Long-Term Outcomes of Nonalcoholic Fatty Liver Disease: From Nonalcoholic Steatohepatitis to Nonalcoholic Steatofibrosis

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The following commentary discusses a landmark article published in CGH and is part of a series that celebrates the journal's 15th year of publication. Landmark articles were chosen by the CGH Board of Editors and represent discoveries that advanced the science and practice of gastroenterology.

Although the term nonalcoholic steatohepatitis (NASH) was coined in 1989, it took another decade to recognize that NASH is a part of the clinicopathologic spectrum of nonalcoholic fatty liver disease (NAFLD) with subtypes with differential potential for progression.[1] In 2009, we published one of the first long-term outcomes study of NAFLD subjects in *Clinical Gastroenterology and Hepatology*.[2] In this study, subjects with biopsy-proven NAFLD with long-term outcomes data from the National Death Index were followed for a maximum of 28.5 years.[2] Although the study showed that the most common cause of death in the NAFLD cohort was cardiac related, subjects with biopsy-proven NASH experienced significantly increased liver-related mortality as compared with NAFLD subjects whose liver biopsies did not indicate steatohepatitis. This and other subsequent studies also documented that presence

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Long-Term Follow-Up of Patients With Nonalcoholic Fatty Liver

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Background & Aims: **Nonalcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of conditions ranging from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH) convincingly. NASH is the only subtype of NAFLD that has been shown to progress relatively, although these findings were reported from studies with short follow-up periods. We assessed the long-term outcomes of a NAFLD cohort.** ***Methods:*** **Patients with NAFLD established by biopsy were identified in databases and categorized as NASH or non-NASH. Mortality data and causes of death were obtained from National Death Index Plus. The nonparametric Kaplan–Meier method with log-rank test and multivariate analyses with a Cox proportional hazard model were used to compare different NAFLD subtypes and to identify independent predictors of overall and liver-related mortality.** ***Results:*** **Of 173 NAFLD patients (age at biopsy, 50.2 ± 14.5 y; 39.9% male; 80.8% Caucasian; 28.9% with type II diabetes), 72 (41.6%) had NASH and 101 (58.4%) had non-NASH NAFLD. Over the follow-up period, the most common causes of death were coronary artery disease, malignancy, and liver-related death. Although overall mortality did not differ between the NAFLD subtypes, liver-related mortality was higher in patients with NASH ($P < .05$). Independent predictors of liver-related mortality included histologic NASH, type II diabetes, older age at biopsy, lower albumin levels, and increased levels of alkaline phosphatase ($P < .05$).** ***Conclusions:*** **This long-term follow-up evaluation of NAFLD patients confirms that NASH patients have increased liver-related mortality compared with non-NASH patients. In addition, patients with NAFLD and type II diabetes are especially at risk for liver-related mortality.**

Nonalcoholic fatty liver disease (NAFLD) is associated with metabolic syndrome and obesity. NAFLD encompasses a wide spectrum of clinicopathologic conditions ranging from simple hepatic steatosis to steatosis with nonspecific inflammation and nonalcoholic steatohepatitis (NASH).[1,2] NAFLD rapidly is becoming one of the most common causes of chronic liver disease worldwide. According to the Third National Health and Nutrition Examination Survey, 23% of Americans may have NAFLD.[3–5] On the other hand, the worldwide prevalence of NAFLD in the general population ranges from 9% to 36.9%, whereas NASH ranges from 3% to 5%.[6–10] Furthermore, in the Dallas Heart Study, using magnetic resonance spectroscopy, the prevalence of NAFLD was 34%.[11] Given the fact that both the clinical definition of NAFLD used in the Third National Health and Nutrition Examination Survey analysis and the imaging studies used in other population studies may not diagnose some patients with NAFLD, this prevalence rate probably underestimates the true prevalence of NAFLD. In fact, in patients undergoing bariatric surgery with a liver biopsy, the prevalence of NAFLD is quite high, ranging from 60% to 95%. In addition, 25% to 30% of these patients had histologic NASH.[12–14]

Current research indicates differential progression for the subtypes of NAFLD.[1,15–20] NASH is the only subtype of NAFLD that has been shown convincingly to progress.[1,15–17] On the other hand, simple steatosis and steatosis with nonspecific inflammation (non-NASH subtypes of NAFLD) do not seem to progress. Nevertheless, most of the published studies of NAFLD have reported a relatively short period of follow-up evaluation. The purpose of this study was to assess the long-term mortality outcome of a cohort of patients with histologically proven NAFLD and its subtypes.

Methods

Patient Population

Data on patients with histologically proven NAFLD were obtained from our fatty liver databases. These databases included our previously reported cohort from the Cleveland Clinic Foundation (CCF),[1] as well as patients with biopsy-proven NAFLD from the Center for Liver Diseases (CLD). To be included in the study, a patient must have had biopsy-proven NAFLD with a minimum of 5 years of follow-up. Patients were excluded for the following reasons: (1) daily alcohol intake greater than 20 g in men and greater than 10 g in women; (2) other forms of chronic liver disease such as viral hepatitis, or medication-induced liver disease; (3) use of medications such as thiazolidinediones or biguanides; (4) bariatric surgery or small-bowel resection; (5) total parenteral nutrition; and (6) malignancy.

