Natural History of Cirrhosis of Liver after First Decompensation: A Prospective Study in India

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Background and aims: As liver cirrhosis is a dynamic condition, it is possible to improve survival in decompensated cirrhosis. Hence, we planned a prospective study to determine the natural history of cirrhosis after first decompensation. **Methods:** We enrolled all patients of liver cirrhosis who presented with first episode of decompensation defined by the presence of ascites, either overt or detected by Ultrasonography (UD), Gastroesophageal Variceal Bleeding (GEVB), and Hepatic Encephalopathy (HE). All patients were followed up to death/liver transplant or at least for the period of 1 year. Multivariable Cox proportional hazards regression was used to analyze the risk of failure (death or Orthotopic Liver Transplantation (OLT)). **Results:** In total of 110 cirrhotic patients (93 males, mean age 50 ± 11 years), the most frequent etiology was alcohol (48%), followed by nonalcoholic steatohepatitis/cryptogenic (26%), hepatitis B (10%), autoimmune hepatitis (7%), and hepatitis C (6%). The distribution of CTP classes was: 4%, 56%, and 41% in class A, B, and C, respectively. Ascites was the most common decompensation found in 88 patients (80%) followed by HE (14%) and GEVB (6%). At 1-year follow up, transplant free survival was 78%, 2 underwent OLT, 4 developed hepatocellular carcinoma, and 24 died. Cumulative incidence of failure (death or OLT) by type of decompensation after 1 year was: 22% overt ascites, 50% GEVB, 28% UD ascites, 20% HE, and 33% ascites and GEVB concomitant. **Conclusions:** Patients with UD ascites do not have a negligible mortality rate as compared to overt ascites. Patients with cirrhosis after first decompensation have better transplant free survival with treatment of etiology and complications than previously mentioned in literature. (J CLIN EXP HEPATOL 2018;8:50–57)

Liver cirrhosis is a dynamic condition where patient can progress from compensated to decompensated stage. Approximate prevalence of clinical cirrhosis in adults is 1 in 1000 and histological cirrhosis 1% in an adult population.¹ Median survival of patients with compensated cirrhosis is 12 years while that of decompensated patients is reduced to less than 2 years. Cirrhosis is accounting for 200,000 deaths per year in India.² Liver transplantation is the only treatment which improves both longevity and quality of life in patients with decompensated liver cirrhosis.³ However, every patient

with decompensated liver cirrhosis is not eligible for transplantation and it is not available for majority of the patients. Our current understanding of natural history, pathophysiology and treatment of complication has resulted in improved management, quality of life and life expectancy in patients with decompensated liver cirrhosis.⁴

The natural history of cirrhosis is characterized by an asymptomatic phase, referred to as “compensated cirrhosis,” followed by a progressive phase marked by the development of complications of portal hypertension and/or liver dysfunction, designated “decompensated cirrhosis.” Decompensation is defined by the development of ascites, portal hypertensive Gastrointestinal (GI) bleeding, encephalopathy, or jaundice.⁵ Cirrhosis is distinguished between compensated and decompensated stages, with different features, prognoses, and predictors of death.⁶

Acute-on-Chronic Liver Failure (ACLF) is an increasingly recognized entity encompassing an acute deterioration of liver function in patients with cirrhosis, which is usually associated with a precipitating event and results in the failure of one or more organs and high short and medium term mortality of 50–90%.⁷ The differentiation between ACLF and decompensated liver cirrhosis may remain difficult. It is likely that the most important difference between both entities is the potentially reversible nature of ACLF, by controlling the precipitating factor.⁸

Keywords: ascites, hepatic encephalopathy, hepatocellular carcinoma, liver transplant, survival

