Original Article

Profile of Patients Admitted with Acute-on-Chronic Liver Disease in a Tertiary Care Hospital

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ABSTRACT

Introduction: Chronic liver disease (CLD) and cirrhosis of liver are 12th leading cause of death. Acute-on-chronic liver failure (ACLF) is an increasingly recognized entity encompassing an acute deterioration of liver function in patients with cirrhosis and it is associated with high mortality.

Methodology: A total of 100 consecutive patients admitted with ACLF were studied. Chronic liver disease was defined as per 2014 ICD-10 CM Diagnosis Code K 76.9. ACLF was defined as per the Asian Pacific Association for the Study of the Liver (APASL) criteria. Grading of severity of ACLF was done as per the CANONIC study. Prognostic scores including Child-Pugh scoring system were also calculated.

Results: Out of 100 patients 84 were males (mean age 44.31±13.58 years) and 16 females (mean age 40.19±19.11 years). Underlying etiology of CLD was alcoholic (76 cases), Hepatitis B virus (HBV) (10 cases), cryptogenic (seven cases), autoimmune (four cases) and Heapatitis C virus (HCV) in (three cases). There were 74% from rural area, 51% illiterate and 82% belonged to the low socio-economic status. Most common presentation of ACLF was hemetemesis (36%) followed by melena (30%), vomiting (30%), sepsis (28%), pain abdomen (27%), hepatic encephalopathy (17%) and hepato-renal syndrome (16%). Mortality rate in our study was 9% and all belonged to the alcoholic group. Severe anemia, hypoalbuminemia, hyperbilirubinemia, renal dysfunction, sepsis, hyponatremia, high PT-INR and high Child Pugh score 10-15 were associated with poor prognosis.

Conclusion: Knowledge and early recognition of various risk factors may help in prevention of acute- on- chronic liver failure and early identification of various prognostic features may help in decreasing the mortality in patients of acute- on- chronic liver failure.

INTRODUCTION

Chronic liver disease (CLD) is an important cause of morbidity and mortality, currently up to 2% of all attribution goes to liver disease and in the clinical context it is defined as a disease process of the liver that involves a process of progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis.[1] The complications of cirrhosis are basically the same regardless of the etiology, it is useful to classify patients by the underlying cause. The most common causes of chronic liver disease (CLD) in general order of frequency are chronic hepatitis C, alcoholic liver disease, nonalcoholic steato-hepatitis, chronic hepatitis B, autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, haemochromatosis and Wilson's disease.[2] However, recently the prevalence of non-alcoholic fatty liver disease (NAFLD) has risen dramatically, affecting up to 40% of all Europeans and more than 50% of patients suffering from type-2 diabetes mellitus.[3]

Acute-on-chronic liver failure (ACLF) is an increasingly recognized entity encompassing an acute deterioration of liver function in patients with cirrhosis[4] either secondary to superimposed liver injury or due to extrahepatic precipitating factors such as infection culminating in the end-organ dysfunction. Occasionally, no specific precipitating event can be found. Although the exact pathophysiology of the development of ACLF remains to be elucidated, unregulated inflammation is thought to be a major contributing factor. A characteristic feature of ACLF is its rapid progression, the requirement for

multiple organ supports and a high incidence of short and medium term mortality.[5] The condition remains undefined but two consensus working definitions for this syndrome exist. The first put forward by the Asia–Pacific Association for the Study of Liver Disease[6] defines it as "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" and a second at a EASL-AASLD single topic symposium[7] which defines it as "acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure". These definitions are too imprecise to allow homogeneous diagnostic criteria and clinical studies are currently underway to reach an evidence-based definition. The latter definition implies that organ failure is a central component of this syndrome and leads to the hypothesis that the organs may behave differently to chronic decompensated liver disease.[8] Data regarding the epidemiology of ACLF are rare.[4]

Since over the last few years there is consistent increase in number of CLD patients requiring hospitalization, we carried out this study to evaluate demographic, clinical profile, risk factor and prognostic indicators of ACLF cases.

METHODS

The present study was carried out on 100 consecutive patients suffering from acute-on-chronic liver disease admitted in the Department of Medicine, S.P. Medical College, P.B.M. and associated group of Hospitals, Bikaner. Chronic liver disease was defined as per 2014 ICD-10 CM Diagnosis Code K 76.9.[9] The diagnosis of cirrhosis of liver was based on previous liver biopsy if available or based on clinical, imaging (heterogenous echotexture of liver with irregular outline, altered liver size or portosystemic collaterals), laboratory (low serum albumin, aspartate aminotransferase/alanine aminotransferase ratio >1, GGT, PT-INR and aPTT) and endoscopic findings ($\geqslant$ grade 2 oesophageal varices). Acute ascites was defined as development of grade 2 to 3 ascites, according to the International Ascites Club Classification within a period of 2 week, either as the first episode or recurrence in a previously controlled patient. Bacterial infections were diagnosed either based on culture positive or with evidence of infection based on chest imaging for pneumonia, urine microscopy showing pus cells for urinary tract infection, ascitic fluid polymorphonuclear count more than 250 cells/ml for spontaneous bacterial peritonitis or clinical examination compatible with cellulitis. Active alcoholism was defined as alcohol consumption for the past three months.

