

Original Research Article

A hospital-based study on acute on chronic liver failure underlying etiology and precipitating factors

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ABSTRACT

Background: Acute-on-chronic liver failure (ACLF) is an increasingly recognised entity that includes the acute deterioration of chronic liver disease usually associated with a precipitating event, development of one or more organ failure and high short-term mortality.

Methods: This is a prospective observational study. Clinical data of patients admitted with ACLF at Goa Medical College between November 2019 to November 2021 are summarized and analyzed using relevant statistical tests.

Results: A total of 70 patient's data was collected. Most common cause of underlying chronic liver disease was alcohol (85.7%) followed by hepatitis B (4.3%), autoimmune diseases (4.3%), cryptogenic (4.3%) and hepatitis C (1.4%). Infections were the most common precipitating factors for ACLF (42.8%) followed by alcohol (28.5%), upper gastrointestinal bleeding (21.42%), drug (AKT) induced (1.42%), unknown cause (10%).

Conclusions: Infection and alcohol were found to be important precipitating factors. A multicentre study involving larger numbers of patients are required to know further details and to form a standard treatment protocol.

Keywords: ACLF, Alcohol, Chronic liver disease, Infections

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a newly recognized category that encompasses the acute declination of chronic liver disease, which is frequently preceded by a triggering factor resulting in the onset of one or more organ failure and a high rate of short-term death. The acronym ACLF was first used in 1995. There are almost thirteen distinct descriptions available. There are two widely accepted definitions.¹ "The first definition, belonging to the Asian Pacific Association for the Study of the Liver (APASL), considers that the ACLF is an "acute hepatic insult manifesting as jaundice and coagulopathy, complicated within four weeks by ascites and/or encephalopathy in a patient with previously

diagnosed or undiagnosed chronic liver disease".² A joint symposium of the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (EASL) formulated a second definition. It defines ACLF as an "acute worsening of pre-existing chronic liver disease, usually related to a causal event, and associated with increased mortality at three months due to multi-system organ failure".

These patients have a rapidly deteriorating course with the development of multiorgan failure and high short-term mortality, in contrast to chronic liver disease. The potential reversibility is a critical concept in this group of patients. The term reversibility means the acute deterioration of the liver function due to the precipitating

event is reversible. It does not mean that underlying chronic liver damage is reversible.

The cause for acute deterioration can be infectious causes like viral hepatitis and non-hepatotropic viruses, sepsis, infections, or non-infectious causes like alcohol, drugs, gastrointestinal bleeding, toxins, and surgery.

Management of ACLF needs good intensive care to avert organ failure development or assist the failing organs. Various studies explored the use of various extracorporeal liver support systems.³ Despite improvements in metabolic markers and hepatic encephalopathy, there is no substantial survival advantage. The only cure is liver transplantation.⁴ With a prevalence of roughly 30%, ACLF is a familiar syndrome.

This cross-sectional study looks at the clinical profile, precipitating factors, and etiology of underlying chronic liver disease in ACLF patients admitted to a tertiary care hospital.

METHODS

This prospective observational study was conducted in department of general medicine, GOA medical college and hospital. The study period was from November 2019 to May 2021. 70 patients of acute on chronic liver failure were enrolled.

Inclusion criteria

Patients with chronic liver disease (diseases of liver which lasts over a period of 6 months or more with compensated or decompensated cirrhosis) [based on deranged LFTs/USG finding/clinical symptoms more than 6 months] who presented with ACLF. Age >18 yrs. Have the capacity to understand and sign an informed consent were included in the study.

Exclusion criteria

Acute liver failure, acute viral hepatitis, age <18 yrs, liver transplantation, pregnant and lactating women, those unwilling to give consent were excluded from the study.

Data collection

Data was collected prospectively on patient's demographics, clinical features, laboratory parameters, disease severity, aetiology of the underlying chronic disease and the acute insult, presence of multi organ dysfunction.