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Abbreviations: ACLF: Acute-on-Chronic Liver Failure; AIH: Autoimmune Hepatitis; APASL: Asian Pacific Association for the Study of the Liver; CI: Confidence Interval; GEVB: Gastroesophageal Variceal Bleeding; GI: Gastrointestinal; HE: Hepatic Encephalopathy; HBV: Hepatitis B Virus; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; HRS: Hepatorenal Syndrome; MELD: Model for End-Stage Liver Disease; NASH: Nonalcoholic Steatohepatitis; OLT: Orthotopic Liver Transplantation; PPI: Proton Pump Inhibitor; SAAG: Serum-Ascites Albumin Gradient; SBP: Spontaneous Bacterial Peritonitis; UD: Ultrasonography
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The increasing clinical awareness that cirrhosis/fibrosis is a dynamic process, not irreversible as thought in the past, have led to the assumption that liver transplantation is no longer the only possible option to increase patient survival.⁹ Evidence of fibrotic or cirrhotic regression has now been documented in the entire spectrum of CLDs, including Autoimmune Hepatitis (AIH), alcohol, biliary obstruction, iron overload, Nonalcoholic Steatohepatitis (NASH), and viral hepatitis B and C.^{10–16} In spite of this overwhelming evidence, the guidelines in the management of cirrhosis are not followed properly. Recent goals of therapy in decompensated cirrhosis are reversal of liver failure, decrease mortality, and decrease need for liver transplant.

METHODS

Study Population and Design

In prospective, longitudinal hospital-based cohort study, we enrolled all consecutive patients with cirrhosis (either followed by periodically surveillance as outpatients or after in-hospital admission) in whom a first episode of liver decompensation defined as (i) ascites (overt or Ultrasound detected alone (UD)), (ii) Gastroesophageal Variceal Bleeding (GEVB), and (iii) Hepatic Encephalopathy (HE) has occurred.¹¹ The follow-up schedules after hospital release were pre-established by the writing committee and they were based on 3-month intervals (clinical and biochemical, ultrasonography). Patients were followed up to death/Orthotopic Liver Transplant (OLT) or for minimum 1 year from inclusion of last patient.

Inclusion Criteria

All patients of cirrhosis of any etiology presented with first episode of decompensation as defined above of any age group.

Exclusion Criteria

All patients with previous episodes of liver decompensation, HIV co-infection, drug addiction, concomitant extra-hepatic neoplasm, hemodialysis, and solid organ or bone marrow transplantation were excluded.

Diagnostic Criteria for Inclusion

Diagnosis of previous compensated cirrhosis (either by histology or based on clinical ground) was available in all patients who had undergone periodical follow-up. For those who were unaware of a pre-existing liver disease, diagnosis was obtained by record (when available) and/or confirmed during hospitalization by ultrasound, computed tomography scan, and upper endoscopy. In the latter group of patients, a detailed history of the prior clinical course of their disease was accurately investigated at study entry in order to confirm the inclusion criteria.

Diagnosis of cirrhosis was based on clinical, biochemical, endoscopic, and imaging/histological findings. Diagnostic paracentesis was performed in all patients with ascites (overt or UD) in order to establish its portal-hypertensive nature by Serum-Ascites Albumin Gradient (SAAG) and to assess the concomitant presence of Spontaneous Bacterial Peritonitis (SBP) by a polymorphonuclear cell count in ascitic fluid >250 cells/mm³ and/or ascitic fluid culture positive. Hepatorenal Syndrome (HRS) and refractory ascites were diagnosed according to the International Ascites Club criteria.¹⁷ Bleeding was attributed to the rupture of GEVB by endoscopic report according to Baveno guidelines.¹⁸ Esophageal varices were classified into 2 grades (small and large) with a cut-off size of 5 mm.¹⁹ HE was defined as an episode of neurological and neuropsychiatric abnormality revertible after an effective ammonia-lowering treatment and graded according to West Haven grading.²⁰ Presence of Hepatocellular Carcinoma (HCC) was assessed by two coincidental imaging techniques. ACLF was defined as per (1) Asian Pacific Association for the Study of the Liver (APASL) group (2009): “acute liver injury manifesting as jaundice (serum bilirubin ≥ 5 mg/dl) and coagulopathy (INR ≥ 1.5 or prothrombin activity of 40%), complicated within 4 weeks by ascites and/or encephalopathy in a patient previously diagnosed or undiagnosed chronic liver disease”²¹ and (2) EASL-CLIF Consortium (2013) and graded as 1, 2, and 3 grade depending on single, two organ, and three or more organ failure, respectively.²² Liver failure as a cause of death was defined by serum bilirubin level ≥ 5 mg/dl and INR ≥ 1.5 with no identifiable cause of death like sepsis, bleeding, or HRS had been documented.

Treatments of complications were carried out according to current guidelines. Written consent of all patients and/

Figure 1 Flowchart of the study. HCC, Hepatocellular Carcinoma; OLT, Orthotopic Liver Transplantation.

