Acute-On-Chronic Liver Failure

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KEYWORDS

• Acute-on-chronic liver failure • Acute liver failure • Organ failure
• Liver transplantation • Cirrhosis

KEY POINTS

- Acute-on-chronic liver failure (ACLF) is characterized by a precipitating event in patients with underlying chronic liver disease, leading to acute deterioration of liver function and often ending in multiorgan system failure.
- The physiology of ACLF can be divided into a 4-part model: (1) predisposition, (2) injury caused by the precipitating event, (3) response to the injury, and (4) organ failure.
- The definition of ACLF, like the definition of acute liver failure, requires liver dysfunction, and the prognosis depends on the number of extrahepatic organs involved (ie, renal, cerebral, circulatory, and pulmonary). Increasing numbers of organ failures with underlying cirrhosis usually portends progressively worse outcomes.
- Acute renal failure in patients with cirrhosis is associated with an almost 8-fold increased risk of death; smaller increases ($\geq$0.3 mg/dL) in creatinine level, some of which occur lower than the 1.0 mg/dL creatinine cutoff for MELD (Model for End-Stage Liver Disease) point allocation, have significant prognostic implications.
- ACLF carries a high mortality in wait-listed patients, and those who survive require prompt transplantation.

INTRODUCTION

According to the US Centers for Disease Control, chronic liver disease and cirrhosis is the 12th leading cause of death in the United States, and liver disease–related mortality has remained unchanged over the last 3 decades, despite dramatic improvements in general medical care, hepatology care, and post–liver transplant outcomes achieved during that time.[1] Chronic liver disease is not only a significant cause of morbidity and mortality but it accounts for a substantial portion of health care

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expenditure in the United States and worldwide.[2] Therefore, to improve prognostication and outcomes in patients with chronic liver disease, the current terminology that defines liver dysfunction must first be evaluated. Although liver dysfunction was often discussed as compensated versus decompensated cirrhosis, quantitation of liver dysfunction was first reasonably and accurately accomplished by the Child-Turcott-Pugh (CTP) score and is now accomplished in a more granular manner by the Model for End-Stage Liver Disease (MELD) score.[3,4] However, when a cirrhotic patient experiences an acute event, such as an infection, their pre-event MELD score does not accurately predict their mortality risk. The concept of acute-on-chronic liver disease emerged, because cirrhotics often experience a nonlinear progression in their liver disease (**Fig. 1**).[5–7] However, this notion has struggled to achieve universal acceptance as a uniform entity. In an effort to understand the concept and describe its implication peritransplant, it is important to distinguish acute-on-chronic liver failure (ACLF) from decompensation.

ACLF IS NOT DECOMPENSATED CIRRHOSIS

ACLF is a distinct entity from compensated and decompensated liver disease (presence of ascites, hepatorenal syndrome, variceal hemorrhage, hepatic encephalopathy, or synthetic dysfunction). In a population-based study, persons with compensated cirrhosis had a 5-fold, and persons with decompensated cirrhosis had a 10-fold, increased risk of death compared with the general population.[8] Most of the deaths among patients with compensated cirrhosis occurred because of a transition to decompensation and resultant complications. However, unlike the simple features of ascites, encephalopathy, hepatorenal syndrome, variceal hemorrhage, and hepatic synthetic dysfunction that characterize hepatic decompensation, ACLF focuses on the acute events (**Box 1**) that move patients from low-risk to high-risk of organ failure and death.

PHYSIOLOGY OF ACLF

Borrowing from the sepsis literature, Jalan and colleagues[6] parsed the pathophysiologic basis of ACLF into a 4-part model: (1) predisposition, (2) injury caused by

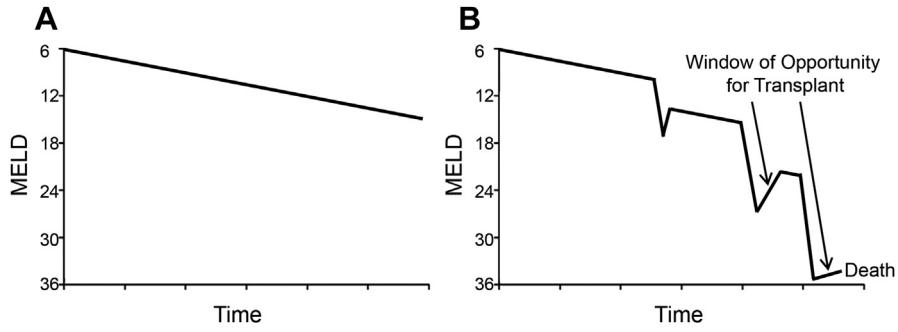

Fig. 1. (*A*) Few patients with cirrhosis experience a smooth and steady increase in MELD score over time. (*B*) Most patients have a background slope of slowly increasing MELD score, which is punctuated by ACLF events, which early on result in recovery, but later on result in longer periods of illness, less recovery potential, and a higher risk of multiorgan system failure. After the acute event has resolved, there is a window of opportunity to transplant patients while their MELD is high enough to receive priority, but they are no longer too sick for transplant.