Clinical profile and course

Once a diagnosis of ACLF has been made, data was collected prospectively on patient demographics, clinical symptoms and signs, laboratory parameters,

complications and outcomes. Extensive history was taken from the patients and the attending relatives. This included history of alcohol intake, other drugs including native medications, abdominal distension, fever, altered sensorium, upper gastrointestinal bleed and focus of infection including previous episodes of decompensation (ascites, encephalopathy, spontaneous bacterial peritonitis, esophageal varices, variceal bleeding or hepatocellular carcinoma) as well etiology of cirrhosis. All patients underwent detailed physical examination and vital signs were recorded. Presence of spider naevi, gynecomastia, hepatomegaly, ascites, abdominal wall collaterals and grade of encephalopathy was noted. Hepatic encephalopathy was graded according to West Haven system into grade 0 to 4.

Blood was collected for complete blood count, urea, creatinine, electrolytes, liver function tests, prothrombin time, INR and viral markers. Ascitic fluid analysis was done for serum ascitic fluid albumin gradient, cell count and culture. Spontaneous bacterial peritonitis was defined by the presence of >250 neutrophils per mm³ or positive ascitic fluid cultures. Other biochemical tests such as ANA etc. done when clinically indicated. All patients underwent USG abdomen and following details were recorded- liver -size, surface nodularity of liver, Size of the spleen, size of portal vein; presence of portal-systemic collaterals, presence of ascites.

Grading of ACLF

ACLF patients were divided into 3 grades according to the type and number of organs affected.¹³

ACLF grade 1: Included patients with single kidney failure; patients with single failure of the liver, coagulation, circulation, or respiration who had a serum creatinine level ranging from 1.5 to 1.9 mg/dl and/or mild to moderate hepatic encephalopathy; and patients with single cerebral failure, who had a serum creatinine level ranging from 1.5 to 1.9 mg/dl.

ACLF grade 2: Included patients with failure of two organs and

ACLF grade 3: Included patients with failure of three or more organs. Organ failures were defined as per the CANONIC study criteria.²

Diagnosis of organ failure

Liver failure was by a serum bilirubin level of ≥ 12.0 mg/dl.

Kidney failure was defined if the serum creatinine level was ≥ 2.0 mg/dl or the need for renal replacement therapy.

Cerebral failure was defined by grade III or IV hepatic encephalopathy as per the West Haven classification.

Coagulation failure included an international normalized ratio of ≥ 2.5 and/or platelet count of $\leq 20000/\text{cc}$.

Circulatory failure was defined by the need for the use of vasopressors like dopamine, dobutamine, or terlipressin at any dose.

Respiratory failure was defined by a PaO_2 to FiO_2 ratio of ≤ 200 or a SpO_2 to FiO_2 ratio of ≤ 200 .³ Clinical characteristics of each group, the presence of precipitating events, potential risk factors for developing ACLF and causes of mortality were analyzed.

Statistical analysis

All the data were entered on a excel sheet. Mean and median were calculated for appropriate variables. Data was analyzed using statistical Package for Social Sciences (SPSS) software and relevant statistical tests. Results were represented in the tabular and graphical forms.

RESULTS

During the study period, 70 patients satisfying the inclusion criteria were enrolled in the study. There were 63 males and 7 females (Male: Female-9:1). The mean age of study participants is 45.69 ± 10.34 yrs. Majority of the study participants were in the age group of 41-50 years (41.4%) followed by 51-60 years (22.9%) (Table 1 and 2).

Table 1: Distribution of study participants according to their sex (n=70).

Sex	No. of patients	Valid percent
Female	7	10
Male	63	90
Total	70	100

Table 2: Distribution of study participants according to their age (n=70).

Age (years)	No. of patients	Valid percent
<30	6	8.6
31-40	15	21.4
41-50	29	41.4
51-60	16	22.9
61-70	3	4.3
>70	1	1.4
Total	70	100

Clinical features and laboratory finding

Jaundice was seen in all patients with median of 10.55 mg/dl(range-2-41.93) (Figure 1). Ascites was seen in 52 patients (74.3%). Encephalopathy was seen in 38 patients (54.3%) (Figure 1). As per West Haven classification, 25

patients had grade II, 12 patients had grade III and 1 patient had grade IV Encephalopathy (Table 3).

