Original Article

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Clinical Profile of Acute on Chronic Liver Failure Patients in a Tertiary Care Centre

Internal Medicine Section

NISHANT SAXENA[1], ANUJ SINGHAL[2], SHANKAR SUBRAMANIAN[3], ARUN KUMAR YADAV[4], ASHITA MATHUR[5]

ABSTRACT

Introduction: In patients of Chronic Liver Disease (CLD), two types of acute decompensation can be seen, Acute on Chronic Liver Failure (ACLF) and Non Acute on Chronic Liver Failure (NACLF). There is difference in presenting symptoms, clinical signs, Ultrasonography (USG) findings and aetiological factors. Complications arising and its severity relayed to mortality also vary between two.

Aim: To assess the difference and define the two types of acute decompensation.

Materials and Methods: This was an observational, descriptive, longitudinal study based on prevalence of ACLF. All subjects meeting the eligibility criteria (acute decompensation was defined as set of jaundice or rise in S. Bilirubin levels >2 mg/dL, encephalopathy, development or increase in ascites, UGI bleed, increase in PT/INR by >1 second or S. Creatinine >0.5 mg/dL) were included in the study. These patients underwent estimation of haemogram, liver function tests, renal function tests, serum electrolytes (Na/K), viral serology (HIV/HBsAg/Anti-HCV/IgM HAV/IgM HEV), urine routine/microscopic examination and culture, stool routine/microscopic examination and culture (in cases of diarrhoea), blood culture, ascitic fluid analysis (if present) including culture/sensitivity, chest X-ray and USG abdomen. Data obtained were analysed qualitatively by Chi-square test and quantitatively by t-test.

Results: In this study of 86 patients suffering from CLD, 71 (82.6%) were males and 49 (57%) patients were above 50 years of age. It was found that abdominal distension was the most common presenting symptom seen in 50 (58.1%) patients and the most evident clinical sign was icterus in 70 (81.4%) patients. The most common deranged laboratory parameter was elevated AST in 61 (70.9%) and anaemia in 51 (59.5%) patients. The most common USG finding was splenomegaly seen in 32 (37.2%) patients. Alcohol turned up to be the most common aetiological factor in 45 (52.3%) patients and HBV in 11 (12.8%) patients. The most common complication seen after three months of follow-up was variceal bleed in 33 (38.4%) patients and encephalopathy in 28 (32.6%) patients. The three months mortality in ACLF patients was 36.36% with overall Odds Ratio of 8.57. The common complications of acute decompensation in 22 cases of ACLF were multi-organ failure.

Conclusion: ACLF as an entity in acute decompensated CLD patients was more common in patients who presented with altered sensorium, jaundice and decreased urine output. On three months of follow-up, Renal failure was most significant complication followed by hepatic encephalopathy and respiratory infections. The overall mortality in ACLF increases with complications.

Keywords: Ascites, Chronic liver disease, Hepatic encephalopathy, Hepato-renal syndrome

INTRODUCTION

Acute on Chronic Liver Failure (ACLF) denotes an acute deterioration of liver function in patients with Chronic Liver Disease (CLD) [1,2]. There is paucity of prospective studies on acute decompensation of chronic liver disease and its short-term outcome in India, especially with no facility for liver transplantation available to majority of these patients. Global literature says most of ACLF in India is caused by infections. With improvement of socio-economic status aetiological cause should be studied for a change in trend. Different factors affect the incidence and prevalence of ACLF in different geographical areas. To study the clinical profile of cases suffering from acute decompensation in chronic liver disease patients as ACLF and Non ACLF.

MATERIALS AND METHODS

The present observational study was conducted at Government Tertiary Care hospital in Pune, India. The study period was from July 2017 to November 2019. The sample size was calculated based on the prevalence of acute decompensation of chronic liver disease in India [1-3] (33.9%), using the standard furmula. Where, n-sample size, z- 1.96 (95 % confidence interval), p-33.9/100, d- absolute error, 10% or 0.1; The final sample size was 86.

