# The Natural History of Nonalcoholic Fatty Liver Disease—An Evolving View

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**KEYWORDS**

• Insulin resistance • Metabolic syndrome • Obesity • Nonalcoholic fatty liver disease • Nonalcoholic steatohepatitis • Fibrosis • Steatosis • Cirrhosis

**KEY POINTS**

- Nonalcoholic fatty liver disease (NAFLD) is a worldwide epidemic, with global prevalence increasing in parallel with rates of obesity, diabetes, and the metabolic syndrome.
- Understanding of the natural history of NAFLD is evolving; recent studies suggest that both patients with steatosis and with steatohepatitis are at risk for progression.
- Patients with NAFLD experience elevated rates of cardiovascular events and higher-than-expected all-cause mortality; fibrosis is the strongest predictor of liver-related complications and mortality.

## INTRODUCTION

Since first described in 1980,[1] nonalcoholic fatty liver disease (NAFLD) is defined as the accumulation of hepatic fat, as evidenced by radiologic or histologic examination, in the absence of a coexisting cause of chronic liver disease or secondary cause of steatosis (including drugs, significant alcohol consumption, or inherited or acquired metabolic states). The spectrum of NAFLD encompasses 2 subtypes: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). Isolated NAFL is characterized by steatosis (which may be associated with mild chronic inflammation) in at least 5% of hepatocytes.

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On the other end of the spectrum, NASH is defined by a pattern of characteristics that include steatosis, lobular and portal inflammation, and liver cell injury in the form of hepatocyte ballooning. Lobular inflammation is classically mild, characterized by a mixed inflammatory cell infiltrate. Other potential histologic findings include Mallory–Denk bodies, iron deposition, periportal hepatocytes with vacuolated nuclei, ductular reaction, megamitochondria, lobular lipogranulomas, periodic acid–Schiff–diastase–resistant Kupffer cells, and acinar zone 3 perisinusoidal/pericellular fibrosis, which may be indistinguishable from alcoholic steatohepatitis.[2,3] In recent years, the NAFLD activity score, developed by the Pathology Committee of the NASH Clinical Research Network, has gained wide acceptance for histologically diagnosing NASH.[4] The NAFLD activity score assesses the degree of steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis. The NAS, however, does not supplant a pathologist's overall histologic evaluation.[5]

Histologically, it is important clinically to establish the distinction between NAFL and NASH, because most NAFLD patients have steatosis without necroinflammation or fibrosis and do not require medical therapy. In its more advanced stages, NAFLD can progress to fibrosis, cirrhosis, and end-stage liver disease with related complications, including hepatocellular carcinoma (HCC).[6]

To understand the clinical relevance of NAFLD, define long-term outcomes, and risk-stratify patients for disease-related complications and mortality, it is important to understand the natural history of the disease. Long-term observational studies, paired liver biopsy studies, and high-quality global meta-analysis have better defined the course of NAFLD. Conflicting data among studies persists, however, with resultant persistent ambiguity in the field. This review attempts to add to the current literature by summarizing recent high-quality evidence supporting the elucidation of the natural history of NAFLD.

## EPIDEMIOLOGY

A recent systematic review and meta-analysis has estimated the global prevalence of NAFLD, as diagnosed by imaging in the absence of significant alcohol use, to be approximately 25%, with the highest prevalence in the Middle East and South America and the lowest prevalence in Africa. Metabolic comorbidities associated with a diagnosis of NAFLD included obesity (51.34%), type 2 diabetes mellitus (22.51%), hyperlipidemia (69.16%), hypertension (39.34%), and the metabolic syndrome (42.54%).[7] In the United States, data from the National Health and Nutrition Examination Surveys (NHANES) conducted between 1988 and 2008 estimate that the prevalence of NAFLD increased from 5.5% to 11%, with concurrent increased prevalence of obesity, type 2 diabetes mellitus, insulin resistance, and hypertension. By contrast, the prevalence of hepatitis B–related, hepatitis C–related, and alcohol-related chronic liver disease remained stable over the same period of time. NAFLD is increasingly diagnosed in the pediatric population, with studies estimating prevalence rates of 3% to 18%.[8–11]

Based on data collected from the United Network for Organ Sharing and the Organ Procurement and Transplantation Network registry from 2004 through 2013, NAFLD is now the most common form of chronic liver disease in the United States and is the second-most common indication for liver transplantation.[12] The same study identified that new liver transplant waitlist registrants with NASH increased by 170%; however, these same patients experienced higher 90-day waitlist mortality and were less likely to undergo liver transplantation. NAFLD is on track to be the most common indication for liver transplantation by the year 2020.[13]