Table 1 Baseline Characteristics of Patients According to the Presence or Absence of ACLF.

Variable ^a	Study population (n = 110)	ACLF (n = 31)	Non ACLF (n = 79)	P value
Age (years)	50.17 ± 10.80 (minimum = 17, maximum = 79)	43.68 ± 9.47	52.72 ± 10.25	.000
Gender				
Male	93 (84.5%)	28 (90%)	65 (82%)	
Female	17 (15.5%)	03 (10%)	14 (18%)	
BMI	25.61 ± 5.23	24.5 ± 5.34	26 ± 5.15	.165
Hemoglobin (g/dl)	10.51 ± 1.72	10.28 ± 1.65	10.6 ± 1.75	.382
Platelets (×10 ³ /mm ³)	148.8 ± 80.2	153 ± 77	147 ± 82	.000
S.bilirubin (mg/dl)	3.33 (0.38, 27)	11.21 ± 5.43	2.84 ± 3.08	.000
S.albumin (g/dl)	2.80 ± 0.55	2.46 ± 0.51	2.92 ± 0.50	.000
Prothrombin time (INR)	1.65 ± 0.56	2.05 ± 0.57	1.49 ± 0.46	.000
ALT	59.56 ± 35.21	73.87 ± 53.09	53.93 ± 23.13	.007
AST	87.63 ± 50.13	123.61 ± 64.90	73.50 ± 34.27	.000
S.creatinine (mg/dl)	1.24 ± 0.86	1.53 ± 1.40	1.11 ± 0.46	.022
S.sodium (meq/L)	134.42 ± 4.44	131.51 ± 4.81	135.55 ± 3.74	.000
Child–Turcotte–Pugh class				
A5/A6	4 (3.6%)	–	04 (5%)	.001
B7/B9	61 (55.5%)	04 (13%)	57 (72%)	
C10/C15	45 (40.9%)	27 (87%)	18 (23%)	
MELD score (median, IQR)	17 (12, 22)	25.80 ± 6.91	15.05 ± 5.32	.000
Gastroesophageal varices				
Small	66 (70.2%)	15	51	.46
Large	28 (29.8%)	05	23	
Etiology				
HBV	11 (10.0%)	01	10	.001
HCV	6 (5.5%)	–	06	
Alcohol	53 (48.2%)	26	27	
AIH	8 (7.3%)	01	07	
NASH/cryptogenic	29 (26.4%)	02	27	
Others ^b	3 (2.7%)	01	02	
In hospital admission	54 (49.1%)	18	36	.24
Outpatients	56 (50.9%)	13	43	

ACLF, Acute On Chronic Liver Failure; AIH, Autoimmune Hepatitis; ALT, Alanine Transaminase; AST, Aspartate Transaminase; BMI, Body Mass Index; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; INR, International Normalized Ratio; IQR, Interquartile Range; MELD, Model for End-Stage Liver Disease; NASH, Nonalcoholic Steatohepatitis.

^aValues are number and percentage, mean ± s.d. or median and IQR.

^bOthers include Wilson disease, Budd–Chiari syndrome and biliary cirrhosis.

or close relatives was taken. Ethical committee clearance had been taken from the institute's ethical review board.

Statistical Analysis

Data was recorded on a predesigned proforma and managed on Microsoft excel spreadsheet. In time-to-event analyses, the considered event of interest was death or OLT. The observation started from the time of first episode of decompensation and data were censored on

the date of the last follow-up visit. The cumulative incidences of death or OLT and HCC were calculated using the method of Kalbfleisch and Prentice and compared across different subgroups using the Gray test.^{23,24} For multivariate analyses, Cox proportional hazard regression modeling was used to analyze the factors associated with the outcomes and hazard ratios and 95% Confidence Intervals (CIs) were calculated for the strength of association. Survival analysis was done using Kaplan–Meier method.

Table 2 Baseline Clinical and Laboratory Characteristics of 110 patients of Decompensated Cirrhosis According to the Features of First Decompensation.

