Classification and Epidemiologic Aspects of Acute Liver Failure

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KEYWORDS

• Acute liver failure • Fulminant liver failure • Classification • Epidemiology • Race

KEY POINTS

- Acute liver failure is a life-threatening condition that requires early recognition and transfer to specialized centers to achieve good outcomes.
- It is not a single disease, but a whole group of varied etiologies, many of which are difficult to diagnose and lack specific treatment modalities.
- Understanding the epidemiologic aspects of the various conditions that lead to acute liver failure and their subtype classifications can help clinicians better identify and manage this condition.

INTRODUCTION

Acute liver failure (ALF) is a devastating condition with a high rate of short-term morbidity and mortality.[1] The disease has been labeled by multiple names, including fulminant hepatic failure, acute hepatic necrosis, fulminant hepatitis, and fulminant necrosis, but the preferred term is ALF.[2] It is a rare condition with a reported incidence of less than 5 cases per million population per year in the developed world and an estimated 2000 cases per year in the United States.[2,3] It should be noted, however, that accurate estimates of both the incidence and the morbidity of ALF are difficult to obtain, because many patients expire before transfer to a referral center and are thus not accounted for by estimated models.[4]

ALF, originally named fulminant hepatic failure, was defined in 1970 by Charles Trey and Charles Davidson as "a potentially reversible condition, the consequence of severe liver injury, with the onset of encephalopathy within 8 weeks of the appearance of the first symptoms and in the absence of pre-existing liver disease."[5]

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Aspects of this original definition are still in use today, although the condition has gone through multiple names and diagnostic criteria over the past 47 years. The most widely accepted definition of ALF is an abnormality in coagulation (practically an International Normalized Ratio of >1.5) with any degree of encephalopathy in a patient without cirrhosis and an illness duration of less than 26 weeks.[6] This review addresses the classification of ALF and the epidemiologic aspects of the disease, with a focus on the underlying etiology and its relationship to incidence and outcomes.

CLASSIFICATION

Since the initial definition by Trey and Davidson, there have been more than 40 different criteria that have attempted to define and subclassify ALF.[7] Of all of these definitions and classification systems, there are 4 that warrant special mention (**Table 1**). The Bernuau system, published in 1986, was the first to classify ALF into 2 subgroups: fulminant, in which less than 2 weeks pass between the onset of jaundice and symptoms of liver failure, and subfulminant, in which liver failure symptoms develop between 2 and 12 weeks after the onset of jaundice.[8]

In 1993, John O'Grady and colleagues[9] published the first classification system that accounted for the etiology, complications, and prognosis of ALF. The O'Grady system, still widely used today, subdivides ALF into hyperacute, acute, and subacute groups. Hyperacute liver failure is defined by hepatic encephalopathy (HE) developing within 1 week of the appearance of jaundice, patients in the acute group develop HE between 1 and 4 weeks, and patients with subacute liver failure develop HE between 4 and 12 weeks.

In an attempt to standardize the nomenclature and classification of ALF, the International Association for the Study of the Liver formed a subcommittee for the nomenclature of ALF and subacute liver failure. This International Association for the Study of the Liver subcommittee published their findings in 1999 and divided ALF and subacute liver failure into 2 distinct entities, rather than as subdivisions of an overarching condition.[10] ALF was defined as HE within 4 weeks of symptom onset, and subacute liver failure was defined as HE or ascites that develop between 5 weeks and 6 months of symptom onset. Because ALF was considered a separate condition from subacute liver failure by the International Association for the Study of the Liver, it was further subdivided into a hyperacute form, with the development of HE within 10 days of symptoms, and a fulminant form, with HE developing between 10 and 30 days from the first onset of symptoms.[10]

Historically, the definition and classification of ALF in Japan was different from that of Europe and the United States.[11] In an attempt to align their definitions, the Intractable Hepato-Biliary Diseases Study Group in Japan established a task force that published its revised definition and classification in 2011.[12] The Japanese defined ALF as an International Normalized Ratio of 1.5 or greater or a prothrombin time of 40% or less of the standardized value within 8 weeks of the onset of symptoms in a patient without prior liver disease. The presence of HE was not required to meet the definition of ALF; thus, ALF was subdivided into ALF with hepatic coma (grade 2 HE or higher) and ALF without hepatic coma (no HE or grade 1 HE). Those patients who had ALF with hepatic coma were further subdivided into an acute type, with HE developing within 10 days of symptoms, and a subacute type, with HE developing between 11 and 56 days after symptom onset. Patients who meet the criteria for ALF with hepatic coma but develop symptoms between 8 weeks (56 days) and 24 weeks are categorized as having late-onset hepatic failure.