ACLF as per the APASL[10] criteria was defined as "acute hepatic insult manifesting as jaundice and coagulopathy, complicated within four week by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease." As per the APASL criteria patients with prior decompensated cirrhosis were not considered to be having ACLF and infections were not included as acute precipitating events.

Definition of ACLF as per CLIF-SOFA system and grading of severity of ACLF was based on number and type of organ failures as per the CLIF acute-on-chronic liver failure in cirrhosis (CANONIC) study.[11] Organ failures were defined as per the CANONIC study criteria. Diagnosis of liver failure was by a serum bilirubin level of $\geqslant$ 12.0 mg/dl. Kidney failure was defined if serum creatinine level was $\geqslant$ 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 $\geqslant$ 2.5 and/or platelet count of $\leqslant$ 20000/cc. Circulatory failure was defined by 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 $\leqslant$ 200 or a SpO_2 to FiO_2 ratio of $\leqslant$ 214.

All patients were evaluated as per proforma including detailed history and physical examination and laboratory evaluation i.e. CBC, LFT (serum bilirubin , AST, ALT, serum total protein, serum albumin, serum globulin), RFT (blood urea, serum creatinine), serum sodium, serum potassium, GGT, alkaline phosphatase (ALP), PT-INR, blood sugar, aPTT. All patients underwent upper gastrointestinal (GI) endoscopy and USG. All patients were treated as per standard guidelines. Investigations for etiology of cirrhosis and cause of acute deterioration were performed as required on a case by case basis. Prognostic scores including Child-Pugh[12] scoring system was calculated as per previously published criteria. All scores and definitions were applied at the time of admission to this institute.

Data analysis was done in terms considering objectives of the study using descriptive and inferential statistics

Table 1: Demographic profile of cases of chronic liver disease (CLD).

	Alcohol	Autoimmune	Cryptogenic	HCV	HBV	Total
Number of cases	76	4	7	3	10	100
Mean age ±SD (years)	47.04±13.58	31.25±5.50	40.43±18.65	28.50±8.75	32.33±5.13	43.58±14.65
Sex (M:F)	76:00	00:04	02:05	01:02	05:05	84:16
Rural:Urban	60:16	00:04	04:03	02:01	08:02	74:26

HCV-Hepatitis C Virus; HBV- Hepatitis B Virus

frequency and percentage distribution were done to analyze demographic variables. Appropriate statistical analysis was applied as when required using SPSS software for statistics version 10.0.

RESULTS

Demographic profile of the CLD cases is shown in Table-1. Out of total 100 patients studied (age ranging 20 years to 82 years) 84 were males (mean age 44.31±13.58 years) and 16 females (mean age 40.19±19.11 years). There were 74% from rural area, 51% illiterate and 82% belonged to low socio-economic status. Underlying etiology of CLD was alcoholic: 76 cases (age ranging 27 years to 82 years, all males, 85% from low socioeconomic status, 57% illiterate, 79% from rural area, 80% belong to farmer or labor class), Hepatitis B Virus related: 10 cases (age ranging 20 years to 48 years, five males, five females, 90% from low socioeconomic status, 40% illiterate, 80% from rural area, five were house wife, four students and one businessman), cryptogenic :seven cases (age ranging 23 years to 65 years, two males, five females, 71% from low socioeconomic status, 29% illiterate, 57% from rural area, four house wife, one each belonging to government servant, student and labor class) , autoimmune: four (age ranging 24 years to 36 years, all females, 25% from low socioeconomic status, 25% illiterate, all from urban area, all house wife) and Hepatitis C virus related in three cases (age ranging 21 years to 38 years, two males, one female, 66% from low socioeconomic status, 33% illiterate, 67% from rural area, two house wife, one labor class)

Clinical profile of CLD cases is shown in table-2. Mean duration of history of CLD was 11.81±12.43 months (ranging from 2 to 72 months) at the time of hospitalization. Important presenting symptoms were upper GI bleed, altered sensorium, fever, pain abdomen, vomiting and decreased urine output.

Laboratory profile of CLD cases is shown in table-3. Although there was no statistical difference in various laboratory parameters depending upon underlying

Table 2: Clinical profile of cases of chronic liver disease (CLD).