Variable ^a	Overt ascites (n = 63)	GEVB (n = 4)	UD ascites (n = 25)	HE (n = 15)	GEVB and ascites (n = 3)
Age (years)	51.92 ± 9.74	51.92 ± 9.74	51.92 ± 9.74	51.92 ± 9.74	51.92 ± 9.74
Gender					
Male	51 (81.0%)	2 (50.0%)	25 (100.0%)	12 (80.0%)	3 (100.0%)
Female	12 (19.0%)	2 (50.0%)	0 (0.0%)	3 (20.0%)	0 (0.0%)
BMI	26.35 ± 6.05	25.84 ± 3.68	24.92 ± 3.81	24.00 ± 3.95	23.50 ± 1.73
S.bilirubin (mg/dl)	5.26 ± 5.77	1.28 ± 0.83	4.65 ± 4.84	6.83 ± 5.48	5.93 ± 4.02
S.albumin (g/dl)	2.85 ± 0.54	2.83 ± 0.73	2.76 ± 0.51	2.66 ± 0.65	2.60 ± 0.44
Prothrombin time (INR)	1.57 ± 0.38	1.20 ± 0.22	1.58 ± 0.43	2.21 ± 0.98	1.86 ± 0.57
ALT	56.44 ± 25.02	56.00 ± 21.76	61.84 ± 35.07	61.47 ± 65.86	71.00 ± 36.01
AST	85.78 ± 37.85	58.25 ± 24.25	92.08 ± 50.29	93.67 ± 90.95	98.33 ± 29.84
Hemoglobin (g/dl)	10.80 ± 1.62	7.83 ± 1.51	10.86 ± 1.68	9.77 ± 1.47	8.87 ± 0.81
Platelets (×10 ³ /mm ³)	157.2 ± 84.7	143.7 ± 102.2	150.4 ± 83.2	117.1 ± 51.1	124.0 ± 22.7
S.creatinine (mg/dl)	1.24 ± 0.80	0.95 ± 0.29	1.28 ± 1.18	1.24 ± 0.65	1.07 ± 0.32
S.sodium (meq/L)	134.54 ± 4.36	136.0 ± 3.74	135.80 ± 3.61	132.33 ± 4.17	128.67 ± 8.74
Child–Turcotte–Pugh class					
A5/A6	2 (3.2%)	1 (25.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)
B7/B9	37 (58.7%)	3 (75.0%)	15 (60.0%)	5 (33.3%)	1 (33.3%)
C10/C15	24 (38.1%)	0 (0.0%)	9 (36.0%)	10 (66.7%)	2 (66.7%)
MELD score (median, IQR)	17.0 (11.0, 21.0)	9.5 (7.5, 13.0)	17.0 (12, 20.5)	23.0 (17.0, 29.0)	23.0 (11.0, 26.0)

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; GEVB, gastroesophageal variceal bleed; HE, hepatic encephalopathy; INR, international normalized ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; UD, ultrasonography detected.

^aValues are number and percentage, mean ± s.d. or median and IQR.

A *P* value of <0.05 was considered statistically significant.

RESULTS

A total of 130 patients were eligible as per inclusion criteria but 20 patients were not willing to adhere to protocol, so a total of 110 patients with first episode of decompensation of cirrhosis were enrolled and followed up. The flowchart of the study is illustrated in Figure 1.

The clinical and laboratory characteristics of the 110 evaluated patients at inclusion are shown in Table 1. There was male preponderance (85%) and mean age was 50.17 ± 10.80 years. The most frequent etiological factor was alcohol abuse (48.2%), followed by NASH/cryptogenic (26.4%). Three-fourth of alcoholic cirrhotics were abstinent at entry and remained abstinent during follow up. The results of biochemical parameters (SGOT > SGPT, low albumin) were consistent with the diagnosis of established cirrhosis. The distribution of CTP classes was: 3.6% class A, 55.5% class B, and 40.9% class C. Compared with patients with Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) etiology, subjects with alcohol-related disease showed a

more advanced stage of their condition (CTP class C: 60.37% vs. 11.76%, *P* < 0.001; median Model for End-Stage Liver Disease (MELD): 20 vs. 13, *P* = 0.003). Gastroesophageal varices were present in 94 patients (66 small and 28 large varices) and, among them, 39 subjects (41.5%) took β-blockers (propranolol or carvedilol) as a primary prophylaxis of variceal bleeding. Half of the patients were in-hospital admissions.