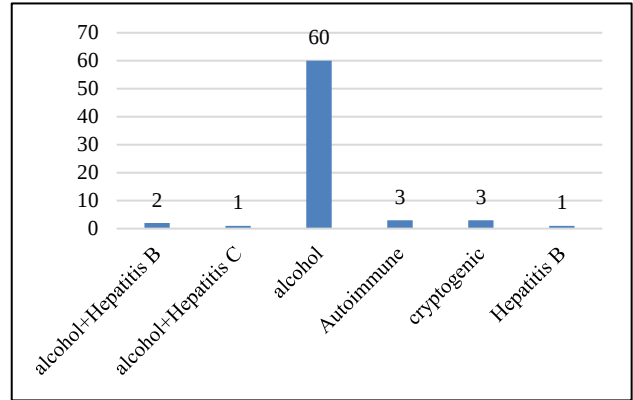


Figure 1: Etiology.

Table 3: Baseline clinical features of study participants.

Clinical feature	No. of patients	Percentage (%)
Jaundice	70	100
Ascites	52	74.3
Encephalopathy (west haven classification)	38	54.3
	Grade 1-00	
	Grade 2-25	
	Grade 3-12	
	Grade 4-01	
Upper GI bleeding	22	31.4
Hepatomegaly	11	15.7
Splenomegaly	36	51.4
SBP	11	15.7
Spider naeve	10	14.28
Parotid enlargement	14	20

Table 4: Baseline laboratory findings of all the patients.

Parameters	Median	Range
Haemoglobin(g/dl)	8.13	1.3 to 14.8
WBC/mm ³	11000	5200 to 46700
Platelets/mm ³	100000	15000 to 340000
Total S. bilirubin (mg/dl)	10.55	2 to 41.3
SGOT (U/l)	99	23 to 618
SGPT (U/l)	37	8 to 447
ALP (U/l)	119	41 to 348
Total proteins (g/dl)	6	3.5 to 8.4
Se.albumin (g/dl)	2	0.7 to 3.9
Se.globulin (g/dl)	3.95	2.3 to 6.5
A:G ratio	0.51	0.25 to 1.25
Blood urea (mg/dl)	53	8 to 337
Se.creatinine (mg/dl)	1.55	0.47 to 8.8
INR	2.11	0.6 to 4.23

A total of 22 patients (31.4%) had history of upper gastrointestinal bleeding in the form of hematemesis or melena (Figure 1). In most of the patients it was related to coagulopathy.

History of fever was found in 9 patients.

SBP was seen in 11 patients (15.7%) (Figure 1). 11 patients had hepatomegaly (15.7%) (Figure 1) and 36 patients had splenomegaly (51.4%) (Figure 1). 14 patients had parotid enlargement and 10 patients had spider naevae (Table 3).

The median hemoglobin was 8.13 g/dl (range-1.3-14.8). The median platelets were 1,00,000/mm³ (range-80,000-1,50,000). Median WBC was 11,000 (range-8545-17500).

Median SGOT and SGPT values were 99 and 37 U/l respectively. Median se.albumin was low -2 mg/dl (range1.78-2.4). Median A:G ratio was 0.51 (range 0.25-1.25). INR was prolonged (median-2.11) No coagulation is seen in 9 patients. Median S. Creatinine was 1.55 mg/dl (range-0.47-8.8) (Table 4).

Infections in ACLF

Out of 70 patients, 30 patients had infections. Most patients had elevated WBC ranging from 12000 to 46700. 9 patients had history of fever. SBP and LRTIs were most common infections followed by UTIs. Among 30 patients, 9 patients had spontaneous bacterial peritonitis (30%), 6 patients had pneumonia (20%) and 3 patients had LRTI (10%), 7 patients had urinary tract infections (23%), 2 patients had cellulitis (7%), 1 patient had folliculitis (3%) and 2 patients had leptospirosis infection (7%) (Table 5).

