Prognostic Models in Acute Liver Failure

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KEYWORDS

• Acute liver failure • Prognostic models • Model for End-Stage Liver Disease • MELD • King's College Criteria

KEY POINTS

- There is a strong imperative to develop valid and accurate prognostic modeling for acute liver failure (ALF).
- Despite the numerous clinical models that have been proposed thus far and the use of some such models, that is, King's College Criteria and Model for End-Stage Liver Disease, in clinical practice to aid decision-making, there is a significant need for improvement for determining patients' clinical course, survival, and requirement for liver transplantation.
- Future prognostic models shall need a stronger statistical foundation and accountability for time and variability in the clinical course of ALF and be applied for pretransplant and posttransplant outcomes.

INTRODUCTION

Acute liver failure (ALF) is the rare and rapid clinical deterioration of liver function in the setting of coagulopathy and worsening mental status. This multisystem clinical syndrome was first reported in the literature by Trey and Davidson in the 1970s.[1] The definition of ALF is widely agreed to be a rapid-onset, severe hepatic dysfunction of less than 26 weeks' duration, coagulation abnormality (international normalized ratio [INR] $\geq$1.5), and encephalopathy in patients without preexisting cirrhosis.[1] Otherwise known as fulminant hepatitis,[2] fulminant hepatic failure,[1] fulminant liver failure,[3] and acute hepatic failure,[4] ALF is associated with high morbidity and mortality with most cases occurring de novo in patients without preexisting liver disease.[5,6]

The clinical presentation of liver failure can vary dramatically. Signs and symptoms include altered mental status or encephalopathy, cerebral edema, jaundice, right

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upper quadrant tenderness, ascites, along with numerous other clinical features that can be seen in any patient with acute-on-chronic liver disease. The most predominant causes of ALF worldwide include viral hepatitis (specifically acute infection with hepatitis A or B), followed by drug-induced liver injury (mostly acetaminophen [*N*-acetyl-*p*-aminophenol (APAP)] overdose), autoimmune-related liver disease, ischemic or shock liver, and hypoperfusion injury.[7] In the United States, APAP-related injury remains the most common cause of ALF.[8] Recent data suggest ALF results in approximately 2000 deaths annually in the United States, a number that has not improved in more than 20 years.[7,9] Given the various causes that contribute to ALF, the variable survival associated with its course, and the numerous clinical complications that occur concomitantly in this syndrome, prognostic models to determine outcomes would be highly useful, though currently have limited success.

It is critical to identify and risk stratify those patients with ALF to rapidly determine who is eligible for liver transplantation. Currently, liver transplantation is the only treatment that has proven survival benefit; however, given the often variable clinical course of ALF and its rapidly progressive nature, it is occasionally not a viable option.[10] Depending on the cause of liver injury, clinical outcomes can be favorable and transplant-free survival can be achieved as high as 70% of the time, whereas other causes of liver failure can lower the likelihood of clinical recovery to less than 30% without a transplantation.[7] Liver transplantation is the cornerstone of the treatment of irreversible fulminant hepatic failure and in the setting of rapid innovation can result in the survival of up to 88% of the patients who undergo it based on the most up-to-date data.[10,11] Currently, the diagnosis of ALF accounts for 8% of liver transplantation cases in both the United States and Europe.[12,13] Thus, to gauge the clinical status of patients and determine their eligibility for orthotopic transplantation, the use of prognostic models is crucial in stratifying the degree of liver failure. It is equally important to identify those patients who are not suitable candidates for transplantation to prevent morbidity associated with transplantation and the lifelong challenges of immunosuppression.

CAUSES OF ACUTE LIVER FAILURE

In order to characterize and determine the course and prognosis of patients with ALF, it is important to identify the cause of the underlying disorder first. Before 1999, the 3 largest studies investigating ALF deemed hepatitis B and non-A, non-B, or non-C hepatitis (ultimately, a largely cryptogenic cause) to be the most common causes for ALF.[6,14,15] In 1999, Schiødt and colleagues[16] conducted a large multicenter study gathering data on 295 patients in 13 hospitals between 1994 and 1996. The investigators of this study identified APAP to be the most frequent cause of ALF in the United States based on drug toxicity in 20% of their patient sample. These data were consistent with the patient data collected from the United Kingdom[17] and Denmark,[18] although there were considerable differences in frequency of APAP hepatotoxicity between the countries. Twenty percent of ALF cases in the United States were attributed to APAP toxicity versus 50% to 70% recorded in the United Kingdom and Denmark. This statistical underestimation of liver injury attributed to APAP toxicity in the United States was likely because data collected in the United States for this study were solely obtained from transplant databases; thus, by default, any patient who had APAP toxicity who was not listed for orthotopic transplantation was not included in the analysis.[19] Similar findings were confirmed in a study conducted by the US Acute Liver Failure Study Group in 2002, specifically that APAP toxicity and drug-induced liver injury were the predominant causes of ALF.[7] Several years later in 2008, another large