ACLF Group at Presentation

Out of 110 patients, 31 (28%) fulfilled the ACLF diagnosis as APASL definition. Precipitating factors for ACLF in decreasing order as follows: (1) active alcoholism in 19 (61%), (2) bacterial infection in 9 (30%), (3) active bleeding in 2 (6%), and (4) flair of Wilson's disease in 1 (3%). Sepsis was considered as precipitant of ACLF. No patient underwent renal replacement or mechanical ventilation. A severe hepatic impairment was very frequent: 87% of these subjects belonged to CTP class C and mean value of MELD was 25.80 ± 6.91. Mortality in ACLF group at 30 and 90 days was 32% and 45%, respectively. According to EASL-CLIF consortium, 10 patients had single organ failure, 8 had two organ, and 3 had three or more organ failure.

Figure 2 Survival probability during 12 months follow up according to type of decompensation.

Hepatic failure was most common followed by coagulation failure, renal failure, and cerebral failure. Ninety-day mortality in ACLF grade 1, 2, and 3 was 35%, 42%, and 48%, respectively.

Non-ACLF Group at Presentation

In comparison with previous subjects, these patients were significantly older, with less severe liver impairment. Mortality on follow up in this group was 10 (13%) as compared to 45% in ACLF group ($P = 0.000$) (Table 1).

Ascites was the most common decompensation (88 cases, 80%). Among them, 63 (72%) had overt ascites while 25 (28%) had UD ascites. Eight patients had SBP and one patient had HRS in ascites group. HE was second most common decompensation (15 cases, 13.64%). Grades of HE among them was: 6.67% grade 1, 66.67% grade 2, 20% grade 3, and 6.66% grade 4. GEVB was seen in 7 patients (6.36%) and among them 3 patients had both GEVB and overt ascites concomitant. Six out of 7 patients among GEVB had undergone endoscopic variceal ligation while one patient had undergone glue injection for gastric varix along with vasoactive therapy. Difference in the median MELD score was significant among different types of decompensation ($P = 0.012$) (Table 2).

Follow-up and Survival Analysis

A total of 110 patients were followed up for 1 year from the date of inclusion as per schedule and during the time of observation, 24 patients died, 2 received OLT, and

4 developed HCC. One-year transplant free survival was 78%. The main causes of death for 24 patients were the following: liver failure ($n = 19$), GEVB ($n = 1$), sepsis ($n = 3$), and HRS ($n = 1$). Cumulative incidence of failure (death or OLT) by type of decompensation was shown in Table 3. Survival analysis had shown that among expired patients, most patients died in first 3 months after decompensation irrespective of type of decompensation (Figure 2).

Alcoholics who remain abstinent on follow up had higher survival rate as compared to who were not abstinent ($P = 0.001$). Use of β -blockers did not differ significantly in patients with ascites who survived. Out of 110 patients, 20 patients had culture positive infections (18.18%) as precipitating event for decompensation with mortality of 45% (9 out of 20 patients). SBP was most common infection ($n = 8$) followed by UTI ($n = 7$), pneumonia ($n = 3$), and cellulitis ($n = 2$). A total of 23 patients were on proton pump inhibitor (PPI) before inclusion of study and all of them were taking minimum once daily dose for minimum 1-year duration, out of that 17 patients developed infections. Among the patients with infections, 13 out of 20 were on PPI and 5 out of 20 were on β -blockers, while 4 patients were on both PPI and β -blockers. Significant correlation between use of PPI and infection was seen ($P < 0.000$).

Predictive Model for Death/OLT

Prognostic factors predictive of mortality at 1 year after decompensation were shown in Table 4.

Table 3 Description of Observed First Clinical Events and Estimated Cumulative Incidence of Failure (Death and OLT) with 95% CI by Type of Decompensation at Baseline.

Group/category (n)	Cause of death				Total deaths	OLT	HCC	Cumulative incidence of failure (death and OLT) (95% CI) 1 year
	Hepatic failure	Bleeding	Sepsis	Hepatorenal syndrome				
Overt ascites (63)	10	0	2	1	13	1	1	22.22% (13.91, 30.54)
GEVB (4)	1	0	0	0	1	0	1	25.00% (15.03, 36.00)
UD ascites (25)	5	1	0	0	5	1	2	28.00% (19.02, 36.98)
HE (15)	3	0	0	0	3	0	0	20.00% (12.00, 28.00)
Ascites with GEVB (3)	0	0	1	0	1	0	0	33.33% (23.91, 42.76)

CI, Confidence Interval; GEVB, Gastroesophageal Variceal Bleeding; HCC, Hepatocellular Carcinoma; HE, Hepatic Encephalopathy; HRS, Hepatorenal Syndrome; OLT, Orthotopic Liver Transplantation; UD, Ultrasonography Detected.