The Asia-Pacific Association for the Study of the Liver (APASL) 2014 criteria were taken to define ACLF and CLIF-C-OF score was calculated to define organ failure [5]. The exclusion criteria were Acute liver failure patients who died within 12-hours of admission or lack of consent or patient on steroids/ or any other immunosuppressive medication or post liver transplantation. All subjects meeting the eligibility criteria were included in the study. The study was conducted after the approval from the Institutional Ethical committee (Institutional Ethical approval letter number is IEC/Oct/2017). After obtaining written consent, a detailed history and clinical examination was performed. These patients underwent estimation of haemogram, liver function tests, renal function tests, serum electrolytes (Na/K), viral serology (HIV/HBsAg/Anti-HCV/IgM HAV/IgM HEV), urine routine/microscopic examination and culture, stool routine/microscopic examination and culture (in cases of diarrhea), blood culture, ascitic fluid analysis (if present) including culture/sensitivity, chest X-ray and ultrasonography abdomen.

STATISTICAL ANALYSIS

Chi-square test was used for calculation of the results. Odds ratio was calculated for ACLF patients. The data were analysed using SPSS 22.0 (IBM, USA).

RESULTS

In this study of 86 patients suffering from CLD, 71 (82.6%) were males and 49 (57%) patients were above 50 years of age [Table/Fig-1]. It was found that abdominal distension was the most common presenting

symptom seen in 50 (58.1%) patients and the most evident clinical sign was icterus in 70 (81.4%) patients; 08/86 patients had caput medusa and engorged abdominal veins [Table/Fig-2,3].

	Age	<30	30-50	<50
Male		8	29	34
Female		2	04	09

[Table/Fig-1]: Depicting age and sex distribution.

Symptoms	ACLF patients		CLD patients	p-value
	Present	Absent		
Haematemesis	4	12	16	0.999
Malena	8	21	29	0.797
Inversion of sleep	4	7	11	0.461
Jaundice	16	28	44	0.026*
Abdominal pain	9	20	29	0.441
Abdominal distension	13	37	50	0.999
Fever	4	17	21	0.569
Breathlessness	5	14	19	0.999
Altered sensorium	12	9	21	<0.001*
Decreased urine output	5	5	10	0.115

[Table/Fig-2]: Distribution of various symptoms in ACLF patients and in 86 acute decompensated CLD patients.
*statistically significant

Signs	ACLF patients		CLD patients	p-value
	Present	Absent		
Icterus	22	48	70	0.009*
Pallor	14	42	56	0.999
Fetor hepaticus	2	2	4	0.568
Pedal oedema	13	37	50	0.999
Asterixis	11	9	20	0.001*
Petechiae	2	1	3	0.160
Ascites	13	41	54	0.799
Splenomegaly	15	27	42	0.048*
Liver span	7	25	32	0.616

[Table/Fig-3]: Distribution of various signs.
*statistically significant

The most common deranged laboratory parametre was elevated AST {in 61 (70.9%)} and anaemia {in 51 (59.5%)}. The various derangements in laboratory parametre are tabulated in [Table/Fig-4]. The most common USG finding was splenomegaly, seen in 32 (37.2%) patients. The various derangements detected in ultrasound in the chronic liver disease patients are tabulated in [Table/Fig-5] and comparison of radiological findings on ACLF patients are shown in [Table/Fig-6].

Lab parameters	ACLF patients		CLD patients	p-value
	Present	Absent		
Abnormal Hb	13	38	51	0.999
Abnormal TLC	6	8	14	0.177
Abnormal PLT	15	35	50	0.322
Abnormal S. CREAT	9	11	20	0.038*

[Table/Fig-4]: Distribution of various deranged lab parameters.
* statistically significant

Alcohol turned up to be the most common aetiological factor in 45 (52.3%) patients and HBV in 11 (12.8%) patients. The details of various aetiological factors are shown in [Table/Fig-7]. The most common complication seen after three months of follow-up was variceal bleed {in 33 (38.4%)} and encephalopathy {in 28 (32.6%)}. The details of various complications seen in ACLF and non ACLF patients are shown in [Table/Fig-8]. Total 14 (16.3 %) out of 86 patients developed Uraemia with criteria of Serum creatinine more than 2 mg/dL.

