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# 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 2017;xx:1–8)**

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]

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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 extrahepatic 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/mm$^3$ 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 $\geq$ 5 mg/dl) and coagulopathy (INR $\geq$ 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 $\geq$5 mg/dl and INR $\geq$ 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/

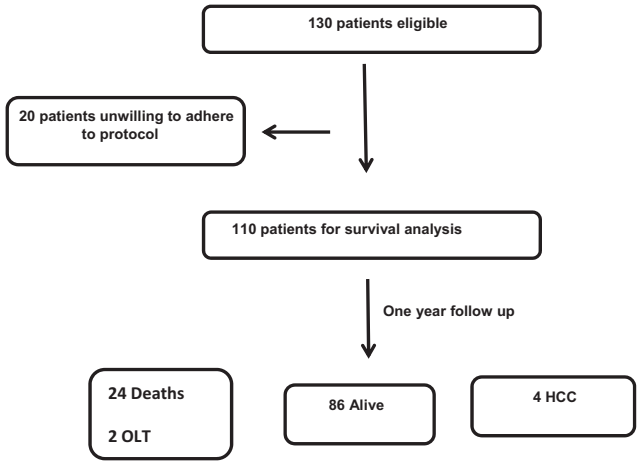


**Figure 1** Flowchart of the study. HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation.




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