Table 5: Source of infection.

Source of infection	No. of patients	Valid percent
LRTI	3	10
SBP	9	30
leptospirosis	2	7
UTI	16	22.9
Folliculitis	1	1.4
Pneumonia	6	20
Cellulitis	2	7

Table 6: Precipitating factors.

Precipitating factors	No. of patients	Valid percent
Infections	30	42.8
Alcohol	20	28.5
UGIB	15	21.4
Drug induced	1	1.4
Unknown	7	10

Underlying etiology of chronic liver disease

During the study underlying cause of chronic liver disease was evaluated. Most common cause of underlying liver disease was alcohol seen in 60 patients (85.7%) followed by Hepatitis B in 3 patients (4.3%) and Autoimmune diseases in 3 patients (4.3%). All the 3 patients were female who had autoimmune disease as cause for underlying liver disease. Hepatitis C along with alcohol seen in 1 patient (1.4%). Cause was uncertain in 3 patients (Figure 1).

Precipitating factors

Infections were the most common precipitating factors for ACLF seen in 30 patients (42.8%), followed by alcohol in 20 patients (28.5%), upper gastrointestinal bleeding in 15 patients (21.42%), drug (AKT) induced seen in 1 patient (1.42%). In 7 patients precipitating factor could not be identified (10%).

A total 3 patients had more than one precipitating factors, out of which one had LRTI and upper GI bleed, second patient had alcohol and upper GI bleed and third patient had SBP and upper GI bleed (Table 6).

Organ involvement

The commonest organ failure was coagulation failure 52.8%. Liver failure and renal failure was observed in 47.1% and 44.2% respectively. Circulatory and cerebral failure was seen in 21.4% and 20%. Respiratory failure in 1.4% (Table 7).

Table 7: Organs.

Organs	No. of patients	Valid percent
Liver	33	47.1
Renal	31	44.2
Coagulation	37	52.8
Cerebral	14	20
Circulatory	15	21.4
Respiratory	1	1.4

ACLF grading

Majority of the patients belonged to grade II. Patients with Grade I ACLF were 25, grade II -31 and grade III-14. Organ failure under ACLF grading depicted in Table 8.

Table 8: ACLF grade.

ACLF grade	No. of patients	Valid percent
I	25	35.7
II	31	44.3
III	14	20
Total	70	100

Table 9: % Organ failure among various studies.

	Liver (%)	Renal (%)	Coagulation (%)	Circulatory (%)	Cerebral (%)	Respiratory (%)
Canonic study	43.6	55.8	27.7	16.8	24.1	9.2
Present study	47.1	44.2	52.8	21.4	20	1.4
Premkumar et al⁵	50	80	40	75.3	74.6	80
Gawande et al⁷	25.9	12.9	29.8	25.4	41.3	12.01
Amarapurkar et al²³	67	32	39	30	15	13

DISCUSSION

This is a prospective study that looks at the clinical profile, precipitating factors and underlying etiology of chronic liver disease in patients with acute on chronic liver failure.

ACLF is a rare condition that differs from chronic decompensation of end-stage liver disease in that it has a rapidly deteriorating course and the possibility to be reversed. Multiorgan failure is the main cause of high mortality. We studied a total of 70 patients who were diagnosed with ACLF as per criteria defined by EASL-CLIF consortium. All patients had cirrhosis of liver; Jaundice was severe in majority of the patients. Encephalopathy was seen in 54.3%, majority of patients belonged to grade II (as per West Haven classification). Ascites was seen in 74.3%.

In our study, it was observed that majority of patients i.e 41.4% were in the age group of 41-50 yrs. Ramachandran et al, Premkumar et al and Gawande et al in their study also showed similar age of presentation, demonstrating that the syndrome generally affects cirrhotic people in their prime and productive years of life, causing severe morbidity and mortality.⁵⁻⁷ Studies from northern India Kumar R et al showed similar age of presentation.⁸

In our study male incidence was 9 times more than females. This finding is consistent with studies by Gawande et al from Jaipur, Radhakrishna et al from Lucknow as well as, Premkumar et al from Chennai.^{5,7,9} Males are more prone than females to become addicted to alcohol since they spend more time outside and have greater social interaction.