DISCUSSION

The present cohort study demonstrates the epidemiology, clinical features, and disease outcome of patients with cirrhosis of liver of any etiology after the onset of their first episode of liver decompensation. The prospective enrollment of consecutive patients starting from their first complication has reduced potential selection bias. Participation of patients from different states provided a representative picture of patients with cirrhosis in India.

Patients with alcoholic cirrhosis were younger than NASH/cryptogenic cirrhosis ($P = 0.01$). Results were consistent with study by Patel et al. and Sarin et al. in India where mean age was same as our study.^{25,26} Patients with HBV infection or alcohol abuse were predominantly men, whereas female gender was highly represented in autoimmune and NASH/cryptogenic diseases. This study showed alcohol as the most common etiology of cirrhosis followed by NASH/cryptogenic cirrhosis, HBV, AIH, and HCV.

Recent epidemic of obesity, diabetes, and high prevalence of metabolic syndrome in India was explaining NASH as the second most common etiology of cirrhosis after alcoholism.²⁷ The number of patients with HBV infection was much lower, confirming that this condition has decreased over the past 20 years in our country, mainly because of the national vaccination plan and efficacy of antiviral therapy.

This study reports prevalence of ACLF as determinant of first decompensation. By using the APASL criteria, we found that 28% of the episodes of first complication in cirrhotic patients could be attributable to ACLF. Bruno et al. had reported 12% prevalence of ACLF as determinant of first decompensation.²⁸ Although it had been described that in the Asia-Pacific region, the majority of ACLF is precipitated by hepatitis B flares and acute hepatitis A or E superimposed on chronic liver disease, our study shows similar results with western studies where active alcoholism and infections were major precipitating events.²⁹ Thirty- and ninety-day mortality in ACLF defined by

Table 4 Comparison Between Model Considering only MELD Score (Model 1), Model also Including Type of Decompensation (Model 2), and Model also Including Type of Decompensation, Age, Sex, BMI, ALT, AST, Hb, Sodium, and Diagnosis of Diabetes (Model 3).

	Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
MELD (5 point increase)	1.46 (1.19, 1.79)	<0.001	1.39 (1.12, 1.85)	0.003	1.32 (0.97, 1.79)	0.002
Overt ascites vs. HE			2.54 (1.22, 4.02)	0.023	2.83 (1.13, 4.96)	0.021
Age (10 year increase)					1.02 (0.97, 1.07)	0.01
Gender (male vs. female)					1.03 (0.28, 3.76)	0.02
BMI (5 unit increase)					0.98 (0.89, 1.08)	0.06
ALT (times u.l.n., 1 unit increase)					0.99 (0.92, 1.00)	0.06
AST (times u.l.n., 1 unit increase)					1.01 (1.00, 1.03)	0.06
Hb (g/dl, 1 unit increase)					1.02 (0.78, 1.33)	0.01
Sodium (meq/L, 1 unit increase)					0.96 (0.87, 1.07)	0.04
Diabetes (yes, no)					1.21 (0.37, 3.93)	0.01

ALT, Alanine Transaminase; AST, Aspartate Transaminase; BMI, Body Mass Index; CI, Confidence Interval; Hb, Hemoglobin; HE, Hepatic Encephalopathy; HR, Hazard Ratio; MELD, Model for End-Stage Liver Disease; u.l.n., upper limit of normal.

APASL criteria in our study was lower than study by Garg et al.³⁰ (32% and 45% vs. 50% and 63%). The bigger group of patients with HBV reactivation, concurrently with the more severe disease stage of patients at presentation (median MELD 29 vs. 25, high proportion of both HRS and multiorgan failure), may justify the different rates of 3-month mortality between our study and Garg et al. study. Ninety-day mortality in ACLF grade 1, 2, and 3 was lower compared to Moreau et al. study (35%, 42%, and 48% vs. 40%, 52%, and 79%, respectively).²² Ninety-day mortality in ACLF group 3 was 48% which is very less as compared to CANONIC study and other Indian studies from various centers. There was a significant difference in the mortality rate between ACLF and non-ACLF group, highlights importance of identify and treat precipitating cause in ACLF.