USG findings	Number of patients	Percentage (%)
Splenomegaly	32	37.2
Shrunken liver	19	22.1
Portal hypertension (Portal pressure >10 cm of H_2O)	15	17.4
Ascites (>100 mL)	25	29.1
Cholelithiasis	3	3.5

[Table/Fig-5]: Depicting ultrasound findings in CLD patients.

USG findings	ACLF patients		CLD patients	p-value
	Present	Absent		
Splenomegaly	10	22	32	0.445
Shrunken liver	4	15	19	0.769
Portal hypertension	2	13	15	0.335
Ascites	18	07	25	
Cholelithiasis	01	03	03	

[Table/Fig-6]: Comparisonof various ultrasound USG findings patients.

Aetiology	ACLF		Total	p-value
	Present	Absent		
Alcohol	19	26	45	< 0.001*
HBV	7	4	11	0.005*
HCV	0	3	3	0.567
Non alcoholic steato hepatitis	0	2	2	0.615
Others	2	11	13	0.501

[Table/Fig-7]: Distribution of various aetiological factors in ACLF patients.
*statistically significant

Complication	ACLF		Total	p-value
	Present	Absent		
Variceal bleed	8	25	33	0.999
Hepato cellular carcinoma	0	2	2	0.615
Spontaneous bacterial peritonitis	4	3	7	0.068
Renal failure (S. Creat. >2 mg/dL)	8	6	14	0.006
Bacteraemia	1	2	3	0.999

[Table/Fig-8]: Distribution of various complications in ACLF and non ACLF patients.

The common precipitating factors of acute decompensation in 86 cases of CLD were alcohol consumption despite CLD (51.16%); Reactivation of HBV infection/HCV/HEV (16.2%); Infections (13.9%); Drug induced injury (1.16%), non-compliance to dietary modifications (5.81%) and non-compliance to prescribed medications e.g., laxatives (11.6) the details are depicted in [Table/Fig-9]. The only case where drug induced injury precipitated ACLF was seen with isoniazid.

Precipitating factor	Prevalence
Alcohol	44 (51.16 %)
Hepatotropic viruses	14 (16.2 %)
Infections	12 (13.9 %)
Drug induced injury (Isoniazid)	01 (1.16 %)
Non-compliant to Dietary modification	05 (5.81 %)
Non-compliant to medication	10 (11.6 %)

[Table/Fig-9]: Showing details of various precipitating factors leading to acute decompensation in Chronic Liver Disease (CLD) cases.

Out of enrolled 86 CLD patients, ACLF was found prevalent in 22 (25.6%) patients.

Odds Ratio (OR) was calculated and amongst the symptoms, most significant was altered sensorium with maximum OR of 7.333 and decreased urine output as 3.471. Icterus was the most significant clinical sign and had the maximum OR as infinity and that of fetor hepaticus was 3.1. The laboratory parameters showed the maximum OR of serum creatinine as 3.336 and that of leukocytosis

were 2.625. The USG findings suggested that splenomegaly had maximum OR of 1.591 and that of shrunken liver was 0.726. In the aetiological factors, alcohol was the most common factor with OR of 9.526; it was followed by HBV infection with OR of 7.0. Renal failure was the most common complication in ACLF patients with OR of 5.524 and second most common complication was Spontaneous Bacterial Peritonitis with OR of 4.519 [Table/Fig-10].

Headings	Odds ratio
Altered sensorium	7.33
Icterus	Infinity (Icterus will always be present)
Serum creatinine	3.33
Splenomegaly	1.59
Alcohol	9.25
Renal failure	5.52

[Table/Fig-10]: Depicting ODDS RATIO of common symptoms, signs, laboratory parameters, aetiology and complications in Acute on Chronic Liver Failure (ACLF) patients.

The common complications of acute decompensation in 22 cases of ACLF were Multi-organ failure (54.5 %) followed by Hepatic encephalopathy (54.5 %) [Table/Fig-11].

