Progression and Natural History of Nonalcoholic Fatty Liver Disease in Adults

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KEYWORDS

• Steatohepatitis • Hepatocellular carcinoma • Type 2 diabetes • Obesity • Cirrhosis

KEY POINTS

- Liver-related mortality is the third cause of death in patients with nonalcoholic fatty liver disease (NAFLD) and is significantly higher in patients with nonalcoholic steatohepatitis (NASH) compared with patients with simple steatosis (7.3% vs 0.9% respectively) within the first 15 years of follow-up.
- The presence and severity of fibrosis on liver biopsy is currently the best indicator of long-term liver outcomes in patients with NAFLD.
- The rate of fibrosis progression is at around 1 stage every 6 to 15 years in patients with NASH but is reduced by half in patients with simple steatosis; however some patients with NAFLD, also with simple steatosis, can progress rapidly to clinically significant fibrosis.
- Patients with NAFLD with cirrhosis have lower rates of liver-related complications but similar overall mortality as compared with patients with hepatitis C virus because of a higher incidence of cardiovascular events.
- Hepatocellular carcinoma incidence is growing in patients with NAFLD with or without cirrhosis, particularly among those with multiple metabolic risk factors.

INTRODUCTION

The three leading causes of death in patients with nonalcoholic fatty liver disease (NAFLD) in descending order are cardiovascular disease, cancer, and liver disease. Although the extrahepatic complications of NAFLD are described elsewhere, this section is focused on the potential liver-related morbidity and mortality that, along with the large prevalence and increasing incidence of this disease in the general population, clearly forecast the future impact of NAFLD on health care.

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The burden of data on the liver-related complications of NAFLD comes from studies addressing both the clinical course and the progression of liver damage through paired liver biopsies, but tackling the natural history of NAFLD is one of the most difficult challenges for researchers. On one hand, the variety of criteria used to define NAFLD from the clinical point of view (abnormal liver enzymes, hepatic ultrasound, indices of liver fat, and liver biopsy), coupled with the lack of sensitivity and specificity of most of the tests used and the composite nature of NAFLD outcomes, has hampered most clinical studies. On the other hand, studies based on repeat biopsies are limited by sampling variability and by the lack of consensus on what is the best definition of nonalcoholic steatohepatitis (NASH). Several scoring systems have been described to classify liver histology in adults with NAFLD.[1–3] The NASH Clinical Research Network (CRN) classification is the most frequently used in recent studies; however, the NAFLD Activity Score (NAS) has often been used as a surrogate for the diagnosis of NASH, although it is not designed for it but rather for crude evaluation of disease severity, once the diagnosis has been established by the overall pathologic assessment. The prospectively designed Steatosis-Activity-Fibrosis score[2] has been recently introduced. Despite these caveats, the threat that NAFLD is going to replace chronic hepatitis C as major cause of liver morbidity and mortality should be no longer overlooked.

LIVER DISEASE PROGRESSION IN SIMPLE STEATOSIS AND NONALCOHOLIC STEATOHEPATITIS

Major prospective cohort studies have been derived from Western populations, whereas data in Asian, African, and Latin American populations are limited (**Table 1**). The overall long-term mortality of Western patients with the whole spectrum of NAFLD is 34% to 69% higher than the general population of the same age and sex within 15 years of follow-up and is mostly due to cardiovascular disease.[4] In a community-based study of 420 patients from the United States, liver disease was the third leading cause of death in patients with NAFLD, as compared with the 13th leading causes of death in the general Minnesota population.[5] However, only 21 (5%) patients were diagnosed with cirrhosis, and 3.1% developed liver-related complications, including one requiring liver transplantation (LT) and 2 developing hepatocellular carcinoma (HCC). Higher mortality was associated with age (hazard ratio [HR] per decade 2.2; 95% confidence interval [CI] 1.7–2.7), impaired fasting glucose (HR 2.6; 95% CI 1.3–5.2), and cirrhosis (HR 3.1; 95% CI 1.2–7.8).

Importantly, there is a prognostic association between the presence of NASH, the stage of liver disease (higher fibrosis stage), and the long-term prognosis of patients with NAFLD. In patients with NASH compared with patients with simple steatosis, both the prevalence of cirrhosis development (10.8% vs 0.7%, respectively) and the liver-related mortality are significantly higher (7.3% vs 0.9%) within the first 15 years of follow-up.[10] These findings have been repeatedly confirmed. In a landmark study,[9] although just 5% of the 129 patients with biopsy-proven NASH enrolled went on to develop end-stage liver disease, including 3 patients with HCC, liver-related mortality was increased 10-fold compared with the reference population. However, in patients with simple steatosis (or steatosis with mild inflammation/cellular injury), the overall and liver-related mortality risk was not different. In the long-term follow-up studies available thus far, only 1% of patients with simple steatosis developed cirrhosis and died a liver-related death after a mean 15.6 years of follow-up, compared with 11% of those with NASH having or developing cirrhosis, and 7.3% of those with NASH dying of a liver-related cause after a similar period of