Parameters	Alcohol		Autoimmune		Cryptogenic		HCV		HBV		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Duration of CLD (months)	11.48±11.49		08.50±04.69		17.71±19.66		08.30±04.58		15.50±16.80		11.81±12.43	
Upper GI bleeding	31	40.8	0	-	2	28.6	0	-	3	30.0	36	36.0
Hepatic encephalopathy	16	21.1	0	-	0	-	0	-	1	10.0	17	17.0
Fever	19	25.0	1	25.0	2	28.6	2	66.7	4	40.0	28	28.0
Vomiting	20	26.3	1	25.0	3	42.9	1	33.3	5	50.0	30	30.0
Melena	25	32.9	1	25.0	1	14.3	1	33.3	2	20.0	30	30.0
Pain Abdomen	15	19.7	1	25.0	4	57.1	1	33.3	6	60.0	27	27.0
Hepato - renal Syndrome	16	21.1	0	-	0	-	0	-	0	-	16	16.0
Anemia	39	51.3	3	75	4	57.1	1	33.3	5	50	52	52
Jaundice	49	64.5	2	50	5	71.4	3	100	6	60	65	65
Ascitis	76	100	4	100	7	100	2	66.7	7	70	96	96
Splenomegaly	52	68.4	4	100	7	100	3	100	9	90	75	75
Flapping tremors	14	18.4	0	0	0	0	1	33.3	1	10	16	16

Table 3: Laboratory profile of cases of chronic liver disease (CLD).

	Alcohol		Autoimmune		Cryptogenic		HCV		HBV		p
Parameters	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Hb (g/dl)	9.38	2.80	8.15	3.36	7.77	1.63	9.21	2.86	10.77	3.01	0.454
TLC (10^3 cmm)	11.55	4.52	7.03	2.69	9.56	3.91	9.37	2.79	10.33	4.90	0.149
Platelet Count (10^3 cmm)	146.92	52.34	127.50	44.80	166.43	56.03	145.40	50.83	183.33	27.02	0.567
Blood Sugar (mg/dl)	95.11	13.05	85.25	3.95	97.47	15.73	102.60	16.15	104.00	7.55	0.169
Sodium (mEq/l)	136.70	3.54	139.50	3.11	138.63	1.94	137.30	1.83	140.00	5.29	0.158
Potassium (mEq/l)	3.76	0.34	3.68	0.15	3.73	0.24	3.77	0.32	3.70	0.30	0.980
S. Bilirubin (T) (mg/dl)	3.51	3.38	2.18	1.44	4.86	2.78	4.98	3.95	6.30	1.82	0.278
S. Bilirubin (C) (mg/dl)	1.97	1.94	1.35	1.18	2.34	1.02	2.75	2.17	3.87	1.01	0.301
Bilirubin (UN) (mg/dl)	1.53	1.52	0.83	0.29	2.51	2.17	2.23	1.79	2.43	1.66	0.236
S. Protein (g/dl)	6.97	5.79	6.40	0.22	6.23	0.44	6.11	0.22	6.13	0.49	0.980
S. Albumin (g/dl)	3.30	0.50	3.55	0.10	3.14	0.51	3.43	0.34	2.80	0.36	0.213
S. Globulin (g/dl)	3.67	5.75	2.85	0.24	3.09	0.39	2.68	0.25	3.33	0.15	0.977
AST (units/l)	90.97	64.06	72.25	17.56	69.43	39.65	49.50	22.26	66.67	21.13	0.253
ALT (units/l)	95.45	93.48	74.25	21.48	55.86	25.27	47.90	20.05	62.67	20.55	0.378
S. ALP (IU/l)	206.84	118.94	126.25	25.51	243.57	247.39	154.20	34.34	183.00	52.31	0.416
aPTT (seconds)	42.64	20.99	29.30	8.82	32.51	10.35	29.44	7.54	32.33	3.51	0.128
PT-INR	17.45	3.15	14.50	2.55	16.21	2.62	16.64	2.11	13.87	0.86	0.086
GGT (units/l)	84.34	84.83	40.00	15.23	71.14	58.97	44.32	11.54	44.67	18.00	0.414
Blood Urea (mg/dl)	41.16	16.43	30.75	2.36	33.86	7.10	36.40	7.14	35.67	4.16	0.416
S. Creatinine (mg/dl)	1.50	1.24	0.78	0.05	0.87	0.15	0.88	0.21	0.90	0.30	0.207

