCV, 16% with HBV, 16% with HCV co-infection, 8% with alcohol abuse, 1% with PBS, 2% with Wilson's disease, along with 5% without any etiologies. In addition, ascites occurred among 59% of cases, portal hypertension in 42%, varicose veins 29%, BPS 29%, acute variceal hemorrhage 27%, HE of various grades 24%, HRS among 9% and HCC among 7% of the patients.<sup>9</sup> A high burden of variceal bleed as the most frequent complication followed by HE was prevalent among patients in our study.

Since cirrhosis is often associated with continually evolving multi-organ dysfunction, the incidence of liver failure in a patient with cirrhosis is a crucial point in medical care and prognosis. Owing to a lack of liver detoxification, metabolic, regulatory functions and an impaired immune response, there are life-threatening threats such as renal failure, increased susceptibility to infection, hepatic coma and systemic hemodynamic dysfunction.<sup>10,11</sup> It's not shocking that the combined impact of these complications leads to mortality rates of 50-90%.<sup>12</sup> As a result, the conundrum is of public concern and further interventions in terms of awareness, prevention, fine-tuning, and renewal of the clinical protocol directed at the earliest stages of viral hepatitis, non-alcoholic liver fat disease and liver alcohol-related disease, which are the most prevalent liver disorders, are required.

A study by Tasneem *et al*, from Pakistan showed a statistically significant mortality in 24 ACLF patients in relation to a CTP score of  $\geq 13$ , a MELD score  $\geq 30$ , older age, ACLD Grade III and the presence of organ failure specifically brain (porto-systemic encephalopathy) and renal failure.<sup>13</sup> The relation of advanced grade of ACLF and mortality is also evident from our study with poor prognosis even after organ transplantation.

A similar study from China on 90 patients with ACLF showed infections to be the most common precipitating event (41.2%), followed by HBV reactivation (26.5%), drugs (17.6%) and alcohol intake (11.8%).<sup>14</sup> Whereas, in our study the most common precipitating factor was drugs (33%), acute viral hepatitis (27%), bacterial infections (7.5%) and alcoholic hepatitis (4.5%). About 25.4% of the patients had no apparent etiology in our study.

It is evident from a clinical viewpoint that only liver transplantation can save the patient in the case of end-stage liver disease, while any effort to move the decompensation back to the crucial threshold of functional liver, is of concern for acute-on-chronic liver

failure. The rising discrepancy between the increasing number of patients qualifying for liver transplantation and the relatively stagnant number of available donor organs strongly motivates these attempts.<sup>15-18</sup>

A study from Pakistan predicting 30-day mortality in ACLF patients reported a high mortality of 43.2%, with the highest mortality seen in  $\geq 3$  organ failure (Grade III and IV ACLF).<sup>19</sup> In contrast, our study reported a mortality of 30%. This rate can be improved by provision of prompt hepatology referrals and high output liver transplant units to avoid any delays and subsequently mortality post organ transplantation.

The aim of this research is to better understand the natural history of acute-on-chronic liver failure, as well as to evaluate its magnitude, precipitating factors, survival and mortality outcomes after liver transplantation. The failure of liver detoxification, metabolic and regulatory functions of the liver contributes to life-threatening complications in acute-on-chronic liver failure and rapidly culminates in multiorgan failure. Current medical therapy includes handling the precipitating incident and treating symptoms before the liver has finally healed, leaving no treatment choices other than transplantation unless these efforts have failed. The lack of cadaveric organs and other problems related to transplants, however, have encouraged the urgency for other approaches for liver support.<sup>20</sup>

Acute-on-chronic liver failure is not uncommon in patients who present with acute decompensation of liver cirrhosis in our set up. The commonest organ failure was liver, followed by coagulation. Majority presented in the window period where they could be salvaged with treatment. Liver transplantation done at the correct time especially in acute-on-chronic liver failure grade II has smooth post operative recovery. Maximum mortality is seen during the first 28 days.

**CONCLUSION**

Acute-chronic-liver failure is common in patients presenting with acute decompensation of liver cirrhosis. Patients undergoing liver transplantation in the correct window period, have good prognosis.

**Conflict of Interest:** None.

**Authors' Contribution**

RSAK: Contributed to main idea, draft and literature review, MSK: Contributed to main idea, draft and literature review, FS: Contributed to critical analysis, SKHK: Contributed to main idea and literature review, FAS: Contributed to manuscript writing, RUD: Contributed to main idea and literature review.

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