Ascites was the commonest decompensation seen in 80% patients. The occurrence of culture positive SBP was 9% and HRS was 1% which was consistent with previous studies who has reported incidence of SBP between 7 and 30%.³¹ Mortality of patients with SBP was 45% in our study; on the contrary the trial in which cefotaxime plus albumin was studied reported an inpatient mortality rate of 10%.³² The finding that the vast majority of these cases received antibiotic prophylaxis according to international recommendations indicates that the epidemiology of bacterial infections has changed over the years and that the level of efficacy of the available therapy schedule has lowered.³³

In comparison with previous estimates reported by D'Amico et al., we found that prevalence of GEVB as a first cause of decompensation was extremely low. This discrepancy can be explained by the following reasons: (1) current widespread use of primary prophylaxis with β -blockers and/or endoscopic variceal ligation, (2) exclusive inclusion of patients at their first decompensation in spite of the presence of patients with previous decompensation, and (3) a collection of prospective cases instead of retrospective cohorts. One-year mortality according to prognostic stages of cirrhosis^{6,34} in our study was 25%, 24%, 33%, and 45% in stages 3, 4, 5, and 6, respectively. In the study by D'Amico et al.,³⁴ 1-year mortality rate was 10%, 21%, and 27% in stages 3, 4, and 5, respectively. Result of both studies suggests a fairly steady increase in death rate across stages.

Survival rates in patients with overt ascites paralleled those reported by Planas et al. and Alvarez et al. in HCV and alcohol-related cirrhosis, respectively.^{35,36} Ascites, more accurately than bleeding, reflects a severe impairment of both circulatory and renal function, giving the justification of the concordance of our results with those obtained in the past.³⁷ One-year mortality rate in patients with UD ascites was 20% in our study which was similar in study done by Bruno et al.²⁸ Results of survival rate in GEVB were consistent with meta-analysis suggesting

improved survival due to use of non-selective β -blockers and endoscopic band ligation as the effective therapies for primary and secondary prophylaxis of variceal bleeding.³⁸ Hepatic failure was the most common cause of death among all patients followed by sepsis.

In our study, 18% patients had culture positive infections as a precipitating event for decompensation and mortality rate of 45%. SBP was the most common infection followed by UTI, pneumonia, and cellulitis. These results paralleled to study done by Fernández et al.³⁹ Significant correlation between use of PPI and infections was seen ($P < 0.000$) in our study. A meta-analysis by Tri kudana- than et al. found a significant association between the use of PPI and the development of SBP which was also represented in this study.⁴⁰ PPI facilitates enteric bacterial colonization, overgrowth, and translocation, which might predispose to SBP.

Use of β -blockers in ascitic patients had not shown increased mortality in our study as contrary to previous study by Sersté et al.⁴¹ Reasons for this difference are: (1) most patients in our study were in the middle stages of cirrhosis when portal hypertension was significant and medium-to-large varices and ascites developed but systemic hemodynamic were still preserved. (2) Patients with refractory ascites were negligible in our study.

An accurate prognosis of 1-year mortality was enabled by combining multiple risk factors like type of complication, older age, male gender, diabetes, and MELD score in patients at the time of onset of first decompensation. There were few limitations of the study like patients with correctable etiology like HBV and AIH are less as compared to NASH and we are not able to analyze results of directly acting antivirals in decompensated HCV patients as it was not approved or available during the study period.

In conclusion, this is the first prospective study in India, which incorporated cirrhotic patients of all etiology from first decompensation and show higher transplant free survival at the end of 1 year with mortality characteristics according to different decompensation. Ascites was the commonest decompensation. Predominant cause of decompensation was infection and patients who were on PPI treatment had higher risk for infections. Patients with UD ascites do not have a negligible mortality rate as compared to overt ascites.

AUTHOR CONTRIBUTIONS

All the authors have contributed equally in conceptualizing, planning, data collection, and preparation of the manuscript.

CONFLICTS OF INTEREST

The authors have none to declare.

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