Clinical, demographic, and pathologic data were available for each patient. The demographic and clinical data included age, sex, race, height, weight, alcohol consumption, history of diabetes (established diagnosis and receiving treatment), history of hyperglycemia, history of hyperlipidemia, serum alanine aminotransferases (ALT), aspartate aminotransferases (AST), glu-

Abbreviations used in this paper: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CCF, Cleveland Clinic Foundation; CLD, Center for Liver Diseases; ICD, International Classification of Diseases; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NDI Plus, National Death Index Plus.

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of type II diabetes in NAFLD is an independent predictor of liver-related and overall mortality.[3,4]

This long-term study was followed by several other similar studies reporting almost identical results. Although our original findings still hold true today, there are several other advances in the field of NAFLD that are worthy of a commentary. In this context, we believe that the burden of NAFLD should be assessed in a comprehensive manner including its impact on clinical, economic, and patient-reported outcomes. The clinical impact of NAFLD relates to its prevalence, incidence, and progression. The global prevalence of NAFLD is estimated to be around 25%.[5] Although fewer studies are available regarding the incidence of NAFLD and NASH, they seem to follow the same trends as the rates for obesity.[5] In terms of progressiveness, there is now consensus that NASH is the subtype of NAFLD that can progress to cirrhosis and its complications.[1–8] There is also significant evidence suggesting that subjects with NAFLD are at increased risk for hepatocellular carcinoma,[9] and a small proportion of these cases of hepatocellular carcinoma can occur in the absence of cirrhosis.[10] Furthermore, there is substantial indirect evidence that most cases of cryptogenic cirrhosis in the United States are related to NASH and NASH can recur after liver transplantation.[11] In the context of increasing trends in its prevalence, NASH has now become the second most common indication for liver transplantation.[12]

In addition to the increasing prevalence in the general population, NAFLD prevalence rates are much higher in those with diabetes and severely obese subjects undergoing weight reduction surgery. Furthermore, the risk of NAFLD and NASH can vary by ethnicity.[13] In the United States, NAFLD has been found to be more common in Mexican Americans as compared with non-Hispanic whites and non-Hispanic blacks.[13] Even within an ethnic group, there are differences according to the country of origin.[13] However, African Americans have the lowest prevalence of NAFLD despite having higher prevalence rates of the risk factors associated with NAFLD (obesity, type 2 diabetes mellitus, and hypertension).[13] These variations suggest that development of NAFLD is influenced by both nature (genetics) and nurture (environment, diet). The exact contribution of these factors to the development of NAFLD and NASH may be different throughout the world and is not well understood. One interesting and intriguing issue is that about 18% of all NAFLD cases in the United States are lean according to body mass index threshold.[14] In contrast, there is higher prevalence of lean NAFLD in certain Asian countries with a higher to lower gradient of lean NAFLD from rural to urban areas. These data suggest that NAFLD and NASH are really just phenotypes reflecting several different underlying pathogenic mechanisms in different regions of the world.

It is important to note that not all subjects with NASH progress to cirrhosis. A small proportion of NASH subjects may even regress spontaneously.[15] Nevertheless, it has become important to determine which pathologic features seen in the liver biopsy of subjects with NASH can predict long-term outcomes of mortality. In this context, our group was the first to show that presence of significant hepatic fibrosis was the only independent predictor of liver-related mortality in NASH.[6] This was subsequently confirmed in another multicenter study and a recent meta-analysis.[7,8] In addition to the importance of hepatic fibrosis in predicting liver-related mortality, it is also the most reliable pathologic feature assessed by pathologists. In contrast, hepatocyte ballooning, Mallory-Denk bodies, and lobular inflammation that are key components of histologic diagnosis of NASH suffer from higher interobserver and intraobserver variability and are less reliable.[16] This makes the histologic outcome of "NASH resolution" quite problematic and emphasizes the superiority of "fibrosis improvement" as the most relevant and reliable histologic outcome. Finally, most efforts to develop the noninvasive radiologic and serum biomarkers for subjects with NASH (wet and dry biomarkers) are focused on determining stage of hepatic fibrosis. Although the current generation of noninvasive biomarkers is unable to replicate the accuracy the liver biopsy, future tests are highly likely to be quite accurate.

While awaiting the availability of new (more accurate) markers, it is prudent to focus on NAFLD with fibrosis as the most clinically relevant and reliable disease entity. In this context, we recently classified our NAFLD cohort as having either nonalcoholic steatofibrosis (steatosis with fibrosis with or without other features) or NASH.[17] The long-term data from this study show that both NASH and nonalcoholic steatofibrosis diagnostic categories are associated with increased liver-related mortality with almost identical fit statistics. In contrast, only steatofibrosis is associated with increased overall mortality.[17] Entering a new era of developing treatment regimens for subjects with NASH, it is important to focus on the type of liver disease that is most clinically relevant. Furthermore, one must choose clinical trial endpoints that represent the best surrogate for mortality in NAFLD and are also most robust and reliable. In this context, subjects with steatofibrosis may be the most clinically relevant and improvement of fibrosis in NASH may be the most robust endpoint.

To capture the comprehensive impact of NAFLD, it is important to assess its economic impact and its burden on patient experience. Studies have shown that patients with NAFLD experience impairment of their health-related quality of life with significant impairment in physical functioning and vitality.[18] Although these assessments have generally been performed using the generic PRO instruments, a disease-specific health-related quality of life tool was recently developed.[19] The disease-specific CLDQ-NAFLD has been fully validated and is currently being used in clinical trials for treatment of NAFLD.