etiology but moderate to severe anemia, leucocytosis, neutrophilia, high red cell distribution width, hyponatremia, hypoalbuminemia, hyperbilirubinemia, high PT-INR and azotemia were important observations in severe cases. Mortality rate in the present study was 9%, all belonged to alcoholic CLD, cause of death were massive upper GI bleed, hepatic encephalopathy, hepato-renal syndrome and sepsis in various combination. Depending upon presentation at the time of hospitalization 11.11% with hematemesis, 29.41%

with hepatic encephalopathy, 21.43% with sepsis and 56.25% with hepato-renal syndrome died. Severe anemia (Hb <8gm%, p<0.001), high blood urea (> 71mg%, p<0.001), serum creatinine (>4.16mg%, p<0.001), aPTT (>55 sec, p<0.008), PT-INR (>2.92 INR, p<0.001), serum bilirubin (>8.33mg%, p<0.001) Child Pugh score (>10) and hypoalbuminemia (<2.58gm%, p<0.001) were associated with mortality risk.

DISCUSSION

We studied 100 hospitalized patients of CLD with acute decompensation. Our observation on age of male and female patients were similar to previously reported studies.[13] We found high prevalence of CLD in males as most of the cases were alcoholic and alcoholism is very common in males in India and rare in females. A high prevalence of ACLF was observed in illiterates, patients belonging to low socioeconomic status and rural area because of the high prevalence of alcoholism, poor nutrition and health unawareness among them.

In our study, out of total 100 patients; 76 patients were alcoholic, out of them only 14 were consuming alcohol <100gm/day while 45 patients were consuming 100-200 gm/day and 17 patients were consuming alcohol >200gm/day. We found that majority of patients developing CLD were consuming alcohol more than 100 gm/day. Norton et al[14] also found that the risk of alcohol related cirrhosis increases with consumption of alcohol >60 gm/day.

Alcoholic liver disease was the most common underlying etiology of CLD in our study. Dhiman et al[15] in 2014 conducted a study on 50 patients to compare the utility of the Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) and Asia-Pacific Association for the Study of Liver (APASL) definitions of acute-on-chronic liver failure (ACLF) in predicting short-term prognosis of patients with ACLF. They also found that majority [43 (86%)] of the patients were male and mean age was 46 ± 13 years (range 22-78 years), alcoholic liver disease (58%) was the most common etiology of cirrhosis followed by cryptogenic (14%), hepatitis C virus (10%), autoimmune liver disease (6%), hepatitis B virus (6%) and Wilson disease (6%). Similar observations were reported by Scott and Garland[16] who performed a structured literature review to detail the frequency and etiology of chronic liver disease in aboriginal North Americans. Alcoholic liver disease was the leading etiology of CLD but viral hepatitis, particularly hepatitis C was an important and growing cause of CLD. High rates of autoimmune hepatitis was reported in regions of coasted British Columbia and South-Eastern Alaska. Recently, non alcoholic fatty liver disease (NAFLD) has emerged as leading cause of CLD in European countries especially in diabetics.[16]

We found that massive upper GI bleed, severe anemia, hepatic encephalopathy and hepato-renal syndrome were associated with a high mortality rate similar to observations made by the other workers.[13,17-20] Hepatic encephalopathy (HE) associated with ACLF occurred in cirrhosis, mostly alcoholics, with severe liver failure and systemic inflammatory reaction and in relation to bacterial infection.[21] We found 36% patients were admitted with bacterial infection out of them 93% patients had child score ≥7, 47.22% patients developed hepatic encephalopathy and 22.22% patients developed hepato renal failure; 22.22% patients died because of infection related acute- on - chronic liver failure (I-ACLF). Similar study was done by Bajaj et al[10] in the year 2014, on infection related acute on chronic liver failure. They included 507 patients with 15.8% infection. During hospitalization 55.7% developed HE, 15.1% required renal replacement therapy and 15.8% needed ventilation and 23% died within 30 days and 21.6% developed secondary infections. I-ACLF was defined as ≥2 organ failure given the significant change in survival probability. Low level of serum sodium, high bilirubin, ascites, high PT-INR and hepatic encephalopathy predict poor outcome in the present study .Similar results were reported by Garg et al[22] in their study on 91 patients of ACLF.

CONCLUSION

Alcoholic liver disease is becoming most common cause of chronic liver disease in Bikaner region. It is found to be common in illiterate and low socioeconomic class therefore it can be prevented by education and health awareness program. Upper GI bleeding and sepsis were the most common cause of acute decompensation in CLD. Hepatorenal syndrome and hepatic encephalopathy were the most common cause of mortality in CLD. We found severe anemia, hyponatremia, high bilirubin, high PT-INR, high serum creatinine, and high child pugh scores were associated with poor outcome. Knowledge and early recognition of various risk factors may help in prevention of acute- on- chronic liver failure and mortality.

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