The most common etiology of chronic liver disease in our study was alcoholic liver disease, which is similar to most western studies i.e Laleman et al, CANONIC study by Moreau et al etc.^{10,11} In a multi-centre study from India i.e Shalimer et al, alcohol was found to be most common cause.^{12,13} According to Netaji Garad et al from Raipur, Premkumar et al from Chennai, Gawande et al from Jaipur, Pati et al from Cuttack also alcohol was the most common underlying etiology. The most prevalent insult, according to Duseja et al from Chandigarh, is alcohol, followed by viral hepatitis and autoimmune hepatitis.¹⁴

While on other hand, HBV infection was revealed to be the most common etiological agent for Chronic Liver Disease in research from north India, China, and Taiwan. Prevalence of Hepatitis B as per studies reported from China by Xia et al and Shi et al was 70% and 75% respectively.^{15,16} Chronic hepatitis B, followed by alcohol and cryptogenic, was the most common aetiology in major prospective research conducted by H Garg et al from Delhi.¹⁷ As per our study hepatitis B was found in 4.3% and Hepatitis C in 1.4%.

In our study, percentage of patients with alcoholic liver disease was significantly very high (85.7%) when compared to above mentioned study i.e Premkumar K et al (58%). This could be related to increased alcohol intake in society as some Goan communities have assimilated the use of alcohol in their daily life and celebrations whereas growing number of younger generations consume alcohol as part of socialization. Alcohol is readily available in Goa at cheaper prices. There is also improved awareness of HBV infection prevention and immunization in our society.^{18,19} Because our hospital is a tertiary care facility that provides patients with entirely free treatment, there is a risk of referral bias, with alcoholics being the most typical cause. Other etiologies observed in our study include autoimmune (4.3%) and cryptogenic (4.3%).

Study by Gawande et al from Jaipur reported autoimmune liver disease in 4.3% and cryptogenic in 13.94% patients.⁷ In another single study by Rachit et al from Jammu revealed 5% patients with autoimmune etiology, which correlates well with our study.

Infections were the most common acute precipitating factors in ACLF observed in 42.8% patients in our study. Infections include pneumonia, lower respiratory tractions, urinary tract infections, spontaneous bacterial peritonitis, cellulitis and folliculitis. Among infections, spontaneous bacteria peritonitis was the most common infection, seen in 30% of our patients, followed by pneumonia (20%), lower respiratory tract infections (10%), and urinary tract infection (23%).

This is consistent with CANONIC Study by Moreau et al where in, spontaneous bacterial peritonitis and pneumonia were the most common infections along with

other bacterial infections (32.6%). In one of the single centre study, Xu et al infections were the most common precipitating factors.¹⁹ Among other studies such as Premkumar et al from Chennai infections (41%) were the most common acute precipitating event.⁵

Khatun et al from Chittagong in their study also reported infections as the most common precipitating factors.²⁰

Other precipitating factors observed in our study include - binge alcohol intake seen in 28.5%, upper GI bleed in 21.4%, drug induced in 1.4%, factors unknown in 10% patients. In CANONIC study by Moreau et al binge alcohol intake was seen in 24.5%, upper GI bleed in 13.2%, factors could not be identified in 43.6%. Similar findings were noted by Premkumar et al.⁵

Infection and its consequences are more common in patients with alcoholic liver disease. These patients have impaired neutrophil activity and phagocytosis, according to Mookerjee et al.²¹ Increased oxidative burst in these neutrophils indicates a functional failure. Patients with chronic liver illness are more susceptible to infection due to increased intestinal permeability, which allows bacteria to enter in the blood circulation. The precipitous decline cannot be attributed solely to bacterial translocation. This is compounded by a faulty immunological response manifested by aberrant neutrophil activity and phagocytosis. Majority of the patients had elevated whole blood count.