Complications	Prevalence
Multi-organ failure	12 (54.5 %)
Hepatorenal syndrome	08 (36.36 %)
Hepatic encephalopathy	12 (54.5 %)
Cardiovascular decompensation	06 (27.7 %)
Respiratory infections	04 (18.1 %)
Provided ventilatory support	01 (4.5 %)
Deep vein thrombosis	01 (4.5 %)
Coagulopathy	11 (51.2 %)

[Table/Fig-11]: Depicting prevalence of complications in Acute on Chronic Liver Failure (ACLF) patients.

The three months mortality in ACLF patients was 08 (36.36%) with overall OR was 8.57 [Table/Fig-12].

		ACLF			Odds ratio
		Yes	No		
Mortality	Yes	8	4	12	8.57
	No	14	60	74	
		22	64	86	

[Table/Fig-12]: Mortality in ACLF patients.

DISCUSSION

Cirrhosis had been classified into two stages- compensated cirrhosis and decompensated cirrhosis [6]. Majority of patients with compensated cirrhosis progress to decompensated disease, which is characterised by jaundice, coagulopathy. Four stages of cirrhosis are: First is cirrhosis without either varices or ascites, second is compensated cirrhosis with varices that have not bled, third is ascites without bleed, fourth is variceal bleed. Cirrhosis with sepsis has been proposed as the fifth stage of cirrhosis [1].

ACLF occurs as a natural history of chronic liver disease. There is a risk for multiple organ failure and an increased mortality [2,4,6,7].

The Asia-Pacific Association for the Study of the Liver (APASL) found reactivation of hepatitis B and superinfection with hepatitis E virus infection on NAFLD are important causes or ACLF in that region, but a significant proportion of cases continue to be due to alcoholic hepatitis [3,5,8-10]. In this study, the most common aetiology was alcohol followed by HBV infection. OR for alcohol was 9.25. There was a study by Arroyo V et al., in which majority of subjects in the setting of alcoholic liver disease had similar findings [6]. In other study, no precipitating factor was found in 44% cases. Even viral or drug-induced hepatitis were described as uncommon precipitating factors [4]. In the present study, the most common precipitating factor was alcohol with p-value <0.001 and OR 9.256.

The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) recently examined survival in sepsis or infection related **ACLF** [1,2]. Nosocomial infection was present in 16% and Hepatitis C was present in overall half of the population (total 507 patients). This study also found that overall Thirty-day mortality was in proportion with number of extrahepatic organ failures. In this study, it was found that significant OR ratio for ACLF was present in renal failure and Spontaneous Bacterial Peritonitis (SBP) signified high mortality in these patients.

In non-cirrhotic chronic liver disease the precipitating event is a major hepatic injury, such as reactivation of chronic hepatitis B, superimposed acute hepatitis A or hepatitis E infection [3,8] in the East, or drug-induced liver injury superimposed upon nonalcoholic fatty liver disease in the West [8]. Alcoholic hepatitis or drug-induced hepatitis are common precipitating events in compensated cirrhosis while infections are common in *decompensated cirrhosis*. Same study suggested that in acute viral hepatitis, underlying diabetes and CLD are at higher risk for development of liver failure. The study demonstrated that patients with underlying diabetes are prone for Drug-Induced Liver Injury (DILI) and further to liver failure. Thereby they concluded ACLF is a common precipitant in NAFLD patient with superadded DILI Almost 50% of patients of cirrhosis admitted to the hospital have evidence of infection or sepsis and a further 25% develop nosocomial infections with high inpatient hospital mortality [11-13]. In the present study it was found that the common precipitating factors were alcohol and HBV infection with significant OR of 9.256 and 7.000 and survival at 03 months was 86%.

ACLF has various definitions, due to which the correct prevalence of ACLF cannot be assessed; but it ranges from 12% to 40% among hospitalised cirrhotic patients, while the European studies revealed a prevalence of 31% [14,15]. In the NACSELD cohort, infection associated ACLF prevalence was 24.4% (>2 organ failures) [16,17]. In the index study it was found that the prevalence of ACLF was 25.6 %.

The infection-associated ACLF mortality may be as high as 50% [11], 50% hospitalisations of cirrhotic patients are due to infections; indeed, a further 20% to 40% of patients develop nosocomial infections [18,19]. Urinary Tract Infection (UTI) and SBP are most common infections in cirrhosis. In this study, it was found that 24.4% patient had SBP and other infections. Elevated surrogate markers of inflammation, C Reactive Protein (CRP) [20-23] and leukocyte count are associated with worse outcomes. The role of the compensatory anti-inflammatory response is important in determining the risk for nosocomial infections and higher mortality. In this study, it was found that there was a similar course with leukocytosis {06 (27.7 %) of 22 ACLF}. The other studies found that death in ACLF patients were due to Immune paralysis leading to sepsis and organ failure. In this study, SIRS and organ failure was there in 22 % patients. In decompensated cirrhosis, it is unlikely to have multisystem organ failure werein number of failing organ systems has prognostic value in ACLF [12,13]. In this study the prevalence of multi organ failure was 54.5 % in ACLF patients.

Prerenal azotemia, acute tubular necrosis, and Hepatorenal Syndrome (HRS) are commonly found causes of AKI in cirrhosis. In cirrhosis, sepsis can precipitate AKI in 30-40 % cirrhotics with one month mortality upto 18.6 %. three- month survival rate was only 31 % in other study. Exact prevalence of HRS in ACLF were not studied in earlier study. The prevalence of hepatorenal syndrome was present in 36.36 % of ACLF patients in the present study.

An added complication, Hepatic Encephalopathy (HE) due to ALF, decompensated cirrhosis and ACLF, is associated with significant in-hospital mortality. Isolated hepatic encephalopathy may occur in

cirrhotic patients without evidence of any extrahepatic organ dysfunction [11,24-27]. In this study the prevalence of HE was in 54.5% of ACLF patients as compared to 45 to 50% in other studies [12,13].

Patients with ACLF have a decrease in mean arterial pressure and systemic vascular resistance, and a significant increase in Hepatic Venous Pressure Gradient (HVPG). These haemodynamic changes improve with resolution of the acute episode [12,21]. In this study the prevalence of cardiovascular decompensation was 27.7 % in ACLF patients.

In cirrhotic, upto 14% to 48% of all infections are respiratory infection which leads to organ failure [18,19]. The patient requiring ventilatory support has higher risk of developing ACLF. Thie use of assisted ventilation also prognosticates ACLF with 89% mortality in 1 year [18,19]. As compared to other studies with prevalence ranging from 4 to 49% [12,13]; In this study the prevalence of respiratory infection was 18.1% and ventilatory support was provided to 4.5% of ACLF patients.

Cirrhosis is a procoagulant state but there is decrease in both pro-coagulation and anticoagulation factors in ACLF. The study could not delineate the risk of bleeding in ACLF.. Decrease in protein C and reduced fibrinolysis result in increased risk for coagulation [11]. In this study the prevalence of DVT was 4.5% and prolongation of INR was seen in 51.2% patients as compared to other studies in which prevalence of DVT was 6.3 % [12,13].

Limitation(s)

The limitation of this study is the less follow-up period of three months. A longer follow-up with 12 months duration of study could have given more accurate results.

CONCLUSION(S)

In this study, ACLF was common cause of three months mortality in CLD. This mortality can be reduced by early identification of clinical signs and focused pathological and radiological investigations. The high index of suspicion for sepsis and early organ failure are key in prevention of mortality in decompensated CLD. It is recommended to institute all corrective measures to control infections in setting of chronic liver disease and prevent ACLF.

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PARTICULARS OF CONTRIBUTORS:
1. Resident, Department of Internal Medicine, AFMC, Pune, Maharashtra, India.
2. Professor, Department of Internal Medicine, AFMC, Pune, Maharashtra, India.
3. Professor and Head, Department of Internal Medicine, AFMC, Pune, Maharashtra, India.
4. Associate Professor, Department of Community Medicine, AFMC, Pune, Maharashtra, India.
5. Medical Officer, Indian Army, Department of Internal Medicine, AFMC, Pune, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Anuj Singhal,
Professor, Department of Internal Medicine, AFMC, Pune, Maharashtra, India.
E-mail: purnimanuj@gmail.com

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