In a multicentre study from India, alcohol was the most common precipitating factor found in 35% patients, followed by sepsis (16.6%), hepatotropic viruses (hepatitis B, A, and E (21.4%), variceal bleed (8.4%), and drugs (5.7%).²² Similarly in one of the studies from northern India Rakesh kumar et al alcohol was most common factor. In our study, 3 patients had more than one precipitating factors. First patient had LRTI with upper GI bleed, second patient had SBP with upper GI bleed and third patient had alcohol with upper GI bleed.

Most important feature of ACLF is development of organ failure. In our study most common organ failure was coagulation failure (52.8%) followed by liver failure (47.1%) and renal failure (44.2%). As per CANONIC study by Moreau et al, renal failure was the most common organ failure (55.8%).

According to Premkumar et al from Chennai, the commonest organ failure was renal failure, whereas as per Gawande et al from Jaipur and Amarapurkar et al cerebral failure was the commonest organ failure (Table 9).^{5,7,23}

This variation in percentage of organ failures can be attributed to the fact that different studies have used different criteria for defining organ failure. Some studies were conducted as per APSAL criteria such as Gawande et al, Kumar R et al.^{7,8} Others including CANONIC Study

by Moreau et al, Premkumar et al, Amarapurkar et al used EASL CLIF Consortium criteria.

In our study, majority of the patients belonged to grade II ACLF (44.3%) followed by grade I (35.7%) and grade III (20%). In Gawande et al, 22.12% and 20.67% belonged to grade II and III ACLF respectively. As per CANONIC study, 64.3% had only one organ involvement i.e grade I. 78% patients belonged to grade III according to Premkumar K et al from Chennai, as this study was conducted in Institute of Hepatobiliary Sciences, a tertiary centre where most of the critical patients are referred.

Majority of the patients admitted in our hospital had advanced liver disease at presentation (64%), hence patients belonged to grade II. Grading of ACLF helps in assessing the severity of the condition as well as the prognosis.

Acute decompensation manifests as variceal haemorrhage, infection, hepatic encephalopathy, and ascites as a result of portal hypertension and chronic liver disease consequences. Many patients are able to recover to a compensated state due to recent advancements in medical care of acute decompensation. However, a percentage of patients develop substantial pathological consequences, such as hepatic and/or extrahepatic organ failure or multi-organ failure, necessitating intensive care and life support. ACLF is a unique illness that typically manifests as organ failure after a triggering event and is linked to a high rate of short-term mortality. While the exact pathophysiology of ACLF is unknown, it appears that unopposed and exacerbated inflammation plays a key role. Multiple organ supportive care is frequently necessary due to the severe inflammation that occurs with ACLF, as well as its rapid advancement, and it is associated with a 45 percent to 90 percent short-term death rate.

Although the underlying cirrhosis in ACLF is irreversible, the disorder is assumed to have a reversible component because it is frequently linked to a triggering stimulus. There is currently a lack of data on the epidemiology of ACLF; nonetheless, the high fatality rates, lengthy hospital stays, and significant financial impact on healthcare systems associated with the condition highlight the necessity of bettering our understanding of the disorder.

Limitation

It was single-centre research with few participants. A larger sample size may give more insight into the relationship among precipitating factors, underlying etiology for chronic liver diseases and ACLF. Despite these limitations, this study strengthens the valid scientific evidence about ACLF. A multicenter study involving larger numbers of patients is required to know the clinical characteristics, other precipitating factors and

to form a standard treatment protocol for this dynamic syndrome.

CONCLUSION

ACLF is a condition in which a patient with chronic liver disease develops single, two, or more organ failure after a triggering event that is associated with a high rate of short-term death. In our hospital, the most common cause of underlying chronic liver disease is alcoholic liver disease (85.7%) followed by Hepatitis B (4.3%) and Autoimmune diseases (4.3%) and other causes. The most common acute precipitating factor is infection. Other factors include alcohol, upper gastrointestinal bleeding, drugs. These study findings bolster up the current knowledge, understanding and management in the field of ACLF.

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